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Mitochondrial Ion Channels

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Abstract

Mitochondria are involved in multiple cellular tasks, such as ATP synthesis, metabolism, metabolite and ion transport, regulation of apoptosis, inflammation, signaling, and inheritance of mitochondrial DNA. The majority of the correct functioning of mitochondria is based on the large electrochemical proton gradient, whose component, the inner mitochondrial membrane potential, is strictly controlled by ion transport through mitochondrial membranes. Consequently, mitochondrial function is critically dependent on ion homeostasis, the disturbance of which leads to abnormal cell functions. Therefore, the discovery of mitochondrial ion channels influencing ion permeability through the membrane has defined a new dimension of the function of ion channels in different cell types, mainly linked to the important tasks that mitochondrial ion channels perform in cell life and death. This review summarizes studies on animal mitochondrial ion channels with special focus on their biophysical properties, molecular identity, and regulation. Additionally, the potential of mitochondrial ion channels as therapeutic targets for several diseases is briefly discussed.

Contents

INTRODUCTION

Proper mitochondrial function is based on the integrity of mitochondrial membranes. Peter Mitchell in his Nobel Lecture delivered in 1978 underlined the low permeability of the inner mitochondrial membrane (IMM) to ions (see 138). Consequently, the discovery of multiple ion channels in the IMM was for many years considered to be an experimental artifact. Nowadays, mitochondrial ion channels present in the outer mitochondrial membrane (OMM) and IMM are recognized as crucial players for regulating mitochondrial function (39, 220). Thus, mitochondrial ion channels have attracted attention for many years, especially in the context of the regulation of life and death processes in the various cell types (88, 117, 148, 221). For example, the activation of mitochondrial potassium channels may induce cytoprotective phenomena in cardiac tissue and in neurons (149, 224). On the contrary, inhibition of mitochondrial potassium channels may cause cell death (119, 149). Mitochondrial ion channels also seem to play a role in inflammatory responses (174).

Two major types of ion channels were identified in mitochondria (220). Channels of the first type, including the majority of mitochondrial potassium channels, display biophysical and pharmacological properties similar to those of their counterparts in the plasma membrane. The molecular identity of these channels also seems to be similar to that of plasma membrane channels. However, some of the mitochondrial ion channels are exclusive for mitochondria, for example, mitochondrial calcium channels (66) or channels of the outer membrane such as mitochondrial porins (91). Additionally, mitochondria constitute a unique environment for the regulation of ion channels (126) by (*a*) metabolic activities leading to reactive oxygen species (ROS) synthesis and (*b*) highly negative membrane potential ($\Delta\psi$). This kind of environmental context is very important for understanding the role of mitochondrial ion channels (**Figure 1*a***) in cell physiology.

Recently, significant advances in the mitochondrial ion channel field have primed a new list of open questions (115). These questions concern, among others, the regulation of channel-forming proteins, their interaction with partners, and specific pharmacological tools affecting channel

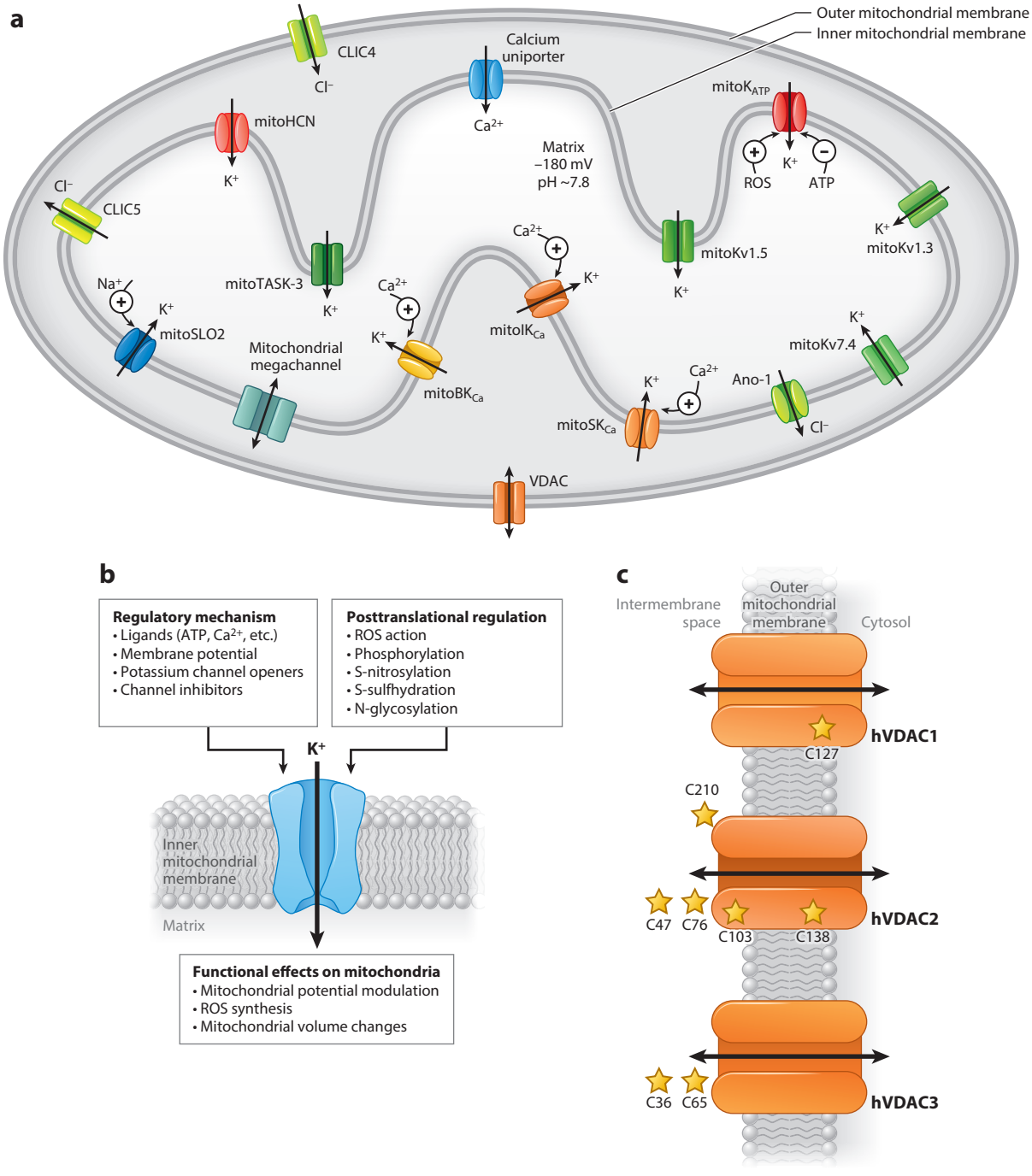

Figure 1

Mitochondrial ion channels. (*a*) Localization and basic properties of ion channels in the outer and inner mitochondrial membranes. (*b*) Summary of regulatory mechanisms and posttranslational modification of mitochondrial potassium channels leading to functional effects on mitochondria. (*c*) Cysteine residues undergoing posttranslational modifications of human VDAC isoforms. Partial or full oxidation of the indicated cysteine residues' sulfhydryl groups to sulfonic acid occur in all three VDAC isoforms. Abbreviations: hVDAC, human VDAC; ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.

activity. In this review, we aim to summarize our current knowledge about mitochondrial ion channels, with a special emphasis on the latest contributions, in the hope that this will help the reader to better understand this fascinating subfield of cellular bioenergetics.

VOLTAGE-DEPENDENT ANION CHANNELS OF THE OUTER MITOCHONDRIAL MEMBRANE

Optimal functioning of the mitochondrial respiratory chain requires an efficient exchange of metabolites including ATP/ADP, Ca^{2+}, and other ions between the cytoplasm and mitochondria. The task of connecting these two compartments is fulfilled by voltage-dependent anion channel (VDAC), also known as mitochondrial porin, an evolutionarily conserved β-barrel membrane protein (129) located in the OMM. VDAC isoforms encoded by distinct genes may be present in mitochondria. Yeast harbors two genes for VDAC isoforms, *YVDAC1* and *YVDAC2*; YVADC1 forms a channel with functional properties closely resembling VDAC1 from other species (122). In vertebrates, three VDAC isoforms (VDAC1, VDAC2, and VDAC3) showing tissue-specific expression have been identified. Although a common transport function may be attributed to all VDAC isoforms, their distinct regulation, expression (263), and posttranslational modifications (169, 183) likely underlie the unique pathophysiological roles that they play in different cell types (e.g., 27, 53, 240).

Information on structure is available for all three isoforms from models (4, 43) and from X-ray crystallization or nuclear magnetic resonance studies (17, 62, 197, 235), even for oligomeric VDAC1 (92) and VDAC3 aggregates (83). These studies revealed a transmembrane pore region composed of a 19-stranded β-barrel with an N-terminal α-helix lining the pore. The main differences among the three isoforms consist of (*a*) the absence of glutamate 73, recently linked to the ability of VDAC2 to control calcium flux across the OMM (201), in VDAC3, and (*b*) the presence of six cysteines in VDAC3 (54), proposed to confer an oxidative stress sensor function to this isoform (180, 266). Thus, although the isoforms are structurally quite similar, subtle primary sequence differences may facilitate isoform-specific roles (e.g., 140, 182). Evidence for the channel-forming ability of VDACs comes from both electrophysiological studies and a *Saccharomyces cerevisiae* complementation assay exploiting a YVDAC1-depleted (Δpor1) mutant, which enabled assessment of the ability of an exogenous protein to recover the physiological growth phenotype of the mutated strain (257).

The main biophysical properties of VDACs are their large conductance [up to 4 nS in 1M KCl in the fully open state (24)]; their bell-shaped voltage dependence, with the highest probability of opening observed around 0 mV; and their anion over cation selectivity in the fully open state, with the presence of cationic conductance substates that become prevalent in the partially closed conformation (220). The physiological consequences of such properties include the passage of even large molecules and metabolites across the OMM where the membrane potential value is considered close to zero. While a consensus has been reached regarding VDAC1 and VDAC2 activities and their regulation, findings regarding VDAC3's biophysical characteristics and likeliness to form channels with high conductance seem to vary depending on the experimental conditions used (40, 147, 177, 257). A thorough study using a thermal shift assay discovered that VDAC3 protein stability is very low when certain detergents are used (176). In addition, VDAC3 cysteines can adopt different oxidation states (SNO, SSH, SOH, SO_2H, SO_3H, S-acylation, S-glutathionylation), contributing to protein heterogeneity during the purification procedure (179, 180) and likely accounting for the low conductance observed in some of the studies. Accordingly, the addition of the reducing agent dithiothreitol during protein purification resulted in large-conductance channel activity (44, 176). Thus, these factors likely account for the observed

differences, although it has to be pointed out that the intermembrane space (IMS) is an oxidative environment, so VDAC3 is not expected to operate in the fully open state most of the time. Most of the biophysical studies on VDACs, with a few exceptions (135, 255), exploited lipid bilayer reconstitution and a nonphysiologically high 1M KCl medium for channel activity measurements. This methodological choice may have an impact on the interaction of regulatory proteins such as tubulin or α-synuclein with VDAC molecules (e.g., 65, 134, 185, 202), as the strength of electrostatic interactions may vary depending on the ionic strength used (29).

A myriad of different functions have been proposed for all three isoforms, based on in vitro and in vivo experiments employing VDAC-deficient cells or organisms. VDAC1 is the most abundant form and, along with VDAC2, is involved in apoptosis regulation (for recent reviews, see, e.g., 140, 202); the function of VDAC3, showing high expression in the testis, is less clear (179). Interestingly, among the VDAC isoforms only deletion of VDAC2 results in early-stage mouse lethality, despite VDAC2's apparent redundancy in function, likely because VDAC2 is crucial for the mitochondrial import of proapoptotic Bak and for truncated Bid (tBid)-induced (141) and Bax-triggered apoptosis (42). In VDAC1$^{-/-}$ mice, tissue-specific alterations in metabolisms (linked to defects in multiple respiratory complex activities) and an altered sensitivity for ADP were observed (5). VDAC1 has been proposed to be a component of the permeability transition pore (PTP), which is crucial for cell death (104, 265); however, the main properties of the PTP are conserved in VDAC1$^{-/-}$ mitochondria (111). In agreement with this, Ca^{2+}- and oxidative stress–induced PTP opening and cell death were not affected in cells deleted for VDAC1/3 and downregulated for VDAC2 (12), questioning the role of VDACs in PTP formation. However, fear conditioning and spatial learning were dysregulated in VDAC1-deficient mice (248), which showed a slight delay in growth. Interestingly, in the VDAC1$^{+/-}$ heterozygous mice, in contrast, an enhanced mitochondrial function was found, as demonstrated by elevated ATP and dampened ROS levels (128). In contrast to VDAC1, deletion of muscle VDAC3 led to decreased activity of complex IV only (6), raising the possibility of tissue- and VDAC isoform–dependent modulation of bioenergetic efficiency. VDAC3-deleted male mice harbor sperm with reduced motility and are thus infertile (191). Recently, Kastor and Polluks, two polypeptides encoded by a testis-specific long noncoding RNA (lncRNA), have been reported to modulate VDAC3 function and spermatogenesis (137); these results open up a new field of research, i.e., linking lncRNA to mitochondrial ion channel modulation and associated metabolic changes.

Indeed, we foresee that the list of regulatory peptides and proteins and possible posttranslational modifications (PTMs) of VDACs is far from complete. The reader is advised to consult a recent, excellent summarizing review about reversible PTMs of VDACs (169). As an example to underline the importance of such regulation, we illustrate in detail the relationship between VDACs and the E3 ligase Parkin: A decade ago, VDACs were proposed to serve as mitochondrial docking sites to recruit Parkin from the cytosol upon mitochondrial dysfunction (214). Following this, it was shown that the R1-in-between-ring-RING2 motif of Parkin (87), as well as a heart-specific RING-finger protein, indeed interacts with VDAC1 (139). Finally, Parkin-mediated VDAC1 polyubiquitination was linked to mitophagy (necessary for removal of damaged mitochondria), while deficient monoubiquitination promoted apoptosis by increasing Ca^{2+} uptake into mitochondria (86). Flies expressing a VDAC1 that could not undergo monoubiquitination showed signs of Parkinson disease (86), indicating that a differential PTM of VDAC1 is able to determine the fate of mitochondria and also of the cell. Another interesting case to cite when describing PTM is that of VDAC3: As mentioned above, this isoform has been reported to adopt different conductance states depending on the oxidation state (183) and was shown to buffer ROS, given that PTMs of its cysteines seem to be indispensable to counteract ROS-induced oxidative stress (181).

MITOCHONDRIAL CALCIUM-PERMEABLE CHANNELS OF THE INNER MEMBRANE

Mitochondria are crucial organelles for shaping the cytosolic Ca^{2+} signals, since they act as buffers by allowing rapid uptake of this second messenger into the matrix (184). The negative $\Delta\psi$ represents a considerable driving force for the uptake of cations, including Ca^{2+}. The pathway mediating Ca^{2+} uptake into energized mitochondria through the so-called mitochondrial calcium uniporter (MCU) complex (MCUC) has been elucidated during the past decade with regards to molecular identification and regulation. The first member of the MCUC identified by an integrative genomics and proteomics approach was MICU1, an EF-hand protein able to modulate Ca^{2+} uptake into the mitochondria (165). Soon after, two groups independently identified the coiled-coiled domain containing CCDC109A as the pore-forming component of the MCUC (16, 55). De Stefani and coworkers (55) provided direct evidence showing activity of the recombinant or in vitro–expressed protein in electrophysiological experiments. The activity resembled the tiny <6pS MCU channel previously identified by patch clamp (106). De Stefani and colleagues (55) also identified the critical glutamate residues in the pore region and confirmed that MCU is able to conduct sodium when calcium is absent. Later, patch-clamp studies performed on mitochondria isolated from cells with RNA interference–mediated knockdown of CCDC109A further confirmed the identity of MCU (37). A dominant-negative pore-forming subunit, MCUb, has also been identified (178). These groundbreaking studies prompted the field to elucidate the role of MCU in various pathophysiological contexts using genetic models (for recent reviews, see, e.g., 2, 130, 156). In addition, numerous groups have dedicated attention to delineating how MCU is regulated and to resolving the 3D structure of the protein (63, 143, 152), highlighting its tetrameric organization.

Several regulatory subunits of the MCUC have been identified besides MICU1. Tissue-dependent expression of a splicing variant of MICU1 (241) was reported, and paralogs MICU2 (e.g., 159, 170) and MICU3 (160, 170) were identified that are able to form heterodimers with MICU1 and exert specific regulatory function on Ca^{2+} fluxes across the IMM. From a biophysical point of view, MICU1 was shown to increase the open probability but not the conductance of the MCU channel in the presence of Ca^{2+} ions, while, in the absence of this ion, MICU2 closed the pore (159), thereby fine-tuning the MCUC. However, later, many contradictory studies appeared regarding the regulation of the MCUC by MICUs, proposing that the MCU pore is plugged by MICU1 (127), mostly based on measurements of Ca^{2+} uptake in cells lacking MICUs. Genetic manipulation of MICUs, however, impacts the expression level of MCUC components as well. Thus, interpretation of these results in the absence of direct demonstration of channel activity gave rise to erroneous conclusions in the field. This issue was recently resolved thanks to the excellent and thorough work of the Kirichok group, who confirmed an increased open probability of MCU by MICU1 at high [Ca^{2+}] and provided evidence, by directly measuring channel activity in mitoplasts, that MICU1 does not occlude the pore (75). In addition, this group provided evidence that (*a*) MICU2 also contributes to allosteric potentiation of MCU in the presence of Ca^{2+}; (*b*) the MCUC is also able to conduct Mn^{2+}, which shows higher affinity for the pore compared to Ca^{2+}; and (*c*) MCU is blocked by Mg^{2+}. In contrast to previous reports (238, 239), they found no inhibition of MCU by elevated matrix [Ca^{2+}]. Further considerations can be taken into account based on the structure of the MCUC holocomplex: As pointed out by Garg and colleagues (75), the structure resolved under the most physiological conditions (ionic strength, presence of cardiolipin) (262), which however lacked Mg^{2+}, shows no occlusion of the MCU pore by MICUs, in contrast to the results of other studies (64, 246). Previous data indicating a direct interaction of MICU1 with the negatively charged aspartate residues in the pore region of MCU (155, 168) have been confirmed.

Another issue related to the MCUC is the exact role of the metazoan-specific protein harboring a single transmembrane domain named essential MCU regulator (EMRE) (192). In mammalian mitochondria, while the lack of EMRE prevented channel activation (75, 192), the low expression level of EMRE in the MICU1 knockout (KO) mitochondria did not affect the calcium current (I_{Ca}), and overexpression of EMRE did not rescue the reduction of I_{Ca} observed upon deletion of MICU1 (75). Thus, apparently, MCU channel activity does not necessarily require a 1:1 MCU:EMRE stoichiometry to be functional, as has also been proven experimentally (247). Accordingly, MCUs from plants that do not express EMRE are able to form functional channels on their own (227, 228, 234). In the heart and kidney, where the MCU-carried Ca^{2+} current is detectable (67, 68), MCU is mainly present as a tetramer without EMRE (247). These recent results may in part explain the observation of single-channel activity in experiments using recombinant MCU in the absence of EMRE (55). Thus, EMRE might be considered more a channel regulator than a channel-forming subunit (262), and it is able to maintain tight MICU regulation of the MCU pore by binding to MICU1 (234). In accordance with this, without MICU1/2, EMRE cannot enhance MCU activity; however, a single-amino-acid mutation in MCU (MCU-R297D) disrupts interaction with EMRE and leads to loss of activity (262).

As to the PTM of MCUC components, it has been reported that MICU1 can be degraded in a Parkin-dependent way (133); acetylated at residue K332, leading to enhanced apoptosis through SIRT1 inhibition (215); and methylated by protein arginine methyl transferase 1, resulting in decreased Ca^{2+} sensitivity of MICU1 (125). In contrast, MCU can be tyrosine phosphorylated by proline-rich tyrosine kinase 2 (151), and the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) was also shown to affect MCU activity (96). However, modulation by CaMKII was not confirmed in subsequent studies (67, 144). Another important regulator of MCU activity is modification of its IMS-located Cys residue: Similarly to VDACs, MCU can sense the IMS oxidative state via Cys-97 S-glutathionylation, which promotes higher-order oligomerization of the channel complex (60). The relevance of this modulation was highlighted in cells expressing an MCU Cys97 mutant: These cells show enhanced Ca^{2+} uptake, ROS synthesis, and cell death. The MCUC complex components are regulated also by the m-AAA protease, which degrades non-assembled EMRE (110). Also in the case of the MCUC, we predict that many further PTMs will come into play in the near future to further implement our knowledge, with the aim of comprehending the function and regulation of this important protein complex.

POTASSIUM CHANNELS OF THE INNER MITOCHONDRIAL MEMBRANE

The mitochondrial K^+ cycle regulates mitochondrial volume to maintain the integrity of the organelle (77, 164). The homeostasis of matrix volume depends on the balance between K^+ uptake and K^+ efflux from mitochondria. Influx of K^+, driven by highly negative $\Delta\psi$, into mitochondria is accompanied by anion flux, followed by water, which results in mitochondrial swelling. The K^+ uptake is compensated by the inner membrane K^+/H^+ antiporter, which catalyzes electroneutral K^+ efflux from mitochondria (77). The process of K^+ influx was for many years known as K^+ uniporter activity without specifying the protein(s) responsible for these activities. Properties of K^+ uniporter, such as its inhibition by adenine nucleotides (18), and the discovery of the mitochondrial ATP-regulated (mitoK_{ATP}) channel suggested that K^+ uniporter activity in fact was mediated by mitochondrial potassium channels (**Figure 1*b***), rather than classical transporters (76).

Mitochondrial ATP-Regulated K^+ Channels

In 1991, a potassium-selective, ATP-sensitive channel (mitoK_{ATP}) was described in the IMM of rat liver mitochondria (94). The channel was recorded using patch-clamp and was inhibited by

ATP and the antidiabetic sulfonylurea glibenclamide. The latter property indicated the potential similarity of the mitochondrial channel with the potassium channel regulated by ATP present in the plasma membrane (PM) of many cells (232). Later studies showed that mitoK_{ATP} channels were present in the mitochondria of various cell types. These channels have been identified in the mitochondria of heart tissue (161, 194), brain tissue (13), skeletal muscles (57), renal tissue (32), human T lymphocytes (47), and skin fibroblasts (19). The presence of the mitoK_{ATP} channel has also been reported in *Trypanosoma cruzi* (46), *Caenorhabditis elegans* (249), and *Acanthamoeba castellani* mitochondria (103), as well as in plant mitochondria (49, 132, 189). All of these observations suggest widespread occurrence of ATP-sensitive transport of K^+ in mitochondria.

Patch-clamp on mitoplasts and planar lipid bilayer techniques have been applied to study the biophysical and pharmacological properties of mitoK_{ATP} channels. The measured channel activity displayed conductance ranging from 10 to 100 pS (220). The observed differences in conductance values most likely depend on the cells or tissue, methods, or experimental conditions applied. However, it cannot be ruled out that ATP-sensitive transport of K^+ ions is carried out by different proteins in different types of cells.

The pharmacology of the mitoK_{ATP} channel is similar to that of the PM K_{ATP} channels (10). The potassium channel opener diazoxide (at μM concentrations) is considered to be a specific activator of the mitoK_{ATP} channel (78, 79). Additionally, the K^+ channel opener BMS191095 is considered to act on mitochondrial potassium channels (82). Among mitoK_{ATP} channel inhibitors, ATP is believed to be the major negative regulator of mitoK_{ATP}. MitoK_{ATP} channels are also inhibited by 5-hydroxydecanoic acid (5-HD) and the antidiabetic sulfonylurea glibenclamide (10, 230). It is believed that 5-HD is highly selective toward the mitoK_{ATP} channel (78, 95). Glibenclamide acts through interaction with the mitochondrial low-affinity sulfonylurea receptor (mitoSUR) subunit to inhibit the mitoK_{ATP} channel (161, 223, 225). Additionally, the mitoK_{ATP} channels can be regulated by Mg^{2+}, quinine, and other nucleotides (10). Application of mitoK_{ATP} activators and inhibitors requires special care in interpreting the results when using intact cells or tissues, since most of the above channel regulators can influence numerous biochemical processes not related to the transport of K^+ through the IMM (254). Besides ATP and nucleotides, a set of endogenous factors regulate mitoK_{ATP} channels. For example, inhibition of mitoK_{ATP} by long-chain acyl-CoA was observed (162). The cardiac mitoK_{ATP} channel is also regulated by multiple phosphorylation events (187) and can be activated by thiol oxidation by ROS (259, 260).

The molecular identity of the mitoK_{ATP} channel has been enigmatic since the first report of its activity in mitochondria. Because of its sensitivity to antidiabetic sulfonylurea, it has been proposed that the channel, similarly to the PM K_{ATP} channel, is composed of an inward rectifier subunit, Kir6.x, and a regulatory sulfonylurea receptor, SUR (23). Binding studies revealed that the mitoSUR receptor differs from its PM counterparts in its affinity to glibenclamide (225). The above hypothesis was rejected because, in mouse cardiac tissue with Kir6.2 deletion, mitoK_{ATP} activity was still present (71). Later, it was proposed that the renal outer medullary potassium channel (ROMK2, also known as Kir1.1) protein represents the pore-forming subunit of mitoK_{ATP} in heart mitochondria (70). Moreover, ROMK2 protein expressed in cardiac H9c2 cells was shown to reach mitochondria (70). The channels were inhibited by 5-HD and by inhibitor of ROMK-type channels, tertiapin Q. Furthermore, mitoK_{ATP} activity in mitochondria overexpressing ROMK2 was inhibited by ATP/Mg^{2+} and activated by diazoxide (114). The role of ROMK2 as the mitoK_{ATP} channel remains unclear because cardiomyocyte-specific global knockout of the ROMK channel was without any effect on ischemia/reperfusion (I/R) injury (157). This was unexpected, as mitoK_{ATP} activation by diazoxide was shown to exert a protective effect against I/R damage (88).

Recently, it was proposed that the protein encoded by the *CCDC51* gene is the pore-forming subunit of mitoK_{ATP} (154). Recombinant CCDC51, along with the mitoSUR protein Abcb8, was

shown to mediate ATP-sensitive K^+ currents and displayed all major characteristics of mitoK_{ATP}. The overexpression of CCDC51 resulted in a decrease of $\Delta\psi$. In contrast, deletion of CCDC51 in HeLa cells also influenced mitochondrial function, including organelle swelling and $\Delta\psi$, and caused decreased oxidative phosphorylation. Importantly, loss of CCDC51 suppressed cardioprotection by diazoxide (154). All of these observations strongly support the conclusion that this protein may constitute the mitoK_{ATP} channel. To obtain further proof, patch-clamp experiments on mitochondria from wild-type (WT) and CCDC51 global KO mice are warranted. Interestingly, it was recently suggested that ATP synthase subunits, modulated by classical activators and inhibitors of mitoK_{ATP}, might form the pore of mitoK_{ATP} (97, 98).

To sum up, we can now indicate a few potential candidates for the proteins giving rise to ATP-regulated potassium channel activity. Whether these different proteins are needed to form mitoK_{ATP} in a tissue-dependent manner needs further clarification.

Mitochondrial Calcium-Activated K^+ Channels

The first mitochondrial calcium-activated potassium channel was described using patch-clamp in glioma cells (203). Potassium selective channel activity increased with increasing Ca^{2+} concentrations and was decreased by the classical peptide inhibitor charybdotoxin. Channel conductance was 295 pS, in line with the values observed for BK_{Ca} channels (203). Later, the small conductance potassium (mitoSK_{Ca}) channel was discovered in cardiac mitochondria (212), and the intermediate-conductance calcium-activated potassium (mitoIK_{Ca}) channel was observed in mitochondria of human colon cancer cells (50, 193).

In recent years, the mitoBK_{Ca} channel has attracted particular attention (15), mainly due to (*a*) its wide occurrence in various types of cells, (*b*) the large number of available BK_{Ca} channel openers, and (*c*) its postulated participation in cytoprotection (81, 210). The mitoBK_{Ca} channels are present in the mitochondria of tissues such as the brain (61), cardiac (72, 206, 210) and skeletal muscle (208), endothelium (21), bronchial epithelium (198), and skin fibroblasts (102).

The biophysical and pharmacological properties of the mitoBK_{Ca} channel are similar to the properties of the PM BK_{Ca} channels (10, 15). Patch-clamp recordings revealed that conductance values range between 150 and 300 pS for mitoBK_{Ca} (14, 72, 210, 256). Activation of the mitoBK_{Ca} channel occurs after the influx of Ca^{2+} into the mitochondrial matrix, suggesting that the C-terminal part of the channel, which contains the calcium-sensing domain, is located in the mitochondrial matrix (203, 256). MitoBK_{Ca} is activated by well-known BK_{Ca} channel openers such as NS1619 and NS11021 and is regulated by the redox state (187). Activation of the channel results in an influx of K^+ into the mitochondrial matrix, causing a decrease in $\Delta\psi$ (depolarization) (101), an increase in oxygen consumption (101), and a decrease in ROS synthesis (90, 101). MitoBK_{Ca} activity is inhibited by the peptides iberiotoxin (207, 208), charybdotoxin (207, 256), and paxilline (14, 72). Additionally, H_2S and CO activate the channel blocked by heme, or hemin (186, 243), shown to be an important regulator of gating of ion channels (74).

Biophysical properties of mitoBK_{Ca} suggest that the pore-forming subunit is encoded by the same gene coding for PM BK_{Ca}. The BK_{Ca} channels are composed of four pore-forming α-subunits encoded by the *KCNMA1* gene (Slo1) (81). Several studies suggested that the VEDEC BK_{Ca} isoform locates to the IMM (73). The specificity of this isoform is defined by the C-terminus modification. The activity of the pore can be regulated by auxiliary β subunits (146). The β1 subunit colocalizes with cardiac mitochondria of mammalian cells (14), likely affecting the biophysical properties of mitoBK_{Ca}. Coexpression with β1 resulted in a higher density of BK_{Ca} in mitochondria (14), although the mechanism of mitochondrial targeting is still unclear.

Interestingly, mitoBK_{Ca} was shown to interact with some mitochondrial proteins. These reports also suggest functional effects of these interactions on mitoBK_{Ca} channel activity. It was

found that the β1 subunit might interact with the respiratory chain in rat cardiac mitochondria (14). Mass spectrometry analysis of the cardiac mitoBK$_{Ca}$ channel revealed interactions with mitochondrial translocases, including the TOM complex and carriers such as adenine nucleotide translocator (ANT) (261). Interestingly, a study describing the global interactome of mouse cochlea BK$_{Ca}$ channels suggests that approximately 20% of the potential channel partners were related to mitochondrial proteins (99), and in glioma cells, respiratory chain activity was found to regulate the mitoBK$_{Ca}$ channels probably via interaction with cytochrome c oxidase (22).

Voltage-Gated K$^+$ Channels

The following voltage-gated potassium channels were described in the IMM: (*a*) the mitoKv1.3 (mitochondrial 1.3 voltage-gated potassium) channel, encoded by *KCNA3* gene (20, 218); (*b*) the mitoKv1.5 (mitochondrial 1.5 voltage-gated potassium) channel, encoded by *KCNA5* gene (120); and (*c*) the mitoKv7.4 (mitochondrial 7.4 voltage-gated potassium) channel, encoded by *KCNQ4* gene (229). While mitoKv1.3 activity was directly observed with patch-clamp by two groups, expression and activity of mitoKv1.5 in macrophages and of mitoKv7.4 in cardiac (229) and neuronal mitochondria (163) are indicated mostly by biochemical and pharmacological experiments.

All three channels have at least dual localization, to the PM and the IMM. Regarding the route they follow to the mitochondria, recent experiments indicate that at least mitoKv1.3 is imported via the classical TOM/TIM-dependent protein import machinery (33). The targeting efficiency of this channel to mitochondria depends on interaction with caveolin-1 (34). Whether such mechanisms apply also to mitoKv1.5 and mitoKv7.4 is an open question. In isolated energized mitochondria, pharmacological modulation of both mitoKv1.3 and mitoKv7.4 leads to changes in $\Delta\psi$m and ROS synthesis, indicating that the channels are open under physiological conditions (163, 218). However, the regulatory mechanisms that allow the opening of these voltage-gated channels (normally open at depolarizing PM voltage) at very negative $\Delta\psi$m are still unknown. Closure of mitoKv1.3 by either specific inhibitors (218) or the proapoptotic protein Bax (217) triggers massive ROS release, probably by virtue of a physical and functional interaction of mitoKv1.3 with complex I of the respiratory chain (166). The relevance of mitoKv1.3 activity in fine-tuning $\Delta\psi$ and ROS release is well illustrated by the observation that a derivative of PAP-1, a specific small molecule inhibitor of Kv1.3 (196) targeted to mitochondria by virtue of a positively charged triphenyl-phosphonium group (209), was able to trigger hyperpolarization followed by elevated ROS release and depolarization due to ROS-triggered opening of the permeability transition pore (see below) (118). In turn, this series of events selectively triggered apoptosis of cancer cells expressing high levels of Kv1.3 and displaying high basal ROS levels, both in vitro and in vivo. As a consequence, the mitochondriotropic mitoKv1.3 inhibitor efficiently and drastically reduced melanoma (118), pancreatic cancer (124), and chronic lymphocytic leukemia (199) in vivo, without signs of toxicity.

Other Cation Selective Channels in Mitochondria

Three other cation selective channels have been described in the IMM: mitoTASK3 channel (encoded by *KCNK9*), a tandem pore-domain acid-sensitive potassium channel type 3 (11, 188, 233, 258); mitoSLO2 (encoded by *KCNT2*), a mitochondrial sodium-activated potassium channel (250, 251); and mitoHCN (encoded by HCN1–4 genes), a mitochondrial hyperpolarization-activated cyclic nucleotide-gated channel (123, 153). The biophysical and functional properties of these channels are described in only a few reports; thus, further studies are warranted to elucidate their pathophysiological relevance.

MITOCHONDRIAL INNER MITOCHONDRIAL MEMBRANE–LOCATED ANION-SELECTIVE CHANNELS

Since the 1960s, it has been known that the IMM contains anion-selective transport systems (30), but an anion-selective, voltage-dependent, mitochondrial channel, the inner membrane anion channel (IMAC), also called the mitochondrial Centum picoSiemens (mCS), which has a mean single channel conductance of 107 pS, was identified by patch-clamping mitochondria (211) only 20 years later. The IMAC is mainly implicated in mitochondrial volume homeostasis and is involved in the heart in electrical and contractile dysfunction after ischemic injury (205). Unfortunately, the molecular identity of the IMAC has not been defined, limiting further progress in understanding the functional role(s) of this channel by genetic means (173).

More is known about mitochondrial anion channels belonging to chloride intracellular channel proteins (CLIC) (84, 173, 244). There are six homologs in mammals (CLIC1–6), four in plants (DHAR1–4), and two in *C. elegans* (Exc4 and Exl1). Mammalian CLICs share approximately 50–60% sequential homology with each other (85). CLIC4 and CLIC5 were recently characterized in mitochondrial membranes (171, 173). CLIC4 is localized to the OMM of cardiac mitochondria, but CLIC5 is found in the IMM (205). The single-channel conductances of CLIC4 and CLIC5 are 15 pS and up to 110 pS, respectively. Both channels are inhibited by indanyloxyacetic acid-94 (IAA-94), an intracellular chloride channel blocker (172). IAA-94 increases myocardial infraction after I/R injury and cardiac cell death, indicating a role for CLIC4 and CLIC5 channels in cardioprotection (172); however, possible off-target effects of IAA-94 have not been excluded.

Anoctamin (Ano), a Ca^{2+}-activated chloride channel (CaCC), performs a multitude of functions including control of cell proliferation, excitability, and the cell cycle; regulation of cell volume; exocrine and endocrine secretion; fertilization; and control of smooth muscle cell contractility (89). CaCCs are the translated products of two members (*ANO1* and *ANO2*, also known as *TMEM16A* and *TMEM16B*) of the Anoctamin family of genes. Recently, the presence of an Ano-1 channel was detected in pulmonary endothelial cells (3), in particular in mitochondria of rat lung microvascular endothelial cells. Ano-1 activation increased mitochondrial ROS synthesis, reduced $\Delta\psi$, and increased p38 phosphorylation, promoting apoptosis of pulmonary endothelial cells (3), although determination of the exact role of Ano-1 in regulation of mitochondrial bioenergetics will require further studies.

In our opinion, anion-selective channels of the IMM constitute an extremely interesting research subject, since their regulation by ATP and pH suggest that they play an important, yet-to-be-discovered role in setting mitochondrial bioenergetic efficiency (108, 136). Additionally, the widespread presence of these channels renders them promising potential targets for drug discovery.

MITOCHONDRIAL MEGACHANNEL AND PERMEABILITY TRANSITION PORE

The permeability transition, i.e., loss of impermeability of the IMM, was originally considered as an unspecific, lipid-mediated event. The idea that it might be due to a regulated pore (93), the so-called PTP, received experimental support from the discovery of Cyclosporine A (CSA), which blocks such a transition, and by the observation of a Ca^{2+}-activated, CSA-sensitive, unselective, large channel with a conductance value of 1.3 nS in 150 mM KCl. The calculated diameter of such a channel fits well to the postulated size of a nonselective PTP pore with a diameter of 2–3 nm in the IMM. The high-conductance channel, named the mitochondrial megachannel (MMC), was indeed later identified as the PTP on the basis of its pharmacological profile, in

particular its (*a*) activation by matrix-side Ca^{2+} (submM range); (*b*) inhibition by CSA (nM range) (219); (*c*) inhibition by divalent cations such as Sr^{2+}, Mn^{2+}, Ba^{2+}, and Mg^{2+} in a Ca^{2+}-competitive manner (μM range) (26, 216); and (*d*) inhibition by mildly acidic matrix pH (216). Interestingly, at very low Ca^{2+} levels, the probability of observing transient MMC activity in a membrane patch is low (51), and upon chelation of Ca^{2+}, MMC activity disappears (216), suggesting that Ca^{2+} is required not only for channel assembly but also for full activation of the pore. Contemporarily with the discovery of the MMC, the group of Kinnally used patch-clamp to reveal activity of the so-called multiple conductance channel (MCC) (105). The major features of the MCC include a peak conductance of up to approximately 1 nS (150 mM KCl) (although in some cases 2.7 nS was recorded), inhibition by CSA, and activation by calcium on the cytoplasmic side (for recent review, see, e.g., 142). While this channel shows slightly distinct biophysical and pharmacological features with respect to the MMC, it is highly likely that the activity of both channels can be ascribed to the same protein. Both the MMC and MCC are characterized by binary cooperative behavior, with a full-conductance state and a prominent half-conductance fast-gating substate, in addition to numerous substates occurring with lower conductance. The half-conductance channel can also be observed as a stand-alone channel (51, 264), suggesting a dimeric structure. Both channels (*a*) are unselective, with the MCC showing a slight selectivity of the smaller substates; (*b*) show voltage dependence with full opening of the channel at depolarizing membrane potential values near to zero; and (*c*) are inhibited by CSA. Further studies performed by several groups revealed that MMC activity in the native IMM is modulated by a series of pathophysiologically relevant agents such as dopaminergic D2-receptor agonist pramipexole (195), ubiquinone analogs (131), and 17β-estradiol (231), as well as by the calpain inhibitor calpeptin (58).

The MMCs described in various studies show very similar biophysical and pharmacological characteristics, independently of the tissue of origin. Interestingly, however, the MMC has been observed in mitoplasts obtained by swelling but not in those prepared using French Press (e.g., 106), suggesting that stripping off of the OMM by swelling may trigger a specific rearrangement of the IMM-located MMC-forming protein(s).

The molecular nature of the MMC/PTP remained a mystery for more than 50 years. Different hypotheses have been put forward (for an excellent recent review, see, e.g., 35), ranging from the involvement of VDAC (but see 111) and the adenine nucleotide carrier (ANT) (but see 107) to the spastic paraplegia 7 (SPG7) protein (200). However, these ideas were discarded because the PTP persisted in cells lacking the above putative components. In recent years, the work of different groups converged on the idea that F-ATP synthase may form MMC/PTP (1, 28, 80). Indeed, the above-mentioned features of the MMC are closely recapitulated by those observed for highly purified F-ATP synthase when reconstituted in planar lipid bilayer experiments (236). Both the mean and maximal conductance values of the F-ATP synthase channel were strictly Ca^{2+} dependent, and the channel operated with full conductance in the presence of the well-known PTP agonist benzodiazepine (Bz)-423 (35). Inhibition of F-ATP synthase–mediated channel activity by CSA could not be observed in bilayer experiments due to the lack of CypD, required for desensitization of the MMC/PTP by CSA (48), casting some doubt on the molecular identification. However, a comparison of MMC activity recorded in WT F-ATP synthase–expressing mitoplasts with that observable in mitoplasts isolated from cells expressing F-ATP synthase with point mutations or subunit deletions represented an elegant way to provide definitive proof in favor of the above hypothesis. This strategy was employed in two studies. First, Antoniel and colleagues (7) identified a specific His mutation conferring sensitivity of MMC to protons. The mutation of the highly conserved histidyl residue (H112) of F-ATP synthase did not alter channel activity itself, but instead rendered MMC insensitive to proton-mediated inhibition. Second, Carrer and colleagues (36) showed that subunits g and e are required for MMC activity in the native membrane. However, when genetically

modifying the F-ATP synthase and measuring channel activity, one has to keep in mind that even single-point mutations in the critical pore-forming regions might collapse a channel, as is the case, for example, in the GYGD pore (P-region) of K^+ channels. Thus, if mutations or deletions impact regions that are fundamental for assembly or stability of the channel-forming protein or protein complex, then erroneous conclusions can be drawn. This risk can be mitigated via a combination of molecular biology, electrophysiology, and structural studies. In addition, a further layer of specificity has to be introduced by exploiting pharmacological tools; as an illustration of this, Carrer and colleagues found it necessary to distinguish the MMC from ANT activity in the native IMM (36).

MITOCHONDRIAL ION CHANNELS AS DRUGGABLE TARGETS

Mitochondrial ion channels are potential therapeutic targets because the function and bioenergetic efficiency of mitochondria are based on the integrity of and ion homeostasis across mitochondrial membranes. Besides contributing to cellular ions homeostasis, and thus affecting energy transducing processes and ROS synthesis, mitochondrial ion channels play an important role in triggering apoptosis (190, 237), in aging (9, 213), and in tumor progression (121, 167). However, modulation of the above processes by inhibiting or activating mitochondrial ion channels using specific agents that lack off-target and/or toxic effects is far from being trivial. Mitochondria are unique targets for pharmacological intervention, given that the highly negative $\Delta\psi$ may lead to accumulation of hydrophobic and positively charged molecules in the mitochondrial matrix. This simple mechanism can be used to selectively target drugs, such as those harboring TPP^+ moiety, to mitochondria (69, 221), but it can also lead to secondary effects (for a review, see, e.g., 221). The alkaline pH of matrix instead causes accumulation of drugs with hydrophobic and weak acidic properties.

Given their fundamental roles in determining the fate of cells, mitochondrial potassium (39, 253) and chloride (173) channels, as well as the mitochondrial calcium channel (calcium uniporter) (2, 56), could be particularly interesting targets for pharmacological intervention. MitoK_{ATP} channels are involved in cytoprotection in both cardiac and neuronal tissue (31, 45, 76). This protective mechanism is triggered by channel activation using potassium channel openers (222, 245). Because there is an enormous set of potassium channel openers, one can expect future identification of specific opener(s) of mitoK_{ATP} channels (116, 175). The mitoBK_{Ca} channels are also believed to be involved in cytoprotective phenomena, especially in cardiac tissue (226). Likewise, there is a large set of specific mitoBK_{Ca} channel openers with potential protective action (224); for example, the use of NS1619, a benzimidazolone that activates BK_{Ca}, together with dehydroepiandrosterone, an inhibitor of the pentose phosphate pathway ensuring antioxidant defense, represented a winning strategy against pediatric T-cell acute lymphoblastic leukemia, at least in a xenograft model (204). Finally, the mitoK_V1.3 channel is important, since upon its inhibition, cancer progression is halted through a ROS-dependent mechanism (38). Currently, a major obstacle to targeting potassium channels to mitochondria is their universal presence in the PM and in different intracellular membranes (41). As a consequence, targeting a unique mitochondrial potassium channel in a specific tissue seems like a hard task these days (112). However, unique properties of mitochondria, such as high membrane potential, may be exploited for successful targeting.

Recent descriptions of the molecular identity of mitochondrial CLICs and mitochondrial CaCC may facilitate the search for specific channel regulators. The pharmacology of mitochondrial chloride channels is currently very limited (158, 242), but, for example, VDAC-based cell-penetrating peptides are of great promise in the context of cancer (202). Regarding VDACs, so crucial for metabolite transport and redox buffering, one interesting possibility would be that of generating molecules acting at the level of different cysteine residues (**Figure 1*c***) and thus able

to modulate channel activity. Considering the important functional role of mitochondrial anion channels, the progress in synthetizing channel regulators may accelerate therapeutic application (205).

Altered MCUC function is crucially linked to several diseases ranging from neuro- and muscle degeneration to stroke, diabetes, and cancer. Thus, identification of small-molecule MCUC regulators has become a priority. Ruthenium Red (RuR), by binding to S259 in MCU, blocks MCU activity (16). A cell-permeable, low-toxicity variant, Ru265, has been synthesized (252) and proven to exert a beneficial effect against brain I/R damage even in vivo (145); however off-target effects were not excluded in these studies. More recently, mitoxantrone (8), DS16570511 (109), and MCU-i4 and MCU-i11 (59) were identified. The latter compound binds to MICU1 and does not induce mitochondrial depolarization in healthy cells, in contrast to the former drugs (for a recent review, see 130). Finally, screening of US Food and Drug Administration–approved drugs identified amorolfine and benzethonium as positive and negative MCU modulators, respectively (52). The latter drug protected breast cancer cells against apoptosis (52), in accordance with the known relevance of mitochondrial calcium overload for cell death (150). To the best of our knowledge, whether a mitochondria-targeted version of the above-mentioned drugs may more efficiently modulate the MCUC is still an unexplored area.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Due to advances in mitochondrial ion channel studies during the past 20 years, there has been a substantial acceleration in understanding mitochondrial channel function in various cell types. Despite this progress, some essential issues remain unclear. The most important open questions in the field regard channels' molecular identity, the protein–protein interaction network of channels (possibly in intact cells), and the import pathways involved in subcellular targeting of mitochondrial ion channels. Likewise, signaling pathways that regulate mitochondrial ion channel activities are of utmost importance but are known only in a few cases (25, 72, 100, 187, 205). Elucidation of the above factors, along with techniques allowing measurement of channel activity in situ, would lead to a better understanding of the physiological role of these proteins. Finally, answering these burning questions may aid in further development of therapeutic strategies based on specific modulation of mitochondrial channels in specific tissues (113).

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