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► **To cite this version:**

Sonia Martial. Involvement of ion channels and transporters in carcinoma angiogenesis and metastasis. *American Journal of Physiology - Cell Physiology*, 2016, 310, pp.710 - 727. 10.1152/ajp-cell.00218.2015 . hal-02375861

HAL Id: hal-02375861

<https://hal.science/hal-02375861v1>

Submitted on 26 Nov 2019

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1 **Involvement of ion channels and transporters in carcinoma angiogenesis**
2 **and metastasis**

3

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9 **Running title:** Ion transport modulates tumor angiogenesis and metastasis

10

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22 **ABSTRACT**

23

24 Angiogenesis is a finely tuned process, which is the result of the equilibrium between pro- and anti-angiogenic
25 factors. In solid tumor angiogenesis, the balance is highly in favor of the production of new, but poorly
26 functional blood vessels, initially intended to provide growing tumors with nutrients and oxygen. Among the
27 numerous proteins involved in tumor development, several types of ion channels are overexpressed in tumor
28 cells, as well as in stromal and endothelial cells. Ion channels thus actively participate in the different hallmarks
29 of cancer, especially in tumor angiogenesis and metastasis. Indeed, from their strategic localization in the
30 plasma membrane, ion channels are key operators of cell signaling, as they sense and respond to environmental
31 changes. This review aims to decipher how ion channels of different families are intricately involved in the
32 fundamental angiogenesis and metastasis hallmarks, which lead from a nascent tumor to systemic
33 dissemination. An overview of the possible use of ion channels as therapeutic targets will also be given,
34 showing that ion channel inhibitors or specific antibodies may provide effective tools, in a near future, in the
35 treatment of carcinomas.

36

37

38 **KEYWORDS:** ion channel, tumor vascularization, cell signaling, ion channel-targeted therapy

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40

41 **ABBREVIATIONS:** HIF, hypoxia-inducible factor; CRC, colorectal carcinoma; ccRCC, clear cell renal cell
42 carcinoma; CAIX, carbonic anhydrase IX; RVD, regulatory volume decrease; PDAC, pancreatic ductal
43 adenocarcinoma; VEGFR, VEGF receptor; TSP, thrombospondine; MMP, matrix metalloproteinase; SOCE,
44 store-operated calcium entry; CRAC, Ca²⁺-release activated channel; ROCE, receptor-operated calcium entry;
45 IP3, inositol 1,4,5-trisphosphate; EMT, epithelial-mesenchymal transition; TME, tumor microenvironment;
46 STIM, stromal interaction molecule; MAM, mitochondrion-associated ER membrane; NMDAR, N-methyl, D-
47 aspartate Receptor; CML, chronic myeloid leukemia; ER, endoplasmic reticulum; BiP, binding immunoglobulin
48 protein; NSAID, non-steroid anti-inflammatory drug; GPCR, G protein-coupled receptor.

49

50 I. Introduction

51 Carcinoma is a solid cancer developing from epithelial cells and is the most widely spread form of human
52 cancer. Among the phenomena leading to the development and progression of this type of cancer, one of the
53 most important is angiogenesis. Indeed, tumor vascularization is essential for a growing tumor to obtain oxygen
54 and nutrients needed for its ongoing growth, *in situ*. Tumor neovascularization is also a means for the tumor to
55 grow away from its primary site towards a remote neo-colonized structure (metastasis).

56 In the last 10 to 15 years, many efforts have been made on the elucidation of which genes might be directly
57 involved or affected during the different steps of tumorigenesis, described by Hanahan and Weinberg as the
58 hallmarks of cancer (95, 96). Multiple studies demonstrated that, among these genes, plasma membrane ion
59 channels and transporters are clearly modulated during carcinogenesis, in different types of carcinomas (9, 20,
60 31, 75, 78, 93, 133, 147, 201, 207). Several different roles have been ascribed to ion channels during
61 carcinogenesis, depending on the step of the tumorization process and on the organ in which it takes place.

62 In this review, we do not intend to make an exhaustive list of channels involved in cancer development. Instead,
63 we choose to focus on the involvement and/or alteration of some ion channels in angiogenesis, from the
64 vascularization of recently formed tumors to the metastasis cascade. Indeed, neo-formation of tumors involves
65 pH changes, which are associated with proton exchange through the plasma membrane (127, 209, 217) and
66 water transport (17, 162). The subsequent tumor growth needs neovascularization, associated with Ca^{2+} , K^+ and
67 Na^+ channels (5, 61, 201). Finally, Na^+ , K^+ , Ca^+ and Cl^- channels are implicated in the transition to metastasis
68 (32, 73, 75).

69 The main ion channels involved in tumor development processes and mentioned in this review are listed in
70 Table 1.

71

72 II. Neangiogenesis

73 A. The fate of new tumors

74 In the early steps of its formation, a tumor depends solely on the host blood vessels (104). However, this initial
75 peripheral vasculature quickly disappears, leaving the tumor and its microenvironment in a hypoxic state (84,
76 97). Folkman (77) was the first to show that, under these conditions, the tumor growth is limited to a few cubic
77 millimeters, unless reorganization of a new blood supply is promoted (neoangiogenesis).

78 The lowered local O_2 pressure (pO_2) observed near cancer cells and the resulting tumor microenvironment
79 acidification activate hypoxia-inducible factors, especially HIF-1 (44, 58, 115). HIF-1 α is stabilized by
80 phosphorylation (172) and dimerizes with the constitutively expressed HIF-1 β to form the transcription factor
81 HIF-1, which in turn stimulates a set of genes involved in tumor development. Conversely, recent reports
82 present HIF-2 as the tumorigenic form of HIF, whereas HIF-1 would be a tumor suppressor (227, 263).

83 Initially, the cancer cells undergo metabolic changes, among which increased glucose consumption and lactate
84 production (the Warburg's effect) lead to acidosis of the cells. In conjunction with the higher need for glucose,
85 several authors report a HIF-dependent expression of the GLUT-1 glucose transporter in breast or colorectal
86 carcinoma cell (CRC) models (25, 84, 132) and a repressed mitochondrial function (175). In clear cell renal cell
87 carcinomas (ccRCC), some isoforms of glucose transporters are equally increased, including the GLUT-5
88 fructose transporter (240). Moreover, in order to prevent acidosis induced by the accumulation of lactate, cancer
89 cells increase the amount and/or activity of several families of acid-extruding plasma membrane proteins. In
90 several carcinoma models, these HIF-1 increased proteins include: NHE1, the Na^+/H^+ exchanger (79, 170, 231),
91 the MCT1 and MCT4 forms of monocarboxylate transporters, dedicated to lactate extrusion (62, 184, 246), the
92 SLC4A4 (NBC) Na^+/HCO_3^- cotransporter (1, 180), involved in the bicarbonate reabsorption which contributes
93 to intracellular pH recovery. Acid-sensing ion channels (ASIC1, 2, 3) are also up-regulated in adenoid cystic
94 carcinomas, following the acidification of the extracellular space (257). Finally, carbonic anhydrases (especially
95 CAIX, the main carbonic anhydrase found in hypoxic tumors (64)), dedicated to microenvironment pH
96 modulation are also upregulated (132, 171, 180). The different ion channels involved at this stage are
97 summarized in Figure 1. Activation of all these transport proteins eventually contribute to a modest elevation of
98 the tumor cell intracellular pH, while the extracellular medium is acidified.

99 Subsequently, the newly constituted tumor will only grow larger if it manages to regenerate a constant blood
100 supply to provide O₂ and nutrients to the tumor cells and to rid the cells of metabolites. Two main families of
101 plasma membrane ion channels have been proposed to be involved in this tumor developmental stage and
102 regulated by HIF. Transient receptor potential (TRP) channels contribute to calcium homeostasis and are
103 upregulated in several cancer cell types, thus playing an important part in Ca²⁺ influx, regulatory volume
104 decrease (RVD) and cell cycle progression (63, 254). A variety of K⁺ channels are also involved in the HIF-
105 induced regulation of proliferation and revascularization, namely the voltage-dependent “ether-à-gogo”
106 potassium channel (EAG1, KCNH1, Kv10.1) (31, 177), and the two-pore domain potassium channels TASK
107 (30) and TREK (243). In pancreatic ductal adenocarcinoma (PDAC), the Ca²⁺-dependent potassium channel of
108 intermediate conductance, IK_{Ca} (K_{Ca}3.1) is up-regulated and contributes to cell proliferation (114).

109

110 B. Angiogenic switch

111 Tumor angiogenesis is the key step for tumor growth, invasion and metastasis. Tumor angiogenesis mostly
112 relies on the same processes as those involved in physiological angiogenesis (27, 45, 176). Particularly,
113 ischemia and hypoxia are in both cases, major initiators of angiogenesis processes (“on” switches). Moreover,
114 tumor angiogenesis and physiological angiogenesis heavily depend on VEGF secretion, as was described
115 elsewhere and as we will describe here for tumor-dependant angiogenesis. The main differences are: 1)
116 Pathological angiogenesis is more dependent upon VEGF than physiological angiogenesis (45); and 2)
117 Physiological angiogenesis events recede when vessel perfusion starts and upon disappearance of the stimuli
118 that gave rise to neoangiogenesis (“off” switch), whereas tumor angiogenesis is a continuous process, fueled by
119 the steady secretion of tumor-induced angiogenesis factors (45).

120 The concept of “angiogenic switch” was formulated in order to characterize angiogenesis as a balance between
121 processes that tend to favor and processes that tend to prevent angiogenesis (94). When tumor cells enter a
122 hypoxic state, activation of HIF leads to the subsequent activation of a multiple array of pro-angiogenic factors;
123 thus, the regular balance of angiogenesis is lost: the angiogenic switch has been turned “ON”. The most studied
124 HIF-regulated pro-angiogenesis factor is probably VEGF, the angiogenesis cytokine that regulates endothelial
125 cell proliferation and blood vessel formation. Both VEGF and its receptors VEGFR1 (FLT-1) and VEGFR2

126 (KDR/FLK1), which are located principally on the surface of endothelial cells, are upregulated by HIF (123,
127 185). Fibroblast Growth Factor (FGF) is also regulated by hypoxia and may act synergistically with VEGF to
128 amplify angiogenesis (125).

129 The “angiogenic switch” is turned “ON”, in several types of cancer cells, including mouse colon carcinoma,
130 mouse melanoma and human neuroblastoma, when several types of ion channels are modulated. P2X₇R, the
131 non-selective cationic pore, has been shown to promote tumor growth and VEGF release (4, 5, 7). TRPC
132 channels are functionally coupled to VEGF or FGF, playing important roles in cancer development steps (76,
133 156). Moreover, in renal cell carcinoma (RCC), the TRPC4 Ca²⁺ channel expression is decreased, which impairs
134 Ca²⁺ metabolism, hence preventing the production of thrombospondin-1 (TSP1), an angiogenesis inhibitor
135 (238). Numerous studies report overexpression of most families of K⁺ channels in human cancers. In particular,
136 the closely related voltage-dependent hERG and EAG1 K⁺ channels are both involved in the processes leading
137 to angiogenesis. Indeed, hERG channels regulate angiogenesis in CRC by increasing the HIF-1 activated VEGF
138 expression and secretion in a β1-integrin-dependent manner and via a PI3K/Akt pathway (46). This regulation
139 has been confirmed in transgenic mice expressing hERG channels and treated with azoxymethane. These mice
140 present increased staining for VEGF in immunohistochemistry (IHC) studies and a higher total number of blood
141 vessels, consistent with neoangiogenesis, as well as colorectal lesions, on the whole showing acceleration of the
142 colorectal cancer phenotype (74). EAG1, but not EAG2 contributes to tumor progression, as demonstrated by
143 xenograft tumor formation resulting from implanted MDA-MB-435S breast cancer cells, EAG1-transfected
144 CHO cells and EAG1- or EAG2-transfected NIH-3T3 cells. Furthermore, EAG1 stimulates VEGF secretion,
145 measured in CHO- or 3T3-transfected cells. Finally, EAG1 increases HIF-1 amount in EAG1-expressing cells,
146 thus demonstrating that EAG1 is involved in the angiogenic switch and the subsequent neoangiogenesis (61).

147 The role of Ca²⁺ channels in conjunction with angiogenic switch is worth to mention. Indeed, it has been
148 demonstrated that VEGF utilizes Ca²⁺ signaling to promote endothelial cell proliferation and subsequent
149 neoangiogenesis, which we largely discuss in the next section. However, it is noteworthy that some Ca²⁺
150 channels, mostly of the TRP family, are upregulated by hypoxia in cancer cells (76). The subsequent increase in
151 intracellular Ca²⁺ concentration is at the basis of cancer cell hallmarks such as cell proliferation or migration
152 (76).

153

154 C. Neovascularization

155 Tumor vasculature is a crucial feature of carcinoma development. New blood vessels develop by sprouting
156 (angiogenesis) or intussusception from pre-existing vessels (144, 199). They can also emerge from the assembly
157 of endothelial precursors derived from the bone marrow (vasculogenesis) (189). Sprouting is a very well studied
158 process, which is involved in tumor blood vessel formation. Angiogenesis is a multistep process that begins
159 when endothelial cell VEGF receptors are stimulated by VEGF (19, 34) to give rise to new blood vessels
160 growing towards the avascular tumor that initially secreted the stimulating cytokine. The different steps of the
161 process are detailed below:

162

163 1. VEGF-induced blood vessel dilatation

164 Most research on tumor angiogenesis has focused on VEGF-A. VEGF-A signaling occurs through two VEGF
165 receptors, VEGFR1 and VEGFR2 (19, 144). Although VEGF-A has the highest affinity for VEGFR1, the
166 higher tyrosine kinase activity of VEGFR2 makes it the primary receptor involved in angiogenesis processes.
167 VEGFR1, conversely, is involved in macrophage chemotaxis, as well as in tumor cell survival and invasion
168 (136, 205, 255). Additionally, VEGFR1 may also have a negative role on angiogenesis and tumorigenesis
169 processes, only acting as a decoy receptor (102, 142). VEGF-A binds to its receptor and this first results in
170 blood vessel dilatation, as recently shown by *in vivo* studies of breast tumors, by sonographic examination (41).
171 Like most mammalian cells, endothelial cells express cell-swelling activated Cl⁻ channels, called the Volume-
172 Regulated Anion Channel (VRAC) (166, 167). Interestingly, receptor tyrosine kinases such as VEGFRs can
173 serve as mechanosensors (40). As such, they are involved in the VRAC signaling pathway. Thus, one might
174 infer that VEGF signaling in endothelial cell is mediated by VRAC Cl⁻ channels, as shown by the suppression of
175 angiogenesis by VRAC inhibitors (146).

176

177 2. Disorganization of the vascular bed

178 Angiogenesis partly proceeds by the VEGF stimulation of endothelial cell matrix metalloproteinases (MMPs)
179 (188). Secretion of these MMPs, more precisely MMP-2 and MMP-9 (18, 250), triggers the dissolution of the
180 basement membrane surrounding these endothelial cells, thus provoking the destabilization of the entire blood

181 vessel wall and leading to vessel leak (34). Among the multiple mechanisms that cooperate for the close
182 regulation of MMP activity, Ca^{2+} signaling is one of the most important (121). The work, led by Kato,
183 demonstrates that under extracellular acidification, B16 mouse melanoma cell line displays increased voltage-
184 gated Ca^{2+} channel expression and activity, resulting in an increase in intracellular Ca^{2+} concentration and in
185 MMP-9 induction. Thus, Ca^{2+} signals and channels are potentially the most important points in the regulation of
186 the VEGF-triggered blood vessel reorganization. However, the work conducted by Kato and colleagues
187 addresses the other types of Ca^{2+} channels that may be involved in the complex processes going from VEGF
188 upregulation to basement membrane disorganization. Indeed, under a hypoxic stimulus, the formation of a
189 VEGF-VEGFR complex at the endothelial cell plasma membrane can also result in intracellular Ca^{2+} increase,
190 due to the release of intracellular Ca^{2+} stores (Fig. 2). The depletion of these stores in turn results in Ca^{2+} influx,
191 via plasma membrane Ca^{2+} channels which results in store-operated calcium entry or SOCE (for review, see
192 (75)). Several Ca^{2+} channels of the transient receptor potential (TRP) superfamily appear to be involved in
193 SOCE and help explain how SOCE contributes to VEGF-induced basement membrane disruption. Among the
194 TRPCs (canonical), TRPC1 activation magnifies the VEGF-induced increase in endothelial cell monolayer
195 transepithelial permeability (111, 178). Conversely, inhibition of the TRPC1 activity reduces this transepithelial
196 permeability increase (111). TRPC4 is a necessary intermediate in the response of human pulmonary artery
197 endothelial cells to VEGF stimulation (71). TRPC6 is also presented as a good candidate in the process of
198 VEGF-induced vascular permeability increase. Indeed, as shown in individually perfused frog microvessels,
199 stimulation of TRPC6 generates an increase in the hydraulic conductivity (L_p) of the vessels (186). The Ca^{2+} -
200 release activated Ca^{2+} (CRAC) channel (composed of the plasma membrane Orai1 subunit coupled with the
201 endoplasmic reticulum STIM subunit) is also involved in VEGF-dependent SOCE (139). Indeed, in human
202 umbilical vein endothelial cells, inhibition or disruption of Orai1 reduces VEGF-induced calcium entry, cell
203 migration and *in vitro* angiogenesis. The increase in transepithelial permeability may result from both in-cell
204 and in-between-cell pore creation (43, 98). Finally, VEGF effects can also occur via receptor-operated-calcium
205 entry (ROCE), as shown on human microvascular endothelial cells (42); TRPC3 and TRPC6 are two examples
206 of channels involved in calcium-mediated vascular permeabilization.

207 In conclusion, VEGF-induced calcium-dependent events leading to the basement membrane disorganization,
208 though resulting in the same final outcome, appear to be the consequence of several calcium entry pathways.

210 3. Endothelial cell proliferation, migration and organization

211 Breakdown of the blood vessels (i.e. dissolution of the basement membrane) leads endothelial cells to be
212 released into the extracellular matrix (ECM) where they proliferate and organize to generate new blood vessels,
213 growing towards the tumor that initially emitted stimulating signals. Angiogenic sprouting is a guided process in
214 which the vasculature expands outwards from the preexisting vessel, following a gradient of angiogenic factors
215 such as VEGF-A (85) or soluble VEGFR1 (38). In this regard, Gerhardt and colleagues demonstrated that the
216 first cell of the column, the so-called “endothelial tip cell,” consists of a single, non-proliferative, highly
217 polarized endothelial cell, which is the sensor of the emitted elongation signal. The cell migration along this
218 signal (chemotaxis) paves a path for the cells that follow, the “stack cells”, which undergo high rate mitosis to
219 form the newly elongating blood vessel. At the endothelial cell level, it is now recognized that VEGFR2 is the
220 main actor of the angiogenic cascade. VEGF, when binding to VEGFR2, activates a signaling cascade starting
221 from auto-phosphorylation of VEGFR2, subsequent phosphorylation and activation of phospholipase C- γ (PLC-
222 γ), increased production of inositol 1,4,5-trisphosphate (IP3) and resulting increase in the Ca^{2+} release from
223 endoplasmic reticulum. The subsequent rise in calcium influx by the aforementioned SOCE process involves
224 TRPC channels, as already discussed (see chapter II.C.2) and promotes endothelial cell migration via a
225 Ca^{2+} /calmodulin/calcineurin pathway (72). The role of SOCE was also established in bovine artery endothelial
226 cells for the different mechanisms of angiogenesis (i.e., cell sprouting, cell proliferation and cell migration) and
227 involves the Ca^{2+} /calmodulin/protein kinase cascade (15).

228 One of the fundamental roles of ion channels in endothelial Ca^{2+} signaling is the fine-tuning of the
229 electrochemical gradient for Ca^{2+} (118). Several types of ion channels cooperate in elaborating the cell
230 membrane potential, which regulates calcium entry into the endothelial cells (118). Among those, K^+ channels,
231 especially Ca^{2+} -activated K^+ channels (251), inwardly rectifying K^+ channels (K_{ir}) and voltage-dependent K^+
232 channels, are the major classes of ion channels involved in setting the membrane potential (165), which in turn
233 influences the driving force for the Ca^{2+} via SOCE. Indeed, blockers of K^+ channels, as well as plasma
234 membrane depolarization, stop the cell cycle in G1 phase, thus reducing cell proliferation (153, 165). However,
235 among the Ca^{2+} -dependent K^+ channels, the Ca^{2+} -dependent intermediate conductance K^+ channel IK1 (SK4,

236 KCNN4) increases cell proliferation with a completely different mechanism, in a HEK overexpressing system.
237 Indeed, the potassium current itself does not seem to mediate the effect, since a non-transporting mutant of the
238 channel induces the same proliferation. So it seems that the IK1-induced proliferative effect is not SOCE-
239 mediated (152). The cell membrane potential is partly regulated by Cl⁻ channels (247). Hence, volume-regulated
240 anion channels (VRAC), Ca²⁺-activated Cl⁻ channels (CaCC), as well as cystic fibrosis transmembrane regulator
241 (CFTR) (145) might be important regulators of SOCE, which drives the proliferation step of angiogenesis.

242

243 4. Maturation of the new blood vessel

244 Two steps are essential for completion of angiogenesis:

245 (1) A new vessel is formed when the elongating sprout lumenizes to create a tube, which will eventually be able
246 to transport fluid and the multiple blood components: this step is called tubulogenesis (117, 143). At least two
247 models of tubulogenesis have been described. The “cell hollowing” model (currently the most studied) evolves
248 from a chain of single endothelial cells (117). This model involves intracellular vesicle formation, then fusion of
249 these vesicles into vacuoles, first intracellularly, and then from cell to cell, all along the sprout, when the
250 vacuoles get bigger. The future lumen vacuole membrane finally acquires hallmarks of an apical membrane,
251 thus defining the apical-basolateral polarity of the neo-formed vessel. In the less studied “cord hollowing”
252 model, which happens in a multi-cellular elongated stack, the cells first lose their initial polarity, then
253 basolateral membrane markers are accumulated at the membrane facing the extracellular matrix, while vesicles
254 are accumulated and get fused on the opposite membrane, hence forming an initial lumen that expands
255 afterwards (179, 248). In the “cell hollowing” model, the formation of vacuoles is linked to the activation of
256 intracellular chloride channels of the CLIC family. The chloride intracellular channel (CLIC) family of proteins
257 contains six mammalian members (CLIC1-6), from which only CLIC1 and CLIC4 are expressed in endothelial
258 cells (230). CLIC proteins can change from a soluble state to a membrane-linked state. In the latter case, when
259 inserted in such organelles as mitochondria, Golgi membranes, nuclear membranes, etc., CLICs function as
260 chloride channels, although very different in structure from the other known Cl⁻ channels (65, 233). In the “cell
261 hollowing” model of tubulogenesis, CLIC4 is present in human umbilical vein endothelial cells and promotes
262 several processes involved in angiogenesis, including luminal formation (229). Particularly, endothelial cells

263 derived from transgenic mice, in which the *Clc4* gene has been invalidated, fail to proceed to the vacuole
264 creation and extension process. Tung and colleagues show that the enlarging vacuoles acidify during their
265 formation, involving an electrogenic vacuolar proton-ATPase (vH^+ -ATPase), and propose that CLIC4 supports
266 this acidification by creating an electrical gradient for the proton transfer. The same article proposes that CLIC1
267 may partially compensate for the absence of CLIC4 in the process of tubulogenesis, although CLIC1 seems
268 mainly committed to proliferation and migration processes rather than to morphogenesis of endothelial cells
269 (230).

270 (2) The new hollow tube thus created is finally stabilized by the formation of a new basement membrane.
271 Indeed, in physiological angiogenesis, accessory cells, such as pericytes and smooth muscle cells are recruited
272 to the newly developed vessel, to form a new basement membrane (54). In tumor angiogenesis, however, the
273 newly formed blood vessels are very heterogeneous in structure and function (54). Their architecture is very
274 chaotic and disorganized, with abnormal branching, inflated cells and tortuous courses. Subsequently, the
275 association between endothelial and mural cells is altered, becoming loose and leading to highly permeable
276 vessels, which, paradoxically, are not adapted to a fluent and regular irrigation of the tumor, hence favoring its
277 dissemination to other, supposedly more welcoming, locations (35). The leaky vessels allow the tumor to escape
278 the noxious environment in which it grows (metastasis). Again, Ca^{2+} channels of the TRP family, namely
279 TRPV4 Ca^{2+} channels, are key determinants in the balance between normal and defective vasculature (2).
280 Indeed, tumoral endothelial cells naturally contain low levels of TRPV4. Conversely, overexpression or
281 pharmacological activation of TRPV4 normalizes the vasculature and restores the endothelial cell layer physical
282 and biophysical properties.

283

284 **III. Metastasis**

285 **A. The tumor microenvironment (TME): role and ion channel profile**

286 The extracellular environment of tumor cells is viewed as a complex network of stromal cells, deregulated
287 vasculature, extracellular membrane (ECM) proteins, growth factors and cytokines, all of which generated or
288 activated by the tumor cells, acting together to influence the growth, behavior and malignancy of the tumor

289 (236), and constantly evolving while the tumor grows and becomes more aggressive. The physical and chemical
290 characteristics of the TME is cancer-type dependent, but there are a number of typical, cancer type-independent
291 features, among which hypoxia, acidic pH, high levels of lactate and low levels of glucose (21, 82). In this
292 context, ion channels and transporters are important specialized proteins involved in the regulation of signaling
293 pathways associated with these properties. All the cells composing the tumor microenvironment (TME) are
294 laden with several types of misexpressed/overexpressed ion channels, which participate in the crosstalk
295 described by Arcangeli, between the tumor and its TME (8). These ion channels also contribute to maintain the
296 harsh conditions that allow tumor growth (33). Concerning the vasculature, we have already discussed the
297 channels involved in neoangiogenesis and mentioned the importance of endothelial cell Ca^{2+} homeostasis
298 throughout this process. Mesenchymal cells (fibroblasts, myofibroblasts, immune cells) also express ion
299 channels, particularly lymphocytes that infiltrate the tumors express K^+ channels of the $\text{K}_v1.3$ and $\text{K}_{Ca}3.1$ types,
300 which are involved in T cell activation via Ca^{2+} signaling (124). Interestingly, tumor-associated macrophages
301 express $\text{P2X}_7\text{R}$ non-selective cation channels and inwardly-rectifying K_{IR} K^+ channels; both families are
302 involved in the Ca^{2+} -dependent activation of macrophages (8).

303

304 B. Role of the epithelial-mesenchymal transition (EMT) in the metastasis process

305 Metastasis of epithelial cancer cells is a multistep process, which involves mobilization of the cells from their
306 original location, migration of the cells, invasion of surrounding locations, intravasation of cancer cells into
307 newly formed tumoral blood vessels, cell survival in the blood flow and seeding to more distant new niches,
308 where the cells start proliferating again, thus creating secondary tumors. Multiple oncogenic signals originating
309 from the TME convert the cells into their new metastatic and invasive phenotype. These signals lead the tumor
310 cells to acquire several biological capabilities described as hallmarks of cancer (95, 96) and mediated by an
311 epithelial-mesenchymal transition (EMT) process, otherwise called the metastatic cascade. During this cascade,
312 cells, which originally display epithelial cell features (i.e., adhesion to each other and to the basement
313 membrane, high level of E-cadherin involved in the epithelial integrity (16)) are progressively transformed into
314 mesenchymal cells (116). Briefly, during this process, polarized epithelial cells acquire a new phenotype, which
315 includes increased resistance to death, enhanced migratory capacities and invasiveness. The complete spectrum

316 of signaling agents that contribute to EMT remains an open question. EMT is a complicated process and ion
317 channels from several different families play a particularly important role in this transition (249).

318

319 1. Mobilization of the cells: involvement of ion channels

320 Loss of cell-cell contacts is the first step of EMT. This phenotype is associated with repression of cell junction
321 proteins, such as E-cadherin, and correlated with stimulation of both vimentin (an intermediate filament protein)
322 and N-cadherin (neural cadherin, normally expressed in migrating non-tumoral cells) synthesis (107, 164, 226).

323 This process has been shown in breast cancer cells to be Ca^{2+} -dependent (52). In fact, induction of EMT is
324 clearly related to the expression of TRPM7, the melastatin-like TRP Ca^{2+} channel. Indeed, upregulation of
325 TRPM7 regulates the expression of the EMT marker vimentin. Conversely, downregulation of the channel
326 prevents EMT induction in breast cancer cells. In colorectal carcinoma cells, the Ca^{2+} -activated KCNN4
327 ($\text{K}_{\text{Ca}3.1}$; SK4) channels have been shown to be involved in EMT promotion, probably through participation in
328 the cell hyperpolarization, subsequent induction of Ca^{2+} entry via voltage-dependent Ca^{2+} channels and an
329 increase in intracellular Ca^{2+} concentration (129).

330 Tumor cell mobilization is the next step in the metastatic cascade. This step involves migration of the cells from
331 their initial site and invasion of the surrounding stroma and vasculature. This is a complex process requiring the
332 coordination of multiple macromolecules involved in adhesion, cytoskeletal dynamics and digestion of the
333 ECM. Among the extracellular elements favoring EMT, hypoxia and microenvironment acidification have been
334 the most studied and are involved in tumor cell mobilization. As discussed earlier in this review, tumor acidity
335 is a direct result of hypoxia (83, 237). Indeed, low pO_2 raises the rate of glycolysis, which produces elevated
336 levels of lactate and protons in tumor cells. In order to maintain pH_i within a tight range ($\text{pH } 7.2 - 7.4$), the
337 tumor cells upregulate H^+ extrusion, which, in turn, results in microenvironmental acidosis, down to $\text{pH } 6.5$ (50)
338 or even to $\text{pH } 5.8$ as shown in highly metastatic MDA-MB-435S breast tumor cells (208). Extracellular acidosis
339 increases even more due to hypoxia-induced activation of carbonic anhydrases, especially CAIX (223).
340 Consequently, tumor cells are equipped with mechanisms that allow them to sense and react to the low pH_e to
341 which they have been exposed. pH sensors of several types are present in the plasma membrane of mammalian
342 tumor cells and these pH sensors are categorized into G-protein coupled receptors (GPCRs) and non-GPCR pH

343 sensors (50). GPCR signaling pathways are manifold: ERK pathway/ Ca^{2+} release (105), G_s -protein/cAMP,
344 $\text{G}_{12/13}$ -protein/Rho, and G_q -protein/phospholipase C pathways (140). pH sensing results in reorganization of the
345 cytoskeleton (e.g. actin rearrangement, stress fiber synthesis, etc.), thus contributing to tumor migration and
346 eventually to tumor progression (39). Non-GPCR proteins include ion channels of several families and
347 participate in migration and invasion phenotypes. Indeed, expression of the tumor cell cation-permeable Acid
348 Sensing Ion Channels (ASICs) is pH-dependent. ASIC1a is associated with tumor cell migration and invasion in
349 hepatocellular carcinoma cells (112); ASIC2a and ASIC3 have been identified in the plasma membrane of
350 adenoid cystic carcinoma cells and proposed to be involved in the acquired invasive capabilities of the cells
351 (257). The Ca^{2+} channel TRPV1 is also activated by low pH (259) and is correlated with tumor cell proliferation
352 in human prostate cancer cell lines (159). Both families of channels are involved in cancer-associated pain (57,
353 259) and plasma membrane phospholipids are proposed to be modulators of ASIC and TRPV1 activities (128).
354 Other acid-sensitive channels comprise several members of the Ca^{2+} channel TRP family, ionotropic
355 purinoceptors (P2X), inward rectifier K^+ channels (K_{ir}), voltage-activated K^+ channels (K_v family), L-type Ca^{2+}
356 channels (Ca_v , CACN), hyperpolarization-activated and cyclic nucleotide-gated cation channels (HCN), gap
357 junction channels, and Cl^- channels. They are involved in the process of tumor cell migration (217).
358 Interestingly, the Ca^{2+} -activated, high conductance, BKCa K^+ channels are not involved in breast cancer
359 progression, as shown by the absence of effect of iberiotoxin (an inhibitor of BKCa) in the processes of
360 proliferation, survival, migration or invasion in several breast cancer cell lines (200).
361 Migratory cells are polarized along their longitudinal axis, with hypoxia- and TME acidosis-dependent
362 protrusion of lamellipodia at the cell front edge and coordinated retraction of the rear edge (213). This process is
363 intracellular Ca^{2+} concentration-sensitive, thus involving Ca^{2+} release from intracellular stores and SOCE
364 channels (228). It creates the amoeboid movement characteristic of migrating tumor cells which is highly
365 dependent on ion and water flux (210). Indeed, the formation of lamellipodia is accompanied by relocalization
366 at the leading edge of a number of plasma membrane transport proteins, among which CAIX, NHE, MCT (all
367 involved in pH modulation), anion exchangers (such as NBC transporters or the anion exchanger AE2) and
368 water channels (aquaporins; AQP). It is proposed that the coordinated action of all these channels and
369 transporters makes it possible for the cells to establish the osmotic gradient that subsequently induces AQP-
370 mediated water flux at the leading edge of the cell. Water extrusion by AQP, at the rear end of the cell, is

371 mediated by the combined activity of Ca^{2+} -activated K^+ channels ($\text{K}_{\text{Ca}3.1}$) and Volume-Regulated Anion
372 Channels (VRACs) and leads to regulatory volume decrease (RVD) and shrinkage of the cells (206).

373

374 2. Invasion of surrounding TME and vasculature

375 Invasion of healthy tissues by tumor cells is critically dependent on the local degradation of ECM and basement
376 membrane, which otherwise would constitute a barrier to tumor metastasis. The degradation process thus creates
377 the escape pathway by which single tumor cells leave their primary location and colonize surrounding areas.
378 This degradation results from the low extracellular pH produced by tumor cells and relies on the secretion or
379 membrane expression of acid-dependent proteases (MMPs and cathepsins). Soluble (MMP2, MMP9) or
380 membrane-bound (MMP14) MMPs are key enzymes in tumor cell invasiveness, involved in both ECM and
381 basement membrane degradation (187, 193, 253) and involved as well in the angiogenic sprouting (18, 53).
382 MMP activity is promoted by low pH_e localized at the front part of migrating cells. As stated above, NHE1 is
383 one of the main actors of this extracellular acidification. While the acidification process appears as a crucial step
384 to weaken and break the ECM barrier, the physical progression of aggressive tumor cells relies on the formation
385 of ECM-degrading protrusions, called invadopodia, at the leading edge of the cells. NHE1 has been localized
386 within these invadopodia (29) and this localization has been correlated with extracellular acidification and MMP
387 expression and activity (88), thus suggesting the invadopodia as the major sites of ECM digestion and NHE1 as
388 the main channel involved in this process.

389 Voltage-gated sodium channels are highly expressed in epithelial tumors. In the MDA-MB-231 breast cancer
390 cell line, the $\text{Na}_\text{v}1.5$ Na^+ channel, by driving Na^+ influx and depolarizing the cells, greatly increases NHE1
391 potency to promote extracellular acidification and tumor invasion (23, 24, 86).

392 Calcium channels are also involved in the migration and invasion processes. Indeed, TRP channels, which
393 mediate SOCE Ca^{2+} entry and regulate intracellular $[\text{Ca}^{2+}]$, especially TRPV2 (158) and TRPM8 (169),
394 positively influence carcinoma invasion by upregulating MMP2 and MMP9 synthesis and production. Thus,
395 MMP production may be an intracellular $[\text{Ca}^{2+}]$ -dependent process. Interestingly, high concentrations of ATP
396 are observed in the TME of most hypoxic solid tumors (181). ATP acts as a signaling agent by activating
397 plasma membrane ligand-gated receptors of the P2X family, namely P2X₇R cation channels promote migration

398 and invasion, as shown in T47D breast cancer cells (253). P2X₇R cation channels mediate Ca²⁺ influx in tumor
399 cells thus contributing to the increase in intracellular [Ca²⁺]. In the breast cancer cell line MDA-MB-435S, ATP
400 activation of P2X₇R cation channels activates Ca²⁺-dependent SK3-mediated potassium currents, thus favoring
401 the elongation of cell protuberances, which, in turn, promote cell migration (110). In this model, the P2X₇R-
402 promoted invasive phenotype also relies on the activation of proteolytic enzymes, essentially cathepsin B.
403 Correlatively, pharmacological inhibition or downregulation of P2X₇R channels in PC-3M human prostate
404 carcinoma-derived cell lines inhibit ATP-driven migration and invasion (193). This Ca²⁺-dependent process
405 requires activation of either PI3/AKT or ERK1/2 signaling pathway. It reduces the expression of proteins
406 involved in the maintenance of cell-cell contacts (e.g. E-cadherin and claudin-1) and correlatively increases the
407 expression of Snail (an inhibitor of E-cadherin), interleukin 8 (IL-8, a promoter of migration and angiogenesis)
408 and MMPs, thus contributing to the invasion phenomenon. The metastasis- and malignancy-promoting status of
409 P2X₇R, however, is still an important field in cancer research. Indeed, recent studies have been designed to
410 explore the effects of P2X₇R on tumor development and metastatic outcome *in vivo*. Hofman and collaborators
411 demonstrate that colitis-associated cancers (colon adenocarcinoma, colon carcinoma) are favored by P2X₇R
412 silencing or pharmacological inhibition (103). A different study reveals that P2X₇R restricts tumor progression
413 by developing antitumoral immunity (4).

414

415 3. Metastasis: transit in blood vessels and extravasation

416 Tumor cell metastasis occurs when the cells successfully escape from their primary location, overcome the step
417 of transit in the circulation as unattached cells and finally disseminate to their secondary sites by extravasation
418 from the vessels and reattachment to a new ECM support.

419 Circulating tumor cells do not always survive long enough to metastasize. It is estimated that only 0.01% of the
420 cells that enter the vasculature will eventually survive the harsh conditions to which they are submitted (87).

421 Tumor cells must resist anoikis whereby apoptosis is triggered by inadequate or loss of cell anchorage. Among
422 the multiple signals involved in anoikis resistance, several types of ion channels have been described (137).

423 Indeed, to effectively resist detachment-induced apoptosis, tumor cells utilize mechanisms that eventually limit
424 the rise in intracellular [Ca²⁺]. Ca²⁺ channels are thus downregulated, especially those acting via SOCE (130).

425 Depletion in other Ca^{2+} channels (TRPM2, TRPV6) also tends to reduce cell apoptosis (211). Activity of
426 caspases and other DNA-degrading enzymes, as well as a decrease in membrane potential have been linked to
427 loss of intracellular $[\text{K}^+]$ by K^+ channels. Cell shrinkage involved in apoptotic volume decrease (AVD) results
428 from a loss of KCl by K^+ and Cl^- channels, with a concomitant loss of water. Thus, downregulation of K^+ (K_v ,
429 K_{Ca} , K_{ATP} , K_{IR} , $\text{K}_{2\text{P}}$) and Cl^- channels also prevents apoptosis (26). Alternatively, anoikis-resistant cells can
430 develop regulatory volume increase (RVI) whereby Cl^- channels of the volume-regulated (VRAC) family,
431 especially prostate cancer cell ClC-3 (138), which are involved in the maintenance of cell volume under
432 hyperosmotic stress, are upregulated in cells that resist apoptosis. Interestingly, Ca^{2+} -activated Cl^- channels
433 (CLCA) may be either activated or not activated in anoikis-resistant cells, as shown in mammary gland cells
434 (67, 244), thus suggesting a different function of these channels in cancer cells.

435 Tumor cells are subjected to mechanical forces resulting from the blood stream, especially in narrow capillaries.
436 Mechanical stress is the main destruction pathway that tumor cells must avoid in order to be able to form
437 metastases. To prevent destruction, they develop integrin-involving adhesion processes and eventually get
438 attached to the endothelial bed of the vessel in which they are traveling (81). This interaction between
439 circulating tumor cells and endothelial cells is fundamental for the rest of the metastasis process, as it
440 determines the site where the cells will eventually exit from the vessel, hence initiating the extravasation
441 process. Gout and Huot have described the whole process of extravasation (87). Briefly, this process involves a
442 first step of tumor cell adhesion to endothelial cells, utilizing specific receptors. Tumor cells rolling along the
443 endothelial layer characterize this “light adhesion” step. A second step of firmer cell attachment then takes
444 place, mediated by cytokines and cell adhesion molecules. Extravasation (or diapedesis) finally occurs when the
445 cells cross the endothelial barrier through cell-cell junctions. As for several steps of the tumorigenesis process,
446 the importance of intracellular $[\text{Ca}^{2+}]$ and of the associated Ca^{2+} channels is also demonstrated for metastasis of
447 tumor cells. Indeed Orai1 , the pore-forming component of the store-operated Ca^{2+} channel and its associated
448 STIM1 Ca^{2+} sensor are associated with cell migration, invasion and metastasis in human breast carcinoma cells
449 (256). *In vivo* studies in a zebrafish model corroborate the importance of the $\text{Orai1}/\text{STIM1}$ partners and of
450 SOCE Ca^{2+} entry in the process of cell extravasation (262). Indeed, inhibition of the store-operated Ca^{2+} entry or
451 knockdown of Orai1 in nasopharyngeal carcinoma cells prevents extravasation of the cells from vasculature in a
452 zebrafish hematogenous metastasis model.

453 Finally, diapedesis is the result of tumor cells passing in between insufficiently tight endothelial cell junctions
454 (due to damaged vasculature). The alterations in cell shape necessary for diapedesis are most likely explained by
455 K^+ and Cl^- fluxes and by the following water fluxes. Indeed, it has been already shown that glioma cell
456 migration and invasion are supported by K^+ and Cl^- channels, which, by governing transmembrane water
457 movements and the resulting cell shape, are important for glioma invasion through narrow spaces (215).
458 Colonization of the secondary site by the tumor is not simply a matter of gaining access to this site. Tumor cells
459 will only be able to colonize compatible target tissues. The host tissue must then adapt to be able to foster the
460 colonizing tumor cells; this is the concept of “pre-metastatic niche” (212). Tumor cells must also adapt to their
461 new stroma and become able to secrete all the molecules necessary for their efficient attachment and ulterior
462 vascularization (91). Hence, there are many barriers to overcome before the tumor actually metastasizes.

463

464 **IV. Sigma 1 receptor: the main organizer?**

465 In the present review, we will skip the long history of sigma-1 receptor (Sig-1R), which has been widely studied
466 on the functional, pharmacological, structural and mechanistic points of view for the last 30 – 40 years (11, 148,
467 245). Similarly, we will not open this discussion to the sigma-2 receptor, which has not been cloned yet,
468 although it was shown to be involved in cancer development (234). Instead, we will focus on the specific role of
469 chaperone of Sig-1R that is of major interest in the context of cancer development.

470 Sig-1R is a 25 kD, endoplasmic reticulum (ER)-resident, ligand-regulated protein, which is involved in many
471 diseases, ranging from toxic substance addiction to stroke and cancer (10, 11, 148). It is mainly present in
472 normal brain, heart and liver, but is highly expressed in tumor cell lines and human cancer tissues of various
473 origins, including lung, colon, prostate carcinomas, sarcomas, breast tumors, brain tumors, and melanomas (10,
474 11, 113, 173, 241), in which it interferes with cell cycle and proliferation (10, 197). Interestingly, in breast
475 cancer cells, Sig-1R positively correlates with the metastatic grade of the cells, i.e. highly metastatic cells
476 contain higher levels of Sig-1R mRNA and protein than their less aggressive counterparts (10).

477 Sig-1R is anchored in the ER membrane, in a specific region called mitochondrion-associated ER membrane
478 (MAM). At rest, it is in a “dormant” state, associated with a chaperone protein, called GRP78 or BiP (100). BiP

479 is a main regulator of ER function: it has a high Ca^{2+} -buffering capacity and serves to store Ca^{2+} , which is
480 essential to many signaling pathways. Under specific ligand stimulation or under prolonged ER stress such as
481 ER Ca^{2+} depletion, Sig-1R is up-regulated, dissociates from BiP and becomes able to act as a chaperone (100)
482 after translocation to other ER areas or to the plasma membrane (101). In the plasma membrane, Sig-1R
483 interacts with – and regulates the activity of – several ion channels (Ca^{2+} , K^+ , Na^+ , Cl^-), receptors (NMDA
484 receptor) or kinases (Src) (148).

485 In the context of cancer development, as we discussed earlier in this review, many ion channels of diverse
486 classes (voltage-gated, calcium-gated, volume activated) are involved in a number of tumor cell processes.
487 Voltage-gated ion channels are involved in cell processes including proliferation, apoptosis, angiogenesis,
488 adhesion to ECM and migration. Interestingly, Sig-1R interacts with most of these channels, as demonstrated in
489 several works (12, 13, 126, 197). Patch-clamp studies and western blot assays in the presence of Sig-1R ligands
490 (e.g. (+)-pentazocine, igmesine, and 1,3-di(2-tolyl)guanidine [DTG]) were conducted in small cell lung cancer
491 (SCLC) derived cell lines (NCI-H146 and NCI-H209) and in T-cell leukemia-derived Jurkat cells. These studies
492 demonstrate that ligand-mediated inhibition of Sig-1R results in cell cycle arrest in G_1 phase with no stimulation
493 of apoptosis (197). This effect correlates with the reduction of voltage-operated K^+ currents in all these cell
494 lines, indicating that Sig-1R-mediated cell growth arrest is the result of the negative regulation of K^+ channels
495 (197). Cell cycle arrest also correlates with the negative modulation of Volume-Regulated Chloride Channels
496 (VRCC), both effects leading to the overall inhibition of the Regulated Volume Decrease (RVD) process, (196),
497 which is known to govern cell cycle progression and numerous cellular functions such as proliferation,
498 apoptosis, migration, ... (202). The *Xenopus* oocyte system allowed direct reconstitution (in the absence of Sig-
499 1R ligands) of the interaction that exists between Sig-1R and potassium channels (Kv1.4 and Kv1.5) and
500 established that Sig-1R directly acts as an auxiliary subunit of a few channels to govern several cell functions
501 (12). In order to provide further evidence of this direct interaction, I participated in a study (47) showing that in
502 chronic myeloid leukemia (CML)-derived cells (K562) – which overexpress Sig-1R – the abnormally expressed
503 cardiac K^+ channel hERG co-immunoprecipitated with Sig-1R. In this model, Sig-1R extinction by a specific
504 shRNA or Sig-1R inhibition by Sig-1R ligands led to the reduction of hERG K^+ currents, whereas co-injection
505 of both hERG and Sig-1R in *Xenopus* oocytes increased hERG current when compared to oocytes injected with

506 hERG alone. This modulation proceeds from the regulation of hERG channel maturation and stability, which is
507 in adequation with the role Sig-1R as a chaperone of hERG K⁺ channel in cancer cells (47).

508 Recently, using the technique of atomic force microscopy, Sig-1R was shown to physically associate, in a four-
509 fold symmetry (1 channel molecule vs. 4 Sig-1R molecules), with the voltage-gated Na⁺ channel Na_v1.5 (13),
510 previously proven to promote invasiveness in breast cancer cells (24, 86). With the same technique, the same
511 team demonstrated physical interaction between Sig-1R and acid-sensing ion channels (ASIC1a; (36)) and
512 provided evidence of Sig-1R association with the heteromeric GluN1/GluN2A NMDA receptor, via specific
513 binding of Sig1R to the GluN1 subunit (14).

514 These data raise the following question: how can an ER protein interact with plasma membrane ion channels of
515 so many different families and govern so many cell functions in oncogenesis? A plausible explanation resides in
516 the following observations: 1) Sig-1R is localized in ER, a cell area where Ca²⁺ signaling is crucial; 2) Sig1R is
517 highly mobile in the ER membrane and Sig-1R overexpression, cellular stress or pharmacological treatment lead
518 to dissociation of Sig-1R from its chaperone BiP and subsequent translocation to the plasma membrane (100,
519 149, 221), where it interacts with its client proteins (ion channels, receptors). Indeed, during cancer progression,
520 the tumor cells undergo harsh conditions (hypoxia, low pH, starvation in nutrients) or even treatments that
521 create cell stress and alter ER protein expression levels or generate abnormal secretion of ER-resident
522 chaperones (157). Indeed, inasmuch as ER chaperones such as Sig-1R contribute to the correct folding of newly
523 synthesized or conformationally distorted proteins, or to protect proteins that are prone to de misfolded, their
524 role becomes crucial in case of cell stress. Moreover, it is worth pointing out that the BiP-Sig-1R association is
525 tightly regulated in an ER Ca²⁺/Mn²⁺-dependent manner. Any cell signal that results in lowering ER Ca²⁺
526 concentration below physiological concentration (0.5 mM) leads to disassembly the two chaperones, thus
527 increasing the activity of each (100). Under cell stress conditions, Sig-1R stabilizes the conformation of type3-
528 IP3 receptor in the ER, thus stimulating Ca²⁺ transport from the ER to the mitochondria (100) and to the cytosol
529 (252). Hence, Sig-1R orchestrates Ca²⁺ signaling between ER and mitochondria, by fueling the production of
530 ATP by the mitochondria, which conversely regulates Ca²⁺ concentration in the ER (99). Sig1R also maintains
531 proper folding and proper function of the plasma membrane proteins challenged by cell stress: it thus plays a
532 major role in cell survival (Figure 3). Sig-1R has since then been proposed as a modulator of inter-organelle
533 signaling (220).

534 Subsequently, several lines of evidence demonstrate that Sig-1R interacts with different types of proteins
535 including ER stress sensors, cytokines, ion channels and that this interaction constitutes the mechanism whereby
536 Sig-1R governs cancer cell behavior in response to alterations of the tumor microenvironment. Sig-1R
537 modulates cell survival (160), apoptosis (60, 151) and cell cycle (196, 197). Recently, I participated in a study
538 presenting evidence that Sig-1R is a key regulator of the signaling events that occur between the tumor cell and
539 its microenvironment. Indeed, in chronic myeloid leukemia- and colon carcinoma-derived cells (resp. K562 and
540 HCT-116 cells), we showed that extracellular matrix triggered a Sig-1R-dependent increase in cell adhesion,
541 cell migration, cell invasiveness, as well as VEGF secretion (48) and that a hERG K⁺ channel-β1 integrin
542 interaction mediated these effects in both cell lines. Silencing of Sig-1R in K562 and HCT-116 cells resulted in
543 *in vivo* reduction of angiogenesis, invasion and extravasation (48). Sig-1R thus appears as a major regulator of
544 tumor development. Further studies are necessary to assess whether Sig-1R might be envisioned as a therapeutic
545 target and whether Sig-1R ligands might be designed as antitumoral treatments.

546

547 **V. Antiangiogenic therapy and therapy resistance**

548 Cancer is one of the deadliest pathologies, with approximately 14 million of new cases and 8 million of cancer-
549 related deaths in 2012; negative WHO predictions expect annual cancer cases to rise from 14 million in 2012 to
550 22 million in the next two decades. Carcinomas (lung, liver, stomach, colorectal, breast, esophageal) are among
551 the most common causes of cancer deaths <http://www.who.int/mediacentre/factsheets/fs297/en/>.

552 Conventional global anti-tumoral therapies (chemotherapies) are only partly efficient because of the lack of
553 responsiveness of some cancers and because these therapies sometimes induce systemic toxicity or resistance,
554 ending up in treatment discontinuation. For vascularized cancers, a more precise strategy of angiogenesis
555 inhibition has been developed, which focuses on the neutralization of the effects of angiogenic factors (FGF,
556 VEGF) or on the inhibition of their receptors (70, 122). This strategy leads to vasculature destruction. Given the
557 drawbacks of such therapies (89, 90), which can lead to more severe condition or even to death (194, 195), solid
558 tumor therapies evolved towards normalization rather than destruction of the abnormal vasculature, the
559 objective being to restore a close to normal blood flux and pO₂, to favor normal immune cell function and

560 finally, to allow efficient delivery of anticancer agents (106, 109, 190, 219). Thus, antiangiogenic therapies were
561 used to treat several vascularized cancers in the last 40 years. However, too many carcinomas are still refractory
562 to antiangiogenic-based treatments.

563 Hence, in parallel to existing therapeutic strategies, it is important to identify predictive biomarkers of stage and
564 aggressiveness for the different types of tumors, as well as further targets for the development of
565 complementary treatments to be used in combination with VEGF-targeted therapies. Carcinogenesis is a
566 multistep process in which each step constitutes a potential angle of attack for a new therapeutic strategy
567 development. Ion channels are implicated in the growth, migration, invasion and metastasis of tumors and
568 therefore cancers can be included in the category of “channelopathies” (pathologies characterized by alterations
569 in channel function). Consequently, recent studies present ion channels as potential targets for the development
570 of future treatments. Several factors are in favor of the use of ion channels as therapeutic targets: i) cell
571 expression of ion channels is often modified in cancers; ii) this expression varies with the type of tumor and, in
572 a given type of tumor, with the specific step of tumor progression; iii) ion channels are accessible from the
573 extracellular side of the cell and the potential pharmacological tools (available or yet to be designed) are
574 multiple.

575 We do not intend here to review how ion channels can be targeted in each step of cancer development or in
576 different cancers to design potential therapeutic strategies. Several excellent reviews have already been written
577 from these standpoints (9, 49, 155, 203, 239). Rather, we will take a few examples of global cancer-associated
578 clinical dysfunctions in which ion channels may be targeted in order to restore normal function or diminish
579 cancer-associated disagreements and, finally, to improve patient’s condition.

580

581 *Restoring a less toxic microenvironment*

582 Concomitant with gradual accumulation of mutations in tumor cells, changes in the physical parameters of the
583 microenvironment also contribute to reinforce the cell aggressiveness. Among these physical changes, as
584 discussed in §II.A of this review, the microenvironment undergoes hostile conditions characterized by low pO₂,
585 high interstitial pressure, low extracellular glucose and high extracellular lactate – all of these create high
586 extracellular acidity. Regulating the establishment of such harsh conditions would reduce the metastatic
587 potential of tumor cells. Cancer therapies thus include trials based on the regulation of extracellular pH. They

588 consist of systemic buffering using sodium bicarbonate to increase extracellular pH or take advantage of the
589 proton transport systems involved in tumor cells (150). For the latter, inhibition of carbonic anhydrases
590 (especially CAIX), of the Na^+/H^+ exchanger, using amiloride or EIPA are efficient but have not been developed
591 for clinical use. Conversely, inhibition of the vacuolar H^+ -ATPase, using omeprazole (already used to suppress
592 gastric acidity) was proven efficient as a pH normalizer in cancer treatment. Interestingly, the opposite treatment
593 consisting in hyperacidification of tumor cells or of their microenvironment is also a promising treatment.
594 Intracellular hyperacidification promotes tumor cell apoptosis whereas extracellular hyperacidification may
595 provide an important tool to deliver therapeutic agents directly to the tumor site using acid-accumulating
596 peptides (69).

597

598 *Normalizing the vasculature*

599 Carcinoma progression is associated with the production, by tumoral and stromal cells, of angiogenic factors,
600 which participate in the development of a non-productive angiogenesis, due to blood vessel disorganization and
601 to vessel wall high permeability. Antiangiogenic treatments, which tend to block the development of new blood
602 vessels and harvest the tumor from oxygen and nutrients, are inadequate or even counter-productive to treat
603 cancers. Other targets are now under scrutiny, which could participate in the emerging process known as
604 vascular normalization, and among these targets are ion channels. Physical properties of the ECM have been
605 shown to influence normal and malignant cell behavior. Especially, angiogenic response is influenced by the
606 stiffness of tumor ECM (134). Ca^{2+} influx is one of the main responses of endothelial cells to the mechanical
607 stress resulting from the growth of new vessel tips in such a stiff environment. In a recent paper, it has been
608 shown that in a model of mouse prostate adenocarcinoma, mechanosensitive transient receptor potential
609 vanilloid 4 (TRPV4) calcium channels regulate angiogenesis and tumor vessel maturation by the regulation of
610 tumor endothelial cell mechanosensitivity via the reduction in basal Rho activity (2). This confirms that ion
611 channels must be included in the set of molecules to be targeted in the design of the new tools aiming at
612 normalizing vasculature, hence allowing better delivery of complementary antitumoral therapies. To further
613 reinforce the biological relevance of Ca^{2+} channels as molecular targets for antitumoral treatments, we can
614 mention that all the families of Ca^{2+} channels have recently been the focus point of researches demonstrating the
615 involvement of these channels in pro-angiogenic processes. Many of these channels are now the object of

616 patents that describe the use of modulators of their function in order to treat the symptoms associated with
617 cancer, i.e., proliferation, angiogenesis and metastasis; for review, see (163). The use of K^+ channel or pH
618 modulators to fight cancer development has been patented as well (49, 198).

619

620 *Fighting cancer-induced pain*

621 Cancer-related pain is one of the most devastating side effects of tumor development. Indeed, hypoxia and,
622 consequently, tumor acidosis are known to be responsible for the generation of pain (108). Cancer-related pain
623 can also be the result of tumor metastasis especially in the case of bone dissemination. Indeed, cytokines
624 produced by the tumor cells or by the bone microenvironment activate osteoclasts and thus contribute to the
625 signaling of cancer-associated pain in bones (225). Anti-tumoral treatment administration can, by itself, be a
626 factor of pain, whether the treatment is traditional chemotherapy, radiation, or surgery.

627 Moreover, it now seems that, except for morphine, for which the study results are not conclusive, conventional
628 pain-reducing therapies (NSAIDs, cannabinoids, opioids, GABA-ergic drugs) may have a negative impact on
629 cancer evolution (135). Consequently, the research of other analgesics and their targets is required. Current
630 research on this topic focuses on ion channels associated with pain, such as ASIC (57, 258), especially ASIC3
631 (56), and such as TRP channels of several sub-families, especially TRPV1 (192). Indeed, both types of channels
632 are known to be expressed in sensory neurons and to be activated by an acid load. These channels represent
633 relevant targets for the future development of new analgesics. Treatments based on TRPV1 pharmacological
634 inhibitors are already being clinically tested with some showing promising results (22). Voltage-gated Ca^{2+}
635 channels and voltage-gated Na^+ channels are also under study, especially $Ca_v2.2$, $Ca_v3.2$, $Na_v1.7$, $Na_v1.8$.
636 Specific antagonists derived from conotoxins have been developed and now seem to have good results in
637 clinical tests (242).

638 This field of research is still wide open and progressing very quickly. It is interesting to note that most of the ion
639 channels involved in the perception of pain are also implicated in one step or another of tumor development.
640 This leaves open the possibility that a specific treatment designed against an ion channel in order to treat cancer-
641 associated pain might also be used to prevent cancer progression. In particular, cannabinoids demonstrate
642 antitumoral effect in several cancer types (hepatocellular carcinoma, ccRCC, etc.), which is not mediated by the
643 regular CB1 and CB2 cannabinoid receptors (131, 235). Since cannabinoids can bind to many different ion

644 channel types, such as GPCR, NMDA receptors, GABA_A receptors (182), any of them can mediate the effect of
645 cannabinoids in tumor cells, thus shedding a new light on the yet unexplained anti-oncogenic effect of
646 cannabinoids.

647 In this topic, it is tempting to propose the potential development of Sig-1R ligands as treatments to fight cancer-
648 induced pain. Indeed, as we mentioned earlier, Sig1R promotes the action of ASIC channels, which are involved
649 with nociception (36). Sig-1R-inhibiting agents might be a way to obtain relief in this matter.

650

651 **VI. Conclusion**

652 A new concept in oncogenesis has emerged for the last 20 to 25 years, which states that ion channels and
653 transporters regulate different aspects of the neoplastic cell physiology. A growing body of evidence now
654 demonstrates that they govern the so-called “hallmarks of cancer”. As for neoangiogenesis, ion channels are
655 involved at all stages, in tumor cells, as well as endothelial cells or stromal cells. Ion channels thus represent a
656 new and promising field of research concerning the development of novel therapeutic agents. TRP channels for
657 instance, which are highly expressed in endothelial cells and involved in thermosensation, osmoregulation and
658 mechanoreception, are under current scrutiny for novel therapeutic strategy developments. Similarly, whereas
659 monocarboxylate transporters (MCT1 and MCT4) have now emerged as anticancer targets, the lactate shuttle
660 mechanism governing tumor cell pH regulation is still under study (55, 59). However, it is important to take into
661 account that most ion channels, though overexpressed in many cancer types, still exist in healthy organs. The
662 use of ion channel inhibitor-based therapies might thus induce many side effects, which will need to be carefully
663 prevented or minimized. As an example, blocking hERG1 K⁺ channel prevents the angiogenic switch in
664 colorectal cancer and, in turn, reduces metastasis (46). However, hERG1 is one of the main heart-expressed K⁺
665 channels, which certainly hinders the use of any of the current hERG1-targeted molecule as a cancer therapeutic
666 agent. It might thus be important to develop non-cardiotoxic hERG1 blockers to be used as complementary anti-
667 angiogenic treatments. The ion channel-based antitumoral therapies, though very attractive and potentially
668 powerful, probably need more research time in order to be carefully designed for safe clinical use. It might be
669 more fruitful to develop pharmacological treatments against Sig-1R, taking into account that this protein is

670 present in many tissues (CNS, lung, liver, pancreas, spleen), in membrane compartments. Targeted
671 pharmacological action on Sig-1R at the MAM or at the plasma membrane represents a potential new axis for
672 the development of therapies against numerous diseases including cancer.

673

674

675 **ACKNOWLEDGEMENTS**

676 I am very grateful to Ryan Arant, Hélène Guizouarn, Gilles Pagès and Olivier Soriani for their careful reading
677 of the manuscript and useful comments.

678

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1319

1320 FIGURE LEGENDS

1321

1322 **Fig. 1:** Schematic representation of the different transport systems activated in tumor cells by hypoxia.

1323 Hypoxia induces activation of the α subunit of HIF1 (hypoxia-induced factor), which dimerizes with HIF1 β to
1324 result in HIF1. HIF1, in turn, stimulates a set of proteins involved in membrane ion or solute transport. NHE:
1325 Na⁺/H⁺ exchanger; ASIC: Acid-Sensing Ion Channel; NBC: Na⁺/HCO₃⁻ cotransporter; CAIX: carbonic
1326 anhydrase type IX; GLUT: Glucose transporter; MCT: Monocarboxylate transporter.

1327

1328 **Fig. 2:** Schematic representation of Ca²⁺ signaling in endothelial cells activated by the tumor environment
1329 physical and biochemical conditions. In a hypoxic environment, acidification of the microenvironment triggers
1330 the synthesis and release of VEGF (blue circles) by both tumor and stromal (CAF) cells. VEGF binds to its
1331 specific endothelial cell receptor (VEGF-R2), which, in turn, activates Ca²⁺ entry by two main processes. Store-
1332 operated Ca²⁺ entry (SOCE) results from 1) activation of Ca²⁺ release from endoplasmic reticulum (ER),
1333 especially via inositol 1,4,5-trisphosphate (IP₃R), and subsequent replenishment of these stores by Ca²⁺ entry via
1334 TRPC1 or TRPC4 channels; 2) activation of the stimulating unit (STIM) of the STIM-ORAI complex and
1335 subsequent Ca²⁺ influx by the ORAI transporting unit. Receptor-operated Ca²⁺ entry (ROCE) results from the
1336 direct activation of TRPC3 or TRPC6 Ca²⁺ channels. The ensuing increase in intracellular [Ca²⁺] is the
1337 mainspring of mobilization, organization and permeabilization of new blood vessels.

1338

1339 **Fig. 3:** Schematic representation of plasma membrane ion channel chaperoning and Ca²⁺ signaling enhancement
1340 by Sig-1R in cancer cells (adapted after Su et al, 2010, Trends Pharmacol. Sci.31: 557-566). During cancer
1341 progression, tumor cells are submitted to stressful conditions caused by low pO₂, low pH, and few nutrients.
1342 Under these conditions, Sig-1R (blue wide arrow) released from its ER co-chaperone BiP, activates the ER
1343 IP₃R3 Ca²⁺ channel, thus enhancing Ca²⁺ flux from the ER to the mitochondria and increasing the production of
1344 energy by the mitochondria. Sig-1R also stimulates the *bcl2* oncogene transcription, which reduces ROS
1345 production by the mitochondria and is in favor of cell survival. Under prolonged conditions of stress, ER
1346 chaperones are up-regulated; Sig-1R is overexpressed and translocates to the plasma membrane area where it
1347 becomes able to chaperone and activate membrane proteins such as ion channels (hERG, Na_v1.5, ASIC1a, ...) or
1348 enzymes (e.g. Src kinase).

Table 1. Main ion channels and solute transporters involved in tumor development and their role in these processes.

TRANSPORT PROTEIN	GENE	OFFICIAL NAME	FUNCTION IN ONCOGENESIS
Water channel			
AQP-1	<i>Aqp1</i>	Aquaporin	Angiogenesis, proliferation, migration (66, 68, 120)
Solute carriers (Na⁺/solute exchangers)			
GLUT-1	<i>Slc2a1</i>	Glucose transporter	Tumor cell glucose metabolism (6, 84, 132)
GLUT-5	<i>Slc2a5</i>	Fructose transporter	Tumor cell glucose metabolism (240, 260)
NHE1	<i>Slc9a1</i>	Na ⁺ /H ⁺ exchanger isoform 1	Cell volume and pH homeostasis (33, 170) Tumor angiogenesis (80) Metastasis (88, 218)
Bicarbonate transporters			
AE1-3	<i>Slc4a1-3</i>	Anion exchangers	pH homeostasis (222) Cell migration (222)
NBC transporters	<i>Slc4a4, 5, 7, 10</i>	Sodium-bicarbonate cotransporters	pH homeostasis (180) Tumor growth (180) Metastasis (180)
MCT family of monocarboxylate transporters			
MCT 1-4	<i>Slc16a1-4</i>	Solute carrier family 16 members 1-4	Cell migration and metastasis (184)
TRP superfamily of cation channels			
TRPA (ankyrin) family	<i>Trpa1</i>	Transient receptor potential cation channel, subfamily A	Cell migration and metastasis (63) Nociception, inflammation (22)
TRPC (canonical) family	<i>Trpc1-7</i>	Transient receptor potential cation channel, subfamily C	Cell migration and metastasis (76) Tumor angiogenesis (261)
TRPM (melastatin) family	<i>Trpm1-8</i>	Transient receptor potential cation channel, subfamily M	Cell migration and metastasis (63) Tumor angiogenesis (75)
TRPV (vanilloid) family	<i>Trpv1-6</i>	Transient receptor potential cation channel, subfamily V	Cell migration and metastasis (119) Tumor angiogenesis (75) Nociception (22)
Voltage-gated family of K⁺ channels			
Kv1.1-1.8	<i>Kcna1-7, 10</i>	Potassium channel, voltage gated, shaker related subfamily A, members 1-7	Proliferation of cancer cells (168) Apoptosis resistance (168) Immunoresponsiveness (224)
EAG1, 2	<i>Kcnh1, 5</i>	Ether-a-go-go K ⁺ channels	Proliferation of cancer cells (31) Migration of breast cancer cells (183)
hERG 1-3 or Kv11.1-11.3	<i>Kcnh2, 6, 7</i>	Ether-a-go-go-related gene K ⁺ channels	Proliferation of cancer cells (214) Crosstalk with cell adhesion molecules (183) Tumor angiogenesis (183)

Table 1. cont'd

Two-Pore K⁺ channel family			
K _{2p} 2.1 or TREK	<i>Kcnk2</i>	Arachidonic acid-sensitive K ⁺ channel	Cell proliferation (243)
K _{2p} 3.1 or TASK	<i>Kcnk3</i>	Acid-sensitive two-pore K ⁺ channel	Cell proliferation (127, 243) Evasion from apoptosis (127)
Calcium-activated K⁺ channels			
K _{Ca} 1.1 or BK _{Ca}	<i>Kcnn1</i>	Large conductance Ca ²⁺ -activated K ⁺ channel	Proliferation (200) Apoptosis (28)
K _{Ca} 2.1-3 or SK1-3	<i>Kcnn1-3</i>	Small conductance Ca ²⁺ -activated K ⁺ channels	Cell migration and metastasis (37, 110, 191)
K _{Ca} 3.1 or IK _{Ca} or SK4	<i>Kcnn4</i>	Intermediate conductance Ca ²⁺ -activated K ⁺ channel	Proliferation of cancer cells (141) Cell migration (141) Tumor angiogenesis (141) Evasion from immune destruction (174)
Voltage-gated Na⁺ channels			
Na _v	<i>Kcnn1</i>	Voltage-gated Na ⁺ channel	Tumor cell migration, invasion, endocytosis (32) Metastasis (32)
Voltage-gated family of Ca²⁺ channels			
Ca _v 1.1-1.4	<i>Cacna1s, c, d, f</i>	L-type Ca ²⁺ current	Tumor angiogenesis (51)
Ca _v 2.1-2.3	<i>Cacna1a, b, e</i>	P/Q-, N-, R-type Ca ²⁺ currents	Tumor angiogenesis (154)
Ca _v 3.1-3.3	<i>Cacna1g, h, i</i>	T-type Ca ²⁺ currents	Tumor angiogenesis (204)
P2X Receptor (P2XR) family of Na⁺, K⁺, Ca²⁺ ion channels			
P2X ₇ receptor	<i>P2rx7</i>	Ligand-gated cation channel	Proliferation of cancer cells (3, 103) Apoptosis resistance (3, 103)
Acid-sensing ion channel family			
ASIC1-3	<i>Asic1-3</i>	Acid-sensing ion channels	pH homeostasis (92) Cell migration and invasion (92)
Chloride intracellular channel family			
CLIC1-6	<i>Clic1-6</i>	Nuclear and intracellular organelle Cl ⁻ channels	Tumor angiogenesis (232)
Calcium release-activated calcium channels (CRAC channels)			
Orai1 (works with STIM)	<i>Orai1</i>	Calcium release-activated calcium channel protein 1	Cell migration and metastasis (161, 216) Tumor angiogenesis (139) Immunosuppression (174)





