Review

The Contribution of Mitochondrial Ion Channels to Cancer Development and Progression

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Abstract

Mitochondria play a central role in cancer development, by contributing to most of the classical hallmarks of cancer, including sustained proliferation, metabolic re-programming, apoptosis resistance, invasion and induction of angiogenesis [1]. In addition, mitochondria affect also the function of anti- and pro-tumoral immune cells in the tumor microenvironment. Mitochondria harbor a plethora of regulated ion channels whose function is related to ion/metabolite transport and to fine-tuning of mitochondrial membrane potential as well as of reactive oxygen species release. As a consequence, growing evidence link ion channels located both in the outer and inner mitochondrial membranes to several cancer hallmarks. The present review summarizes our recent knowledge about the participation and role of mitochondrial channels leading to acquisition of cancer hallmarks and thus to cancer progression.

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Introduction

Mitochondria are bioenergetic organelles of endosymbiontic origin, where oxidative phosphorylation takes place in the inner mitochondrial membrane (IMM) leading to the generation of a proton motive force that can be exploited then for the synthesis of ATP. Although the chemi-osmotic hypothesis apparently contradicts the possibility of the presence of ion channels operating in the IMM, over the last three decades a number of highly-regulated ion channels have been identified in this membrane by using various techniques ranging from biochemistry to electrophysiology. Despite the fact that their identification in terms of genes encoding the proteins giving rise to channel activities in these membranes is not fully clear for each channel, a detailed pharmacological characterization helped to hypothesize their functions in mitochondrial physiology (for recent review see [2]). For the cases where

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molecular identity has been clarified, a combination of genetic and pharmacological tools allowed elucidation of the roles of these channels not only for cell physiology but also in pathological contexts, such as cancer development [3], chemo-resistance [4] and neurodegenerative diseases [5]. The field underwent a particularly intense development regarding calcium signaling in the above processes (e.g. [6]), mediated by mitochondrial Calcium-transporting channels/ transporters following the recent molecular identification of the mitochondrial calcium uniporter (MCU) [7, 8] and of the Ca^{2+}/Na^+ exchanger [9]. In the present review we give an overview of how specific mitochondrial ion channels affect specific hallmarks of cancer development and progression. First, ion channels of both the outer and inner mitochondrial membranes

Fig. 1. Contribution of mitochondrial ion channels to cancer hallmarks. The main hallmarks where participation of ion channels in mitochondria has been documented are listed. The crucial role of the mitochondrial uniporter and the porins (VDAC) in promoting cancer progression by acting on several different hallmark process is evident. A putative role for some ion channels in angiogenesis is indicated with question marks. See text for details.

(OMM and IMM, respectively) will be listed. Description of the specific ion channels' contribution to cancer hallmarks, where known, follows (Fig. 1). In many cases, more than one hallmark processes are regulated by a given mitochondrial channel, highlighting an especially important role for the OMM-located porin (VDAC), MCU and some potassium channels.
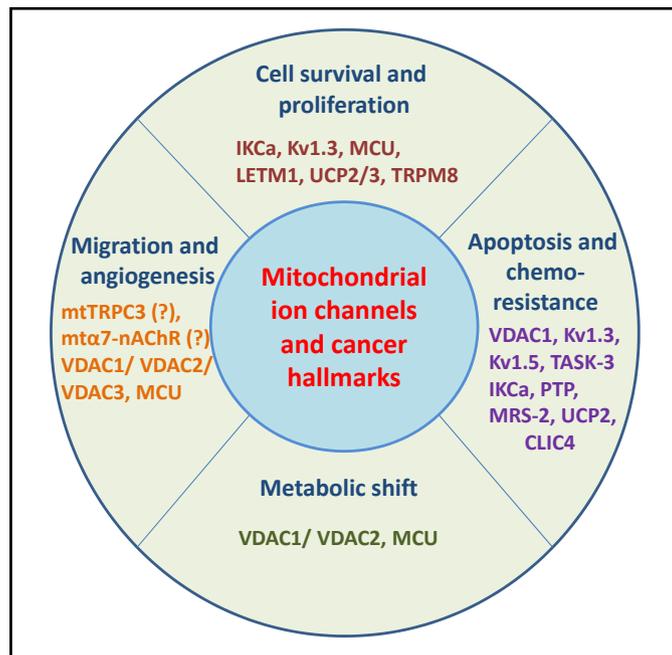
Mitochondrial outer membrane channels

The most extensively studied mitochondrial channels of the outer mitochondrial membrane (OMM) are the three isoforms of the β-barrel Voltage-Dependent Anion Channel (VDAC), or "mitochondrial porin" family (reviews: [10-12], namely VDAC1, VDAC2 and VDAC3. The most abundant mammalian isoform is VDAC1 [13]), present both in the OMM, in the plasma membrane (PM) [14, 15], in endosomes [16] and in the sarco/endoplasmic reticulum [17, 18]. Beside the three VDAC isoforms, electrophysiological or biochemical studies indicate that the OMM harbors also an inward rectifying potassium channel (Kir) [19], the nicotinic acetylcholine receptor α7 AChR found prevalently in the PM [20] and CLIC4, a member of the intracellular chloride channel family [21, 22].

Mitochondrial inner membrane channels

The inner membrane harbours a plethora of potassium channels, many of them being active in various membranes within the cells [10, 23-25]. The Big conductance potassium channel (BKCa)[26], Intermediate-conductance K^+ channel (IKCa)[27], Small conductance K^+ channel (SKCa)[28], the voltage-gated shaker type K^+ channels Kv1.3 [29], Kv1.5 [30], Kv7.4 [31] as well as a renal outwardly rectifying channel ROMK [32, 33] and the two-pore potassium channel TASK-3 [34] are all present both in the mitochondria and in the PM. Ca^{2+} channels that might contribute to mediation of Ca^{2+} fluxes across IMM include the TRPC3 channel [35, 36] and the mitochondrial ryanodine receptor (mRyR1), both showing multiple localization within the cell. Mitochondria-specific channels also exist, including the main pathway for calcium, the calcium uniporter MCU coiled-coiled helix-containing protein CCDC109A [7, 8], the magnesium-transporting channel Mrs2 [37], the Inner Membrane Anion Channel (IMAC), the uncoupler proteins (UCPs) and the mitochondrial permeability transition pore (MPTP) (for a summarizing review see [10]). Finally, a mitochondria-specific component of the ATP-dependent potassium channel (mitoKATP) [38], the coiled-coiled protein CCD51 has been recently identified [39]. Regarding the presence of chloride channels, CLIC5 was shown to be active in the IMM [22].

Mitochondrial ion channels and regulation of proliferation in cancer cells

Limitless cell proliferation, typical of cancer cells is supported by mitochondrial function, since tumor cells need to upregulate macromolecular biosynthesis while maintaining energy production [40]. Our knowledge about the role of mitochondrial channels in promoting proliferation is rather limited. Among potassium channels, IKCa has been shown to regulate oxidative phosphorylation (OxPhos) in pancreatic ductal adenocarcinoma where the channel is functional in both the plasma membrane and mitochondria. Knock-down experiments and channel inhibition by rac-16, a specific small molecule inhibitor pointed to its role in regulating oxygen consumption, ATP production and, as a consequence, cellular proliferation [41]. In particular, in different cell lines tested, inhibition of the channel had no or only minor effects on cell proliferation in the presence of glucose, but forcing the cells to generate ATP exclusively via oxidative phosphorylation by culturing them in galactose, allowed to understand that inhibition of the channel decreased proliferation. Although the underlying mechanism has not been fully elucidated a decrease in ATP synthesis may account for the reduced proliferation rate. Also, a PM IKCa-triggered signalling cascade leading to altered mitochondrial function cannot be fully excluded.

Another mitochondrial potassium channel whose inhibition at sub-lethal concentrations affected cell cycle progression and cell proliferation is mitochondrial Kv1.3. In this case, the drugs inhibiting this channel slightly increased the percentage of cells in S phase and decreased the population at G0/G1 stage of cells, presumably related to a slightly increased ROS levels within the cells [42]. On the other hand, sub-lethal concentrations of the same Kv1.3 inhibitors reduced Wnt signaling [43] that plays an important role in the uncontrolled proliferation of cancer cells, when it is constitutively activated (e.g. [44]). In this paper, the role of AMPK that is regulated by ATP:AMP ratio as well as that of AKT, a serine-threonine kinase has been explored in linking K^+ channel modulation to Wnt signaling, but no significant change in these signaling pathways occurred upon inhibition of channel activity [43].

In addition to K^+ channels, mitochondrial calcium fluxes also affect proliferation. A recent work revealed that a cell cycle-dependent rapid, mitochondrial Ca^{2+} transient mediated by MCU is able to link energy sensing to mitochondrial activity during mitosis, since inhibition of MCU caused a spindle checkpoint-dependent mitotic delay. Cellular ATP levels drop during early mitosis, causing an AMPK-dependent phosphorylation of MCU, its activation, Ca^{2+} uptake into mitochondria and consequent boost of mitochondrial respiration in order to restore energy homeostasis within the cell [45]. A constitutively active Ca^{2+} transfer from the endoplasmic

reticulum (ER) to mitochondria plays a crucial role to ensure viability of tumorigenic cells [46]. In particular, upon a decreased calcium transfer between the two organelles, ATP levels fall since calcium is necessary for the function of some metabolic enzymes (e.g. of the Krebs cycle). As a consequence, impairment of Ca^{2+} uptake into mitochondria prevents cancer cell survival, while healthy cells cope with this fall in ATP by activating autophagy via the energy-sensing AMP kinase (AMPK), therefore allowing cell survival. In general, cancer cell death correlates with inefficient bioenergetics. Interestingly, the transient receptor potential M8 (TRPM8) (a cold receptor), which is located in the ER membrane in keratinocyte, functions as ER Calcium-release channel and thus controls mitochondrial matrix Ca^{2+} level, is able to modulate mitochondrial ATP and superoxide synthesis in a cold-dependent manner. ATP is an inducer of keratinocyte proliferation, whereas superoxide anion triggers differentiation. The authors observed that regulation of these factors controls the balance between keratinocyte proliferation and differentiation [47]. No information is available about whether this mechanism might play a role in the uncontrolled proliferation of epithelial cancer cells and whether the ATP-sensing mitoKATP also contributes to fine tuning of proliferation. In addition, K^+ channels, by affecting membrane potential and thus the driving force for Ca^{2+} uptake, might contribute to the above signaling events that depend on Ca^{2+} levels in the matrix. However, to our knowledge, a possible cross-talk between K^+ channel and MCU activity has not been systematically addressed so far. Instead, a clear effect of the putative K^+/H^+ transporter LETM1 has been shown on Calcium influx/efflux into/from mitochondria [48] and silencing of LETM1 promoted AMPK activation, cell cycle arrest and autophagy [49].

Finally, activation of uncoupling proteins that induce futile mitochondrial respiration that becomes uncoupled from ATP synthesis, results in nutrient wasting and opposes high proliferation rate. Thus, activation of UCP would be expected to counteract cancer cell growth and proliferation. Indeed, forced mitochondrial uncoupling obtained by UCP3 overexpression was shown to inhibit skin carcinogenesis [50]. Interestingly, AKT activation was markedly inhibited in UCP3 overexpressing primary human keratinocytes as well as in cancer cells of epithelial origin. Uncoupling has the effect of increasing fatty acid oxidation and membrane phospholipid catabolism, and at the same time impairs recruitment of AKT to the plasma membrane. Indeed, overexpression of AKT can overcome the effects of UCP3, rescuing carcinogenesis [50]. Likewise, overexpression of the mitochondrial UCP2 in cancer cells is sufficient to repress malignant phenotypes via upregulation of AMPK expression. In addition, UCP2 overexpression led to down-regulation of hypoxia-induced factor (HIF1-α) expression. These two events are contributing thus to restore a balance toward oxidative phosphorylation by altering expression of glycolytic and oxidative enzymes [51]. Altogether, these results point to the regulation of metabolism in an AKT/AMPK dependent way through a non-canonical function of UCP proteins.

The above examples point to the hypothesis that in principle, any of the mitochondrial channels whose function modulates respiration, ATP production and ROS release might exert a regulatory effect on cell proliferation, involving AMPK and/or AKT kinase-related signaling downstream events. Indeed, low levels of ROS were shown to activate AMPK and AKT as well as apoptosis signal-regulating kinase/c-Jun N-terminal kinase (JNK) pathways. In addition, ROS released from ER and/or mitochondria at sub-lethal concentrations directly modulate the activities of transcriptional factors such as NF-κB, p53, and nuclear factor (erythroid-derived) 2-like (Nrf2) [52], thereby controlling proliferation.

Mitochondrial ion channels and metabolic shift of cancer cells

In order to sustain their proliferation, most cancer cells are characterized by a peculiar metabolism, namely aerobic glycolysis, called also Warburg effect. This type of metabolism ensures a high, uncontrolled cell proliferation rate even under relatively low nutrient availability. These pathologic cells prefer to convert pyruvate, produced by glycolysis, to lactate rather than to Acetyl-CoA, even in the presence of molecular oxygen that would allow complete oxidation of pyruvate through the Krebs cycle and oxidative phosphorylation [53, 54]. This metabolic shift toward glycolysis gives a selective advantage to the tumor cells and can occur thanks to an upregulation of the glucose transporter and high rate glycolysis [55, 56]. Reversal of the Warburg effect may offer a general anticancer strategy. However, many cancer cell types need fully functional mitochondria to maintain their homeostasis and produce pivotal metabolites: some type of cancer cells, including cancer stem cells, rely on oxidative phosphorylation for their survival (e.g. [57-59]).

Ion channels modulate metabolic efficiency of mitochondria [60], both by permitting flux of metabolites (in the case of VDAC and specific transporters) and by affecting efficiency of the respiratory chain and complex V (ATP synthase) in synthesizing ATP (see above). VDAC1 allows direct tunneling of ATP, synthesized in the mitochondrial matrix and exported to the inter-membrane space (delimited by the two mitochondrial membranes) via the adenine nucleotide carrier, to the first enzyme of the glycolytic pathway, hexokinase. This enzyme contributes to the maintenance of the Warburg effect, as it catalyzes phosphorylation of glucose and permits the production of glycolytic metabolic intermediates that can be used by the cancer cells for several biosynthetic processes (e.g., [55, 61, 62]). Both VDAC1 and certain hexokinase isoforms are overexpressed in several types of cancer cells [12, 63] and give a selective advantage to these cells by controlling cellular energy homeostasis. The role of VDAC1 in cancer cell metabolism has been proven by silencing its expression, resulting in inhibition of cancer cell growth, both *in vitro* and *in vivo*. VDAC1 silencing induced metabolic rewiring of the cancer cells and triggered their differentiation. Knockdown of VDAC1 inhibited stemness as well, through changes in transcription factor expression levels (increased expression of p53 and decreased expression of HIF1-α and c-Myc upon VDAC silencing) associated with cancer hallmarks [64].

VDAC1 and VDAC2 allow also the flux of calcium from/to the cytosol into/from mitochondria [11, 65, 66]. Calcium is a key regulator of several essential processes for mitochondrial metabolism, for example is required for the function of key enzymes of the Krebs cycle [67]. Transfer of this ion into mitochondria from the endoplasmic reticulum through MCU, that is overexpressed in several cancer cell types, seems to be essential for the maintenance of mitochondrial function and cellular energy balance [68]. Upregulation of MCU that enhanced the Ca^{2+} uptake into mitochondria promoted ROS production by affecting $NAD^+/NADH$ ratio via modulation of Krebs cycle enzymes [69]. In turn, activities of NAD^+-dependent deacetylase sirtuin 3 and of downstream superoxide dismutase 2 (SOD2) were reduced, finally leading to increased ROS release. An increased ROS in turn may modulate hexokinase II expression via stabilization of HIF1-α [70], contributing to enhanced proliferation. A recent paper reports that MCU has an explicit role in shifting metabolism of cancer cells [71]. First, this paper assessed MCU expression by immunohistochemistry in tumor samples from breast cancer patients and found it to be highly expressed. Following, microRNA-340, which suppressed breast cancer cell motility by inhibiting glycolysis was identified as a modulator of MCU. Thus, this study indicates that upregulated MCU promotes breast cancer metastasis via enhancing glycolysis.

Mitochondrial ion channels and apoptosis

Mitochondria are central organelles for apoptosis and, in general, for regulated cell death in different organisms [72]. Release of pro-apoptogenic factors, such as cytochrome c, SMAC/Diablo (Second Mitochondria-derived Activator of Caspases/ Direct IAP-Binding protein with Low PI) and AIF (apoptosis-inducing factor) from the mitochondrial inter-membrane space represents the point of no return of the intrinsic mitochondrial programmed cell death signaling pathway. Mitochondrial ion channels are emerging oncological targets [3], as modulation of these ion-transporting proteins may impact on mitochondrial membrane potential, efficiency of oxidative phosphorylation and reactive oxygen production. In turn, these factors affect the release of cytochrome c, which is the point of no return during mitochondrial apoptosis (for reviews see e.g. [73, 74]).

Recent reviews (also in this issue) summarize the role of different mitochondrial channels in modulating apoptosis and also of cancer cell chemoresistance due to defective apoptosis [4, 75, 76]. Therefore, we will focus only on the recent developments in the field and summarize only very briefly early observations.

VDAC contributes to apoptosis-resistance by preventing outer membrane permeabilization (see e.g. [77, 78]), while in the inner membrane a defective permeability transition pore opening accounts for chemo-resistance (for reviews see e.g. [79, 80]). Mitochondria can undergo a Ca^{2+}-dependent increase of inner membrane permeability (the permeability transition, MPT) causing inner membrane depolarization and interruption of ATP synthesis (see e.g., [81, 82]). The PT has been ascribed later on to the opening of a proteic pore, the MPTP, based on the ability of Cyclosporin A (CSA) to specifically block the PT [83].

Other channels involved in the apoptotic pathway have also been identified, for example TASK-3, IKCa and Kv1.3/Kv1.5 (for reviews see e.g. [4, 84-86]). In general, these latter channels are overexpressed in many tissues and either their activation protects against apoptosis or their pharmacological inhibition sensitizes the cells to apoptotic stimuli.

MPTP opening (that is associated with different forms of cell death) can be triggered by Ca^{2+} overload in the matrix, while other bivalent cations such as Mg^{2+}, Sr^{2+} and Ba^{2+} have an inhibitory effect on pore opening [80]. In this context, it is important to mention that deletion of the Mg^{2+} channel MRS2 prevents influx of this cation into mitochondria, resulting in cell death. In contrast, MRS2-overexpressing cells became less sensitive to apoptosis inducers [87]. Overexpression of MCU allowing Ca^{2+} influx into mitochondria and occurring in several cancer cell types might instead trigger MPTP opening. Indeed, for example microRNA-mediated (miR-25) downregulation of MCU has been linked to chemo-resistance in colon and prostate cancer lines [88]. On the other hand, inhibition of Ca^{2+} transfer from ER to mitochondria also causes cell death through ill-defined mechanisms [68]. In fact, a recent work reported that acute treatment with the death receptor ligand TRAIL rapidly increased mitochondrial Ca^{2+} concentration. Ca^{2+} chelators and the MCU inhibitor ruthenium 360, as well as MPTP openers (since this pore may mediate release of calcium) decreased the Ca^{2+} content in the matrix but at the same time sensitized these tumor cells to TRAIL cytotoxicity. The authors therefore suggest that mitochondrial Ca^{2+} removal can be exploited to overcome the resistance of cancer cells to TRAIL treatment [89]. Overall, the role of calcium in mitochondrial matrix and at the level of ER/OMM contact sites is not fully clarified in the context of sensitivity towards apoptotic stimuli.

In addition to the above players, UCP2 regulates apoptosis: its overexpression prevented death induced by chemotherapy [90-92] due to a reduction of ROS level, linked to mild uncoupling triggered by UCP2. Upon inhibition of UCP2 expression, a decrease in cell viability and clonogenicity was observed [93]. Among chloride channels, knockdown of CLIC4 enhanced ATP-induced apoptosis in head and neck squamous carcinoma HN4 cells. In accordance with the dual localization of CLIC4 to ER and mitochondria, both organelles were involved in CLIC4-mediated cell apoptosis [94]. In addition, CLIC4 expression has been associated with apoptosis induced by hydrogen peroxide in C6 glioma cells, as suppression

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of CLIC4 expression enhanced apoptosis, similarly to the above-mentioned example. Dissipation of mitochondrial membrane potential and nuclear translocation of CLIC4 was observed during apoptosis but how these events are linked to CLIC4 function is not fully understood [95, 96]. What was observed is that knockdown of CLIC4 increased the expression of Bax, active caspase-3, active caspase-4 by a still unclarified mechanism and sensitized cells to apoptosis [94].

Altogether these results illustrate that a plethora of ion channels are modulating apoptosis indirectly, by modulating oxidative stress or by triggering opening of MPTP.

Ion channels and angiogenesis

Endothelial cells (ECs) line blood vessels and are essential for normal functioning of the vascular system. Under physiological conditions, ECs are normally quiescent while in response to injury or in pathological conditions they are activated to sprout from the pre-existing vessels, in a tightly regulated process called angiogenesis [97]. Inadequate or excessive vascular growth is implicated in many pathological settings, including carcinogenesis. A better understanding of the molecular mechanisms regulating the angiogenic process is therefore crucial to find effective therapies.

A great number of ion channels and transporters present in the plasma membrane of ECs mediate the fluxes of ions, water and other small molecules associated with the complex sequence of events driving the angiogenesis [98]. The ion channels expressed in endothelial cells include voltage-gated channels (VOCs), transient receptor potential channels (TRPs), nicotinic receptors (nAChRs), volume-regulated anion channels and water channels (acquaporin). Beyond their general role in setting the membrane potential, signal transduction and vascular tone, some of them are directly involved in the angiogenic process and they have been related to tumor angiogenesis, in particular, upon angiogenic stimulus (such as VEGF) the intracellular concentration of Ca^{2+} is increased through activated ion channels. Although, except for VDAC, direct evidence that mitochondrial ion channels can indeed affect angiogenesis is missing, we list here the ion channels which may potentially contribute, given their dual (or multiple) localization within the cells.

The voltage-gated K^+ channels (Kv) are the most represented ones among the cancer-related ion channel families. In cancer cells, Kv11 regulates the expression and secretion of the vascular endothelial growth factor (VEGF-A) potentially inducing angiogenesis [99]. In human endothelium the Kv1.3 channel is present and mediates the proliferation of ECs in culture via membrane hyperpolarization by VEGF-A, resulting in Ca^{2+} influx [100]. The crosstalk between tumor cells and endothelium via VEGF emerges for other endothelial ion channels as well. The voltage-gated Na^+ (Nav) channels are upregulated in metastatic tumor cells and the isoforms Nav1.5 and Nav1.7 expressed in HUVECs modulate VEGF signaling resulting in increased cellular growth and migration [101]. Transient receptor potential (TRP) channels that regulate Ca^{2+} influx into cells represent another family of cation-permeable channels widely expressed in ECs and whose activity plays a relevant role in VEGF mediated signaling and angiogenesis [102]. TRP channels have been reported to be activated and/or modulated by different chemical and physical stimuli. Among several signaling molecules, angiogenic growth factors such as VEGF and bFGF are found to activate specific TRP isoforms in endothelial cells, causing a subsequent rise in endothelial $[Ca^{2+}]i$ and modulating different angiogenic processes. It has been reported that TRPC3 inhibition or silencing with siRNA impairs VEGF activation of ERK1/2, suppresses endothelial tube formation and proliferation [103]. Experiments using dominant-negative mutant of TRPC6 reduce EC proliferation, migration and sprouting in matrigel assay [104]. Interestingly it was observed that Ca^{2+}influx through TRP channels may stimulate endothelial cells to produce and release the angiogenic growth factors VEGF and PDGF, which consequently stimulate angiogenesis. Beside regulating the Ca^{2+} influx, the specific TRPM6 and -M7 channels allow the influx of Mg^{2+} and they are crucial for Mg^{2+} homeostasis. Although there is still little

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information, they may participate in the angiogenic process since Mg^{2+} is an essential player in cellular proliferation.

Nicotinic acetylcholine receptors (nAChRs) are the first cholinergic receptors expressed in the endothelium described to be involved in the angiogenesis [105]. nAChRs are pentameric ligand-gated ion channels opened by the binding of acetylcholine or other specific agonists such as nicotine. When activated, nAChRs function as multifunctional receptors employing different kinds of signaling related to proliferation, survival, adhesion and motility. Nicotine has been reported to be a potent inducer of angiogenesis activating ECs through nAChRs. Experimental evidences indicate that the α7 subunit forming functional homomeric receptor permeable to Ca^{2+} plays an important role in angiogenesis. It increases EC survival, which is associated with upregulation of AKT and downregulation of BAD activity, as well as the synthesis of NO. Selective inhibitors of α7-nAChR abrogate endothelial tube formation and migration. *In vivo,* pharmacological inhibition of α7-nAChR as well as its genetic disruption significantly inhibited inflammatory angiogenesis and reduced ischemia-induced angiogenesis and tumor growth [106]. Recent findings revealed that some endothelial ion channels can be localized also in the mitochondrial membranes and may play a role in the angiogenic process. The α7-nAChR represents the first example of functioning receptor found in the mitochondria. α7-nAChR localizes in the outer membrane directly interacting with VDAC and regulates the release of pro-apoptotic molecules such as cytochrome c [107]. Using specific agonist and antagonist molecules on isolated mitochondria it was reported that α7-nAChR affects intra-mitochondrial protein kinases (activation of intra-mitochondrial PI3K/AKT pathway and inhibition of calcium-calmodulin-dependent or Src-kinase-dependent signaling pathways) [108].

Perturbations of mitochondrial functions affect proliferation and migration in ECs in culture and ultimately lead to impaired or aberrant angiogenesis. The most well-studied ion channel within the mitochondria is the protein voltage-dependent anion channel (VDAC) which regulates the passage of ions and small metabolites through the outer mitochondrial membrane. It has been found that different compounds targeting the mitochondrial VDAC inhibit angiogenesis with various mechanisms affecting cellular survival and proliferation. The endogenous endostatin promotes apoptosis of endothelial cells by up-regulating VDAC1 expression [109]. Itraconazole, a common antifungal drug, binds to VDAC1 causing an increase in the AMP:ATP ratio, which in turn activates AMPK that down-regulates mTOR pathway and ultimately inhibits endothelial cell proliferation [110].

Mitochondrial ion channels and migration

VDAC was amongst the first channels whose activity has been linked to migration thanks to its ability to transfer Ca^{2+} into mitochondria. In particular, VDAC1 and VDAC3 interact with Mcl-1, an antiapoptotic member of the Bcl-2 family that is frequently upregulated in non-small cell lung carcinoma. Reducing Mcl-1 expression levels or application of peptides that specifically prevent interaction of VDAC1 with Mcl-1 limited uptake of Calcium into the mitochondrial matrix, with a consequent inhibition of ROS generation and reduction of cell migration, without affecting cell proliferation. Migration was rescued in Mcl-1 knockdown cells by restoring ROS levels, consistent with a model in which ROS production drives increased migration. These data suggest that an interaction between Mcl-1 and VDAC promotes lung cancer cell migration by a ROS and calcium-dependent mechanism [111]. In accordance with this hypothesis, knockdown of MCU in triple negative breast cancer cells significantly reduced cell migration and invasion *in vitro* and even lung metastasis *in vivo.* In contrast, overexpression of MCU in non-metastatic MCF-7 breast cancer cells increased migration and invasion *in vitro* and lung metastasis *in vivo* by enhancing glycolysis [71]. MCU silencing was shown to decrease migration and metastasis by changing the antioxidant capacity of the cells and by decreasing the steady-state levels of ROS. As a result, altered HIF1-α stabilization decreased expression of its target genes that are critical factors for migration [70]. Inhibition

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of the Ca^{2+} communication between mitochondria and ER was also shown to reduce cancer cell migration *in vitro* and *in vivo* [112]. MCU silencing was reported to decrease migration through a still unclear mechanism that implies a reduction of the store-operated Ca^{2+} entry into the cells. In agreement with the above studies, MCU-dependent mitochondrial Ca^{2+} uptake was shown to promote mitochondrial matrix metalloproteinase-2 activity and cell migration by ROS-activated JNK pathway. Altogether these studies suggest that MCU may be a potential therapeutic target against metastatic spread [69].

In addition to MCU and VDAC, other mitochondrial channels might be of relevance for promoting migration. For example, IKCa of the plasma membrane is intimately linked to invasiveness [113], but whether the mitochondrial counterpart of IKCa may also contribute to this effect, is presently unexplored. Likewise, a potential role for mitochondrial BKCa, SKCa and TASK-3 potassium channels as well as CLICs in migration cannot be excluded.

Conclusions and future perspectives

As summarized above, mitochondrial ion channels are emerging oncological targets as they are able to profoundly alter processes related to various hallmarks of cancer. The great advantage of these channels is that many of them can be pharmacologically targeted by membrane-permeable inhibitors. However, for specific targeting of mitochondrial channels only, chemical strategies that allow accumulation of ion channel inhibitors in mitochondria can be especially useful [74, 114].

A further important point in this field is to improve our understanding regarding the signaling mechanisms that link mitochondrial inner membrane ion channels to cytoplasmic signaling. Although it is by now recognized that key kinases, such as the c-Jun N-terminal kinase (JNK), protein kinase A (PKA), PTEN-induced kinase-1 (PINK1), and AMPK, readily translocate to the outer mitochondrial membrane (OMM), the interface of mitochondria-cell communication, much remains to be discovered concerning the mechanisms of how ion channels may modulate the action of these kinases. As mentioned above, one possibility is signaling via ATP concentration (in the case for example of AMPK) while another possibility envisions ROS (Fig. 2).

The role of mitochondrial ion channels in other hallmarks than those discussed here should also be addressed. To our knowledge, no information is available regarding a link between mitochondrial ion channel function and evasion of growth suppressors as well as between ion channels and the so-called cancer enabling characteristics such as genome instability and tumor-promoting inflammation [1]. In this respect it is interesting to note that in human monocyte-derived macrophages the mitochondrial calcium uptake via MCU was fundamental for M2 macrophage polarization, suggesting that mitochondrial calcium homeostasis might be relevant also for the tumor microenvironment [115]. Likewise, regulation of the NLRP3 inflammasome by mitochondrial Ca^{2+} has been observed, pointing to calcium-dependent control of inflammation [116].

Altogether, the present review reports data that further point to the importance of pharmacologically targeting mitochondrial ion channels in order to contrast cancer development.
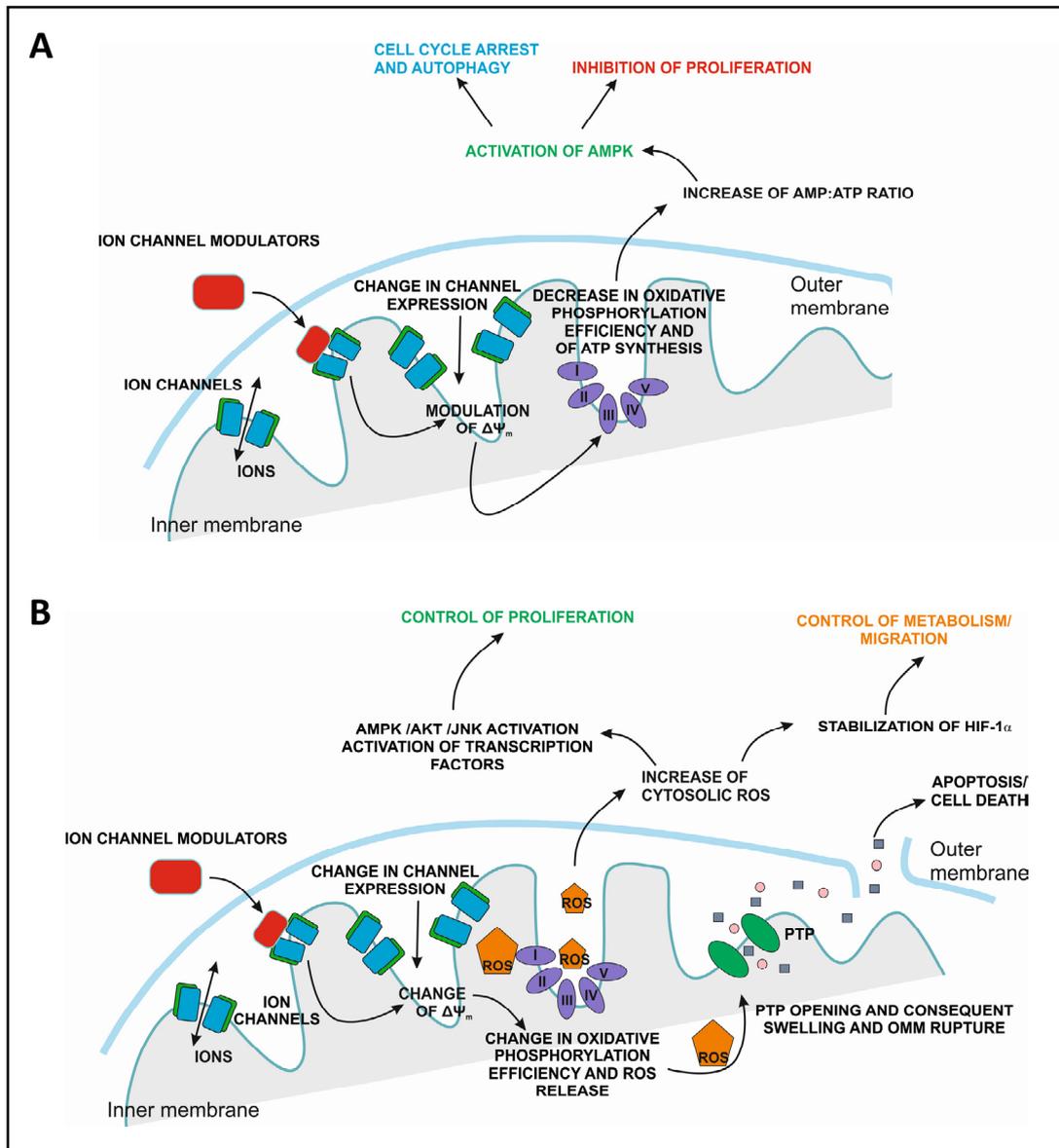
Fig. 2. Possible mechanisms linking ion channel function to signalling events affecting cancer progression. A) A change in ion channel function or in channel expression might affect the efficiency of respiration by modulating the mitochondrial membrane potential. If efficiency decreases, less ATP is produced and as a consequence, the AMP: ATP ratio increases leading to AMPK activation. In turn, phosphorylation of downstream targets may modulate different signalling pathways inducing cell cycle arrest and inhibition of proliferation. B) Ion channel function, by a similar mechanism as shown in A) might affect ROS release prevalently at respiratory chain complexes I and III (but ROS production occurs also at the level of complex II to a lesser extent). Sustained ROS release in the matrix might trigger opening of the permeability transition (MPTP) leading to depolarization, swelling, rupture of the outer mitochondrial membrane and release of pro-apoptotic factors from mitochondria. ROS, when produced at sub-lethal concentration and released to the cytosol, might activate various kinases, transcription factors, and stabilize HIF1-α (although non-canonical, ROS-independent mechanism also contribute). Thereby, ROS controls proliferation, migration, metabolic shift and possibly angiogenesis. See text for further details.

Abbreviations

AIF (apoptosis-inducing factor); AMPK (AMP-activated protein kinase); BAD (BCL2-associated agonist of cell death); BKCa (big conductance potassium channel); CLIC (chloride intracellular channel); CSA (cyclosporin A); EC (endothelial cells); ER (endoplasmic reticulum); ERK (extracellular signal-related kinase); FGF (fibroblast growth factor); HIF1-α (hypoxia-inducible factor 1-alpha); HUVEC (human umbilical vein endothelial cells); IKCa (intermediate conductance potassium channel); IMAC (inner membrane anion channel); IMM (inner mitochondrial membrane); JNK (c-Jun N-terminal kinase); KATP (ATP-dependent potassium channel); Kir (inward rectifying potassium channel); Kv (voltage-gated potassium channel); MCU (mitochondrial calcium uniporter); MPTP (mitochondrial permeability transition pore); mTOR (mammalian target of rapamycin); nAChR (nicotinic acetylcholine receptor); Nav (voltage-gated sodium channel); NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells); NO (nitric oxide); Nrf2 (Nuclear factor erythroid 2-related factor 2); OMM (outer mitochondrial membrane); OxPhos (oxidative phosphorylation); PDGF (platelet-derived growth factor); PI3K (phosphoinositide 3-kinase); PINK1 (PTEN-induced kinase 1); PKA (protein kinase A); PM (plasma membrane); ROMK (renal outwardly rectifying channel); ROS (reactive oxygen species); RyR (ryanodine receptor); SKCa (small conductance potassium channel); SMAC/Diablo (second mitochondria-derived activator of caspases/direct IAP binding protein with low pI); SOD2 (superoxide dismutase); TASK (Twik-related acid sensitive potassium channel); TRAIL (TNF-related apoptosis-inducing ligand); TRPC (transient receptor potential channel); UCP (uncoupling protein); VDAC (voltage-dependent anion channel); VEGF (vascular endothelial growth factor); VOC (voltage-gated channels).

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Disclosure Statement

The authors declare that they have no conflict of interests.

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