



HAL
open science

Mesenchymal stromal cells for improvement of cardiac function following acute myocardial infarction: a matter of timing

Stéphanie Barrère-Lemaire, Anne Vincent, Christian Jorgensen, Christophe Piot, Joël Nargeot, Farida Djouad

► To cite this version:

Stéphanie Barrère-Lemaire, Anne Vincent, Christian Jorgensen, Christophe Piot, Joël Nargeot, et al.. Mesenchymal stromal cells for improvement of cardiac function following acute myocardial infarction: a matter of timing. *Physiological Reviews*, In press, 10.1152/physrev.00009.2023 . hal-04189475

HAL Id: hal-04189475

<https://hal.science/hal-04189475>

Submitted on 28 Aug 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Mesenchymal stromal cells for improvement of cardiac function following**
2 **acute myocardial infarction: a matter of timing**

3

4 **Stéphanie Barrère-Lemaire^{1,2#}, Anne Vincent^{1,2}, Christian Jorgensen^{3,4},**
5 **Christophe Piot^{1,5}, Joël Nargeot^{1,2}, Farida Djouad³.**

6 1- Institut de Génomique Fonctionnelle, Université Montpellier, CNRS, INSERM,
7 Montpellier, France.

8 2- LabEx Ion Channel Science and Therapeutics (ICST), Université de Nice, France.

9 3- IRMB, Université de Montpellier, INSERM, Montpellier, France;

10 4- CHU Montpellier, Montpellier, F-34295 France.

11 5- Département de Cardiologie Interventionnelle, Clinique du Millénaire; Montpellier, France;

12

13 # corresponding author:

14 Stéphanie Barrère-Lemaire

15 IGF, CNRS UMR-5203

16 Team “Cardioprotection, pathophysiology of heart rhythm and ischemia”

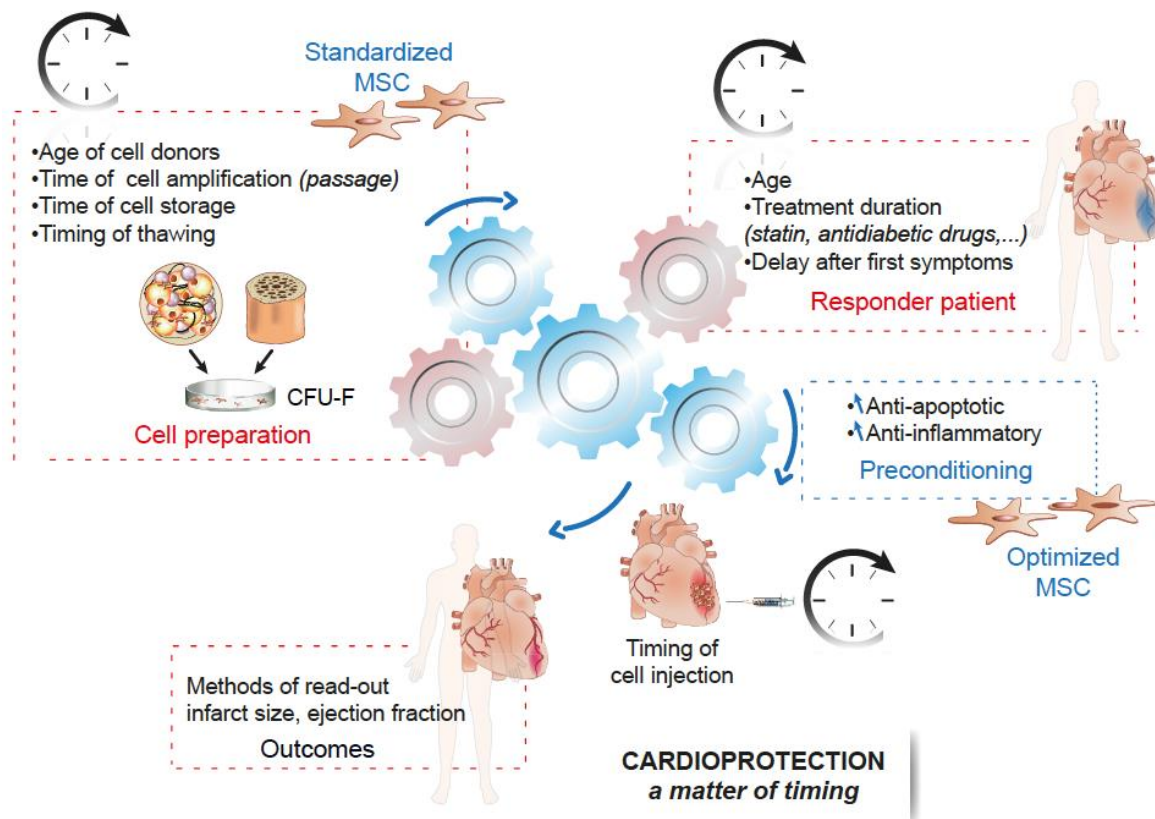
17 Department of Physiology and Cancer

18 141, rue de la Cardonille - F-34094 Montpellier, France

19 e-mail : Stephanie.Barrere@igf.cnrs.fr

20

21



22 **Clinical highlights**

23 The use of mesenchymal stromal/stem cells (MSC) in clinical trials has provided inconsistent outcomes
24 in patients with acute myocardial infarction (AMI), which contrasts with their promising results shown
25 in preclinical studies. The challenge for achieving success in the clinical setting is to generate an
26 optimized cell therapeutic product able to prevent cardiac injury because fully activated to release
27 cardioprotective molecules in the infarcted myocardium. In this context, data from the literature
28 highlighted the "matter of timing" as a critical parameter for the success of MSC therapy. Indeed, the
29 notion of time is involved in different ways such as between MSC culture and administration to patients,
30 the age of MSC donors and the age of AMI patients, and identified as a major parameter for the success
31 of MSC-based therapy. Current efforts are focused on MSC optimization in particular to circumvent the
32 effects related to an inappropriate timing.

33

34 **Abstract**

35 Acute myocardial infarction (AMI) is the leading cause of cardiovascular death and remains the most
36 common cause of heart failure (HF). Re-opening of the occluded artery i.e., reperfusion, is the only way
37 to save the myocardium. However, the expected benefits on infarct size are disappointing due to the
38 reperfusion paradox, which also induces specific cell death. These ischemia-reperfusion (IR) lesions can
39 account for up to 50% of final infarct size, a major determinant for both mortality and the risk of heart
40 failure (morbidity). In this review, we first provide a detailed description of the cell death and
41 inflammation mechanisms as features of IR injury, cardioprotective strategies such as ischemic
42 postconditioning (PostC) as well as their underlying mechanisms. Due to their biological properties, the
43 use of Mesenchymal Stromal/Stem Cells (MSC) has been considered as a potential therapeutic approach
44 in AMI. Despite promising results and evidence of safety in preclinical studies using MSC, the effects
45 reported in clinical trials are not conclusive and even inconsistent. These discrepancies were attributed
46 to many parameters such as donor age, *in vitro* culture and storage time as well as injection time window
47 after AMI, which alter MSC therapeutic properties. In the context of AMI, future directions will be to
48 generate MSC with enhanced properties in order to limit cell death in myocardial tissue, thereby reduce
49 infarct size, and improve the healing phase to increase post-infarct myocardial performance.

50

51 **Running head:** MSC to decrease cardiac injury

52

53 **Keywords:** mesenchymal stromal/stem cells; cardioprotection; apoptosis; myocardial infarction;
54 conditioning; inflammation.

55

56	Table of contents	
57	I- INTRODUCTION.....	p5
58		
59	II- Myocardial injury and aspects of cardioprotection.....	p6
60		
61	A. Mechanisms of cardiac injury	p6
62	1. Historical consideration and definitions	
63	2. Cell death mechanisms	
64	3. Contribution of inflammation to cardiac injury	
65	4. Temporal wave-front of cardiac injury	
66		
67	B. Endogenous mechanisms of cardioprotection	p21
68	1. Ischemic conditioning stimuli	
69	<i>1.1. Preconditioning</i>	
70	<i>1.2. Postconditioning</i>	
71	<i>1.3. Remote conditioning</i>	
72	2. Mechanisms underlying endogenous cardioprotection	
73	<i>1.1. Molecular mediators</i>	
74	<i>1.2. Remote mechanisms</i>	
75	3. Therapeutic time window of cardioprotection.	
76		
77	III- Generalities on mesenchymal stem cells (MSC).....	p32
78		
79	A. MSC definition	p32
80		
81	B. MSC developmental origins.....	p33
82		
83	C. MSC heterogeneity.....	p34
84		
85	D. MSC homing/biodistribution in the heart.....	p35
86		
87	E. MSC properties.....	p36
88		
89	1. Anti-apoptotic properties	
90	<i>1.1. Soluble factors</i>	
91	<i>1.2. Extracellular vesicles</i>	
92	<i>1.3. Tunneling nanotubes and organelle exchange</i>	
93	2. Anti-inflammatory/immunoregulatory properties	
94	<i>2.1. MSC priming/activation with inflammatory cytokines</i>	
95	<i>2.2. Anti-inflammatory properties</i>	
96	<i>2.3. MSC immunoregulatory properties</i>	
97		
98		
99	IV- MSC for the treatment of acute myocardial infarction.....	p48
100	A. Results obtained in preclinical studies and clinical trials	p48
101	1. In preclinical models	
102	2. In AMI patients	
103		
104	B. Origin of the gap for the clinical translation.....	p51
105	1. Influence of the cell therapy product and the recipient	
106	<i>1.1 Regarding the cells</i>	
107	<i>1.2. Regarding patients</i>	
108	2. Various MSC doses	
109	<i>2.1 Preclinical studies</i>	

110	2.2. <i>Clinical trials</i>	
111	3. Various timings of administration	
112	3.1. <i>Preclinical studies</i>	
113	3.2. <i>Clinical studies</i>	
114	4. Various routes of administration	
115	4.1. <i>Preclinical studies</i>	
116	4.2. <i>Clinical studies</i>	
117		
118	C. Strategies to improve MSC-based cell therapy.....	p59
119	1. How to overcome the influence of time on MSC-based therapy?	
120	1.1. <i>Which patients and protocol for the best benefits?</i>	
121	1.2. <i>Which protocol(s) to obtain MSC with optimal function?</i>	
122	2. Which protocol(s) to enhance MSC functions?	
123	2.1. <i>MSC preconditioning to improve their therapeutic potential</i>	
124	2.2. <i>MSC genetic modifications</i>	
125	2.3. <i>Use of MSC-derived EV or microparticles</i>	
126	2.4. <i>Combined therapies</i>	
127		
128	V- CONCLUSION.....	p66
129		
130	VI- GRANTS.....	p67
131		
132	VII- DISCLOSURES.....	p67
133		
134	VIII- ACKNOWLEDGEMENTS.....	p67
135		
136	IX-AUTHOR NOTES.....	p67
137		
138	X- AUTHOR CONTRIBUTIONS	p67
139		
140	XI- REFERENCES.....	p67
141		

142 I- INTRODUCTION

143 Acute myocardial infarction (AMI) ranks first in the leading cause of cardiovascular death and
144 is a strong provider of heart failure. According to the *World Health Organization*, cardiovascular
145 diseases are predicted to stay at the first rank until 2030 and this burden will be worsened due to an
146 aging population, an exponential growing number of diabetic patients and the COVID-19 pandemic
147 leading to cardiovascular complications. In 2023, prompt revascularization of the culprit artery to
148 reperfuse the myocardium is the only treatment for the care of AMI patients recommended by the
149 societies of cardiology in Europe and in USA. While timely reperfusion is crucial for AMI patients, still
150 15 to 30% of patients are admitted too late at the hospital for reperfusion therapy to be effective. In
151 addition, there is also a significant number of patients for whom reperfusion is not effective at all.
152 Optimized techniques of angioplasty and care management of patients have allowed to decrease infarct
153 size, a major determinant of mortality. However, for the patients surviving after AMI, morbidity rate for
154 heart failure is still rising. There is an urgent need to develop cardioprotective strategies to reduce the
155 high morbidity and mortality rates and the total burden in terms of public health and societal costs.
156 This review gathers authors with complementary expertise with the goal of identifying in the large panel
157 of studies in the field, the best conditions for providing a successful cell therapy tool able to prevent the
158 complex myocardial injury following AMI and for which no effective treatment is available. Section II
159 describes the main mechanisms involved in ischemia and reperfusion injury that are targeted by
160 mesenchymal stem/stromal cell-based therapy. While the goal of reperfusion is to save the myocardium
161 and decrease infarct size, it has deleterious effects, paradoxically exacerbating cardiac cell death at the
162 time of patient care and leading to specific so-called ischemia-reperfusion (IR) injury. In this review,
163 we describe the historical context of the discovery of both ischemic injury and reperfusion injury as well
164 as the mechanisms of regulated cell death (RCD) and inflammation as features of myocardial infarction
165 and reperfusion. We also describe the endogenous mechanisms of cardioprotection involved in ischemic
166 conditioning, in particular ischemic postconditioning (PostC), which is clinically relevant and also
167 represents a major concept attesting the existence of IR injury. Remote conditioning is also described
168 since it allows a non-invasive care of the patient. However, it is striking that in over 30 years of research,
169 all monotherapies tested in AMI patients have failed and that nowadays there is still no clinical treatment
170 for reperfusion injury. This explains why multi-target therapies such as inhibition of both apoptosis and
171 inflammation, identified as main contributors of PostC and mesenchymal stromal/stem cell (MSC)
172 therapeutic effects, have been explored and have provided promising results. This section highlights the
173 complexity of the mechanisms underlying the lesions and their unfolding in time highlighting the fact
174 that the treatments, to be effective, must be applied in a compatible and optimal temporal window.
175 Section III describes the various embryonic origins and the heterogeneity of MSC that exists at different
176 levels. The properties of MSC, in particular their anti-apoptotic, immunoregulatory effects and anti-
177 inflammatory potential, are discussed by highlighting the underlying mechanisms, including their ability

178 to release bioactive molecules and transfer organelles such as mitochondria and extracellular vesicles
179 (EV). The description of the phenotypic and functional heterogeneity of MSC is addressed in order to
180 identify strategies to generate standardized and optimized cells to achieve their maximal therapeutic
181 effect in AMI patients. Among these strategies, the enhancement of MSC survival rate and engraftment
182 in the damaged tissue as well as their anti-apoptotic properties on cardiac cells appears as a promising
183 approach.

184 Section IV is focused on the results achieved with MSC during acute myocardial infarction. We report
185 the promising issues obtained in preclinical studies by contrast to the clinical trials that reveal
186 heterogeneous and inconsistent outcomes, although the safety and efficacy of MSC in phase I and II
187 have been demonstrated. The second part of section IV analyzes the factors that could explain such an
188 heterogeneity of results in patients compared to preclinical data i.e., the source of MSC and the *in vitro*
189 amplification process of MSC obtained from patients. Finally, this section describes the methods used
190 to optimize MSC therapeutic potential and bring them into the routine clinical practice. In addition,
191 analysis and identification of the critical parameters including MSC doses, their routes and timing of
192 administration, should allow to further enhance the success of MSC-based therapies.

193

194

195 **II- Myocardial injury and aspects of cardioprotection**

196 In this section will be described the elements helping to understand the mechanisms of action of the
197 MSC involved in their cardioprotective effects. In particular, since MSC have been reported to protect
198 the heart in the context of AMI through an inhibition of both regulated cell death cascades and
199 inflammation. All the mechanisms underlying cardiac injury at the acute and subacute phases of
200 myocardial infarction as well as those mediating cardioprotection will be described.

201

202 **A- Mechanisms of cardiac injury**

203 **1- Historical consideration and definitions**

204 Myocardial infarction (MI) originates with an ischemic injury (**FIGURE 1A**) induced by the complete
205 occlusion or a severe reduction of the blood flow in a coronary artery. Ischemia, whose Greek etymology,
206 *ισχημια*, means “withholding blood”, generates alterations in the deprived cardiac region, which,
207 depending on the severity of the reduction of the coronary blood flow, will lead to the death of cells and
208 hence the heart muscle. The area perfused by the coronary artery downstream the site of occlusion
209 corresponds to the area at risk of infarction. Within a given area at risk, both the severity and duration
210 of the reduction in coronary blood flow will determine the amount of injury.

211

212 **Ischemic injury (FIGURE 1A)** In fact, infarct size depends on several parameters (1) including
213 the site of occlusion (proximal *versus* distal), which will determine the extent of area at risk (2), the

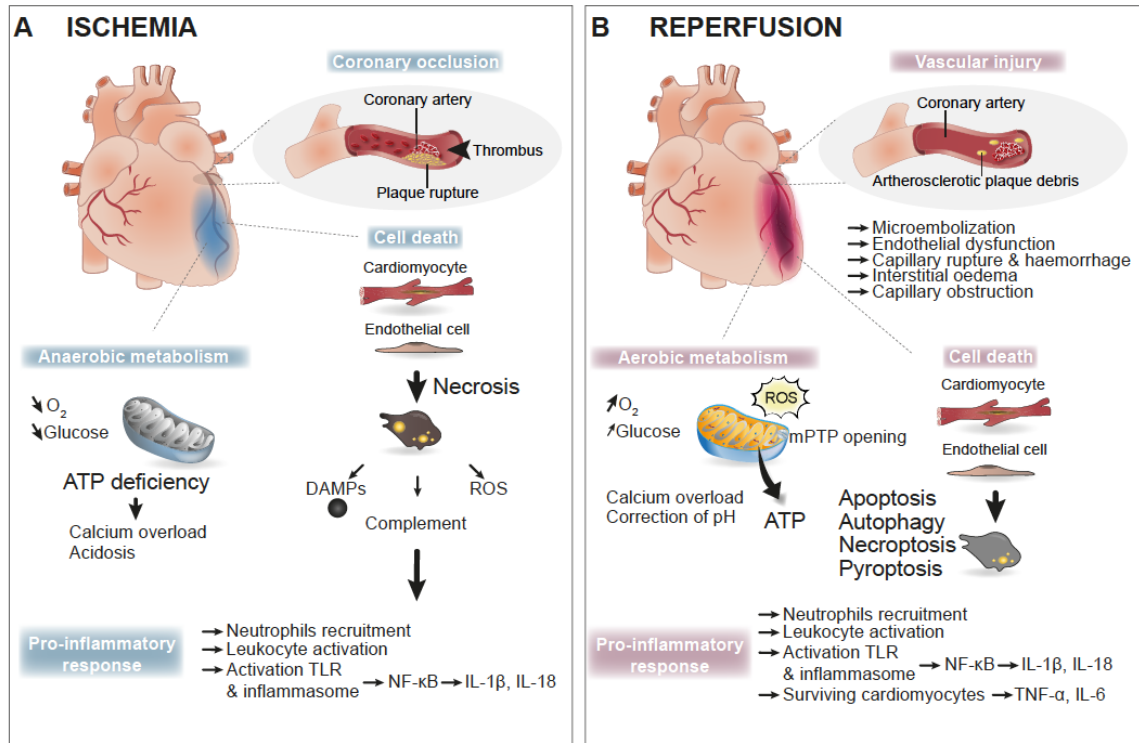
214 density of the collateral capillary network involved in the coronary circulation (1, 3, 4), the ischemia
215 duration (3, 5) as well as the haemodynamic parameters during ischemia such as heart rate (6, 7).
216 As a result of the interruption or reduction of blood supply, the lack in oxygen in the ischemic tissue
217 leads to the cessation of the respiratory chain in the mitochondria shifting their metabolism from aerobic
218 to anaerobic (8) *via* mechanisms well detailed in a previous review published in *Physiological Reviews*
219 in 2008 (9). The metabolic changes result in ATP deficiency leading to an increased production of
220 reactive oxygen species (ROS), acidosis and to impaired ion homeostasis (10). In particular, increased
221 cell resting membrane potential, reduced excitability associated to an increased potassium (K^+) efflux,
222 shorten action potential duration and decrease conduction velocity. These electrophysiological
223 modifications generate a potential substrate for the generation of arrhythmias leading to ventricular
224 fibrillation and sudden cardiac death (11, 12). Severe ischemic conditions during MI induce cardiac cell
225 death mainly by necrosis leading to the disruption of the cell membrane and the passive release of
226 DAMPS (*Danger associated molecular patterns*) (13).

227 In fact, both reversible and irreversible injuries are induced during myocardial ischemia. R.B. Jennings
228 was the first to clearly show that all myocytes of the sub-endocardium of the canine heart survived when
229 occlusion of the circumflex artery was maintained less than 15 minutes, due to reversible injury (13).
230 However, when the ischemic period was prolonged until 60 minutes, most of the subendocardial tissue
231 was dead, resulting in an irreversible injury. In those experiments, dead cells were evidenced due to their
232 degraded architecture with either membrane disruption, prominent “contraction bands”, or calcified
233 mitochondria. This princeps study clearly evidenced two major results: first, the notion of irreversibility
234 because some myocytes after reperfusion did not survive and second, restoration of arterial blood flow
235 after revascularization allowing the salvage of ischemic myocytes still alive, constituting the basis of
236 the actual reperfusion therapy (13, 14). K. Reimer and R. Jennings reported both the time line and the
237 wavefront of cell death within the transmural myocardium, starting from the sub-endocardium and
238 ending in the sub-epicardium (3). Following MI, around 1 billion cardiac cells die in response to
239 ischemia (15). The resulting “infarct size”, corresponding to the dead tissue, is mainly correlated with
240 the duration of the coronary occlusion (3, 5, 13, 16) and constitutes a major determinant of myocardial
241 functional recovery and mortality after MI (17).

242 Ischemic injury is also associated with functional changes in the infarcted tissue due to the lack of high-
243 energy phosphates. These metabolic changes take place following the switch from aerobic to anaerobic
244 glycolysis providing new high energy phosphates from glucose issued from glycogen stores. As a result
245 of lactate accumulation, the cytosol becomes acidic, the pH dumping from 6.6 after 10 minutes to 5.8
246 after 50 minutes of ischemia (18). Disturbance in calcium homeostasis is also a main characteristic of
247 ischemic injury due to the lack of ATP and the shutdown of ion pumps or channels leading to a defect
248 in contractile performance of the myocardium (19). At the acute phase, necrotic cardiac cells release
249 their cytosolic contents into the extracellular space, activating innate immune pathways, which have
250 been previously described in details by Xu et al. in *Physiological Review* (20). This resulting transient

251 but intense inflammatory response (see section II-A-3 below: *Contribution of inflammation*) allows
 252 repair of injured tissue through wound resorption and scar formation, but was also reported to prevent
 253 cardiac regeneration in adult mammals (21-23).

254



255

256 **FIGURE 1: Mechanisms of ischemia and reperfusion injury.**

257 **A:** Ischemia results from coronary occlusion, leading to a shift from aerobic to anaerobic metabolism.
 258 The lack of ATP induces the shutdown of ion channels and pumps leading to calcium overload. Acidosis
 259 results from the accumulation of lactate in the cytosol. Necrotic cells release DAMPs, produce ROS,
 260 and activate the complement cascade, inducing a burst of sterile inflammation: neutrophils and
 261 leukocytes are recruited, the inflammasome activates in circulating cells leading to the release of IL-1β
 262 and IL-18.

263 **B:** Upon reperfusion, aerobic metabolism is restored and mitochondria again produce ATP.
 264 Reperfusion injury is complex and multifactorial involving ROS, calcium (Ca^{2+}) overload, mPTP
 265 opening, vascular complications and cardiac cell death mediated by apoptosis, necroptosis, autophagy
 266 and pyroptosis. The pro-inflammatory response is exacerbated and mediated by TLR (2, 4, and 9) and
 267 NLRP3 signaling cascades. Activation of the inflammasome in circulating cells leads to release of IL-
 268 1β and IL-18 and to caspase-1 mediated pyroptosis in cardiomyocytes. Surviving cardiomyocyte in the
 269 border zone produce TNF-α and IL-6 pro-inflammatory cytokines.

270

271

272

273 **Reperfusion injury (FIGURE 1B)** J. Ross' laboratory was the first in 1972 to describe in a
 274 preclinical dog model of AMI that reperfusion, after 180 min coronary occlusion, reduced infarct size
 275 and restored contractile function, a cardioprotective effect maintained during 1 week after reperfusion
 276 (24, 25). With the aim to limit infarct size and improve cardiac function in patients after AMI,
 277 reperfusion therapy was translated into the clinics in the early 80's, first using intracoronary (IC)
 streptokinase infusion that allowed to restore coronary flow in 70 % to 90% of the cases and improved

278 left ventricular function compared to the non-reperused myocardium groups (26-29). However, despite
279 treatment with thrombolytics, the coronary stenoses that contributed to the infarction could only be
280 treated surgically by coronary bypass. Hartzler et al. reported the first experience in AMI patients using
281 percutaneous transluminal coronary angioplasty as an alternative to bypass surgery, alone or in addition
282 to thrombolysis (30). Percutaneous coronary intervention (PCI) later provided benefits in terms of both
283 myocardial salvage and clinical outcome, i.e. post-myocardial infarction (post-MI) recovery and patient
284 survival (31). Reperfusion therapy, preferably by PCI but also by thrombolysis, stays nowadays the only
285 treatment recommended for all types of MI (32-35).

286 The first evidence of coronary no-reflow phenomenon as a vascular complication by R. Kloner
287 highlighted the dark side of myocardial reperfusion (36, 37). In addition, the death of myocardial cells
288 in this dog model was reported to occur before the onset of capillary damage due to the lower energy
289 requirements of endothelial cells for their structural integrity conservation (36). In areas of no-reflow,
290 oxygenated blood and pharmacological agents cannot enter the ischemic region, thus preventing any
291 therapy to save the muscle in this area. A few years later, obvious signs of irreversible myocardial injury
292 such as rupture of cell sarcolemma were described in the same dog model (3, 5).

293 Despite clear evidence of direct cardiac cell injury upon restoration of the blood flow, the
294 existence of reperfusion injury has been a matter of debate since more than 30 years until the proof-of-
295 concept of PostC was provided, a main issue, which will be described in section I-B (38, 39). Ischemia-
296 reperfusion (IR) injury (see **FIGURE 1B**) includes both reversible mechanisms, such as myocardial
297 stunning, endothelial dysfunction and most of arrhythmias (with the exception of ventricular
298 fibrillations), but also irreversible damage characterized by cardiac cell death occurring in contractile
299 cardiomyocytes and vascular cells.

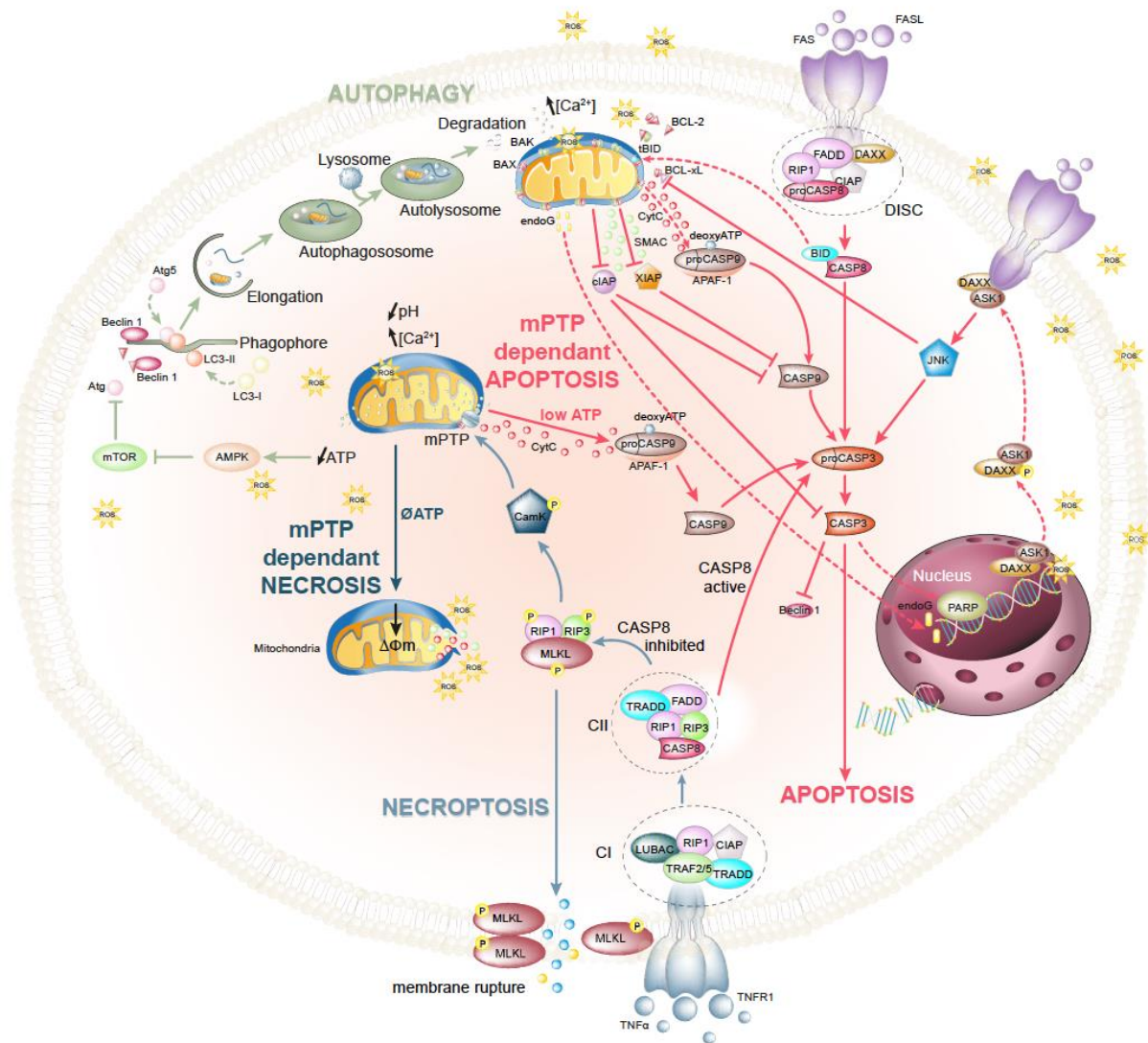
300 Upon reperfusion, the abrupt return of oxygen allows mitochondria to provide ATP after switching from
301 an anaerobic to an aerobic metabolism (**FIGURE 1B**). Due to the accumulation of the substrate
302 succinate, an overproduction of ROS occurs, leading to oxidative stress (around 6-fold more than in
303 ischemic conditions) (40, 41). As a result, IR injury includes metabolic alterations, ROS overproduction,
304 autophagy deregulation, mitochondrial dysfunction, cytosolic and mitochondrial calcium overload,
305 cardiomyocyte hyper contracture as well as apoptosis (**FIGURE 2**). At the tissue level, IR is associated
306 with a dysfunction of the microcirculation, an influx of inflammatory cells and edema (42). We will
307 focus our review on irreversible damage mediated by RCD mechanisms including necrosis, apoptosis,
308 necroptosis and autophagy.

309

310 **2- Cell death mechanisms**

311 MI is defined as cardiac cell death caused by both ischemia and reperfusion resulting from
312 necrosis, apoptosis, necroptosis, autophagy and pyroptosis cell death mechanisms as illustrated in
313 **FIGURE 2**.

314

315
316

317 **FIGURE 2: RCD mechanisms activated upon IR injury.**

318 Apoptotic or necrotic pathways activate during severe IR injury by contrast to autophagic cell death
 319 activating during moderate injury to ensure survival. Mitochondria are stimulated by various stresses
 320 including ischemia-reperfusion, oxidative/proteotoxic stress, DNA damage or increased cytosolic
 321 concentrations of Ca^{2+} . The **intrinsic pathway of apoptosis** is characterized by MOMP under the control
 322 of proteins from the BCL-2 family. Oligomerization (hetero- or homo-) of BAX and BAK to form pores
 323 in the outer membrane is dependent on BH3-only protein regulators and leads to the release of Cyt C,
 324 that binds to APAF-1 with dATP to constitute the apoptosome, in which procaspase-9 is activated and
 325 SMAC binding XIAP or cIAP, preventing them to inhibit caspase-3 and -9. Caspase-9 subsequently
 326 activates downstream procaspase-3. Active Caspase-3 cleaves PARP in the nucleus leading to DNA
 327 fragmentation. EndoG, released by mitochondria, contributes also to DNA fragmentation. In parallel,
 328 mPTP opening is triggered at the onset of reperfusion by the burst of ROS, a further increase in
 329 mitochondrial Ca^{2+} and the restoration of a physiological pH. In these conditions, the H^+ gradient
 330 across the inner mitochondrial membrane is lost, leading to the depolarization of the mitochondrial
 331 membrane potential, $\Delta\psi_m$. The permeabilization of the inner membrane leads to a swelling of the matrix
 332 due to osmotic pressure, inducing the rupture of the OMM and the release of pro-apoptotic Cyt C in the
 333 cytosol. BAX and BAK regulate or participate in the formation of the mPTP as proteins from the outer
 334 membrane.

335 The **extrinsic pathway** is mediated by the FAS receptor (TNF family) activated by external stimuli
 336 (FASL). Homotrimers of FAS undergo a conformational change favoring homotypic interactions with

337 intracellular death domain-containing proteins such as FADD. This pathway recruits pro-Caspase-8 in
 338 the DISC protein complex formed by FAS, FADD and RIP1, leading to its auto-proteolytic cleavage.
 339 Activated caspase 8 will in turn active caspase 3 directly or indirectly via the cleavage of cytosolic BID.
 340 tBID translocates and inserts into the mitochondrial outer membrane where it contributes to the release
 341 of Cyt C through mechanisms either involving BAX or independently of BAX.
 342 The nuclear protein DAXX also plays a crucial role in the intracellular signaling cascade of the FAS
 343 membrane receptor. DAXX nucleocytoplasmic export is triggered by oxidative stress during reperfusion
 344 and mediated by the MAPK kinase ASK1. DAXX possesses a critical role in FAS-mediated cell
 345 death to optimally form the DISC. The activation of ASK1 results in the phosphorylation and activation
 346 of JNK to induce cell apoptosis through the JNK-BAX-dependent mitochondrial pathway.
 347 **Necroptosis** is defined as a regulated death mechanism triggered by TNF, FasL and TRAIL ligands.
 348 Following activation of complex I (TNFR, RIP1, TRADD, cIAP1/2, LUBAC), complex II (TRADD,
 349 FADD, RIP1 and pro-caspase 8) activates and triggers initiation of apoptosis or necroptosis (no
 350 cleavage of RIP1 in case of caspase-8 inhibition). The association of RIP3/RIP1 with MLKL within the
 351 necrosome complex leads to MLKL phosphorylation and membrane permeabilization. CAM kinase is a
 352 substrate of RIP3 leading to activation of the mPTP-dependent mitochondrial pathway.
 353 **Autophagy** is activated in the heart during ischemia with ATP depletion and subsequent activation of
 354 AMPK to eliminate intracellular waste from proteins, lipids and organelles damaged during stress.
 355 Autophagy is inhibited by the survival proteins AKT or mTOR. Beclin-1 controls the initiation of
 356 autophagosomes, ATG their elongation and recruit the cytosolic protein LC3-I which, once transformed
 357 into LC3-II, will be integrated into the autophagosome membrane. Functional autophagy invariably
 358 culminates in lysosomal degradation. Beclin-1 is cleaved by caspases, showing the existence of a
 359 crosstalk between autophagy and apoptosis.

360
 361
 362 **During ischemic injury**, passive mechanisms of cell death are triggered due to the lack of ATP.

363 Necrosis is the first mechanism described initially to occur during this phase in cardiomyocytes. It is
 364 characterized by plasma membrane permeability and the release of DAMPS in the extracellular space
 365 (13). By contrast to RCD mechanisms, this form of apoptosis cannot be prevented.

366 Lethal reperfusion injury is defined as the death of cardiac cells, viable at the end of the ischemic period,
 367 that occurs within the first minutes of reperfusion in cells (43, 44). This concept was supported by studies
 368 showing that the mitochondrial permeability transition pore (mPTP) opening, considered as the key
 369 event responsible for cardiomyocyte death, opens within the first 5 minutes of reperfusion (45). In fact,
 370 either apoptosis, necrosis, necroptosis or autophagy cell death mechanisms can all be activated upon IR
 371 injury, depending on the intensity of the stress (46): if the lesions are moderate, autophagy will be
 372 activated to ensure cell survival; if ischemia is more intense, cell death will be induced mainly by
 373 apoptotic or necrotic route, with a continuum between the two mechanisms. Intensive research in the
 374 last 30 years has been conducted to inhibit IR-induced cell death, however no treatment has been yet
 375 validated for its use in the clinical setting (47).

376 The existence of apoptotic mechanisms in the IR myocardium, described first by Gottlieb et al. in an *in*
 377 *vivo* rabbit model, was evidenced in different animal models and human ischemic heart disease, and
 378 considered of potential interest for therapeutic intervention in cardioprotection (48-51). Moreover,
 379 numerous studies have shown the beneficial effect *in vivo* of specific anti-apoptotic interventions against
 380 myocardial IR injury (see below in section I-C-1) (52-59). By contrast, another study using *in vivo*
 381 models of cardiac-specific caspase-3 deficient/full, caspase-7-deficient mice (Casp3/7DKO) reported

382 that caspases-3 and -7, known as executioner caspases since they can cleave target proteins leading to
 383 characteristic apoptotic breakdown of a cell, do not significantly contribute to cardiomyocyte death
 384 induced by transient coronary occlusion (60). These discrepancies on caspase contribution were
 385 explained by a global reduction of the whole caspase-dependent pathway expression in terminally
 386 differentiated cardiac cells (61). However, an immunohistochemical study performed on post-mortem
 387 human hearts slices clearly showed that caspase 3-dependent apoptosis is an important mode of
 388 cardiomyocyte cell death in MI in the early period (less than 24h) in particular in infarcted heart tissues
 389 who received reperfusion therapy. When analysis was performed on samples taken later (more than 48h),
 390 caspase-3 activity was detected in neutrophil granulocytes and inflammatory cells (62).

391

392 **Apoptosis** is a highly regulated, energy-dependent form of RCD defined as “*type I cell death*
 393 *or apoptosis, exhibiting cytoplasmic shrinkage, chromatin condensation (pyknosis), nuclear*
 394 *fragmentation (karyorrhexis), and plasma membrane blebbing, culminating with the formation of*
 395 *apparently intact small vesicles (commonly known as apoptotic bodies) that are efficiently taken up by*
 396 *neighboring cells with phagocytic activity and degraded within lysosomes” (46). The dependence on*
 397 *ATP production makes apoptosis incompatible with ischemic conditions and makes it specific to the*
 398 *reperfusion phase: apoptotic cascades pre-activate during ischemia and are fully executed during*
 399 *reperfusion, in the presence of ATP, leading to specific DNA fragmentation (63). Apoptosis retains the*
 400 *integrity of the plasma membrane and the metabolic activity until the final stage where the plasma*
 401 *membrane breaks down and the cells acquires a necrotic morphotype (secondary necrosis) (46). Two*
 402 *main apoptotic pathways, the intrinsic (or mitochondrial) and the extrinsic (depending on death*
 403 *receptors), are activated during IR injury.*

404 **The intrinsic, or mitochondrial pathway** has been described in detail in 2019 by Del Re et al. (64) in
 405 *Physiological Reviews*. It is defined as a type of RCD initiated by perturbations of both the extracellular
 406 or intracellular microenvironment. It is characterized by the permeabilization of the mitochondrial outer
 407 membrane (MOMP) and precipitated by executioner caspases, mainly Caspase-3 (**FIGURE 2**) (46, 65,
 408 66). MOMP is mediated by homo/hetero oligomers of BCL-2 associated to X apoptosis regulator (BAX),
 409 and/or BCL2 antagonist/killer 1 (BAK1 or BAK) transmembrane proteins with BH domains
 410 (Homologous to *B-cell lymphoma 2*, BCL-2) (67), that form pores across the outer mitochondrial
 411 membrane (OMM) and lead to a large increase in outer mitochondrial permeability (68, 69).
 412 Permeabilization results in the release into the cytoplasm of the pro-apoptotic factors: (i) SMAC (Second
 413 Mitochondrial Activator of Caspases)/DIABLO that binds and inhibits XIAP (X-linked Inhibitor of
 414 Apoptosis); (ii) endonuclease G that cleaves DNA (caspase-independent mechanism), and (iii)
 415 cytochrome c (Cyt C), the loss of which in the mitochondrial respiratory chain leads to the dissipation
 416 of the mitochondrial transmembrane potential ($\Delta\psi_m$) and cessation of mitochondrial functions such as
 417 ATP synthesis (70). Cyt C binds to and stimulates the oligomerization of APAF-1 (*Apoptotic peptidase*
 418 *activating factor 1*) and the subsequent recruitment and activation of caspase-9. In turn, executioner

419 caspases 3/6/7 activate, leading to specific DNA fragmentation and cell apoptosis (71). The
420 characteristic apoptotic morphology results from the caspase-mediated cleavage of key proteins such as
421 poly (ADP-ribose) polymerase (PARP), actin, or lamins (72).

422 An increase in inner mitochondrial membrane permeability occurs when the mega channel mPTP (73),
423 maintained closed in acidic ischemic conditions, opens upon reperfusion. The molecular identity of the
424 mPTP is still not fully unraveled despite significant progress in the recent years (74). The adenine
425 nucleotide translocator (ANT) was proposed first as candidate for mPTP channel formation. Several
426 proteins from the different compartments have been described also as contributors: VDAC (voltage-
427 dependent anion channel), BCL-2 family proteins, Translocator protein (TSPO) called benzodiazepine
428 receptor from the OMM, and the IMM protein F1Fo ATPase as well as CyPD (cyclophilin D) from the
429 matrix (for review (75)). mPTP opening is triggered by the cellular stress generated by the burst of ROS,
430 an increase in mitochondrial Ca^{2+} and the restoration of a physiological pH (76-83). This
431 permeabilization of the inner membrane leads to a swelling of the matrix due to osmotic pressure caused
432 by the high concentration of proteins in the matrix relative to the outer component of mitochondria.

433 It is important to note that the mPTP and BAX/BAK proteins together contribute to both the
434 mitochondrial pathway and the mPTP-driven necrosis RCD mechanisms, suggesting a crosstalk
435 between apoptosis and regulated necrosis (46, 64, 84). In fact, the time frame of mPTP opening
436 determines the mechanism of RCD: short-term opening allowing restoration of ATP levels leads to
437 apoptosis while long term opening induces irreversible damage leading to necrosis (85). The
438 pathological role for PTP opening during IR injury was highlighted by pharmacological or genetic
439 approaches inducing cardioprotection (45, 86-88). Many animal studies have shown that the
440 administration of drugs interacting with cyclophilin D (CyPD), such as cyclosporin A (CsA), at the time
441 of reperfusion to target PTP opening, reduces infarct size, although studies in pig AMI models have
442 been puzzling (89). In summary, only the full elucidation of the mPTP structure would probably to solve
443 the uncertainties on mPTP involvement in the pathophysiology of IR injury.

444 **The extrinsic pathway** is activated by external stimuli (specific ligands) binding to death receptors
445 belonging to the TNF receptor superfamily such as FAS (*First Apoptosis Signal*; TNFRSF6/CD95/APO-
446 1) (90). FAS receptors are pre-associated as homotrimers in the cell membrane and undergo, after
447 stimulation by FAS ligand (FASL), a conformational change favoring homotypic interactions with
448 intracellular death domain-containing proteins (91). Among them, two adaptor proteins FADD (*FAS-*
449 *Associated protein with Death Domain* or MORT 1) and DAXX (*Death-domain associated protein-6*)
450 initiate the intracellular cascades of FAS that will converge to a common caspase cascade leading to
451 specific DNA fragmentation and cell destruction (92-95). The extrinsic pathway has been less explored
452 in the myocardium as compared to the intrinsic mitochondrial pathway. Indeed, previous experiments
453 in various knockout mouse models with inactivated FAS receptor or non-functioning FASL, have shown
454 inconsistent results on cardioprotection (96-99). In addition, FASL alone is not sufficient to induce
455 apoptosis *in vitro* in cardiac cells unless a pre-exposition to oxidative stress, suggesting that hypoxia

456 sensitizes cardiac cells to the effects of FASL (100), probably through the recruitment of key
457 contributors (such as DAXX) as additional locks for a maximal safety to trigger apoptotic cell death.
458 Furthermore, the release of FASL in the plasma of patient during the early phases of AMI and in
459 postischemic hearts *ex vivo* after the onset of reperfusion provides strong evidence for the contribution
460 of the FAS-dependent pathway in IR injury (96, 101).

461 Activation of the FAS receptor initiates the caspase cascade *via* the formation of the DISC (*Death*
462 *inducing signaling complex*) proteinase complex formed by FAS, FADD, RIP1 (*Receptor interacting*
463 *protein kinase 1*) and pro-caspase 8 (102). This FAS-FADD signaling cascade has been widely described
464 by many authors and reviewed in detail by Del Re et al. 2019 (64). Efficient DISC assembly induces an
465 auto-proteolytic cleavage of caspase-8, which in turns activates caspase 3 directly or indirectly *via* the
466 cleavage of cytosolic BID (*BH3 interacting-domain death agonist*). Truncated BID (tBID, p15)
467 translocates and inserts into the mitochondrial outer membrane where it contributes to the release of Cyt
468 C through mechanisms either involving BAX or independently of BAX (103-107). As a result, FAS-
469 mediated apoptosis is amplified by the activation of the mitochondrial pathway *via* a subsequent release
470 of Cyt C leading to the complete processing of caspases-3. The amount of caspase-8 recruited to the
471 DISC allows to define cells as Type I cells when they execute FAS-induced apoptosis by a largely
472 mitochondrial-independent pathway and type II cells when FAS-apoptosis is also dependent on the
473 mitochondrial pathway. Importantly, cardiomyocyte restricted deletion of FADD significantly reduced
474 the infarct size *in vivo* in a mouse model of IR injury (108).

475 Independently of the cascade involving FADD, the nuclear protein DAXX also plays a crucial role in
476 the intracellular signaling cascade of the FAS membrane receptor (92), allowing to optimally form the
477 DISC even in myocardial tissue (59, 92). The dual role of DAXX as an antiapoptotic transcriptional
478 repressor in the nucleus (109, 110) and as a pro-apoptotic signal mediator in the cytoplasm depends on
479 the subcellular localization of the protein (92). DAXX nucleocytoplasmic export is triggered by
480 oxidative stress or UV irradiation in cardiac cells (100, 111) or by glucose deprivation (112). The MAPK
481 kinase kinase ASK1 (*Apoptosis signal-regulating kinase 1*) insures DAXX-shuttling into the cytoplasm
482 during nucleo-cytoplasmic transport (112, 113). The activation of ASK1 results in the phosphorylation
483 and activation of JNK to induce cell apoptosis through the JNK-BAX-dependent mitochondrial pathway
484 (106, 114). Finally, JNK activates a variety of transcription factors, such as c-JUN and p53, and regulates
485 mitochondrial proteins, such as BCL-2 and BCL-XL, through phosphorylation, resulting in DNA
486 damage and apoptosis (see for review (115)). DAXX *via* its FAS-binding domain binds the death domain
487 of FAS after oligomerization (92). Interestingly, our group has shown that blocking this specific
488 interaction by either genetical and pharmacological approaches appears as a very promising
489 cardioprotective strategy against IR injury because both extrinsic and intrinsic (mitochondrial) apoptotic
490 cascades are inhibited (57, 59, 116).

491 Importantly, both intrinsic and extrinsic apoptosis generate a lot of apoptotic debris, which has
492 to be rapidly eliminated to avoid the release of cytotoxic particles after the loss of their membrane

493 integrity that are not always immunologically silent. This process serves as a waste disposal mechanism
494 and promotes resolution of inflammation (117). In addition, apoptotic cells have to be cleared by
495 phagocytes, predominantly macrophages that represent 7% of the noncardiomyocytes cells, a process
496 known as programmed cell removal or “efferocytosis” (118-121).

497
498 **Necroptosis** is another form of RCD involved in IR injury triggered by oxidative stress or death
499 receptor activation by TNF, FasL and TRAIL (*Tumor necrosis factor-related apoptosis-inducing ligand*)
500 ligands (**FIGURE 2**) (122). Despite its similarity with necrosis, necroptosis depends on caspase 8
501 activity, a feature found also in apoptosis. RIP1 and RIP3 protein kinases as well as death receptors play
502 a crucial role at the crossroads of necroptosis and apoptosis. In fact, following activation of complex I
503 including TNFR, RIP1, TRADD (*TNFR-Associated Death Domain*) and cIAP1/2 (*cellular inhibitor of*
504 *apoptosis proteins 1 and 2*), complex II (TRADD, FADD, RIP1 and pro-caspase 8) activates and triggers
505 initiation of apoptosis or necroptosis. The latter will only be triggered if caspase 8, responsible for the
506 cleavage of RIP1, is inhibited. The association RIP3/RIP1 with MLKL (*mixed lineage kinase domain*
507 *like pseudokinase*) within the necrosome complex leads to permeabilization and rupture of the plasma
508 membrane under the action of MLKL.

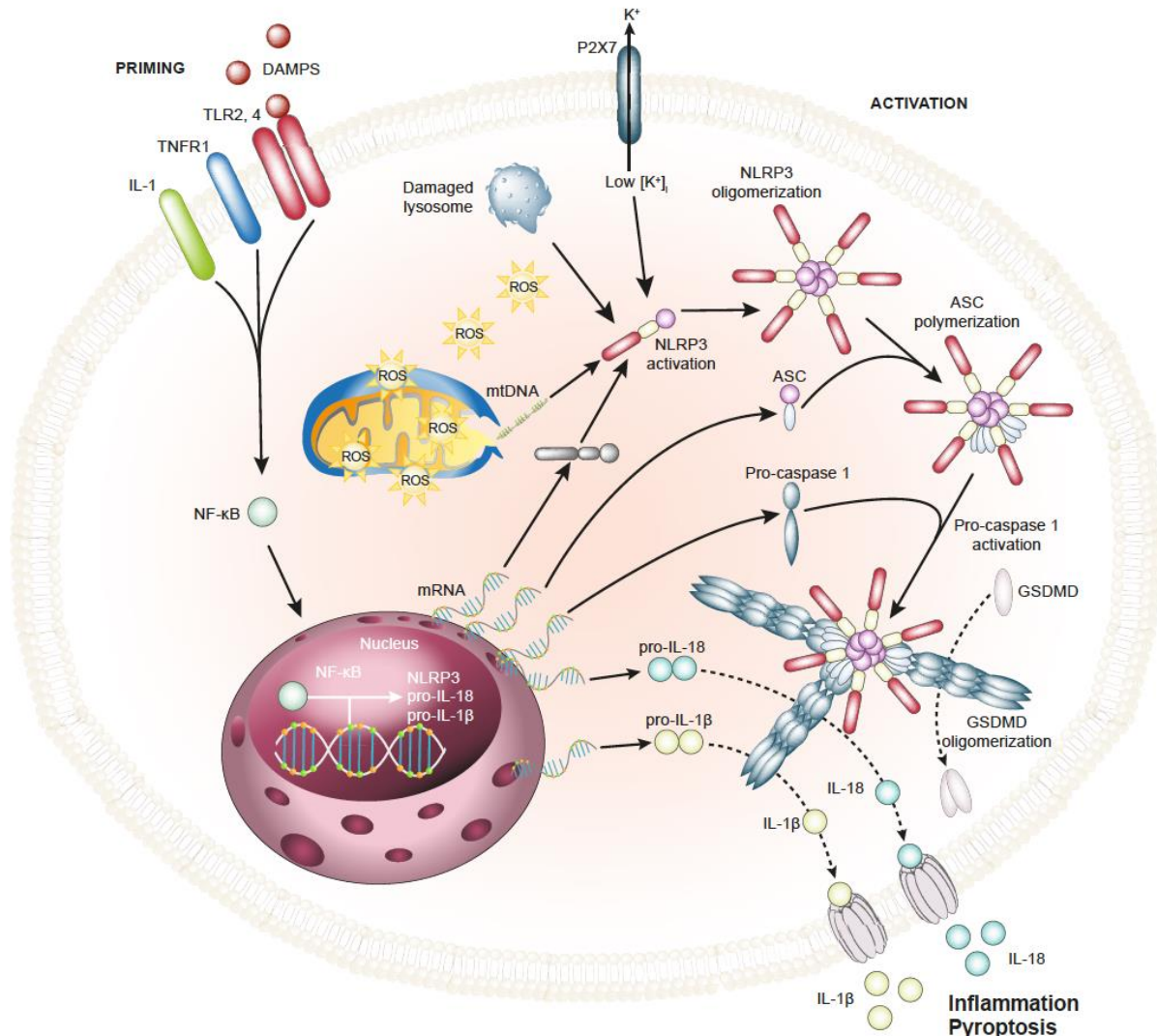
509
510 **Autophagy and autophagic cell death** Autophagy is activated in the heart to eliminate
511 intracellular waste from proteins, lipids and organelles damaged during stress (123). During ischemia,
512 autophagy is a cardioprotective mechanism activated by ATP depletion and subsequent activation of
513 AMPK (**FIGURE 2**). However, during reperfusion, autophagy and apoptosis can occur in the same cell
514 and usually autophagy occurs before apoptosis because stress often stimulates an autophagic response,
515 especially if the stimulus is not lethal (124). As a negative feedback loop, increased caspase activity in
516 apoptosis can cleave Beclin-1 to inactivate Beclin1-mediated autophagy (125). Reduced activity is also
517 controlled by BCL-2 or BCL-XL, by the survival proteins AKT (protein kinase B) (126, 127) or mTOR
518 (mammalian Target Of Rapamycin) (128). Autophagic cell death in cardiac cells after reperfusion has
519 been reported and can even spiral out of control in the final phase of reperfusion, leading to autosis (129,
520 130). The BH3-only protein Beclin-1, a core component of the class III PI3K (phosphatidylinositol-3
521 kinase) complex, controls autophagosome formation, which is the main step in autophagy. Beclin-1 is
522 reported to be activated during reperfusion. However, conflicting results have been obtained concerning
523 the role of Beclin-1 in cardiac cell death, since cardioprotection was observed both in Beclin-1^{+/-} mutant
524 mice or after administration of a Tat-Beclin1 peptide during myocardial IR injury (129, 131).

525
526 **Pyroptosis** corresponds to a pro-inflammatory programmed cell death (Greek roots: πυρο for
527 fire and πτοσις meaning falling). Pyroptosis is characterized by the generation of pores in the plasma
528 membrane by gasdermin D (GSDMD) activated through a cleavage by inflammatory caspases such as
529 caspase-1 (**FIGURE 3**). To form pores, GSDMD-NT, the NH₂-terminal cleavage product, oligomerizes

530 in the plasma membrane inner leaflet and causes the release of intracellular material inducing cell death
 531 (64).

532

533



534 **FIGURE 3: NLRP3 Inflammasome and pyroptosis.**

535 The first priming signal is triggered by DAMPS binding to TLR (Toll-like Receptors) and by cytokines
 536 activating their receptors. Subsequent activation of the NF-κB cascade leads to the transcription of
 537 target genes encoding for pro-IL-1β, pro-IL-18 and NLRP3. Activation of NLRP3 is triggered by K⁺
 538 efflux, DAMPS, lysosomal rupture and mitochondrial ROS, and subsequent release of oxidized
 539 mitochondrial DNA into the cytosol. Active NLRP3 oligomerizes into NLRP3-ASC-Caspase1
 540 inflammasome, forming a circular structure functioning as a platform for the polymerization of ASC
 541 into filaments, which in turn work as a central core from which caspase 1 filaments branch, forming a
 542 star-like structure. Active caspase 1 cleaves the inactive pro-IL-1β and pro-IL-18 into the active IL-1β
 543 and IL-18. GSDMD is an additional substrate of caspase 1 that oligomerizes upon cleavage and forms
 544 pores in the cell membrane with the N-terminal fragments, which allow the extracellular release of
 545 active IL-1β and IL-18. The mature NLRP3 inflammasome works as an activation platform for caspase-
 546 1 that, in circulating cells, processes and releases IL-1β and IL-18 cytosolic inflammatory cytokines
 547 and, in cardiomyocytes, leads to caspase-1 mediated pyroptosis.
 548

549 During IR injury, the expression of ASC (*Apoptosis-associated speck-like protein containing a CARD*)
550 and NLRP3 (*Nucleotide-binding oligomerization domain-Like Receptor family Pyrin domain*
551 *containing 3*) inflammasome components are upregulated as well as the activation of caspase-1 and the
552 release of pro-inflammatory cytokines IL-1 β and IL-18 mainly in fibroblasts and to a less extent in
553 cardiomyocytes (132, 133). Activation of the inflammasome in circulating cells leads to IL-1 β and IL-
554 18 release but its activation in cardiomyocytes leads to caspase-1 mediated pyroptosis (134). GSDMD-
555 mediated cardiomyocyte pyroptosis is a key event during IR injury (135) Recently, Zhang et al.
556 demonstrated that GSDMD inhibition allows to reduce IR injury by blocking pyroptosis (136). However,
557 cardiac function was worsened by activation of poly(ADP-ribosyl)ation through the interaction of
558 GSDMD with PARP-1, leading to apoptosis of cardiomyocytes. This suggests a cross-talk between
559 pyroptosis and apoptosis.

560
561

562 Understanding cell death mechanisms underlying the acute phase of MI as well during
563 reperfusion is crucial for the development of therapeutic strategies inhibiting specifically these cascades
564 and save cardiomyocytes. It is worth noting that RCD mechanisms are interconnected as illustrated by
565 FIGURE 2, thanks to regulator proteins playing key roles in the intricate complex interplay between
566 apoptosis, necrosis, necroptosis, pyroptosis and autophagy. RCD mechanisms activate during
567 reperfusion, which coincides with the therapeutic time window of MSC administration. At the onset of
568 reperfusion, autophagy is triggered to save cellular components and steer the cell towards a survival fate.
569 Then, apoptosis is triggered when the injury is more severe during reperfusion. In parallel, the
570 inflammatory RCD mechanism pyroptosis activates. In this context of cardiac injury, targeting of
571 multiple mechanisms should offer greater efficacy in improving the outcome of MI. MSC are relevant
572 to provide a multiple target strategy because targeting either apoptosis, autophagy, necroptosis and
573 pyroptosis (see below sections III and IV).

574

575 **3- Contribution of inflammation to cardiac injury**

576 During AMI, inflammation is necessary for myocardial healing and the formation of a scar thus
577 preventing wall rupture. The inflammatory response includes both a local and a systemic component.

578

579 **Local inflammatory response** The burst of inflammation induced by necrotic cells through
580 production of ROS, complement cascade activation and the release of DAMPS by necrotic cells, has
581 been referred as sterile inflammation since it occurs in the absence of pathogenic infection (137).
582 DAMPS (or alarmins; previously detailed in a review by Sarhan et al., (138))- such as HMGB1 (*High*
583 *Mobility Group Box 1*), eATP (extracellular ATP), pro-IL1 α , heat-shock proteins, S100-proteins and
584 histones- bind to PRRs (*Pattern Recognition Receptors*) in cardiomyocytes, fibroblasts, endothelial cells
585 and leukocytes, to induce inflammatory pathways and stimulate cytokine secretion (**FIGURE 3**) (139,

586 140). In particular, among the PRRs, the TLRs (*Toll Like Receptors*) lead to the production of cytokines
587 as well as the activation and recruitment of neutrophils to the site of injury (141, 142). In addition, the
588 cytoplasmic PRR NLRP3 is activated during the first step of priming by endogenous or exogenous
589 signals leading to the activation of NF- κ B and the transcription of inflammasome components in
590 circulating inflammatory cells and in cardiomyocytes, fibroblasts, and endothelial cells (22, 143).
591 Following the production of inflammasome components during the priming step, full activation of the
592 NLRP3 is triggered by K⁺ efflux but also DAMPS, lysosomal rupture, mitochondrial ROS, and
593 subsequent release of oxidized mitochondrial DNA into the cytosol. Thus, NLRP3 inflammasome
594 assembles into the multimeric complex of inflammasome NLRP3-ASC-Caspase 1 (143-145). NLRP3,
595 ASC, and procaspase 1 are associated to form a mature NLRP3 inflammasome functioning as an
596 activation platform for caspase-1 that controls the processing and release of cytosolic inflammatory
597 cytokines, including IL-1 β (**FIGURE 3**). Furthermore, NLRP3 inflammasome activates also caspase-8
598 in addition to caspase-1, leading to both apoptotic and pyroptotic cell death (146). Mast cells and soluble
599 complement proteins are also important initiators of inflammation. The activation of the complement
600 cascade and the release of cytokines and chemokines (TNF-alpha, IL-1 β , IL-18) induce the recruitment
601 of neutrophils and then monocytes to the injured area (142).
602 Upon reperfusion, the pro-inflammatory response is exacerbated and will contribute to cardiomyocyte
603 death and IR injury within 6 and 24 h post-reperfusion. TLR2, TLR4, and TLR9 stimulated by HMGB1
604 and NLRP3 in the NLRP3-ASC-caspase 1 inflammasome contribute to this strong inflammatory burst
605 following reperfusion through mediators such as IL-1, IL-6 and active caspase-1 acting *via* the NF- κ B
606 pathway (23).

607
608 ***Systemic inflammation*** In addition to a local inflammatory response, myocardial injury triggers
609 also systemic inflammation, stimulating the release of bone marrow-derived leukocytes. The
610 complement activates within 2 hours after AMI leading to the recruitment of neutrophils and monocytes
611 at the site of the lesion in animal models and in patients (147). Neutrophils activated in the peripheral
612 circulation infiltrate into the ischemic myocardium across the vessel wall within 6 to 8 hours after AMI,
613 produce extensive ROS and pro-inflammatory factors to attract monocytes (148). In the injured
614 myocardium, neutrophils will polarize upon activation of TLR4. Hours after AMI, the massive
615 recruitment of neutrophils peaking at 1-3 days is followed by the infiltration of monocytes and
616 macrophages with phagocytic and proteolytic functions promoting the digestion of the infarcted tissue
617 and the removal of necrotic debris (149, 150). Monocyte recruitment to the infarcted myocardium is
618 biphasic with classical proinflammatory monocytes being the predominant monocyte subset recruited
619 within the first 48h (peaking at day 3 to 4) and the anti-inflammatory populations with Ly-6C^{low} and
620 non-classical anti-inflammatory monocytes starting 4-7 days post-MI (peaking about day 7 post-MI).
621 Within the infarcted tissue, inflammatory monocytes differentiate into inflammatory macrophages that
622 will remove the cell debris after injury. They play a crucial role in the early inflammatory phase,

623 producing a variety of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases. It has
624 been shown that following AMI, B lymphocytes infiltrate the infarcted area (peaking at day 5 post-AMI),
625 and augment the pro-inflammatory response by secreting the chemokine CCL7, which in turn induces
626 mobilization from the bone marrow of pro-inflammatory Ly6C^{hi} monocytes (151). In addition, the
627 polarization of inflammatory towards anti-inflammatory macrophages is finely tuned by cytokines (152).
628 Then, anti-inflammatory macrophages produce a variety of anti-inflammatory, pro-angiogenic, and pro-
629 repair factors contributing to the resolution of inflammation by also removing cell debris (152).
630 Beside their role in immune response, macrophages participate in the crosstalk with other cells
631 (including cardiomyocytes, fibroblasts, immune cells, and vascular endothelial cells) to coordinate post-
632 MI processes within cardiac tissue. Activated monocytes and macrophages are the major source of
633 cytokines but all nucleated cell types within the myocardium including endothelial cells, smooth muscle
634 cells and cardiac myocytes also secrete themselves cytokines locally in the heart or systemically (153,
635 154). Finally, a limited short-term up-regulation of stress-activated cytokines such as TNF α , IL-6 and
636 IL-1 β leads to an inflammatory process necessary for wound repair, scar formation and compensatory
637 hypertrophy after MI. This inflammatory cytokine response mediates cardioprotection by activating the
638 survivor activating factor enhancement (SAFE) pathway (155).

639 However, an excessive, persistent and expanded pro-inflammatory response after AMI due to a
640 delay in resolution of inflammation will contribute to expand the infarcted area (23). Prolonged
641 expression of cytokines leads also to myocardial deleterious effects including myocyte hypertrophy,
642 alterations in fetal gene expression, myocyte apoptosis and subsequent adverse LV remodeling leading
643 to heart failure (154). Splenic B lymphocytes are reported to play a key role in cardiac remodeling after
644 AMI and have been identified as putative cardiac therapeutic strategy (156). Vascular complication
645 occurs during AMI when neutrophils exert detrimental effects on endothelial function and together with
646 platelets cause plugging of the coronary microcirculation. Distal microthrombus embolization
647 (microvascular obstruction) and microvascular damages during PCI lead to the no-reflow phenomenon
648 in up to 40% of patients (157), which is associated with larger infarct size and worse outcomes including
649 a higher incidence of death (158). Both no-reflow and hemorrhage carry an adverse prognosis for
650 patients after reperfusion (159).

651 In summary, a complex inflammatory response during AMI is organized by different
652 contributors leading to both pro-inflammatory and anti-inflammatory reparative phases, allowing wound
653 repair. A number of anti-inflammatory strategies have failed to reduce MI size in patients. Combining
654 multiple targets approaches such as MSC-based therapy for this complex phenomenon and using an
655 appropriate timing of administration should provide beneficial results.

656

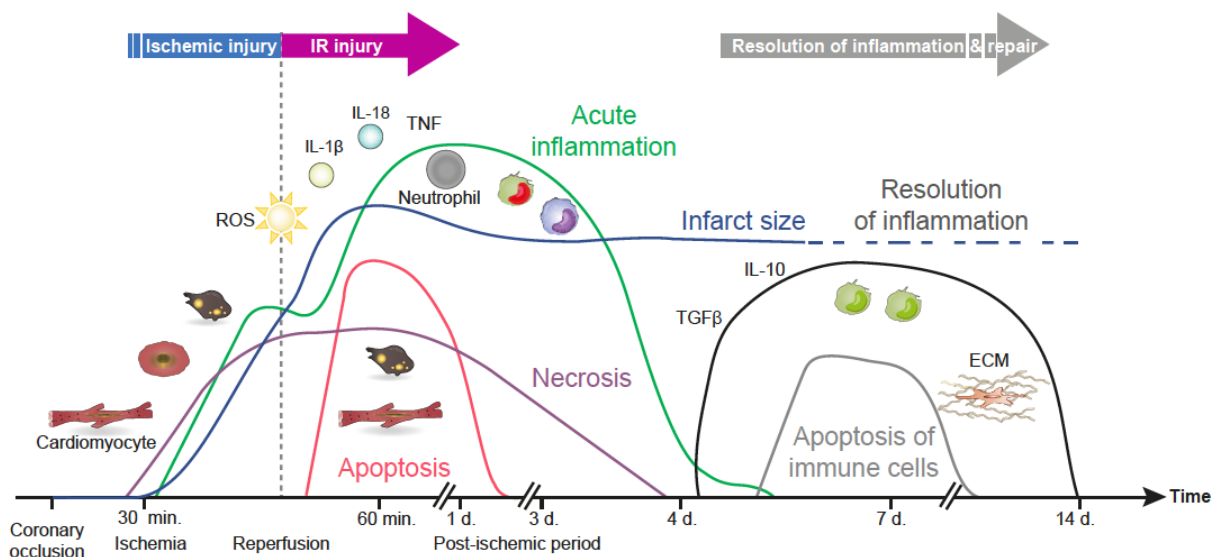
657 **4- Temporal wave-front of cardiac injury**

658 Beside a spatial progression of cardiac injury, a dynamic wave-front of cell death occurs and
659 develops over time after reperfusion (50, 160, 161). Our group described for the first time the

660 progression over time of apoptosis after the onset of reflow in the mouse heart. A slight delay (around
 661 10 minutes) was evidenced between infarct size and apoptosis kinetics (**FIGURE 4**). Such a delay
 662 suggests that a degree of necrosis takes place in the very first minutes of reperfusion before apoptosis
 663 as previously hypothesized by other groups (38, 50). In the mouse model, the apoptotic wave-front
 664 progresses during the first 60 minutes after the onset of reperfusion to reach a plateau phase
 665 corresponding to the final infarct size. Regarding necrosis, it is predominant during ischemia and at the
 666 onset of reperfusion (38, 50) but progresses also in human hearts after infarction more than expected
 667 regarding the guidelines for timely reperfusion. Indeed, a study by Greulich et al. revealed that in their
 668 cohort of ST segment-elevation MI patients, time to reperfusion to salvage myocardium was less than
 669 suggested by current guidelines since a symptom-to-balloon time of >121 minutes causes a high grade
 670 of transmural necrosis. This study strongly suggests that immediate reperfusion is vital (162).

671 Knowing the time window of reperfusion injury i.e., exploring the timing of activation of the
 672 potential targets of interest, is essential to develop an appropriate and efficient therapeutic strategy
 673 adapted to each specific phase.

674



675

676 **FIGURE 4: Temporal wavefront of IR injury.**

677 *Simplified diagram of the development of injury in the myocardium as a function of time, after the*
 678 *coronary occlusion leading to ischemia. Necrosis develops first during ischemia. The wavefront of*
 679 *apoptosis is very rapid, triggered by the exacerbated production of ROS due to the abrupt return of*
 680 *oxygenated blood in the artery at the onset of reperfusion. After reperfusion, the pro-inflammatory*
 681 *response is exacerbated and will contribute to cardiomyocyte death (necrosis) and IR injury within 6*
 682 *and 24 h post-reperfusion.*

683 *After the ischemic period (AMI), acute inflammation is triggered by DAMPS and is characterized by the*
 684 *massive recruitment of neutrophils peaking at 1-3 days and followed by the infiltration of monocytes*
 685 *and macrophages with phagocytic and proteolytic functions promoting the digestion of the infarcted*
 686 *tissue. The removal of necrotic debris is dominated by Ly-6Chigh monocytes activity, peaking day 3-4*
 687 *post-MI, and the anti-inflammatory phase with Ly-6Clow monocytes (peak at day 7, post-MI). The*
 688 *immune cells are eliminated in the injured tissue by apoptosis, thus contributing to the resolution of the*
 689 *inflammation. The temporal window of cardioprotection to prevent reperfusion injury is, for anti-*

690 apoptotic strategies, limited to the first 30 minutes of reperfusion. Regarding anti-inflammatory
691 strategies, this window could be extended to the first days (< at 5 days) of the post-ischemic period to
692 avoid any interference with the healing process.

693

694

695 **B- Endogenous mechanisms of cardioprotection**

696

697 **1- Ischemic conditioning stimuli**

698 Making the myocardium briefly ischemic before a more severe ischemia increases the tolerance
699 of the myocardium to ischemic injury by activating endogenous protective mechanisms (163).
700 Myocardial ischemic conditioning is an intervention protecting the heart from damages caused by
701 prolonged exposure to ischemic conditions (infarction). Conditioning protocols can be applied at
702 different times: before, during and after the ischemic period. They act as triggers of endogenous
703 mechanisms of cardioprotection.

704

705 **1.1. Preconditioning**

706 Murry et al. were the first to describe in a dog model that the application of repeated brief
707 episodes of ischemia followed by reperfusion can protect myocardial tissue from the deleterious effects
708 of a subsequent prolonged episode of ischemia by reducing the amount of necrosis (164). This
709 phenomenon was called ischemic preconditioning (PreC) and its effectiveness has been demonstrated
710 both in reducing infarct size and in limiting ventricular rhythm disorders in many animal models *in vivo*
711 (165). Piot et al. provided evidence that ischemic PreC reduces ischemic injury and infarct size after
712 prolonged ischemia and reperfusion in the rat heart *in vivo* (166). There is substantial evidence that this
713 phenomenon also occurs in humans, including the observation that the AMI patients suffering from
714 angina pectoris have decreased infarct size due to the repetitive episodes of short ischemia within one
715 vascular bed during prodromal angina compared to those who do not have pre-infarction angina before
716 the acute phase of MI (167, 168). Angina pectoris before infarction, comparable to PreC, was
717 associated with a reduction in death, cardiogenic shock and heart failure (168). Unfortunately,
718 outside of specific situations such as cardiac surgery, the application of ischemic PreC in the human
719 clinic is not feasible because, by definition, the occurrence of a MI being unpredictable.

720

721 **1.2. Postconditioning**

722 While PreC suffered from its lack of clinical application, the description by Vinten-Johansen's
723 group of PostC revolutionized the world of cardioprotection by demonstrating that application of brief
724 repeated episodes of ischemia-reperfusion immediately after coronary reopening, i.e., at the very
725 beginning of reperfusion allowed to inhibit specifically IR injury (39). Zhao et al. reported a significant
726 reduction in infarct size in the postconditioned group (3 periods of 30 seconds of ischemia and 30

727 seconds of reperfusion immediately after 60 minutes of sustained ischemia) compared with the
728 unconditioned control group. The cardioprotection conferred by PostC was identical to that induced by
729 PreC, corresponding to a reduction in infarct size (15% and 14% of the area at risk, respectively)
730 compared with 25% for the control group. Furthermore, this decrease in infarct size was corroborated
731 by a decrease in creatine kinase (CK) activity, and reduced tissue edema in the area at risk identical to
732 that observed with PreC (39). A lower amount of malondialdehyde (MDA) level in the plasma was
733 described for the PostC group compared to the control group indicating less lipid peroxidation (39).
734 Thus, the work of Zhao et al. highlighted that modifying the hydrodynamic conditions during the early
735 period of reperfusion provides powerful cardioprotection by reducing reperfusion injury, comparable to
736 PreC. Since its original description, many experimental studies have been carried out, and benefits of
737 PostC were then confirmed both *in vitro* and *in vivo* in rats, mice, and rabbits, and *in vivo* in pigs and
738 dogs (165). PostC, by contrast to PreC, is clinically applicable in AMI patients. In a "proof-of-concept"
739 clinical study in AMI patients, Staat et al. highlighted that PostC consisting in 4 episodes of 1-minute
740 inflation/1-minute deflation of the angioplasty balloon performed just after a direct stenting of the
741 occluded coronary artery lowers the release of CK, a classic marker of infarct size (169). Moreover,
742 PostC applied during PCI leads to a persistent reduction in infarct size and to an improvement in long-
743 term functional recovery (170).

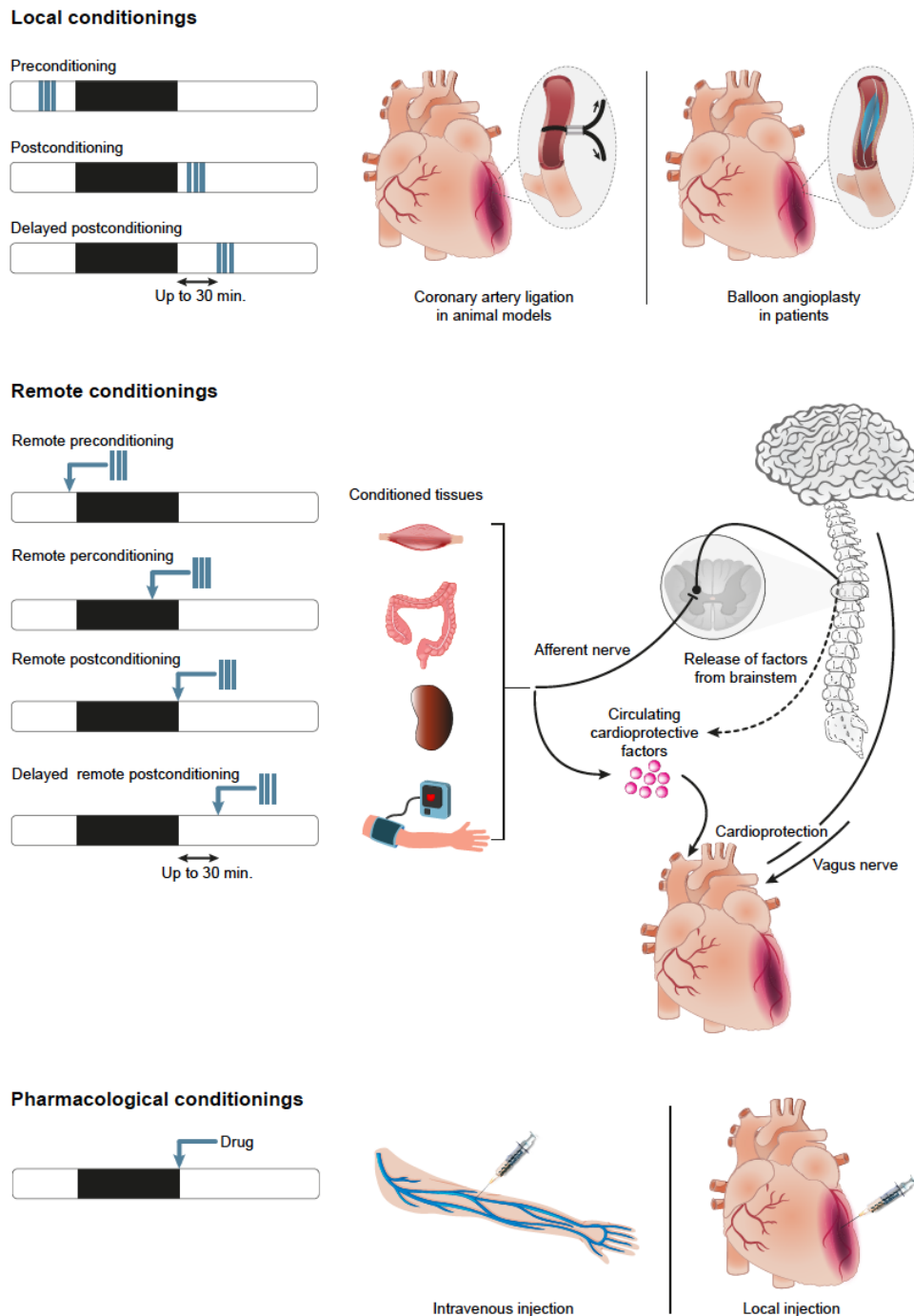
744 The potent inhibition of myocardial injury by PostC suggests a clinically applicable strategy suitable
745 with certain surgical revascularization procedures. PostC was then considered by scientists and
746 physicians as an attractive approach to protect the myocardium against IR injury and was therefore the
747 subject of many studies aimed at exploring its efficacy in different animal models and understanding its
748 underlying mechanisms of action (for review (171-173)).

749

750 **1.3. Remote conditioning**

751 The major disadvantage of PostC treatments is the need to perform an invasive procedure
752 directly into the heart (**FIGURE 5**). Przyklenk et al. demonstrated, in a canine model, that remote
753 ischemic preconditioning (RIPC) in the circumflex artery bed, prior to a 60 min left anterior descending
754 (LAD) occlusion protected the LAD vascular bed against severe ischemia, leading to a markedly smaller
755 (38%-reduction) infarct size compared to control hearts (174). This work highlighted that ischemic
756 conditioning also applied at a distance from the heart was able to provide cardioprotection (hence the
757 term "remote" ischemic conditioning, RIC) through the production of diffusible protective factors
758 released in the circulation reaching the myocardium (174). Gho et al. demonstrated that brief anterior
759 mesenteric artery occlusion/reperfusion to induce a brief period of intestinal IR stimulus immediately
760 reduces myocardial infarct size by 28% in a rat model (175). RIPC could be applied to a number of
761 different tissues or organs far from the heart (i.e. skeletal muscle, kidney, liver and brain). It could
762 protect any other organ or tissue against a prolonged lethal episode of acute IR injury and was termed
763 inter-organ preconditioning (176). RIC has been demonstrated to be effective if applied before ischemia

764 (remote ischemic preconditioning) (175), during ischemia (remote ischemic preconditioning) (177) or
 765 as a PostC stimulus (178-184). A large number of experimental studies have established that brief
 766 ischemic events in a limb can protect the heart and reduce infarct size (see for review (185)).
 767



769 **FIGURE 5: Illustrative scheme of cardioprotective strategies in acute myocardial infarction.**
 770 Local preconditioning (PreC), postconditioning (PostC), delayed postconditioning (Delayed PostC),
 771 are applied at various time points through a coronary artery within the myocardium. PreC consists of
 772 applying occlusion-reperfusion cycles administered before the ischemic event. For PostC the stimulus
 773 is applied at the onset of reperfusion and can be achieved in animal models by reversible coronary
 774 artery ligation. PostC in patients with AMI can be applied by repeated balloon inflation during the

775 coronary angioplasty procedure. PostC induces cardioprotection even if delayed until 30 minutes after
 776 the onset of culprit coronary artery reperfusion (Delayed PostC).
 777 Remote conditionings (RIC) stimuli could be applied to a number of different tissues or organs remote
 778 from the heart (i.e., skeletal muscle, mesentery, kidney) to protect against a prolonged lethal episode of
 779 acute IR injury. In patient, RIC could be initiated by simply inflating and deflating a blood pressure cuff
 780 placed on the arm or leg for a few minutes then deflating the cuff and performing the procedure several
 781 more times to induce brief cycles of IR. Regarding the timing, protection with RIC can be accomplished
 782 when the stimulus is applied before sustained coronary occlusion (remote preconditioning), during the
 783 sustained ischemic insult (remote perconditioning), or at the time of reperfusion (remote
 784 postconditioning). The conditioning stimulus induces the release of both circulating factors and factors
 785 activating local sensory neurons leading to activation of the parasympathetic innervation.
 786 Pharmacological conditionings are induced by drugs administered intravenously or intracoronary just
 787 before or at early reperfusion.
 788 The black rectangle indicates severe ischemia and the three blue lines the conditioning stimulus.
 789

790

791 In the clinical setting, the fact that RIC can be applied by simply inflating and deflating a blood
 792 pressure cuff placed on the arm or leg of human patients makes it attractive to patients in the acute phase
 793 of their infarction, as part of perconditioning or postconditioning (186, 187). Various small clinical
 794 studies reported inconsistent data with limb RIC applied prior to, or after the PCI, showing improved
 795 myocardial recovery (188-191) and/or reduced infarct size (192-194) or no protection (190). Long-term
 796 clinical outcomes in patients with ST-elevation myocardial infarction were also improved including hard
 797 clinical endpoint of cardiac mortality and hospitalization for heart failure (195, 196). As shown by
 798 several recent meta-analyses, most of the clinical studies indicated a positive effect of RIC on decreasing
 799 IR injury in particular in patients treated by PCI (197, 198). Despite these promising studies, a recent
 800 international multicenter, single-blind, randomized controlled trial (CONDI-2/ERIC-PPCI) including
 801 5401 STEMI patients who underwent PCI indicated that RIC did not report improved clinical outcomes
 802 (cardiac death or hospitalization for heart failure) at one year in STEMI patients (199).

803

804 **2- Mechanisms underlying endogenous cardioprotection**

805 Reduction of infarct size compared with reperfusion alone is a common feature of the three
 806 types of ischemic conditioning (i.e., PreC, PostC and RIC), despite temporal and spatial differences (200,
 807 201). Experiments in animal models allowed to demonstrate that decreased infarct size was related to
 808 an inhibition of IR injury. Indeed, Piot et al. provided the first evidence that ischemic PreC decreases
 809 specific DNA fragmentation as an hallmark of apoptosis in the rat heart (166). PostC has also been
 810 shown to decrease apoptosis *in vivo* (202, 203) in addition to necrosis, both of them contributing
 811 ostensibly to overall infarct size (202, 203). Indeed, PostC diminishes known triggers of apoptosis such
 812 as oxidants (i.e. ROS, peroxynitrite), calcium overload (203, 204), and also inhibits pro-apoptotic
 813 pathways and regulatory factors *in vivo* (205). Our group evidenced that more than 80% of the cell
 814 death-related genes regulated by PreC or PostC are involved in apoptosis (206). An anti-inflammatory

815 effect is also described but the studies have been focused only on evaluation of TNF α production and
816 neutrophil infiltration (202, 207, 208).

817 Although PreC and PostC have been reported to protect the heart against cardiac injury after
818 AMI, a greater cardioprotection was reported for PreC than for PostC in the rat heart *in vivo* with several
819 differences been highlighted (209, 210). Combining PreC and PostC was reported to offer a greater
820 cardioprotection in an *in vivo* rabbit model but this additivity was not retrieved in both *ex vivo* rat heart
821 or *in vivo* canine models (211-213). The non-additive cardioprotection during combined application of
822 PreC and PostC could indicate either that the effects of the “conditionings” are species dependent, or
823 might be related to the number and duration of the sequences of the algorithms (often different between
824 studies) or that these two stimuli could activate common pathways. In this context, a large-scale
825 differential transcriptomic study comparing gene expression levels revealed that only 5 of the 16 463
826 mouse genes explored were jointly regulated upon both PreC and PostC after 1 hour of reperfusion (206).

827

828 The underlying mechanisms of protection by ischemic conditioning are multifactorial and include all
829 mediators of cardioprotection, from the physical stimulus (conditioning maneuver) to the cascades
830 blocking IR-induced damages (see **FIGURE 6**).

831

832 **2.1. Molecular mediators**

833 In summary, the currently accepted paradigm suggests that, in response to the ischemic
834 conditioning stimulus, cells release autacoid substances. Endogenously released chemical stimuli
835 triggering cardioprotection include conventional ligands that, after binding to their respective receptor
836 (*G protein-coupled receptors*, GPCR), will induce the activation of downstream pro-survival signaling
837 pathways (214). Liu et al. demonstrated that 8-sulfophenyltheophylline (8-SPT), a nonspecific blocker
838 of the adenosine receptor, blocks ischemic conditioning, and that IC administration of adenosine or an
839 adenosine A1 receptor agonist can decrease myocardial infarct size (215). Subsequently, more GPCR
840 ligands have been reported as triggering ischemic conditioning, such as acetylcholine (216),
841 catecholamines (217), opioids (218), bradykinin (219), angiotensin II (220), endothelin-1 (221) and
842 glutamate (222). Other inducers of ischemic conditioning include small molecules, as calcium ions, ROS,
843 nitric oxide (NO), hydrogen sulfide and the mitochondrial K_{ATP} channel (see for review (173)).

844 Ischemic conditioning cardioprotective effects are mediated by the activation of signaling cascades, in
845 particular, RISK (*reperfusion injury salvage kinase*), SAFE (223) and cGMP/PKG (*cyclic Guanosine*
846 *Mono Phosphate /Proteine Kinase G*) pathways (224). Finally, it is proposed that this set of receptor-
847 mediated signals converges on mitochondria (end effector) and confers myocardial protection by
848 stabilizing mitochondrial membranes, inhibiting the opening the mPTP, and thereby attenuating
849 mitochondrial swelling and rupture (9, 42, 200).

850 **RISK pathway** The RISK pathway designates a group of pro-survival protein kinases, conferring
851 cardioprotection when they are specifically activated at the time of reperfusion (225, 226). The RISK

852 pathway is carried by the PI3K-AKT and p42/44 extracellular signal-regulated kinase (ERK1/2)
853 cascades. The cardioprotective benefit of both PreC and PostC is fully reversed by inhibition of the
854 RISK pathway suggesting that the RISK pathway commonly mediates ischemic PreC and PostC at the
855 time of reperfusion (212, 223, 225).

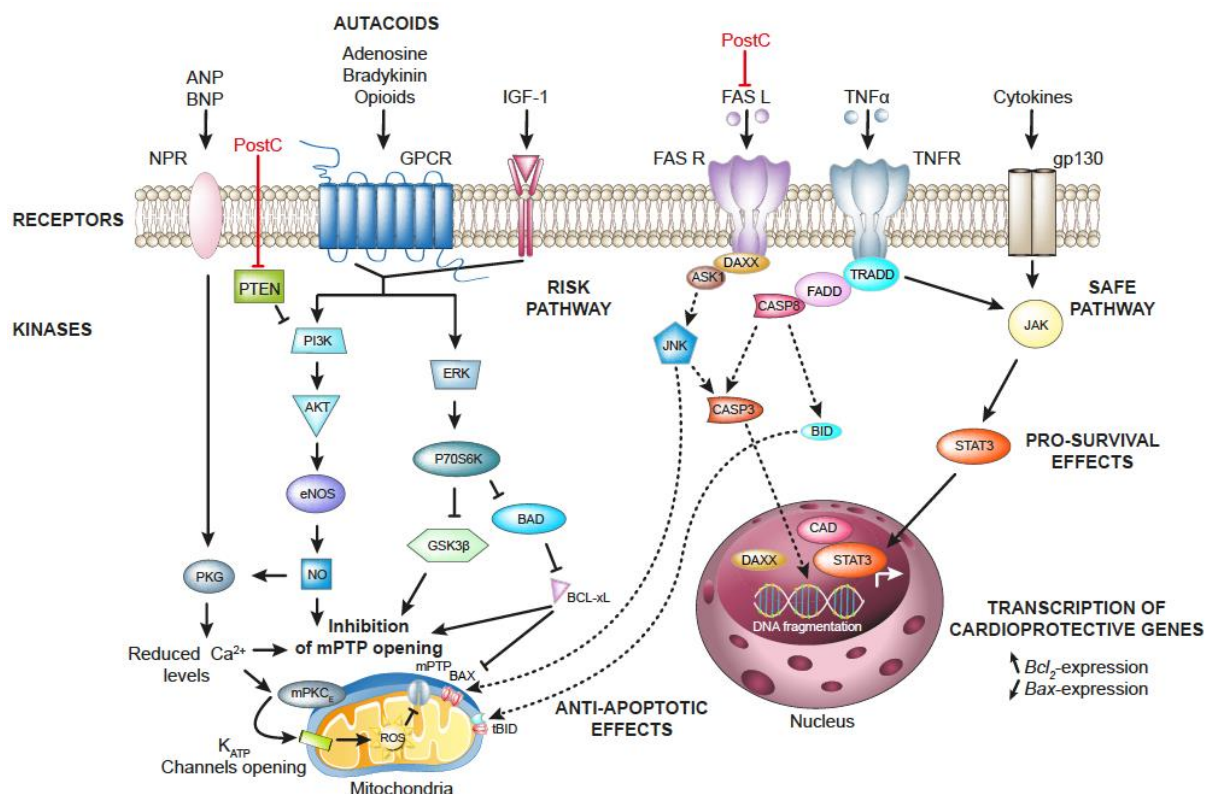
856 - The PI3K/AKT pathway is activated by G-coupled receptors reported to be involved in
857 cardioprotection, such as adenosine, opioid and glutamate receptors (222, 227). The mechanism by
858 which cell survival is mediated is essentially the inhibition of apoptosis after phosphorylation of BAD
859 (*BCL-2 associated agonist of cell death*) by PI3K (228). At the cardiac level, its protective role against
860 IR injury is mediated by the activation of the serine-threonine kinase AKT (or protein kinase B) (229,
861 230). In fact, although AKT activation follows PI3K activation, both enzymes are capable independently
862 to acutely inhibit apoptosis in cardiomyocytes (229). Furthermore, AKT, in addition to its anti-apoptotic
863 effects, preserves cardiac function *in vivo* following an episode of ischemia and decreases infarct size *in*
864 *vivo* (231). Another study showed that overexpression of AKT *in vivo* also improves calcium
865 mobilization, in particular by increasing the expression and phosphorylation of SERCA2a
866 (*sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase 2a*), a mechanism that could explain the beneficial
867 effects on cardiac function (232). While transient activation of PI3K-AKT is cardioprotective, chronic
868 activation of AKT can be deleterious as described in human cardiac tissue samples at advanced stages
869 of heart failure characterized by high levels of phosphorylated AKT. This suggests that either high levels
870 of AKT are deleterious or that, despite significant activation of AKT, there was no beneficial effect
871 against the consequences of myopathic deterioration (233). In mouse models of *Akt* overexpression
872 specifically in the myocardium, concentric ventricular hypertrophy and, in the most severe cases,
873 significant cardiac dilatation have been observed (234, 235). However, an interesting study revealed that
874 the deleterious effects of chronic AKT activation can be antagonized *via* PI3K activation (236). Indeed,
875 this study conducted on a transgenic mouse model of an activated form of AKT (Myr-Akt-Tg), reports
876 that in this case, a negative feedback mechanism inhibits upstream PI3K activity. Restoration of PI3K
877 function by gene transfer in these transgenic mouse hearts was reported to reduce the deleterious effects
878 generated by a myocardial IR episode (236).

879 PTEN *Phosphatase and tensin homologue deleted chromosome 10*) is a powerful negative regulator of
880 PI3K activity in various cell types and plays an important role in myocardial IR injury, as well as in
881 myocardial remodeling, hypertrophy, and fibrosis (237-240). PTEN inhibition is therefore an effective
882 potential target for reducing infarct size and improving cardiac function in animal models (241). By
883 dephosphorylating the product of PI3K i.e., PIP3, PTEN inhibits the activity of several downstream
884 molecules in the signaling pathway, the most important of these molecules being AKT. PTEN activity
885 is reduced upon PreC and restored as the protective effect of PreC is lost (242). PostC treatment
886 decreases also PTEN level, activates PI3K/AKT prosurvival kinase pathway and decreases significantly
887 myocardial apoptosis in an *in vivo* rat model (243).

888 The PI3K/AKT pro-survival kinase pathway has a crucial influence on the opening of mPTP by
 889 inhibiting its opening in the first minutes of reperfusion, thus preventing cell death by apoptosis or
 890 necrosis (244-246). Numerous studies have evidenced that mPTP opening is prevented at the onset of
 891 reperfusion in hearts subjected to PreC (86, 164, 247, 248) or PostC (39, 249) but not in the case of RIC
 892 (see for review (250, 251)).

893 - ERK1/2 or p42/44, members of the MAP kinase (*mitogen activated protein kinase*) family, are serine-
 894 threonine kinases involved in the regulation of cell proliferation, differentiation and survival. Among
 895 the five ERK isoforms identified, ERK1 and ERK2 are the most abundantly expressed forms in the heart.
 896 Numerous studies have shown that the MEK (*MAPK-ERK kinase*)-ERK pathway can have anti-
 897 apoptotic effects following stimulation by IGF-1, cardiotrophin-1 or catecholamines (252-254).
 898 Activation of ERK1/2 plays a protective role against reperfusion injury *in vitro* and *in vivo* (255, 256).
 899 The work of Lips et al. in the *erk2^{+/-}* and *erk1^{-/-}* mouse models, suggests that ERK1 and ERK2 would
 900 have specific roles and that only the MEK1-ERK2 pathway would protect the myocardium from IR-
 901 induced apoptosis. However, there are some differences reported between PreC and PostC, such as the
 902 fact that ERK1/2 is involved in PostC but not in PreC (257).

903



904

905

906 **FIGURE 6: Endogenous mechanisms of cardioprotection.**

907 Upon postconditioning stimulus autacoids (adenosine, bradykinin, endogenous opioids) are released
 908 and bind to their specific receptors belonging to the superfamily of GPCR. Other receptors are able to
 909 mediate the response to growth factors such as IGF-1 or cytokines (IL-6). RISK signaling pathways
 910 comprising survival kinases such as PI3K/AKT and ERK1/2 (p42/44) are downstream cascades
 911 activated upon PostC stimulus. PTEN is a powerful negative regulator of PI3K activity. The final

912 *endpoint of this intracellular cascade is the inhibition of MPTP opening via inhibition of GSK3 β ,*
 913 *increased NO (via AKT) and PKG activity (via natriuretic peptides receptors) and reduced intracellular*
 914 *Ca²⁺ levels. The opening of mitochondrial K_{ATP} channels is part of the endpoints of the postconditioning*
 915 *mechanisms.*

916 *The SAFE pathway mediated by JAK-STAT3 is also responsible for postconditioning induced-*
 917 *cardioprotective effects. STAT3 relocates to the nucleus in order to control the transcription of*
 918 *cardioprotective genes such as Bcl-xl.*

919 *The cardioprotective effects of PostC results also from the inhibition of apoptotic pathways (dotted*
 920 *lines) mediated by the extrinsic pathway involving death receptors such as FAS and TNF receptors.*
 921

922 **SAFE pathway.** The conditioning stimulus also activates the SAFE pathway involving the cytokine
 923 TNF- α and STAT3 (*Signal Transducer and Activator of Transcription-3*) (258). Indeed, Lecour et al.
 924 demonstrated the cardioprotective effect of the administration of TNF- α before the ischemic insult
 925 without involvement of the RISK signaling cascade (258). Later, they showed that TNF- α administration
 926 during reperfusion activated an alternative pathway, termed the SAFE pathway (259-261), and they also
 927 established a link between preconditioning and the activation of this pathway (262). In humans, it seems
 928 that STAT5 (*Signal Transducer and Activator of Transcription-5*), instead of STAT3, may play a
 929 relevant role in cardioprotection (263). Activation of STAT3 has a role in the long-term transcriptional
 930 regulation of cardioprotective proteins (264), but also has acute effects by enhancing mitochondrial
 931 respiration (265) particularly during PostC (266) and by attenuating apoptosis. Indirect evidence proves
 932 the involvement of STAT3 in RIC. Indeed, Apolipoprotein A has been proposed as a humoral transfer
 933 signal RIPC (267), and the decrease in infarct size by RIPC and exogenous apolipoprotein A was
 934 mitigated by blocking PI3K, ERK, and STAT 3 (268).

935 **cGMP/PKG or PKG/NO pathway** This signaling cascade involving protein kinase G (PKG) and NO
 936 has also been identified as a contributor in cardioprotection (269, 270). NO produced downstream of
 937 PI3K/AKT emerges as a key signaling element in the reperfusion salvage pathway activated by many
 938 classes of agents capable of safeguarding the organism's integrity. Activation of soluble guanylyl cyclase
 939 (sGC) and PKG depends on activation of the PI3K/AKT pathway and appears as crucial for many
 940 different forms of cardioprotection (see for review (224)). Several studies indicate that this pathway is
 941 negatively impacted in cardiomyocytes by IR injury and its activation is essential for the
 942 cardioprotective effects of PostC (211, 271, 272). However, another study shows that blockade of NOS
 943 (*Nitric oxide synthase*), sGC, and PKG, but not PI3K, abolishes the cardioprotective effects of PostC,
 944 further suggesting that activation of the cGMP/PKG pathway is NOS-dependent but independent of
 945 PI3K/AKT signaling (273).

946 In fact, PostC mitigates ROS generation at reperfusion probably by decreasing the delivery of oxygen
 947 during the controlled reperfusion (209, 213, 274) that limits tetrahydrobiopterin (BH₄) oxidation and
 948 increases endothelial NOS (eNOS) activity. The subsequent activation of the cGMP/PKG pathway leads
 949 to PKG-dependent inhibition of Na⁺/H⁺ exchanger (NHE), slowing intracellular pH normalization
 950 during reperfusion. In addition, the cGMP/PKG has a direct effect on calcium oscillations and
 951 mitochondrial permeability transition (224).

952 Despite available evidence supporting that the cGMP/PKG pathway is involved in PostC protection,
953 only a limited number of studies have identified PKG-phosphorylated target proteins that are implicated
954 in the molecular mechanisms of cardioprotection. It has been proposed that PKG activation inhibits
955 mPTP through GSK3 β phosphorylation (275, 276). Nevertheless, double GSK-3 α/β knockin mice
956 lacking GSK3 phosphorylation sites that lead to kinase inactivation could still be protected by both PreC
957 and PostC (277), proving that GSK3 β inhibition is unlikely to serve as a downstream mediator of the
958 cardioprotection induced by cGMP/PKG activation. Results from an *in situ* pig model and in *ex vivo* rat
959 hearts confirm that GSK3 β phosphorylation does not play a causal role in PostC protection (273, 278).

960

961 **2.2. Remote mechanisms**

962 The identified common mechanistic threads identified for PreC and PostC appear to extend to
963 remote conditioning (176, 214, 279-281), with a significant contribution from PKC, the RISK pathway
964 and mitochondrial function (173).

965 Unlike PreC and PostC, RIC stimulus differs considerably in that protection begins in the remote organ
966 or tissue and the cardioprotective signal must be transferred from the remote organ to the heart via
967 different pathways. Several mechanisms have been proposed in many animal studies: communication
968 via (i) circulating blood and humoral mediators (176, 282, 283), (ii) neuronal mechanisms (175, 284)
969 and (iii) modification of circulating immune cells (279, 281, 285, 286).

970 A humoral mechanism for RIC has been reported with the demonstration of perfusate transfer-
971 mediated cardioprotection between isolated perfused hearts (179, 282, 287-289). This cardioprotection
972 can be transferred by perfusing plasma into an isolated heart from a different animal species suggesting
973 cross-species protection (289, 290). In addition, it is mediated by RISK and SAFE pathways since for
974 example, blocking these cascades abolished the protection provided after infusion of plasma from pigs
975 that had been subjected to remote PostC in isolated rat hearts (290). The identification of humoral
976 mediators has been the subject of numerous studies using proteomic approaches in both animals and
977 humans, but also led to some contradictory results (267, 291, 292). Examples of proteins that may be
978 involved include apolipoprotein A-I, kallistatin, and stromal-derived factor 1 α (see for review (293)).

979 The neural hypothesis of RIC postulates that IR cycles in remote tissues or organs can promote
980 a neural reflex leading to myocardial protection against subsequent myocardial insult (294). Additional
981 mechanisms have been suggested as contributing to the remote signal, such as activation of peripheral
982 nociceptive fibers releasing unidentified molecules into the systemic circulation and/or through the
983 spinal cord activating the autonomic nervous system to release cardioprotective factors (see for review
984 (251)). Donato et al. pointed out that RIPC activates a neural afferent pathway involving the vagus nerve,
985 which releases ACh and triggers downstream cascades via a muscarinic receptor (295), resulting in
986 eNOS stimulation and elevated cGMP production (296). Humoral factors can stimulate also the
987 cGMP/PKG pathway through activation of PI3K/AKT cascade (179, 297). Intact neural connection is
988 thus necessary between the remote organ and the heart, as demonstrated in different animal models. In

989 rabbits, renal RIPC was associated with an increased sympathetic nerve activity and abrogated when the
 990 renal nerve was sectioned before IR *in vivo* (298, 299). Likewise, in a mouse model, combined resection
 991 of the femoral and sciatic nerves abolished the cardioprotective effect of RIPC (284). Cardioprotection
 992 was abolished also after pharmacological autonomic ganglia blockade in the case of RIPC through the
 993 mesenteric artery but not in the case of PreC (175). Mastitskaya et al. demonstrated that vagal pre-
 994 ganglionic neurons residing in the dorsal motor nucleus of the vagus nerve (DMVN) have a crucial role
 995 in RIC-induced cardioprotection.(300). The involvement of sensory nerves in the propagation of
 996 protection also has been directly evidenced. Activation of sensitive fibers by nociceptive stimuli or
 997 topical capsaicin results in the release of cardioprotective substances into the bloodstream, mimicking
 998 the cardioprotection induced by RIPC in a rabbit model (301). Intramesenteric bradykinin, by
 999 stimulating local sensory nerves, leads to RIPC-like protection, which is abolished by hexamethonium
 1000 in a rat model suggesting the involvement of the autonomic nervous system in addition to sensory nerves
 1001 (302). Communication between distant organs and the heart may be multifactorial, and the overlap
 1002 between neural pathways and humoral mediators has also been suggested in rodents (172, 284, 299).
 1003 In healthy humans, inhibition of RIPC by the autonomic ganglia blocker trimethaphan was reported but
 1004 not observed after IV administration of a bradykinin-2 receptor antagonist suggesting that the
 1005 mechanisms may be different in humans (303, 304).

1006 . The systemic response theory is supported by the existence of several blood-derived factors (e.g.,
 1007 cytokines, nitrites, autacoids,..) constituting the "remote signal" to be delivered to the heart *via* the
 1008 systemic circulation (see for review (181, 305)). Opioids are thought to be responsible for remote
 1009 myocardial salvage by modulating CCR1 (C-C chemokine receptor type 1)-triggered leukocyte
 1010 infiltration in the myocardium or by stimulating CCR5-mediated regulatory T cell (Treg) recruitment
 1011 (286). RIC through transient forearm ischemia may alter gene expression in circulating leukocytes and
 1012 suppresses their activation in human patients (306).

1013

1014 **3- Therapeutic time window of cardioprotection**

1015 AMI is an absolute emergency and recommendations in clinical practice are to reperfuse the
 1016 myocardium as soon as possible in agreement with the concept
 1017 that "time is muscle" (6). Whereas a 2-hour delay was recommended to obtain a beneficial effect from
 1018 thrombolysis in early studies of coronary artery reopening, reperfusion therapy, mainly PCI, must now
 1019 be performed within 3 hours for maximum efficacy (32, 307). Early proof-of-concept studies established
 1020 the dogma that PostC, to be efficient, must be applied within the first minute after the onset of
 1021 reperfusion (39, 209, 211). Since then, most PostC maneuvers have been initiated within 1 minute of
 1022 the onset of reperfusion in the majority of studies, including clinical trials (169, 308, 309). A significant
 1023 decrease in infarct size was demonstrated when the PostC stimulus was applied immediately after the
 1024 onset of reperfusion following a prolonged ischemic insult *in vivo* in a dog (310) and rabbit models
 1025 (211). Meanwhile, another study in a rat model of myocardial IR reported that PostC was effective in

1026 reducing infarct size only if applied no later than 1 min after the onset of reperfusion (209). It was then
1027 considered that PostC should be applied in the time immediately after the onset of reperfusion to be able
1028 to decrease myocardial reperfusion injury.

1029 However, several years later, our group provided evidence that PostC, delayed up to 30 minutes after
1030 the onset of culprit coronary artery reperfusion in the mouse heart *in vivo*, was still able to reduce the
1031 wave-front of reperfusion injury and prevent apoptotic cell death occurring during the first minutes of
1032 reperfusion (50). In addition, delayed PostC also exhibits a time-dependent degree of protection (50).

1033 The wave-front of apoptosis occurs as a “burst”, and prolonging the application time of anti-apoptotic
1034 strategies from 1 to 6 days was reported to be deleterious, leading to cardiac rupture, since apoptosis
1035 during the healing process is an absolute necessary mechanism (50, 311). When applied later, PostC is
1036 not able to prevent necrotic processes that occur in the late stage of apoptosis (46, 50). A very narrow
1037 therapeutic window is suggested for both preclinical and clinical studies. Many studies confirmed this
1038 idea and reported also that delaying the time point of application of the conditioning stimulus or
1039 pharmacological cardioprotective strategies is still able to preserve some cardioprotective effect (59,
1040 160, 312, 313) even in the case of anti-inflammatory strategies (314, 315). Other studies describe that,
1041 to be effective, pharmacological strategies must be applied before reperfusion, as reported for
1042 cyclosporine A administration (316).

1043 Altogether, these data clearly show that anti-apoptotic strategies need to be administered as soon as
1044 possible at the onset of reperfusion or even prior to reperfusion reinforcing the concept that
1045 cardioprotection is a matter of timing. Anti-inflammatory strategies must be administered at the same
1046 time as the pro-inflammatory burst. Indeed, colchicine has been reported to reduce infarct size when
1047 administered before ischemia (317) or 25 min. prior to reperfusion in a mouse model of AMI (318).
1048 Administered during one week post-reperfusion in mice, colchicine prevented the increased expression
1049 of inflammatory cytokines and NLRP3 activation and improved cardiac function, heart failure and
1050 survival after MI (319). In patients, colchicine administered during PCI and the 5 following days was
1051 associated either with a smaller infarct size (320) or an absence of cardioprotective effects (321). In fact,
1052 the timing to treatment initiation influences the beneficial effect of colchicine. Results of the COLCOT
1053 study have shown that early colchicine administration within 3 days after AMI allows reducing future
1054 events including major adverse cardiovascular events, cerebrovascular accidents, and need for
1055 revascularization compared to standard therapy alone (322).

1056 The therapeutic time window for treating patients with AMI appears to be crucial for targeting specific
1057 signals and should be tailored according to their targets. In conclusion, the therapeutic time window for
1058 treating patients with AMI appears to be crucial and must be adapted to each target.

1059
1060
1061
1062

1063 **III- Generalities on mesenchymal stem cells (MSC)**

1064 As described above, apoptotic mechanisms are of major importance in IR injury as evidenced
1065 in various animal models and in human ischemic heart disease.

1066 A major reason for the failure to translate cardioprotection in the clinical setting may have been the use
1067 of a monotherapy approach focused on a single target involved either in IR injury or in an endogenous
1068 cardioprotective pathway. Unfortunately, this strategy might be insufficient to address the multifaceted
1069 components of myocardial reperfusion injury, comprising mitochondrial and endothelial dysfunction,
1070 oxidative stress, calcium overload and inflammation as well as microvascular obstruction (323-325).
1071 This awareness has paved the way for new multi-targeted therapies, including mesenchymal stromal cell
1072 (MSC)-based therapy, which relies on the pleiotropic properties of MSC. In this chapter, we will
1073 summarize the properties of MSC that are mainly relevant in the treatment of AMI.

1074

1075 **A- MSC definition**

1076 The acronym MSC has been used for multiple meanings that include, mesenchymal stem cell,
1077 mesenchymal stromal cell, and multipotent stromal cell. MSC have been initially discovered by
1078 Friedenstein *et al.* who identified in the bone marrow (BM) of mouse and guinea pig a fibroblastic cell
1079 type that gives rise to clonal colonies and that generates bone and reticular tissue when transplanted
1080 heterotopically (326, 327). BM-MSC represent 1/10 000 of the mononuclear cells in the BM and can be
1081 easily isolated and expanded *in vitro*. Given that a stem cell is defined for its clonal self-renewal potential
1082 and multilineage differentiation potential, the term “mesenchymal stem cells” has for a long time been
1083 criticized (328) although their self-renewal capacities have been demonstrated (329). The international
1084 society for cellular therapy (ISCT) recommends to distinguish between the self-renewing fraction within
1085 the BM that exhibits a multipotent differentiation potential *in vivo* and mesenchymal stromal cells
1086 identified in multiple tissue types and that exhibit multipotent differentiation potential *in vitro* (328).
1087 Cells that display a multipotent potential *in vitro* have been identified in the adipose tissue (AT-MSC)
1088 (330-332), dental pulp (333), cartilage (334), synovial membrane (335), tendon (336), heart (337) and
1089 lungs (338) as well as in perinatal tissues including the placenta (339), umbilical cord blood (340),
1090 umbilical cord (341) and fetal sources such as fetal tissue and amniotic fluid (342).

1091 Regardless of the niche, these multipotent cells referred all to MSC as multipotent mesenchymal
1092 stromal cells in accordance with 3 criteria established by the ISCT (343). First, MSC adhere to the plastic
1093 when cultured in standard conditions. Second, MSC are positive for a panel of surface molecules,
1094 individually not specific, that includes CD105, CD73 and CD90, and are negative for hematopoietic
1095 lineage markers such as CD45, CD34, CD14 or CD11b, CD79 α or CD19 and HLA-DR. Third, MSC
1096 are multipotent cells that can differentiate *in vitro* into osteoblasts, adipocytes and chondroblasts. In
1097 2019, the minimal criteria defined by the ISCT were updated to classify a cell as a MSC and to
1098 rationalize the use of the MSC nomenclature in laboratories. On this occasion, the board re-emphasized

1099 the necessity of MSC nomenclature and the need for additional reportable criteria such as their tissue of
1100 origin and functional assays performed to better qualify these cells (344). Similarly, Renesme et al. have
1101 pointed to the need for increased efforts to ensure the agreement of a consensus definition of MSC and
1102 reporting guidelines to improve the robustness, repeatability, and clarity of the MSC literature and,
1103 eventually, the safe application of effective MSC-based therapies (345).

1104

1105

1106 **B- MSC developmental origins**

1107 The high number of MSC sources has highlighted the possibility that MSC might derive from
1108 different embryonic origins. Indeed, although bone marrow and adipose tissue were thought, for a long
1109 time, to host MSC originating from the mesoderm (346), elegant and convincing studies have evidenced
1110 that these two tissues also host neural crest-derived MSC (**FIGURE 7**). The first study was carried out
1111 in 2007 by Takashima and colleagues (347) by means of lineage tracing approaches. They show that the
1112 trunk of E9.5 mouse embryos possesses cells positive for Sox1, a marker for neural stem cells, that gave
1113 rise to MSC positives for PDGFR α (PDGF receptor alpha), a marker of paraxial mesoderm. They
1114 evidenced also that in postnatal BM, neural crest-derived MSC are still present, even at a low extent,
1115 suggesting that the first wave of MSC in the embryo derives from the neural crest and that following
1116 birth, a second wave of MSC from another source takes place (347). The origin of adult MSC is still an
1117 open question and the function of MSC from different developmental origins has been addressed more
1118 recently. While neural crest-derived stem cells are quiescent in the BM where they exhibit a
1119 hematopoietic stem cell niche function during the *in-utero* development and after birth, mesoderm-
1120 derived MSC participate in fetal skeletogenesis and lose their activity after birth (348). Similarly, the
1121 subcutaneous fat of adult mice was shown to contain neural crest-derived MSC that are phenotypically
1122 and functionally distinct from MSC derived from non-neural crest (349).

1123 These studies that improve our knowledge on the developmental origin of MSC found in
1124 different adult tissues are critical for the optimal use of MSC in clinic. Indeed, MSC from different tissue
1125 sources, with no regard to their embryonic origin, have been or are currently used in 663 clinical trials
1126 enrolling patients with heart disorders. However, the studies described above have brought to our
1127 attention that depending on their embryonic origin, MSC might exhibit different functions once injected
1128 *in vivo*. Of note, for clinical applications, neural crest-derived MSC may be of interest, given recent
1129 studies demonstrating the contribution of the neural crest to several cardiovascular structures in
1130 vertebrates, such as cardiomyocytes and to cardiac regeneration in adult zebrafish (350, 351). Moreover,
1131 these studies raise the question about the intrinsic properties of MSC from a given embryonic origin and
1132 the subsequent phenotypic and functional heterogeneity among MSC within a same tissue source that
1133 are ontogenically distinct.

1134

1135

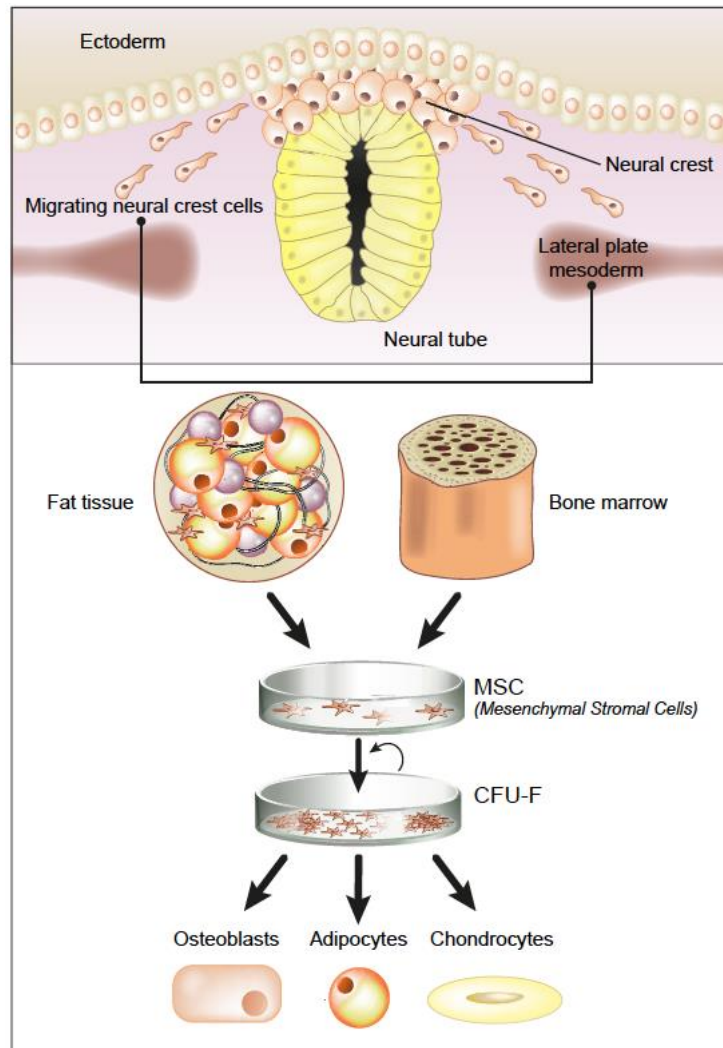


FIGURE 7: Embryonic origin, isolation, and differentiation potential of MSC derived from adipose tissue (AT-MSC) and bone marrow (BM-MSC).

AT-MSC and BM-MSC originate from both neural crest cells and the lateral plate mesoderm. Both AT-MSC and BM-MSC display the capacity to adhere to the plastic, to form CFU-F (CFU-fibroblasts), and to differentiate into osteoblasts, adipocytes, and chondrocytes.

C- MSC heterogeneity

MSC heterogeneity exists at different levels. First, MSC derived from different donors exhibit phenotypic and functional differences that are well documented (352). Second, MSC derived from different tissue sources display features that refer to their tissue of origin (353, 354). Finally, as discussed above, MSC derived from the same tissue may show differences that can be explained by the fact that MSC from the same source may have different embryonic origins (348, 349).

At the functional level, MSC from different tissue sources exhibit different properties. Regarding MSC immunoregulatory properties, while BM and umbilical cord (UC) have similar immunosuppressive capacities, placenta-derived MSC exhibit a lower capacity to inhibit CD4⁺ and

1174 CD8⁺ T cells (for review (355)). Compared to BM-MSC, AT-MSC display a stronger suppressive
1175 potential on IFN γ -producing Th1 (*T helper 1*) cells (for review (355)). Similarly, superior suppressive
1176 effects of AT-MSC were reported on macrophages compared to BM-MSC (356). With regard to MSC
1177 differentiation potential, tissue-specific abilities have been reported. For example, in a comparative
1178 study using donor-matched AT-MSC and BM-MSC, while AT-MSC showed significantly higher
1179 proliferation rate and adipogenic potential, BM-MSC showed significantly higher osteogenic and
1180 chondrogenic potential (352). Of note, a significant heterogeneity among the donors regarding the
1181 proliferation and differentiation potential of the two MSC types was observed in this study.

1182 Heterogeneity is also reported between MSC from a same tissue sample. Indeed, multiple
1183 studies from the early 2000s report variations in phenotype, proliferation and differentiation properties
1184 (330, 357-359). While 30% of BM-MSC clones display a tri-lineage differentiation potential, 70%
1185 exhibit a bi-lineage or uni-lineage potential (359). For AT-MSCs, only 1.4% of the clonal
1186 subpopulations were tripotent and the rest were either bipotent or unipotent (330).

1187 MSC heterogeneity has direct consequences on MSC phenotype, functions and therapeutic
1188 potential. MSC exert different functions including immunomodulation, anti-apoptotic, anti-fibrotic and
1189 pro-angiogenic properties (360). Thus, one can speculate that either a single subpopulation of MSC
1190 would exert these pleiotropic activities and thus effectively treat multifaceted IR lesions, or that each
1191 subpopulation would exert a specific function explaining the pleiotropy of this heterogeneous cell panel.
1192 This would explain that the use of MSC in clinical trials have led to various results going from moderate
1193 to inconsistent benefits (361-363). The frequency of MSC derived from NC or mesoderm might vary
1194 among the tissue sources, tissue donors and clonal subpopulations. Amplification protocols and culture
1195 media used for MSC could also favor the enrichment of one subpopulation of MSC rather than another.
1196 Thus, verification of the way that culture conditions can impact on the frequency and the functions of
1197 MSC subpopulation is critical step of quality control. Altogether, the multiple sources of variations
1198 would explain, in part, the phenotypic and functional heterogeneity found among MSC isolated from
1199 different tissues, donors and different laboratories. Thus, to overcome the subsequent clinical
1200 inconsistencies obtained with MSC and guarantee the therapeutic potential of these cells administrated
1201 into the patient a current strategy consists in standardizing and even enhancing the MSC therapeutic
1202 product.

1203 The development of assays to evaluate MSC functions and predict their efficacy *in vivo* before
1204 their administration in patients is essential to guarantee trustworthy and reproducible results. Thus, assay
1205 development and standardization are ongoing to facilitate the choice between different sources and
1206 improve safety and efficacy of MSC-based therapies.

1207

1208 **D- MSC homing/biodistribution in the heart**

1209 Since the first demonstrations of cardiac differentiation, data from *in vivo* studies based on cell
1210 tracking techniques have clearly shown that only very few transplanted MSC differentiate into

1211 cardiomyocytes to directly repopulate cardiac tissue. A few data evidenced that transplanted MSC can
1212 fuse with recipient cardiomyocytes (364, 365). Thus, recent investigations focus mainly on MSC
1213 paracrine effects as the main underlying mechanisms mediating cardiac repair. In this context,
1214 substantial efforts have been made to define the biodistribution and fate of MSC after their
1215 administration. IV administration of stem cells to increase the pool of endogenous stem cells homing to
1216 injured myocardium was first assessed by post-mortem histology. However, the dynamic redistribution
1217 of peripherally infused stem cells as well as cell trafficking was investigated using the high sensitivity
1218 of the combined single-photon emission computed tomography technology after IV injection of MSC
1219 after AMI. Focal and diffuse recruitment of MSC in the infarcted myocardium was visible on images
1220 within the first 24 hours and remained up to 7 days after but also in the lungs and non-target organs
1221 including the kidney, spleen and liver within 24 to 48 hours after injection (366). By contrast, MRI was
1222 unable to detect MSC after IV injection within the heart in part because of the lower sensitivity of the
1223 technique (366). MSC engraftment into the heart was significantly increased with their local
1224 administration (367, 368). Thus, currently, two main delivery strategies are used in cardiac MSC-based
1225 therapies: IC and intramyocardial (IM) injection. Because IM cell injection is a more invasive approach,
1226 IC infusion is more attractive for the clinic. However, relying on bioluminescent signals for live MSC
1227 imaging, high focal intensity signal was reported after IM delivery, while obviously a weaker signal was
1228 observed after IC delivery. These results suggest a poor retention of MSC after IC delivery compared to
1229 IM delivery (369, 370). Whether the reduced number of “homing” MSC in the myocardium contributed
1230 to higher rate of MSC biodistribution into remote organs (spleen, lung, liver...) remains to be
1231 investigated.

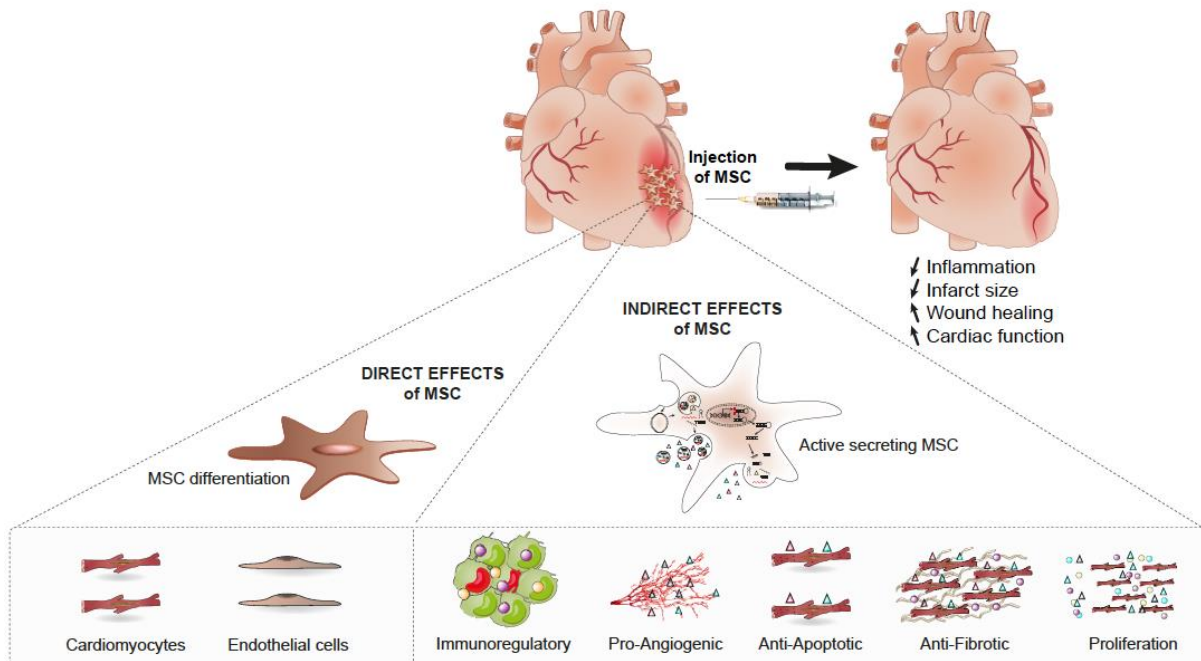
1232

1233 **E- MSC properties**

1234 The cardioprotective effects of MSC, through direct or indirect mechanisms, are multifactorial
1235 and lead to a decrease in both infarct size and post-infarction remodeling (**FIGURE 8**). However, it is
1236 well-admitted that MSC interest resides less in their differentiation abilities into cardiomyocytes and
1237 endothelial cells than in their aptitude to modulate their microenvironment by targeting injured cells
1238 through the release of a plethora of mediators.

1239 *In vitro*, MSC require induction with appropriate factors to differentiate into cells of the three
1240 main components of the cardiovascular system including cardiomyocytes, endothelial cells and vascular
1241 smooth muscle cells (371, 372). Over the last two decades, different strategies have been developed to
1242 induce MSC differentiation into cardiomyocytes, including the use of growth factors (373), chemical
1243 inducers (374), and coculture with primary cardiomyocytes (375). However, these reports also argue
1244 against the use of certain chemical inducers, such as 5-azacytidine, and highlight the necessity to identify
1245 alternative induction procedures. In this context, using sternal marrow-derived MSC, the
1246 cardiomyogenic potential of bFGF (*basic FGF*) combined to hydrocortisone was compared with that of

1247 5-azacytidine, revealing that induction with bFGF and hydrocortisone results in the differentiation of
 1248 MSC into cardiomyocytes with a slightly higher efficiency (376).
 1249
 1250



1251
 1252 **FIGURE 8: MSC-based therapy of AMI relies on the pleiotropic properties of the cells.**
 1253 *MSC cardioprotective effects can be mediated through direct effects relying on the capacity of MSC to*
 1254 *differentiate into cardiac cells or by indirect effects limiting the immune response and apoptosis while*
 1255 *increasing angiogenesis and cardiac cell proliferation. When in presence of specific differentiation*
 1256 *inducers, MSC differentiate both in vitro and in vivo in cardiomyocytes and endothelial cells which*
 1257 *contribute, at least in part, to their ability to repair injured myocardium.*
 1258

1259
 1260 ***In vivo***, MSC engraftment and further differentiation into cardiomyocytes and endothelial cells
 1261 after MI have been demonstrated. The efficacy of AT-MSC and BM-MSC has been compared in a
 1262 porcine AMI model showing a similar beneficial effect of the two cell types on cardiac function and
 1263 angiogenesis but a better effect of AT-MSC on left ventricular (LV) remodeling. This therapeutic effect
 1264 was associated with the engraftment of the cells positive for CD31, a marker of endothelial cell, 4 weeks
 1265 after their transplantation (377). Also, the retrograde infusion of bFGF into the coronary vein increases
 1266 the graft uptake and differentiation potential of implanted MSC, thereby restoring cardiac function and
 1267 preventing unwanted remodeling (378).

1268 However, although the differentiation of MSC into cardiomyocytes has been documented, it is
 1269 important to note that a substantial proportion of transplanted MSC is rapidly lost mainly through
 1270 apoptotic mechanisms and that a modest fraction of MSC engraftment happened without differentiation.
 1271 Therefore, paracrine effects have been proposed as the main effect of transplanted MSC for the treatment

1272 of cardiac tissues. The multiple trophic factors produced by MSC are able to repress cardiomyocyte
1273 apoptosis, favor angiogenesis, induce the recruitment and proliferation of endogenous stem cells,
1274 decrease inflammatory oxidative stress as well as fibrosis in the border zone of the scar (379). In 2009,
1275 Shabbir et al. showed for the first time that non-invasive delivery of MSC or their trophic factors by IM
1276 injection can be successful in rescuing the failing heart (380). This study, which reveals that the MSC-
1277 conditioned milieu is as effective as MSC per se in treating experimental heart failure, offered the
1278 definitive proof of the major role of trophic factors in the field of MSC-based therapy for the
1279 myocardium. The set of factors secreted by MSC, also referred to as the MSC secretome, acts on
1280 neighboring cells through a paracrine phenomenon. MSC secretome is a complex product released *in*
1281 *vitro* in the conditioned medium and *in vivo* in the extracellular medium, consisting mainly in soluble
1282 factors and EV (extracellular vesicles). MSC EV and organelles can also be transferred from MSC to
1283 another cell *via* tunneling nanotubes.

1284

1285 **1- Anti-apoptotic properties**

1286 We will discuss the paracrine effects of MSC, which appear to be the primary mechanism by
1287 which they promote cardiomyocyte viability and protect them from apoptosis (**FIGURE 9**).

1288

1289 **1.1. Soluble factors**

1290 MSC release paracrine factors such as cytokines, chemokines and growth factors that can bind
1291 to their specific receptors on cardiac injured cells and regulate processes such as stress-induced apoptotic
1292 pathways to promote cell survival. Among the factors secreted by MSC, we will focus on the role of
1293 VEGF, IGF-1 and HGF (*Hepatocyte Growth Factor*) that display anti-apoptotic properties.

1294 **VEGF**, a vascular osmotic molecule, belongs to the family of the vascular endothelial growth
1295 factor and exhibits various physiological functions including pro-angiogenic properties and the capacity
1296 to enhance cell proliferation, differentiation, and viability. VEGF released by MSC (381) is significantly
1297 upregulated in MSC treated with pro-inflammatory cytokines such as IFN- γ and IL-1 β (382). VEGF
1298 overexpression by MSC has been shown to activate stromal cell-derived factor-1 α (SDF-1 α)/CXCR4
1299 axis and to induce cardiac stem cell mobilization and migration into infarcted areas (383) resulting in
1300 an enhanced angiogenesis. The high level of VEGF released by MSC provides multiple beneficial
1301 effects, ranging from their angiogenic effect and anti-hypertrophic properties to their anti-apoptotic
1302 properties on injured cardiomyocytes (382). The paracrine factor of VEGF is mediated through the
1303 downregulation of microRNA-23a (miRNA-23a) and miRNA-92a in injured cardiomyocytes (384).

1304 **IGF-1** displays an important role in cell growth and differentiation and was reported to prevent
1305 apoptosis of myocardial cells, ventricular dilation and wall stress in infarcted hearts (385). IGF-1,
1306 through the activation of IGF-1R, prevents oxidative stress and cardiac cell apoptosis by repressing
1307 DNA fragmentation, decreasing BAX induction, and inhibiting caspase 3 activity (386). IGF-1
1308 protective mechanisms also involve the preservation of the mitochondrial potential and the retention of

1309 Cyt C, preventing mitochondrial dysfunctions (387). IGF-1 is released by MSC and has been described
1310 to be involved in their cytoprotective effects. *In vitro*, IGF-1 increases cardiomyocyte proliferation and
1311 migration while inhibiting their apoptosis induced by hypoxia (388). In addition, IGF-1 ameliorates the
1312 healing capacity of MSC by improving angiogenesis, decreasing scar formation and accelerating muscle
1313 structure reconstitution (389). Furthermore, the exposition of MSC to a combination of IGF-1 and HGF
1314 decreased their rate of apoptosis after transplantation and promoted their protective effects by
1315 attenuating LV remodeling and improving cardiac function (390). In line with these studies, Wnt11
1316 overexpression in MSC was shown to enhance their anti-apoptotic and anti-necrotic properties on
1317 cardiomyocytes exposed to hypoxia. This increased effect of MSC was associated with the significantly
1318 greater release of VEGF and IGF-1 by MSC overexpressing Wnt11 (391). The addition of anti-VEGF
1319 and anti-IGF-1 antibodies in the co-cultures inhibited this protective effect.

1320 **Basic FGF** (bFGF) is an important mitogen factor that protects cardiomyocytes from iNOS-
1321 mediated apoptosis through the MEK-1-ERK pathway (392). Although MSC are not important
1322 producers of bFGF, they are regularly supplemented with bFGF to, in part, maintain their multipotent
1323 differentiation ability, enhance their expansion and their secretory profile (393). Moreover, bFGF
1324 represses apoptosis in human MSC and *bFGF*-transfected MSC (394, 395). *In vivo*, in a canine model
1325 of coronary ligation, the combined therapy with bFGF and MSC promoted neovascularization and
1326 reduced apoptosis in the infarct border zone. This was associated with an increased engraftment of
1327 transplanted MSC resulting in decreased myocardial fibrosis, an improved recovery of cardiac function
1328 and prevention of post-MI LV remodeling (378). Among the modifications of the secretory profile
1329 induced by bFGF on MSC, HGF secretion ability was significantly increased (393). HGF, a pleiotropic
1330 cytokine, is known to regulate several biological processes including angiogenesis, inflammation and
1331 cell survival. HGF overexpression in MSC resulted in an optimization of MSC therapeutic effect in MI
1332 (396). This enhanced therapeutic effect was due to the enhanced survival of MSC linked to HGF
1333 overexpression under hypoxic conditions and mediated by the regulation of the AKT signaling pathway.
1334 Moreover, the transplantation of MSC overexpressing HGF reduces cardiomyocyte apoptosis, increases
1335 cardiomyocyte proliferation and enhances angiogenesis presumably by augmenting their paracrine
1336 effects. Indeed, via the activation of the Akt pathway, HGF increases VEGF production as well as bFGF
1337 and EGF.

1338

1339 **1.2. Extracellular vesicles**

1340 Extracellular vesicles (EV) represent important intercellular messengers involved in the transfer
1341 to recipient cells of biological signals, especially proteins, lipids and RNA. EV derived from MSC
1342 (MSC-EV) have shown promising protective properties on injured cardiac cells, in part, through the
1343 transfer of mitochondria. The anti-apoptotic effect of EV derived from MSC was shown in coculture
1344 experiments with induced pluripotent stem cell-derived cardiomyocytes (iCM) exposed to doxorubicin
1345 (DOX) using a transwell system allowing to physically separate the two cell types (397). In these

1346 experiments, the authors showed that MSC protect stressed iCM from apoptosis and improved their
1347 viability. This anti-apoptotic effect exerted by the secretome of MSC was mediated by their capacity to
1348 release large EV (>200 nm) enriched in mitochondria and up-taken by iCM. Indeed, DOX-injured iCM
1349 receiving mitochondria contained in MSC-EV exhibited improved both biogenesis and contractility as
1350 well as increased ATP production and PGC-1 α (Peroxisome proliferator-activated receptor gamma
1351 coactivator 1-alpha) transcription. The inhibition of the mitochondrial functions in MSC-derived EV
1352 using 1-methyl-4-phenylpyridinium (MPP⁺) decreased their beneficial effect on injured iCM (397).

1353 The cardioprotective effects of EV are also mediated by transferring growth factors and various
1354 micro-RNA (miR) to recipient cardiac cells. A large body of evidence suggests that miR contained in
1355 MSC-derived EV could be a promising cardioprotective therapy. For instance, miR-144 contained in
1356 MSC-derived EV decreases the expression of PTEN and increases levels of pAKT in cardiomyocytes
1357 and thereby protects them against hypoxia-induced cell apoptosis (398). Of note, miR-144 was described
1358 to promote mitochondrial biogenesis and reduce cardiomyocyte apoptosis through the activation of
1359 AMPK phosphorylation and PGC-1 α deacetylation by targeting RAC1 (RAC family small gtpase 1)
1360 (399). In ischemic hearts, anti-apoptotic effect of MSC-EV was reported to be mediated by miR-19a,
1361 which down-regulates PTEN activation, increases BCL-2 protein expression and enhances AKT
1362 phosphorylation (400, 401). PTEN was also shown to be decreased in cardiomyocytes receiving miR-
1363 21a-5p contained in MSC-EV. Consistently, the delivery of miR-21a-5p in recipient cardiac cells targets
1364 genes products involved in cell survival or apoptosis including PDCD4 (*Programmed Cell Death 4*),
1365 PTEN, FASL and PELI1 (Pellino E3 Ubiquitin Protein Ligase 1) and decreased apoptosis (402).
1366 Similarly, miR-22-enriched EV, secreted from MSC following a PreC stimulus, were shown to be up-
1367 taken by cardiomyocytes and to reduce apoptosis in neonate cardiomyocyte subjected to an ischemic
1368 stress (403). miR-210 and miR-4732-3p were also shown to be enriched in MSC-EV and able to protect,
1369 in a paracrine manner, hypoxic cardiomyocytes against apoptosis by decreasing the expression levels of
1370 BAX, BAD, and cleaved caspase 3 and increasing BCL-2 expression (404, 405). Exosomal miR-25-3p,
1371 is another example of miRNA from MSC that confers cardioprotective effects in MI by targeting pro-
1372 apoptotic proteins (406).

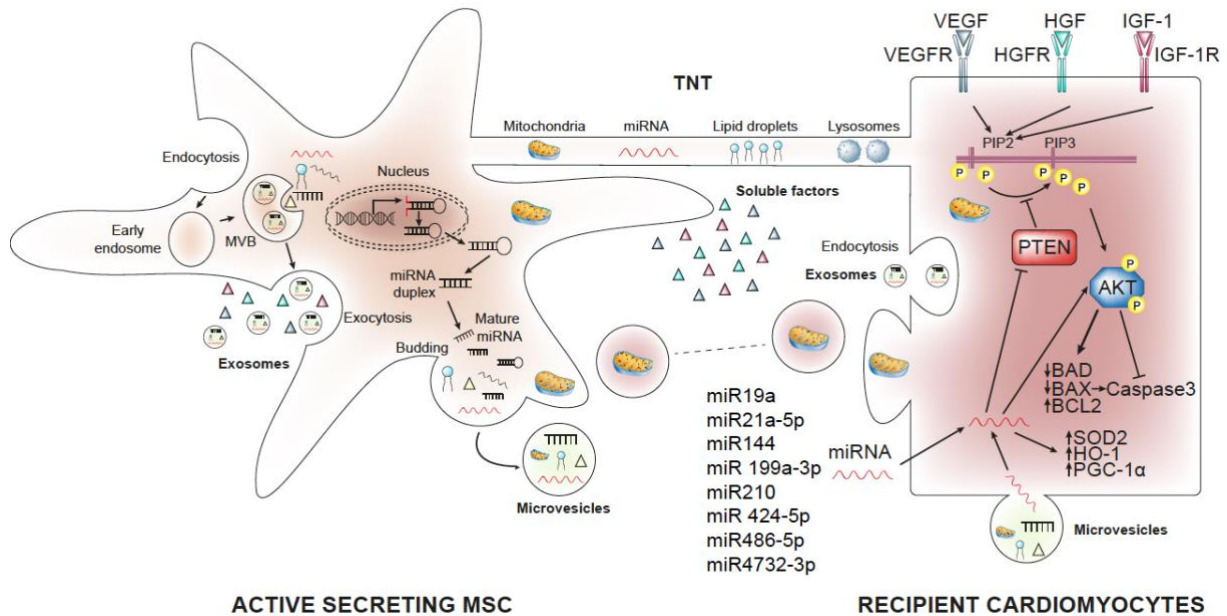
1373 Altogether, these studies strongly suggests that EV derived from MSC could be a potent
1374 therapeutic vehicle to protect injured cardiac cells from apoptosis in ischemic conditions through the
1375 delivery of multiple anti-apoptotic miRNAs.

1376

1377 ***1.3. Tunneling nanotubes and organelle exchange***

1378 Tunneling nanotubes (TNT) are the structures allowing the selective transfer of membrane
1379 vesicles and organelles (407). These structures can be formed between MSC and many other cell types
1380 including endothelial cells (408) and cardiomyocytes (409). TNT allow the transfer of organelles such
1381 as mitochondria, lysosomes, microRNA and lipid droplets (**FIGURE 9**). The transfer of mitochondrial
1382 DNA from stem cells to hypoxic endothelial cells leads to a restoration of their aerobic respiration and

1383 the prevention of apoptosis (410). In addition, mitochondria from BM-MSC provided anti-apoptotic and
 1384 anti-degenerative effects through the rescue of endogenous mitochondrial function restoring SOD2,
 1385 BCL-2, BAX and PGC-1 α expression and inhibiting ROS production (411).



1386

1387 **FIGURE 9: Mechanisms involved in MSC anti-apoptotic effects of cardiomyocytes.**

1388 MSC promote cardiomyocyte viability and protect them from apoptosis through a variety of mechanisms
 1389 that include organelles (mitochondria, lipid droplets, lysosomes) transfer via the formation of TNT as
 1390 well as the secretion of various trophic factors or EV such as exosomes and microvesicles. Microvesicles
 1391 are generated by plasma membrane budding. The MSC extracellular constituents and surface proteins
 1392 form the early sorting endosome by endocytosis with internal budding of the plasma membrane. The
 1393 early sorting endosome gives rise to the late sorting endosome and multivesicular bodies (MVB). The
 1394 MVB release their vesicles into the extracellular zone in the form of exosomes. Exosomes can release
 1395 cargo to recipient cardiomyocytes by three modes: endocytosis, direct membrane fusion, and receptor-
 1396 ligand binding. MSC microvesicles and exosomes can contain a number of different molecules as cargo
 1397 such as proteins, chemokines, growth factors (VEGF, IGF-1 and HGF), cytokines, DNA, mRNA, miR
 1398 (miR19a, miR21a-5p, miR144, miR199&-3p, miR210, miR424-5p, miR486-5p and miR4732-3p) and
 1399 other nucleic acids as well as organelles (mitochondria, lipid droplets, lysosomes) which will protect
 1400 the injured/stressed cardiomyocytes from apoptosis. These molecules and organelles will target genes
 1401 involved in cell survival or apoptosis, in part, through Akt activation.

1402

1403

1404 In the injured tissue, suffering cells release DAMPS to promote the adaptative MSC reparative
 1405 response. Anti-apoptotic functions of MSC are also triggered, in part, via mitochondria transfer to
 1406 injured cardiomyocytes (412). As a response, MSC donate their healthy mitochondria to help injured
 1407 cells to overcome oxidative stress injury, in part, through the cytoprotective heme-oxygenase 1 (HO-1)
 1408 enzyme stimulating mitochondrial biogenesis (412). HO-1 is an inducible stress protein that protects
 1409 cells from oxidative stress, apoptosis, and inflammation. MSC pre-treatment with a potent inducer of
 1410 HO-1, haemin, was shown to inhibit mitochondrial fragmentation and apoptosis of MSC induced by

1411 serum deprivation and hypoxia. At 4-week after transplantation, compared with naïve MSC, haemin-
1412 treated MSC significantly enhanced cardiac function in mice subjected to MI. This therapeutic benefit
1413 was associated with decreased apoptosis of cardiomyocytes, improved angiogenesis and higher cell
1414 survival (413). Therefore, pharmacological pre-treatment might improve MSC survival rate under
1415 ischemic conditions through the repression of mitochondrial fission and then improve MSC-based
1416 therapy for MI treatment.

1417 To conclude, MSC have strong anti-apoptotic effects mediated by different mechanisms. They
1418 can increase pro-survival pathway by direct or indirect effects to limit oxidative stress and inflammation
1419 and increase angiogenesis. However, the main benefits observed in MSC-based therapy including their
1420 anti-apoptotic properties, are provided by their secretome.

1421

1422 **2- Anti-inflammatory/Immunoregulatory properties**

1423 MSC have also been of high interest for the treatment of cardiovascular diseases because of their
1424 immunoregulatory and anti-inflammatory properties. Indeed, MSC not only exert immunoregulatory
1425 properties through the innate and/or the adaptive immune system but also regulate the trafficking of
1426 inflammatory immune cells. To exert such functions, MSC need to be “primed”/activated with pro-
1427 inflammatory molecules. Indeed, in response to their environmental stimuli, MSC can adopt different
1428 phenotypes, morphologies, a migratory potential, anti-inflammatory and immunoregulatory functions.

1429

1430 **2.1. MSC priming/activation with inflammatory cytokines**

1431 Pro-inflammatory factors released in the local injured milieu, massively impact on MSC
1432 properties and thus modulate the outcome of MSC-based therapies. MSC express several receptors
1433 among which the inflammation sensing receptors and the toll-like receptors enabling them to sense and
1434 respond to tissue damage (414). Thus, MSC stimulation with a specific ligand effectively prime MSC
1435 to induce and/or modulate one or more of their functions and their therapeutic effects (415).

1436 Several studies have shown the pivotal role of IFN- γ for MSC activation (416-418). Indeed,
1437 IFN- γ , a proinflammatory cytokine produced by activated T cells, primes the immunomodulatory
1438 property of MSC by upregulation of PD-L1 (*Programed Death-Ligand 1*), an inhibitory surface
1439 molecule. Conversely, PD-L1 knockdown using siRNA abolished MSC immunosuppressive potential.
1440 In line with these studies, it was shown that IFN- γ induces MSC immunosuppressive properties alone
1441 or in combination with others pro-inflammatory cytokines including IL-1 β , IL-1 α and TNF- α (416).
1442 These pro-inflammatory cytokines induce, in part, the expression of VCAM-1 and ICAM-1 in MSC
1443 (419). Thus, when MSC are cocultured with activated T cells producing high levels of pro-inflammatory
1444 cytokines, they significantly increase the adhesion capacity of T cells to their surface via their increased
1445 expression of VCAM-1 and ICAM-1. Consistently, MSC immunoregulatory properties were
1446 significantly reduced *in vitro* and *in vivo* when VCAM-1 and ICAM-1 were functionally inactivated or
1447 genetically silenced. TNF/TNFR1 axis also enhances the production of molecules referred as mediators

1448 of MSC immunosuppressive properties such as PGE₂ by inducing the expression of COX2
1449 (*cyclooxygenase 2*) in MSC. In turn, PGE₂ released by primed MSC stimulates the production of IL-10
1450 by macrophages through the prostaglandin EP2 and EP4 receptors (420). In addition, TNF- α and
1451 hypoxia priming of MSC enhances the production of paracrine factors including b-FGF, VEGF and
1452 TGF- β (*Transforming Growth Factor- β*) that work in synergy to regulate the microenvironment and
1453 reduce inflammation in MI (421).

1454 More recently, our group and others showed that MSC activation with IFN- γ and TNF α induces
1455 their metabolic switch towards glycolysis (422-424). Going further we demonstrated that this metabolic
1456 reprogramming significantly enhanced MSC immunoregulatory properties *in vitro* and *in vivo* in an
1457 AMPK- and HIF-1 α (*Hypoxia Inducible Factor-1 alpha*)-dependent manner (422). Indeed, we showed
1458 that the significant increased level of AMPK phosphorylation in MSC after TNF α and IFN- γ stimulation
1459 induced their glycolytic switch. The inhibition of AMPK activity abolished the enhancement of
1460 glycolytic MSC suppressive activity. TNF- α and IFN- γ stimulation of MSC also significantly increased
1461 the expression and the nuclear translocation of HIF-1 α (425). HIF-1 α knockdown in MSC induced a
1462 metabolic switch from glycolysis to OXPHOS, a decrease of the immunoregulatory potential and a
1463 reduction of the expression or production of some MSC immunosuppressive mediators including ICAM,
1464 IL-6, and NO respectively (425).

1465 Among the master regulators of cell metabolism, mitochondria are key organelles that have been
1466 shown to orchestrate MSC immunoregulatory potential. MSC have the unique ability to export their
1467 own mitochondria to neighboring cells in response to inflammation. Indeed, the pro-inflammatory
1468 environment induced by TNF promotes TNT formation and mitochondrial transfer between MSC and
1469 cardiomyocytes to rescue cardiomyopathy (426). Moreover, mitochondrial transfer induced by pro-
1470 inflammatory stimuli between MSC and immune cells has been shown to regulate the immune response
1471 (427, 428). Altogether these studies indicate that the inflammatory microenvironment may be a critical
1472 factor to reprogram the metabolic status of MSC and enhance their paracrine effects and mitochondrial
1473 transfer to modulate their anti-inflammatory and immunoregulatory properties.

1474

1475 **2.2. Anti-inflammatory properties**

1476 During MI, distant inflammatory cell-generating organs, including the spleen and bone marrow,
1477 are stimulated, thereby maintaining a continuous supply of monocytes to the site of inflammation (429,
1478 430). Thus, the systemic response can transfer the inflammation to organs that are not initially involved
1479 (430). While systemic and local inflammatory responses after MI are well described, the mechanisms
1480 of infarct zone containment have been addressed recently. The authors showed that serum of patients
1481 with AMI exerts anti-inflammatory actions on healthy cardiomyocytes, thereby contributing to limit
1482 infarct size and protecting healthy tissue. However, ventricular fibrillation, a complication of MI,
1483 promotes the switch of healthy cardiomyocytes towards a proinflammatory phenotype (431). During MI,

1484 tissue injury-related signals including DAMPs released from dying or stressed cells are detected by MSC
1485 leading to increased pro-repair abilities and anti-inflammatory outcomes (432).

1486

1487 **Effect of MSC on inflammation** Experiments on cultured naive human BM-MSC spheroids
1488 exposed to TNF α , and cocultured with adult human cardiomyocytes, or with conditioned media pooled
1489 from TNF α -stimulated adult cardiomyocytes, showed that TNF α -induced inflammation altered BM-
1490 MSC survival and differentiation into mature cardiomyocytes, while promoting matrix protein synthesis
1491 and cytokine release conducive to the MI remodeling (433). While inflammation repressed naïve MSC
1492 functions, different results were reported using primed MSC. Indeed, the increased expression of
1493 inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 in the ischemic heart was shown to be inhibited
1494 upon the transplantation of IGF-1-primed MSC, which also reduced cardiac dysfunction, increased cell
1495 engraftment and reduced apoptosis of myocardium cells (434). Similarly, MSC overexpressing HGF
1496 down-regulate inflammatory cytokine secretion and up-regulate anti-inflammatory cytokine release,
1497 suggesting that HGF is a critical contributor to the regulation of cytokine secretion by MSC (435).

1498

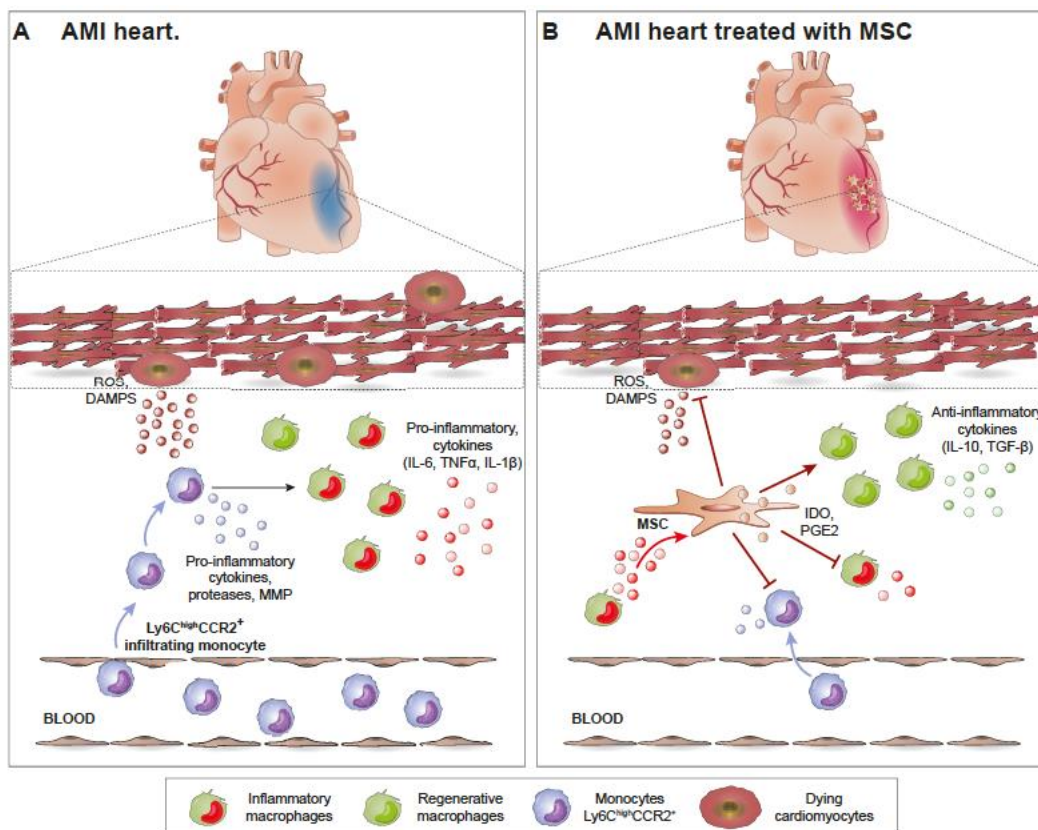
1499 **Effect of MSC administration on the monocyte response** Pro-inflammatory cytokines are
1500 mainly derived from monocyte-derived macrophages, the most abundant immune cells in the heart after
1501 MI and IR injury (436). After MI, monocytes migrate to the infarct area and differentiate into
1502 macrophages that release chemokines, growth factors and cytokines, to clear injured and apoptotic
1503 myocardial cells (**FIGURE 10**). Macrophages after MI are activated and polarized towards different
1504 subsets with different immune functions, mainly into pro-inflammatory macrophages producing IFN- γ ,
1505 TNF- α and IL-23 and promoting the destruction of the extracellular matrix (437). Therefore, the
1506 regulation of monocyte trafficking and mobilization has emerged as an attractive therapeutic approach
1507 for myocardial inflammation and fibrosis. In an experimental model of myocarditis, the capacity of MSC
1508 to decrease the severity of the disease in mice was associated with a reduced percentage of pro-
1509 inflammatory Ly6C^{high} and Ly6C^{middle} monocytes and an increased percentage of Ly6C^{low} monocytes in
1510 the heart and the blood. This study demonstrates that MSC promote the resolution of cardiac
1511 inflammation by repressing the cardiac infiltration of pro-inflammatory monocytes while enhancing
1512 cardiac influx of anti-inflammatory monocytes (438).

1513 More recently, the combined treatment with MSC and anti-CCR2 significantly reduced monocyte
1514 accumulation at the site of infarction in AMI mice by comparison with injection of MSC or anti-CCR2
1515 alone. In addition, the reduced monocyte infiltration was associated with a decreased secretion of pro-
1516 inflammatory cytokines at the injury sites, a better tissue regeneration and an enhanced improvement in
1517 cardiac function (439).

1518

1519 **Effect of MSC-EV on inflammation** Similarly, to their parental cells, MSC-EV were shown
1520 to regulate cardiac inflammation and ameliorate cardiac function in preclinical studies through the same

1521 pathway. Indeed, EV can inhibit the monocyte influx into the injured region via different mechanisms.
 1522 The first evidence of the anti-inflammatory effect of MSC-EV was provided by a study in a mouse
 1523 model of myocardial IR injury, where the EV were injected intravenously before reperfusion (440).
 1524 Similarly, MSC-EV administered in rat hearts after permanent ligation significantly reduced the
 1525 percentage of macrophages in the peri-infarct zone one week after MI (441). These anti-inflammatory
 1526 effects of EV might be mediated through the transfer of different molecules including miRNA and
 1527 therefore regulate leukocyte influx in the heart. For instance, miR-24 was shown to regulate vascular
 1528 inflammation by controlling macrophage behavior (442, 443). Moreover, miR-24-3p was suggested to
 1529 repress the recruitment of bone marrow-leukocytes by downregulating their CCR2 expression level
 1530 (444).
 1531



1532

1533 **FIGURE 10: MSC anti-inflammatory and immunoregulatory effects in hearts after ischemic injury.**
 1534 **A.** The death of cells induced by ischemic injury leads to the release of DAMPs and ROS, which induces
 1535 the inflammatory phase. Indeed, dying cardiomyocytes produce pro-inflammatory cytokines and
 1536 chemokines resulting to a substantial inflammatory monocytes influx into the cardiac ischemic area,
 1537 responsible for phagocytosis of the dying cells and the generation of an inflammatory environment
 1538 promoted by the presence of pro-inflammatory macrophages and Ly6C^{high}CCR2⁺ infiltrating monocytes
 1539 that adopt transcriptional active states and participate to adverse cardiac remodeling. **B.** MSC
 1540 administrated in the ischemic hearts will receive pro-inflammatory signals from injured cardiac cells
 1541 and the inflammatory monocytes/macrophages and an active secreting phenotype. The subsequent
 1542 primed secreting MSC will release soluble factors, microvesicles and exosomes that will mediate anti-
 1543 inflammatory and immunoregulatory properties. First, primed MSC will regulate the influx of CCR2⁺
 1544 infiltrating macrophages derived from circulating monocytes. Second, primed MSC will promote
 1545 resident or monocyte-derived macrophages polarization towards an anti-inflammatory phenotype.

1546

1547 **2.3. MSC immunoregulatory properties**

1548 In addition to their capacity to control monocyte trafficking and mobilization, MSC can also
 1549 potentially regulate the immune response. MSC immunoregulatory properties have been discovered in the
 1550 early 2000s. MSC have been initially described for their capacity to inhibit T cell proliferation and
 1551 functions both *in vitro* and *in vivo* (445). A few years after, the inhibitory potential of MSC on other
 1552 adaptative immune cells such as B cells (446) and innate immune cells, including dendritic cells (DCs)
 1553 (447), natural killer cells (NK cells) (448) and macrophages (449), was reported.

1554 MSC and macrophage interactions increase the expression of CD206 and the production of IL-10 by
 1555 macrophages while reducing IL-12 and TNF- α . Thus, it was proposed that these MSC-trained
 1556 macrophages constitute a new type of alternatively activated macrophages that would play a potential
 1557 important role in tissue repair (450).

1558

1559 **Priming of MSC immunoregulatory properties** To exert such immunoregulatory properties
 1560 and switch the inflammatory immune response into a balanced immune response, MSC sense danger
 1561 signals *via* receptors including TLR and respond to excessive pro-inflammatory signals *via* TNF- α and
 1562 IFN- γ receptors. MSC immunoregulatory properties have been described by our group and others to be
 1563 mediated through both direct cell contacts and soluble factors. Thus, MSC need to be primed by
 1564 inflammatory conditions or also hypoxia to exert their immunoregulatory functions. For example, MSC
 1565 do not exhibit at steady state any indoleamine 2,3-dioxygenase (IDO) activity, pivotal for their
 1566 immunosuppressive functions, while IFN- γ induces it. Similarly, the production of PGE₂ by MSC (451),
 1567 a soluble mediator of MSC immunoregulatory properties, is stimulated by inflammatory cytokines such
 1568 as the combination of IFN- γ and TNF- α (452). IDO and PGE₂ produced by MSC induce the switch
 1569 from pro-inflammatory to anti-inflammatory macrophages (453). However, PGE₂ can modulate both
 1570 the innate and adaptive immunity, with either beneficial or adverse effects (454). Indeed, PGE₂ produced
 1571 by MSC can, on one hand, promotes an inflammatory response by enhancing LPS (lipopolysaccharide)-
 1572 induced IL-23 production by dendritic cells, which favors Th1 and Th17 cell differentiation (for review
 1573 see (455)). On the other hand, PGE₂ produced by MSC can generate an anti-inflammatory response
 1574 through its binding to its receptors EP2 and EP4 on macrophages that enhances their polarization toward
 1575 anti-inflammatory macrophages (420).

1576

1577 **Factors involved in the immunoregulatory properties of MSC on monocytes/macrophages** In
 1578 a mouse model of AMI, the injection of MSC, 2 days after MI induction reduced the proportion of
 1579 macrophage/monocyte including pro-inflammatory macrophages, while increasing the percentage of
 1580 anti-inflammatory and reparative macrophages (F4/80⁺CD206⁺) both in the circulation and in infarcted
 1581 heart (456, 457). The increased immunoregulatory effect on macrophages observed in response to MSC
 1582 treatment in cardiomyopathies is lost when MSC are pretreated with a COX-2 inhibitor prior their

1583 injection (458). Anti-inflammatory macrophage polarization promoted by MSC *via* the COX-2-PGE2
1584 pathway will increase the concentration levels of TGF β , IL-10, HGF, PGE2 and IDO in the infarcted
1585 myocardium and thus suppress the proinflammatory state of the tissue. This paradoxical effect exerted
1586 by PGE2 depends on its concentration (for review see (455)). Other soluble factors produced by MSC
1587 such as IL-1Ra (*Interleukin-1 receptor antagonist*), IL-6 and granulocyte macrophage-colony
1588 stimulating factor (GM-CSF) mediate, in part, the shift of macrophages toward an anti-inflammatory
1589 phenotype (420, 459, 460). Recently, it has been shown that the intracardiac injection of living or dead
1590 stem cells similarly provides an accumulation of macrophage positives for CCR2 and CX3CR1 inducing
1591 a functional repair process of the injured myocardium (461). This latter study suggests that stem-cell
1592 based therapy in cardiac ischemic injury promotes wound healing response and restores the mechanical
1593 properties of infarcted heart *via*, in part, an acute immune response. However, the recent findings
1594 indicating a functional distinction between CCR2⁺ and CX3CR1⁺CCR2⁻ macrophage subsets in cardiac
1595 wound healing (462, 463) raise the question of the role of MSC-based therapy on these macrophage
1596 subsets.

1597 Modified MSC were shown to display enhanced immunoregulatory potential and subsequently
1598 improved therapeutic properties for MI. Indeed, in an experimental model of MI, MSC overexpressing
1599 IL-33 (MSC-IL-33) were shown to decrease inflammation in the hearts with MI, to increase the
1600 expression of CD206 and reduce the expression of iNOS. Moreover, genes related to inflammation
1601 including IL-6, TNF- α , and IL-1 β were found to be reduced in the border zone of hearts treated with
1602 MSC-IL-33 compared to the heart treated with control MSC (464).

1603 More recently, the role of hypoxia on MSC immunoregulatory properties was investigated. First,
1604 the authors showed that hypoxia increase the expression levels of HIF-1 α and TGF- β 1 in MSC and that
1605 the hypoxic conditioned media of MSC promotes macrophage polarization towards an anti-
1606 inflammatory-like phenotype through TGF- β 1/Smad3 signaling pathway. Finally, they report that these
1607 macrophages attenuate cardiac fibrosis and apoptosis and increase the density of the microvessels
1608 density after MI (465).

1609 Therefore, MSC based-therapy of MI is, in part, mediated through the control of the monocyte
1610 trafficking and mobilization and the regulation of macrophage polarization.

1611

1612

1613 **IV- MSC for the treatment of IR injury**

1614

1615 **A- Results obtained in preclinical studies and clinical trials**

1616

1617

1618 **1- In preclinical models**

1619

1620

1621

1622

1623

1624

1625

1626

1627

1628

1629

1630

1631

1632

1633

1634

1635

1636

1637

1638

1639

1640

1641

1642

1643

1644

1645

1646

1647

Highly encouraging results were obtained from pioneering studies in preclinical models in the early 2000s showing that MSC in the adult heart were able to replace damaged tissue after engraftment although contested thereafter (466). Then, MSC-based cardiomyoplasty was investigated in different animal models, showing the differentiation of MSC into cardiomyocytes, endothelial and smooth vascular cells (467-469). Evidence of MSC differentiation into functional cardiomyocytes (CM-MSC) was reported *in vitro* after treatment with various drugs such as 5-azacytidine (an hypomethylating agent) and *in vivo* with improvement of contractile function (470, 471). However, due to safety concerns, this differentiation protocol has been replaced by insulin, dexamethasone and ascorbic acid (472) or bone morphogenetic protein-2 associated with FGF (473). In addition, the risk of immune response more pronounced with differentiated MSC led researchers to use undifferentiated MSC instead for *in vivo* studies (474, 475). The safety of undifferentiated MSC was subsequently demonstrated, with the exception of one report of arrhythmias in a porcine model of AMI (476), as well as their efficacy on infarct size and heart function.

Effects of MSC administration on cardiac performance Ejection fraction parameter (EF, %), the simplest and most widely used parameter for the global assessment of myocardial function in patients (477), was measured in animals either using echocardiography (in most cases), MRI or SPECT (*Single Photon Emission Computed Tomography*). Kanelidis' metanalysis reports a 12%-overall increase in EF in rodents after MSC administration compared to the untreated group (478). Results in large species such as pigs showed a 7%-improved EF obtained from only 7 out 16 studies revealing MSC positive impact. Jansen Of Lorkeers' analysis confirmed that MSC treatment was able to increase EF by an average of 8.7% in 832 treated animals of large species including pigs, dogs, and sheep *versus* 583 control animals (479). Accordingly, a 8%-decrease in infarct size was evidenced in 50% of the preclinical studies performed in rodents (mouse and rat) (478) and a 6.4%-reduction in pig hearts (mean obtained from 7 positive *versus* 5 neutral studies) (478). Cardiac remodeling was also prevented by MSC therapy as assessed by the decreased volume of the cardiac chamber (LVEDV, *Left Ventricular End-Diastolic Volume* and LVESV, *Left Ventricular End-Systolic Volume*), the absence of hypertrophy and also a less extent in cardiac fibrosis (479-483).

1648 **Immune response following MSC administration** For technical reasons, the most frequently
 1649 used MSC source are allogeneic in preclinical models but also autologous usually in large species (484),
 1650 or xenogeneic MSC (481, 485, 486) have been studied, showing similar efficacy (for review see (478,
 1651 479). Both autologous and allogeneic cell therapies have been reported to be safe in preclinical studies
 1652 on large animals (pig, sheep, dog) (479). The risk of immune rejection after transplantation has been
 1653 widely discussed since MSC exhibit an immune evasion phenotype marked by low MHC (*Major*
 1654 *Histocompatibility Complex*) class I levels and the absence of expression of MHC class II (474, 487).
 1655 MSC, due to their low immunogenicity, can survive for more than one month after transplantation in
 1656 allogeneic hearts by contrast to differentiated MSC that are not immune-privileged (474, 475). Their
 1657 short lifespan (<1month) after injection could be explained by immune rejection due to expression of
 1658 MHC class II *in vivo* (488). However, despite the existence of an immune response, an improvement in
 1659 the left ventricle EF was evidenced even with xenogeneic MSC (489).

1660

1661 **2- In AMI patients**

1662 Results obtained in clinical trials evaluating the benefits of MSC for cardiac repair in AMI
 1663 patients are variable and sometimes even contradictory (see **Table**). Safety was the first primary clinical
 1664 outcome evaluated in those studies, clearly showing the near absence of complications during either the
 1665 procedure (except for one case of periprocedural complication of coronary artery obstruction) or the
 1666 follow-up (490-492). Importantly, neither tumorigenicity nor ectopic tissue formation was reported 24
 1667 months after allogeneic MSC injection (493).

1668

1669 **Heterogenous protocols of MSC administration** EF (%) parameter was also measured to
 1670 evaluate cardiac function using echocardiography in most cases (490, 492-501), MRI (493, 494) or
 1671 SPECT (490, 492, 494-497, 499, 502). A highly significant 3.78%-increase in EF for the MSC group
 1672 *versus* control was evidenced by Attar's metanalysis (13 clinical trials), confirming the results of a
 1673 previous metanalysis (3.22%-increase) (503, 504). Remarkably, a record 5%-increase in EF was
 1674 reported also with the combination of 6.10^6 MSC injected *via* the IC route, 1-week post-MI (<1 week
 1675 and $<10^7$) suggesting that the finely tuned combination of the right timing and the right dose injected is
 1676 determinant for the effectiveness of MSC therapy (495). However, considering the positive results
 1677 obtained with a treatment protocol of timing of injection <1-week combined to a dose of MSC $<10^7$
 1678 (495, 502) or the protocol with a timing <1-week and a dose $>10^7$) (493, 494) and the negative ones
 1679 obtained with a timing of injection >1 -week and a dose of MSC $>10^7$) (490, 497, 500), the "timing of
 1680 injection" seems to be the crucial parameter for success. Importantly, cardiac function improvement was
 1681 stable for up to 24 months after MSC-based therapy (505).

1682

1683

1684

Author, year	Source of MSC	Origin	Route	Timing (days after PCI)	Number /Age	Dose	Readout	Follow-up duration (months)	Results	LVEF Treated	LVEF placebo
Chen, 2004	Autologous	BM-MSC, fresh	IC	18 ± 0.5	69 / 57,5	8-10 .10 ⁹	ECHO, PET	6 m	-Increased EF (vs placebo) -Decreased perfusion defects, LVEDV and LVESV	At 3 months 67 ±11	At 3 m : 53±8
Hare, 2009	Allogeneic	BM-MSC	IV	<7	53 / 57	80 . 10 ⁶	ECHO/MRI	12 m	-safety of hMSC allogeneic -Improved EF vs baseline -reduced ventricular tachycardia	5.2 ± 1.9 changes vs placebo (p*)	1.8 ± 1.5 changes vs baseline
Yang, 2010	Autologous	BM-MSC Vs BM-MSC (no control group)	IC via the LAD (group I) or via a non-infarct coronary artery (group II)	21	16 / 60.2	12.2±17.7 (group I) or 13.2 ±17.6 10 ⁶ (group II)	ECHO, SPECT	6 m	Increased LVEF + myocardial viability vs baseline	52.0 ± 8.9	50.5 ±9.1
Penn, 2012	Allogeneic	BM-MSC	IC	3.3	25 / 53	20. 10 ⁶ , 50. 10 ⁶ 100. 10 ⁶	ECHO, Angiography	4 m	improved EF vs baseline (50 10 ⁶). Improved EF + stroke volume for doses ≥50 10 ⁶ in patients with EF<45%	8.7 % Absolute change (vs baseline) (50 10 ⁶)	
Houtgraaf, 2012	Autologous	Adipose : first study	IC	<1	13 / 58	17.4 ±4.1 x10 ⁶	SPECT/CMR	6 m	-Safety - decreased infarct size and perfusion defects vs placebo - no change in EF	56.1%	50.3%
Gao, 2013	Autologous	BM-MSC	IC	17.1	43 / 56.8	3.08. 10 ⁶	ECHO, SPECT	12 m	- no change in EF	54.9 ±1.6	55.1± 1.8
Rodrigo, 2013	Autologous	BM-MSC	IM	17 to 25	54 / 58.5	46. 10 ⁶	ECHO, SPECT	60 m	-safety /5 years - no change in EF vs placebo	57.0 ± 3	50 ± 12
Wang, 2014	Autologous	BM-MSC no control group	IC	14	58/57	10 ⁸	ECHO, angiography	6 m	-decreased Adverse events and rehospital rates -no change in EF	50.1 ± 3.4	49.1 ± 2.3
Lee, 2014	Autologous	BM-MSC	IC	28.8	69/54	72. 10 ⁶	ECHO, SPECT	6 m	-Safety -Improvement of EF vs baseline	50.0 ± 8.4 (5.9% ± 8.5% vs baseline)	50.4 ± 9.4 (1.6% ± 7.0% vs baseline)
Chullikana, 2015	Allogeneic	BM-MSC	IV	2	19/47,5	2.10 ⁹ /kg of body weight	ECHO, MRI, SPECT	24 m	Safety and tolerance - No improvement in EF	46.96 ±7.56	45 ±10.21
Musialek, 2015	Allogeneic	WJ-MSC	IC	5-7	10 / 55	30. 10 ⁶	Safety procedural	12 m	Safety		
Gao, 2015	Allogeneic	umbilical	IC	6.2	116/57	6. 10 ⁶	ECHO / PET / SPECT	18 m	- increase in EF -decreased infarct size and remodeling	7.8 ± 0.9 vs baseline (+ vs placebo)	2.8 ± 1.2 Vs baseline
Kim, 2018	Autologous	BM-MSC	IC	25	26/56.5	72 ± 9 x 10 ⁶	ECHO, SPECT	12 m	-improved EF vs baseline and vs placebo	8.8 ± 2.9% vs baseline	4.8 ± 1.9% vs baseline
Zhang, 2021	Autologous	BM-MSC	IC	14.07 ± 9.53	43/59	3.31 ± 1.7 .10 ⁶	ECHO	12 m	- no change in EF	57.2 ± 10.2	62.0 ± 6.8

1685 **Table: summary table of clinical trials conducted on AMI patients with MSC-based therapy**

1686

1687 **Effects of MSC on patient prognosis** Outcomes on infarct size were assessed by cardiac
 1688 magnetic resonance (CMR) (502), MRI (494) or ventriculography (500). In most cases, a lack of effect
 1689 was reported using either allogeneic (494) or autologous BM-MSC (500) except in one study showing a
 1690 decreased infarct size with an IC injection of freshly prepared autologous AT-MSC (502). Contrasting
 1691 results were reported also for myocardial viability after autologous BM-MSC administration showing
 1692 either improvements (506) or neutral effects (492, 501). Regarding myocardial perfusion, improvements
 1693 were observed after injection of autologous AT-MSC and BM-MSC (490, 502, 506) or Wharton's jelly-
 1694 derived MSC (495) but an absence of effects was also described despite quite similar protocols (492,
 1695 494, 501). By contrast to preclinical studies, long-term progression towards heart failure was quoted in
 1696 patients, showing a reduction LVEDV or LVESV measurements as indicators of LV remodeling (490,
 1697 493, 495) and in the number of rehospitalizations for heart failure (500). However, no change was
 1698 observed for the six-min walk test at 6-month post-MI (493) and also, more importantly, in the survival
 1699 rate (499, 500).

1700

1701 **Allogeneic versus autologous MSC** For a clinical application, bone marrow and adipose
 1702 human tissues are the two main sources of cells widely used to ensure large amounts of MSC (507) even

1703 though umbilical cord-derived stem cells have been shown recently to have a more positive effect on
 1704 EF (503). Both autologous (490, 492, 496, 497, 499-502, 508) and allogeneic (493-495, 509) MSC have
 1705 been tested in AMI patients. After a pioneering study showing safety and promising results using
 1706 autologous MSC (490), puzzling data have been reported in following studies with either positive results
 1707 (496, 497, 500, 502) or a lack of efficacy (492, 499, 501). Because autologous stem cells must be
 1708 amplified *ex vivo* for several weeks (1 to 4) to obtain a sufficient number for the treatment (496, 501),
 1709 they cannot be easily used in the acute phase of MI to treat reperfusion injury. Thus, the use of allogeneic
 1710 MSC appear more adapted and less expensive than autologous cells that require cell expansion, product
 1711 characterization and batch release testing for each patient. More importantly, allogeneic MSC in AMI
 1712 patients are safe and provide promising results (362, 493, 509) highlighting the difference in quality of
 1713 MSC from young and healthy donors compared to AMI patients. For these reasons, allogeneic MSC
 1714 therapy is preferred over autologous MSC therapy (510). They come from healthy donors by contrast to
 1715 autologous ones and, as “off-the-shelf” product, they are immediately available for urgent treatment.

1716

1717

1718 **B. Origin of the gap for the clinical translation**

1719

1720 While MSC is a promising cell therapy product, the heterogeneity of results raises the question
 1721 of how to use them optimally to guarantee positive results to the patients. To this end, it is necessary to
 1722 analyze the reasons underlying this heterogeneity.

1723

1724 **1- Influence of the cell therapy product and the recipient**

1725 The difference between the results obtained in the preclinical studies and those reported in the
 1726 large-scale clinical trials could be explained by several issues including the heterogeneity of cell
 1727 preparations, the injected doses and the therapeutic time window of administration.

1728

1729 ***1.1 Regarding the cells***

1730 ***Age of cell donors*** The first investigations performed with patient-derived cells revealed a
 1731 decreased number of cells and an impaired functional activity as compared to healthy cells (511). In
 1732 AMI patients, disease and/or age reduce the impact of BM-MSK on their function (492) as compared
 1733 with other studies using allogeneic MSC from young and healthy donors (493-495, 512). As a result,
 1734 most clinical trials used allogeneic MSC instead of autologous MSC coming from patients with age-
 1735 related diseases that have decreased regenerative capacities (513, 514). In fact, compared with aged
 1736 donors, MSC derived from young donors have a higher proliferation rate, a slower progression toward
 1737 senescence during the *in vitro* expansion phase (515) and a lower rate of trophic factor secretion (for
 1738 review see (516)). For instance, decreased secretion of brain-derived neurotrophic factor (BDNF) and
 1739 PDGF in human MSC derived from aged donors was associated with less atrophy-preventing capacities,

1740 anti-inflammatory effects, vessel maturation and lower levels of MCP-1 in peri-infarct tissue compared
1741 to MSC derived from young donors since PDGF is a potent inducer of MCP-1 and the PDGF family is
1742 closely related to the VEGF family (516). The same negative correlation was reported for age and
1743 immunoregulatory potential of BM- and AT-MSC (517). Old MSC display a reduced expression of TNF
1744 receptor (TNFR), IFN- γ receptor (IFNGR), and CCR7, required for their activation by TNF- α and IFN-
1745 γ , which stimulate/prime their immunosuppressive properties (518).

1746 Therefore, disadvantageous characteristics of MSC from aged donors could adversely affect the success
1747 of cell therapy for MI and consequently allogenic source of MSC from young and healthy donors are
1748 preferred in clinical trials. Further investigations are ongoing to elucidate the mechanisms associated to
1749 MSC aging in order to find new directions for counteracting cell age loss.

1750 **Anatomical depots** In mammals, white adipose tissue, involved in energy storage, is anatomically
1751 classified into two major fat deposits, visceral adipose tissue (e.g., epididymal adipose tissue (EAT))
1752 and subcutaneous adipose tissue (e.g., inguinal adipose tissue (IAT)). The different characteristics of
1753 EAT and IAT are mediated, in part, by the distinct properties of ASC. For instance, IAT-derived ASC
1754 actively repress monocyte infiltration via secreted molecules, thereby inhibiting inflammatory responses
1755 in IAT (519). Moreover, in a study comparing the biology of ASC from 5 different subcutaneous adipose
1756 locations (superficial abdominal, deep abdominal, arm, thigh, and trochanteric), it was shown that the
1757 susceptibility to apoptosis was lowest in the superficial abdominal depot and in the younger age groups
1758 (520). This observation was in line with a study showing that the superficial abdominal depot was less
1759 susceptible to apoptosis when compared with adipose stem cells from the omental depot (521).

1760 In addition to differences in susceptibility to apoptosis, different functions have been associated to the
1761 ASC subsets identified in response to obesogenic stimuli. Indeed, ASC positive for syndecan 1 (SDC1)
1762 predominant in EAT promote fibrotic remodeling, while IAT-derived ASC positive for CXCL14 inhibit
1763 macrophage infiltration (522).

1764 The most commonly used source of adipose tissue for isolating ASCs is subcutaneous white adipose
1765 tissue harvested from the abdomen, hips, thighs or buttocks, usually during plastic surgery procedures.
1766 However, there are no preclinical studies comparing the therapeutic potential of these different types of
1767 adipose tissue.

1768 **Conditions and time of cell amplification** Preclinical murine models use adapted MSC in
1769 culture, whereas clinical trials rely on MSC stored in different conditions (bio- or cryo-preserved) and
1770 thawed just before administration without a culture period allowing recovery. Deleterious effects of
1771 immediate thawing on MSC properties such as their immunomodulatory properties have been described
1772 *in vitro* (523). In addition, certain functions of MSC such as their differentiation potential decline after
1773 sustained passages due to the average decrease in CFU (*Colony Forming Unit*) and colony size observed
1774 *in vitro* (524). After multiple serial passages in culture (30-40 population doublings), MSC cease to
1775 divide and enter a state of *in vitro* aging, also known as replicative senescence or the Hayflick limit
1776 (525). Moreover, MSC start to become hypertrophic (MSC size about 4-fold larger at passage 6 than at

1777 passage 1) and their stemness gene expression profile is altered (526, 527). Regarding the expression
1778 profile of markers characteristics for MSC including CD73, CD90, CD105, and CD106, they were
1779 shown to be down-regulated during culture expansion compared to MSC in the stromal fraction (527,
1780 528). Thus, for the use of MSC in the clinic, the dilemma comes from the fact that the culture of MSC
1781 for the clinical application must have few passages while it is necessary to amplify them in a sufficient
1782 number (529). MSC amplification in a large scale will inevitably confront MSC with epigenetic, genetic,
1783 phenotypic, metabolic, functional modifications and their senescence being associated to reduced
1784 proliferative, regenerative capabilities and decreased life expectancy.

1785 A standardized manufacturing process for successful clinical trials is required. Surface marker
1786 profiling is one method to detect and isolate *in vitro* aging senescent cells. For instance, CD264, is a
1787 surface marker of *in vitro* MSC aging that is not linked to donor age (530). Compared to MSC negative
1788 for CD264, MSC expressing CD264 exhibit increased SA- β -gal (*Senescence-Associated beta-*
1789 *galactosidase*) activity as well as a reduced differentiation potential and colony-forming ability (531).
1790 In contrast, CD146, downregulated in MSC derived from aged donors (*versus* young donors), is also
1791 decreased in MSC after prolonged *in vitro* expansion (532). The decreased expression of CD146 in MSC
1792 was suggested to be associated with their reduced migratory potential in degenerative tissues (533).
1793 Although some molecules are expressed to different extents during aging and may be related with
1794 functional changes, there is no current consensus that a molecule can serve as a gold standard for young
1795 or aged MSC population selective purification. Senolysis, the process that consists in clearing senescent
1796 cells from a proliferative cell niche using specific agents called senolytic drugs, is currently tested in
1797 preclinical studies and the translation of this process to the clinical field is a promising topic to improve
1798 MSC-based therapy in MI (534).

1799
1800 ***Time of manufacturing process and storage*** Following the *European Union (EU) Regulation*
1801 *1394/2007*, MSC are an advanced therapy medicinal product that must be manufactured according to
1802 the standards of good manufacturing practices (GMP). About 21 to 28 days of manufacturing process is
1803 necessary from the BM collection to the obtention of P2-frozen/thawed MSC that will be either
1804 administrated to the patients or stored (535). Furthermore, this process must ensure an efficient long-
1805 term storage without altering MSC properties. Existing cryopreservation procedures consist in storing
1806 MSC in cryopreservation solutions at temperatures below -135°C and include cooling and thawing steps,
1807 avoiding rapid temperature changes that lead to stress and changes in material characteristics. Slow rate
1808 freezing results in cell dehydration with related stress and osmotic imbalances leading to oxidative stress
1809 and apoptotic cell death by contrast to fast MSC freezing that improves osmolality but increases the
1810 intracellular ice content. In general, a uniform rate of cooling of -1.0°C per minute has been shown to
1811 be effective for the majority of cells. The current standard practice for cell recovery in cryovials is to
1812 promote rapid thawing using a 37°C water bath (536). Of note, the effect of an inappropriate baseline
1813 cryopreservation process can be noticed within the first 36 hours after thawing (537).

1814 Several investigations have been carried out to validate cultures and study the short- and long-
1815 term stability of fresh or thawed products. In a recent study, Lechanteur et al. reported their efforts to
1816 implement GMP standards in their manufacturing process of allogeneic MSC (529) allowing to obtain,
1817 in an academic setting, a GMP license. To validate the steps of freezing and thawing steps, P2 (*Passage*
1818 2)- frozen MSC were thawed and seeded for one week prior the predefined quality criteria (QC) analysis
1819 including viability, sterility, mycoplasma, endotoxin, doubling time, population doubling time,
1820 phenotypic identity (CD73, CD90 and CD105), karyotype, viability, potency and morphology (535).
1821 MSC from three different donors were thawed and QC assessments were conducted at 0, 1, 2 and 4
1822 hours. Results show that one hour was the maximum time from the end of the MSC thawing step to
1823 administration to the patient (535).

1824

1825 ***1.2. Regarding patients***

1826 Among the critical factors impacting the results of MSC-based therapy, one needs also to
1827 consider the recipient of the cell transplantation. AMI patients, as generally elderly patients, are
1828 frequently multi-morbid and are often treated with multiple therapies that can modify the intracellular
1829 cascades of endogenous mechanisms of cardioprotection.

1830

1831 ***Aging of recipients*** is an immutable cardiovascular risk factor that is attracting increasing
1832 attention due to its rising prevalence (538). If many studies have highlighted aspects of MSC aging, only
1833 a few studies have shown that aging significantly impedes the effectiveness of MSC migration and
1834 transplantation in both preclinical and clinical studies in other applications (539, 540). Preclinical studies
1835 described that aging impairs the angiogenic response of implanted cells after ischemic injury (541) while
1836 by contrast, a clinical trial with a small cohort of 49 patients showed that the recipient's age does not
1837 influence MSC efficiency for the treatment of patients with ischemic cardiomyopathy (511). However,
1838 it is critical to study the impact of aging since MI preferentially affects old patients, with an average age
1839 of about 65 years in men and 72 in women, and that all the preclinical studies of both cardioprotection
1840 and biotherapy are performed on young adult laboratory animals. For the treatment of AMI in old
1841 patients, allogenic transplantation of stem cells derived from young donors should be considered to
1842 potentially overcome aging-related limitations since autologous MSC will be less efficient (542). This
1843 is particularly relevant in view of the increased susceptibility to IR injury reported in old animals in
1844 preclinical studies as a result of the attenuation of the RISK/SAFE signaling cascades without any
1845 changes reported for PKG or PKA pathways (543). Indeed, Akt, ERK1/2, PKC and STAT3 undergo
1846 post-translational modifications and altered expression, leading to impaired endogenous mechanisms of
1847 cardioprotection in the elderly (544, 545). In particular, impaired Akt activation is related to a higher
1848 vulnerability to hypoxic injury and impaired paracrine efficiency of BM-MS (546).

1849

1850 **Diabetes** Diabetic patients are at high risk of MI due to increased adverse cardiovascular events.
1851 It is currently admitted that diabetic hearts are more sensitive to IR injury in human but contrasting
1852 results have been obtained in preclinical models (for review see (547)). Hyperglycemia is an important
1853 inducer of cardiac injury, and even in nondiabetic patients, hyperglycemia on hospital admission is
1854 associated with increased infarct size and should be considered a prognostic marker in all patients with
1855 AMI (548). Hyperglycemia and increased oxidative stress probably contribute to the impairment of
1856 PTEN-Akt signaling in human cardiac tissues (549). As a result, a resistance of diabetic hearts to
1857 cardioprotective strategies such as ischemic conditionings is observed both in preclinical models (for
1858 review see (547)) and in patients (550). Similar loss of cardioprotection was obtained after
1859 transplantation of human MSC in the infarcted border zone of a preclinical model of IR injury showing
1860 that diabetes impacts negatively MSC-induced cardioprotection (551).

1861
1862 **Treatments** Pharmacological treatments should be considered since they can interfere with
1863 MSC properties. Indeed, most of the patients at risk of AMI are usually treated for a coronary artery
1864 disease. In the arsenal of drugs prescribed in this case, statins (3-hydroxy-3-methylglutaryl-CoA
1865 reductase inhibitors) allowing to lower cholesterol amounts in the blood of patients, have shown
1866 contrasting results in cardioprotection depending on their duration of administration. For instance,
1867 chronic atorvastatin prevents the cardioprotective effect of PostC, while an acute treatment in
1868 combination with PostC is cardioprotective (552). In addition, atorvastatin or rosuvastatin increase
1869 proliferation rates of human MSC upon hypoxic conditions *in vitro*, and have a beneficial impact on
1870 transplanted MSC activity in preclinical studies (553-556). The impact of chronic statin treatment in
1871 AMI patients receiving MSC therapy is questioned because it has been reported that statins, evaluated
1872 as a cardioprotective drug against IR injury, are not protective when chronically administered due to an
1873 up-regulation of PTEN expression (557). Since cardioprotection by MSC therapy is mediated through
1874 downregulation of PTEN expression (398, 400, 401), it is uncertain whether MSC treatment will be
1875 strong enough to counteract the effect of statins on the PI3K pathway.

1876 Another example of treatment given to patients at risk of infarction concerns antidiabetic drugs,
1877 including metformin (biguanide) and gliflozins (*sodium-glucose cotransporter 2*, SGLT2 inhibitors)
1878 described as reversing diabetes-induced alterations in the signaling pathways, leading *per se* to
1879 cardioprotection (558-560). Indeed, metformin has been reported to induce apoptosis in MSC and
1880 impede their therapeutic when co-administered in hearts during AMI (561).

1881 All these treatments given to the population of AMI patients can compromise the therapeutic
1882 effect of MSC in clinical trials, so they need to be considered.

1883

1884 **2- Various MSC doses**

1885 **2.1 Preclinical studies**

1886 Dose-response was obtained for the improvement of cardiac function with allogeneic MSC
1887 tested at various doses 10^3 , 10^4 , 10^5 and 10^6 cells *per* kg body weight in the MI pig model. Only the
1888 highest doses provided significant benefits for cardiac function but not for a decrease in infarct size,
1889 where a U-curve was observed (562). An apparent dose-response was also observed for the values of
1890 systolic function (assessed by pressure-volume analysis) in a pig model of IR injury after IV
1891 administration of allogeneic MSC at 1, 3 and 10 millions of cells, the highest dose giving the best
1892 benefits (563). However, in another study, the highest dose of MSC, 10 million/kg, was reported to
1893 induce cardiopulmonary collapse and a subsequent loss in cardioprotection as evidenced by infarct size
1894 measurement (563). Similarly, an absence of dose-response was reported for allogeneic BM-MSCs after
1895 transendocardial (TE) injection (20, 240 or 440 million) in pigs submitted to IR injury (564). These
1896 studies raise controversies regarding the dose-dependence of the therapeutic potential of MSC and an
1897 inverted U-shaped dose-response curve showing poorer results with both lower and higher doses has
1898 been described. In agreement with this observation, we reported a U-shaped curve for infarct size
1899 reduction induced by MSC treatment in a mouse model of IR injury treated with allogeneic MSC (565).

1900

1901 **2.2. Clinical trials**

1902 A recent meta-analysis of clinical trials evaluating MSC therapy for AMI patients revealed that
1903 the number of cells injected, mostly intracoronary in 10 of 13 studies, ranged from 2.3 to $85 \cdot 10^6$ cells
1904 (503). This contrasts with the higher doses inducing cardioprotection in patients with ischemic
1905 cardiomyopathy, ranging from 100 to $150 \cdot 10^6$ cells, and mostly injected intramyocardially (566). The
1906 meta-analysis also points out that the dose to be injected in patients with AMI should be less than 10^7
1907 MSC, within 1 week of AMI (combination timing/dose), to improve EF (503) and that administration
1908 of more than 10 million MSC has an opposite effect (504). A randomized clinical trial BOOSTER-
1909 TAHA7 is currently ongoing and recruiting patients with the aim to evaluate if increasing the frequency
1910 of cell injections will induce greater beneficial effects. This study will evaluate the paracrine theory of
1911 MSC: increasing the number of cells will increase the amount of paracrine stimuli in the recipient heart
1912 (567).

1913

1914 **3- Various timings of administration**

1915 **3.1. Preclinical studies**

1916 The time window to prevent IR injury after MI is very narrow and endogenous mechanisms or
1917 strategies of cardioprotection must be activated before the full activation of cell death mechanisms, in
1918 particular apoptosis (50, 568). The optimal timing for MSC injection to generate therapeutic benefit in
1919 AMI is unknown. In preclinical models of MI, various timing for the administration of the same dose of
1920 MSC have been tested leading to variable and contrasting results in large species. Three studies were
1921 performed using an injection protocol of autologous BM-MSCs (30 million) at 30 min after reperfusion.
1922 The first one reports no beneficial effects on EF or reduction of infarct size and a poor survival rate of

1923 implanted cells in the post-infarct environment (554). The second describes only a decreased infarct size
1924 and no changes in EF (555) and the last one reports an improvement of both EF and infarct size (480).
1925 An earlier time point of injection, 15 min after the onset of reperfusion, underlined that early IV injection
1926 of allogeneic BM-MSc is effective for the treatment of IR injury (563). Later administrations, 3 days
1927 post-MI or 3 months after complete infarct healing, promoted significant reversed remodeling in pig
1928 hearts (486, 569). However, in a more recent study in rats, a detrimental effect of the adverse ventricular
1929 remodeling at 30-day post-MI on MSC survival and function was evidenced (570).
1930 The environment of the injured tissue impacts MSC function after their injection, either by positively
1931 priming them or by inducing apoptosis. We can therefore assume that, according to the timing of
1932 injection, MSC might encounter either a favorable or a detrimental tissular environment that will
1933 respectively either promote/prime their therapeutic properties or induce their apoptosis and clearance.

1934

1935

3.2. Clinical studies

1936

1937

1938

1939

1940

1941

1942

1943

1944

1945

1946

1947

1948

1949

1950

1951

1952

1953

1954

1955

1956

1957

1958

1959

The “timing” parameter appears to be critical for the efficacy of stem cell therapy in AMI patients. The metanalysis from Attar et al. comparing 13 clinical trials showed that MSC improve EF when injected within 1 week after MI (503). Similar results were obtained using allogeneic Wharton’s jelly derived-MSc evidencing positive results for EF, myocardial perfusion and viability parameters, when cells were injected 5 to 7 days post-PCI (495). For early injections, within 24 hours after AMI, contrasting results were obtained since Houtgraaf et al. by contrast with Zang et al evidenced reduced infarct size using autologous freshly prepared adipose-derived regenerative cells comprising large amounts of MSC without any vascular complications (502, 571).

In conclusion, most authors recommend that MSC should not be injected after one week to achieve beneficial effects. Indeed, injecting MSC earlier, in the acute phase or up to 5 days after infarction, will impair the survival and functions of transplanted cells due to the hostile environment of the injured myocardial tissue. These results are based on naive MSC that have not been modified to optimize their resistance to the hostile conditions of the immediate post-MI period. Section IV-C will describe strategies to improve the therapeutic effects of MSC through the generation of an optimized and standardized “MSC 2.0” therapeutic product guarantying a benefit whatever the conditions.

4- Various routes of administration

4.1 Preclinical studies

A meta-analysis performed on 58 studies (n=1165 mice, rats and pigs) using MSC in AMI and chronic ischemic cardiomyopathy reveals that the efficacy of MSC depends on the routes of injection (IM, IV, TE and IC) although all of them provide EF improvement (478). After analysis, TE administration appears to provide better results in terms of infarct size decrease and EF improvement, probably due to specific myocardial beneficial effects in addition to MSC systemic immunomodulatory functions (478). Moreover, TE injection was reported to be safe, well tolerated and associated with a

1960 decreased remote engraftment compared to IC and IV deliveries. TE injection resulted in a higher cell
 1961 retention in the canine heart (clusters of MSC in the core infarct) associated with a greater functional
 1962 improvement compared to the IC route (572). In addition, IC administration was associated with a higher
 1963 incidence of decreased coronary blood flow after injection, obviating the advantage of such a delivery
 1964 approach. Regarding IV injection of MSC, studies in the pig model of reperfused MI have described
 1965 beneficial effects (476, 563) despite a low engraftment rate within the infarcted area compared to other
 1966 routes (573). The decreased efficiency after systemic IV delivery of MSC results from their entrapment
 1967 in lungs as reported in rodent AMI model. Accordingly, a short half-life of about 24 hours was evidenced
 1968 for human MSC injected in mice (574, 575). The retention in the lungs is related to both, MSC adhesion
 1969 to the pulmonary vasculature endothelium through the expression of VCAM-1 (576) and a size issue
 1970 because the 20 μm diameter of cultured MSC is larger than the size of pulmonary microcapillaries (577).
 1971 Accordingly, *in vivo* experiments studying the distribution and homing of MSC after IV injection
 1972 showed that vasodilator sodium nitroprusside prior to MSC injection allowed MSC to clear the lungs
 1973 and reach the target organs in greater quantity (578). Surprisingly, instead of providing negative effects,
 1974 retention in the lung activates MSC, which in turn express TNF- α -induced protein 6 (TNAIP6 or TSG-
 1975 6) that suppresses the excessive inflammatory response induced by MI, the subsequent fibrotic scarring
 1976 and impaired cardiac function (575).
 1977 More studies comparing the routes of MSC injection are required to validate these observations and
 1978 define the most effective route for the design of clinical trials.

1979

1980 **4.2 Clinical trials**

1981 Probably in relation with PCI procedures used for reperfusion therapy, most MSC were injected
 1982 using the IC route in AMI patients at the acute phase (STEMI patients) whatever their autologous or
 1983 allogeneic nature, using the culprit artery (490, 492, 495-497, 500, 502, 503, 509) or through a remote
 1984 coronary artery (506). In addition, IC infusion in the culprit artery is minimally invasive and allows to
 1985 concentrate the cell product at the site of the lesion, facilitating the homing of MSC. Furthermore,
 1986 inflation of the angioplasty balloon at a low pressure downstream the stent allows maximizing the
 1987 contact time of MSC with micro-circulation of the infarction territory, the only precaution being to
 1988 infuse the cells through various short periods to avoid periprocedural MI. Some limitations to this
 1989 procedure are reported, such as the rapid release of MSC into the systemic circulation and the issue of
 1990 applying a PostC stimulus with angioplasty balloon inflation-deflation sequences (579).

1991 Local injection is also performed through IM administration using the *NOGA* system. This
 1992 system allows injecting cells directly into the infarct border zone (8–12 IM injections) as reported by one
 1993 study showing both feasibility and long-term (up to 5 years) safety (499).

1994 However, for the clinic, a simple IV approach would be ideal, due to its easy access and the
 1995 absence of time constraints. Thus, IV administration of allogeneic MSC cells was tested in patients
 1996 showing EF improvement only in one study (493, 494).

1997 First, the heterogeneity of results obtained with MSC therapy might be related to the design of
1998 both preclinical studies and to the protocols used in clinical trials. Second, in clinical trials, the
1999 heterogeneity of the patients arises from other parameters such as the age of the patients, the severity of
2000 their infarction, chronic treatments, comorbidities, etc... Finally, focusing on additive parameters
2001 including the cell source, amplification protocols, storage and thawing conditions, it appears obvious
2002 that the heterogeneity observed between studies occurs at multiple levels and that a standardization of
2003 the protocols becomes mandatory.

2004

2005

2006 **C. Strategies to improve MSC-based cell therapy**

2007

2008 **1- How to overcome the influence of time on MSC-based therapy?**

2009 Although the transfer of MSC from the laboratory to the bedside is theoretically feasible, many clinical
2010 trials have failed at early and late stages due in part to time-related issues that need to be clarified and
2011 resolved in the short term. These issues will be discussed in this section.

2012 ***1.1. Which patients and protocol for the best benefits?***

2013 Several factors have been described as contributing to clinical trial failure in cardioprotection,
2014 including those related to patients who are included in trials evaluating MSC therapeutic effects. Then,
2015 to design future clinical trials capable of showing the therapeutic effects of MSCs, it is necessary to take
2016 into account the factors that may compromise their cardioprotective role.

2017

2018 ***Co-morbidities*** A careful selection of the patient population is needed to avoid inclusion of
2019 patients with confounding factors including age, diabetes, cardiovascular risk and medications that could
2020 alter both MSC therapeutic properties and the response of the target tissue i.e., the myocardium to the
2021 transplanted cells as already discussed above.

2022

2023 ***Clinical protocol*** The protocol of MSC administration needs to be carefully designed and
2024 standardized among centers for clinical trials to provide data that can be compared. For inclusion of
2025 AMI patients likely to be good responders to MSC therapy, cardiac lesions must be compatible with
2026 myocardial salvage by reperfusion and additional MSC-based therapy that would be applied to further
2027 decrease the infarct size. However, ischemia duration must also not be too long for a possibility to rescue
2028 the targeted tissue. An ideal window for revealing cardioprotective effects in human would be within a
2029 range of 2 to 3 hours between the onset of symptoms and the application of the cardioprotective strategy,
2030 as previously demonstrated for PostC (580-582).

2031 The optimal timing of MSC injection within the first week post-PCI seems to be optimal, in
 2032 particular within the 4- to 7-day time window. The route of administration could be preferentially IM or
 2033 IC, both methods have their advantages and disadvantages. An appropriate method for the evaluation of
 2034 the clinical outcomes should be also chosen, probably new 3-D echocardiography and strain evaluation,
 2035 methods that will compete with CMR, for limited access and cost at the moment. Finally, the important
 2036 point is that the method used must be always the same.

2037 However, since it is rarely possible to select patients, MSC therapy must be open to as many
 2038 patients as possible and on the other side, researchers and clinicians are developing protocols to prime
 2039 MSC in order to provide a standardized cell product capable of delivering the highest benefit to any
 2040 patients.

2041

2042 ***1.2 - Which protocol(s) to obtain MSC with optimal functions?***

2043 ***Strategies for overcoming MSC age-related issues*** MSC used in the clinic are obtained from
 2044 donors of different ages and some studies have reported an effect of age on MSC functions. In this
 2045 context, efforts have to be made to elucidate the molecular mechanisms of MSC aging in order to
 2046 develop new methods to prevent this negative effect and rejuvenate aged altered MSC. Pharmacological
 2047 priming and genetic modifications have been investigated to increase the expression level of
 2048 genes/molecules decreased in aged MSC such as BDNF, PDGF-BB (PDGF with two B subunits) and
 2049 MCP-1 and that impact their therapeutic properties. The system for gene editing, CRISPR/Cas9, has
 2050 also been explored as a way to improve MSC potential in treating diseases such as MI (583). Targeted
 2051 *pdgfra* knock-in promoted MSC differentiation capacity and in turn, favored the functional insufficiency
 2052 of local cells (584). Although genetically modified MSC have been tested in clinical trials showing their
 2053 safety, further investigations are still required to produce unequivocal evidence of an enhanced
 2054 therapeutic effect of MSC.

2055 Another way to overcome the age-related problems of MSC is to study other tissue sources.
 2056 Autologous BM- and AT-derived MSC are relatively easier to collect compared to UC-MSC. However,
 2057 it is also important to consider the patient age, gender and health status when using BM- and AT-derived
 2058 MSC. Moreover, compared to these latter cells, UC-MSC show higher lifespan, proliferation and
 2059 differentiation capacities as well as an enrichment in angiogenic factors (585-588). Moreover, given the
 2060 advantages of UC-MSC, the therapeutic properties of their vesicles and trophic factors are currently
 2061 subject to intense research.

2062 As an alternative to aged tissue-derived MSC, the generation of functional MSC from induced
 2063 pluripotent stem (iPS) cells is presently a main issue (589-591). A great advantage of iPS-derived MSC
 2064 (iMSC) is that a high number of cells can be produced using *in vitro* culture based systems, an important
 2065 requirement for cell therapy. While iMSC are very similar to primary MSC isolated from diverse human
 2066 tissues in terms of morphology, phenotype, immunoregulatory and differentiation capacities, they
 2067 possess a greater regenerative potential as shown in animal disease models (For review see (592)). In

2068 addition, iPSC can be expanded almost indefinitely, so the source of iMSC can be unlimited and iMSC
2069 generated from one iPSC cell or clone are more homogeneous in theory and their biological properties
2070 are more predictable because their molecular signature is minimally different between batches. The final
2071 iMSC product quality is stable, easily controlled, and can reach the highest therapeutic efficacy for
2072 specific clinical applications and personalized patient treatment (For review see (592)). In this context,
2073 *Cynata Therapeutics* received the approval in 2016 to initiate the first trial using allogeneic iPSC (CYP-
2074 001) for the treatment of steroid-resistant acute GVHD (*Graft Versus Host Disease*). Based on positive
2075 safety and outcomes, iMSC are consider in Phase II trials for the treatment of critical limb ischemia and
2076 in a Phase III trial with 440 osteoarthritic patients (593-595). Therefore, iMSC outstanding properties
2077 enable their preferential commercial applications beyond other types of primary MSC isolated from
2078 diverse human tissues with their guaranteed quality control. However, the functions of these cells have
2079 to be further investigated in different preclinical models of MI in order to compare their therapeutic
2080 capacity when administrated in different experimental protocols when several “time” parameters are
2081 changed (including injection time, injection duration, etc.). iMSC offer the possibility to produce
2082 millions of “off-the-shelf” copies under Good Manufacturing Practice (GMP) procedures for further
2083 therapeutic applications to treat complex and multifactorial diseases. However, properties of iMSC need
2084 to be further optimized to warrant their therapeutic efficacy to treat patients with MI whatever their age,
2085 the timing of patient care and the timing of injection (after reperfusion). To that end, the production of
2086 iMSC should be perhaps combined to the MSC preconditioning protocols as discussed below.

2087

2088 ***Strategies for overcoming MSC storage-related issues*** The availability of human MSC off-
2089 the-shelf to treat patients with cardiac IR injury requires the development of cryopreservation protocols
2090 that are nontoxic, safe, and efficient to maintain MSC survival and functions. However, negative impacts
2091 of MSC cryopreservation on their therapeutic efficacy have been reported (596).

2092 To avoid physical damages of freezing and thawing, the most commonly followed steps include freezing
2093 MSC at a slow cooling rate and thawing them at a high rate as well as cryoprotecting MSC. To do this,
2094 trehalose (597), anti-freezing protein mimics (598, 599) and plant proteins (600) have been mixed with
2095 low DMSO concentrations to improve the cryopreservation of MSC (601). MSC vitrification with a low
2096 cryoprotectant concentration was accomplished *via* the introduction of microfluidic-based hydrogel
2097 microencapsulation or droplet-based cell printing technology (602, 603). Although promising, these
2098 MSC cryopreservation advances have not considered MSC properties and functions *in vivo*. More
2099 recently, protocols for cryopreservation of MSC without DMSO have been developed such as using
2100 zwitterionic compounds combined with electroporation able to retain normal *in vitro* proliferation and
2101 differentiation functions, as well as *in vivo* distribution potential (604). MSC long-term low-temperature
2102 storage has a significant impact on the recovery and function of MSC due to repeated exposure to room
2103 temperature (605). In this context, the effect of minimizing ambient temperature fluctuations on stored

2104 cells by designing an automatic cryopreservation system that handles cells in controlled temperatures
2105 was evaluated and identified as a priority to maintain MSC survival and functions (606).
2106 Of note, the detrimental effects caused by cryopreservation and reported in clinical trials using
2107 cryopreserved MSC thawed immediately prior to infusion (523, 607) were shown to be reversible.
2108 Indeed, to counteract the adverse effects of cryopreservation, the successful phase 3 clinical trial of
2109 Alofisel for perianal fistulas used “rescued” MSC in cell culture for a period of at least 24 hours after
2110 thawing, to allow “recovery” of the freshly thawed MSC before administration to the patients (608).

2111

2112 **2- Which protocol(s) to enhance MSC functions**

2113

2114 To guarantee a therapeutic effect of the MSC injected to the patients and to get over the
2115 limitations discussed above, efforts are being made to (i) protect MSC during their administration to
2116 patients in particular against apoptosis and, (ii) standardize and improve their therapeutic effects in order
2117 to decrease the number of MSC needed to obtain an optimal beneficial effect for the patients. We will
2118 then discuss below the strategies currently developed to address this clinical challenge.

2119

2120 ***2.1. MSC preconditioning to improve their therapeutic potential***

2121 MSC display a poor survival and engraftment rate *in vivo*. Moreover, the results obtained in
2122 clinical studies using MSC in various applications have often reported worse outcomes when MSC were
2123 injected at the highest dose, resulting in an inverted U-shaped dose response curve (for review see (609)).
2124 To overcome these limitations, extensive studies aimed at generating MSC with a better therapeutical
2125 potential to reduce the dose of injected cells. The enhancement of cell survival and homing to improve
2126 the paracrine activity of MSC has been also investigated as well as strategies to protect both MSC and
2127 cardiomyocytes from apoptosis. Different preconditioning protocols applied to MSC (hypoxia,
2128 pharmacological and chemical agents) and novel approaches (engineered MSC, MSC-derived EV and
2129 MSC trapped on innovative biomaterial/patches) have been developed. Among these strategies, the “*in*
2130 *vitro*” priming of MSC is a simple and attractive approach.

2131

2132 ***Hypoxic preconditioning*** MSC death and caspase-3 activation were significantly lower (40%-
2133 decrease) in an hypoxic situation when compared with MSC cultured under normoxic conditions both
2134 *in vitro* and *in vivo*, leading to a better vascularization in the infarcted myocardium and better therapeutic
2135 efficacy in rat hearts (610). This preconditioning increased pro-survival and pro-angiogenic factor
2136 expression levels such as HIF-1 α , VEGF and its receptor, BCL-2, and BCL-xL. As a preconditioning
2137 stimulus, moderate hypoxia induces MSC proliferation, while severe hypoxia promotes MSC glycolytic
2138 metabolism and quiescence, and short exposures are better than longer (611, 612). Under hypoxia

2139 exposure, MSC exhibit an increased expression level of leptin, which is pivotal for enhancing survival,
 2140 chemotaxis, and therapeutic properties of MSC (613).

2141

2142 **Chemical and pharmacological preconditioning** Biological compounds and drugs, including
 2143 hormones, growth factors, pharmacological and chemical substances, have been employed as an
 2144 alternative to hypoxia-preconditioned MSC for the preconditioning of MSC to optimize their properties.

2145 **Hormones** The priming of MSC with adipokines has been shown to enhance their survival in an
 2146 ischemic microenvironment (614, 615). The role of adipokines on MSC survival was first discovered in
 2147 a study of hypoxia preconditioning of MSC, which evidenced their capacity to enhance their therapeutic
 2148 properties (615). Five years later, the protective role of resistin, another adipokine, on MSC was reported
 2149 (614). The injection of MSC pretreated with resistin in a murine model of IR injury significantly
 2150 increased angiogenesis and reduced myocardial apoptosis and fibrosis resulting in improved cardiac
 2151 performance, as compared to vehicle-treated MSC. Also, an enhanced homing of the cells into the
 2152 damaged heart in a ERK1/2-dependent manner was observed. In line with these studies, it was shown
 2153 that asprosin, a newly-discovered adipokine, also increases the survival of MSC in MI, improved their
 2154 homing and significantly improved EF (616). *In vitro*, the authors showed that asprosin-pretreatment of
 2155 MSC generates a protective effect on H₂O₂-induced damage and apoptosis of MSCs *via* the activation
 2156 of the ERK1/2-SOD2 pathway. Similarly, the priming of MSC with haemin, a potent HO-1 inducer,
 2157 before their transplantation into the peri-infarct region in MI mice, promotes the survival of MSC and
 2158 enhances their cardioprotective properties (413).

2159 **Growth factors** IGF-1 pretreatment of MSC had a positive effect on survival, adverse infarct outcomes
 2160 including infarct size and ventricular remodeling and the release of pro-inflammatory cytokines (373,
 2161 434). This current trend to augment MSC viability is mediated through various pathways including PI3K,
 2162 HIF-1, MAP Kinase and Hippo (617). More recently, it was described that SDF-1 α MSC pretreatment
 2163 resulted in improved vasculogenesis and recovery of cardiac function in infarcted myocardium 6 weeks
 2164 after treatment (618). However, the priming effect is not retained during cryopreservation/thawing
 2165 because pro-survival factor expression levels are largely dependent on the environment. Of note the use
 2166 of a hypothermic preservation solution allowed to keep the benefit of preconditioning.

2167 **Pharmacological substances** Statin preconditioning were shown to improve the therapeutic effects of
 2168 MSC: atorvastatin was reported to enhance CXCR4 expression in MSCs and promote them homing
 2169 toward the injured myocardium, leading to an improved cardiac function in an AMI rat model (619).

2170 Sevoflurane preconditioning decreases MSC apoptosis, the loss of mitochondrial membrane potential
 2171 and upregulates VEGF, HIF-1 α , HIF-2 α protein levels and pAKT/AKT ratio (620).

2172 In line with this study, we have recently evidenced that optimization of the anti-apoptotic properties of
 2173 MSCs has a substantial impact on their therapeutic effects in myocardial IR injury. Indeed, by using a
 2174 PPAR β/δ (*Peroxisome Proliferator-Activated Receptor β/δ*) agonist to prime MSC, we found a
 2175 significant increase in the survival of MSCs when exposed to an IR-simulated stress as well as an

2176 enhancement of their anti-apoptotic properties on cardiomyocytes and endothelial cells exposed to
2177 oxidative stress compared with naive MSC. In addition, we observed that priming MSC with the
2178 PPAR β/δ agonist permitted us to halve the dose of cell injected into the heart since the cardioprotective
2179 effect obtained *ex vivo* using PPAR β/δ -primed MSC injected at a dose of $3.75 \cdot 10^5$ MSC was comparable
2180 to that observed with untreated control MSC injected at the optimal dose of $7.5 \cdot 10^5$ MSC (565).
2181 Concerning the clinical translation, the C-CURE trial reported that MSC pretreated with a cardiogenic
2182 cocktail-based priming medium showed improved ventricular function and physical performance and
2183 quality of life (361). While the injection of MSC is well tolerated by patients with MI, their therapeutic
2184 benefit still deserves to be improved. Such a possibility relies on a full understanding of the molecular
2185 mechanisms underlying the cardioprotective effects of MSC.

2186

2187 **2.2. MSC genetic modifications**

2188 Genetic modifications consist in upregulating the expression of specific genes involved in the
2189 therapeutic properties of MSCs in order to reduce premature senescence, increase their survival and then
2190 their therapeutic effects *in vivo*. For example, the overexpression of *EphB2* (ephrin receptor B2)
2191 inhibited premature senescence by repressing mitochondrial ROS accumulation that triggers senescence
2192 in MSC (621). A main target was also apoptosis and overexpression of *Bcl-2* in MSCs injected after MI
2193 significantly increases MSC survival for up to 6 weeks compared to control MSCs and potentiates their
2194 efficacy on vascular density, cardiac function, infarct size and myocardial fibrosis (622). *In vitro*, *Bcl-2*
2195 overexpression decreased the apoptosis of MSC by 32% and increased the secretion of VEGF by more
2196 than 60% under hypoxic conditions (622). Moreover, *Hgf* overexpression in MSC was shown to increase
2197 the expression of BCL-2 while reducing BAX and Caspase-3 levels in response to hypoxia *in vitro*. *In*
2198 *vivo*, the engraftment and survival of MSC was enhanced when the cells were both overexpressing HGF
2199 and encapsulated in a small molecular hydrogel (20).

2200 MSC overexpressing CCR1, the receptor for CCL7 significantly upregulated in the heart post-MI, are
2201 more protected from apoptosis and are more prone to accumulate in the infarcted myocardium as well
2202 as to reduce the infarct size and cardiomyocytes apoptosis in injured myocardium as compared to their
2203 control counterpart (475).

2204 The overexpression of the macrophage migration inhibitory factor (MIF), a proinflammatory cytokine,
2205 in aged MSC rejuvenated them by activating autophagy and increased their therapeutic potential in MI
2206 (616). In line with this study, EV from MSC overexpressing MIF significantly, were shown to increase
2207 heart function and reduce heart remodeling, apoptosis and ROS production as compared to EV from
2208 naïve MSC (623).

2209 Altogether these studies reveal that MSC priming to protect them from apoptosis once administrated *in*
2210 *vivo* not only prolongs their presence and survival in the injured heart but also increases their therapeutic
2211 efficacy in MI.

2212

2213 **2.3. Use of MSC-derived EV or microparticles**

2214 One of the particularities of MSC is their plasticity and versatility. Indeed, according the
2215 inflammatory environment, MSC are going to adopt different phenotypes and functions. *In vivo*, MSC
2216 versatility can represent an advantage since the cell can sense and adapt their properties to their
2217 environment but in some cases this versatility/plasticity can lead to an unpredictable response. To
2218 overcome this limitation, experimental animal models have addressed the therapeutic benefits of MSC-
2219 derived EV in the context of AMI.

2220 EV enriched with miR-22 secreted by MSC exposed to PreC and applied to cardiomyocytes
2221 were shown to inhibit their ischemia-induced apoptosis. EV derived from MSC exposed to PreC
2222 significantly reduced infarct size and myocardial fibrosis *in vivo* by targeting *Mecp2* *via* miR-22 (403).
2223 Similarly, miR-221 overexpression in EV derived from MSC transduced with GATA-4 (MSC-GATA4)
2224 displayed increased cardioprotective effects by reducing the expression of p53 upregulated modulator
2225 of apoptosis (PUMA) in cardiomyocytes (624). In line with this study, EV-derived from MSC-GATA4
2226 were shown to be a reservoir of anti-apoptotic miRNA responsible for activation of the cell survival
2227 signaling pathway and thus cardioprotection (625).

2228 Concerning the MSC-mediated promotion of angiogenesis and subsequent improvement of impaired
2229 infarcted cardiac function, MSC-EV were found to mediate this property through a miR-210-Efna3-
2230 dependent mechanism (626). Overall, these studies suggest that MSC-EV may exert greater
2231 cardioprotective effects (627) and a lower risk of tumorigenicity (628) compared with MSC-based
2232 therapies. This therapeutic effect mediated by EV might be more dependent on the administration
2233 window since MSC-EV will not be able to adapt to their pathological environment in contrast to their
2234 parental cells and thus will have to possess the required properties *per se* to be therapeutically useful.
2235 Indeed, one study showed that administering EV 30 min post-MI had no beneficial effect (629). Also,
2236 EV have a short lifetime and restricted efficacy due to their poor persistence in the myocardium (630-
2237 632).

2238 A new concept with synthetic MSC has been evaluated for the treatment of AMI in mice, showing
2239 enhanced therapeutic effects compared to native MSC. These synthetic MSC were obtained by
2240 packaging factors secreted by human BM-MSC into Poly (lactic-co-glycolic acid) PLGA microparticles
2241 and coating them with MSC membranes. This novel particle exhibited similar surface antigen and
2242 secretome profiles than MSC. When injected in mouse heart with MI, angiogenesis, improved cardiac
2243 function and attenuated LV remodeling were observed. Furthermore, their high stability to both
2244 cryopreservation and lyophilization and their immune privilege, makes this concept attractive for
2245 various applications in different organs (633).

2246

2247 **2.4. Combined therapies**

2248 Combinatorial delivery of MSC with their derived EV was assessed in rat hearts. In particular,
2249 the sequential administration of EV (30 min post-MI) and then MSC (3 days post-MI) effectively

2250 decreased scar size and restored cardiac function after AMI (634). The authors proposed that the
2251 beneficial effect of the combinatorial treatment was due to an improved inflammatory microenvironment
2252 induced by the EV administration resulting in a better recruitment and retention of MSC. Regarding
2253 combination of cells with drugs, a new clinical trial evaluating the association of atorvastatin and
2254 injected BM-MSC is ongoing. These patients undergoing PCI will receive autologous BM-MSC with
2255 regular or high dose of Atorvastatin treatment to improve the survival of implanted cells (635).

2256

2257

2258 **V- CONCLUSION**

2259

2260 Acute myocardial infarction is a leading cause of cardiovascular disease in the world. With the
2261 improvement of the revascularization techniques and patient care, the rates of the mortality have
2262 decreased by contrast to the rising rates of morbidity leading to heart failure. The World Health
2263 Organization predicts that this burden will be worsened since cardiovascular disease are expected to stay
2264 at the first rank until 2030 because of the aging of the population and an exponential growing number
2265 of diabetic patients. Therefore, the challenge is to discover new treatments with cardioprotective activity
2266 in particular able to reduce IR injury to further decrease infarct size which is a major determinant for
2267 the morbi-mortality rates.

2268 In this context, MSC are appropriate for this challenge because their pleiotropic properties appear
2269 relevant to overcome this multifaceted IR injury. The description of the kinetics of the events leading to
2270 IR injury in regard to the underlying mechanisms of action of MSC should allow the design of the most
2271 appropriate protocols to fully benefit from the pleiotropic properties of MSC of interest for AMI patients.
2272 While the mechanisms underlying the therapeutic properties of MSCs are not exclusively limited to their
2273 survival rate, it is necessary to identify the optimal timing conditions (duration of culture, age of MSC
2274 donors, duration of cell storage, timing of thawing) to obtain the most effective MSC possible endowed
2275 with optimal therapeutic properties. Moreover, these cells must be delivered at the right time to the
2276 damaged heart tissue to enable them to reverse the pathways that trigger cell death. Finally, AMI patients
2277 are expected be good responders to MSC, providing a status for MSC to deliver their therapeutic
2278 properties. Analyzing the various critical points to be overcome and developing protocols to enhance
2279 MSC therapeutic properties including their own survival in the cardiac tissue, will facilitate the success
2280 of clinical translation.

2281 Application of various strategies of conditioning appears as a way to provide a standardized cell product
2282 capable of delivering the highest benefit to any patients, whatever their age, status and treatments.

2283 In this context, our review suggests that cardioprotection is a matter of timing.

2284

2285

2286 **VI- GRANTS**

2287 This study was supported by CNRS (S.B.-L. and J.N.), l'Agence Nationale de Recherche (ANR-11-
2288 LABX-0015) (to S.B.-L., A.V., J.N.), la Fondation de France # 00096298 (to S.B.-L.), la Région
2289 Occitanie Prématuration 2021 prEVAMI # 211553 (to S.B.-L. and F.D.).

2290

2291

2292 **VII- DISCLOSURES**

2293 No conflicts of interest, financial or otherwise, are declared by the authors.

2294

2295

2296 **VIII- ACKNOWLEDGEMENTS**

2297 We are grateful to Muriel Asari (IGF- Genopolys, Montpellier, France) for her professional
2298 drawing of the figures of the manuscript.

2299

2300

2301 **IX- AUTHOR NOTES**

2302 Correspondence: S. Barrère-Lemaire

2303

2304

2305 **X- AUTHOR CONTRIBUTIONS**

2306 S.B.-L., F.D. and A.V. drafted manuscript; S.B.-L., F.D., A.V. prepared figures with the support of
2307 Muriel Asari ; C.P., J.N. and C.J. corrected and revised manuscript ; S.B.-L., F.D., A.V., C.P., J.N. and
2308 C.J. approved final version of manuscript.

2309

2310 **XI- REFERENCES**

- 2311 1. **Miura T, Yellon DM, Hearse DJ, and Downey JM.** Determinants of infarct size during permanent
2312 occlusion of a coronary artery in the closed chest dog. *J Am Coll Cardiol* 9: 647-654, 1987.
- 2313 2. **Jugdutt BI, Hutchins GM, Bulkley BH, and Becker LC.** Myocardial infarction in the conscious dog:
2314 three-dimensional mapping of infarct, collateral flow and region at risk. *Circulation* 60: 1141-1150, 1979.
- 2315 3. **Reimer KA, and Jennings RB.** The "wavefront phenomenon" of myocardial ischemic cell death. II.
2316 Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral
2317 flow. *Laboratory investigation; a journal of technical methods and pathology* 40: 633-644, 1979.
- 2318 4. **Heusch G.** The Coronary Circulation as a Target of Cardioprotection. *Circulation research* 118: 1643-
2319 1658, 2016.
- 2320 5. **Reimer KA, Lowe JE, Rasmussen MM, and Jennings RB.** The wavefront phenomenon of ischemic
2321 cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56: 786-794, 1977.

- 2322 6. **Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J, Jr., and Braunwald E.** Factors
 2323 influencing infarct size following experimental coronary artery occlusions. *Circulation* 43: 67-82, 1971.
- 2324 7. **Heusch G, Skyschally A, Gres P, van Caster P, Schilawa D, and Schulz R.** Improvement of regional
 2325 myocardial blood flow and function and reduction of infarct size with ivabradine: protection beyond heart rate
 2326 reduction. *Eur Heart J* 29: 2265-2275, 2008.
- 2327 8. **Bing RJ.** CARDIAC METABOLISM. *Physiol Rev* 45: 171-213, 1965.
- 2328 9. **Murphy E, and Steenbergen C.** Mechanisms underlying acute protection from cardiac ischemia-
 2329 reperfusion injury. *Physiol Rev* 88: 581-609, 2008.
- 2330 10. **Kalogeris T, Baines CP, Krenz M, and Korthuis RJ.** Cell biology of ischemia/reperfusion injury. *Int*
 2331 *Rev Cell Mol Biol* 298: 229-317, 2012.
- 2332 11. **Ferrero JM, Gonzalez-Ascaso A, and Matas JFR.** The mechanisms of potassium loss in acute
 2333 myocardial ischemia: New insights from computational simulations. *Front Physiol* 14: 1074160, 2023.
- 2334 12. **Janse MJ, and Kléber AG.** Electrophysiological changes and ventricular arrhythmias in the early phase
 2335 of regional myocardial ischemia. *Circulation research* 49: 1069-1081, 1981.
- 2336 13. **Jennings RB, Sommers HM, Smyth GA, Flack HA, and Linn H.** Myocardial necrosis induced by
 2337 temporary occlusion of a coronary artery in the dog. *Archives of pathology* 70: 68-78, 1960.
- 2338 14. **Jennings RB.** Historical perspective on the pathology of myocardial ischemia/reperfusion injury.
 2339 *Circulation research* 113: 428-438, 2013.
- 2340 15. **Laflamme MA, and Murry CE.** Regenerating the heart. *Nat Biotechnol* 23: 845-856, 2005.
- 2341 16. **Redel A, Jazbutyte V, Smul TM, Lange M, Eckle T, Eltzhig H, Roewer N, and Kehl F.** Impact of
 2342 ischemia and reperfusion times on myocardial infarct size in mice in vivo. *Experimental biology and medicine*
 2343 *(Maywood, NJ)* 233: 84-93, 2008.
- 2344 17. **Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger**
 2345 **CB, Jenkins PL, Nichols M, and Ben-Yehuda O.** Relationship Between Infarct Size and Outcomes Following
 2346 Primary PCI: Patient-Level Analysis From 10 Randomized Trials. *J Am Coll Cardiol* 67: 1674-1683, 2016.
- 2347 18. **Kübler W, and Spieckermann PG.** Regulation of glycolysis in the ischemic and the anoxic myocardium.
 2348 *J Mol Cell Cardiol* 1: 351-377, 1970.
- 2349 19. **Carmeliet E.** Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiol Rev* 79:
 2350 917-1017, 1999.
- 2351 20. **Xu M, Liu PP, and Li H.** Innate Immune Signaling and Its Role in Metabolic and Cardiovascular
 2352 Diseases. *Physiol Rev* 99: 893-948, 2019.
- 2353 21. **Laflamme MA, and Murry CE.** Heart regeneration. *Nature* 473: 326-335, 2011.
- 2354 22. **Toldo S, and Abbate A.** The NLRP3 inflammasome in acute myocardial infarction. *Nat Rev Cardiol* 15:
 2355 203-214, 2018.
- 2356 23. **Ong SB, Hernandez-Resendiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY, Cabrera-**
 2357 **Fuentes HA, and Hausenloy DJ.** Inflammation following acute myocardial infarction: Multiple players, dynamic
 2358 roles, and novel therapeutic opportunities. *Pharmacol Ther* 186: 73-87, 2018.
- 2359 24. **Maroko PR, Libby P, Ginks WR, Bloor CM, Shell WE, Sobel BE, and Ross J, Jr.** Coronary artery
 2360 reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *J Clin Invest* 51:
 2361 2710-2716, 1972.
- 2362 25. **Ginks WR, Sybers HD, Maroko PR, Covell JW, Sobel BE, and Ross J, Jr.** Coronary artery reperfusion.
 2363 II. Reduction of myocardial infarct size at 1 week after the coronary occlusion. *J Clin Invest* 51: 2717-2723, 1972.
- 2364 26. **Ganz W, Buchbinder N, Marcus H, Mondkar A, Maddahi J, Charuzi Y, O'Connor L, Shell W,**
 2365 **Fishbein MC, Kass R, Miyamoto A, and Swan HJ.** Intracoronary thrombolysis in evolving myocardial
 2366 infarction. *Am Heart J* 101: 4-13, 1981.
- 2367 27. **Reduto LA, Smalling RW, Freund GC, and Gould KL.** Intracoronary infusion of streptokinase in
 2368 patients with acute myocardial infarction: effects of reperfusion on left ventricular performance. *Am J Cardiol* 48:
 2369 403-409, 1981.
- 2370 28. **Rentrop KP, Blanke H, Karsch KR, Wiegand V, Köstering H, Oster H, and Leitz K.** Acute
 2371 myocardial infarction: intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol* 2: 354-363, 1979.
- 2372 29. **Rentrop P, Blanke H, Karsch KR, Kaiser H, Köstering H, and Leitz K.** Selective intracoronary
 2373 thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 63: 307-317, 1981.
- 2374 30. **Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, Jr., McCallister BD, Gura GM, Jr.,**
 2375 **Conn RC, and Crockett JE.** Percutaneous transluminal coronary angioplasty with and without thrombolytic
 2376 therapy for treatment of acute myocardial infarction. *Am Heart J* 106: 965-973, 1983.
- 2377 31. **Braunwald E.** Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction,
 2378 and improved survival. Should the paradigm be expanded? *Circulation* 79: 441-444, 1989.
- 2379 32. **Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F,**
 2380 **Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M,**
 2381 **Varenhorst C, Vranckx P, and Widimský P.** 2017 ESC Guidelines for the management of acute myocardial

- 2382 infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute
 2383 myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology
 2384 (ESC). *Eur Heart J* 39: 119-177, 2018.
- 2385 33. **O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM,**
 2386 **Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby**
 2387 **LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, and Zhao DX.**
 2388 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American
 2389 College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll*
 2390 *Cardiol* 61: e78-e140, 2013.
- 2391 34. **Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons**
 2392 **C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D,**
 2393 **Storey RF, and Windecker S.** 2015 ESC Guidelines for the management of acute coronary syndromes in patients
 2394 presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary
 2395 Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology
 2396 (ESC). *Eur Heart J* 37: 267-315, 2016.
- 2397 35. **Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP,**
 2398 **Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM,**
 2399 **Sibbing D, Stefanini GG, Windecker S, Yadav R, and Zembala MO.** 2018 ESC/EACTS Guidelines on
 2400 myocardial revascularization. *Eur J Cardiothorac Surg* 55: 4-90, 2019.
- 2401 36. **Kloner RA, Ganote CE, and Jennings RB.** The "no-reflow" phenomenon after temporary coronary
 2402 occlusion in the dog. *J Clin Invest* 54: 1496-1508, 1974.
- 2403 37. **Krug A.** Alterations in myocardial hydrogen ion concentration after temporary coronary occlusion: a sign
 2404 of irreversible cell damage. *Am J Cardiol* 36: 214-217, 1975.
- 2405 38. **Garcia-Dorado D, Ruiz-Meana M, and Piper HM.** Lethal reperfusion injury in acute myocardial
 2406 infarction: facts and unresolved issues. *Cardiovasc Res* 83: 165-168, 2009.
- 2407 39. **Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, and Vinten-Johansen J.**
 2408 Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic
 2409 preconditioning. *Am J Physiol Heart Circ Physiol* 285: H579-588, 2003.
- 2410 40. **Zweier JL, Kuppusamy P, Williams R, Rayburn BK, Smith D, Weisfeldt ML, and Flaherty JT.**
 2411 Measurement and characterization of postischemic free radical generation in the isolated perfused heart. *J Biol*
 2412 *Chem* 264: 18890-18895, 1989.
- 2413 41. **Hearse DJ, Humphrey SM, and Chain EB.** Abrupt reoxygenation of the anoxic potassium-arrested
 2414 perfused rat heart: a study of myocardial enzyme release. *J Mol Cell Cardiol* 5: 395-407, 1973.
- 2415 42. **Yellon DM, and Hausenloy DJ.** Myocardial reperfusion injury. *N Engl J Med* 357: 1121-1135, 2007.
- 2416 43. **Piper HM, and Garcia-Dorado D.** Prime causes of rapid cardiomyocyte death during reperfusion. *Ann*
 2417 *Thorac Surg* 68: 1913-1919, 1999.
- 2418 44. **Zhao ZQ, Velez DA, Wang NP, Hewan-Lowe KO, Nakamura M, Guyton RA, and Vinten-Johansen**
 2419 **J.** Progressively developed myocardial apoptotic cell death during late phase of reperfusion. *Apoptosis* 6: 279-290,
 2420 2001.
- 2421 45. **Griffiths EJ, and Halestrap AP.** Mitochondrial non-specific pores remain closed during cardiac
 2422 ischaemia, but open upon reperfusion. *Biochem J* 307 (Pt 1): 93-98, 1995.
- 2423 46. **Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L,**
 2424 **Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA,**
 2425 **Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P,**
 2426 **Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH,**
 2427 **Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE,**
 2428 **D'Angiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ,**
 2429 **Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS,**
 2430 **Elrod JW, Fimia GM, Fulda S, Garcia-Saez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb**
 2431 **E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner**
 2432 **MO, Hetz C, Ichijo H, Jaattela M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O,**
 2433 **Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A,**
 2434 **Lipton SA, Lockshin RA, Lopez-Otin C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz**
 2435 **M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S,**
 2436 **Miao EA, Molkentin JD, Moll UM, Munoz-Pinedo C, Nagata S, Nunez G, Oberst A, Oren M, Overholtzer**
 2437 **M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini**
 2438 **M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP,**
 2439 **Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A,**
 2440 **Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y,**
 2441 **Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH,**

- 2442 **Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky**
 2443 **B, Zitvogel L, Melino G, and Kroemer G.** Molecular mechanisms of cell death: recommendations of the
 2444 Nomenclature Committee on Cell Death 2018. *Cell Death Differ* 25: 486-541, 2018.
- 2445 47. **Davidson SM, Arjun S, Basalay MV, Bell RM, Bromage DI, Botker HE, Carr RD, Cunningham J,**
 2446 **Ghosh AK, Heusch G, Ibanez B, Kleinbongard P, Lecour S, Maddock H, Ovize M, Walker M, Wiart M,**
 2447 **and Yellon DM.** The 10th Biennial Hatter Cardiovascular Institute workshop: cellular protection-evaluating new
 2448 directions in the setting of myocardial infarction, ischaemic stroke, and cardio-oncology. *Basic Res Cardiol* 113:
 2449 43, 2018.
- 2450 48. **Gottlieb RA, Burlison KO, Kloner RA, Babior BM, and Engler RL.** Reperfusion injury induces
 2451 apoptosis in rabbit cardiomyocytes. *J Clin Invest* 94: 1621-1628, 1994.
- 2452 49. **Kajstura J, Cheng W, Reiss K, Clark WA, Sonnenblick EH, Krajewski S, Reed JC, Olivetti G, and**
 2453 **Anversa P.** Apoptotic and necrotic myocyte cell deaths are independent contributing variables of infarct size in
 2454 rats. *Laboratory investigation; a journal of technical methods and pathology* 74: 86-107, 1996.
- 2455 50. **Roubille F, Franck-Miclo A, Covinhas A, Lafont C, Cransac F, Combes S, Vincent A, Fontanaud**
 2456 **P, Sportouch-Dukhan C, Redt-Clouet C, Nargeot J, Piot C, and Barrere-Lemaire S.** Delayed
 2457 postconditioning in the mouse heart in vivo. *Circulation* 124: 1330-1336, 2011.
- 2458 51. **Logue SE, Gustafsson AB, Samali A, and Gottlieb RA.** Ischemia/reperfusion injury at the intersection
 2459 with cell death. *J Mol Cell Cardiol* 38: 21-33, 2005.
- 2460 52. **Holly TA, Drincic A, Byun Y, Nakamura S, Harris K, Klocke FJ, and Cryns VL.** Caspase inhibition
 2461 reduces myocyte cell death induced by myocardial ischemia and reperfusion in vivo. *J Mol Cell Cardiol* 31: 1709-
 2462 1715, 1999.
- 2463 53. **Saraste A, Pulkki K, Kallajoki M, Henriksen K, Parvinen M, and Voipio-Pulkki LM.** Apoptosis in
 2464 human acute myocardial infarction. *Circulation* 95: 320-323, 1997.
- 2465 54. **Chen Z, Chua CC, Ho YS, Hamdy RC, and Chua BH.** Overexpression of Bcl-2 attenuates apoptosis
 2466 and protects against myocardial I/R injury in transgenic mice. *Am J Physiol Heart Circ Physiol* 280: H2313-2320,
 2467 2001.
- 2468 55. **Miao W, Luo Z, Kitsis RN, and Walsh K.** Intracoronary, adenovirus-mediated Akt gene transfer in
 2469 heart limits infarct size following ischemia-reperfusion injury in vivo. *J Mol Cell Cardiol* 32: 2397-2402, 2000.
- 2470 56. **Piot CA, Martini JF, Bui SK, and Wolfe CL.** Ischemic preconditioning attenuates
 2471 ischemia/reperfusion-induced activation of caspases and subsequent cleavage of poly(ADP-ribose) polymerase in
 2472 rat hearts in vivo. *Cardiovasc Res* 44: 536-542, 1999.
- 2473 57. **Roubille F, Combes S, Leal-Sanchez J, Barrere C, Cransac F, Sportouch-Dukhan C, Gahide G,**
 2474 **Serre I, Kupfer E, Richard S, Hueber AO, Nargeot J, Piot C, and Barrere-Lemaire S.** Myocardial expression
 2475 of a dominant-negative form of Daxx decreases infarct size and attenuates apoptosis in an in vivo mouse model of
 2476 ischemia/reperfusion injury. *Circulation* 116: 2709-2717, 2007.
- 2477 58. **Yaoita H, Ogawa K, Maehara K, and Maruyama Y.** Attenuation of ischemia/reperfusion injury in rats
 2478 by a caspase inhibitor. *Circulation* 97: 276-281, 1998.
- 2479 59. **Boisguérin P, Covinhas A, Gallot L, Barrère C, Vincent A, Busson M, Piot C, Nargeot J, Lebleu B,**
 2480 **and Barrère-Lemaire S.** A novel therapeutic peptide targeting myocardial reperfusion injury. *Cardiovasc Res*
 2481 116: 633-644, 2020.
- 2482 60. **Inserte J, Cardona M, Poncelas-Nozal M, Hernando V, Vilardosa Ú, Aluja D, Parra VM, Sanchis**
 2483 **D, and Garcia-Dorado D.** Studies on the role of apoptosis after transient myocardial ischemia: genetic deletion
 2484 of the executioner caspases-3 and -7 does not limit infarct size and ventricular remodeling. *Basic Res Cardiol* 111:
 2485 18, 2016.
- 2486 61. **Bahi N, Zhang J, Llovera M, Ballester M, Comella JX, and Sanchis D.** Switch from caspase-
 2487 dependent to caspase-independent death during heart development: essential role of endonuclease G in ischemia-
 2488 induced DNA processing of differentiated cardiomyocytes. *J Biol Chem* 281: 22943-22952, 2006.
- 2489 62. **Zidar N, Dolenc-Strazar Z, Jeruc J, and Stajer D.** Immunohistochemical expression of activated
 2490 caspase-3 in human myocardial infarction. *Virchows Arch* 448: 75-79, 2006.
- 2491 63. **Freude B, Masters TN, Robicsek F, Fokin A, Kostin S, Zimmermann R, Ullmann C, Lorenz-Meyer**
 2492 **S, and Schaper J.** Apoptosis is initiated by myocardial ischemia and executed during reperfusion. *J Mol Cell*
 2493 *Cardiol* 32: 197-208, 2000.
- 2494 64. **Del Re DP, Amgalan D, Linkermann A, Liu Q, and Kitsis RN.** Fundamental Mechanisms of Regulated
 2495 Cell Death and Implications for Heart Disease. *Physiol Rev* 99: 1765-1817, 2019.
- 2496 65. **Tait SW, and Green DR.** Mitochondria and cell death: outer membrane permeabilization and beyond.
 2497 *Nat Rev Mol Cell Biol* 11: 621-632, 2010.
- 2498 66. **Kroemer G, Galluzzi L, and Brenner C.** Mitochondrial membrane permeabilization in cell death.
 2499 *Physiol Rev* 87: 99-163, 2007.
- 2500 67. **Westphal D, Kluck RM, and Dewson G.** Building blocks of the apoptotic pore: how Bax and Bak are
 2501 activated and oligomerize during apoptosis. *Cell Death Differ* 21: 196-205, 2014.

- 2502 68. **Luna-Vargas MPA, and Chipuk JE.** Physiological and Pharmacological Control of BAK, BAX, and
 2503 Beyond. *Trends Cell Biol* 26: 906-917, 2016.
- 2504 69. **Czabotar PE, Lessene G, Strasser A, and Adams JM.** Control of apoptosis by the BCL-2 protein family:
 2505 implications for physiology and therapy. *Nat Rev Mol Cell Biol* 15: 49-63, 2014.
- 2506 70. **Liu X, Kim CN, Yang J, Jemmerson R, and Wang X.** Induction of apoptotic program in cell-free
 2507 extracts: requirement for dATP and cytochrome c. *Cell* 86: 147-157, 1996.
- 2508 71. **Stennicke HR, and Salvesen GS.** Properties of the caspases. *Biochim Biophys Acta* 1387: 17-31, 1998.
- 2509 72. **Thornberry NA, and Lazebnik Y.** Caspases: enemies within. *Science* 281: 1312-1316, 1998.
- 2510 73. **Szabo I, and Zoratti M.** Mitochondrial channels: ion fluxes and more. *Physiol Rev* 94: 519-608, 2014.
- 2511 74. **Bernardi P, Carraro M, and Lippe G.** The mitochondrial permeability transition: Recent progress and
 2512 open questions. *Febs j* 289: 7051-7074, 2022.
- 2513 75. **Boyenle ID, Oyedele AK, Ogunlana AT, Adeyemo AF, Oyelere FS, Akinola OB, Adelusi TI, Ehigie
 2514 LO, and Ehigie AF.** Targeting the mitochondrial permeability transition pore for drug discovery: Challenges and
 2515 opportunities. *Mitochondrion* 63: 57-71, 2022.
- 2516 76. **Crompton M.** The mitochondrial permeability transition pore and its role in cell death. *Biochem J* 341
 2517 (Pt 2): 233-249, 1999.
- 2518 77. **Halestrap AP, McStay GP, and Clarke SJ.** The permeability transition pore complex: another view.
 2519 *Biochimie* 84: 153-166, 2002.
- 2520 78. **Halestrap AP, and Brenner C.** The adenine nucleotide translocase: a central component of the
 2521 mitochondrial permeability transition pore and key player in cell death. *Curr Med Chem* 10: 1507-1525, 2003.
- 2522 79. **Bernardi P, and Petronilli V.** The permeability transition pore as a mitochondrial calcium release
 2523 channel: a critical appraisal. *J Bioenerg Biomembr* 28: 131-138, 1996.
- 2524 80. **Zoratti M, and Szabò I.** The mitochondrial permeability transition. *Biochim Biophys Acta* 1241: 139-
 2525 176, 1995.
- 2526 81. **Hirsch T, Susin SA, Marzo I, Marchetti P, Zamzami N, and Kroemer G.** Mitochondrial permeability
 2527 transition in apoptosis and necrosis. *Cell Biol Toxicol* 14: 141-145, 1998.
- 2528 82. **Halestrap AP.** Calcium, mitochondria and reperfusion injury: a pore way to die. *Biochem Soc Trans* 34:
 2529 232-237, 2006.
- 2530 83. **Murphy E, and Steenbergen C.** What makes the mitochondria a killer? Can we condition them to be
 2531 less destructive? *Biochim Biophys Acta* 1813: 1302-1308, 2011.
- 2532 84. **Patel P, Mendoza A, Robichaux DJ, Wang MC, Wehrens XHT, and Karch J.** Inhibition of the Anti-
 2533 Apoptotic Bcl-2 Family by BH3 Mimetics Sensitize the Mitochondrial Permeability Transition Pore Through Bax
 2534 and Bak. *Front Cell Dev Biol* 9: 765973, 2021.
- 2535 85. **Halestrap AP, Clarke SJ, and Javadov SA.** Mitochondrial permeability transition pore opening during
 2536 myocardial reperfusion—a target for cardioprotection. *Cardiovasc Res* 61: 372-385, 2004.
- 2537 86. **Hausenloy DJ, Maddock HL, Baxter GF, and Yellon DM.** Inhibiting mitochondrial permeability
 2538 transition pore opening: a new paradigm for myocardial preconditioning? *Cardiovasc Res* 55: 534-543, 2002.
- 2539 87. **Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E,
 2540 Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, Andre-Fouet X, Revel D, Kirkorian
 2541 G, Monassier JP, Derumeaux G, and Ovize M.** Effect of cyclosporine on reperfusion injury in acute myocardial
 2542 infarction. *N Engl J Med* 359: 473-481, 2008.
- 2543 88. **Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, Hambleton MA, Brunskill EW, Sayen
 2544 MR, Gottlieb RA, Dorn GW, Robbins J, and Molkentin JD.** Loss of cyclophilin D reveals a critical role for
 2545 mitochondrial permeability transition in cell death. *Nature* 434: 658-662, 2005.
- 2546 89. **Bernardi P, and Di Lisa F.** The mitochondrial permeability transition pore: molecular nature and role as
 2547 a target in cardioprotection. *J Mol Cell Cardiol* 78: 100-106, 2015.
- 2548 90. **Dostert C, Grusdat M, Letellier E, and Brenner D.** The TNF Family of Ligands and Receptors:
 2549 Communication Modules in the Immune System and Beyond. *Physiol Rev* 99: 115-160, 2019.
- 2550 91. **Siegel RM, Frederiksen JK, Zacharias DA, Chan FK, Johnson M, Lynch D, Tsien RY, and Lenardo
 2551 MJ.** Fas preassociation required for apoptosis signaling and dominant inhibition by pathogenic mutations. *Science*
 2552 288: 2354-2357, 2000.
- 2553 92. **Yang X, Khosravi-Far R, Chang HY, and Baltimore D.** Daxx, a novel Fas-binding protein that
 2554 activates JNK and apoptosis. *Cell* 89: 1067-1076, 1997.
- 2555 93. **Salomoni P, and Khelifi AF.** Daxx: death or survival protein? *Trends Cell Biol* 16: 97-104, 2006.
- 2556 94. **Chen LY, and Chen JD.** Daxx silencing sensitizes cells to multiple apoptotic pathways. *Mol Cell Biol*
 2557 23: 7108-7121, 2003.
- 2558 95. **Torii S, Egan DA, Evans RA, and Reed JC.** Human Daxx regulates Fas-induced apoptosis from nuclear
 2559 PML oncogenic domains (PODs). *EMBO J* 18: 6037-6049, 1999.
- 2560 96. **Jeremias I, Kupatt C, Martin-Villalba A, Habazettl H, Schenkel J, Boekstegers P, and Debatin KM.**
 2561 Involvement of CD95/Apo1/Fas in cell death after myocardial ischemia. *Circulation* 102: 915-920, 2000.

- 2562 97. **Lee P, Sata M, Lefer DJ, Factor SM, Walsh K, and Kitsis RN.** Fas pathway is a critical mediator of
2563 cardiac myocyte death and MI during ischemia-reperfusion in vivo. *Am J Physiol Heart Circ Physiol* 284: H456-
2564 463, 2003.
- 2565 98. **Gomez L, Chavanis N, Argaud L, Chalabresse L, Gateau-Roesch O, Ninet J, and Ovize M.** Fas-
2566 independent mitochondrial damage triggers cardiomyocyte death after ischemia-reperfusion. *Am J Physiol Heart*
2567 *Circ Physiol* 289: H2153-2158, 2005.
- 2568 99. **Tekin D, Xi L, and Kukreja RC.** Genetic deletion of fas receptors or Fas ligands does not reduce infarct
2569 size after acute global ischemia-reperfusion in isolated mouse heart. *Cell Biochem Biophys* 44: 111-117, 2006.
- 2570 100. **Yaniv G, Shilkrot M, Lotan R, Berke G, Larisch S, and Binah O.** Hypoxia predisposes neonatal rat
2571 ventricular myocytes to apoptosis induced by activation of the Fas (CD95/Apo-1) receptor: Fas activation and
2572 apoptosis in hypoxic myocytes. *Cardiovasc Res* 54: 611-623, 2002.
- 2573 101. **Shimizu M, Fukuo K, Nagata S, Suhara T, Okuro M, Fujii K, Higashino Y, Mogi M, Hatanaka Y,
2574 and Ogihara T.** Increased plasma levels of the soluble form of Fas ligand in patients with acute myocardial
2575 infarction and unstable angina pectoris. *J Am Coll Cardiol* 39: 585-590, 2002.
- 2576 102. **Krammer PH.** CD95's deadly mission in the immune system. *Nature* 407: 789-795, 2000.
- 2577 103. **Li H, Zhu H, Xu CJ, and Yuan J.** Cleavage of BID by caspase 8 mediates the mitochondrial damage in
2578 the Fas pathway of apoptosis. *Cell* 94: 491-501, 1998.
- 2579 104. **Grinberg M, Sarig R, Zaltsman Y, Frumkin D, Grammatikakis N, Reuveny E, and Gross A.** tBID
2580 Homooligomerizes in the mitochondrial membrane to induce apoptosis. *J Biol Chem* 277: 12237-12245, 2002.
- 2581 105. **Gross A, Yin XM, Wang K, Wei MC, Jockel J, Milliman C, Erdjument-Bromage H, Tempst P, and
2582 Korsmeyer SJ.** Caspase cleaved BID targets mitochondria and is required for cytochrome c release, while BCL-
2583 XL prevents this release but not tumor necrosis factor-R1/Fas death. *J Biol Chem* 274: 1156-1163, 1999.
- 2584 106. **Luo X, Budihardjo I, Zou H, Slaughter C, and Wang X.** Bid, a Bcl2 interacting protein, mediates
2585 cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* 94: 481-490,
2586 1998.
- 2587 107. **Kim TH, Zhao Y, Barber MJ, Kuharsky DK, and Yin XM.** Bid-induced cytochrome c release is
2588 mediated by a pathway independent of mitochondrial permeability transition pore and Bax. *J Biol Chem* 275:
2589 39474-39481, 2000.
- 2590 108. **Fan Q, Huang ZM, Boucher M, Shang X, Zuo L, Brinks H, Lau WB, Zhang J, Chuprun JK, and
2591 Gao E.** Inhibition of Fas-associated death domain-containing protein (FADD) protects against myocardial
2592 ischemia/reperfusion injury in a heart failure mouse model. *PLoS One* 8: e73537, 2013.
- 2593 109. **Michaelson JS, Bader D, Kuo F, Kozak C, and Leder P.** Loss of Daxx, a promiscuously interacting
2594 protein, results in extensive apoptosis in early mouse development. *Genes Dev* 13: 1918-1923, 1999.
- 2595 110. **Michaelson JS, and Leder P.** RNAi reveals anti-apoptotic and transcriptionally repressive activities of
2596 DAXX. *J Cell Sci* 116: 345-352, 2003.
- 2597 111. **Jung YS, Kim HY, Lee YJ, and Kim E.** Subcellular localization of Daxx determines its opposing
2598 functions in ischemic cell death. *FEBS Lett* 581: 843-852, 2007.
- 2599 112. **Song JJ, and Lee YJ.** Role of the ASK1-SEK1-JNK1-HIPK1 signal in Daxx trafficking and ASK1
2600 oligomerization. *J Biol Chem* 278: 47245-47252, 2003.
- 2601 113. **Chang HY, Nishitoh H, Yang X, Ichijo H, and Baltimore D.** Activation of apoptosis signal-regulating
2602 kinase 1 (ASK1) by the adapter protein Daxx. *Science* 281: 1860-1863, 1998.
- 2603 114. **Song JJ, and Lee YJ.** Daxx deletion mutant (amino acids 501-625)-induced apoptosis occurs through
2604 the JNK/p38-Bax-dependent mitochondrial pathway. *J Cell Biochem* 92: 1257-1270, 2004.
- 2605 115. **Dhanasekaran DN, and Reddy EP.** JNK signaling in apoptosis. *Oncogene* 27: 6245-6251, 2008.
- 2606 116. **Covinhas A, Gallot L, Barrère C, Vincent A, Sportouch C, Piot C, Lebleu B, Nargeot J, Boisguérin
2607 P, and Barrère-Lemaire S.** Anti-apoptotic peptide for long term cardioprotection in a mouse model of myocardial
2608 ischemia-reperfusion injury. *Sci Rep* 10: 18116, 2020.
- 2609 117. **Elliott MR, Koster KM, and Murphy PS.** Efferocytosis Signaling in the Regulation of Macrophage
2610 Inflammatory Responses. *J Immunol* 198: 1387-1394, 2017.
- 2611 118. **Pinto AR, Ilinykh A, Ivey MJ, Kuwabara JT, D'Antoni ML, Debuque R, Chandran A, Wang L,
2612 Arora K, Rosenthal NA, and Tallquist MD.** Revisiting Cardiac Cellular Composition. *Circulation research* 118:
2613 400-409, 2016.
- 2614 119. **Boada-Romero E, Martinez J, Heckmann BL, and Green DR.** The clearance of dead cells by
2615 efferocytosis. *Nat Rev Mol Cell Biol* 21: 398-414, 2020.
- 2616 120. **Li Y, Li Q, and Fan GC.** Macrophage Efferocytosis in Cardiac Pathophysiology and Repair. *Shock* 55:
2617 177-188, 2021.
- 2618 121. **Rizzo G, Gropper J, Piollet M, Vafadarnejad E, Rizakou A, Bandi SR, Arampatzi P, Krammer T,
2619 DiFabion N, Dietrich O, Arias-Loza AP, Prinz M, Mack M, Schlepckow K, Haass C, Silvestre JS, Zerneck
2620 A, Saliba AE, and Cochain C.** Dynamics of monocyte-derived macrophage diversity in experimental myocardial
2621 infarction. *Cardiovasc Res* 2022.

- 2622 122. **Zhe-Wei S, Li-Sha G, and Yue-Chun L.** The Role of Necroptosis in Cardiovascular Disease. *Front*
 2623 *Pharmacol* 9: 721, 2018.
- 2624 123. **Sciarretta S, Maejima Y, Zablocki D, and Sadoshima J.** The Role of Autophagy in the Heart. *Annu*
 2625 *Rev Physiol* 80: 1-26, 2018.
- 2626 124. **Mariño G, Niso-Santano M, Baehrecke EH, and Kroemer G.** Self-consumption: the interplay of
 2627 autophagy and apoptosis. *Nat Rev Mol Cell Biol* 15: 81-94, 2014.
- 2628 125. **Gottlieb RA, and Mentzer RM.** Autophagy during cardiac stress: joys and frustrations of autophagy.
 2629 *Annu Rev Physiol* 72: 45-59, 2010.
- 2630 126. **Wu S, Chang G, Gao L, Jiang D, Wang L, Li G, Luo X, Qin S, Guo X, and Zhang D.** Trimetazidine
 2631 protects against myocardial ischemia/reperfusion injury by inhibiting excessive autophagy. *J Mol Med (Berl)* 96:
 2632 791-806, 2018.
- 2633 127. **Ye G, Fu Q, Jiang L, and Li Z.** Vascular smooth muscle cells activate PI3K/Akt pathway to attenuate
 2634 myocardial ischemia/reperfusion-induced apoptosis and autophagy by secreting bFGF. *Biomed Pharmacother* 107:
 2635 1779-1785, 2018.
- 2636 128. **Sciarretta S, Forte M, Frati G, and Sadoshima J.** The complex network of mTOR signalling in the
 2637 heart. *Cardiovasc Res* 118: 424-439, 2022.
- 2638 129. **Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, Asano T, Levine B, and Sadoshima J.** Distinct
 2639 roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin
 2640 1 in mediating autophagy. *Circulation research* 100: 914-922, 2007.
- 2641 130. **Liu Y, Shoji-Kawata S, Sumpter RM, Jr., Wei Y, Ginet V, Zhang L, Posner B, Tran KA, Green**
 2642 **DR, Xavier RJ, Shaw SY, Clarke PG, Puyal J, and Levine B.** Autosis is a Na⁺,K⁺-ATPase-regulated form of
 2643 cell death triggered by autophagy-inducing peptides, starvation, and hypoxia-ischemia. *Proc Natl Acad Sci U S A*
 2644 110: 20364-20371, 2013.
- 2645 131. **Xie M, Cho GW, Kong Y, Li DL, Altamirano F, Luo X, Morales CR, Jiang N, Schiattarella GG,**
 2646 **May HI, Medina J, Shelton JM, Ferdous A, Gillette TG, and Hill JA.** Activation of Autophagic Flux Blunts
 2647 Cardiac Ischemia/Reperfusion Injury. *Circulation research* 129: 435-450, 2021.
- 2648 132. **Kawaguchi M, Takahashi M, Hata T, Kashima Y, Usui F, Morimoto H, Izawa A, Takahashi Y,**
 2649 **Masumoto J, Koyama J, Hongo M, Noda T, Nakayama J, Sagara J, Taniguchi S, and Ikeda U.** Inflammasome
 2650 activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation* 123: 594-604,
 2651 2011.
- 2652 133. **Sandanger Ø, Ranheim T, Vinge LE, Bliksøen M, Alfsnes K, Finsen AV, Dahl CP, Askevold ET,**
 2653 **Florholmen G, Christensen G, Fitzgerald KA, Lien E, Valen G, Espevik T, Aukrust P, and Yndestad A.** The
 2654 NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion
 2655 injury. *Cardiovasc Res* 99: 164-174, 2013.
- 2656 134. **Silvis MJM, Demkes EJ, Fiolet ATL, Dekker M, Bosch L, van Hout GPJ, Timmers L, and de Kleijn**
 2657 **DPV.** Immunomodulation of the NLRP3 Inflammasome in Atherosclerosis, Coronary Artery Disease, and Acute
 2658 Myocardial Infarction. *J Cardiovasc Transl Res* 14: 23-34, 2021.
- 2659 135. **Shi H, Gao Y, Dong Z, Yang J, Gao R, Li X, Zhang S, Ma L, Sun X, Wang Z, Zhang F, Hu K, Sun**
 2660 **A, and Ge J.** GSDMD-Mediated Cardiomyocyte Pyroptosis Promotes Myocardial I/R Injury. *Circulation*
 2661 *research* 129: 383-396, 2021.
- 2662 136. **Zhang ZH, Zhang ZG, Chen MW, Yang Y, Li RJ, Xu JJ, Yang C, Li YY, Chen HW, Liu SX, Li**
 2663 **YL, Luo P, Liu YJ, Chen WB, Shan ZG, and Huang ZR.** Inhibition of GSDMD Activates Poly(ADP-
 2664 ribosylation) and Promotes Myocardial Ischemia-Reperfusion Injury. *Oxid Med Cell Longev* 2022: 1115749, 2022.
- 2665 137. **Epelman S, Liu PP, and Mann DL.** Role of innate and adaptive immune mechanisms in cardiac injury
 2666 and repair. *Nat Rev Immunol* 15: 117-129, 2015.
- 2667 138. **Sarhan M, Land WG, Tonnus W, Hugo CP, and Linkermann A.** Origin and Consequences of
 2668 Necroinflammation. *Physiol Rev* 98: 727-780, 2018.
- 2669 139. **Deftereos S, Angelidis C, Bouras G, Raisakis K, Gerckens U, Cleman MW, and Giannopoulos G.**
 2670 Innate immune inflammatory response in the acutely ischemic myocardium. *Med Chem* 10: 653-662, 2014.
- 2671 140. **Frangogiannis NG.** The inflammatory response in myocardial injury, repair, and remodelling. *Nat Rev*
 2672 *Cardiol* 11: 255-265, 2014.
- 2673 141. **Vilahur G, and Badimon L.** Ischemia/reperfusion activates myocardial innate immune response: the key
 2674 role of the toll-like receptor. *Front Physiol* 5: 496, 2014.
- 2675 142. **Lin L, and Knowlton AA.** Innate immunity and cardiomyocytes in ischemic heart disease. *Life Sci* 100:
 2676 1-8, 2014.
- 2677 143. **Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes-Alnemri T,**
 2678 **Wu J, Monks BG, Fitzgerald KA, Hornung V, and Latz E.** Cutting edge: NF-kappaB activating pattern
 2679 recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J*
 2680 *Immunol* 183: 787-791, 2009.

- 2681 144. **Zhou R, Yazdi AS, Menu P, and Tschopp J.** A role for mitochondria in NLRP3 inflammasome
 2682 activation. *Nature* 469: 221-225, 2011.
- 2683 145. **Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ,**
 2684 **Vergnes L, Ojcius DM, Rentsendorj A, Vargas M, Guerrero C, Wang Y, Fitzgerald KA, Underhill DM,**
 2685 **Town T, and Arditi M.** Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis.
 2686 *Immunity* 36: 401-414, 2012.
- 2687 146. **Sagulenko V, Thygesen SJ, Sester DP, Idris A, Cridland JA, Vajjhala PR, Roberts TL, Schroder**
 2688 **K, Vince JE, Hill JM, Silke J, and Stacey KJ.** AIM2 and NLRP3 inflammasomes activate both apoptotic and
 2689 pyroptotic death pathways via ASC. *Cell Death Differ* 20: 1149-1160, 2013.
- 2690 147. **Bavia L, Lidani KCF, Andrade FA, Sobrinho M, Nisihara RM, and de Messias-Reason IJ.**
 2691 Complement activation in acute myocardial infarction: An early marker of inflammation and tissue injury?
 2692 *Immunol Lett* 200: 18-25, 2018.
- 2693 148. **Carbone F, Nencioni A, Mach F, Vuilleumier N, and Montecucco F.** Pathophysiological role of
 2694 neutrophils in acute myocardial infarction. *Thromb Haemost* 110: 501-514, 2013.
- 2695 149. **Nahrendorf M, Pittet MJ, and Swirski FK.** Monocytes: protagonists of infarct inflammation and repair
 2696 after myocardial infarction. *Circulation* 121: 2437-2445, 2010.
- 2697 150. **Frangogiannis NG, Smith CW, and Entman ML.** The inflammatory response in myocardial infarction.
 2698 *Cardiovasc Res* 53: 31-47, 2002.
- 2699 151. **Zouggari Y, Ait-Oufella H, Bonnin P, Simon T, Sage AP, Guérin C, Vilar J, Caligiuri G, Tsiantoulas**
 2700 **D, Laurans L, Dumeau E, Kotti S, Bruneval P, Charo IF, Binder CJ, Danchin N, Tedgui A, Tedder TF,**
 2701 **Silvestre JS, and Mallat Z.** B lymphocytes trigger monocyte mobilization and impair heart function after acute
 2702 myocardial infarction. *Nat Med* 19: 1273-1280, 2013.
- 2703 152. **Jian Y, Zhou X, Shan W, Chen C, Ge W, Cui J, Yi W, and Sun Y.** Crosstalk between macrophages
 2704 and cardiac cells after myocardial infarction. *Cell Commun Signal* 21: 109, 2023.
- 2705 153. **Kapadia S, Lee J, Torre-Amione G, Birdsall HH, Ma TS, and Mann DL.** Tumor necrosis factor-alpha
 2706 gene and protein expression in adult feline myocardium after endotoxin administration. *J Clin Invest* 96: 1042-
 2707 1052, 1995.
- 2708 154. **Mann DL.** Inflammatory mediators and the failing heart: past, present, and the foreseeable future.
 2709 *Circulation research* 91: 988-998, 2002.
- 2710 155. **Lecour S, and James RW.** When are pro-inflammatory cytokines SAFE in heart failure? *Eur Heart J*
 2711 32: 680-685, 2011.
- 2712 156. **Sun Y, Pinto C, Camus S, Duval V, Alayrac P, Zlatanova I, Loyer X, Vilar J, Lemitre M, Levoye**
 2713 **A, Nus M, Ait-Oufella H, Mallat Z, and Silvestre JS.** Splenic Marginal Zone B Lymphocytes Regulate Cardiac
 2714 Remodeling After Acute Myocardial Infarction in Mice. *J Am Coll Cardiol* 79: 632-647, 2022.
- 2715 157. **Harrison RW, Aggarwal A, Ou FS, Klein LW, Rumsfeld JS, Roe MT, and Wang TY.** Incidence and
 2716 outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute
 2717 myocardial infarction. *Am J Cardiol* 111: 178-184, 2013.
- 2718 158. **Ito H.** No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract*
 2719 *Cardiovasc Med* 3: 499-506, 2006.
- 2720 159. **Betgem RP, de Waard GA, Nijveldt R, Beek AM, Escaned J, and van Royen N.** Intramyocardial
 2721 haemorrhage after acute myocardial infarction. *Nat Rev Cardiol* 12: 156-167, 2015.
- 2722 160. **Barrere-Lemaire S, Nargeot J, and Piot C.** Delayed postconditioning: not too late? *Trends Cardiovasc*
 2723 *Med* 22: 173-179, 2012.
- 2724 161. **Opie LH, and Lecour S.** Delayed postconditioning: cardioprotection at the limit? *Circulation* 124: 1315-
 2725 1318, 2011.
- 2726 162. **Greulich S, Mayr A, Gloekler S, Seitz A, Birkmeier S, Schaufele T, Bekeredjian R, Zuern CS, Seizer**
 2727 **P, Geisler T, Muller KAL, Krumm P, Nikolaou K, Klug G, Reinstadler S, Pamminger M, Reindl M, Wahl**
 2728 **A, Traupe T, Seiler C, Metzler B, Gawaz M, Windecker S, and Mahrholdt H.** Time-Dependent Myocardial
 2729 Necrosis in Patients With ST-Segment-Elevation Myocardial Infarction Without Angiographic Collateral Flow
 2730 Visualized by Cardiac Magnetic Resonance Imaging: Results From the Multicenter STEMI-SCAR Project. *J Am*
 2731 *Heart Assoc* 8: e012429, 2019.
- 2732 163. **Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D, and Rusticali F.** Prodromal
 2733 angina limits infarct size. A role for ischemic preconditioning. *Circulation* 91: 291-297, 1995.
- 2734 164. **Murry CE, Jennings RB, and Reimer KA.** Preconditioning with ischemia: a delay of lethal cell injury
 2735 in ischemic myocardium. *Circulation* 74: 1124-1136, 1986.
- 2736 165. **Skyschally A, van Caster P, Iliodromitis EK, Schulz R, Kremastinos DT, and Heusch G.** Ischemic
 2737 postconditioning: experimental models and protocol algorithms. *Basic Res Cardiol* 104: 469-483, 2009.
- 2738 166. **Piot CA, Padmanaban D, Ursell PC, Sievers RE, and Wolfe CL.** Ischemic preconditioning decreases
 2739 apoptosis in rat hearts in vivo. *Circulation* 96: 1598-1604, 1997.

- 2740 167. **Yellon DM, Alkhulaifi AM, and Pugsley WB.** Preconditioning the human myocardium. *Lancet* 342:
2741 276-277, 1993.
- 2742 168. **Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, Burstein S, Gibson M, Poole**
2743 **WK, Cannon CP, and et al.** Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to
2744 preconditioning? *Circulation* 91: 37-45, 1995.
- 2745 169. **Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, Andre-**
2746 **Fouet X, and Ovize M.** Postconditioning the human heart. *Circulation* 112: 2143-2148, 2005.
- 2747 170. **Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, Cung TT, Bonnefoy E,**
2748 **Angoulvant D, Aupetit JF, Finet G, Andre-Fouet X, Macia JC, Raczka F, Rossi R, Itti R, Kirkorian G,**
2749 **Derumeaux G, and Ovize M.** Long-term benefit of postconditioning. *Circulation* 117: 1037-1044, 2008.
- 2750 171. **Shi W, and Vinten-Johansen J.** Endogenous cardioprotection by ischaemic postconditioning and remote
2751 conditioning. *Cardiovasc Res* 94: 206-216, 2012.
- 2752 172. **Hausenloy DJ.** Cardioprotection techniques: preconditioning, postconditioning and remote conditioning
2753 (basic science). *Curr Pharm Des* 19: 4544-4563, 2013.
- 2754 173. **Heusch G.** Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote
2755 conditioning. *Circulation research* 116: 674-699, 2015.
- 2756 174. **Przyklenk K, Bauer B, Ovize M, Kloner RA, and Whittaker P.** Regional ischemic 'preconditioning'
2757 protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 87: 893-899, 1993.
- 2758 175. **Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, and Verdouw PD.** Myocardial protection
2759 by brief ischemia in noncardiac tissue. *Circulation* 94: 2193-2200, 1996.
- 2760 176. **Hausenloy DJ, and Yellon DM.** Remote ischaemic preconditioning: underlying mechanisms and clinical
2761 application. *Cardiovasc Res* 79: 377-386, 2008.
- 2762 177. **Schmidt MR, Smerup M, Konstantinov IE, Shimizu M, Li J, Cheung M, White PA, Kristiansen SB,**
2763 **Sorensen K, Dzavik V, Redington AN, and Kharbanda RK.** Intermittent peripheral tissue ischemia during
2764 coronary ischemia reduces myocardial infarction through a KATP-dependent mechanism: first demonstration of
2765 remote ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 292: H1883-1890, 2007.
- 2766 178. **Andreka G, Vertesaljai M, Szantho G, Font G, Piroth Z, Fontos G, Juhasz ED, Szekely L, Szolid Z,**
2767 **Turner MS, Ashrafian H, Frenneaux MP, and Andreka P.** Remote ischaemic postconditioning protects the
2768 heart during acute myocardial infarction in pigs. *Heart* 93: 749-752, 2007.
- 2769 179. **Breivik L, Helgeland E, Aarnes EK, Mrdalj J, and Jonassen AK.** Remote postconditioning by
2770 humoral factors in effluent from ischemic preconditioned rat hearts is mediated via PI3K/Akt-dependent cell-
2771 survival signaling at reperfusion. *Basic Res Cardiol* 106: 135-145, 2011.
- 2772 180. **Gritsopoulos G, Iliodromitis EK, Zoga A, Farmakis D, Demerouti E, Papalois A, Paraskevaidis IA,**
2773 **and Kremastinos DT.** Remote postconditioning is more potent than classic postconditioning in reducing the
2774 infarct size in anesthetized rabbits. *Cardiovasc Drugs Ther* 23: 193-198, 2009.
- 2775 181. **Heusch G, Botker HE, Przyklenk K, Redington A, and Yellon D.** Remote ischemic conditioning. *J*
2776 *Am Coll Cardiol* 65: 177-195, 2015.
- 2777 182. **Kerendi F, Kin H, Halkos ME, Jiang R, Zatta AJ, Zhao ZQ, Guyton RA, and Vinten-Johansen J.**
2778 Remote postconditioning. Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces
2779 myocardial infarct size via endogenous activation of adenosine receptors. *Basic Res Cardiol* 100: 404-412, 2005.
- 2780 183. **Wei M, Xin P, Li S, Tao J, Li Y, Li J, Liu M, Li J, Zhu W, and Redington AN.** Repeated remote
2781 ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model
2782 of myocardial infarction. *Circulation research* 108: 1220-1225, 2011.
- 2783 184. **Zhu SB, Liu Y, Zhu Y, Yin GL, Wang RP, Zhang Y, Zhu J, and Jiang W.** Remote preconditioning,
2784 preconditioning, and postconditioning: a comparative study of their cardio-protective properties in rat models.
2785 *Clinics (Sao Paulo)* 68: 263-268, 2013.
- 2786 185. **Bromage DI, Pickard JM, Rossello X, Ziff OJ, Burke N, Yellon DM, and Davidson SM.** Remote
2787 ischaemic conditioning reduces infarct size in animal in vivo models of ischaemia-reperfusion injury: a systematic
2788 review and meta-analysis. *Cardiovasc Res* 113: 288-297, 2017.
- 2789 186. **Oxman T, Arad M, Klein R, Avazov N, and Rabinowitz B.** Limb ischemia preconditions the heart
2790 against reperfusion tachyarrhythmia. *Am J Physiol* 273: H1707-1712, 1997.
- 2791 187. **Kharbanda RK, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschitzky JA, Vogel**
2792 **M, Sorensen K, Redington AN, and MacAllister R.** Transient limb ischemia induces remote ischemic
2793 preconditioning in vivo. *Circulation* 106: 2881-2883, 2002.
- 2794 188. **Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kalsoft AK, Terkelsen CJ, Munk K, Andersen**
2795 **NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen**
2796 **SS, Rehling M, Sorensen HT, Redington AN, and Nielsen TT.** Remote ischaemic conditioning before hospital
2797 admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial
2798 infarction: a randomised trial. *Lancet* 375: 727-734, 2010.

- 2799 189. **Eitel I, Stiermaier T, Rommel KP, Fuernau G, Sandri M, Mangner N, Linke A, Erbs S, Lurz P,**
 2800 **Boudriot E, Mende M, Desch S, Schuler G, and Thiele H.** Cardioprotection by combined intrahospital remote
 2801 ischaemic preconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA
 2802 CONDITIONING trial. *Eur Heart J* 36: 3049-3057, 2015.
- 2803 190. **Verouhis D, Sorensson P, Gourine A, Henareh L, Persson J, Saleh N, Settergren M, Sundqvist M,**
 2804 **Tornvall P, Witt N, Bohm F, and Pernow J.** Effect of remote ischemic conditioning on infarct size in patients
 2805 with anterior ST-elevation myocardial infarction. *Am Heart J* 181: 66-73, 2016.
- 2806 191. **White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, Tehrani S, Flett AS,**
 2807 **Meier P, Ariti C, Davies JR, Moon JC, Yellon DM, and Hausenloy DJ.** Remote ischemic conditioning reduces
 2808 myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc*
 2809 *Interv* 8: 178-188, 2015.
- 2810 192. **Crimi G, Pica S, Raineri C, Bramucci E, De Ferrari GM, Klersy C, Ferlini M, Marinoni B, Repetto**
 2811 **A, Romeo M, Rosti V, Massa M, Raisaro A, Leonardi S, Rubartelli P, Oltrona Visconti L, and Ferrario M.**
 2812 Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely
 2813 reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc*
 2814 *Interv* 6: 1055-1063, 2013.
- 2815 193. **Prunier F, Angoulvant D, Saint Etienne C, Vermes E, Gilard M, Piot C, Roubille F, Elbaz M, Ovize**
 2816 **M, Biere L, Jeanneteau J, Delepine S, Benard T, Abi-Khalil W, and Furber A.** The RIPOST-MI study,
 2817 assessing remote ischemic preconditioning alone or in combination with local ischemic postconditioning in ST-
 2818 segment elevation myocardial infarction. *Basic Res Cardiol* 109: 400, 2014.
- 2819 194. **Yellon DM, Ackbarkhan AK, Balgobin V, Bulluck H, Deelchand A, Dhuny MR, Domah N,**
 2820 **Gaoneadry D, Jagessur RK, Joonas N, Kowlessur S, Lutchoo J, Nicholas JM, Pauvaday K, Shamloll O,**
 2821 **Walker JM, and Hausenloy DJ.** Remote Ischemic Conditioning Reduces Myocardial Infarct Size in STEMI
 2822 Patients Treated by Thrombolysis. *J Am Coll Cardiol* 65: 2764-2765, 2015.
- 2823 195. **Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, Pedersen L,**
 2824 **Sorensen HT, Botker HE, and Investigators C.** Improved long-term clinical outcomes in patients with ST-
 2825 elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous
 2826 coronary intervention. *Eur Heart J* 35: 168-175, 2014.
- 2827 196. **Gaspar A, Lourenco AP, Pereira MA, Azevedo P, Roncon-Albuquerque R, Jr., Marques J, and**
 2828 **Leite-Moreira AF.** Randomized controlled trial of remote ischaemic conditioning in ST-elevation myocardial
 2829 infarction as adjuvant to primary angioplasty (RIC-STEMI). *Basic Res Cardiol* 113: 14, 2018.
- 2830 197. **McLeod SL, Iansavichene A, and Cheskes S.** Remote Ischemic Preconditioning to Reduce Reperfusion
 2831 Injury During Acute ST-Segment-Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis. *J*
 2832 *Am Heart Assoc* 6: 2017.
- 2833 198. **Niu X, Zhang J, Chen D, Wan G, Zhang Y, and Yao Y.** Remote ischaemic conditioning in
 2834 percutaneous coronary intervention: a meta-analysis of randomised trials. *Postepy Kardiol Interwencyjnej* 10: 274-
 2835 282, 2014.
- 2836 199. **Hausenloy DJ, Kharbanda RK, Moller UK, Ramlall M, Aaroe J, Butler R, Bulluck H, Clayton T,**
 2837 **Dana A, Dodd M, Engstrom T, Evans R, Lassen JF, Christensen EF, Garcia-Ruiz JM, Gorog DA, Hjort J,**
 2838 **Houghton RF, Ibanez B, Knight R, Lippert FK, Lonborg JT, Maeng M, Milasinovic D, More R, Nicholas**
 2839 **JM, Jensen LO, Perkins A, Radovanovic N, Rakhit RD, Ravkilde J, Ryding AD, Schmidt MR, Riddervold**
 2840 **IS, Sorensen HT, Stankovic G, Varma M, Webb I, Terkelsen CJ, Greenwood JP, Yellon DM, Botker HE,**
 2841 **and Investigators C-E-P.** Effect of remote ischaemic conditioning on clinical outcomes in patients with acute
 2842 myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. *Lancet* 394: 1415-1424,
 2843 2019.
- 2844 200. **Przyklenk K.** Reduction of myocardial infarct size with ischemic "conditioning": physiologic and
 2845 technical considerations. *Anesth Analg* 117: 891-901, 2013.
- 2846 201. **Heusch G.** Cardioprotection: chances and challenges of its translation to the clinic. *Lancet* 381: 166-175,
 2847 2013.
- 2848 202. **Kin H, Wang NP, Mykytenko J, Reeves J, Deneve J, Jiang R, Zatta AJ, Guyton RA, Vinten-**
 2849 **Johansen J, and Zhao ZQ.** Inhibition of myocardial apoptosis by postconditioning is associated with attenuation
 2850 of oxidative stress-mediated nuclear factor-kappa B translocation and TNF alpha release. *Shock* 29: 761-768, 2008.
- 2851 203. **Sun HY, Wang NP, Halkos M, Kerendi F, Kin H, Guyton RA, Vinten-Johansen J, and Zhao ZQ.**
 2852 Postconditioning attenuates cardiomyocyte apoptosis via inhibition of JNK and p38 mitogen-activated protein
 2853 kinase signaling pathways. *Apoptosis* 11: 1583-1593, 2006.
- 2854 204. **Wang HC, Zhang HF, Guo WY, Su H, Zhang KR, Li QX, Yan W, Ma XL, Lopez BL, Christopher**
 2855 **TA, and Gao F.** Hypoxic postconditioning enhances the survival and inhibits apoptosis of cardiomyocytes
 2856 following reoxygenation: role of peroxynitrite formation. *Apoptosis* 11: 1453-1460, 2006.

- 2857 205. **Penna C, Perrelli MG, Raimondo S, Tullio F, Merlino A, Moro F, Geuna S, Mancardi D, and**
 2858 **Pagliari P.** Postconditioning induces an anti-apoptotic effect and preserves mitochondrial integrity in isolated rat
 2859 hearts. *Biochim Biophys Acta* 1787: 794-801, 2009.
- 2860 206. **Vincent A, Gahide G, Sportouch-Dukhan C, Covinhes A, Franck-Miclo A, Roubille F, Barrere C,**
 2861 **Adda J, Dantec C, Redt-Clouet C, Piot C, Nargeot J, and Barrere-Lemaire S.** Down-regulation of the
 2862 transcription factor ZAC1 upon pre- and postconditioning protects against I/R injury in the mouse myocardium.
 2863 *Cardiovasc Res* 94: 351-358, 2012.
- 2864 207. **Xiong J, Wang Q, Xue FS, Yuan YJ, Li S, Liu JH, Liao X, and Zhang YM.** Comparison of
 2865 cardioprotective and anti-inflammatory effects of ischemia pre- and postconditioning in rats with myocardial
 2866 ischemia-reperfusion injury. *Inflammation research : official journal of the European Histamine Research Society*
 2867 *[et al]* 60: 547-554, 2011.
- 2868 208. **Fang J, Fan L, Chen L, Chen X, and Wu L.** Coronary effluent from postconditioned hearts promotes
 2869 survival of mesenchymal stem cells under hypoxia. *Scandinavian cardiovascular journal : SCJ* 48: 120-127, 2014.
- 2870 209. **Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, and Vinten-**
 2871 **Johansen J.** Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early
 2872 minutes of reperfusion. *Cardiovasc Res* 62: 74-85, 2004.
- 2873 210. **Dow J, and Kloner RA.** Postconditioning does not reduce myocardial infarct size in an in vivo regional
 2874 ischemia rodent model. *J Cardiovasc Pharmacol Ther* 12: 153-163, 2007.
- 2875 211. **Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, and Cohen MV.** Multiple, brief coronary
 2876 occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. *J Am Coll Cardiol*
 2877 44: 1103-1110, 2004.
- 2878 212. **Tsang A, Hausenloy DJ, Mocanu MM, and Yellon DM.** Postconditioning: a form of "modified
 2879 reperfusion" protects the myocardium by activating the phosphatidylinositol 3-kinase-Akt pathway. *Circulation*
 2880 *research* 95: 230-232, 2004.
- 2881 213. **Halkos ME, Kerendi F, Corvera JS, Wang NP, Kin H, Payne CS, Sun HY, Guyton RA, Vinten-**
 2882 **Johansen J, and Zhao ZQ.** Myocardial protection with postconditioning is not enhanced by ischemic
 2883 preconditioning. *Ann Thorac Surg* 78: 961-969; discussion 969, 2004.
- 2884 214. **Hausenloy DJ, and Yellon DM.** Preconditioning and postconditioning: underlying mechanisms and
 2885 clinical application. *Atherosclerosis* 204: 334-341, 2009.
- 2886 215. **Liu GS, Thornton J, Van Winkle DM, Stanley AW, Olsson RA, and Downey JM.** Protection against
 2887 infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* 84: 350-
 2888 356, 1991.
- 2889 216. **Yao Z, and Gross GJ.** Acetylcholine mimics ischemic preconditioning via a glibenclamide-sensitive
 2890 mechanism in dogs. *Am J Physiol* 264: H2221-2225, 1993.
- 2891 217. **Tsuchida A, Liu Y, Liu GS, Cohen MV, and Downey JM.** alpha 1-adrenergic agonists precondition
 2892 rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase C. *Circulation*
 2893 *research* 75: 576-585, 1994.
- 2894 218. **Schultz JE, Rose E, Yao Z, and Gross GJ.** Evidence for involvement of opioid receptors in ischemic
 2895 preconditioning in rat hearts. *Am J Physiol* 268: H2157-2161, 1995.
- 2896 219. **Goto M, Liu Y, Yang XM, Ardell JL, Cohen MV, and Downey JM.** Role of bradykinin in protection
 2897 of ischemic preconditioning in rabbit hearts. *Circulation research* 77: 611-621, 1995.
- 2898 220. **Liu Y, Tsuchida A, Cohen MV, and Downey JM.** Pretreatment with angiotensin II activates protein
 2899 kinase C and limits myocardial infarction in isolated rabbit hearts. *J Mol Cell Cardiol* 27: 883-892, 1995.
- 2900 221. **Wang P, Gallagher KP, Downey JM, and Cohen MV.** Pretreatment with endothelin-1 mimics ischemic
 2901 preconditioning against infarction in isolated rabbit heart. *J Mol Cell Cardiol* 28: 579-588, 1996.
- 2902 222. **Vincent A, Sportouch C, Covinhes A, Barrere C, Gallot L, Delgado-Betancourt V, Lattuca B,**
 2903 **Solecki K, Boisguerin P, Piot C, Nargeot J, and Barrere-Lemaire S.** Cardiac mGluR1 metabotropic receptors
 2904 in cardioprotection. *Cardiovasc Res* 113: 644-655, 2017.
- 2905 223. **Hausenloy DJ, and Yellon DM.** Reperfusion injury salvage kinase signalling: taking a RISK for
 2906 cardioprotection. *Heart failure reviews* 12: 217-234, 2007.
- 2907 224. **Insarte J, and Garcia-Dorado D.** The cGMP/PKG pathway as a common mediator of cardioprotection:
 2908 translatability and mechanism. *Br J Pharmacol* 172: 1996-2009, 2015.
- 2909 225. **Hausenloy DJ, Tsang A, and Yellon DM.** The reperfusion injury salvage kinase pathway: a common
 2910 target for both ischemic preconditioning and postconditioning. *Trends Cardiovasc Med* 15: 69-75, 2005.
- 2911 226. **Schulman D, Latchman DS, and Yellon DM.** Urocortin protects the heart from reperfusion injury via
 2912 upregulation of p42/p44 MAPK signaling pathway. *Am J Physiol Heart Circ Physiol* 283: H1481-1488, 2002.
- 2913 227. **Hausenloy DJ.** Signalling pathways in ischaemic postconditioning. *Thromb Haemost* 101: 626-634, 2009.
- 2914 228. **Franke TF, and Cantley LC.** Apoptosis. A Bad kinase makes good. *Nature* 390: 116-117, 1997.

- 2915 229. **Matsui T, Li L, del Monte F, Fukui Y, Franke TF, Hajjar RJ, and Rosenzweig A.** Adenoviral gene
 2916 transfer of activated phosphatidylinositol 3'-kinase and Akt inhibits apoptosis of hypoxic cardiomyocytes in vitro.
 2917 *Circulation* 100: 2373-2379, 1999.
- 2918 230. **Fujio Y, Nguyen T, Wencker D, Kitsis RN, and Walsh K.** Akt promotes survival of cardiomyocytes
 2919 in vitro and protects against ischemia-reperfusion injury in mouse heart. *Circulation* 101: 660-667, 2000.
- 2920 231. **Matsui T, Tao J, del Monte F, Lee KH, Li L, Picard M, Force TL, Franke TF, Hajjar RJ, and
 2921 Rosenzweig A.** Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in
 2922 vivo. *Circulation* 104: 330-335, 2001.
- 2923 232. **Kim YK, Kim SJ, Yatani A, Huang Y, Castelli G, Vatner DE, Liu J, Zhang Q, Diaz G, Zieba R,
 2924 Thaisz J, Drusco A, Croce C, Sadoshima J, Condorelli G, and Vatner SF.** Mechanism of enhanced cardiac
 2925 function in mice with hypertrophy induced by overexpressed Akt. *J Biol Chem* 278: 47622-47628, 2003.
- 2926 233. **Haq S, Choukroun G, Lim H, Tymitz KM, del Monte F, Gwathmey J, Grazette L, Michael A,
 2927 Hajjar R, Force T, and Molkentin JD.** Differential activation of signal transduction pathways in human hearts
 2928 with hypertrophy versus advanced heart failure. *Circulation* 103: 670-677, 2001.
- 2929 234. **Condorelli G, Drusco A, Stassi G, Bellacosa A, Roncarati R, Iaccarino G, Russo MA, Gu Y, Dalton
 2930 N, Chung C, Latronico MV, Napoli C, Sadoshima J, Croce CM, and Ross J, Jr.** Akt induces enhanced
 2931 myocardial contractility and cell size in vivo in transgenic mice. *Proc Natl Acad Sci U S A* 99: 12333-12338, 2002.
- 2932 235. **Matsui T, Li L, Wu JC, Cook SA, Nagoshi T, Picard MH, Liao R, and Rosenzweig A.** Phenotypic
 2933 spectrum caused by transgenic overexpression of activated Akt in the heart. *J Biol Chem* 277: 22896-22901, 2002.
- 2934 236. **Nagoshi T, Matsui T, Aoyama T, Leri A, Anversa P, Li L, Ogawa W, del Monte F, Gwathmey JK,
 2935 Grazette L, Hemmings BA, Kass DA, Champion HC, and Rosenzweig A.** PI3K rescues the detrimental effects
 2936 of chronic Akt activation in the heart during ischemia/reperfusion injury. *J Clin Invest* 115: 2128-2138, 2005.
- 2937 237. **Crackower MA, Oudit GY, Kozieradzki I, Sarao R, Sun H, Sasaki T, Hirsch E, Suzuki A, Shioi T,
 2938 Irie-Sasaki J, Sah R, Cheng HY, Rybin VO, Lembo G, Fratta L, Oliveira-dos-Santos AJ, Benovic JL, Kahn
 2939 CR, Izumo S, Steinberg SF, Wymann MP, Backx PH, and Penninger JM.** Regulation of myocardial
 2940 contractility and cell size by distinct PI3K-PTEN signaling pathways. *Cell* 110: 737-749, 2002.
- 2941 238. **Parajuli N, Yuan Y, Zheng X, Bedja D, and Cai ZP.** Phosphatase PTEN is critically involved in post-
 2942 myocardial infarction remodeling through the Akt/interleukin-10 signaling pathway. *Basic Res Cardiol* 107: 248,
 2943 2012.
- 2944 239. **Oudit GY, Kassiri Z, Zhou J, Liu QC, Liu PP, Backx PH, Dawood F, Crackower MA, Scholey JW,
 2945 and Penninger JM.** Loss of PTEN attenuates the development of pathological hypertrophy and heart failure in
 2946 response to biomechanical stress. *Cardiovasc Res* 78: 505-514, 2008.
- 2947 240. **Stiles B, Groszer M, Wang S, Jiao J, and Wu H.** PTENless means more. *Dev Biol* 273: 175-184, 2004.
- 2948 241. **Keyes KT, Xu J, Long B, Zhang C, Hu Z, and Ye Y.** Pharmacological inhibition of PTEN limits
 2949 myocardial infarct size and improves left ventricular function postinfarction. *Am J Physiol Heart Circ Physiol* 298:
 2950 H1198-1208, 2010.
- 2951 242. **Cai Z, and Semenza GL.** PTEN activity is modulated during ischemia and reperfusion: involvement in
 2952 the induction and decay of preconditioning. *Circulation research* 97: 1351-1359, 2005.
- 2953 243. **Li CM, Shen SW, Wang T, and Zhang XH.** Myocardial ischemic post-conditioning attenuates ischemia
 2954 reperfusion injury via PTEN/Akt signal pathway. *Int J Clin Exp Med* 8: 15801-15807, 2015.
- 2955 244. **Hausenloy DJ, and Yellon DM.** The mitochondrial permeability transition pore: its fundamental role in
 2956 mediating cell death during ischaemia and reperfusion. *J Mol Cell Cardiol* 35: 339-341, 2003.
- 2957 245. **Lim SY, Davidson SM, Hausenloy DJ, and Yellon DM.** Preconditioning and postconditioning: the
 2958 essential role of the mitochondrial permeability transition pore. *Cardiovasc Res* 75: 530-535, 2007.
- 2959 246. **Yellon DM, Beikoghli Kalkhoran S, and Davidson SM.** The RISK pathway leading to mitochondria
 2960 and cardioprotection: how everything started. *Basic Res Cardiol* 118: 22, 2023.
- 2961 247. **Hausenloy DJ, and Yellon DM.** New directions for protecting the heart against ischaemia-reperfusion
 2962 injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* 61: 448-460, 2004.
- 2963 248. **Javadov SA, Clarke S, Das M, Griffiths EJ, Lim KH, and Halestrap AP.** Ischaemic preconditioning
 2964 inhibits opening of mitochondrial permeability transition pores in the reperfused rat heart. *J Physiol* 549: 513-524,
 2965 2003.
- 2966 249. **Argaud L, Gateau-Roesch O, Raitsky O, Loufouat J, Robert D, and Ovize M.** Postconditioning
 2967 inhibits mitochondrial permeability transition. *Circulation* 111: 194-197, 2005.
- 2968 250. **Ong SB, Samangouei P, Kalkhoran SB, and Hausenloy DJ.** The mitochondrial permeability transition
 2969 pore and its role in myocardial ischemia reperfusion injury. *J Mol Cell Cardiol* 78: 23-34, 2015.
- 2970 251. **Basalay MV, Davidson SM, Gourine AV, and Yellon DM.** Neural mechanisms in remote ischaemic
 2971 conditioning in the heart and brain: mechanistic and translational aspects. *Basic Res Cardiol* 113: 25, 2018.
- 2972 252. **Parrizas M, Saltiel AR, and LeRoith D.** Insulin-like growth factor 1 inhibits apoptosis using the
 2973 phosphatidylinositol 3'-kinase and mitogen-activated protein kinase pathways. *J Biol Chem* 272: 154-161, 1997.

- 2974 253. **Sheng Z, Knowlton K, Chen J, Hoshijima M, Brown JH, and Chien KR.** Cardiotrophin 1 (CT-1)
 2975 inhibition of cardiac myocyte apoptosis via a mitogen-activated protein kinase-dependent pathway. Divergence
 2976 from downstream CT-1 signals for myocardial cell hypertrophy. *J Biol Chem* 272: 5783-5791, 1997.
- 2977 254. **Shizukuda Y, and Buttrick PM.** Subtype specific roles of beta-adrenergic receptors in apoptosis of adult
 2978 rat ventricular myocytes. *J Mol Cell Cardiol* 34: 823-831, 2002.
- 2979 255. **Yue TL, Wang C, Gu JL, Ma XL, Kumar S, Lee JC, Feuerstein GZ, Thomas H, Maleeff B, and**
 2980 **Ohlstein EH.** Inhibition of extracellular signal-regulated kinase enhances Ischemia/Reoxygenation-induced
 2981 apoptosis in cultured cardiac myocytes and exaggerates reperfusion injury in isolated perfused heart. *Circulation*
 2982 *research* 86: 692-699, 2000.
- 2983 256. **Lips DJ, Bueno OF, Wilkins BJ, Purcell NH, Kaiser RA, Lorenz JN, Voisin L, Saba-El-Leil MK,**
 2984 **Meloche S, Pouyssegur J, Pages G, De Windt LJ, Doevendans PA, and Molckentin JD.** MEK1-ERK2 signaling
 2985 pathway protects myocardium from ischemic injury in vivo. *Circulation* 109: 1938-1941, 2004.
- 2986 257. **Hausenloy DJ, and Yellon DM.** Survival kinases in ischemic preconditioning and postconditioning.
 2987 *Cardiovasc Res* 70: 240-253, 2006.
- 2988 258. **Lecour S, Suleman N, Deuchar GA, Somers S, Lacerda L, Huisamen B, and Opie LH.**
 2989 Pharmacological preconditioning with tumor necrosis factor-alpha activates signal transducer and activator of
 2990 transcription-3 at reperfusion without involving classic prosurvival kinases (Akt and extracellular signal-regulated
 2991 kinase). *Circulation* 112: 3911-3918, 2005.
- 2992 259. **Lacerda L, Somers S, Opie LH, and Lecour S.** Ischaemic postconditioning protects against reperfusion
 2993 injury via the SAFE pathway. *Cardiovasc Res* 84: 201-208, 2009.
- 2994 260. **Lecour S.** Activation of the protective Survivor Activating Factor Enhancement (SAFE) pathway against
 2995 reperfusion injury: Does it go beyond the RISK pathway? *J Mol Cell Cardiol* 47: 32-40, 2009.
- 2996 261. **Lecour S.** Multiple protective pathways against reperfusion injury: a SAFE path without Aktion? *J Mol*
 2997 *Cell Cardiol* 46: 607-609, 2009.
- 2998 262. **Suleman N, Somers S, Smith R, Opie LH, and Lecour SC.** Dual activation of STAT-3 and Akt is
 2999 required during the trigger phase of ischaemic preconditioning. *Cardiovasc Res* 79: 127-133, 2008.
- 3000 263. **Davidson SM, and Yellon DM.** STAT5 fits the RISK profile for cardioprotection. *JAKSTAT* 1: 73-76,
 3001 2012.
- 3002 264. **Bolli R, Stein AB, Guo Y, Wang OL, Rokosh G, Dawn B, Molckentin JD, Sanganalmath SK, Zhu Y,**
 3003 **and Xuan YT.** A murine model of inducible, cardiac-specific deletion of STAT3: its use to determine the role of
 3004 STAT3 in the upregulation of cardioprotective proteins by ischemic preconditioning. *J Mol Cell Cardiol* 50: 589-
 3005 597, 2011.
- 3006 265. **Wegrzyn J, Potla R, Chwae YJ, Sepuri NB, Zhang Q, Koeck T, Derecka M, Szczepanek K, Szelag**
 3007 **M, Gornicka A, Moh A, Moghaddas S, Chen Q, Bobbili S, Cichy J, Dulak J, Baker DP, Wolfman A, Stuehr**
 3008 **D, Hassan MO, Fu XY, Avadhani N, Drake JI, Fawcett P, Lesnfsky EJ, and Larner AC.** Function of
 3009 mitochondrial Stat3 in cellular respiration. *Science* 323: 793-797, 2009.
- 3010 266. **Heusch G, Musiolik J, Gedik N, and Skyschally A.** Mitochondrial STAT3 activation and
 3011 cardioprotection by ischemic postconditioning in pigs with regional myocardial ischemia/reperfusion. *Circulation*
 3012 *research* 109: 1302-1308, 2011.
- 3013 267. **Hibert P, Prunier-Mirebeau D, Beseme O, Chwastyniak M, Tamareille S, Lamou D, Furber A,**
 3014 **Pinet F, and Prunier F.** Apolipoprotein a-I is a potential mediator of remote ischemic preconditioning. *PLoS One*
 3015 8: e77211, 2013.
- 3016 268. **Kalakech H, Hibert P, Prunier-Mirebeau D, Tamareille S, Letournel F, Macchi L, Pinet F, Furber**
 3017 **A, and Prunier F.** RISK and SAFE signaling pathway involvement in apolipoprotein A-I-induced
 3018 cardioprotection. *PLoS One* 9: e107950, 2014.
- 3019 269. **Burley DS, Ferdinandy P, and Baxter GF.** Cyclic GMP and protein kinase-G in myocardial ischaemia-
 3020 reperfusion: opportunities and obstacles for survival signaling. *Br J Pharmacol* 152: 855-869, 2007.
- 3021 270. **Cohen MV, and Downey JM.** Cardioprotection: spotlight on PKG. *Br J Pharmacol* 152: 833-834, 2007.
- 3022 271. **Penna C, Rastaldo R, Mancardi D, Raimondo S, Cappello S, Gattullo D, Losano G, and Pagliaro P.**
 3023 Post-conditioning induced cardioprotection requires signaling through a redox-sensitive mechanism,
 3024 mitochondrial ATP-sensitive K⁺ channel and protein kinase C activation. *Basic Res Cardiol* 101: 180-189, 2006.
- 3025 272. **Inserte J, Barba I, Poncelas-Nozal M, Hernando V, Agullo L, Ruiz-Meana M, and Garcia-Dorado**
 3026 **D.** cGMP/PKG pathway mediates myocardial postconditioning protection in rat hearts by delaying normalization
 3027 of intracellular acidosis during reperfusion. *J Mol Cell Cardiol* 50: 903-909, 2011.
- 3028 273. **Inserte J, Hernando V, Vilardosa U, Abad E, Poncelas-Nozal M, and Garcia-Dorado D.** Activation
 3029 of cGMP/protein kinase G pathway in postconditioned myocardium depends on reduced oxidative stress and
 3030 preserved endothelial nitric oxide synthase coupling. *J Am Heart Assoc* 2: e005975, 2013.
- 3031 274. **Fan Q, Yang XC, Liu Y, Wang LF, Liu SH, Ge YG, Chen ML, Wang W, Zhang LK, Irwin MG,**
 3032 **and Xia Z.** Postconditioning attenuates myocardial injury by reducing nitro-oxidative stress in vivo in rats and in
 3033 humans. *Clin Sci (Lond)* 120: 251-261, 2011.

- 3034 275. **Juhaszova M, Zorov DB, Kim SH, Pepe S, Fu Q, Fishbein KW, Ziman BD, Wang S, Ytrehus K,**
3035 **Antos CL, Olson EN, and Sollott SJ.** Glycogen synthase kinase-3beta mediates convergence of protection
3036 signaling to inhibit the mitochondrial permeability transition pore. *J Clin Invest* 113: 1535-1549, 2004.
- 3037 276. **Gomez L, Paillard M, Thibault H, Derumeaux G, and Ovize M.** Inhibition of GSK3beta by
3038 postconditioning is required to prevent opening of the mitochondrial permeability transition pore during
3039 reperfusion. *Circulation* 117: 2761-2768, 2008.
- 3040 277. **Nishino Y, Webb IG, Davidson SM, Ahmed AI, Clark JE, Jacquet S, Shah AM, Miura T, Yellon**
3041 **DM, Avkiran M, and Marber MS.** Glycogen synthase kinase-3 inactivation is not required for ischemic
3042 preconditioning or postconditioning in the mouse. *Circulation research* 103: 307-314, 2008.
- 3043 278. **Skyschally A, van Caster P, Boengler K, Gres P, Musiolik J, Schilawa D, Schulz R, and Heusch G.**
3044 Ischemic postconditioning in pigs: no causal role for RISK activation. *Circulation research* 104: 15-18, 2009.
- 3045 279. **Lim SY, and Hausenloy DJ.** Remote ischemic conditioning: from bench to bedside. *Front Physiol* 3: 27,
3046 2012.
- 3047 280. **Przyklenk K, and Whittaker P.** Remote ischemic preconditioning: current knowledge, unresolved
3048 questions, and future priorities. *J Cardiovasc Pharmacol Ther* 16: 255-259, 2011.
- 3049 281. **Przyklenk K, and Whittaker P.** Genesis of remote conditioning: action at a distance--"hypotheses non
3050 fingo"? *J Cardiovasc Med (Hagerstown)* 14: 180-186, 2013.
- 3051 282. **Dickson EW, Reinhardt CP, Renzi FP, Becker RC, Porcaro WA, and Heard SO.** Ischemic
3052 preconditioning may be transferable via whole blood transfusion: preliminary evidence. *J Thromb Thrombolysis*
3053 8: 123-129, 1999.
- 3054 283. **Veighey K, and Macallister RJ.** Clinical applications of remote ischemic preconditioning. *Cardiol Res*
3055 *Pract* 2012: 620681, 2012.
- 3056 284. **Lim SY, Yellon DM, and Hausenloy DJ.** The neural and humoral pathways in remote limb ischemic
3057 preconditioning. *Basic Res Cardiol* 105: 651-655, 2010.
- 3058 285. **Saxena P, Newman MA, Shehatha JS, Redington AN, and Konstantinov IE.** Remote ischemic
3059 conditioning: evolution of the concept, mechanisms, and clinical application. *J Card Surg* 25: 127-134, 2010.
- 3060 286. **Weber C.** Far from the heart: Receptor cross-talk in remote conditioning. *Nat Med* 16: 760-762, 2010.
- 3061 287. **Serejo FC, Rodrigues LF, Jr., da Silva Tavares KC, de Carvalho AC, and Nascimento JH.**
3062 Cardioprotective properties of humoral factors released from rat hearts subject to ischemic preconditioning. *J*
3063 *Cardiovasc Pharmacol* 49: 214-220, 2007.
- 3064 288. **Huffman LC, Koch SE, and Butler KL.** Coronary effluent from a preconditioned heart activates the
3065 JAK-STAT pathway and induces cardioprotection in a donor heart. *Am J Physiol Heart Circ Physiol* 294: H257-
3066 262, 2008.
- 3067 289. **Shimizu M, Tropak M, Diaz RJ, Suto F, Surendra H, Kuzmin E, Li J, Gross G, Wilson GJ, Callahan**
3068 **J, and Redington AN.** Transient limb ischaemia remotely preconditions through a humoral mechanism acting
3069 directly on the myocardium: evidence suggesting cross-species protection. *Clin Sci (Lond)* 117: 191-200, 2009.
- 3070 290. **Skyschally A, Gent S, Amanakis G, Schulte C, Kleinbongard P, and Heusch G.** Across-Species
3071 Transfer of Protection by Remote Ischemic Preconditioning With Species-Specific Myocardial Signal
3072 Transduction by Reperfusion Injury Salvage Kinase and Survival Activating Factor Enhancement Pathways.
3073 *Circulation research* 117: 279-288, 2015.
- 3074 291. **Hepponstall M, Ignjatovic V, Binos S, Monagle P, Jones B, Cheung MH, d'Udekem Y, and**
3075 **Konstantinov IE.** Remote ischemic preconditioning (RIPC) modifies plasma proteome in humans. *PLoS One* 7:
3076 e48284, 2012.
- 3077 292. **Hibert P, Prunier-Mirebeau D, Beseme O, Chwastyniak M, Tamareille S, Pinet F, and Prunier F.**
3078 Modifications in rat plasma proteome after remote ischemic preconditioning (RIPC) stimulus: identification by a
3079 SELDI-TOF-MS approach. *PLoS One* 9: e85669, 2014.
- 3080 293. **Aimo A, Borrelli C, Giannoni A, Pastormerlo LE, Barison A, Mirizzi G, Emdin M, and Passino C.**
3081 Cardioprotection by remote ischemic conditioning: Mechanisms and clinical evidences. *World J Cardiol* 7: 621-
3082 632, 2015.
- 3083 294. **Gill R, Kuriakose R, Gertz ZM, Salloum FN, Xi L, and Kukreja RC.** Remote ischemic
3084 preconditioning for myocardial protection: update on mechanisms and clinical relevance. *Mol Cell Biochem* 402:
3085 41-49, 2015.
- 3086 295. **Donato M, Buchholz B, Rodriguez M, Perez V, Inserte J, Garcia-Dorado D, and Gelpi RJ.** Role of
3087 the parasympathetic nervous system in cardioprotection by remote hindlimb ischaemic preconditioning. *Exp*
3088 *Physiol* 98: 425-434, 2013.
- 3089 296. **Downey JM, Davis AM, and Cohen MV.** Signaling pathways in ischemic preconditioning. *Heart failure*
3090 *reviews* 12: 181-188, 2007.
- 3091 297. **Xin P, Zhu W, Li J, Ma S, Wang L, Liu M, Li J, Wei M, and Redington AN.** Combined local ischemic
3092 postconditioning and remote preconditioning recapitulate cardioprotective effects of local ischemic
3093 preconditioning. *Am J Physiol Heart Circ Physiol* 298: H1819-1831, 2010.

- 3094 298. **Pell TJ, Baxter GF, Yellon DM, and Drew GM.** Renal ischemia preconditions myocardium: role of
3095 adenosine receptors and ATP-sensitive potassium channels. *Am J Physiol* 275: H1542-1547, 1998.
- 3096 299. **Ding YF, Zhang MM, and He RR.** Role of renal nerve in cardioprotection provided by renal ischemic
3097 preconditioning in anesthetized rabbits. *Sheng Li Xue Bao* 53: 7-12, 2001.
- 3098 300. **Mastitskaya S, Marina N, Gourine A, Gilbey MP, Spyer KM, Teschemacher AG, Kasparov S,**
3099 **Trapp S, Ackland GL, and Gourine AV.** Cardioprotection evoked by remote ischaemic preconditioning is
3100 critically dependent on the activity of vagal pre-ganglionic neurones. *Cardiovasc Res* 95: 487-494, 2012.
- 3101 301. **Redington KL, Disenhouse T, Strantzas SC, Gladstone R, Wei C, Tropak MB, Dai X, Manlihot C,**
3102 **Li J, and Redington AN.** Remote cardioprotection by direct peripheral nerve stimulation and topical capsaicin is
3103 mediated by circulating humoral factors. *Basic Res Cardiol* 107: 241, 2012.
- 3104 302. **Schoemaker RG, and van Heijningen CL.** Bradykinin mediates cardiac preconditioning at a distance.
3105 *Am J Physiol Heart Circ Physiol* 278: H1571-1576, 2000.
- 3106 303. **Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, and MacAllister**
3107 **RJ.** Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion
3108 injury in humans: role of the autonomic nervous system. *J Am Coll Cardiol* 46: 450-456, 2005.
- 3109 304. **Pedersen CM, Schmidt MR, Barnes G, Botker HE, Kharbanda RK, Newby DE, and Cruden NL.**
3110 Bradykinin does not mediate remote ischaemic preconditioning or ischaemia-reperfusion injury in vivo in man.
3111 *Heart* 97: 1857-1861, 2011.
- 3112 305. **Bernhagen J.** Protective cardiac conditioning by an atypical cytokine. *Clin Sci (Lond)* 133: 933-937,
3113 2019.
- 3114 306. **Konstantinov IE, Arab S, Kharbanda RK, Li J, Cheung MM, Cherepanov V, Downey GP, Liu PP,**
3115 **Cukerman E, Coles JG, and Redington AN.** The remote ischemic preconditioning stimulus modifies
3116 inflammatory gene expression in humans. *Physiol Genomics* 19: 143-150, 2004.
- 3117 307. **Boersma E, Maas AC, Deckers JW, and Simoons ML.** Early thrombolytic treatment in acute
3118 myocardial infarction: reappraisal of the golden hour. *Lancet* 348: 771-775, 1996.
- 3119 308. **Mewton N, Thibault H, Roubille F, Lairez O, Rioufol G, Sportouch C, Sanchez I, Bergerot C, Cung**
3120 **TT, Finet G, Angoulvant D, Revel D, Bonnefoy-Cudraz E, Elbaz M, Piot C, Sagraoui I, Croisille P, and**
3121 **Ovize M.** Postconditioning attenuates no-reflow in STEMI patients. *Basic Res Cardiol* 108: 383, 2013.
- 3122 309. **Thibault H, Piot C, and Ovize M.** Postconditioning in man. *Heart failure reviews* 12: 245-248, 2007.
- 3123 310. **Zhao ZQ, Morris CD, Budde JM, Wang NP, Muraki S, Sun HY, and Guyton RA.** Inhibition of
3124 myocardial apoptosis reduces infarct size and improves regional contractile dysfunction during reperfusion.
3125 *Cardiovasc Res* 59: 132-142, 2003.
- 3126 311. **Zhang Y, Kohler K, Xu J, Lu D, Braun T, Schlitt A, Buerke M, Muller-Werdan U, Werdan K, and**
3127 **Ebelt H.** Inhibition of p53 after acute myocardial infarction: Reduction of apoptosis is counteracted by disturbed
3128 scar formation and cardiac rupture. *J Mol Cell Cardiol* 2010.
- 3129 312. **Barsukevich V, Basalay M, Sanchez J, Mrochek A, Whittle J, Ackland GL, Gourine AV, and**
3130 **Gourine A.** Distinct cardioprotective mechanisms of immediate, early and delayed ischaemic postconditioning.
3131 *Basic Res Cardiol* 110: 452, 2015.
- 3132 313. **Basalay M, Barsukevich V, Mastitskaya S, Mrochek A, Pernow J, Sjoquist PO, Ackland GL,**
3133 **Gourine AV, and Gourine A.** Remote ischaemic pre- and delayed postconditioning - similar degree of
3134 cardioprotection but distinct mechanisms. *Exp Physiol* 97: 908-917, 2012.
- 3135 314. **Tan H, Lin D, Wang Z, Yang Y, and Ma J.** Cardioprotective time-window of Penethylidide
3136 hydrochloride postconditioning: A rat study. *Eur J Pharmacol* 812: 48-56, 2017.
- 3137 315. **Zuurbier CJ, Abbate A, Cabrera-Fuentes HA, Cohen MV, Collino M, De Kleijn DPV, Downey JM,**
3138 **Pagliari P, Preissner KT, Takahashi M, and Davidson SM.** Innate immunity as a target for acute
3139 cardioprotection. *Cardiovasc Res* 115: 1131-1142, 2019.
- 3140 316. **Trankle C, Thurber CJ, Toldo S, and Abbate A.** Mitochondrial Membrane Permeability Inhibitors in
3141 Acute Myocardial Infarction: Still Awaiting Translation. *JACC Basic Transl Sci* 1: 524-535, 2016.
- 3142 317. **Bakhta O, Blanchard S, Guihot AL, Tamareille S, Mirebeau-Prunier D, Jeannin P, and Prunier F.**
3143 Cardioprotective Role of Colchicine Against Inflammatory Injury in a Rat Model of Acute Myocardial Infarction.
3144 *J Cardiovasc Pharmacol Ther* 23: 446-455, 2018.
- 3145 318. **Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, Leclercq F, Macia JC,**
3146 **Gervasoni R, Cung TT, Cade S, Cransac F, Labour J, Dupuy AM, and Roubille F.** COLIN trial: Value of
3147 colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. *Arch*
3148 *Cardiovasc Dis* 110: 395-402, 2017.
- 3149 319. **Fujisue K, Sugamura K, Kurokawa H, Matsubara J, Ishii M, Izumiya Y, Kaikita K, and Sugiyama**
3150 **S.** Colchicine Improves Survival, Left Ventricular Remodeling, and Chronic Cardiac Function After Acute
3151 Myocardial Infarction. *Circ J* 81: 1174-1182, 2017.
- 3152 320. **Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G,**
3153 **Goudevenos J, Alexopoulos D, Pyrgakis V, Cleman MW, Manolis AS, Tousoulis D, and Lekakis J.** Anti-

- 3154 Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. *Circulation* 132: 1395-
3155 1403, 2015.
- 3156 321. **Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, Ivanos F, Dubreuil O, Biere L,**
3157 **Hayek A, Derimay F, Akodad M, Alos B, Haider L, El Jonhy N, Daw R, De Bourguignon C, Dhelens C,**
3158 **Finet G, Bonnefoy-Cudraz E, Bidaux G, Boutitie F, Maucort-Boulch D, Croisille P, Rioufol G, Prunier F,**
3159 **and Angoulvant D.** Effect of Colchicine on Myocardial Injury in Acute Myocardial Infarction. *Circulation* 144:
3160 859-869, 2021.
- 3161 322. **Bouabdallaoui N, Tardif JC, Waters DD, Pinto FJ, Maggioni AP, Diaz R, Berry C, Koenig W,**
3162 **Lopez-Sendon J, Gamra H, Kiwan GS, Blondeau L, Orfanos A, Ibrahim R, Grégoire JC, Dubé MP, Samuel**
3163 **M, Morel O, Lim P, Bertrand OF, Kouz S, Guertin MC, L'Allier PL, and Roubille F.** Time-to-treatment
3164 initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular
3165 Outcomes Trial (COLCOT). *Eur Heart J* 41: 4092-4099, 2020.
- 3166 323. **Hausenloy DJ, Garcia-Dorado D, Botker HE, Davidson SM, Downey J, Engel FB, Jennings R,**
3167 **Lecour S, Leor J, Madonna R, Ovize M, Perrino C, Prunier F, Schulz R, Sluijter JPG, Van Laake LW,**
3168 **Vinten-Johansen J, Yellon DM, Ytrehus K, Heusch G, and Ferdinandy P.** Novel targets and future strategies
3169 for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular
3170 Biology of the Heart. *Cardiovasc Res* 113: 564-585, 2017.
- 3171 324. **Lecour S, Bøtker HE, Condorelli G, Davidson SM, Garcia-Dorado D, Engel FB, Ferdinandy P,**
3172 **Heusch G, Madonna R, Ovize M, Ruiz-Meana M, Schulz R, Sluijter JP, Van Laake LW, Yellon DM, and**
3173 **Hausenloy DJ.** ESC working group cellular biology of the heart: position paper: improving the preclinical
3174 assessment of novel cardioprotective therapies. *Cardiovasc Res* 104: 399-411, 2014.
- 3175 325. **Davidson SM, Ferdinandy P, Andreadou I, Botker HE, Heusch G, Ibanez B, Ovize M, Schulz R,**
3176 **Yellon DM, Hausenloy DJ, Garcia-Dorado D, and Action CC.** Multitarget Strategies to Reduce Myocardial
3177 Ischemia/Reperfusion Injury: JACC Review Topic of the Week. *J Am Coll Cardiol* 73: 89-99, 2019.
- 3178 326. **Friedenstein AJ, Piatetzky S, II, and Petrakova KV.** Osteogenesis in transplants of bone marrow cells.
3179 *J Embryol Exp Morphol* 16: 381-390, 1966.
- 3180 327. **Friedenstein AJ, Chailakhjan RK, and Lalykina KS.** The development of fibroblast colonies in
3181 monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet* 3: 393-403, 1970.
- 3182 328. **Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, Deans RJ,**
3183 **Krause DS, Keating A, and International Society for Cellular T.** Clarification of the nomenclature for MSC:
3184 The International Society for Cellular Therapy position statement. *Cytotherapy* 7: 393-395, 2005.
- 3185 329. **Colter DC, Sekiya I, and Prockop DJ.** Identification of a subpopulation of rapidly self-renewing and
3186 multipotential adult stem cells in colonies of human marrow stromal cells. *Proc Natl Acad Sci U S A* 98: 7841-
3187 7845, 2001.
- 3188 330. **Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim**
3189 **P, and Hedrick MH.** Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 13: 4279-4295,
3190 2002.
- 3191 331. **Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, Taureau C, Cousin B, Abbal M,**
3192 **Laharrague P, Penicaud L, Casteilla L, and Blancher A.** Immunomodulatory effect of human adipose tissue-
3193 derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol* 129: 118-129,
3194 2005.
- 3195 332. **Corre J, Barreau C, Cousin B, Chavoïn JP, Caton D, Fournial G, Penicaud L, Casteilla L, and**
3196 **Laharrague P.** Human subcutaneous adipose cells support complete differentiation but not self-renewal of
3197 hematopoietic progenitors. *J Cell Physiol* 208: 282-288, 2006.
- 3198 333. **Huang GT, Sonoyama W, Chen J, and Park SH.** In vitro characterization of human dental pulp cells:
3199 various isolation methods and culturing environments. *Cell Tissue Res* 324: 225-236, 2006.
- 3200 334. **Alsalameh S, Amin R, Gemba T, and Lotz M.** Identification of mesenchymal progenitor cells in normal
3201 and osteoarthritic human articular cartilage. *Arthritis Rheum* 50: 1522-1532, 2004.
- 3202 335. **De Bari C, Dell'Accio F, Tylzanowski P, and Luyten FP.** Multipotent mesenchymal stem cells from
3203 adult human synovial membrane. *Arthritis and rheumatism* 44: 1928-1942, 2001.
- 3204 336. **Salingerboriboon R, Yoshitake H, Tsuji K, Obinata M, Amagasa T, Nifuji A, and Noda M.**
3205 Establishment of tendon-derived cell lines exhibiting pluripotent mesenchymal stem cell-like property. *Exp Cell*
3206 *Res* 287: 289-300, 2003.
- 3207 337. **Monsanto MM, White KS, Kim T, Wang BJ, Fisher K, Ilves K, Khalafalla FG, Casillas A,**
3208 **Broughton K, Mohsin S, Dembitsky WP, and Sussman MA.** Concurrent Isolation of 3 Distinct Cardiac Stem
3209 Cell Populations From a Single Human Heart Biopsy. *Circ Res* 121: 113-124, 2017.
- 3210 338. **Karoubi G, Cortes-Dericks L, Breyer I, Schmid RA, and Dutly AE.** Identification of mesenchymal
3211 stromal cells in human lung parenchyma capable of differentiating into aquaporin 5-expressing cells. *Laboratory*
3212 *investigation; a journal of technical methods and pathology* 89: 1100-1114, 2009.

- 3213 339. **Tran TC, Kimura K, Nagano M, Yamashita T, Ohneda K, Sugimori H, Sato F, Sakakibara Y,**
3214 **Hamada H, Yoshikawa H, Hoang SN, and Ohneda O.** Identification of human placenta-derived mesenchymal
3215 stem cells involved in re-endothelialization. *J Cell Physiol* 226: 224-235, 2011.
- 3216 340. **Sibov TT, Severino P, Marti LC, Pavon LF, Oliveira DM, Tobo PR, Campos AH, Paes AT, Amaro**
3217 **E, Jr., L FG, and Moreira-Filho CA.** Mesenchymal stem cells from umbilical cord blood: parameters for
3218 isolation, characterization and adipogenic differentiation. *Cytotechnology* 64: 511-521, 2012.
- 3219 341. **Wang HS, Hung SC, Peng ST, Huang CC, Wei HM, Guo YJ, Fu YS, Lai MC, and Chen CC.**
3220 Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. *Stem cells* 22: 1330-1337, 2004.
- 3221 342. **Gucciardo L, Lories R, Ochsenbein-Kolble N, Done E, Zwijsen A, and Deprest J.** Fetal mesenchymal
3222 stem cells: isolation, properties and potential use in perinatology and regenerative medicine. *BJOG* 116: 166-172,
3223 2009.
- 3224 343. **Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating**
3225 **A, Prockop D, and Horwitz E.** Minimal criteria for defining multipotent mesenchymal stromal cells. The
3226 International Society for Cellular Therapy position statement. *Cytotherapy* 8: 315-317, 2006.
- 3227 344. **Viswanathan S, Shi Y, Galipeau J, Krampera M, Leblanc K, Martin I, Nolte J, Phinney DG, and**
3228 **Sensebe L.** Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®)
3229 Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy* 21: 1019-1024, 2019.
- 3230 345. **Renese L, Pierro M, Cobey KD, Mital R, Nangle K, Shorr R, Lalu MM, and Thébaud B.** Definition
3231 and Characteristics of Mesenchymal Stromal Cells in Preclinical and Clinical Studies: A Scoping Review. *Stem*
3232 *Cells Transl Med* 11: 44-54, 2022.
- 3233 346. **Dennis JE, and Charbord P.** Origin and differentiation of human and murine stroma. *Stem cells* 20:
3234 205-214, 2002.
- 3235 347. **Takashima Y, Era T, Nakao K, Kondo S, Kasuga M, Smith AG, and Nishikawa S.** Neuroepithelial
3236 cells supply an initial transient wave of MSC differentiation. *Cell* 129: 1377-1388, 2007.
- 3237 348. **Isern J, Garcia-Garcia A, Martin AM, Arranz L, Martin-Perez D, Torroja C, Sanchez-Cabo F, and**
3238 **Mendez-Ferrer S.** The neural crest is a source of mesenchymal stem cells with specialized hematopoietic stem
3239 cell niche function. *eLife* 3: e03696, 2014.
- 3240 349. **Sowa Y, Imura T, Numajiri T, Takeda K, Mabuchi Y, Matsuzaki Y, and Nishino K.** Adipose stromal
3241 cells contain phenotypically distinct adipogenic progenitors derived from neural crest. *PLoS one* 8: e84206, 2013.
- 3242 350. **Tang W, Martik ML, Li Y, and Bronner ME.** Cardiac neural crest contributes to cardiomyocytes in
3243 amniotes and heart regeneration in zebrafish. *eLife* 8: 2019.
- 3244 351. **Cavanaugh AM, Huang J, and Chen JN.** Two developmentally distinct populations of neural crest cells
3245 contribute to the zebrafish heart. *Dev Biol* 404: 103-112, 2015.
- 3246 352. **Mohamed-Ahmed S, Fristad I, Lie SA, Suliman S, Mustafa K, Vindenes H, and Idris SB.** Adipose-
3247 derived and bone marrow mesenchymal stem cells: a donor-matched comparison. *Stem cell research & therapy* 9:
3248 168, 2018.
- 3249 353. **Reinisch A, Etchart N, Thomas D, Hofmann NA, Fruehwirth M, Sinha S, Chan CK, Senarath-Yapa**
3250 **K, Seo EY, Wearda T, Hartwig UF, Beham-Schmid C, Trajanoski S, Lin Q, Wagner W, Dullin C, Alves F,**
3251 **Andreoff M, Weissman IL, Longaker MT, Schallmoser K, Majeti R, and Strunk D.** Epigenetic and in vivo
3252 comparison of diverse MSC sources reveals an endochondral signature for human hematopoietic niche formation.
3253 *Blood* 125: 249-260, 2015.
- 3254 354. **Schellenberg A, Stiehl T, Horn P, Jousen S, Pallua N, Ho AD, and Wagner W.** Population dynamics
3255 of mesenchymal stromal cells during culture expansion. *Cytotherapy* 14: 401-411, 2012.
- 3256 355. **Mattar P, and Bieback K.** Comparing the Immunomodulatory Properties of Bone Marrow, Adipose
3257 Tissue, and Birth-Associated Tissue Mesenchymal Stromal Cells. *Front Immunol* 6: 560, 2015.
- 3258 356. **Li JZ, Cao TH, Han JC, Qu H, Jiang SQ, Xie BD, Yan XL, Wu H, Liu XL, Zhang F, Leng XP,**
3259 **Kang K, and Jiang SL.** Comparison of adipose and bone marrow-derived stem cells in protecting against
3260 oxLDL-induced inflammation in M1 macrophage-derived foam cells. *Mol Med Rep* 19: 2660-2670, 2019.
- 3261 357. **Baksh D, Yao R, and Tuan RS.** Comparison of proliferative and multilineage differentiation potential
3262 of human mesenchymal stem cells derived from umbilical cord and bone marrow. *Stem cells* 25: 1384-1392, 2007.
- 3263 358. **Baksh D, Song L, and Tuan RS.** Adult mesenchymal stem cells: characterization, differentiation, and
3264 application in cell and gene therapy. *Journal of cellular and molecular medicine* 8: 301-316, 2004.
- 3265 359. **Muraglia A, Cancedda R, and Quarto R.** Clonal mesenchymal progenitors from human bone marrow
3266 differentiate in vitro according to a hierarchical model. *J Cell Sci* 113 (Pt 7): 1161-1166, 2000.
- 3267 360. **Luque-Campos N, Contreras-Lopez RA, Jose Paredes-Martinez M, Torres MJ, Bahraoui S, Wei**
3268 **M, Espinoza F, Djouad F, Elizondo-Vega RJ, and Luz-Crawford P.** Mesenchymal Stem Cells Improve
3269 Rheumatoid Arthritis Progression by Controlling Memory T Cell Response. *Front Immunol* 10: 798, 2019.
- 3270 361. **Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El Nakadi B, Banovic**
3271 **M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tenders M,**
3272 **Waldman S, Wijns W, and Terzic A.** Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic

- 3273 stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. *J Am Coll*
 3274 *Cardiol* 61: 2329-2338, 2013.
- 3275 362. **Hare JM, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, Tracy**
 3276 **M, Gherlin E, Johnston PV, Brinker JA, Breton E, Davis-Sproul J, Schulman IH, Byrnes J, Mendizabal**
 3277 **AM, Lowery MH, Rouy D, Altman P, Wong Po Foo C, Ruiz P, Amador A, Da Silva J, McNiece IK, Heldman**
 3278 **AW, George R, and Lardo A.** Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem
 3279 cells delivered by transcatheter injection in patients with ischemic cardiomyopathy: the POSEIDON
 3280 randomized trial. *Jama* 308: 2369-2379, 2012.
- 3281 363. **Bartunek J, Davison B, Sherman W, Povsic T, Henry TD, Gersh B, Metra M, Filippatos G, Hajjar**
 3282 **R, Behfar A, Homsy C, Cotter G, Wijns W, Tendera M, and Terzic A.** Congestive Heart Failure Cardiopoietic
 3283 Regenerative Therapy (CHART-1) trial design. *European journal of heart failure* 18: 160-168, 2016.
- 3284 364. **Gyongyosi M, Blanco J, Marian T, Tron L, Petnehazy O, Petrasi Z, Hemetsberger R, Rodriguez J,**
 3285 **Font G, Pavo IJ, Kertesz I, Balkay L, Pavo N, Posa A, Emri M, Galuska L, Kraitchman DL, Wojta J, Huber**
 3286 **K, and Glogar D.** Serial noninvasive in vivo positron emission tomographic tracking of percutaneously
 3287 intramyocardially injected autologous porcine mesenchymal stem cells modified for transgene reporter gene
 3288 expression. *Circ Cardiovasc Imaging* 1: 94-103, 2008.
- 3289 365. **Noiseux N, Gneccchi M, Lopez-Illasaca M, Zhang L, Solomon SD, Deb A, Dzau VJ, and Pratt RE.**
 3290 Mesenchymal stem cells overexpressing Akt dramatically repair infarcted myocardium and improve cardiac
 3291 function despite infrequent cellular fusion or differentiation. *Mol Ther* 14: 840-850, 2006.
- 3292 366. **Kraitchman DL, Tatsumi M, Gilson WD, Ishimori T, Kedziorek D, Walczak P, Segars WP, Chen**
 3293 **HH, Fritzges D, Izbudak I, Young RG, Marcelino M, Pittenger MF, Solaiyappan M, Boston RC, Tsui BM,**
 3294 **Wahl RL, and Bulte JW.** Dynamic imaging of allogeneic mesenchymal stem cells trafficking to myocardial
 3295 infarction. *Circulation* 112: 1451-1461, 2005.
- 3296 367. **Hill JM, Dick AJ, Raman VK, Thompson RB, Yu ZX, Hinds KA, Pessanha BS, Guttman MA,**
 3297 **Varney TR, Martin BJ, Dunbar CE, McVeigh ER, and Lederman RJ.** Serial cardiac magnetic resonance
 3298 imaging of injected mesenchymal stem cells. *Circulation* 108: 1009-1014, 2003.
- 3299 368. **Hale SL, Dai W, Dow JS, and Kloner RA.** Mesenchymal stem cell administration at coronary artery
 3300 reperfusion in the rat by two delivery routes: a quantitative assessment. *Life Sci* 83: 511-515, 2008.
- 3301 369. **Hou D, Youssef EA, Brinton TJ, Zhang P, Rogers P, Price ET, Yeung AC, Johnstone BH, Yock PG,**
 3302 **and March KL.** Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde
 3303 coronary venous delivery: implications for current clinical trials. *Circulation* 112: 1150-1156, 2005.
- 3304 370. **Zlabinger K, Lukovic D, Hemetsberger R, Gugerell A, Winkler J, Mandic L, Traxler D,**
 3305 **Spannbauer A, Wolbank S, Zanoni G, Kaun C, Posa A, Gyenes A, Petrasi Z, Petnehazy Ö, Repa I, Hofer-**
 3306 **Warbinek R, de Martin R, Gruber F, Charwat S, Huber K, Pavo N, Pavo IJ, Nyolczas N, Kraitchman DL,**
 3307 **and Gyöngyösi M.** Matrix Metalloproteinase-2 Impairs Homing of Intracoronary Delivered Mesenchymal Stem
 3308 Cells in a Porcine Reperfused Myocardial Infarction: Comparison With Intramyocardial Cell Delivery. *Front*
 3309 *Bioeng Biotechnol* 6: 35, 2018.
- 3310 371. **Planat-Benard V, Silvestre JS, Cousin B, André M, Nibbelink M, Tamarat R, Clergue M,**
 3311 **Manneville C, Saillan-Barreau C, Duriez M, Tedgui A, Levy B, Pénicaud L, and Casteilla L.** Plasticity of
 3312 human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. *Circulation* 109:
 3313 656-663, 2004.
- 3314 372. **Sid-Otmane C, Perrault LP, and Ly HQ.** Mesenchymal stem cell mediates cardiac repair through
 3315 autocrine, paracrine and endocrine axes. *J Transl Med* 18: 336, 2020.
- 3316 373. **Hahn JY, Cho HJ, Kang HJ, Kim TS, Kim MH, Chung JH, Bae JW, Oh BH, Park YB, and Kim**
 3317 **HS.** Pre-treatment of mesenchymal stem cells with a combination of growth factors enhances gap junction
 3318 formation, cytoprotective effect on cardiomyocytes, and therapeutic efficacy for myocardial infarction. *J Am Coll*
 3319 *Cardiol* 51: 933-943, 2008.
- 3320 374. **Antonitsis P, Ioannidou-Papagiannaki E, Kaidoglou A, and Papakonstantinou C.** In vitro
 3321 cardiomyogenic differentiation of adult human bone marrow mesenchymal stem cells. The role of 5-azacytidine.
 3322 *Interact Cardiovasc Thorac Surg* 6: 593-597, 2007.
- 3323 375. **Labovsky V, Hofer EL, Feldman L, Fernández Vallone V, García Rivello H, Bayes-Genis A,**
 3324 **Hernando Insúa A, Levin MJ, and Chasseing NA.** Cardiomyogenic differentiation of human bone marrow
 3325 mesenchymal cells: Role of cardiac extract from neonatal rat cardiomyocytes. *Differentiation* 79: 93-101, 2010.
- 3326 376. **Hafez P, Jose S, Chowdhury SR, Ng MH, Ruzymah BH, and Abdul Rahman Mohd R.**
 3327 Cardiomyogenic differentiation of human sternal bone marrow mesenchymal stem cells using a combination of
 3328 basic fibroblast growth factor and hydrocortisone. *Cell Biol Int* 40: 55-64, 2016.
- 3329 377. **Valina C, Pinkernell K, Song YH, Bai X, Sadat S, Campeau RJ, Le Jemtel TH, and Alt E.**
 3330 Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function,
 3331 perfusion, and remodelling after acute myocardial infarction. *Eur Heart J* 28: 2667-2677, 2007.

- 3332 378. **Wang X, Zhen L, Miao H, Sun Q, Yang Y, Que B, Lopes Lao EP, Wu X, Ren H, Shi S, Lau WB,**
 3333 **Ma X, Ma C, and Nie S.** Concomitant Retrograde Coronary Venous Infusion of Basic Fibroblast Growth Factor
 3334 Enhances Engraftment and Differentiation of Bone Marrow Mesenchymal Stem Cells for Cardiac Repair after
 3335 Myocardial Infarction. *Theranostics* 5: 995-1006, 2015.
- 3336 379. **Ward MR, Abadeh A, and Connelly KA.** Concise Review: Rational Use of Mesenchymal Stem Cells
 3337 in the Treatment of Ischemic Heart Disease. *Stem Cells Transl Med* 7: 543-550, 2018.
- 3338 380. **Shabbir A, Zisa D, Suzuki G, and Lee T.** Heart failure therapy mediated by the trophic activities of
 3339 bone marrow mesenchymal stem cells: a noninvasive therapeutic regimen. *Am J Physiol Heart Circ Physiol* 296:
 3340 H1888-1897, 2009.
- 3341 381. **Cai B, Tan X, Zhang Y, Li X, Wang X, Zhu J, Wang Y, Yang F, Wang B, Liu Y, Xu C, Pan Z,**
 3342 **Wang N, Yang B, and Lu Y.** Mesenchymal Stem Cells and Cardiomyocytes Interplay to Prevent Myocardial
 3343 Hypertrophy. *Stem Cells Transl Med* 4: 1425-1435, 2015.
- 3344 382. **Philipp D, Holthaus M, Basoah V, Pfannkuche K, Suhr L, Wahlers T, and P funnel-Görgülü A.**
 3345 VEGF Contributes to Mesenchymal Stem Cell-Mediated Reversion of Nor1-Dependent Hypertrophy in iPS Cell-
 3346 Derived Cardiomyocytes. *Stem Cells Int* 2021: 8888575, 2021.
- 3347 383. **Tang JM, Wang JN, Zhang L, Zheng F, Yang JY, Kong X, Guo LY, Chen L, Huang YZ, Wan Y,**
 3348 **and Chen SY.** VEGF/SDF-1 promotes cardiac stem cell mobilization and myocardial repair in the infarcted heart.
 3349 *Cardiovasc Res* 91: 402-411, 2011.
- 3350 384. **Song YS, Joo HW, Park IH, Shen GY, Lee Y, Shin JH, Kim H, and Kim KS.** Bone marrow
 3351 mesenchymal stem cell-derived vascular endothelial growth factor attenuates cardiac apoptosis via regulation of
 3352 cardiac miRNA-23a and miRNA-92a in a rat model of myocardial infarction. *PloS one* 12: e0179972, 2017.
- 3353 385. **Davis ME, Hsieh PC, Takahashi T, Song Q, Zhang S, Kamm RD, Grodzinsky AJ, Anversa P, and**
 3354 **Lee RT.** Local myocardial insulin-like growth factor 1 (IGF-1) delivery with biotinylated peptide nanofibers
 3355 improves cell therapy for myocardial infarction. *Proc Natl Acad Sci U S A* 103: 8155-8160, 2006.
- 3356 386. **Wang L, Ma W, Markovich R, Lee WL, and Wang PH.** Insulin-like growth factor I modulates
 3357 induction of apoptotic signaling in H9C2 cardiac muscle cells. *Endocrinology* 139: 1354-1360, 1998.
- 3358 387. **Hao CN, Geng YJ, Li F, Yang T, Su DF, Duan JL, and Li Y.** Insulin-like growth factor-1 receptor
 3359 activation prevents hydrogen peroxide-induced oxidative stress, mitochondrial dysfunction and apoptosis.
 3360 *Apoptosis* 16: 1118-1127, 2011.
- 3361 388. **Zhang GW, Gu TX, Guan XY, Sun XJ, Qi X, Li XY, Wang XB, Lv F, Yu L, Jiang DQ, and Tang**
 3362 **R.** HGF and IGF-1 promote protective effects of allogeneic BMSC transplantation in rabbit model of acute
 3363 myocardial infarction. *Cell Prolif* 48: 661-670, 2015.
- 3364 389. **Pumberger M, Qazi TH, Ehrentraut MC, Textor M, Kueper J, Stoltenburg-Didinger G, Winkler**
 3365 **T, von Roth P, Reinke S, Borselli C, Perka C, Mooney DJ, Duda GN, and Geißler S.** Synthetic niche to
 3366 modulate regenerative potential of MSCs and enhance skeletal muscle regeneration. *Biomaterials* 99: 95-108, 2016.
- 3367 390. **Zhang J, Cado D, Chen A, Kabra NH, and Winoto A.** Fas-mediated apoptosis and activation-induced
 3368 T-cell proliferation are defective in mice lacking FADD/Mort1. *Nature* 392: 296-300, 1998.
- 3369 391. **Li HX, Lin J, Jiang B, and Yang XJ.** Wnt11 preserves mitochondrial membrane potential and protects
 3370 cardiomyocytes against hypoxia through paracrine signaling. *J Cell Biochem* 121: 1144-1155, 2020.
- 3371 392. **Iwai-Kanai E, Hasegawa K, Fujita M, Araki M, Yanazume T, Adachi S, and Sasayama S.** Basic
 3372 fibroblast growth factor protects cardiac myocytes from iNOS-mediated apoptosis. *J Cell Physiol* 190: 54-62, 2002.
- 3373 393. **Fujimoto Y, Yokozeki T, Yokoyama A, and Tabata Y.** Basic fibroblast growth factor enhances
 3374 proliferation and hepatocyte growth factor expression of feline mesenchymal stem cells. *Regen Ther* 15: 10-17,
 3375 2020.
- 3376 394. **Nawrocka D, Kornicka K, Szydlarska J, and Marycz K.** Basic Fibroblast Growth Factor Inhibits
 3377 Apoptosis and Promotes Proliferation of Adipose-Derived Mesenchymal Stromal Cells Isolated from Patients with
 3378 Type 2 Diabetes by Reducing Cellular Oxidative Stress. *Oxid Med Cell Longev* 2017: 3027109, 2017.
- 3379 395. **Song H, Kwon K, Lim S, Kang SM, Ko YG, Xu Z, Chung JH, Kim BS, Lee H, Joung B, Park S,**
 3380 **Choi D, Jang Y, Chung NS, Yoo KJ, and Hwang KC.** Transfection of mesenchymal stem cells with the FGF-2
 3381 gene improves their survival under hypoxic conditions. *Mol Cells* 19: 402-407, 2005.
- 3382 396. **Zhao L, Liu X, Zhang Y, Liang X, Ding Y, Xu Y, Fang Z, and Zhang F.** Enhanced cell survival and
 3383 paracrine effects of mesenchymal stem cells overexpressing hepatocyte growth factor promote cardioprotection in
 3384 myocardial infarction. *Exp Cell Res* 344: 30-39, 2016.
- 3385 397. **O'Brien CG, Ozen MO, Ikeda G, Vaskova E, Jung JH, Bayardo N, Santoso MR, Shi L, Wahlquist**
 3386 **C, Jiang Z, Jung Y, Zeng Y, Egan E, Sinclair R, Gee A, Witteles R, Mercola M, Svensson KJ, Demirci U,**
 3387 **and Yang PC.** Mitochondria-Rich Extracellular Vesicles Rescue Patient-Specific Cardiomyocytes From
 3388 Doxorubicin Injury: Insights Into the SENECA Trial. *JACC CardioOncol* 3: 428-440, 2021.
- 3389 398. **Wen Z, Mai Z, Zhu X, Wu T, Chen Y, Geng D, and Wang J.** Mesenchymal stem cell-derived exosomes
 3390 ameliorate cardiomyocyte apoptosis in hypoxic conditions through microRNA144 by targeting the PTEN/AKT
 3391 pathway. *Stem Cell Res Ther* 11: 36, 2020.

- 3392 399. **Tao L, Huang X, Xu M, Yang L, and Hua F.** MiR-144 protects the heart from hyperglycemia-induced
 3393 injury by regulating mitochondrial biogenesis and cardiomyocyte apoptosis. *Faseb j* 34: 2173-2197, 2020.
- 3394 400. **Wang S, Li L, Liu T, Jiang W, and Hu X.** miR-19a/19b-loaded exosomes in combination with
 3395 mesenchymal stem cell transplantation in a preclinical model of myocardial infarction. *Regen Med* 15: 1749-1759,
 3396 2020.
- 3397 401. **Huang L, Yang L, Ding Y, Jiang X, Xia Z, and You Z.** Human umbilical cord mesenchymal stem cells-
 3398 derived exosomes transfers microRNA-19a to protect cardiomyocytes from acute myocardial infarction by
 3399 targeting SOX6. *Cell Cycle* 19: 339-353, 2020.
- 3400 402. **Luther KM, Haar L, McGuinness M, Wang Y, Lynch Iv TL, Phan A, Song Y, Shen Z, Gardner G,
 3401 Kuffel G, Ren X, Zilliox MJ, and Jones WK.** Exosomal miR-21a-5p mediates cardioprotection by mesenchymal
 3402 stem cells. *J Mol Cell Cardiol* 119: 125-137, 2018.
- 3403 403. **Feng Y, Huang W, Wani M, Yu X, and Ashraf M.** Ischemic preconditioning potentiates the protective
 3404 effect of stem cells through secretion of exosomes by targeting Mecp2 via miR-22. *PLoS One* 9: e88685, 2014.
- 3405 404. **Cheng H, Chang S, Xu R, Chen L, Song X, Wu J, Qian J, Zou Y, and Ma J.** Hypoxia-challenged
 3406 MSC-derived exosomes deliver miR-210 to attenuate post-infarction cardiac apoptosis. *Stem Cell Res Ther* 11:
 3407 224, 2020.
- 3408 405. **Sánchez-Sánchez R, Gómez-Ferrer M, Reinal I, Buigues M, Villanueva-Bádenas E, Ontoria-Oviedo
 3409 I, Hernández A, González-King H, Peiró-Molina E, Dorronsoro A, and Sepúlveda P.** miR-4732-3p in
 3410 Extracellular Vesicles From Mesenchymal Stromal Cells Is Cardioprotective During Myocardial Ischemia. *Front
 3411 Cell Dev Biol* 9: 734143, 2021.
- 3412 406. **Peng Y, Zhao JL, Peng ZY, Xu WF, and Yu GL.** Exosomal miR-25-3p from mesenchymal stem cells
 3413 alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2. *Cell Death Dis* 11: 317, 2020.
- 3414 407. **Rustom A, Saffrich R, Markovic I, Walther P, and Gerdes HH.** Nanotubular highways for
 3415 intercellular organelle transport. *Science* 303: 1007-1010, 2004.
- 3416 408. **Liu K, Ji K, Guo L, Wu W, Lu H, Shan P, and Yan C.** Mesenchymal stem cells rescue injured
 3417 endothelial cells in an in vitro ischemia-reperfusion model via tunneling nanotube like structure-mediated
 3418 mitochondrial transfer. *Microvasc Res* 92: 10-18, 2014.
- 3419 409. **Zhang Y, Yu Z, Jiang D, Liang X, Liao S, Zhang Z, Yue W, Li X, Chiu SM, Chai YH, Liang Y,
 3420 Chow Y, Han S, Xu A, Tse HF, and Lian Q.** iPSC-MSCs with High Intrinsic MIRO1 and Sensitivity to TNF-
 3421 alpha Yield Efficacious Mitochondrial Transfer to Rescue Anthracycline-Induced Cardiomyopathy. *Stem Cell
 3422 Reports* 7: 749-763, 2016.
- 3423 410. **Ham PB, 3rd, and Raju R.** Mitochondrial function in hypoxic ischemic injury and influence of aging.
 3424 *Prog Neurobiol* 157: 92-116, 2017.
- 3425 411. **Konari N, Nagaishi K, Kikuchi S, and Fujimiya M.** Mitochondria transfer from mesenchymal stem
 3426 cells structurally and functionally repairs renal proximal tubular epithelial cells in diabetic nephropathy in vivo.
 3427 *Scientific reports* 9: 5184, 2019.
- 3428 412. **Mahrouf-Yorgov M, Augeul L, Da Silva CC, Jourdan M, Rigolet M, Manin S, Ferrera R, Ovize M,
 3429 Henry A, Guguin A, Meningaud JP, Dubois-Rande JL, Motterlini R, Foresti R, and Rodriguez AM.**
 3430 Mesenchymal stem cells sense mitochondria released from damaged cells as danger signals to activate their rescue
 3431 properties. *Cell Death Differ* 24: 1224-1238, 2017.
- 3432 413. **Deng R, Liu Y, He H, Zhang H, Zhao C, Cui Z, Hong Y, Li X, Lin F, Yuan D, Liang X, and Zhang
 3433 Y.** Haemin pre-treatment augments the cardiac protection of mesenchymal stem cells by inhibiting mitochondrial
 3434 fission and improving survival. *J Cell Mol Med* 24: 431-440, 2020.
- 3435 414. **Delarosa O, Dalemans W, and Lombardo E.** Toll-like receptors as modulators of mesenchymal stem
 3436 cells. *Front Immunol* 3: 182, 2012.
- 3437 415. **Najar M, Krayem M, Meuleman N, Bron D, and Lagneaux L.** Mesenchymal Stromal Cells and Toll-
 3438 Like Receptor Priming: A Critical Review. *Immune Netw* 17: 89-102, 2017.
- 3439 416. **Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, Zhao RC, and Shi Y.** Mesenchymal stem cell-
 3440 mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. *Cell stem cell* 2: 141-
 3441 150, 2008.
- 3442 417. **Van Linthout S, Savvatis K, Miteva K, Peng J, Ringe J, Warstat K, Schmidt-Lucke C, Sittlinger M,
 3443 Schultheiss HP, and Tschöpe C.** Mesenchymal stem cells improve murine acute coxsackievirus B3-induced
 3444 myocarditis. *Eur Heart J* 32: 2168-2178, 2011.
- 3445 418. **Sheng H, Wang Y, Jin Y, Zhang Q, Zhang Y, Wang L, Shen B, Yin S, Liu W, Cui L, and Li N.** A
 3446 critical role of IFN γ in priming MSC-mediated suppression of T cell proliferation through up-regulation of
 3447 B7-H1. *Cell Res* 18: 846-857, 2008.
- 3448 419. **Ren G, Zhao X, Zhang L, Zhang J, L'Huillier A, Ling W, Roberts AI, Le AD, Shi S, Shao C, and
 3449 Shi Y.** Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1
 3450 in mesenchymal stem cells are critical for immunosuppression. *J Immunol* 184: 2321-2328, 2010.

- 3451 420. **Németh K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG,**
 3452 **Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, and Mezey E.** Bone marrow stromal
 3453 cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their
 3454 interleukin-10 production. *Nat Med* 15: 42-49, 2009.
- 3455 421. **Selvasandran K, Makhoul G, Jaiswal PK, Jurakhan R, Li L, Ridwan K, and Cecere R.** A Tumor
 3456 Necrosis Factor- α and Hypoxia-Induced Secretome Therapy for Myocardial Repair. *Ann Thorac Surg* 105: 715-
 3457 723, 2018.
- 3458 422. **Contreras-Lopez R, Elizondo-Vega R, Luque-Campos N, Torres MJ, Pradenas C, Tejedor G,**
 3459 **Paredes-Martínez MJ, Vega-Letter AM, Campos-Mora M, Rigual-Gonzalez Y, Oyarce K, Salgado M,**
 3460 **Jorgensen C, Khoury M, Garcia-Robles M, Altamirano C, Djouad F, and Luz-Crawford P.** The ATP
 3461 synthase inhibition induces an AMPK-dependent glycolytic switch of mesenchymal stem cells that enhances their
 3462 immunotherapeutic potential. *Theranostics* 11: 445-460, 2021.
- 3463 423. **Jitschin R, Böttcher M, Saul D, Lukassen S, Bruns H, Loschinski R, Ekici AB, Reis A, Mackensen**
 3464 **A, and Mougiakakos D.** Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem
 3465 cells via STAT1 glycosylation. *Leukemia* 33: 1783-1796, 2019.
- 3466 424. **Liu Y, Yuan X, Muñoz N, Logan TM, and Ma T.** Commitment to Aerobic Glycolysis Sustains
 3467 Immunosuppression of Human Mesenchymal Stem Cells. *Stem Cells Transl Med* 8: 93-106, 2019.
- 3468 425. **Contreras-Lopez R, Elizondo-Vega R, Paredes MJ, Luque-Campos N, Torres MJ, Tejedor G,**
 3469 **Vega-Letter AM, Figueroa-Valdés A, Pradenas C, Oyarce K, Jorgensen C, Khoury M, Garcia-Robles MLA,**
 3470 **Altamirano C, Djouad F, and Luz-Crawford P.** HIF1 α -dependent metabolic reprogramming governs
 3471 mesenchymal stem/stromal cell immunoregulatory functions. *Faseb j* 34: 8250-8264, 2020.
- 3472 426. **Zhang Y, Yu Z, Jiang D, Liang X, Liao S, Zhang Z, Yue W, Li X, Chiu SM, Chai YH, Liang Y,**
 3473 **Chow Y, Han S, Xu A, Tse HF, and Lian Q.** iPSC-MSCs with High Intrinsic MIRO1 and Sensitivity to TNF- α
 3474 Yield Efficacious Mitochondrial Transfer to Rescue Anthracycline-Induced Cardiomyopathy. *Stem Cell Reports*
 3475 7: 749-763, 2016.
- 3476 427. **Luz-Crawford P, Hernandez J, Djouad F, Luque-Campos N, Caicedo A, Carrère-Kremer S,**
 3477 **Brondello JM, Vignais ML, Pène J, and Jorgensen C.** Mesenchymal stem cell repression of Th17 cells is
 3478 triggered by mitochondrial transfer. *Stem Cell Res Ther* 10: 232, 2019.
- 3479 428. **Court AC, Le-Gatt A, Luz-Crawford P, Parra E, Aliaga-Tobar V, Bátiz LF, Contreras RA, Ortúzar**
 3480 **MI, Kurte M, Elizondo-Vega R, Maracaja-Coutinho V, Pino-Lagos K, Figueroa FE, and Khoury M.**
 3481 Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response.
 3482 *EMBO Rep* 21: e48052, 2020.
- 3483 429. **Kim EJ, Kim S, Kang DO, and Seo HS.** Metabolic activity of the spleen and bone marrow in patients
 3484 with acute myocardial infarction evaluated by 18f-fluorodeoxyglucose positron emission tomographic imaging.
 3485 *Circ Cardiovasc Imaging* 7: 454-460, 2014.
- 3486 430. **Fang L, Moore XL, Dart AM, and Wang LM.** Systemic inflammatory response following acute
 3487 myocardial infarction. *J Geriatr Cardiol* 12: 305-312, 2015.
- 3488 431. **Sattler K, El-Batrawy I, Zhao Z, Schrottenberg C, Yücel G, Lan H, Li X, Lang S, Zimmermann**
 3489 **WH, Cyganek L, Utikal J, Wieland T, Ravens U, Bieback K, Borggreffe M, Zhou X, and Akin I.** Serum of
 3490 patients with acute myocardial infarction prevents inflammation in iPSC-cardiomyocytes. *Sci Rep* 9: 5651, 2019.
- 3491 432. **Auletta JJ, Deans RJ, and Bartholomew AM.** Emerging roles for multipotent, bone marrow-derived
 3492 stromal cells in host defense. *Blood* 119: 1801-1809, 2012.
- 3493 433. **Joshi J, and Kothapalli CR.** Role of Inflammatory Niche and Adult Cardiomyocyte Coculture on
 3494 Differentiation, Matrix Synthesis, and Secretome Release by Human Bone Marrow Mesenchymal Stem Cells.
 3495 *Appl Biochem Biotechnol* 194: 1938-1954, 2022.
- 3496 434. **Guo J, Zheng D, Li WF, Li HR, Zhang AD, and Li ZC.** Insulin-like growth factor 1 treatment of MSCs
 3497 attenuates inflammation and cardiac dysfunction following MI. *Inflammation* 37: 2156-2163, 2014.
- 3498 435. **Wang H, Sun RT, Li Y, Yang YF, Xiao FJ, Zhang YK, Wang SX, Sun HY, Zhang QW, Wu CT,**
 3499 **and Wang LS.** HGF Gene Modification in Mesenchymal Stem Cells Reduces Radiation-Induced Intestinal Injury
 3500 by Modulating Immunity. *PLoS One* 10: e0124420, 2015.
- 3501 436. **Mentkowski KI, Euscher LM, Patel A, Alevriadou BR, and Lang JK.** Monocyte recruitment and fate
 3502 specification after myocardial infarction. *Am J Physiol Cell Physiol* 319: C797-c806, 2020.
- 3503 437. **Lambert JM, Lopez EF, and Lindsey ML.** Macrophage roles following myocardial infarction. *Int J*
 3504 *Cardiol* 130: 147-158, 2008.
- 3505 438. **Miteva K, Pappritz K, El-Shafeey M, Dong F, Ringe J, Tschöpe C, and Van Linthout S.**
 3506 Mesenchymal Stromal Cells Modulate Monocytes Trafficking in Cocksackievirus B3-Induced Myocarditis. *Stem*
 3507 *Cells Transl Med* 6: 1249-1261, 2017.
- 3508 439. **Wang Q, Wang K, and Zhao X.** Monocytes recruitment blocking synergizes with mesenchymal stem
 3509 cell transplantation for treating myocardial infarction. *Regen Med* 16: 9-17, 2021.

- 3510 440. **Arslan F, Lai RC, Smeets MB, Akeroyd L, Choo A, Agnor EN, Timmers L, van Rijen HV,**
3511 **Doevendans PA, Pasterkamp G, Lim SK, and de Kleijn DP.** Mesenchymal stem cell-derived exosomes increase
3512 ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent
3513 adverse remodeling after myocardial ischemia/reperfusion injury. *Stem Cell Res* 10: 301-312, 2013.
- 3514 441. **Shao L, Zhang Y, Lan B, Wang J, Zhang Z, Zhang L, Xiao P, Meng Q, Geng YJ, Yu XY, and Li Y.**
3515 MiRNA-Sequence Indicates That Mesenchymal Stem Cells and Exosomes Have Similar Mechanism to Enhance
3516 Cardiac Repair. *Biomed Res Int* 2017: 4150705, 2017.
- 3517 442. **Di Gregoli K, Jenkins N, Salter R, White S, Newby AC, and Johnson JL.** MicroRNA-24 regulates
3518 macrophage behavior and retards atherosclerosis. *Arterioscler Thromb Vasc Biol* 34: 1990-2000, 2014.
- 3519 443. **Maegdefessel L, Spin JM, Raaz U, Eken SM, Toh R, Azuma J, Adam M, Nakagami F, Heymann**
3520 **HM, Chernogubova E, Jin H, Roy J, Hultgren R, Caidahl K, Schrepfer S, Hamsten A, Eriksson P,**
3521 **McConnell MV, Dalman RL, and Tsao PS.** miR-24 limits aortic vascular inflammation and murine abdominal
3522 aneurysm development. *Nat Commun* 5: 5214, 2014.
- 3523 444. **Qiao S, Zhang W, Yin Y, Wei Z, Chen F, Zhao J, Sun X, Mu D, Xie J, and Xu B.** Extracellular
3524 vesicles derived from Krüppel-Like Factor 2-overexpressing endothelial cells attenuate myocardial ischemia-
3525 reperfusion injury by preventing Ly6C(high) monocyte recruitment. *Theranostics* 10: 11562-11579, 2020.
- 3526 445. **Djouad F, Plence P, Bony C, Tropel P, Apparailly F, Sany J, Noel D, and Jorgensen C.**
3527 Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. *Blood* 102:
3528 3837-3844, 2003.
- 3529 446. **Bocelli-Tyndall C, Bracci L, Spagnoli G, Braccini A, Bouchenaki M, Ceredig R, Pistoia V, Martin**
3530 **I, and Tyndall A.** Bone marrow mesenchymal stromal cells (BM-MSCs) from healthy donors and auto-immune
3531 disease patients reduce the proliferation of autologous- and allogeneic-stimulated lymphocytes in vitro.
3532 *Rheumatology (Oxford)* 46: 403-408, 2007.
- 3533 447. **Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, Apparailly F, Cantos C, Jorgensen**
3534 **C, and Noel D.** Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-
3535 dependent mechanism. *Stem cells* 25: 2025-2032, 2007.
- 3536 448. **Aggarwal S, and Pittenger MF.** Human mesenchymal stem cells modulate allogeneic immune cell
3537 responses. *Blood* 105: 1815-1822, 2005.
- 3538 449. **Francois M, Romieu-Mourez R, Li M, and Galipeau J.** Human MSC suppression correlates with
3539 cytokine induction of indoleamine 2,3-dioxygenase and bystander M2 macrophage differentiation. *Mol Ther* 20:
3540 187-195, 2012.
- 3541 450. **Kim J, and Hematti P.** Mesenchymal stem cell-educated macrophages: a novel type of alternatively
3542 activated macrophages. *Exp Hematol* 37: 1445-1453, 2009.
- 3543 451. **Jarvinen L, Badri L, Wettlaufer S, Ohtsuka T, Standiford TJ, Toews GB, Pinsky DJ, Peters-Golden**
3544 **M, and Lama VN.** Lung resident mesenchymal stem cells isolated from human lung allografts inhibit T cell
3545 proliferation via a soluble mediator. *J Immunol* 181: 4389-4396, 2008.
- 3546 452. **English K, Barry FP, Field-Corbett CP, and Mahon BP.** IFN-gamma and TNF-alpha differentially
3547 regulate immunomodulation by murine mesenchymal stem cells. *Immunol Lett* 110: 91-100, 2007.
- 3548 453. **Melief SM, Schrama E, Brugman MH, Tiemessen MM, Hoogduijn MJ, Fibbe WE, and Roelofs H.**
3549 Multipotent stromal cells induce human regulatory T cells through a novel pathway involving skewing of
3550 monocytes toward anti-inflammatory macrophages. *Stem cells* 31: 1980-1991, 2013.
- 3551 454. **Kalinski P.** Regulation of immune responses by prostaglandin E2. *J Immunol* 188: 21-28, 2012.
- 3552 455. **Sreeramkumar V, Fresno M, and Cuesta N.** Prostaglandin E2 and T cells: friends or foes? *Immunol*
3553 *Cell Biol* 90: 579-586, 2012.
- 3554 456. **Dayan V, Yannarelli G, Billia F, Filomeno P, Wang XH, Davies JE, and Keating A.** Mesenchymal
3555 stromal cells mediate a switch to alternatively activated monocytes/macrophages after acute myocardial infarction.
3556 *Basic Res Cardiol* 106: 1299-1310, 2011.
- 3557 457. **Ben-Mordechai T, Holbova R, Landa-Rouben N, Harel-Adar T, Feinberg MS, Abd Elrahman I,**
3558 **Blum G, Epstein FH, Silman Z, Cohen S, and Leor J.** Macrophage subpopulations are essential for infarct repair
3559 with and without stem cell therapy. *J Am Coll Cardiol* 62: 1890-1901, 2013.
- 3560 458. **Jin L, Deng Z, Zhang J, Yang C, Liu J, Han W, Ye P, Si Y, and Chen G.** Mesenchymal stem cells
3561 promote type 2 macrophage polarization to ameliorate the myocardial injury caused by diabetic cardiomyopathy.
3562 *J Transl Med* 17: 251, 2019.
- 3563 459. **Zhang QZ, Su WR, Shi SH, Wilder-Smith P, Xiang AP, Wong A, Nguyen AL, Kwon CW, and Le**
3564 **AD.** Human gingiva-derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance
3565 cutaneous wound healing. *Stem cells* 28: 1856-1868, 2010.
- 3566 460. **Luz-Crawford P, Djouad F, Toupet K, Bony C, Franquesa M, Hoogduijn MJ, Jorgensen C, and**
3567 **Noel D.** Mesenchymal Stem Cell-Derived Interleukin 1 Receptor Antagonist Promotes Macrophage Polarization
3568 and Inhibits B Cell Differentiation. *Stem cells* 34: 483-492, 2016.

- 3569 461. **Vagnozzi RJ, Maillet M, Sargent MA, Khalil H, Johansen AKZ, Schwanekamp JA, York AJ,**
3570 **Huang V, Nahrendorf M, Sadayappan S, and Molkentin JD.** An acute immune response underlies the benefit
3571 of cardiac stem cell therapy. *Nature* 577: 405-409, 2020.
- 3572 462. **Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, Mohan J, Ivey B, Hsiao HM,**
3573 **Weinheimer C, Kovacs A, Epelman S, Artyomov M, Kreisel D, and Lavine KJ.** Tissue Resident CCR2- and
3574 CCR2+ Cardiac Macrophages Differentially Orchestrate Monocyte Recruitment and Fate Specification Following
3575 Myocardial Injury. *Circulation research* 124: 263-278, 2019.
- 3576 463. **Dick SA, Macklin JA, Nejat S, Momen A, Clemente-Casares X, Althagafi MG, Chen J, Kantores**
3577 **C, Hosseinzadeh S, Aronoff L, Wong A, Zaman R, Barbu I, Besla R, Lavine KJ, Razani B, Ginhoux F,**
3578 **Husain M, Cybulsky MI, Robbins CS, and Epelman S.** Self-renewing resident cardiac macrophages limit
3579 adverse remodeling following myocardial infarction. *Nat Immunol* 20: 29-39, 2019.
- 3580 464. **Chen Y, Zuo J, Chen W, Yang Z, Zhang Y, Hua F, Shao L, Li J, Chen Y, Yu Y, and Shen Z.** The
3581 enhanced effect and underlying mechanisms of mesenchymal stem cells with IL-33 overexpression on myocardial
3582 infarction. *Stem Cell Res Ther* 10: 295, 2019.
- 3583 465. **Kim R, Song BW, Kim M, Kim WJ, Lee HW, Lee MY, Kim J, and Chang W.** Regulation of
3584 alternative macrophage activation by MSCs derived hypoxic conditioned medium, via the TGF- β 1/Smad3
3585 pathway. *BMB Rep* 53: 600-604, 2020.
- 3586 466. **Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard**
3587 **B, Bodine DM, Leri A, and Anversa P.** Bone marrow cells regenerate infarcted myocardium. *Nature* 410: 701-
3588 705, 2001.
- 3589 467. **Shake JG, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, Redmond JM, Pittenger MF, and**
3590 **Martin BJ.** Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional
3591 effects. *Ann Thorac Surg* 73: 1919-1925; discussion 1926, 2002.
- 3592 468. **Toma C, Pittenger MF, Cahill KS, Byrne BJ, and Kessler PD.** Human mesenchymal stem cells
3593 differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation* 105: 93-98, 2002.
- 3594 469. **Zimmet JM, and Hare JM.** Emerging role for bone marrow derived mesenchymal stem cells in
3595 myocardial regenerative therapy. *Basic Res Cardiol* 100: 471-481, 2005.
- 3596 470. **Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, Sano M, Takahashi T, Hori S, Abe**
3597 **H, Hata J, Umezawa A, and Ogawa S.** Cardiomyocytes can be generated from marrow stromal cells in vitro. *J*
3598 *Clin Invest* 103: 697-705, 1999.
- 3599 471. **Tomita S, Li RK, Weisel RD, Mickle DA, Kim EJ, Sakai T, and Jia ZQ.** Autologous transplantation
3600 of bone marrow cells improves damaged heart function. *Circulation* 100: Ii247-256, 1999.
- 3601 472. **Shim WS, Jiang S, Wong P, Tan J, Chua YL, Tan YS, Sin YK, Lim CH, Chua T, Teh M, Liu TC,**
3602 **and Sim E.** Ex vivo differentiation of human adult bone marrow stem cells into cardiomyocyte-like cells. *Biochem*
3603 *Biophys Res Commun* 324: 481-488, 2004.
- 3604 473. **Yoon J, Min BG, Kim YH, Shim WJ, Ro YM, and Lim DS.** Differentiation, engraftment and functional
3605 effects of pre-treated mesenchymal stem cells in a rat myocardial infarct model. *Acta Cardiol* 60: 277-284, 2005.
- 3606 474. **Xia C, and Cao J.** Imaging the survival and utility of pre-differentiated allogeneic MSC in ischemic heart.
3607 *Biochem Biophys Res Commun* 438: 382-387, 2013.
- 3608 475. **Huang XP, Sun Z, Miyagi Y, McDonald Kinkaid H, Zhang L, Weisel RD, and Li RK.** Differentiation
3609 of allogeneic mesenchymal stem cells induces immunogenicity and limits their long-term benefits for myocardial
3610 repair. *Circulation* 122: 2419-2429, 2010.
- 3611 476. **Price MJ, Chou CC, Frantzen M, Miyamoto T, Kar S, Lee S, Shah PK, Martin BJ, Lill M, Forrester**
3612 **JS, Chen PS, and Makkar RR.** Intravenous mesenchymal stem cell therapy early after reperfused acute
3613 myocardial infarction improves left ventricular function and alters electrophysiologic properties. *Int J Cardiol* 111:
3614 231-239, 2006.
- 3615 477. **Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS,**
3616 **Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, and Thys**
3617 **DM.** ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography--summary article: a
3618 report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines
3619 (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J*
3620 *Am Coll Cardiol* 42: 954-970, 2003.
- 3621 478. **Kanelidis AJ, Premer C, Lopez J, Balkan W, and Hare JM.** Route of Delivery Modulates the Efficacy
3622 of Mesenchymal Stem Cell Therapy for Myocardial Infarction: A Meta-Analysis of Preclinical Studies and
3623 Clinical Trials. *Circulation research* 120: 1139-1150, 2017.
- 3624 479. **Jansen Of Lorkeers SJ, Eding JE, Vesterinen HM, van der Spoel TI, Sena ES, Duckers HJ,**
3625 **Doevendans PA, Macleod MR, and Chamuleau SA.** Similar effect of autologous and allogeneic cell therapy for
3626 ischemic heart disease: systematic review and meta-analysis of large animal studies. *Circulation research* 116: 80-
3627 86, 2015.

- 3628 480. **Fan CQ, Leu S, Sheu JJ, Zhen YY, Tsai TH, Chen YL, Chung SY, Chai HT, Sun CK, Yang JL,**
3629 **Chang HW, Ko SF, and Yip HK.** Prompt bone marrow-derived mesenchymal stem cell therapy enables early
3630 porcine heart function recovery from acute myocardial infarction. *Int Heart J* 55: 362-371, 2014.
- 3631 481. **Williams AR, Hatzistergos KE, Addicott B, McCall F, Carvalho D, Suncion V, Morales AR, Da**
3632 **Silva J, Sussman MA, Heldman AW, and Hare JM.** Enhanced effect of combining human cardiac stem cells
3633 and bone marrow mesenchymal stem cells to reduce infarct size and to restore cardiac function after myocardial
3634 infarction. *Circulation* 127: 213-223, 2013.
- 3635 482. **Mazo M, Hernández S, Gavira JJ, Abizanda G, Araña M, López-Martínez T, Moreno C, Merino**
3636 **J, Martino-Rodríguez A, Uixeira A, García de Jalón JA, Pastrana J, Martínez-Caro D, and Prósper F.**
3637 Treatment of reperfused ischemia with adipose-derived stem cells in a preclinical Swine model of myocardial
3638 infarction. *Cell Transplant* 21: 2723-2733, 2012.
- 3639 483. **Wang J, Chen Z, Dai Q, Zhao J, Wei Z, Hu J, Sun X, Xie J, and Xu B.** Intravenously delivered
3640 mesenchymal stem cells prevent microvascular obstruction formation after myocardial ischemia/reperfusion injury.
3641 *Basic Res Cardiol* 115: 40, 2020.
- 3642 484. **Schuleri KH, Amado LC, Boyle AJ, Centola M, Saliaris AP, Gutman MR, Hatzistergos KE,**
3643 **Oskouei BN, Zimmet JM, Young RG, Heldman AW, Lardo AC, and Hare JM.** Early improvement in cardiac
3644 tissue perfusion due to mesenchymal stem cells. *Am J Physiol Heart Circ Physiol* 294: H2002-2011, 2008.
- 3645 485. **Amado LC, Saliaris AP, Schuleri KH, St John M, Xie JS, Cattaneo S, Durand DJ, Fitton T, Kuang**
3646 **JQ, Stewart G, Lehrke S, Baumgartner WW, Martin BJ, Heldman AW, and Hare JM.** Cardiac repair with
3647 intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. *Proc Natl Acad Sci U*
3648 *S A* 102: 11474-11479, 2005.
- 3649 486. **Hatzistergos KE, Quevedo H, Oskouei BN, Hu Q, Feigenbaum GS, Margitich IS, Mazhari R, Boyle**
3650 **AJ, Zambrano JP, Rodriguez JE, Dulce R, Pattany PM, Valdes D, Revilla C, Heldman AW, McNiece I, and**
3651 **Hare JM.** Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation.
3652 *Circulation research* 107: 913-922, 2010.
- 3653 487. **Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, and Ringdén O.** HLA expression and
3654 immunologic properties of differentiated and undifferentiated mesenchymal stem cells. *Exp Hematol* 31: 890-896,
3655 2003.
- 3656 488. **Abu-El-Rub E, Sareen N, Lester Sequiera G, Ammar HI, Yan W, ShamsEldeen AM, Rubinchik I,**
3657 **Moudgil M, Shokry HS, Rashed LA, and Dhingra S.** Hypoxia-induced increase in Sug1 leads to poor post-
3658 transplantation survival of allogeneic mesenchymal stem cells. *Faseb j* 34: 12860-12876, 2020.
- 3659 489. **Luger D, Lipinski MJ, Westman PC, Glover DK, Dimastromatteo J, Frias JC, Albelda MT, Sikora**
3660 **S, Kharazi A, Vertelov G, Waksman R, and Epstein SE.** Intravenously Delivered Mesenchymal Stem Cells:
3661 Systemic Anti-Inflammatory Effects Improve Left Ventricular Dysfunction in Acute Myocardial Infarction and
3662 Ischemic Cardiomyopathy. *Circulation research* 120: 1598-1613, 2017.
- 3663 490. **Chen SL, Fang WW, Qian J, Ye F, Liu YH, Shan SJ, Zhang JJ, Lin S, Liao LM, and Zhao RC.**
3664 Improvement of cardiac function after transplantation of autologous bone marrow mesenchymal stem cells in
3665 patients with acute myocardial infarction. *Chin Med J (Engl)* 117: 1443-1448, 2004.
- 3666 491. **Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, and Dreka K.** Challenges and
3667 Controversies in Human Mesenchymal Stem Cell Therapy. *Stem Cells Int* 2019: 9628536, 2019.
- 3668 492. **Gao LR, Pei XT, Ding QA, Chen Y, Zhang NK, Chen HY, Wang ZG, Wang YF, Zhu ZM, Li TC,**
3669 **Liu HL, Tong ZC, Yang Y, Nan X, Guo F, Shen JL, Shen YH, Zhang JJ, Fei YX, Xu HT, Wang LH, Tian**
3670 **HT, Liu DQ, and Yang Y.** A critical challenge: dosage-related efficacy and acute complication intracoronary
3671 injection of autologous bone marrow mesenchymal stem cells in acute myocardial infarction. *Int J Cardiol* 168:
3672 3191-3199, 2013.
- 3673 493. **Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, Gerstenblith G, DeMaria**
3674 **AN, Denktas AE, Gammon RS, Hermiller JB, Jr., Reisman MA, Schaer GL, and Sherman W.** A randomized,
3675 double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells
3676 (prochymal) after acute myocardial infarction. *J Am Coll Cardiol* 54: 2277-2286, 2009.
- 3677 494. **Chullikana A, Majumdar AS, Gottipamula S, Krishnamurthy S, Kumar AS, Prakash VS, and**
3678 **Gupta PK.** Randomized, double-blind, phase I/II study of intravenous allogeneic mesenchymal stromal cells in
3679 acute myocardial infarction. *Cytotherapy* 17: 250-261, 2015.
- 3680 495. **Gao LR, Chen Y, Zhang NK, Yang XL, Liu HL, Wang ZG, Yan XY, Wang Y, Zhu ZM, Li TC,**
3681 **Wang LH, Chen HY, Chen YD, Huang CL, Qu P, Yao C, Wang B, Chen GH, Wang ZM, Xu ZY, Bai J, Lu**
3682 **D, Shen YH, Guo F, Liu MY, Yang Y, Ding YC, Yang Y, Tian HT, Ding QA, Li LN, Yang XC, and Hu X.**
3683 Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-
3684 blind, randomized controlled trial. *BMC Med* 13: 162, 2015.
- 3685 496. **Kim SH, Cho JH, Lee YH, Lee JH, Kim SS, Kim MY, Lee MG, Kang WY, Lee KS, Ahn YK, Jeong**
3686 **MH, and Kim HS.** Improvement in Left Ventricular Function with Intracoronary Mesenchymal Stem Cell

- 3687 Therapy in a Patient with Anterior Wall ST-Segment Elevation Myocardial Infarction. *Cardiovasc Drugs Ther* 32:
3688 329-338, 2018.
- 3689 497. **Lee JW, Lee SH, Youn YJ, Ahn MS, Kim JY, Yoo BS, Yoon J, Kwon W, Hong IS, Lee K, Kwan J,**
3690 **Park KS, Choi D, Jang YS, and Hong MK.** A randomized, open-label, multicenter trial for the safety and
3691 efficacy of adult mesenchymal stem cells after acute myocardial infarction. *J Korean Med Sci* 29: 23-31, 2014.
- 3692 498. **Penn MS, Ellis S, Gandhi S, Greenbaum A, Hodes Z, Mendelsohn FO, Strasser D, Ting AE, and**
3693 **Sherman W.** Adventitial delivery of an allogeneic bone marrow-derived adherent stem cell in acute myocardial
3694 infarction: phase I clinical study. *Circulation research* 110: 304-311, 2012.
- 3695 499. **Rodrigo SF, van Ramshorst J, Hoogslag GE, Boden H, Velders MA, Cannegieter SC, Roelofs H, Al**
3696 **Younis I, Dibbets-Schneider P, Fibbe WE, Zwaginga JJ, Bax JJ, Schaliij MJ, Beerens SL, and Atsma DE.**
3697 Intramyocardial injection of autologous bone marrow-derived ex vivo expanded mesenchymal stem cells in acute
3698 myocardial infarction patients is feasible and safe up to 5 years of follow-up. *J Cardiovasc Transl Res* 6: 816-825,
3699 2013.
- 3700 500. **Wang X, Xi WC, and Wang F.** The beneficial effects of intracoronary autologous bone marrow stem
3701 cell transfer as an adjunct to percutaneous coronary intervention in patients with acute myocardial infarction.
3702 *Biotechnol Lett* 36: 2163-2168, 2014.
- 3703 501. **Zhang R, Yu J, Zhang N, Li W, Wang J, Cai G, Chen Y, Yang Y, and Liu Z.** Bone marrow
3704 mesenchymal stem cells transfer in patients with ST-segment elevation myocardial infarction: single-blind,
3705 multicenter, randomized controlled trial. *Stem Cell Res Ther* 12: 33, 2021.
- 3706 502. **Houtgraaf JH, den Dekker WK, van Dalen BM, Springeling T, de Jong R, van Geuns RJ, Geleijnse**
3707 **ML, Fernandez-Aviles F, Zijlsta F, Serruys PW, and Duckers HJ.** First experience in humans using adipose
3708 tissue-derived regenerative cells in the treatment of patients with ST-segment elevation myocardial infarction. *J*
3709 *Am Coll Cardiol* 59: 539-540, 2012.
- 3710 503. **Attar A, Bahmanzadegan Jahromi F, Kavousi S, Monabati A, and Kazemi A.** Mesenchymal stem
3711 cell transplantation after acute myocardial infarction: a meta-analysis of clinical trials. *Stem Cell Res Ther* 12: 600,
3712 2021.
- 3713 504. **Wang Z, Wang L, Su X, Pu J, Jiang M, and He B.** Rational transplant timing and dose of mesenchymal
3714 stromal cells in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. *Stem*
3715 *Cell Res Ther* 8: 21, 2017.
- 3716 505. **Yu J, Zhang RF, Mao YL, and Zhang H.** Efficacy and Safety of mesenchymal stem cell therapy in
3717 patients with acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials.
3718 *Curr Stem Cell Res Ther* 2021.
- 3719 506. **Yang Z, Zhang F, Ma W, Chen B, Zhou F, Xu Z, Zhang Y, Zhang D, Zhu T, Wang L, Wang H,**
3720 **Ding Z, and Zhang Y.** A novel approach to transplanting bone marrow stem cells to repair human myocardial
3721 infarction: delivery via a noninfarct-related artery. *Cardiovasc Ther* 28: 380-385, 2010.
- 3722 507. **Karantalis V, and Hare JM.** Use of mesenchymal stem cells for therapy of cardiac disease. *Circulation*
3723 *research* 116: 1413-1430, 2015.
- 3724 508. **Wang X, Zhang X, Ren XP, Chen J, Liu H, Yang J, Medvedovic M, Hu Z, and Fan GC.** MicroRNA-
3725 494 targeting both proapoptotic and antiapoptotic proteins protects against ischemia/reperfusion-induced cardiac
3726 injury. *Circulation* 122: 1308-1318, 2010.
- 3727 509. **Musialek P, Mazurek A, Jarocho D, Tekieli L, Szot W, Kostkiewicz M, Banys RP, Urbanczyk M,**
3728 **Kadzielski A, Trystula M, Kijowski J, Zmudka K, Podolec P, and Majka M.** Myocardial regeneration strategy
3729 using Wharton's jelly mesenchymal stem cells as an off-the-shelf 'unlimited' therapeutic agent: results from the
3730 Acute Myocardial Infarction First-in-Man Study. *Postepy Kardiologii Interwencyjnej* 11: 100-107, 2015.
- 3731 510. **Durand N, and Zubair AC.** Autologous versus allogeneic mesenchymal stem cell therapy: The pros and
3732 cons. *Surgery* 171: 1440-1442, 2022.
- 3733 511. **Golpanian S, El-Khorazaty J, Mendizabal A, DiFede DL, Suncion VY, Karantalis V, Fishman JE,**
3734 **Ghersin E, Balkan W, and Hare JM.** Effect of aging on human mesenchymal stem cell therapy in ischemic
3735 cardiomyopathy patients. *J Am Coll Cardiol* 65: 125-132, 2015.
- 3736 512. **Banfi A, Bianchi G, Notaro R, Luzzatto L, Cancedda R, and Quarto R.** Replicative aging and gene
3737 expression in long-term cultures of human bone marrow stromal cells. *Tissue Eng* 8: 901-910, 2002.
- 3738 513. **Kretlow JD, Jin YQ, Liu W, Zhang WJ, Hong TH, Zhou G, Baggett LS, Mikos AG, and Cao Y.**
3739 Donor age and cell passage affects differentiation potential of murine bone marrow-derived stem cells. *BMC Cell*
3740 *Biol* 9: 60, 2008.
- 3741 514. **Yu JM, Wu X, Gimble JM, Guan X, Freitas MA, and Bunnell BA.** Age-related changes in
3742 mesenchymal stem cells derived from rhesus macaque bone marrow. *Aging Cell* 10: 66-79, 2011.
- 3743 515. **Stenderup K, Justesen J, Clausen C, and Kassem M.** Aging is associated with decreased maximal life
3744 span and accelerated senescence of bone marrow stromal cells. *Bone* 33: 919-926, 2003.
- 3745 516. **Yamaguchi S, Horie N, Satoh K, Ishikawa T, Mori T, Maeda H, Fukuda Y, Ishizaka S, Hiu T,**
3746 **Morofuji Y, Izumo T, Nishida N, and Matsuo T.** Age of donor of human mesenchymal stem cells affects

- 3747 structural and functional recovery after cell therapy following ischaemic stroke. *J Cereb Blood Flow Metab* 38:
 3748 1199-1212, 2018.
- 3749 517. **Wu LW, Wang YL, Christensen JM, Khalifian S, Schneeberger S, Raimondi G, Cooney DS, Lee**
 3750 **WP, and Brandacher G.** Donor age negatively affects the immunoregulatory properties of both adipose and bone
 3751 marrow derived mesenchymal stem cells. *Transpl Immunol* 30: 122-127, 2014.
- 3752 518. **Bustos ML, Huleihel L, Kapetanaki MG, Lino-Cardenas CL, Mroz L, Ellis BM, McVerry BJ,**
 3753 **Richards TJ, Kaminski N, Cerdenes N, Mora AL, and Rojas M.** Aging mesenchymal stem cells fail to protect
 3754 because of impaired migration and antiinflammatory response. *Am J Respir Crit Care Med* 189: 787-798, 2014.
- 3755 519. **Hwang I, Jo K, Shin KC, Kim JI, Ji Y, Park YJ, Park J, Jeon YG, Ka S, Suk S, Noh HL, Choe SS,**
 3756 **Alfadda AA, Kim JK, Kim S, and Kim JB.** GABA-stimulated adipose-derived stem cells suppress subcutaneous
 3757 adipose inflammation in obesity. *Proc Natl Acad Sci U S A* 116: 11936-11945, 2019.
- 3758 520. **Schipper BM, Marra KG, Zhang W, Donnenberg AD, and Rubin JP.** Regional anatomic and age
 3759 effects on cell function of human adipose-derived stem cells. *Ann Plast Surg* 60: 538-544, 2008.
- 3760 521. **Kelly IE, Han TS, Walsh K, and Lean ME.** Effects of a thiazolidinedione compound on body fat and
 3761 fat distribution of patients with type 2 diabetes. *Diabetes Care* 22: 288-293, 1999.
- 3762 522. **Nahngoong H, Jeon YG, Park ES, Choi YH, Han SM, Park J, Ji Y, Sohn JH, Han JS, Kim YY,**
 3763 **Hwang I, Lee YK, Huh JY, Choe SS, Oh TJ, Choi SH, Kim JK, and Kim JB.** Distinct properties of adipose
 3764 stem cell subpopulations determine fat depot-specific characteristics. *Cell Metab* 34: 458-472.e456, 2022.
- 3765 523. **Moll G, Alm JJ, Davies LC, von Bahr L, Heldring N, Stenbeck-Funke L, Hamad OA, Hinsch R,**
 3766 **Ignatowicz L, Locke M, Lönnes H, Lambris JD, Teramura Y, Nilsson-Ekdahl K, Nilsson B, and Le Blanc**
 3767 **K.** Do cryopreserved mesenchymal stromal cells display impaired immunomodulatory and therapeutic properties?
 3768 *Stem cells (Dayton, Ohio)* 32: 2430-2442, 2014.
- 3769 524. **Liu L, DiGirolamo CM, Navarro PA, Blasco MA, and Keefe DL.** Telomerase deficiency impairs
 3770 differentiation of mesenchymal stem cells. *Exp Cell Res* 294: 1-8, 2004.
- 3771 525. **Baxter MA, Wynn RF, Jowitt SN, Wraith JE, Fairbairn LJ, and Bellantuono I.** Study of telomere
 3772 length reveals rapid aging of human marrow stromal cells following in vitro expansion. *Stem cells (Dayton, Ohio)*
 3773 22: 675-682, 2004.
- 3774 526. **Ng CP, Sharif AR, Heath DE, Chow JW, Zhang CB, Chan-Park MB, Hammond PT, Chan JK, and**
 3775 **Griffith LG.** Enhanced ex vivo expansion of adult mesenchymal stem cells by fetal mesenchymal stem cell ECM.
 3776 *Biomaterials* 35: 4046-4057, 2014.
- 3777 527. **Zhang L, Mack R, Breslin P, and Zhang J.** Molecular and cellular mechanisms of aging in
 3778 hematopoietic stem cells and their niches. *J Hematol Oncol* 13: 157, 2020.
- 3779 528. **Kim JH, Shin SH, Li TZ, and Suh H.** Influence of in vitro biomimicked stem cell 'niche' for regulation
 3780 of proliferation and differentiation of human bone marrow-derived mesenchymal stem cells to myocardial
 3781 phenotypes: serum starvation without aid of chemical agents and prevention of spontaneous stem cell
 3782 transformation enhanced by the matrix environment. *J Tissue Eng Regen Med* 10: E1-13, 2016.
- 3783 529. **Lechanteur C, Briquet A, Giet O, Delloye O, Baudoux E, and Beguin Y.** Clinical-scale expansion of
 3784 mesenchymal stromal cells: a large banking experience. *J Transl Med* 14: 145, 2016.
- 3785 530. **Madsen SD, Russell KC, Tucker HA, Glowacki J, Bunnell BA, and O'Connor KC.** Decoy TRAIL
 3786 receptor CD264: a cell surface marker of cellular aging for human bone marrow-derived mesenchymal stem cells.
 3787 *Stem Cell Res Ther* 8: 201, 2017.
- 3788 531. **Madsen SD, Jones SH, Tucker HA, Giler MK, Muller DC, Discher CT, Russell KC, Dobek GL,**
 3789 **Sammarco MC, Bunnell BA, and O'Connor KC.** Survival of aging CD264(+) and CD264(-) populations of
 3790 human bone marrow mesenchymal stem cells is independent of colony-forming efficiency. *Biotechnol Bioeng* 117:
 3791 223-237, 2020.
- 3792 532. **Gnani D, Crippa S, Della Volpe L, Rossella V, Conti A, Lettera E, Ravis S, Ometti M, Frascini G,**
 3793 **Bernardo ME, and Di Micco R.** An early-senescence state in aged mesenchymal stromal cells contributes to
 3794 hematopoietic stem and progenitor cell clonogenic impairment through the activation of a pro-inflammatory
 3795 program. *Aging Cell* 18: e12933, 2019.
- 3796 533. **Wangler S, Menzel U, Li Z, Ma J, Hoppe S, Benneker LM, Alini M, Grad S, and Peroglio M.**
 3797 CD146/MCAM distinguishes stem cell subpopulations with distinct migration and regenerative potential in
 3798 degenerative intervertebral discs. *Osteoarthritis Cartilage* 27: 1094-1105, 2019.
- 3799 534. **Al-Azab M, Safi M, Idiattullina E, Al-Shaebi F, and Zaky MY.** Aging of mesenchymal stem cell:
 3800 machinery, markers, and strategies of fighting. *Cell Mol Biol Lett* 27: 69, 2022.
- 3801 535. **Lechanteur C, Briquet A, Bettonville V, Baudoux E, and Beguin Y.** MSC Manufacturing for
 3802 Academic Clinical Trials: From a Clinical-Grade to a Full GMP-Compliant Process. *Cells* 10: 2021.
- 3803 536. **Kilbride P, Lamb S, Gibbons S, Bundy J, Erro E, Selden C, Fuller B, and Morris J.** Cryopreservation
 3804 and re-culture of a 2.3 litre biomass for use in a bioartificial liver device. *PLoS One* 12: e0183385, 2017.
- 3805 537. **Baust JG, Gao D, and Baust JM.** Cryopreservation: An emerging paradigm change. *Organogenesis* 5:
 3806 90-96, 2009.

- 3807 538. **Nanayakkara S, Marwick TH, and Kaye DM.** The ageing heart: the systemic and coronary circulation. *Heart* 104: 370-376, 2018.
- 3808
- 3809 539. **Fabian C, Naaldijk Y, Leovsky C, Johnson AA, Rudolph L, Jaeger C, Arnold K, and Stolzing A.** Distribution pattern following systemic mesenchymal stem cell injection depends on the age of the recipient and neuronal health. *Stem Cell Res Ther* 8: 85, 2017.
- 3810
- 3811
- 3812 540. **Zhang K, Sun H, Cao H, Jia Y, Shu X, Cao H, Zhang Y, and Yang X.** The impact of recipient age on the effects of umbilical cord mesenchymal stem cells on HBV-related acute-on-chronic liver failure and liver cirrhosis. *Stem Cell Res Ther* 12: 466, 2021.
- 3813
- 3814
- 3815 541. **Zhuo Y, Li SH, Chen MS, Wu J, Kinkaid HY, Fazel S, Weisel RD, and Li RK.** Aging impairs the angiogenic response to ischemic injury and the activity of implanted cells: combined consequences for cell therapy in older recipients. *J Thorac Cardiovasc Surg* 139: 1286-1294, 1294.e1281-1282, 2010.
- 3816
- 3817
- 3818 542. **Liang H, Hou H, Yi W, Yang G, Gu C, Lau WB, Gao E, Ma X, Lu Z, Wei X, Pei J, and Yi D.** Increased expression of pigment epithelium-derived factor in aged mesenchymal stem cells impairs their therapeutic efficacy for attenuating myocardial infarction injury. *Eur Heart J* 34: 1681-1690, 2013.
- 3819
- 3820
- 3821 543. **Vessey DA, Kelley M, Li L, and Huang Y.** Sphingosine protects aging hearts from ischemia/reperfusion injury: Superiority to sphingosine 1-phosphate and ischemic pre- and post-conditioning. *Oxid Med Cell Longev* 2: 146-151, 2009.
- 3822
- 3823
- 3824 544. **Boengler K, Schulz R, and Heusch G.** Loss of cardioprotection with ageing. *Cardiovasc Res* 83: 247-261, 2009.
- 3825
- 3826 545. **Ruiz-Meana M, Bou-Teen D, Ferdinandy P, Gyongyosi M, Pesce M, Perrino C, Schulz R, Sluijter JPG, Tocchetti CG, Thum T, and Madonna R.** Cardiomyocyte ageing and cardioprotection: consensus document from the ESC working groups cell biology of the heart and myocardial function. *Cardiovasc Res* 116: 1835-1849, 2020.
- 3827
- 3828
- 3829
- 3830 546. **Zhang Z, Zhao C, Liu B, Liang D, Qin X, Li X, Zhang R, Li C, Wang H, Sun D, and Cao F.** Inositol pyrophosphates mediate the effects of aging on bone marrow mesenchymal stem cells by inhibiting Akt signaling. *Stem Cell Res Ther* 5: 33, 2014.
- 3831
- 3832
- 3833 547. **Penna C, Andreadou I, Aragno M, Beauloye C, Bertrand L, Lazou A, Falcão-Pires I, Bell R, Zurbier CJ, Pagliaro P, and Hausenloy DJ.** Effect of hyperglycaemia and diabetes on acute myocardial ischaemia-reperfusion injury and cardioprotection by ischaemic conditioning protocols. *Br J Pharmacol* 177: 5312-5335, 2020.
- 3834
- 3835
- 3836
- 3837 548. **Paolisso P, Foà A, Bergamaschi L, Angeli F, Fabrizio M, Donati F, Toniolo S, Chiti C, Rinaldi A, Stefanizzi A, Armillotta M, Sansonetti A, Magnani I, Iannopolo G, Rucci P, Casella G, Galiè N, and Pizzi C.** Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA. *Cardiovasc Diabetol* 20: 192, 2021.
- 3838
- 3839
- 3840
- 3841 549. **Wang B, Raedschelders K, Shrivah J, Hui Y, Safaei HG, Chen DD, Cook RC, Fradet G, Au CL, and Ansley DM.** Differences in myocardial PTEN expression and Akt signalling in type 2 diabetic and nondiabetic patients undergoing coronary bypass surgery. *Clin Endocrinol (Oxf)* 74: 705-713, 2011.
- 3842
- 3843
- 3844 550. **Yetgin T, Magro M, Manintveld OC, Nauta ST, Cheng JM, den Uil CA, Simsek C, Hersbach F, van Domburg RT, Boersma E, Serruys PW, Duncker DJ, van Geuns RJ, and Zijlstra F.** Impact of multiple balloon inflations during primary percutaneous coronary intervention on infarct size and long-term clinical outcomes in ST-segment elevation myocardial infarction: real-world postconditioning. *Basic Res Cardiol* 109: 403, 2014.
- 3845
- 3846
- 3847
- 3848
- 3849 551. **Liu Y, Li Z, Liu T, Xue X, Jiang H, Huang J, and Wang H.** Impaired cardioprotective function of transplantation of mesenchymal stem cells from patients with diabetes mellitus to rats with experimentally induced myocardial infarction. *Cardiovasc Diabetol* 12: 40, 2013.
- 3850
- 3851
- 3852 552. **Fan Y, Yang S, Zhang X, Cao Y, and Huang Y.** Comparison of cardioprotective efficacy resulting from a combination of atorvastatin and ischaemic post-conditioning in diabetic and non-diabetic rats. *Clin Exp Pharmacol Physiol* 39: 938-943, 2012.
- 3853
- 3854
- 3855 553. **Sienko D, Klimczak-Tomaniak D, Kulesza A, Symonides H, Kuch M, Paczek L, and Burdzinska A.** The influence of oxygen deprivation and donor age on the effect of statins on human mesenchymal stromal cells. *Tissue Cell* 67: 101427, 2020.
- 3856
- 3857
- 3858 554. **Yang YJ, Qian HY, Huang J, Geng YJ, Gao RL, Dou KF, Yang GS, Li JJ, Shen R, He ZX, Lu MJ, and Zhao SH.** Atorvastatin treatment improves survival and effects of implanted mesenchymal stem cells in post-infarct swine hearts. *Eur Heart J* 29: 1578-1590, 2008.
- 3859
- 3860
- 3861 555. **Song L, Yang YJ, Dong QT, Qian HY, Gao RL, Qiao SB, Shen R, He ZX, Lu MJ, Zhao SH, Geng YJ, and Gersh BJ.** Atorvastatin enhance efficacy of mesenchymal stem cells treatment for swine myocardial infarction via activation of nitric oxide synthase. *PLoS One* 8: e65702, 2013.
- 3862
- 3863
- 3864 556. **Park A, Barrera-Ramirez J, Ranasinghe I, Pilon S, Sy R, Fergusson D, and Allan DS.** Use of Statins to Augment Progenitor Cell Function in Preclinical and Clinical Studies of Regenerative Therapy: a Systematic Review. *Stem Cell Rev Rep* 12: 327-339, 2016.
- 3865
- 3866

- 3867 557. **Mensah K, Mocanu MM, and Yellon DM.** Failure to protect the myocardium against
3868 ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment: a
3869 potential role for phosphatase and tensin homolog deleted on chromosome ten? *J Am Coll Cardiol* 45: 1287-1291,
3870 2005.
- 3871 558. **Sanit J, Prompunt E, Adulyarittikul P, Nokkaew N, Mongkolpathumrat P, Kongpol K,**
3872 **Kijjawornrat A, Petchdee S, Barrere-Lemaire S, and Kumphune S.** Combination of metformin and p38
3873 MAPK inhibitor, SB203580, reduced myocardial ischemia/reperfusion injury in non-obese type 2 diabetic Goto-
3874 Kakizaki rats. *Exp Ther Med* 18: 1701-1714, 2019.
- 3875 559. **Chen Q, Thompson J, Hu Y, and Lesnefsky EJ.** Chronic metformin treatment decreases cardiac injury
3876 during ischemia-reperfusion by attenuating endoplasmic reticulum stress with improved mitochondrial function.
3877 *Aging (Albany NY)* 13: 7828-7845, 2021.
- 3878 560. **Andreadou I, Bell RM, Bøtker HE, and Zuurbier CJ.** SGLT2 inhibitors reduce infarct size in
3879 reperused ischemic heart and improve cardiac function during ischemic episodes in preclinical models. *Biochim*
3880 *Biophys Acta Mol Basis Dis* 1866: 165770, 2020.
- 3881 561. **He X, Yao MW, Zhu M, Liang DL, Guo W, Yang Y, Zhao RS, Ren TT, Ao X, Wang W, Zeng CY,**
3882 **Liang HP, Jiang DP, Yu J, and Xu X.** Metformin induces apoptosis in mesenchymal stromal cells and dampens
3883 their therapeutic efficacy in infarcted myocardium. *Stem Cell Res Ther* 9: 306, 2018.
- 3884 562. **Wolf D, Reinhard A, Seckinger A, Katus HA, Kuecherer H, and Hansen A.** Dose-dependent effects
3885 of intravenous allogeneic mesenchymal stem cells in the infarcted porcine heart. *Stem Cells Dev* 18: 321-329, 2009.
- 3886 563. **Halkos ME, Zhao ZQ, Kerendi F, Wang NP, Jiang R, Schmarkey LS, Martin BJ, Quyyumi AA,**
3887 **Few WL, Kin H, Guyton RA, and Vinten-Johansen J.** Intravenous infusion of mesenchymal stem cells
3888 enhances regional perfusion and improves ventricular function in a porcine model of myocardial infarction. *Basic*
3889 *Res Cardiol* 103: 525-536, 2008.
- 3890 564. **Hashemi SM, Ghods S, Kolodgie FD, Parcham-Azad K, Keane M, Hamamdziec D, Young R, Rippey**
3891 **MK, Virmani R, Litt H, and Wilensky RL.** A placebo controlled, dose-ranging, safety study of allogenic
3892 mesenchymal stem cells injected by endomyocardial delivery after an acute myocardial infarction. *Eur Heart J* 29:
3893 251-259, 2008.
- 3894 565. **Sarre C, Contreras-Lopez R, Nernpermpisooth N, Barrere C, Bahraoui S, Terraza C, Tejedor G,**
3895 **Vincent A, Luz-Crawford P, Kongpol K, Kumphune S, Piot C, Nargeot J, Jorgensen C, Djouad F, and**
3896 **Barrere-Lemaire S.** PPAR β/δ priming enhances the anti-apoptotic and therapeutic properties of mesenchymal
3897 stromal cells in myocardial ischemia-reperfusion injury. *Stem Cell Res Ther* 13: 167, 2022.
- 3898 566. **Razeghian-Jahromi I, Matta AG, Canitrot R, Zibaeezhad MJ, Razmkhah M, Safari A, Nader V,**
3899 **and Roncalli J.** Surfing the clinical trials of mesenchymal stem cell therapy in ischemic cardiomyopathy. *Stem*
3900 *Cell Res Ther* 12: 361, 2021.
- 3901 567. **Attar A, Nouri F, Yazdanshenas A, Hessami K, Vosough M, Abdi-Ardekani A, Izadpanah P, Ramzi**
3902 **M, Kojouri J, Pouladfar G, and Monabati A.** Single vs. double intracoronary injection of mesenchymal stromal
3903 cell after acute myocardial infarction: the study protocol from a randomized clinical trial: BOOSTER-TAHA7
3904 trial. *Trials* 23: 293, 2022.
- 3905 568. **Piper HM, Abdallah Y, and Schäfer C.** The first minutes of reperfusion: a window of opportunity for
3906 cardioprotection. *Cardiovasc Res* 61: 365-371, 2004.
- 3907 569. **Schuleri KH, Feigenbaum GS, Centola M, Weiss ES, Zimmet JM, Turney J, Kellner J, Zviman**
3908 **MM, Hatzistergos KE, Detrick B, Conte JV, McNiece I, Steenbergen C, Lardo AC, and Hare JM.**
3909 Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. *Eur*
3910 *Heart J* 30: 2722-2732, 2009.
- 3911 570. **Tang XL, Wysoczynski M, Gumpert AM, Li Y, Wu WJ, Li H, Stowers H, and Bolli R.** Effect of
3912 intravenous cell therapy in rats with old myocardial infarction. *Mol Cell Biochem* 477: 431-444, 2022.
- 3913 571. **Zhang S, Sun A, Xu D, Yao K, Huang Z, Jin H, Wang K, Zou Y, and Ge J.** Impact of timing on
3914 efficacy and safety of intracoronary autologous bone marrow stem cells transplantation in acute myocardial
3915 infarction: a pooled subgroup analysis of randomized controlled trials. *Clin Cardiol* 32: 458-466, 2009.
- 3916 572. **Perin EC, Silva GV, Assad JA, Vela D, Buja LM, Sousa AL, Litovsky S, Lin J, Vaughn WK, Coulter**
3917 **S, Fernandes MR, and Willerson JT.** Comparison of intracoronary and transendocardial delivery of allogeneic
3918 mesenchymal cells in a canine model of acute myocardial infarction. *J Mol Cell Cardiol* 44: 486-495, 2008.
- 3919 573. **Freyman T, Polin G, Osman H, Cray J, Lu M, Cheng L, Palasis M, and Wilensky RL.** A
3920 quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial
3921 infarction. *Eur Heart J* 27: 1114-1122, 2006.
- 3922 574. **Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori**
3923 **D, Kedes LH, Kloner RA, and Leor J.** Systemic delivery of bone marrow-derived mesenchymal stem cells to
3924 the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation* 108: 863-868, 2003.

- 3925 575. **Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, Semprun-Prieto L, Delafontaine P, and Prockop DJ.** Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. *Cell stem cell* 5: 54-63, 2009.
- 3926 576. **Fischer UM, Harting MT, Jimenez F, Monzon-Posadas WO, Xue H, Savitz SI, Laine GA, and Cox CS, Jr.** Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. *Stem Cells Dev* 18: 683-692, 2009.
- 3927 577. **Crop MJ, Baan CC, Korevaar SS, Ijzermans JN, Pescatori M, Stubbs AP, van Ijcken WF, Dahlke MH, Eggenhofer E, Weimar W, and Hoogduijn MJ.** Inflammatory conditions affect gene expression and function of human adipose tissue-derived mesenchymal stem cells. *Clin Exp Immunol* 162: 474-486, 2010.
- 3928 578. **Gao J, Dennis JE, Muzic RF, Lundberg M, and Caplan AI.** The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion. *Cells Tissues Organs* 169: 12-20, 2001.
- 3929 579. **Penicka M, Widimsky P, Kobylka P, Kozak T, and Lang O.** Images in cardiovascular medicine. Early tissue distribution of bone marrow mononuclear cells after transcatheter transplantation in a patient with acute myocardial infarction. *Circulation* 112: e63-65, 2005.
- 3930 580. **Gersh BJ, Stone GW, White HD, and Holmes DR, Jr.** Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? *Jama* 293: 979-986, 2005.
- 3931 581. **Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, and Stone GW.** Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J* 27: 2400-2405, 2006.
- 3932 582. **Manintveld OC, Te Lintel Hekkert M, van den Bos EJ, Suurenbroek GM, Dekkers DH, Verdouw PD, Lamers JM, and Duncker DJ.** Cardiac effects of postconditioning depend critically on the duration of index ischemia. *Am J Physiol Heart Circ Physiol* 292: H1551-1560, 2007.
- 3933 583. **Golchin A, Shams F, and Karami F.** Advancing Mesenchymal Stem Cell Therapy with CRISPR/Cas9 for Clinical Trial Studies. *Adv Exp Med Biol* 1247: 89-100, 2020.
- 3934 584. **Miwa H, and Era T.** Tracing the destiny of mesenchymal stem cells from embryo to adult bone marrow and white adipose tissue via Pdgfra expression. *Development* 145: 2018.
- 3935 585. **Hass R, Kasper C, Böhm S, and Jacobs R.** Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Commun Signal* 9: 12, 2011.
- 3936 586. **Jin HJ, Bae YK, Kim M, Kwon SJ, Jeon HB, Choi SJ, Kim SW, Yang YS, Oh W, and Chang JW.** Comparative analysis of human mesenchymal stem cells from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. *Int J Mol Sci* 14: 17986-18001, 2013.
- 3937 587. **Mastrolia I, Foppiani EM, Murgia A, Candini O, Samarelli AV, Grisendi G, Veronesi E, Horwitz EM, and Dominici M.** Challenges in Clinical Development of Mesenchymal Stromal/Stem Cells: Concise Review. *Stem Cells Transl Med* 8: 1135-1148, 2019.
- 3938 588. **Shang Y, Guan H, and Zhou F.** Biological Characteristics of Umbilical Cord Mesenchymal Stem Cells and Its Therapeutic Potential for Hematological Disorders. *Front Cell Dev Biol* 9: 570179, 2021.
- 3939 589. **Luo L, Zhou Y, Zhang C, Huang J, Du J, Liao J, Bergholt NL, Bünger C, Xu F, Lin L, Tong G, Zhou G, and Luo Y.** Feeder-free generation and transcriptome characterization of functional mesenchymal stromal cells from human pluripotent stem cells. *Stem Cell Res* 48: 101990, 2020.
- 3940 590. **Kang R, Zhou Y, Tan S, Zhou G, Aagaard L, Xie L, Bünger C, Bolund L, and Luo Y.** Mesenchymal stem cells derived from human induced pluripotent stem cells retain adequate osteogenicity and chondrogenicity but less adipogenicity. *Stem Cell Res Ther* 6: 144, 2015.
- 3941 591. **Pichard L, Brondelo JM, Becker F, Desprat R, De Ceuninck F, Pastoureaux P, Noel D, Jorgensen C, and Lemaitre JM.** Generation of human pluripotent stem cell lines (iPSCs) from mesenchymal stem cells (MSCs) from three elderly patients with osteoarthritis. *Stem Cell Res* 44: 101721, 2020.
- 3942 592. **Zhang J, Chen M, Liao J, Chang C, Liu Y, Padhiar AA, Zhou Y, and Zhou G.** Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Hold Lower Heterogeneity and Great Promise in Biological Research and Clinical Applications. *Front Cell Dev Biol* 9: 716907, 2021.
- 3943 593. **Ozay EI, Vijayaraghavan J, Gonzalez-Perez G, Shanthalingam S, Sherman HL, Garrigan DT, Jr., Chandiran K, Torres JA, Osborne BA, Tew GN, Slukvin, II, Macdonald RA, Kelly K, and Minter LM.** Cymerus™ iPSC-MSCs significantly prolong survival in a pre-clinical, humanized mouse model of Graft-vs-host disease. *Stem Cell Res* 35: 101401, 2019.
- 3944 594. **Saetersmoen ML, Hammer Q, Valamehr B, Kaufman DS, and Malmberg KJ.** Off-the-shelf cell therapy with induced pluripotent stem cell-derived natural killer cells. *Semin Immunopathol* 41: 59-68, 2019.
- 3945 595. **Bloor AJC, Patel A, Griffin JE, Gillece MH, Radia R, Yeung DT, Drier D, Larson LS, Uenishi GI, Hei D, Kelly K, Slukvin I, and Rasko JEJ.** Production, safety and efficacy of iPSC-derived mesenchymal stromal cells in acute steroid-resistant graft versus host disease: a phase I, multicenter, open-label, dose-escalation study. *Nat Med* 26: 1720-1725, 2020.

- 3984 596. **Couto PS, Shatirishvili G, Bersenev A, and Verter F.** First decade of clinical trials and published
3985 studies with mesenchymal stromal cells from umbilical cord tissue. *Regen Med* 14: 309-319, 2019.
- 3986 597. **Ntai A, La Spada A, De Blasio P, and Biunno I.** Trehalose to cryopreserve human pluripotent stem
3987 cells. *Stem Cell Res* 31: 102-112, 2018.
- 3988 598. **He Z, Liu K, and Wang J.** Bioinspired Materials for Controlling Ice Nucleation, Growth, and
3989 Recrystallization. *Acc Chem Res* 51: 1082-1091, 2018.
- 3990 599. **Biggs CI, Bailey TL, Ben G, Stubbs C, Fayter A, and Gibson MI.** Polymer mimics of
3991 biomacromolecular antifreezes. *Nat Commun* 8: 1546, 2017.
- 3992 600. **Singh AK, Jha A, Bit A, Kiassov AP, Rizvanov AA, Ojha A, Bhoi P, Patra PK, Kumar A, and
3993 Bissoyi A.** Selaginella bryopteris Aqueous Extract Improves Stability and Function of Cryopreserved Human
3994 Mesenchymal Stem Cells. *Oxid Med Cell Longev* 2017: 8530656, 2017.
- 3995 601. **Zenhäusern R, Tobler A, Leoncini L, Hess OM, and Ferrari P.** Fatal cardiac arrhythmia after infusion
3996 of dimethyl sulfoxide-cryopreserved hematopoietic stem cells in a patient with severe primary cardiac amyloidosis
3997 and end-stage renal failure. *Ann Hematol* 79: 523-526, 2000.
- 3998 602. **Massood E, Maryam K, Parvin S, Mojgan M, and Nouredin NM.** Vitrification of human umbilical
3999 cord Wharton's jelly-derived mesenchymal stem cells. *Cryo Letters* 34: 471-480, 2013.
- 4000 603. **Fu X, Yan Y, Li S, Wang J, Jiang B, Wang H, Duan Y, Tan T, Gao F, Gong D, Niu Y, Ji W, Zheng
4001 B, and Si W.** Vitrification of Rhesus Macaque Mesenchymal Stem Cells and the Effects on Global Gene
4002 Expression. *Stem Cells Int* 2017: 3893691, 2017.
- 4003 604. **Gao L, Zhou Q, Zhang Y, Sun S, Lv L, Ma P, Yang J, Liu M, Zhang L, Wang X, and Zhan L.**
4004 Dimethyl Sulfoxide-Free Cryopreservation of Human Umbilical Cord Mesenchymal Stem Cells Based on
4005 Zwitterionic Betaine and Electroporation. *Int J Mol Sci* 22: 2021.
- 4006 605. **Hubel A, Spindler R, Curtsinger JM, Lindgren B, Wiederoder S, and McKenna DH.** Postthaw
4007 characterization of umbilical cord blood: markers of storage lesion. *Transfusion* 55: 1033-1039, 2015.
- 4008 606. **Xu Y, Li-Ying Chan L, Chen S, Ying B, Zhang T, Liu W, Guo H, Wang J, Xu Z, Zhang X, and He
4009 X.** Optimization of UC-MSCs cold-chain storage by minimizing temperature fluctuations using an automatic
4010 cryopreservation system. *Cryobiology* 99: 131-139, 2021.
- 4011 607. **François M, Copland IB, Yuan S, Romieu-Mourez R, Waller EK, and Galipeau J.** Cryopreserved
4012 mesenchymal stromal cells display impaired immunosuppressive properties as a result of heat-shock response and
4013 impaired interferon- γ licensing. *Cytotherapy* 14: 147-152, 2012.
- 4014 608. **Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, Dignass A,
4015 Nachury M, Ferrante M, Kazemi-Shirazi L, Grimaud JC, de la Portilla F, Goldin E, Richard MP,
4016 Leselbaum A, and Danese S.** Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex
4017 perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet* 388: 1281-1290,
4018 2016.
- 4019 609. **Galipeau J, and Sensebe L.** Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic
4020 Opportunities. *Cell stem cell* 22: 824-833, 2018.
- 4021 610. **Hu X, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA, and Wei L.** Transplantation of hypoxia-
4022 preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells
4023 and angiogenesis. *J Thorac Cardiovasc Surg* 135: 799-808, 2008.
- 4024 611. **Matta A, Nader V, Lebrin M, Gross F, Prats AC, Cussac D, Galinier M, and Roncalli J.** Pre-
4025 Conditioning Methods and Novel Approaches with Mesenchymal Stem Cells Therapy in Cardiovascular Disease.
4026 *Cells* 11: 2022.
- 4027 612. **Moniz I, Ramalho-Santos J, and Branco AF.** Differential Oxygen Exposure Modulates Mesenchymal
4028 Stem Cell Metabolism and Proliferation through mTOR Signaling. *Int J Mol Sci* 23: 2022.
- 4029 613. **Yu Y, Hu S, Li G, Xue J, Li Z, Liu X, Yang X, Dong B, Wang D, Wang X, Liu S, Liu J, Chen B,
4030 Wang L, Liu S, Chen Q, Shen C, Wang Z, and Wang Y.** Comparative effectiveness of Di'ao Xin Xue Kang
4031 capsule and Compound Danshen tablet in patients with symptomatic chronic stable angina. *Sci Rep* 4: 7058, 2014.
- 4032 614. **He Y, Guo Y, Xia Y, Guo Y, Wang R, Zhang F, Guo L, Liu Y, Yin T, Gao C, Gao E, Li C, Wang S,
4033 Zhang L, Yan W, and Tao L.** Resistin promotes cardiac homing of mesenchymal stem cells and functional
4034 recovery after myocardial ischemia-reperfusion via the ERK1/2-MMP-9 pathway. *Am J Physiol Heart Circ
4035 Physiol* 316: H233-H244, 2019.
- 4036 615. **Hu X, Wu R, Jiang Z, Wang L, Chen P, Zhang L, Yang L, Wu Y, Chen H, Chen H, Xu Y, Zhou Y,
4037 Huang X, Webster KA, Yu H, and Wang J.** Leptin signaling is required for augmented therapeutic properties
4038 of mesenchymal stem cells conferred by hypoxia preconditioning. *Stem cells (Dayton, Ohio)* 32: 2702-2713, 2014.
- 4039 616. **Zhang KJ, Zheng Q, Zhu PC, Tong Q, Zhuang Z, Zhu JZ, Bao XY, Huang YY, Zheng GQ, and
4040 Wang Y.** Traditional Chinese Medicine for Coronary Heart Disease: Clinical Evidence and Possible Mechanisms.
4041 *Front Pharmacol* 10: 844, 2019.
- 4042 617. **Shende P, and Gandhewar N.** Current Trend and Pro-survival Approaches for Augmenting Stem Cell
4043 Viability. *Curr Pharm Biotechnol* 21: 1154-1164, 2020.

- 4044 618. **Esmaeili R, Darbandi-Azar A, Sadeghpour A, Majidzadeh AK, Eini L, Jafarbeik-Iravani N,**
4045 **Hoseinpour P, Vajhi A, Oghabi Bakhshaiesh T, Masoudkabar F, and Sadeghizadeh M.** Mesenchymal Stem
4046 Cells Pretreatment With Stromal-Derived Factor-1 Alpha Augments Cardiac Function and Angiogenesis in
4047 Infarcted Myocardium. *Am J Med Sci* 361: 765-775, 2021.
- 4048 619. **Li N, Yang YJ, Qian HY, Li Q, Zhang Q, Li XD, Dong QT, Xu H, Song L, and Zhang H.** Intravenous
4049 administration of atorvastatin-pretreated mesenchymal stem cells improves cardiac performance after acute
4050 myocardial infarction: role of CXCR4. *Am J Transl Res* 7: 1058-1070, 2015.
- 4051 620. **Sun X, Fang B, Zhao X, Zhang G, and Ma H.** Preconditioning of mesenchymal stem cells by
4052 sevoflurane to improve their therapeutic potential. *PLoS One* 9: e90667, 2014.
- 4053 621. **Jung YH, Lee HJ, Kim JS, Lee SJ, and Han HJ.** EphB2 signaling-mediated Sirt3 expression reduces
4054 MSC senescence by maintaining mitochondrial ROS homeostasis. *Free Radic Biol Med* 110: 368-380, 2017.
- 4055 622. **Li W, Ma N, Ong LL, Nesselmann C, Klopsch C, Ladilov Y, Furlani D, Piechaczek C, Moebius JM,**
4056 **Lützow K, Lendlein A, Stamm C, Li RK, and Steinhoff G.** Bcl-2 engineered MSCs inhibited apoptosis and
4057 improved heart function. *Stem cells (Dayton, Ohio)* 25: 2118-2127, 2007.
- 4058 623. **Liu X, Li X, Zhu W, Zhang Y, Hong Y, Liang X, Fan B, Zhao H, He H, and Zhang F.** Exosomes
4059 from mesenchymal stem cells overexpressing MIF enhance myocardial repair. *J Cell Physiol* 2020.
- 4060 624. **Yu B, Gong M, Wang Y, Millard RW, Pasha Z, Yang Y, Ashraf M, and Xu M.** Cardiomyocyte
4061 protection by GATA-4 gene engineered mesenchymal stem cells is partially mediated by translocation of miR-
4062 221 in microvesicles. *PLoS One* 8: e73304, 2013.
- 4063 625. **Yu B, Kim HW, Gong M, Wang J, Millard RW, Wang Y, Ashraf M, and Xu M.** Exosomes secreted
4064 from GATA-4 overexpressing mesenchymal stem cells serve as a reservoir of anti-apoptotic microRNAs for
4065 cardioprotection. *Int J Cardiol* 182: 349-360, 2015.
- 4066 626. **Wang N, Chen C, Yang D, Liao Q, Luo H, Wang X, Zhou F, Yang X, Yang J, Zeng C, and Wang**
4067 **WE.** Mesenchymal stem cells-derived extracellular vesicles, via miR-210, improve infarcted cardiac function by
4068 promotion of angiogenesis. *Biochim Biophys Acta Mol Basis Dis* 1863: 2085-2092, 2017.
- 4069 627. **de Abreu RC, Fernandes H, da Costa Martins PA, Sahoo S, Emanuelli C, and Ferreira L.** Native
4070 and bioengineered extracellular vesicles for cardiovascular therapeutics. *Nat Rev Cardiol* 17: 685-697, 2020.
- 4071 628. **Barkholt L, Flory E, Jekerle V, Lucas-Samuel S, Ahnert P, Bisset L, Büscher D, Fibbe W, Foussat**
4072 **A, Kwa M, Lantz O, Mačiulaitis R, Palomäki T, Schneider CK, Sensebé L, Tachdjian G, Tarte K, Tosca L,**
4073 **and Salmikangas P.** Risk of tumorigenicity in mesenchymal stromal cell-based therapies--bridging scientific
4074 observations and regulatory viewpoints. *Cytotherapy* 15: 753-759, 2013.
- 4075 629. **Lee JY, Chung J, Byun Y, Kim KH, An SH, and Kwon K.** Mesenchymal Stem Cell-Derived Small
4076 Extracellular Vesicles Protect Cardiomyocytes from Doxorubicin-Induced Cardiomyopathy by Upregulating
4077 Survivin Expression via the miR-199a-3p-Akt-Sp1/p53 Signaling Pathway. *Int J Mol Sci* 22: 2021.
- 4078 630. **Dougherty JA, Mergaye M, Kumar N, Chen CA, Angelos MG, and Khan M.** Potential Role of
4079 Exosomes in Mending a Broken Heart: Nanoshuttles Propelling Future Clinical Therapeutics Forward. *Stem Cells*
4080 *Int* 2017: 5785436, 2017.
- 4081 631. **Prabhu SD, and Frangogiannis NG.** The Biological Basis for Cardiac Repair After Myocardial
4082 Infarction: From Inflammation to Fibrosis. *Circulation research* 119: 91-112, 2016.
- 4083 632. **Chen CW, Wang LL, Zaman S, Gordon J, Arisi MF, Venkataraman CM, Chung JJ, Hung G,**
4084 **Gaffey AC, Spruce LA, Fazelinia H, Gorman RC, Seeholzer SH, Burdick JA, and Atluri P.** Sustained release
4085 of endothelial progenitor cell-derived extracellular vesicles from shear-thinning hydrogels improves angiogenesis
4086 and promotes function after myocardial infarction. *Cardiovasc Res* 114: 1029-1040, 2018.
- 4087 633. **Luo L, Tang J, Nishi K, Yan C, Dinh PU, Cores J, Kudo T, Zhang J, Li TS, and Cheng K.** Fabrication
4088 of Synthetic Mesenchymal Stem Cells for the Treatment of Acute Myocardial Infarction in Mice. *Circulation*
4089 *research* 120: 1768-1775, 2017.
- 4090 634. **Huang P, Wang L, Li Q, Xu J, Xu J, Xiong Y, Chen G, Qian H, Jin C, Yu Y, Liu J, Qian L, and**
4091 **Yang Y.** Combinatorial treatment of acute myocardial infarction using stem cells and their derived exosomes
4092 resulted in improved heart performance. *Stem Cell Res Ther* 10: 300, 2019.
- 4093 635. **Xu JY, Qian HY, Huang PS, Xu J, Xiong YY, Jiang WY, Xu Y, Leng WX, Li XD, Chen GH, Tang**
4094 **RJ, Huang CR, Hu MJ, Jin C, Wu Y, Zhang J, Qian J, Xu B, Zhao SH, Lu MJ, Shen R, Fang W, Wu WC,**
4095 **Chen X, Wang Y, Li W, Lu XF, Jiang XF, Ma CC, Li JW, Geng YJ, Qiao SB, Gao RL, and Yang YJ.**
4096 Transplantation efficacy of autologous bone marrow mesenchymal stem cells combined with atorvastatin for acute
4097 myocardial infarction (TEAM-AMI): rationale and design of a randomized, double-blind, placebo-controlled,
4098 multi-center, Phase II TEAM-AMI trial. *Regen Med* 14: 1077-1087, 2019.
- 4099
4100
4101
4102
4103