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1 **Metabolic reprogramming in atherosclerosis: opposed interplay between the canonical**
2 **WNT/ β -catenin pathway and PPAR γ**
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5 **Running title:** Metabolic reprogramming in atherosclerosis
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Abstract

Atherosclerosis, a chronic inflammatory and age-related disease, is a complex mechanism presenting a dysregulation of vessel structures. During this process, the canonical WNT/ β -catenin pathway is increased whereas PPAR γ is downregulated. The two systems act in an opposite manner. This paper reviews the opposing interplay of these systems and their metabolic-reprogramming pathway in atherosclerosis. Activation of the WNT/ β -catenin pathway enhances the transcription of targets involved in inflammation, endothelial dysfunction, the proliferation of vascular smooth muscle cells, and vascular calcification. This complex mechanism, which is partly controlled by the WNT/ β -catenin pathway, presents several metabolic dysfunctions. This phenomenon, called aerobic glycolysis (or the Warburg effect), consists of a shift in ATP production from mitochondrial oxidative phosphorylation to aerobic glycolysis, leading to the overproduction of intracellular lactate. This mechanism is partially due to the injury of mitochondrial respiration and an increase in the glycolytic pathway. In contrast, PPAR γ agonists downregulate the WNT/ β -catenin pathway. Therefore, the development of therapeutic targets, such as PPAR γ agonists, for the treatment of atherosclerosis could be an interesting and innovative way of counteracting the canonical WNT pathway.

Keywords: WNT pathway; PPAR gamma; atherosclerosis; Warburg effect; aerobic glycolysis

61 **Introduction**

62 Atherosclerosis is a chronic inflammatory and age-related disease [1,2]. The origin of the
63 atherosclerosis process is found in a dysfunction of the endothelial cells (ECs) through the
64 secretion of several inflammatory cytokines/chemokines, leading to the recruitment of peripheral
65 monocytes. Adherence and then aggregation of these monocytes into the subendothelial space of
66 the arterial wall enhance the differentiation of monocytes into macrophages and then into foam
67 cells through the modification of low-density lipoprotein [3]. This accumulation of cholesterol-
68 engorged macrophages, known as foam cells [4], is a major factor in atheromatous plaque
69 formation [5]. The process of atherosclerosis is a complex mechanism that presents a
70 dysregulation of vessel structures. The process is initiated during childhood and progressively
71 develops with age. Three layer structures make up the artery, i.e, tunica intima, media and
72 adventitia. The intima is formed by subendothelial collagen and a single layer of endothelial
73 cells. Endothelial cells are key factors in determining vascular pattern and the recruitment of
74 smooth muscle cells (SMCs) during embryogenesis [6,7]. The intima is particularly important
75 during atherosclerosis due to its physical properties. The media is composed of SMCs and elastin.
76 The elasticity of arterial blood vessels is supported by elastin lamellae, a proteoglycan-rich
77 extracellular matrix, SMCs and collagen fibers. The adventitia is made of a collagen-rich
78 extracellular matrix produced by myofibroblasts [8]. The role of this structure is to prevent
79 rupture of the vessel wall at very high pressures.

80 During the initial stage of atherosclerosis, the accumulation of lipids, SMC infiltration,
81 proliferation and deposition of the extracellular matrix (ECM) occur under the intima [9]. This
82 accumulation leads to a gradual impairment of the vessel through a dysregulation between the
83 three concentric layers. The intima is infiltrated by SMCs and then recruits lymphocytes and
84 macrophages to become an inflammatory site. Inflammation and immunity reactions are then
85 exacerbated by the increased accumulation of cholesterol-rich lipoproteins. An atheromatous
86 plaque is gradually formed and then the vessel lumen can be encroached, leading to diminished
87 blood flow and even myocardial infarction due to coronary artery thrombosis [10–12]. During the
88 final stage, the atheromatous plaques are characterized by an increase in macrophages, the
89 appearance of calcification and a reduction in extracellular matrix (ECM) deposition, which
90 renders them unstable (**Figure 1**) [10,11].

91 The canonical WNT/ β -catenin pathway controls numerous pathways involved in development

92 and tissue homeostasis. The pathway is modulated by transcriptional and post-transcriptional
93 levels. The WNT/ β -catenin pathway is upregulated in atherosclerosis and participates in different
94 stages of this process, from endothelial dysfunction to vascular calcification [12]. Moreover, the
95 canonical WNT/ β -catenin pathway plays a key role in both cell fate decision and inflammation in
96 the initiation of atherosclerosis [13–15].

97 In contrast, the peroxisome proliferator-activated receptor γ (PPAR γ) is downregulated in
98 atherosclerosis [16]. PPAR γ agonists, by inhibiting inflammation and vascular smooth muscle
99 cell (VSMC) proliferation, appear as an interesting therapeutic way of treating numerous
100 diseases, especially cardiovascular diseases [17,18]. In several tissues, activation of the canonical
101 WNT/ β -catenin pathway induces downregulation of PPAR γ , while PPAR γ activation inhibits
102 expression of canonical WNT/ β -catenin signaling [19]. Indeed, PPAR γ agonists induce
103 repression of canonical WNT/ β -catenin signaling in several pathophysiological states. We focus
104 this review on the opposing interplay between the canonical WNT/ β -catenin pathway and PPAR γ
105 in the metabolic-reprogramming pathway during atherosclerosis.

106

107

108 **1. Canonical WNT/ β -catenin pathway**

109 The term WNT refers to Wingless drosophila melanogaster and its mouse homolog, Int. WNT
110 pathway, is involved in numerous signaling and regulating pathways, such as embryogenesis, cell
111 proliferation, migration and polarity, apoptosis, and organogenesis [20]. However, during
112 numerous pathological states, the WNT pathway can be dysregulated by developments such as
113 inflammatory, metabolic and neurological disorders, tissue fibrosis and cancers [21]. Recent
114 studies used the WNT pathway for cell therapy-bioengineering processes [22].

115 WNT ligands are lipoproteins that activate specific co-receptors. These WNT ligands activate the
116 canonical WNT pathway through the action of β -catenin. WNT ligands activate Frizzled (FZD)
117 receptor and low-density lipoprotein receptor-related protein 5 and 6 (LRP 5/6) [23]. The
118 complex formed by extracellular WNT ligands and FZD/LRP5/6 stimulates intracellular
119 Disheveled (DSH). This activation inactivates the destruction complex of β -catenin in the
120 cytosol. β -catenin accumulates in the cytosol and then translocates to the nucleus. Nuclear β -
121 catenin interacts with the T-Cell factor/lymphoid enhancer factor (TCF/LEF) to stimulate gene
122 transcription, such as c-Myc and cyclin D1 [24].

123 During the “off-state” of the WNT/ β -catenin pathway, WNT ligands do not bind FZD and LRP
124 5/6. The β -catenin destruction complex, which is formed by AXIN, APC (adenomatous polyposis
125 coli) and GSK-3 β (glycogen synthase kinase 3 β), phosphorylates the β -catenin. Thus,
126 phosphorylated β -catenin is degraded into the proteasome.

127 Several WNT inhibitors inactivate the canonical WNT/ β -catenin pathway. Activated GSK-3 β is
128 the major inhibitor of the WNT pathway. GSK-3 β is an intracellular serine-threonine kinase which
129 regulates several pathways such as inflammation, neuronal polarity or other cell membrane
130 signaling [25]. GSK-3 β inhibits β -catenin cytosolic stabilization and nuclear migration. Dickkopf
131 (DKK) and soluble Frizzled-related proteins (SFRP) are also WNT inhibitors and bind FZD,
132 LRP5 and LRP6 (**Figure 2**) [26].

133

134

135 **2. PPAR γ**

136 PPARs are ligand-activated transcription factors that bind PPRE (PPAR-response elements). In
137 the nucleus, PPARs form a heterodimer with the retinoid X receptor (RXR) [27]. They are
138 composed of a ligand-binding domain that interacts with a DNA-binding domain to modulate it
139 [28]. PPARs are involved in numerous pathophysiological processes, such as cell differentiation,
140 protein metabolism, lipid metabolism, carcinogenesis [29,30], adipocyte differentiation, insulin
141 sensitivity and inflammation [31,32]. PPARs are subdivided into three isoforms PPAR α , PPAR γ
142 and PPAR β/δ [33]. PPAR γ is highly expressed in adipose tissue and macrophages [16]. PPAR γ
143 ligands can be synthetic or natural. PPAR γ ligands have hypoglycemic and hypocholesterolemic
144 roles, such as glitazones, which have been used in the treatment of type 2 diabetes [34]. PPAR γ
145 ligands, such as thiazolidinediones (TZDs), can also decrease inflammatory activity [34]. Natural
146 ligands include prostaglandins and unsaturated fatty acids [35].

147

148

149 **3. Opposing interplay between PPAR γ and the WNT/ β -catenin pathway**

150 In several diseases, PPAR γ expression is decreased by β -catenin signaling over-activation [36–
151 38]. Indeed, PPAR γ is considered as a negative β -catenin target gene [39,40]. The WNT/ β -
152 catenin pathway and PPAR γ interact through a TCF/LEF domain of β -catenin and a catenin-
153 binding domain within PPAR γ [41,42]. Through this link, a decrease in the WNT/ β -catenin

154 pathway enhances the stimulation of PPAR γ [43], whereas PPAR γ over-expression decreases the
155 β -catenin signaling [44].

156 Numerous studies have shown that the canonical WNT/ β -catenin pathway and PPAR γ act in an
157 opposing manner, such as in cancers, neurodegenerative diseases and fibrosis processes [45–47].

158 PPAR γ agonists are considered to offer promising treatment through the action of this crosstalk
159 [48–50]. Pioglitazone attenuates the expression of WNT/ β -catenin signaling to prevent the
160 development of left ventricular fibrosis [51]. PPAR γ agonists stimulate synaptic plasticity by
161 interacting with the WNT/ β -catenin/PI3K/Akt pathway [52]. Troglitazone, a PPAR γ agonist, can
162 decrease c-Myc levels [53]. PPAR γ agonists activate Dickkopf-1 (DKK1) activity to decrease the
163 canonical WNT/ β -catenin pathway and then inhibit fibroblast differentiation [54]. Furthermore,
164 PPAR γ agonists activate GSK-3 β to decrease β -catenin expression [55]. In adipocytes,
165 adiponectin increases PPAR γ expression and then downregulates LPS-induced NF- κ B
166 expression and IL-6 production [56].

167 Conversely, β -catenin signaling activates the Akt pathway to decrease PPAR γ expression in
168 adipocytes and 2T2-L1 preadipocytes [44,57]. Several inflammatory cytokines, chemokines and
169 intracellular signaling downregulate PPAR γ expression, such as the canonical WNT/ β -catenin
170 pathway, TNF- α , interleukin (IL)-1 and IL-13 [58,59].

171 Another aspect is the regulation of PPAR γ insulin sensitizing activity by the interaction with β -
172 catenin in bone marrow. Degradation of β -catenin positively correlates with increased expression
173 of PPAR γ -controlled markers of insulin signaling [60].

174

175 **4. Canonical WNT/ β -catenin pathway and the atherosclerosis process**

176

177 ***Inflammation (Figure 3)***

178 Inflammation plays a key role in the mediation of the different phases of the atherosclerosis
179 process [61]. Several cytokines participate in atherosclerosis, such as interleukin (IL-1 and IL-4),
180 interferon-gamma (IFN- γ) and TNF- α [62]. TNF- α activation leads directly to the process of
181 calcification and to the proliferation and migration of VSMCs [63]. IL-1 is strongly expressed by
182 macrophages and ECs [64], and IL-1 overexpression stimulates the atherosclerosis process [61].
183 TNF- α acts through bone morphogenetic protein (BMP2), a canonical WNT target [65] and by
184 activating NF- κ B [66] to facilitate multiplication of VSMCs and mineralization of the

185 extracellular matrix (ECM). Moreover, the overexpression of the WNT/ β -catenin pathway in
186 VSMCs increases inflammation by activating the NF- κ B pathway and TNF- α [67].

187

188 *Endothelial dysfunction (Figure 3)*

189 Dysfunction of ECs is observed at the onset of atherosclerosis. The boundary between the
190 circulating tissue and the underlying tissue is constituted by ECs. ECs have a major role in
191 hemodynamic regulation through the release of several vasoactive mediators. Lesions on these
192 ECs induce the expression of inflammatory and pro-thrombotic genes leading to the enhanced
193 recruitment of inflammatory cells to the subendothelial space, an important characteristic of the
194 initiation of atherosclerosis [68].

195 In association with EC lesions, a high level of circulating LDLs infiltrates specific zones of the
196 arterial wall. Although LRP5 is normally expressed in monocytes, macrophages, SMCs and ECs,
197 the overexpression of LRP5 is only observed during inflammatory processes by modified lipids
198 [12,23]. WNT pathway activation promotes the internalization of LDL by macrophages [23].
199 LRP5 is overexpressed by macrophages, aggregated LDLs enhancing lipid uptake, and foam cells
200 [69].

201 The subendothelial space shows aggregation and/or oxidation of LDL, which triggers
202 inflammation in response to the overexpression of cytokines/chemokines, leading to molecular
203 adhesion. This phenomenon is characterized by the presence of immunity cells, such as
204 macrophages, monocytes, T cells, neutrophils and dendritic cells, which participate in the
205 development of the atherosclerotic plaque [11]. These proatherogenic processes increase the
206 endothelial permeability turnover and then alter the interplay between ECs and VSMCs.

207 ECs are the site of the expression of several WNT proteins and WNT receptors [70]. Proliferation
208 of ECs is favored by the over-activation of the canonical WNT/ β -catenin pathway [71].
209 Activation of the canonical WNT/ β -catenin pathway is observed after stimulation of monocyte
210 adhesion to endothelial cells (as opposed to unstimulated monocytes) [72]. Furthermore, the
211 WNT co-receptor LRP5 is involved in the differentiation of monocytes into macrophages [69].
212 The migration of monocytes and macrophages is modulated by activation of the WNT/ β -catenin
213 pathway [23,73,74]. The release of inflammatory factors, such as interleukin 18 (IL-18) during
214 the atherosclerosis process inhibits the activity of GSK-3 β and then increases the expression of
215 WNT target genes to initiate SMC proliferation [75,76].

216

217 ***VSMC proliferation (Figure 3)***

218 Due to EC dysfunction, VSMCs proliferate and migrate toward the intima. They then induce
219 thickening of the subendothelial space [77]. VSMC migration from the media towards the intima
220 is considered as one of the main characteristics of the atherosclerosis process [78]. Thus, the
221 proliferation of VSMCs also contributes to the production of cytokines/chemokines and
222 deposition of ECM [79].

223 Activation of WNT/ β -catenin signaling by WNT2 and WNT3a ligands, β -catenin accumulation
224 and inactivation of GSK-3 β , induces VSMC proliferation [80–82]. The up-regulated WNT/ β -
225 catenin pathway enhances in-vitro pathways of arterial VSMC remodeling [83]. Inhibition of the
226 WNT co-receptor LRP 5/6 reduces arterial VSMC proliferation [84]. The WNT target gene,
227 cyclin D1, is overexpressed after the denudation of the carotid artery [85,86]. Dysregulation of
228 cell adhesion mechanisms releases β -catenin from its nuclear translocation and then, through the
229 activation of cyclin D1, activates the proliferation of VSMCs [85,86].

230

231 ***ECM deposition (Figure 3)***

232 Proliferated and migrated VSMCs synthesize an abundant array of ECM elements, such as
233 collagen and metalloproteinases, which leads to a fibrosis process encroaching on the vessel
234 lumen [87]. One of the key drivers of ECM deposition is TGF- β signaling, which enhances the
235 secretion of ECM proteins. In the endothelium, activated TGF- β signaling enhances the
236 transformation of fibroblasts into α -SMA-expressing myofibroblasts [46]. Myofibroblasts are
237 contractile non-muscle cells that present bundles of α -SMA actin filament [88]. During
238 differentiation into protomyofibroblasts, these cells synthesize ECM and collagen proteins [89]
239 that contain α -SMA and non-muscle myosin II, responsible for myofibroblast retraction [90].
240 TGF- β signaling interacts with fibronectin extra domain A (EDA) leading to differentiation of
241 fibroblasts into myofibroblasts [89]. Moreover, TGF- β interacts with the Smad pathway in
242 myofibroblasts by phosphorylating Smad2 and SMad3 through TGF- β receptor 1 (TGF- β R1).
243 Thus, the formed dimer interacts with TGF- β R2 (receptor 2) to create a heterotetramer for
244 Smad2 and 3 phosphorylation. The complex formed by Smad2/3 binds Smad4 and translocates to
245 the nucleus and then activates a Smad binding element (SBE) responsible for the fibrosis process
246 [91]. In parallel, TGF- β signaling activates the PI3K/Akt pathway [92] and participates in

247 collagen synthesis. By activating the epidermal growth factor receptor (EGFR) and thus the
248 PI3K/Akt pathway, TGF- β signaling enhances the expression of PAI-1 (potent fibrotic
249 matricellular plasminogen activator inhibitor). PAI-1 is responsible for the encoding of ECM
250 elements, i.e. collagen, metalloproteinases and fibronectin. Matrix cellular elements accumulate
251 in the endothelium through activation of PAI-1, one of the main precursors of the fibrosis process
252 [46].

253 The WNT/ β -catenin pathway, through the inhibition of GSK-3 β activity, is a well-known
254 upstream path of the PI3K/Akt pathway [46]. The WNT/ β -catenin pathway activates TGF- β
255 expression through a β -catenin dependent Smad2 signal responsible for the differentiation of
256 myofibroblasts [93]. Stimulation of TGF- β signaling leads to inactivation of the WNT inhibitor,
257 DKK1 [94].

258

259 *Vascular calcification (Figure 3)*

260 Vascular calcification is a major factor in cardiovascular morbidity and mortality. The
261 overexpression of WNT ligands promotes the WNT target gene BMP2. BMP2 is induced by ECs
262 that are oxidized by LDL and TNF- α [95]. BMP2 activation promotes vascular calcification by
263 acting through the osteogenic transcription factor Msh Homeobox 2 (MSX2), which induces
264 WNT3a and WNT7a activation and DKK1 downregulation [96].

265 Moreover, the chondrogenic differentiation of pericytes is observed at sites of calcification in the
266 intima and media of arteries. This suggests a relationship between pericytes and vascular cell
267 calcification, indicating that pericytes play a role in the different stages of vascular diseases [97].

268 The WNT pathway increases osteogenic and chondrogenic differentiation and decreases
269 adipogenic differentiation of pericytes [98]. Thus, over-activation of the canonical WNT pathway
270 can stimulate progenitor cell differentiation in the vascular wall, leading to cartilage deposition
271 and bone in vessels [97]. Indeed, the WNT/ β -catenin pathway plays a major role in the
272 remodeling and formation of bone [99].

273

274

275 **5. Metabolic reprogramming: the Warburg effect**

276 The Warburg effect, also called aerobic glycolysis, was discovered in 1930 by Otto Warburg
277 [100]. It was initially observed in cancer cells, which were found to have a high glycolytic rate

278 compared with normal cells, even in a normoxic environment. This phenomenon involves a shift
279 in ATP production from mitochondrial oxidative phosphorylation to aerobic glycolysis, leading
280 to an overproduction of intracellular lactate. This mechanism is partially due to injury of
281 mitochondrial respiration and an increase in the glycolytic pathway [101]. A heightening of
282 glycolytic activity is typically indicative of a metabolic response to oxygen privation. However,
283 in cancer cells, this occurs in the presence or absence of oxygen and then leads to the
284 accumulation of lactic acid. Metabolites produced through this phenomenon also participate, far
285 beyond ATP production, in the regulation of cell proliferation, apoptosis, autophagy and
286 extracellular matrix production [101]. Thus, through activation of several glycolytic enzymes and
287 related metabolic markers, the Warburg effect induces numerous processes such as fibrosis [46],
288 cancers [45], neurodegenerative disease [47] and atherosclerosis [102].

289 Per unit of glucose, aerobic glycolysis is an inefficient means of generating adenosine
290 triphosphate (ATP) compared to the amount obtained by mitochondrial chain respiration [103].
291 Nevertheless, the rate of glucose metabolism by aerobic glycolysis is higher such that the lactate
292 production from glucose occurs 10 to 100 times faster than the complete oxidation of glucose in
293 mitochondria [104]. Cells with a higher rate, but lower yield, of ATP production could gain a
294 selective advantage when competing for shared and limited energy resources [105]. Moreover,
295 when ATP demand increases by altering the demand of ATP-dependent membrane, aerobic
296 glycolysis is rapidly stimulated [106].

297

298 ***Biosynthetic aspects of the Warburg effect***

299 The Warburg Effect has been considered as an adaptation mechanism to support the biosynthetic
300 requirements of uncontrolled proliferation. Aerobic glycolysis generates amount of metabolites
301 involved in the regulation of cellular functions, such as proliferation, extracellular matrix
302 production, autophagy and apoptosis [107]. The increase in glucose consumption is used as a
303 carbon source for anabolic processes needed to support cell proliferation [108]. This excess
304 carbon is used for the *de novo* generation of proteins, lipids and nucleotides. Thus, this excess is
305 diverted into numerous branching pathways that emanate from glycolysis. Proliferating cells have
306 a rate-limiting demand for ATP and a greater need of reducing equivalents in the form of
307 nicotinamide adenine dinucleotide phosphate (NADPH). The increase in glucose uptake allows
308 for greater synthesis of these reducing equivalents in the oxidative branch of pentose phosphatase

309 pathway, which are then used in reductive biosynthesis, most notably in *de novo* lipid synthesis
310 [103,109].

311 Moreover, the regeneration of NAD⁺ from NADH in the pyruvate to lactate step completes the
312 aerobic glycolysis signaling. NADH, produced by glyceraldehyde phosphate dehydrogenase
313 (GAPDH), is consumed to generate NAD⁺ to keep glycolysis active.

314

315 ***Mechanisms involved in the Warburg effect (Figure 4)***

316 Glycolysis is induced by the WNT/ β -catenin pathway activation via direct stimulation of WNT
317 target genes (as pyruvate dehydrogenase kinase 1 (PDK1) and mono-carboxylate transporter 1
318 (MCT-1)) and via the stabilization of the hypoxia-inducible factor 1 alpha (HIF-1 α) [110–112].

319 HIF-1 α stabilization is sustained in a hypoxia-independent manner through the activation of
320 WNT/ β -catenin target genes (c-Myc and cyclin D1), the PI3K/Akt pathway and β -catenin-
321 induced c-Myc [113].

322 HIF-1 α is a heterodimeric nuclear transcription factor which is composed by two subunits: HIF-
323 1alpha and HIF-1 β . HIF-1 α stabilization results in its nuclear translocation, dimerization with
324 HIF-1 β , and the transcription of genes encoding glycolysis enzymes [114]. Aberrant HIF
325 signaling involves a metabolic reprogramming by increasing glycolysis and then decreasing the
326 entry of glucose-derived carbons into the **Krebs** cycle leading to reduce the mitochondrial
327 oxidative phosphorylation metabolism [115].

328 HIFs also promotes glutamine metabolism. HIF-1 α stabilization increases glycolysis by the
329 stimulation of glucose transporters (Glut) mediating increased glucose uptake and the stimulation
330 of glycolytic enzymes including HK2, PKM2, LDH-A, and PDK1 [116,117]. Thus, HIF-1 α leads
331 to promote lactate production by increasing LDH-A activity and decreasing the conversion of
332 pyruvate into acetyl-CoA through the upregulation of PDK1 and then the decrease of PDH
333 activity [118]. PI3K/Akt signaling is stimulated by cytosolic accumulation of β -catenin [119].
334 Activation of PI3K/Akt pathway induces HIF-1 α stabilization to increase the rate of glucose
335 metabolism [120].

336 After glucose entered the cell, the final step of glycolysis is the conversion of the
337 phosphoenolpyruvate (PEP) and ADP into pyruvate and ATP, a reaction catalyzed by the enzyme
338 pyruvate kinase M2 (PKM2). PKM2 presents low affinity with PEP [121]. Under high glucose
339 concentration, PKM2 is acetylated and translocated to the nucleus through the action of the

340 peptidyl-prolyl isomerase 1 (Pin1) [122], reducing its activity and targeting PKM2 towards a
341 lysosome-dependent degradation [123]. Nuclear PKM2 binds nuclear β -catenin and then induces
342 c-Myc-mediated expression of glycolytic enzymes in a positive feedback loop, thus strengthening
343 aerobic glycolysis [124].

344 The shunting of glucose carbons far from the **Krebs** cycle results in glutamine metabolism
345 reprogramming. c-Myc stimulates glutaminolysis and drives glutamine uptake into the cytosol
346 and the mitochondria [125]. c-Myc-activated HIF shifts from oxidative decarboxylation to
347 reductive carboxylation of glutamine to generate citrate and acetyl-CoA for lipid synthesis [126–
348 128]. c-Myc-induced glutamine enhances aspartate and nucleotide synthesis [125]. Then, a minor
349 part of the pyruvate is converted into acetyl-CoA which enters the **Krebs** cycle and then become
350 citrate for promoting protein and lipid synthesis. Through this complex mechanism, the Warburg
351 effect supports a metabolic environment that allows for the rapid biosynthesis to support growth
352 and proliferation [129].

353

354

355 **6. Interaction between WNT/ β -catenin pathway and the Warburg effect**

356 A partial explanation of the contrast observed between proliferating and quiescent metabolism
357 may be the level of glucose uptake controlled by the growth factor signal transduction [130].
358 Activation of the WNT pathway largely suppresses the pyruvate oxidation in the **Krebs** cycle
359 [131]. In parallel, the PI3K/Akt pathway rewires the glucose metabolism to enhance protein
360 synthesis [103], leading to inhibition of the oxidative metabolism and protection against ROS
361 stress by activation of HIF-1 α [132]. The WNT pathway synergizes with the PI3K/Akt
362 pathway to enhance cell proliferation [133]. PDK-1 (pyruvate dehydrogenase kinase 1), HK-2
363 (hexokinase 2) and MCT-1 (monocarboxylate transporter 1) are considered as important WNT
364 targets, and activation of the LDH-A (lactate dehydrogenase A) gene diverts glycolytic pyruvate
365 away from the **Krebs** cycle through the conversion of pyruvate into lactate [133].

366

367

368 **7. Warburg effect in atherosclerosis**

369 Several metabolic dysregulations have been observed in the atherosclerotic process [134]. The
370 phenomenon of aerobic glycolysis is increased in atheromatous plaques of ApoE $-/-$ mice [135]

371 and in rabbit atherosclerosis arteries [136]. Few recent studies have indicated that the process of
372 the Warburg effect is involved in the proliferation of VSMCs, inflammation and dysregulation of
373 ECs (**Figure 3**) [102].

374

375 ***Warburg effect and inflammation***

376 The process of atherosclerosis is largely associated with inflammation [137]. Recent studies have
377 shown a relationship between inflammation and metabolic dysfunction in atherosclerosis [138].
378 The aerobic glycolysis drives the M1-like pro-inflammatory macrophage phenotype leading to
379 the stimulation of inflammation and then atherosclerosis [139]. Several key integrators of
380 inflammation, such as IL-1 α are induced by aerobic glycolysis [140]. These integrators promote
381 lipid plaque formation and their destabilization in ApoE $-/-$ mice [141]. Moreover, HIF-1 α
382 activation during aerobic glycolysis promotes the differentiation of TH17 cells to aggravate the
383 inflammatory process [142]. In atherosclerosis, the increase of glycolytic enzymes is associated
384 with activation of circulating monocytes [143].

385

386 ***Warburg effect and the dysfunction of endothelial cells (ECs)***

387 EC dysfunction enhances the accumulation of lipids and thus the formation of atherosclerotic
388 plaques [144]. The rate of aerobic glycolysis is high in normal ECs whereas the level of miR-143
389 is very low. A recent study has shown that during the atherosclerotic process, the level of miR-
390 143 and mRNA levels of key enzymes (HK2, LDHA, PKM2) of aerobic glycolysis are increased
391 [145]. The increase of miR-143 is associated with the dysfunction of ECs.

392

393 ***Warburg effect and the promotion of VSMC proliferation***

394 Several studies have shown that increased glycolytic metabolism with a bioenergetics shift occurs
395 during VSMC proliferation and migration [146,147]. The metabolism of aerobic glucose directly
396 affects the proliferation of VSMCs [148] and increases the PDGF-BB (platelet derived growth
397 factor brain barrier)-induced VSMC proliferation [149]. The PKK-1 (phosphofructokinase 1)
398 could have a major role in this determination of glucose flux through the aerobic glycolysis
399 process. VSMC proliferation is associated with an increase in energy demand [150]. This
400 observation may be associated with ATP production by aerobic glycolysis. Upregulation of LDH-
401 A during aerobic glycolysis stimulates the proliferation and migration of VSMCs [151]. This

402 upregulation is associated with an increase of lactate and ATP production.

403

404

405 **8. PPAR γ agonists: potential therapeutic implications**

406

407 *PPAR γ and Warburg effect*

408 Few studies have examined the role of PPAR γ in the regulation of the glycolytic pathway
409 [45,152,153]. However, it has been found that the PPAR γ shift, through a Ski oncogene, takes
410 place through a glycolysis oxidative metabolic metabolism [154]. Administration of GW1929, a
411 PPAR γ agonist, increases the expression of PPAR γ target genes involved in lipid oxidation in
412 adipose tissue [155]. CD36 and FATP-1, two PPAR γ target genes, enhance palmitate oxidation
413 into mitochondria [156].

414

415 *PPAR γ and atherosclerosis*

416 Numerous studies have shown the beneficial effect of PPAR γ agonists in the treatment of
417 atherosclerosis by reducing inflammation, regulating endothelial function and improving the
418 thrombosis process [157–159].

419 PPAR γ regulates the process of change in the immune system by modifying macrophage
420 polarization toward an anti- or pro-inflammatory (M2 or M1) phenotype [160]. PPAR γ agonists
421 inhibit M1 phenotype and decrease the expression of inflammatory cytokines, such as TNF- α , IL-
422 1 and IL-6 [161]. In contrast, the differentiation of M2 macrophages (with anti-inflammatory
423 properties) results in increased expression of PPAR γ [162]. The mechanism of macrophage
424 polarization can be regulated by PPAR γ agonists, underlying their anti-inflammatory and anti-
425 atherosclerosis activities [16]. Moreover, PPAR γ regulates the inflammatory involvement of the
426 immunogenicity of dendritic cells observed in atherosclerosis [163,164], but this mechanism is
427 not yet fully understood [16]. TZDs can suppress thromboxane synthase and receptor expression
428 in both macrophages and VSMCs [165,166]. Thromboxane, an arachidonic acid metabolite, plays
429 a major role in the atherosclerosis process by acting on VSMC proliferation and the aggregation
430 of platelets. PPAR γ overexpression decreases VSMC proliferation [167,168] by arresting the
431 VSMC re-entry cell cycle [169] and diminishes VSMC migration by reducing the mitogen-
432 activated protein kinase (MAPK) pathway [32]. PPAR γ activation reduces inflammation by

433 inhibiting NF-kappaB activity [161]. Lobeglitazone and pioglitazone reduce NF-kappaB activity
434 and then decrease VSMC proliferation [17].

435

436

437 **Conclusion**

438 The canonical WNT/ β -catenin pathway plays a key role in several pathophysiological
439 mechanisms that are involved in cardiovascular diseases, such as inflammation, calcification,
440 fibrosis and lipid infiltration. The dysregulation of this pathway in ECs results in damage to the
441 arterial wall through a cascade of interactions between its molecular targets. Enhancing our
442 knowledge of this pathway leads to a better understanding of the complex network of the
443 different molecular components involved in the reprogramming of the metabolic pathway
444 observed during the atherosclerosis process. This metabolic mechanism, known as the Warburg
445 effect, appears to be a central element in the atherosclerosis process. Numerous studies have
446 shown that the WNT/ β -catenin pathway and PPAR γ act in an opposing manner. Therefore, the
447 development of therapeutic targets, such as PPAR γ agonists, for the treatment of atherosclerosis
448 could be an interesting and innovative way to counteract the influence of the canonical WNT
449 pathway.

450

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452

453 **Abbreviations**

454 Acetyl-coA: Acetyl-coenzyme A; APC: Adenomatous polyposis coli; EC: endothelial cell; ECM:
455 Extracellular-matrix; FZD: Frizzled; Glut: Glucose transporter; GSK-3 β : Glycogen synthase
456 kinase-3 β ; HIF-1 α : Hypoxia induce factor 1 alpha; LDH: Lactate dehydrogenase; LRP 5/6: Low-
457 density lipoprotein receptor-related protein 5/6; MCT-1: Monocarboxylate lactate transporter-
458 1;NF- κ B: nuclear factor kappaB; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate
459 dehydrogenase kinase; PKM2: Pyruvate kinase M2; PPAR γ : Peroxisome proliferator-activated
460 receptor gamma; PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B; TCF/LEF: T-cell
461 factor/lymphoid enhancer factor; TNF- α : tumor necrosis factor alpha; TZD: Thiazolidinedione,
462 VSMC: vascular smooth muscle cell.

463

464 **Author contributions**

465 All authors listed, have made substantial, direct and intellectual contribution to the work, and
466 approved it for publication

467

468 **Conflict of Interest statement**

469 The authors declare that the research was conducted in the absence of any commercial or
470 financial relationship that could be construed as a potential conflict of interest.

471

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973 **Figure 1: Atherosclerosis process in blood vessel**

974 Endothelial cells present impaired conversion in vascular smooth cells (VSMCs), inflammatory
975 processes, differentiation in monocytes and fibroblasts, and foam cell formation.

976

977 **Figure 2: Schematic representation of the canonical WNT pathway ('activated' state and**
978 **'inactivated' state)**

979

980 **Figure 3: Central role of the canonical WNT/beta-catenin pathway in atherosclerosis**

981 Abbreviations: EC: endothelial cell; ECM: extra matrix cellular; Glut: Glucose transporter; LDH:
982 Lactate dehydrogenase; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase
983 kinase; PKM2: Pyruvate kinase M2; VSMC, vascular smooth cell

984

985 **Figure 4: Mechanisms involved in the Warburg effect.**

986 WNT target gene transcription is activated by cytosolic accumulation and then nuclear β -catenin
987 (PDK, c-Myc, cyclin D1, MCT-1). MCT-1 favors lactate expulsion out of the cell. WNT/ β -
988 catenin pathway activates tyrosine kinase receptors (TKRs) activity. Stimulation of HIF-1 α
989 activity, by PI3K/Akt and β -catenin, activates the expression of the glycolytic enzymes (GLUT,
990 HK, PKM2, LDH-A). Aerobic glycolysis is observed with the increase of lactate production and
991 the decrease of mitochondrial respiration. HIF-1 α induced PDK phosphorylates PDH, which
992 resulting in cytosolic pyruvate being shunted into lactate by inducing LDH-A activation. PDK
993 inhibits the PDH complex into the mitochondria, thus pyruvate cannot be fully converted into
994 acetyl-CoA and enter the [Krebs](#) cycle. c-Myc and cyclin D1 also stimulates LDH-A activity
995 which converts cytosolic pyruvate into lactate. Activated PKM2 translocates to the nucleus to

996 bind β -catenin and then to induce the expression of c-Myc. Glucose metabolism over-activation
997 leads to nucleotide synthesis; glutaminolysis to lipid and amino-acid synthesis and lactate release.
998 Abbreviations: Acetyl-coA: Acetyl-coenzyme A; Glut: Glucose transporter; HIF-1 α : Hypoxia
999 induce factor 1 alpha; LDH: Lactate dehydrogenase; MCT-1: Monocarboxylate lactate
1000 transporter-1; PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B; PDH: Pyruvate
1001 dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PKM2: Pyruvate kinase M2.





