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Review

Small-Molecule Modulators of Mitochondrial Channels as Chemotherapeutic Agents

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Abstract
Ion channels residing in the inner (IMM) and outer (OMM) mitochondrial membranes are emerging as noteworthy pharmacological targets in oncology. While these aspects have not been investigated for all of them, a role in cancer growth and/or metastasis and/or drug resistance has been shown at least for the IMM-residing Ca^{2+} uniporter complex and K^+-selective mtK_V1.3, mtIK_{Ca}, mtSK_{Ca} and mtTASK-3, and for the OMM Voltage-Dependent Anion Channel (mitochondrial porin). A special case is that of the Mitochondrial Permeability Transition Pore, a large pore which forms in the IMM of severely stressed cells, and which may be exploited to precipitate the death of cancerous cells. Here we briefly discuss the oncological relevance of mitochondria and their channels, and summarize the methods that can be adopted to selectively target these intracellular organelles. We then present an updated list of known mitochondrial channels, and review the pharmacology of those with proven relevance for cancer.

Introduction

Targeting mitochondria to antagonize cancer has ceased to be an oncological side-show to become a major play, with the emergence of a whole new field of pharmacology based on so-called "mitocans" [1]. The mitochondria of cancerous cells acquire specific characteristics and functions [2, 3]. Thus, for example, the Krebs' cycle becomes a key provider of biosynthetic intermediates and modulators of enzymes, epigenomic control and thus gene expression [4]. An increased production of reactive oxygen species (ROS) by mitochondria contributes to the rapid and limitless growth phenotype [5], and it also constitutes a cellular

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Achilles' heel, since it brings the threshold for oxidative cell death within reach for redox stress-inducing drugs [6]. Mitochondrial alterations, and/or alterations in pro-apoptotic signaling to mitochondria, make cancer cells resistant to extrinsic apoptosis induction. Mitochondrial fusion/fission dynamics have been related to cancer cell invasiveness and maintenance of "stemness" [7]. The bioenergetic characteristics of cancer stem cells [8, 9] point to mitochondrial intervention for their eradication [10]. In summary, the prominence of the mitochondrial role in cancer and the alterations of the mitochondrial characteristics and functions in cancerous cells provide a clear rationale for the "mitocan" approach [1].

Mitochondrial ion channels provide one of the features that can be exploited [11-13]. As discussed elsewhere [12, 14] (Szabò et al, this Special Issue), alterations in their expression levels are commonplace in cancer. They are of special interest in many cases of chemoresistance [15] and possibly for the elimination of cancer stem cells [16, 17]. An updated list of the channels reported to be present in mitochondria is shown in Table 1. This is an expanding field, and the list will probably become longer and more detailed in the next few years. Obviously, not all these channels are necessarily functioning in all cells, and not all of them have a major role in any given cancer. Those for which evidence of such a role has been provided are identified in Table 1. Much, actually most, remains to be learned and understood. Some of the mitochondrial channels have been studied in more depth than others in this context. This can be said for example of mtK_V1.3, which is covered by another contributed paper (Leanza et al., this Special Issue), and of Voltage-Dependent Anion Channel (VDAC)-1. The latter, the mitochondrial porin, serves to show that outer mitochondrial membrane (OMM) channels may be of key importance in this context, laying to rest the vision of the OMM as a passive sieve. Another key point is that while a few of these channels are endemic to mitochondria, several reside in the plasma membrane (PM) and other intracellular membranes as well [11], and this may complicate the pharmacology. The logical move to counteract this difficulty is to engineer the specific accumulation of the drug at mitochondria: non-mitochondrial channels in both normal and cancerous cells will thus

Table 1. Ion channels with mitochondrial location and their involvement in cancer

Channel	Selectivity	Mito location	Link to cancer	Other location(s)	Notes
VDAC1	cations, Ca^{2+} variable	[275, 349, 350]	[293, 351-354]	Plasma membrane, ER/SR, endosomes	Flow of small metabolites is also allowed
VDAC2	cations	[355]	[293, 325]	Plasma membrane	
K_{ATP}	cations, K^+	[356]	/	/	
BK_{Ca}	Ca^{2+}, K^+	[200, 357-359]	[202, 203]	Plasma membrane, ER membrane, nuclear envelope, lysosomal membrane, Golgi	
IK_{Ca}	Ca^{2+}, K^+	[214, 215]	[211, 212, 360, 361]	Plasma membrane	
SK_{Ca}	Ca^{2+}, K^+	[231, 232]	[230]	Plasma membrane, ER membrane	Neurons, cardiomyocytes
TASK-3	K^+	[246]	[246, 249]	Plasma membrane	
MCU	Ca^{2+}	[362]	[108, 109]	/	
Ryr	Ca^{2+}	[363]	/	Sarcoplasmic reticulum, nuclear envelope	
Mrs2	cations, Mg^{2+}	[364]	[365]		
MPTP	/	[66, 67, 366-368]	[73, 369, 370]	/	
K_V1.3	K^+	[371]	[151, 157, 186, 372]	Plasma membrane, ER, Golgi, nuclear envelope	
K_V1.5	K^+	[187]	[186]	Plasma membrane	
K_V7.4	K^+	[373]	/		Auditory neurons, skeletal muscle
ROMK2	K^+	[374]	/	Plasma membrane	Renal epithelia
TRPC3	Ca^{2+}	[375]	[376]	Plasma membrane	
nAChRs	Na^+, Ca^{2+}	[377-379]	[380, 381]	Plasma membrane	
ASIC1	Na^+	[382]	/	Plasma membrane	
IMAC	anions	[383]	/		
CLIC4	Cl^-	[335, 384, 385]	[347, 386]	Cytosol, nuclear membrane, ER	Cardiomyocytes, keratinocytes
CLIC5	Cl^-	[335]	/	Cytosol, nuclear membrane, ER	

be largely spared, and this may help limit side-effects. Drug action on mitochondrial targets will on the other hand have a stronger, selective effect in cancer cells. Target specificity is in principle easier to achieve for inner mitochondrial membrane (IMM) residents, because advantage can be taken of the electrical potential and concentration gradients maintained across the IMM but not across the OMM. The issue of drugging a specific component of an intracellular organelle is superimposed on the upstream problem of selective delivery to the cancerous tissue. This latter topic is not covered here (for reviews see, e.g.: [18-21]).

We provide a summary of the strategies and difficulties involved in selectively aiming at mitochondrial targets, then individually discuss the pharmacology of the mitochondrial channels with a recognized role in cancer.

Mitochondrial targeting

Targeting a drug to mitochondria – or for that matter to any subcellular compartment - can rely on two strategies: a) attaching an "address" moiety to the active principle (Fig. 1) or b) arranging for transportation by a nanostructured targeted carrier. Within the first approach a distinction can be made between molecules in which the targeting moiety is attached permanently and prodrugs based on a labile linker, whose splitting will regenerate the parent active portion. Chemical modification entails new pharmacologically relevant properties which need to be taken into consideration. Moderate lipophilicity and molecular weight are required for an optimal membrane permeation [22].

In most cases mitochondrial targeting relies on the transmembrane potential to drive drugs engineered to carry - stably or temporarily (prodrugs) - a positive charge into the matrix or IMM. Accumulation of membrane-permeant cations into regions at negative electrochemical potential is mandated by the laws of thermodynamics, a principle first applied in this setting by Skulachev's group 50 years ago [23] and later used in any number of biomedical studies (revs., e.g: [24, 25]). In order for the cation to cross biomembranes, in the absence of a specific carrier, the positive charge needs to be delocalized and the molecule as a whole needs to be sufficiently lipophilic. This very often translates into the incorporation

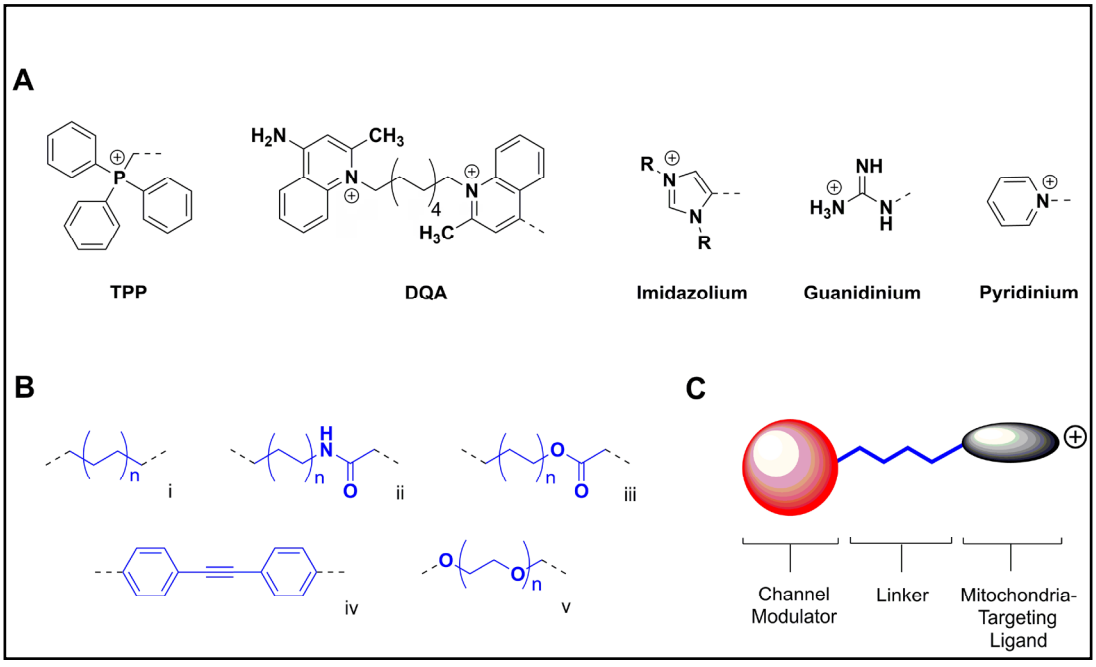

Fig. 1. A) Common mitochondria-targeting ligands; B) examples of linkers between the targeting moiety and the drug; C) typical mitochondria-targeting conjugate scheme.

into the mitochondriotropic molecule of a triphenylphosphonium (TPP) group connected to the pharmacologically active moiety via a linker (which may contain a "bioreversible" bond system if a prodrug is desired). Besides providing a well-tested, reliable stratagem, using TPP facilitates the chemist's task, because – possible complications aside - it can be easily produced by reacting a good and easy-to-handle nucleophile, triphenylphosphine, with an electrophilic center carrying a good leaving group, such as a iodide or tosylate (p-toluensulfonate). On the down side, any lipophilic group is bound, by definition, to have a significant affinity for biomembranes. The positive charge furthermore favors interactions with negatively charged cell components, such as phospholipid headgroups and DNA. Not to be forgotten, it also determines accumulation into the cytosol, which – while electrically positive in comparison to the mitochondrial matrix - is at a more negative potential than the extracellular space. Unsurprisingly, TPP-containing compounds exhibit extensive binding also to non-mitochondrial structures [26]. Because of this tendency to give pleiotropic interactions, off-targets are a possibility to be considered even more seriously than for drugs in general. In fact, at relatively high (several μM) concentrations some TPP conjugates seem to cause mitochondrial dysfunction. This has been observed with TPP surfactants [27] but also phenolic derivatives [28] and other seemingly nondescript TPP-comprising molecules [29-31]. At least in some cases the disrupting effect appears to be associated with an interaction with Complex I of the respiratory chain and the ensuing upregulation of ROS production [32, 33]. ROS in turn can affect some intracellular channels [34]. However, emphatically, not all TPP-comprising compounds produce such effects (e.g. [28, 29]), and specifically this is not the case of the psoralenic derivatives discussed below. Controls are clearly needed in each case.

These shortcomings of the TPP group prompt consideration of alternative mitochondria-targeting groups, including dequalinium (DQA), imidazolium, guanidinium, pyridinium, rhodamine, and triethylammonium groups [35] (Fig. 1A). DQA is a dicationic lipophilic compound formed by two quinaldinium rings linked by ten methylene groups. It can self-assemble into vesicle-like liposomes referred to as DQAsomes [36], which have been used to deliver chemotherapeutics drugs and genetic material to mitochondria [37]. Imidazolium cations have been used to convey fluorophores to the mitochondria of cultured cells [38], and could be exploited, in principle, to target pharmaceuticals as well. Conjugation of porphyrins with guanidinium/biguanidinium determined a "clean" mitochondrial localization in cultured cells [39]. Both Rhodamine 123 and Rhodamine 19 are mitochondria-targeting moieties because of their delocalized positive charge and ability to cross biomembranes. Rhodamine 19 has been tested in substitution of TPP to form a mitochondriotropic rhodamine 19–plastoquinone conjugate [40]. Pyridinium has been used as the targeting group, for example, in compound F16 and its derivatives, which act as anticancer mitochondrial uncouplers [41] and in the rhodocyanine dye MKT-077, a mtHsp70 inhibitor evaluated in an oncological clinical trial [42, 43].

Peptides can also be used as mitochondria-targeting devices [24, 44, 45]. These belong to the family of cell-penetrating peptides (CPPs): positively-charged aminoacid sequences capable of entering the cell and, at least in principle, to carry along a "cargo" as well, e.g. in a prodrug (e.g. [45]). Unsurprisingly, the best-performing Mitochondria Penetrating Peptides (MPPs) alternate charged and lipophilic residues [44]. As for TPP-comprising molecules, some of these peptides may act as mitochondria-disrupting agents, with potential direct anti-cancer applications. This "mitotoxic" activity increases with charge and lipophilicity [44]. Analogously, mitochondrial demise may be brought about by peptide-lipid conjugates [46]. In other studies, MPPs have been used to ferry cytotoxic – DNA-damaging – agents to mitochondria (e.g.: [47, 48]). The peptide may be tailored to engage the mitochondrial protein import system. This option has been, perhaps surprisingly, rather neglected so far, with only a few studies aimed at the mitochondrial delivery of DNA [49, 50] or supramolecular systems [51, 52].

In order to achieve both selective mitochondrial targeting and optimal binding affinity and specificity for the desired mitochondrial ion channel, the position of the targeting

moiety needs to be optimized through structure-activity relationship (SAR) studies. The spacer between the targeting moieties and the pharmacophores can be of various types (Fig. 1B): an alkyl chain with saturated C-C bonds (Fig. 1B, i), or comprise amide (Fig. 1B, ii), ester (Fig. 1B, iii) and disulfide functionalities. Phenylethynyl (Fig. 1B, iv) and polyethylene glycol (Fig. 1B, v) linkers have also been used. Different linkers will provide different chemical and spatial properties to the conjugate, i.e. a phenylethynyl linker is characterized by its rigidity and a polyethylene glycol linker provides higher water solubility. A spacer between the channel modulator and the targeting ligand allows for an optimal recognition.

In the second alternative – using nanocarriers for selective mitochondrial delivery - the targeting problem is obviously shifted from the single molecule to the supramolecular structure, but the principles applied remain much the same. This approach may offer a number of advantages: it may incorporate various components acting in synergy to optimize delivery; it makes it unnecessary to modify the active principle, and protects it from metabolic modifications; it may be used to deliver an assortment of "cargos". On the other hand nanocarriers may encounter difficulties in crossing biomembranes, or use complex and "dangerous" processes, such endocytosis, to do so. This may however turn out to be an advantage for the specific delivery to tumor masses through "defects" of vascular epithelia. This field, born more than 20 years ago with Weissig's dequalinium liposomes [36] is blooming (revs.: [24, 53]), although results in *in vivo* cancer models have yet to meet expectations [54]. The surface of nanovehicles has been decorated with TPP (e.g. [55-57]; the synthesis of TPP-lipid conjugates has been described by [58]) and peptides (e.g. [59, 60]). The possibility of introducing cooperating targeting structures has been taken full advantage of in the development of Multi-Functional Envelope-Type Nano Devices (MENDs) by Harashima's group (rev.s, e.g.: [61]). The various components of these systems act to limit recognition by the reticuloendothelial system, favor uptake into cells and exit from endosomes, and selective delivery to the target compartment. In cultured cells, MENDs can achieve the delivery of small molecules to the mitochondrial matrix [62].

Both strategies – structural modification, packaging – can be used, perhaps in combination, to deliver known or novel channel modulators to mitochondria. This approach has been adopted so far only in a few studies, and the potential for further development is great. We give below a concise overview - limited to matters of oncological interest - of the state of the art.

The Mitochondrial Permeability Transition Pore

Whether the Mitochondrial Permeability Transition Pore (MPTP; recent revs., e.g.: [63-65]) ought to be considered a channel in the same sense as the others mentioned in this review may be a moot point. This is a variable-size (up to very large) pore believed to fulfill physiological roles via transient brief openings, and of major biomedical interest because its full activation leads to mitochondrial depolarization, loss of key soluble matrix components, and cell death. After decades of debates, its molecular identity may now have been settled: the pore is believed to be formed, under the appropriate conditions, by the dimeric F_oF_1 ATP synthase [66, 67]; permissive conditions are a high matrix Ca^{2+} concentration, and oxidative stress (e.g.: [68, 69]). Given its involvement in major pathologies – e.g. infarct, dystrophy, neurodegeneration – in which it plays the villain, pharmacological research has so far concentrated on inhibitors (e.g. [70]). However, the MPTP is of major relevance also in cancer. Cancerous cells have altered Ca^{2+} [71] and ROS [72] homeostasis. They adapt to stressful conditions and defend their survival and proliferation by repressing MPT-mediated death [73]. Although this is not always realized by the researchers, facilitating MPTP opening in cancerous cells may therefore underlie – completely or in part – the effects of drugs ranging from traditional medicine preparations [74] to organometallic gold complexes [75, 76]. The connection is the pro-oxidant effect of the drugs, which increases oxidative stress to the point where a critical death-induction threshold is exceeded in already-stressed cancer

cells, but not – or to a more limited extent – in normal cells. Since the redox sensitivity of Ca^{2+} channels and transporters of the ER, mitochondria and PM links redox alterations and Ca^{2+} levels [77], oxidative stress implies Ca^{2+} stress, the key factors leading to MPTP opening and hence cell death. Anti-cancer strategies based on the upregulation of ROS production are currently receiving much attention [78], with the possible repurposing of several drugs as anti-cancer agents precisely because of their pro-oxidant action (e.g. [79, 80]). The possibility of overcoming chemoresistance by this approach is an important consideration. The down-side is the possibility that redox action may have an undesirable impact on normal cells and organs, for example the heart [81].

It follows that any drug capable of inducing "excess" oxidative stress in cancer cells can be considered as indirectly acting, at least potentially and in part, via the MPTP. Redox stress inducers are plentiful. The already-mentioned metal complexes, including, besides gold compounds, platinum, palladium, copper, silver, ruthenium, tin etc. ones inhibit the thioredoxin reductase (TrxR) system, which is potentiated by cancer cells in order to maintain a degree of redox homeostasis (rev.s, e.g.: [82-85]). Polyphenols, generally considered as anti-oxidants, can actually behave as pro-oxidants and induce cancer cell death by this mechanism (as well as others) (e.g.: [86, 87]). Some, like for example curcumin, myricetin, baicalein, EGCG also are potent TrxR inhibitors [88, 89]. Autoxidation and interaction with the mitochondrial respiratory chain provide further mechanisms of redox stress induction. Redox cyclers such as quinones, paraquat or pyocyanin can act similarly. Redox stress and MPTP activation are also induced by berberine. Methyl jasmonate, a plant hormone, acts likewise and is cytotoxic for cancerous cells while sparing normal ones [90]. The list could go on. The occurrence and relevance of these processes depend on several factors, one of which is the concentration of the active species. Thus, they are expected to be enhanced when a concentrative effect is obtained by coupling to a mitochondria-targeting moiety (see above). Mitochondriotropic derivatives of quercetin, resveratrol, pterostilbene, honokiol, gallic acid, caffeic acid, plastoquinone, menadione and other potentially redox-active compounds have been synthesized and tested, and indeed they show an increased tendency to act as pro-oxidants [24]. The studies with these compounds so far have been limited to *in vitro* protocols. When applied to cultured cancer cells they do exhibit remarkable cytotoxicity. Their usefulness in *in vivo* cancer models remains however to be put to test. *In vivo* models have on the other hand been used to test the efficacy of mitochondriotropic psoralen derivatives, which according to the current mechanistic model act by inducing oxidative stress downstream of the inhibition of a mitochondrial K^+ channel, and are discussed below.

The MPTP thus serves as the executioner for a number of redox-active compounds with anti-cancer potential. It may be indirectly modulated through the signaling cascades that have been identified to have an impact on its activity [65]. Examples of this approach are provided by hirsutine, an alkaloid, and the synthetic compound GSK1059615. What is lacking – and may not be easy to find, given the molecular nature of the pore – is a useful direct activator (for an overview of PT inducers and inhibitors see, e.g., [91]). Polyphosphate, in complex with poly-hydroxybutyrate, has been proposed to act as such [92]. Atractyloside and carboxyatractyloside, two inhibitors of the mitochondrial ADP/ATP exchanger (ANT) stabilizing it in the "C" conformation, have long been observed to induce IMM permeabilization [93] (while bongkrekate, another inhibitor blocking the carrier in the "M" conformation, antagonizes it). Ebselen, a seleno compound, has been reported to do the same [94]. Logically, the ANT has been proposed to be involved, pointing to the possibility that more than one mechanism of IMM permeabilization may exist [95]. Resminostat, an HDAC inhibitor, triggers the MPT via interaction with Cyclophilin D (a modulatory component of the MPTP) and the ANT [96]. Benzodiazepine 423 binds to the Oligomycin Sensitivity Conferring Protein (OSCP) subunit of the F_0F_1 ATP synthase and facilitates the opening of the MPTP, a finding that was instrumental for the identification of ATP synthase dimers as the molecular substrate of the permeability transition [66, 97]. Various ligands of the OMM-located peripheral benzodiazepine receptor / Translocator Protein (TSPO) have been found

to have analogous effects on mitochondria [98], although the underlying mechanism is at present unclear.

The Mitochondrial Calcium Uniporter Complex

That mitochondrial Ca^{2+} handling is of prime importance in cancer follows, if for no other reason, from the role this ion has in precipitating the MPT and cell death (see above). As mentioned, this role belongs to matrix Ca^{2+}. Mitochondrial Ca^{2+} uptake also modulates (increases) ROS production by the organelles [99] (and is in turn modulated by it; [100]). ROS are an intracellular messenger of the utmost importance in cancer cells, in which, as already mentioned (see above), they are upregulated and contribute to cell proliferation, spreading and metastasis, survival, accumulation of oncogenic mutations, adaptation to hypoxia [101, 102]. Mitochondria contribute to shaping cytosolic Ca^{2+} signaling [103, 104], which, again, is altered in cancer cells and is profoundly involved in such aspects as growth, metastasis, autophagy, drug resistance, escape of immune surveillance, "stemness" [105, 106]. Ca^{2+} uptake by mitochondria through the ER-mitochondria axis ("ER-mitochondrial Ca^{2+} fueling") stimulates mitochondrial metabolism thus providing the cancerous cells with an adequate supply of metabolic building. It follows that the mitochondrial machinery for Ca^{2+} uptake/release is a key character on the oncological stage [107-109]. Its centerpiece is the Mitochondrial Calcium Uniporter Complex (MCUC), comprising various regulatory subunits (rev.s: [107, 110]). Not only the expression level but also the composition of the MCUC have been found to be altered in several cancer types, and these variations appear to be cancer type-specific (revs.: [107, 109]). Post-translational modifications also intervene. It should also be mentioned that the stoichiometric composition of the MCUC varies from organ to organ under normal circumstances as well [111]. Pharmacological interventions aimed at the MCUC therefore ought to be planned case-by-case. Besides the pore-forming MCU, one may target regulatory subunits, or, conceivably, oligomerization – a process favored by oxidative conditions.

Historically, Ca^{2+} uptake by mitochondria has been blocked by Ruthenium complexes (Ru360) and lanthanides. These Ruthenium complexes appear to be specific blockers of the MCU and can be utilized in studies with cultured cells, including cancer ones but also *in vivo* (e.g. [112]). Serious drawbacks are the tendency to bind to polysaccharides and difficulty in diffusing across biomembranes. Their use as a possible therapeutic agent in animal cancer models seems to have been limited so far to some studies in the 1970's [113]. A new Ruthenium compound with good permeation and selectivity, Ru265, has been recently reported [114]. Cancer-targeted prodrugs of Ru complexes have been produced and may provide a lead to more useful forms of this type of inhibitors [115]. Other inorganics inhibiting Ca^{2+} uptake by mitochondria are the lanthanides [116], which would however need much work to be turned into useful drugs.

Among organic compounds, two tetracycline analogues - minocycline and doxocycline - were found to inhibit mitochondrial Ca^{2+} uptake when applied in the 50 μM range, protecting rat hepatocytes from chemical hypoxia-induced death [117]. These antibiotics have shown activity against various cancers (e.g. [118]) as well as for several other conditions. DS16570511 has been identified in a large high-throughput screening [119]. This is a membrane-permeant MCU inhibitor, effective in the μM range. It appears however to have as yet unidentified mitochondrial off-targets [120]. We are unaware of any tests in cancer models so far. The thiourea derivative KB-R7943, an inhibitor of the PM Na^+/Ca^{2+} exchanger 1, has also been reported to inhibit mitochondrial Ca^{2+} uptake (μM range) [121], but whether this reflects a direct effect on the MCUC is unclear, since this drug also has mitochondrial off-targets [122]. Mitoxantrone (a topoisomerase inhibitor with oncological applications) has also emerged as an MCUC inhibitor (IC_{50} in the μM range) from a screening study [123]. Another anticancer drug, proteasome inhibitor Bortezomib, stimulates instead mitochondrial Ca^{2+} uptake in a Ru360-sensitive manner, and this may contribute to its anti-

cancer effects [124]. Polyamines, e.g. spermine, also stimulate Ca^{2+} uptake by mitochondria [125], a finding that may be worth scrutinizing now that the MCUC has been molecularly defined. Aminoglucoside antibiotics also can activate [125]. Activation of the MCUC has also been proposed as the mechanism of anti-cancer action of AG311 [126], which however seems more likely to act by inhibiting complex I of the respiratory chain [127]. An analogous suggestion has been made for Necrox-5 [128], but also in this case subsequent reports point to other targets [129, 130]. Several plant flavonoids upregulate mitochondrial Ca^{2+} uptake *in vitro* [131]. The most effective among those tested was kaempferol, which nearly doubled the rate of mito-aequorin response increase at 1 μM in HeLa cells [131].

With the exceptions of Ru360, which has been shown to bind to the aspartate "ring" at the mouth of the MCU channel [132], of Ru265, which involves MCU Cys97 [114] and of oxidative stress, which leads to glutathionylation of Cys97 and formation of higher oligomers [133], the mechanisms of action of these various compounds remain to be explored.

The MCU complex would be fully expected to undergo regulation by cellular signaling cascades (rev.: [133]). Mitochondrial Ca^{2+} uptake has been reported to be modulated downstream of p38 MAPK, PKC, PKD, CaMK-II [134, 135] but how this comes about needs to be investigated further (see, e.g., [136]). In summary, the pharmacology of the MCUC is still fairly primitive – not surprisingly since the system has been first identified only about 9 years ago [137, 138] – but offers excellent perspectives for development and applications, and certainly not only in oncology.

Mitochondrial K_V channels

K^+ is the most abundant cation in both cytosol and mitochondrial matrix; it is used by mitochondria to control volume and some functions [139]; K^+ channels are the most diversified superfamily of ion channels in nature [140]. It is not surprising therefore that several representatives of the class are present, besides other cell membranes, in the IMM (see Table 1; [141]). The processes involved in regulating the distribution of multiple-location channels are now beginning to be understood [142]. And given the pervasive roles of ion channels, in general, in cell life, it is also not surprising that altered expression profiles / functions are often found in cancer (e.g.: [3, 14]; for K^+ channels: [143]) and may concern ion-conducting but also regulatory subunits [144]. The intersection of these concepts makes it likely that some mitochondrial channels are relevant for cancer, and this is indeed the case (see Table 1; [12, 13]). Again, this is work in progress, and it may well be that in the future an oncological relevance may emerge for some mitochondrial channels not currently known to have one, and therefore not discussed here.

So far, mitochondrial K_V channels have been used to precipitate cancerous cell death downstream of their inhibition (see below). It may be considered, however, that an alternative way to reach the same goal may be via their activation by K^+ channel openers. If sustained, so as to overwhelm the counteracting electroneutral K/H exchange, and if the transmembrane electrical potential were maintained, to an extent, by the organelles, activation would be expected to lead to K^+ influx into the matrix, swelling, and, eventually, OMM rupture and cytochrome c release. As far as we know, this approach has not yet been considered.

K_V1.3

K_V1.3 is likely to be the mitochondrial K^+ channel to which the most attention has been paid in an oncological context. Its expression and functions in cell life and death are covered in detail in another review of this Special Issue (Leanza et al) and elsewhere [13]. We therefore provide here only a summary.

PM K_V1.3 is well known to be the target of peptide toxins which block it due to the interaction of a lysine residue with the "ring" of negative charges formed by four aspartate residues in the channel vestibule [145, 146]. This inhibition can block cell proliferation, and since PM K_V1.3 is particularly crucial for lymphocytes, it offers hope for the treatment

of autoimmune disorders [146]. However, these toxins do not enter cells. IMM $K_V1.3$ can likewise be blocked by Lys128 of pro-apoptotic protein Bax following incorporation of the latter into the OMM [147]. Hyperpolarization, ROS production, cytochrome c release and apoptosis follow. These findings suggested that pharmacological inhibition of IMM $K_V1.3$ might well produce the same outcome. Wulff, Chandy and coworkers had developed a family of membrane-permeant K_V inhibitors – including Psora-4 and its derivative PAP-1 - based on the psoralenic (furocoumarinic) ring system [148]. These drugs probably act by inserting "sidewise" into the ion-conducting pore with their coumarinic moieties [149]. Clofazimine, an antimycobacterial drug, was also found to be a permeant $K_V1.3$ inhibitor [150]. The compounds proved to have some efficacy against various cancerous cells *in vitro*, in *in vivo* models of melanoma and pancreatic ductal adenocarcinoma (PDAC) and against B cells from the blood of chronic lymphocytic leukemia (CLL) patients [151-153]. Mitochondriotropic PAP-1 derivatives PAPTP and PCARBTP (a carbamate prodrug) were produced and tested with the goal of improving efficacy and target specificity [154]. The strategy proved successful, achieving important reductions of tumor mass in murine models of melanoma and PDAC and eliminating a very high fraction of *ex vivo* human CLL cells and of various cultured cell lines. Importantly, they were essentially without effect on healthy tissues. Despite killing glioma cells *in vitro*, they were however unable to antagonize the tumor *in vivo*, because they were excluded from the central nervous system by the blood-brain barrier (BBB) [155]. A similar cytotoxicity was exerted by PCTP, a prodrug analogous to PCARBTP but comprising a carbonate group, rather than a carbamate, as labile bond system [156]. The activity of these compounds is sensitive to structural details. Thus, shortening the linker between the furocoumarin system and the "driving" triphenylphosphonium group resulted in a compound (P5TP) with only about the same efficacy as the parent, non-mitochondriotropic PAP-1 [156]. At low doses (< 1 μM), they may activate pro-survival pathways (Bergermann et al., this Special Issue), thus acting in "hormetic" fashion, or alter the cell cycle [157]. Both effects have been tentatively attributed to the induction of a mild oxidative stress.

Much work has been directed towards the discovery of $K_V1.3$ inhibitors because of the role of this channel in inflammatory and autoimmune disorders [158, 159]. A number of natural and synthetic compounds have been found to inhibit PM $K_V1.3$, and might serve as leads for mitochondria-targeted new drugs. These include other psoralen derivatives [160], and the prenylated flavonoids xanthohumol, isoxanthohumol and 6- and 8-prenylnaringenin (EC_{50} in the 3-8 μM range) [161, 162]. Some derivatives of khellinone inhibited with K_d < 1 μM [163-165]. Diphenylphosphine oxide inhibited the channel with an IC_{50} of ~ 3 μM [166]. Sibutramine (a discontinued appetite suppressant), did the same with IC_{50} ~ 3.7 μM [167]. Less potent were trifluoperazine, thioridazine, tamoxifen [168], acacetin, chrysin [162, 169], genistein [170], resveratrol [171], simple derivatives of naringenin and piceatannol [172], 18β-glycyrrhetinic acid [173], lovastatin [174] and other statins [175], verapamil, diltiazem [176]. Derivatives of correolide, a pentacyclic natural compound, have been the object of a SAR study [177]. Patent applications seek to protect whole classes of synthetic $K_V1.3$ blockers, based on an amide [178] or an oxazolidinedione [179] core.

Interestingly, PM $K_V1.3$ is inhibited downstream of ceramide production by acid sphingomyelinase (ASM) [180]. Localization of the channel in lipid rafts is involved in this phenomenon [181]. Ceramide [182] and ASM [183] are present in the mitochondria (at least those of some cells under stressful circumstances), and affect processes of the IMM [184, 185].

$K_V1.5$

$K_V1.5$ is a first-degree cousin of $K_V1.3$, with which it forms heterotetramers. Its expression appears to be altered in several cancers, and to be involved – analogously to $K_V1.3$ – in cell proliferation and metastasis [186]. PAP-1 (see above) was selected among a group of psoralen derivatives because of its (rather modest) selectivity for $K_V1.3$ over $K_V1.5$. $K_V1.5$ is present in the IMM of macrophages [187], but a mitochondrial localization has not been reported for other cell types.

Especially because of its involvement in cardiac function, $K_V1.5$ has been the focus of a considerable pharmacological research effort (e.g. [188]). Among the molecules identified as inhibitors are ortho,ortho-disubstituted bisaryl compounds [189], anthranilic amides [190], pyrazolodihydropyrimidine derivatives [191], S0100176 [192], AVE0118 [193], the phosphatidylinositol 3-kinase inhibitor LY294002 [194], verapamil [195], the anesthetic propofol [196], the lipoxygenase inhibitors cinnamyl-3, 4-dihydroxy-alpha-cyanocinnamate and nordihydroguaiaretic acid [197], diphenylphosphine oxide [198]. At least some of these inhibitors act also on $K_V1.3$. The structural similarity among voltage-dependent K^+ channels clearly makes selective targeting difficult.

Mitochondrial K_{Ca} channels

Ca^{2+}-activated K^+ channels are present in the IMM of several cell types, including some cancer lines (Table 1; [11, 13, 141, 199, 200]). They are believed to participate in the regulation of trans-IMM potential, ROS production and Ca^{2+} homeostasis. According to their conductance, they are named "Big" (BK_{Ca}, a.k.a. $K_{Ca}1.1$), "Intermediate" (IK_{Ca}, a.k.a. $K_{Ca}3.1$) and "Small" (SK_{Ca}, a.k.a. $K_{Ca}2.1$-3). $mtBK_{Ca}$ [200] and $mtSK_{Ca}$ (e.g [201].) have been much studied because of their role in cardiac ischemic preconditioning. Less attention has been paid to their possible role in cancer.

BK_{Ca}

$mtBK_{Ca}$ is present in human LN229 glioma and U-87 MG astrocytoma cell lines. CGS7184, a BK_{Ca} channel opener, induced mitochondrial depolarization and death of these cells, but the effect seems actually to involve Ca^{2+} release from the ER and to be independent of $mtBK_{Ca}$ opening [202, 203]. Ophiobolin A, a fungal metabolite, is instead a (weak; IC_{50} ~ 10 μM) BK_{Ca} channel inhibitor, and it also induced death of a cancer (glioblastoma) line [204]. The correlation between the two effects would however need strengthening also in this case.

Besides the compounds just mentioned, many other small molecule BK_{Ca} agonists have been identified or synthesized. For detailed reviews please see [205, 206]. These compounds are not, in general, either very powerful (typically they act in the several-μM range) or specific. One of the most powerful may be the triterpenoid glycoside dehydrosaponin, which reportedly acted (unfortunately from the intracellular side) at concentrations as low as 10 nM in planar bilayer experiments [207].

Selective antagonists of BK_{Ca} have also been sought, without much luck. For a review please see [208]. Most of the compounds identified – which include, e.g., paxilline, verapamil, quinine, clotrimazole - act also on other K^+ channels, in particular IK_{Ca}. A possibly selective one is Penitrem A [209], which acts via subunit β1. It is one of a set of indole diterpene alkaloids produced by Penicillium sp., reported to have anti-proliferative and anti-invasive properties against various cancers. Penitrems are however known to act also via the Wnt/β-catenin pathway [210].

IK_{Ca}

The role of IK_{Ca} in cancer is, instead, well supported. The channel is involved with cell migration, proliferation, and invasion, and it has been studied in particular in the context of cancers of the pancreas and breast and gliomas (revs.: [211, 212]). It may furthermore confer radioresistance [213]. The mitochondrial population has been discovered in cancer cell lines [214, 215]. IK_{Ca} has been found to regulate oxidative phosphorylation in some PDAC cell lines [216], and treatment with a membrane-permeant inhibitor (TRAM-34) sensitized melanoma cells to TRAIL-induced apoptosis [217] and reduced the proliferation rate in a murine breast cancer model [218].

Mitochondria-targeted IK_{Ca} inhibitors have not yet been developed. A few membrane-permeant inhibitors exist which might serve as leads. One difficulty is the tendency of K^+ channel modulators to act on more than one member of the superfamily, a problem due

to the intrinsic similarity of these channels. The most hopeful for mtIK$_{Ca}$ may well be the tetrarylmethane inhibitors TRAM-34, considered to be selective for IK$_{Ca}$ [219, 220] and clotrimazole (an antimycotic) [221], both of which inhibit the mitochondrial population in cultured cells [214], and activator 1-EBIO [222]. Several other activators [223] are available as lead compounds. Activators generally have low selectivity, acting on small- as well as intermediate-conductance K$_{Ca}$ channels as well as on other channels. However, a SAR study of the benzothiazole pharmacophore of SKA-31 has led to significantly IK$_{Ca}$-selective compounds [224]. Among inhibitors, some natural products, e.g. caffeic acid, are also rather weak and unselective [225]. Some synthetic dibenzoates worked in the nM range, but did not distinguish between IK$_{Ca}$ and SK$_{Ca}$'s [226]. However TRAM-34, Senicapoc (ICA-17043), NS6180 and a derivative of nifedipine have nM-range potency as well as good selectivity [223, 227], and may be the first-choice candidates for elaborations. Dequalinium-related UCL1407, UCL1440, UCL1438 had IC$_{50}$ values in the ~1μM range [228]. The peptide toxin with the best combination of selectivity and potency for IK$_{Ca}$ is maurotoxin [229].

It may well happen – it remains to be investigated in depth – that the mitochondria of a given cancer type might harbour only one or few types of K$^+$ channels. Thus, for example, that of IK$_{Ca}$ was the only significant activity by K$^+$ channels we observed in HCT116 mitochondria [214]. Thus, a mitochondriotropic compound may achieve a sort of "topological selectivity" despite having itself an intrinsically low ability to distinguish among K$^+$ channels.

SK$_{Ca}$

A role of small-conductance Ca^{2+}-activated K$^+$ channels (SK$_{Ca}$2.1-3) in cancer has been documented mainly for SK3 (SK$_{Ca}$2.3) [230]. SK channels are present in the IMM of neurons [231] and of cardiomyocytes [232], where they influence transmembrane potential and respiration and have a protective role. Their possible involvement in cancer cell physiology has not – to our knowledge – been studied, but that their modulation may have (an) effect(s) is a distinct possibility.

The pharmacology of these channels [223] overlaps that of the other K$_{Ca}$ channels to a considerable extent. Activators NS309, SKA-31, 1-EBIO/DCEB, SKS-11, SKS-14 [233] are shared with IK$_{Ca}$. CyPPA activates instead rather specifically on SK2 and SK3 [234], but also modulates the β-catenin/GSK3β pathway [235]. Antagonists include NS8593 [201], which however acts on quite distinct channels as well [236]. More SK-selective selective blockers are the small neurotoxin apamin – which was instrumental in the characterization of SK channels themselves [237], but also blocks K$_V$1.3 with an IC$_{50}$ of 13 nM [238] - BBP [239], UCL1684 [228]. SK3 is also inhibited by edelfosine, an ether-linked phospholipid with anti-cancer properties [240].

TASK

TASK-3 (Twik-related acid-sensitive K$^+$ channel 3; KCNK9; K$_{2P}$9.1) is a member of the two-pore K$^+$ channel (K$_{2P}$) family. PM TASK channels are involved – with other members of the K$_{2P}$ group - in the conduction of a "background" or "leak" K$^+$ current (and hence in setting membrane potential). It has a large role in O_2 (respiration) and pH sensing, apoptosis, the sleep-wake cycle, anesthesia, pain signaling, and various other functions (revs on K$_{2P}$ channels: [241, 242]). It is well known to form heteromeric channels at least with TASK-1, with which it shares about 50% of the sequence, and TWIK-1. Since it's "designed" to control membrane potential, TASK-3 is strongly expressed in the nervous and cardiovascular systems, but it has been found to be upregulated in several cancer types (e.g.: [243, 244]) and it is recognized to have a role in tumorigenesis [245]. The existence of a mitochondrial population has been known for more than 10 years [246, 247], and suppression of TASK-3 expression has deleterious consequences for mitochondria and (cancerous) cells [248, 249]. These observations suggest that mitochondrial TASK-3 may be a target of oncological relevance.

TASK channels (and in general K_{2P} channels) however are not the easiest of pharmacological targets (for recent reviews: [250, 251]). Selectivity in particular has turned out to be a problem (a common one for small-molecule K^+ channel inhibitors). Inhibitors have been sought especially for use as respiratory stimulants. The channel changes its selectivity (i.e., K^+ transport is inhibited) upon extracellular acidification [252], it is blocked by Zn^{2+} (which has no effect on TASK-1 and -2) [253], Ruthenium Red [254, 255], by high concentrations (~10μM) of anandamide (which at lower concentrations is selective for TASK-1) [256] and by a host of other molecules acting in the tens-of-μM units (or higher) range (tabulated in [250]). TASK-3 is a target of anesthetics [257] and breathing stimulants [258]. One of the latter is Doxapram, which actually selects TASK-1 (IC_{50} ~ 0.4 μM) over TASK-3 (IC_{50} ~ 37 μM) or hybrid TASK-1/3 channels (IC_{50} ~ 9 μM) in mouse, whereas it is about equipotent vs. TASK-1 and TASK-3 in human cells (IC_{50} ~ 4 and ~ 2.5 μM, respectively) [259, 260]. Among relatively weak inhibitors one may mention molecules derived from dihydropyrrolo [2, 1-a] isoquinoline [261]. Physiologically, the channel can be inhibited downstream of G protein-coupled receptors (GPCRs) acting via phospholipase C and diacylglycerol, the ultimate modulator [262].

Well-performing antagonists have been identified by SAR studies of series of compounds based on the THPP (5, 6,7, 8 tetrahydropyrido [4, 3-d]pyrimidine) scaffold [263-265]. The most poweful of these derivatives (PK-THPP) exhibited an IC_{50} of 10-35 nM vs. TASK-3, and little discrimination between TASK-1 and TASK-3 [258, 263]. A1899, is also a selective TASK-1 inhibitor. It acts in the nM range, blocking also TASK-3 at approximately 10-fold higher concentrations [266]. These compounds probably share a binding site inside the pore, reached through "fenestrations" in the channel structure [258, 266, 267]. Flaherty and coworkers [268] have developed another series of powerful inhibitors, based on the 1, 3-bis-amide structure. These drugs actually preferentially inhibit TASK-1, which may not be very relevant if the target is mitochondrial TASK(s). The most active towards TASK-3 showed an IC_{50} of 38 nM in patch-clamp assays. The thiotriazole ML308, developed by the same group, worked with an IC_{50} of ~ 0.4 μM, and a >50-fold selectivity for TASK-3 over TASK-1 [269]. Two small-molecule activators have also been identified: NPBA [270] and terbinafine and analogs [271]. In patch-clamp experiments, NPBA increased TASK-3 current with an EC_{50} of 6.7 μM (but the current was increased up to 6-fold at 10 μM). The allilamine terbinafine, a commercial antifungal medication, acts in the single-digit μM range. Schewe et al [272]. have recently described negatively charged activators (e.g. BL-1249) acting on multiple K_{2P} channels, but TASKs are not mentioned in the paper.

VDAC

VDAC1

Long-studied VDAC1, or porin (revs.: [141, 273-275]), is a predominantly mitochondrial outer membrane protein, although its presence has been reported also in the ER/SR [276], endosomes [277] and PM [278-280]. From a pharmacological point of view, the challenge in this case may be not so much to selectively hit the mitochondrial population, as to spare the others. VDAC1 is by now well understood to exert control functions in the transport of Ca^{2+} [281], ATP [282], other metabolites [283], lipids [284] and (at least in yeast) precursors of mitochondrial proteins [285]. Its status thus impacts respiration and cellular ATP levels. It is furthermore at the center of a network of interactions – mediated mainly by the N-terminal - reaching up to 150 partners at a recent count [286]. It has been proposed to be heavily involved in apoptosis [287, 288]. It comes as no surprise that such a pivotal protein plays a major role in cancer (revs.: [274, 289-293]). In this context, two interactions of major relevance are those with Hexokinase (HK) [294, 295] and tubulin [296, 297] (rev.: [298, 299]). Both are understood to contribute to the "Warburg phenotype" of cancerous cells and to repress apoptosis. Disrupting these interactions is therefore a strategy worth considering. In the former case, methyl jasmonate, a plant hormone, has been found to do the job, but

only at mM concentrations [300]. A more efficient approach was based on cell-penetrating peptides copying sequences of the VDAC N-terminal and competing with VDAC itself for binding of HK and possibly other proteins [301-303]. An analogous approach targeted VDAC-Bcl2/Bcl-xL interactions [302, 303]. The peptide agents were remarkably successful also in *in vivo* models.

A long list of small molecules has been found to act on VDAC reducing its conductance for ions and favoring apoptosis when supplied to cells. These include avicins – a family of plant stress metabolites [304], aspirin – which also induces hexokinase detachment from VDAC [305], erastin and erastin-like compounds – which interfere with tubulin binding [306, 307], Fluoxetine (Prozac) [308], Oblimersen (G3139) – a phosphorothioate [309]. Anion transport inhibitors such as DIDS and SITS interact with VDAC and have been reported to inhibit oligomerization and thus antagonize apoptosis [310]. These agents may all act through other pathways as well, and further investigations are needed. For example, DIDS was found to directly inhibit caspase-3, -8 and -9 activity in HeLa cell lysates [311].

VDAC2 and 3

While VDAC1 is the most studied and best known of mitochondrial porins, two others exist. They are relatively minor: in HeLa cells for example VDAC2 expression is about 1/10, and VDAC3's about 1/100, of VDAC1 [312]. Whether they form channels has been in doubt for a long time, and whether this is their main function is still an open question (e.g. [313]). In any case, purified VDAC2 can form large pores resembling those of VDAC1 [314, 315], while VDAC3 can yield mostly smaller conductances under reducing conditions [316]. The significance of these proteins in cell life and cancer seems to derive mainly from some specific functions (e.g. [293, 317, 318]), and in particular from their interactome [319]. Thus, in 2003 VDAC2 was found to bind Bak, preventing its oligomerization [320], an interaction confirmed in various subsequent studies (e.g.: [321, 322]). Indeed, WEHI-9625, a newly discovered tricyclic sulfone which binds VDAC2, prevented Bak-driven apoptosis [323]. However VDAC2 seems to play an opposite, pro-apoptotic role in Bax-mediated apoptosis [324, 325]. The porin reportedly forms with Bax and Bak complexes involving different domains. Deletion of VDAC2 impaired the association of Bax and Bak with mitochondria, and inhibited Bax (but not Bak) function and cell killing by anti-cancer drugs acting via Bax (Etoposide, Venetoclax, BH3-mimetics) [325]. VDAC2 can also bind the mitochondria targeting domain of pro-death Noxa, and a peptide mimicking this domain has been reported to induce the mitochondrial permeability transition and necrotic cell death [326]. It has also been reported to provide the docking site for GSK-3β, an MPTP-activating kinase [327]. VDAC2 seems also to be co-responsible for apoptosis induction by ceramide, which it binds at a site present also in VDAC1. Deletion or mutation of this binding site in VDAC2, but not in VDAC1, made colon cancer cells resistant to ceramide-induced apoptosis [328, 329]. Such a deep involvement in the mechanisms of extrinsic apoptosis makes VDAC2 a clear candidate for pharmacological intervention. Activity in this direction has however been limited so far. Besides WEHI-9625, one compound binding VDAC2 (and VDAC1) is sulindac sulfone, a metabolite of the nonsteroidal anti-inflammatory drug sulindac [330]. VDAC2 is also involved in cell death induced by artesunate, a derivative of the antimalarian herbal drug artemisin [331]. A whole set of compounds, from resveratrol to paclitaxel to artesunate, act via Bak, and their action may therefore involve VDAC2. The possibility of an involvement of VDAC3 in cancer has received so far little attention. The protein has been proposed to function as a redox sensor, and may thus respond to the oxidizing conditions normally found in cancerous cells [332].

CLIC

Chloride intracellular channels (CLIC1-6) are one of the two classes of chloride channels identified in the IMM. They are still only partially understood [333]. CLICs exist in both soluble and membrane forms and are structurally similar to a family of glutathione

S-transferases, but they can insert into membranes to form ion channels [334]. Membrane-associated CLICs are localized in the nuclear membrane, trans-Golgi network, endoplasmic reticulum and mitochondria, and their distribution is tissue specific. They participate in membrane trafficking, cytoskeletal function, apoptosis, cell cycle control, tubulogenesis and other cellular processes. It has been demonstrated that CLIC1, CLIC4 and CLIC5 are present in adult cardiac mitochondria [335]. Since a sub-fraction of CLIC4 has been identified in the IMM, it has been proposed to have a role in the regulation of membrane potential [335, 336]. CLIC4 has also been observed in the mitochondria of keratinocytes [337].

CLICs definitely have a role in cancerogenesis, but our knowledge is still spotty [338]. Both up- and down-regulation have been reported in cancer cell lines, and the various members of the family clearly have different characteristics and functions. Thus, e.g., a correlation was found between tumor grade and percentage of CLIC1 positive cells in renal carcinoma [339]. CLIC1 expression was elevated in glioblastoma in comparison with low-grade glioma [340] and its downregulation by shRNA or antibody treatment in neurospheres reduced the proliferation and tumorigenicity of cancer stem cells [341]. Biguanide drugs (including metformin) selectively inhibit CLIC1 in glioblastoma stem cells and oppose their proliferation and invasiveness, with little effect on normal stem cells [342, 343]. Over-expression of CLIC-4 was reported in malignant pleura mesothelioma patients [344]. CLIC4 was instead downregulated in several epithelial cancers and squamous cancer cell lines. The expression of the protein was inversely correlated with the malignancy of these tumors. CLIC4 expression is controlled by p53 and TNFα and the protein has been observed to translocate from the cytosol to the nucleus under conditions of oxidative stress. Auranofin, an inhibitor of thioredoxin reductase, induced this migration in v-ras^{Ha}-transformed primary keratinocytes but not normal primary keratinocytes [345]. ROS trigger the up-regulation of CLIC4 expression in ovarian cancers [346]. Other studies reported, upon an increase in oxidative stress, an increase of CLIC4 protein expression in the glioma C6 cell line. This behavior was paralleled by an increased Bax/Bcl-2 ratio, cytochrome c and cleaved caspase-3 protein expression upon H_2O_2-induced C6 cell apoptosis, indicating that CLIC4 could be involved in oxidative stress-triggered apoptosis [347]. CLIC4 is thus considered to be a tumor suppressor protein.

The pharmacology of these proteins is, unsurprisingly, still underdeveloped. In addition to the biguanide drugs mentioned above, Indanyloxyacetic acid (IAA)-94 (a chloride channel inhibitor) reduced colon cancer cell migration and invasion, and the effect was attributed to inhibition of CLIC1 [348].

Summarizing, the knowledge on CLICs implications in cancer is still insufficient, especially with regard to mitochondrial populations of the channels. Despite the lack of causal evidences, variations in the expression pattern of (some of) these proteins in cancer makes them interesting topics for further mechanistic and pharmacological investigation.

Conclusion

Collectively, mitochondrial channels have an outstanding potential as targets for innovative chemotherapeutic approaches. Their location allows them to influence aspects of cell biochemistry/physiology of peculiar relevance in cancer, so that drugs targeting them have a selective impact on cancerous cells. In most cases (exceptions: MCUC, K_{ATP}) the mitochondrial population is only a fraction of the total amount expressed by the cell. Focalized targeting thus requires fielding appropriately modified drugs, usually containing a lipophilic cation, and/or specially equipped nanovehicles. It should also be kept firmly in mind that each cancer has its own specific features, and this applies to mitochondrial channels as well as to many other aspects.

The progress made to date towards a possible clinical use varies greatly from case to case. For some mitochondrial channels the connection with cancer has hardly been made, and might not be significant (e.g. K_{ATP}, BK_{Ca}). In other cases it is known to exist, but it is

still insufficiently defined and/or there is essentially no pharmacology to build on (e.g., CLIC4). For a few channels definite steps forward have been made or are being taken. These are MCUC and VDAC, for which mitochondrial targeting is no – or a secondary – problem, and some of the IMM K^+ channels. The latter have counterparts elsewhere in the cell, and thus a pharmacological approach directed specifically to mitochondria may be fruitful. A detailed investigation of the characteristics and functions of mitochondrial channels in cancer cell lines, including those that are known to exist but have been rather neglected thus far, is a prerequisite for the expansion and development of this emerging branch of onco-pharmacology.

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