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Mitochondrial Ca^{2+} channels: Great unknowns with important functions

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Abstract

Mitochondria process local and global Ca^{2+} signals. Thereby the spatiotemporal patterns of mitochondrial Ca^{2+} signals determine whether the metabolism of these organelles is adjusted or cell death is executed. Mitochondrial Ca^{2+} channels of the inner mitochondrial membrane (IMM) actually implement mitochondrial uptake from cytosolic Ca^{2+} rises. Despite great efforts in the past, the identity of mitochondrial Ca^{2+} channels is still elusive. Numerous studies aimed to characterize mitochondrial Ca^{2+} uniport channels and provided a detailed profile of these great unknowns with important functions. This mini-review revisits previous research on the mechanisms of mitochondrial Ca^{2+} uptake and aligns them with most recent findings.

Keywords

Calcium signaling; ER Ca^{2+} release; grp75; IP_3 receptor; Letm1; mCa1; mCa2; MiCa; MCU; Mitochondrial Ca^{2+} uniporter; Mitofusin; p38MAPK; Uncoupling protein; UCP2/3

1. Introduction

Mitochondria have been recently recognized as multifunctional organelles that elementary impact on many different signaling pathways, thus, putting a new complexion on the long-known cellular power houses [1–4]. One distinguished feature of mitochondria that became evident by the utilization of newly developed mitochondria-targeted protein-based Ca^{2+} sensors [5,6] is the organelle's active involvement during physiological Ca^{2+} signaling [7–10].

Herein, mitochondria were discovered to be far more than a passive Ca^{2+} sink that stores Ca^{2+} ions as Ca^{2+}-$(poly)_x$-phosphate[11,12]. Indeed, mitochondrial Ca^{2+} handling turned out to represent a highly sophisticated mechanism that has multiple consequences for cells (Fig. 1A):

First, mitochondria themselves constitute a Ca^{2+} target as these organelles house several Ca^{2+}-sensitive proteins among which key metabolic enzymes, such as the

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dehydrogenases of the Krebs-cycle, translate Ca^{2+} elevation in the mitochondrial matrix to increased respiration and ATP production [13–17].

Second, mitochondria crucially contribute to Ca^{2+} signaling by their ability to take up and release large amount of Ca^{2+} ions. By their potential to sequester cytosolic Ca^{2+}, mitochondria are able to buffer Ca^{2+} in distinct region of the cell and keep spatial Ca^{2+} concentration low even under conditions of strong global Ca^{2+} mobilization upon cell stimulation, which significantly impacts on Ca^{2+}-sensitive signal transduction within a cell [18–20]. Moreover, mitochondria are able to funnel Ca^{2+} to endoplasmic reticulum (ER) Ca^{2+} uptake sites [21,22] and accomplish ER Ca^{2+} replenishment during and after cell stimulation [22], an important process that ensures proper activity of the Ca^{2+}-dependent ER chaperons of the protein folding machinery [23–26].

Third, an excessive mitochondrial Ca^{2+} load sweeps cells to death by triggering either apoptosis or necrotic cell death [27–29], thus, signifying that mitochondrial Ca^{2+} uptake in any case of cellular Ca^{2+} mobilization essentially needs to be precisely regulated [27–29].

Substantial studies over the last decades demonstrated that Ca^{2+} channels and Ca^{2+} exchanger in the inner mitochondrial membrane (IMM) establish Ca^{2+} transfer across the organelle's inner membrane, while the ion transfer across the outer mitochondrial membrane (OMM) was thought to represent a rather uncontrolled process [30–33]. However, the latter view has been changed recently as regulatory mechanisms of the main Ca^{2+}-permeable channels in the OMM, the voltage-dependent anion selective channels (VDAC1, 2 and 3), have been demonstrated [34–36] and their functional involvement in apoptosis was described [37–41]. While with the VDAC family the proteins for the Ca^{2+} transfer across the OMM are most likely identified, the proteins that are responsible for Ca^{2+} movements across the IMM are not completely identified so far (Fig. 1A). However, these mitochondrial Ca^{2+}-shuttling proteins have been functionally well characterized although in many studies isolated mitochondria were used (reviewed in [42]) and the translations of such results to respective processes in intact cells, where mitochondria are embedded into an highly interactive environment, need cautiousness [43]. In this review we consider these aspects and intend to summarize recent progresses in the identification of functional and structural properties of mitochondrial Ca^{2+} channels of the IMM.

2. Characterization and identification of mitochondrial Ca^{2+} channels

Energized, respiring mitochondria are naturally destined to sequester Ca^{2+} due to their great negative membrane potential of the IMM (ψ_{mito}) that establishes a strong driving force for Ca^{2+} uptake into this organelle [9,44]. Moreover, mitochondrial are capable to store high amounts of Ca^{2+} in the mitochondrial matrix by the formation of Ca^{2+}-$(poly)_x$-phosphates [12,31]. Mitochondrial Ca^{2+} uptake stimulates ATP production, but can also initiate cell death. Accordingly, the molecular mechanisms of mitochondrial Ca^{2+} uptake gained much attention during the last years.

2.1. Electrophysiological characterization of distinct mitochondrial Ca^{2+} channels

Recently, in two landmark publications that described the electrophysiological characterization of three highly selective Ca^{2+} channels in the IMM, which presumably account for the mitochondrial Ca^{2+} uniporter (MCU) phenomenon, were presented (Fig. 1B).

2.1.1. The MiCa—Applying the patch-clamp technique on mitoplasts (isolated mitochondria lacking their OMM) from COS-7 cells, the existence of a highly specific Ca^{2+} channel in the IMM has been convincingly demonstrated in 2004 by the laboratory of Clapham et al. [45]. This unique mitochondrial Ca^{2+} channel was referred to as MiCa. The electrophysiological characterization of MiCa showed that this channel is inwardly rectifying with a very high Ca^{2+} transport capacity making it very effective for Ca^{2+} uptake into energized mitochondria. These findings confirm visionary earlier studies in which the mitochondrial electrophoretic Ca^{2+} uniport was explored in isolated energized mitochondria [46,47] and reports that described the hexavalent cation ruthenium red (RR) and its related compound Ru360 as efficient inhibitors of the mitochondrial Ca^{2+} uniport in the nanomolar range [48]. Moreover, as expected for the MCU the permeability of MiCa to various divalent cations shows the following order: $Ca^{2+} \approx Sr^{2+} >> Mn^{2+} \approx Ba^{2+}$, whereas MiCa is impermeable for Mg^{2+} ions. The monovalent ions K^+ and Na^+ do not contribute to the MiCa current in the presence of Ca^{2+}, indicating the high Ca^{2+} selectivity of this mitochondrial Ca^{2+} channel. Notably, in this study 3–7 active channels per patch were found, which is a surprisingly high density of mitochondrial Ca^{2+} channels. Moreover, this study was of utmost significance as it was the first direct measurement of a mitochondrial Ca^{2+} channel in the IMM, thus, approving that mitochondrial Ca^{2+} uptake is indeed accomplished via a Ca^{2+} channel allowing the fast uniport of Ca^{2+} ions across the IMM (Fig. 1B).

2.1.2. The mCa1 and mCa2—In an outstanding work, two distinct mitochondrial Ca^{2+} channels have been recently electrophysiologically characterized in mitoplasts that were prepared from human ventricular myocytes [49]. These Ca^{2+}-selective channels of the IMM are referred to as mCa1 and mCa2 and significantly differ in their single-channel amplitudes, opening times, open probabilities and their sensitivity to Ru360. Although the human mCa1 [49] share some characteristics such as its sensitivity to Ru360 with the MiCa [45] from COS-7 cells (an African Green Monkey SV40-transf'd kidney fibroblast cell line), the gating properties of both mitochondrial Ca^{2+} channels are considerable different, thus, possibly pointing to species and or tissue-specific heterogeneities among mitochondrial Ca^{2+} channels. Moreover, the coexistence of distinct mitochondrial Ca^{2+} currents, i.e. the Ru360-sensitive I_{mCa1} and the rather Ru360-insensitive I_{mCa2}, in mitoplasts from the same origin (human ventricular myocytes) emphasize the need of different mitochondrial Ca^{2+} uptake pathways, which might be essential to properly integrate diverse cytosolic Ca^{2+} signals to mitochondrial Ca^{2+}-induced metabolism in one given cell type. In this context the biophysical properties described for the mCa1 perfectly fit to the necessity of a mitochondrial Ca^{2+} channel facing the rapid and strong ER Ca^{2+} release sites. However, mCa2 with its lower single-channel amplitude, longer opening time and a higher open probability represents an ideal candidate to achieve efficient mitochondrial uptake of Ca^{2+} that rather slowly increases at mitochondrial Ca^{2+} uptake sites upon, e.g. Ca^{2+} entry via the

store-operated Ca^{2+} entry (SOCE) pathway [2,50] (Fig. 1B). Notably, both mCa1 and mCa2 exhibit a high Ca^{2+} selectivity as it was reported for the MiCa. The relative divalent ion conductance of mCa1 and mCa2 for Sr^{2+}, Mn^{2+}, Ba^{2+} and Mg^{2+} has however not been tested so far.

2.1.3. Ca^{2+} carriers and exchangers—Besides the Ca^{2+}-permeable channels there are data describing the existence of Ca^{2+} carriers and exchangers in the IMM that are thought to achieve mitochondrial Ca^{2+} efflux under physiological conditions [51]. Notably, the mitochondrial Ca^{2+}/Na^{+} exchanger (NCX_{mito}) not only represent the main route for mitochondrial Ca^{2+} extrusion (for reviews see [2,51]) but may also contribute to mitochondrial Ca^{2+} uptake under certain conditions [43]. However, substantial novel findings regarding the physiological roles of the NCX_{mito} would require the molecular identification of this Ca^{2+}-shuttling protein.

2.2. Molecular identification of mitochondrial Ca^{2+} channels

Already more than 30 years ago, attempts to isolate and purify Ca^{2+} channels from isolated mitochondria were initiated [52,53]. However, despite many efforts the mitochondrial Ca^{2+} channels of the IMM have not been explicitly identified on the molecular level so far. The clarification of the molecular identities of mitochondrial Ca^{2+} channels is a great challenge for the future and would be essential for the understanding of mitochondrial Ca^{2+} signaling as a fundamental physiological process that essentially contributes to various intracellular signaling pathways. Moreover, recent studies demonstrated the great participation of mitochondrial Ca^{2+} uptake to various pathological processes [1,10,54,55] in, e.g. neurodegeneration [56,57] and cardio-vascular diseases [58,59], thus, pointing to mitochondrial Ca^{2+} channels as attractive targets for the development of novel therapeutic strategies against different diseases [60] (Fig. 1C).

2.2.1. Glycoproteins as early potential candidates for mitochondrial Ca^{2+} channels—Early studies in the 1970s and 1980s that aimed to isolate and purify the mitochondrial Ca^{2+} uniporter suggested that glycoproteins might be elementary involved in the transfer of Ca^{2} across the IMM [32,52,53,61]. Thereby, a almost 90% purified 18 and 75 kD fraction were isolated using affinity chromatography with labeled ^{103}Ru360 and Ca^{2+} uptake into phospholipids vesicles reconstituted with such preparations could be observed [62]. However, the purification and subsequent identification of mitochondrial Ca^{2+} channels has turned out to be difficult and has not been accomplished yet. Notably, in course of these attempts antisera against mitochondrial glycoprotein preparations were obtained that inhibited the Ca^{2+} uniport in isolated liver mitoplasts and reconstituted phospholipids vesicles (reviewed in [33]), thus, indicating the potential importance of these findings.

2.2.2. The novel uncoupling proteins (UCPs) 2 and 3 are fundamental for mitochondrial Ca^{2+} uniport—Uncoupling is a process that dissipates the proton gradient across the IMM of energized mitochondria whereby heat instead of ATP is generated [63]. The UCP1, also referred to as thermogenin, is a protein of the IMM that accomplishes uncoupling of respiration from ATP production, while the exact molecular mechanism by which UCP1 funnels protons from the inter membrane space into the mitochondrial matrix is

still debated [64]. After the identification of UCP1 the so-called novel UCP2 and UCP3 were discovered [65–67]. Although these proteins share certain sequence homology with UCP1, their contribution to uncoupling and thermoregulation under physiological conditions could not be confirmed so far [68]. However, recently the impact of protein overexpression and siRNA-mediated knock-down of UCP2 and UCP3 on mitochondrial Ca^{2+} uptake in intact endothelial cells was tested in response to physiological Ca^{2+} mobilization [69]. Surprisingly, these experiments revealed that both proteins are fundamental for mitochondrial Ca^{2+} uniport as the capacity as well as the velocity of mitochondrial Ca^{2+} sequestration strictly correlated with the expression level of UCP2 and UCP3. Expression of UCP2/3 mutants confirmed the important role of these proteins for mitochondrial Ca^{2+} uptake and pointed to the predicted inter membrane loop 2 (IML2) to be elementary for the mitochondrial Ca^{2+} transport function of these proteins. Notably, in the IML2 domain, UCP2 and UCP3 share high sequence homology whereas this sequence considerable differs from that of UCP1. Very recently we continued experiments with UCP3 mutants and discovered two distinct sites in the IML2 that are essential for the mitochondrial Ca^{2+} transport function of UCP3. Interestingly one site in the IML2 of UCP3 emerged to be specifically required for mitochondrial uptake of intracellularly released Ca^{2+}, while another distinct position was essential for mitochondrial sequestration of entering Ca^{2+} (manuscript submitted). The obvious importance of UCP2/3 for mitochondrial Ca^{2+} uniport was further validated by experiments using isolated liver mitochondria from $UCP2^{-/-}$ mice [43,69]. In summary these data suggest that UCP2/3 are conductive subunits of a Ca^{2+}-selective mitochondrial ion channel at the IMM, though further work is required to challenge this hypothesis (Fig. 1C).

2.2.3. Letm1 as mitochondrial Ca^{2+}/H^{+} antiporter contributing to mitochondrial Ca^{2+} uptake—As a result of a very recent siRNA screening to identify mitochondrial Ca^{2+} shuttling proteins in *Drosophila* S2 cells, Letm1 was identified as a Ca^{2+}/H^{+} antiporter of the IMM, while respective candidates for mitochondrial Ca^{2+} channels have not been described [70]. Letm1 was previously associated with the Wolf–Hirschhorn syndrome, a complex congenital syndrome that is caused by a monoallelic deletion of chromosome 4 [71]. Although Letm1 has been referred to as a mitochondrial protein with unclear function, initially Letm1 was characterized to contribute to electroneutral K^{+}/H^{+} exchange in mitochondria thereby controlling the mitochondrial K^{+} homeostasis and volume [72]. At a first glance the findings that Letm1 particularly contributes to mitochondrial Ca^{2+} uptake at low cytosolic Ca^{2+} raises (<1 μM), while at higher Ca^{2+} concentration another uptake pathway, presumably the MCU got activated [70], is surprising as one would rather expect that a Ca^{2+}/H^{+} antiporter preferentially exports Ca^{2+} from mitochondria (Fig. 1C). However, these findings are in line with other reports suggesting the existence of MCU-independent uptake pathways that are presumably accomplished by mitochondrial exchangers working in their reversed mode [43,50,73,74].

2.2.4. Assembly of protein complexes that establish mitochondrial Ca^{2+} channels—Little is known whether mitochondrial Ca^{2+} channels are protein complexes or not. However our recent finding that an expression of human UCP2/3 was ineffective to affect mitochondrial uptake in yeast [69] suggest that additional proteins are necessary to

constitute Ca^{2+}-permeable channels in the IMM. Thus, it is reasonable to speculate that additional proteins/factors are necessary to reassemble the Ca^{2+} transport function of UCP2 and UCP3 in artificial or heterologous systems. In line with these findings and in analogy to the so called mitochondrial transition pore (MTP), a large conductance pore that upon opening makes the mitochondrial membranes suddenly permeable for molecules with a molecular weight up to appr. 1.5 kDa [75,76], it seems feasible that the mitochondrial Ca^{2+} uniport channels also exhibit multiprotein complexes of IMM and OMM proteins (Fig. 1D).

Overexpression of the adenine nucleotide translocase (ANT), which is also known to be a component of the MTP [77], was shown to significantly reduce mitochondrial Ca^{2+} uptake in intact cells [78]. Although the overexpression of ANT might cause MTP opening and, thus, depolarization of the IMM, it is tempting to speculate that the reduced mitochondrial Ca^{2+} signals in ANT overexpressing cells are at least in part, the result of a disturbed composition of a presumable mitochondrial Ca^{2+} channel complex. The most prominent candidate of a protein of the OMM that probably physically interact with proteins of the IMM to constitute a mitochondrial Ca^{2+} channel spanning the IMM and OMM is VDAC [79]. Overexpression of VDAC in HeLa cells and skeletal myotubes enhanced mitochondrial Ca^{2+} uptake, indicating that this OMM porines are involved in the transfer of cytosolic Ca^{2+} into the lumen of mitochondria [80]. Notably, the chaperone glucose-regulated protein 75 (grp75) was found to link the inositol 1,4,5-trisphosphate receptor (IP_3R) to VDAC, which presumably enhances the transfer of Ca^{2+} from the ER towards mitochondria [81]. The exploration of the molecular basis of structural components of ER-mitochondria contact sites is currently a matter of intensive research [82,83]. Recently, mitofusin 2 was identified as a molecular component of such tethers that connect the ER with mitochondria, which was also elementary for mitochondrial Ca^{2+} uniport of Ca^{2+} that was mobilized from the ER [84]. The physical alliance between ER and mitochondria is also referred to as mitochondrial-associated ER membrane (MAM), which emerges to have important roles for Ca^{2+} signaling [83]. Interestingly, a recent study using electron tomography showed that in MAM the distance between ER and mitochondria is in the range of 10–25 nm, which would allow a direct interaction of proteins of the ER with proteins of the OMM [85]. Accordingly, it is reasonable that mitochondrial Ca^{2+} conducting proteins of the IMM might be assembled in a complex with MAM proteins, which substantially contribute to the gating of mitochondrial Ca^{2+} channels in intact cells (Fig. 1D).

3. Modulation of mitochondrial Ca^{2+} channels

3.1. Phosphorylation of mitochondrial Ca^{2+} channels

First conspicuous evidence that mitochondrial Ca^{2+} channels are targets of kinases came from the observation that an inhibition of the p38 mitogen-activated kinase (MAPK) with SB 202190 increased mitochondrial Ca^{2+} uptake in response to cell stimulation with an IP_3 generating agonist [86]. At a first glance this finding would indicate that mitochondrial Ca^{2+} channels exhibit serine/threonine-phosphorylation sites that, once phosphorylated negatively regulated the channel's activity. Because other inhibitors of the p38MAPK failed to mimic the effect of SB 202190 [87], while structural related compounds without affecting this kinase activity, such as plant flavanoids, enhanced mitochondrial Ca^{2+} loading [88], the

contribution of p38MAPK to the regulation of mitochondrial Ca^{2+} uniport was questioned and an alternative explanation suggesting that compounds such as SB 202190 directly bind to mitochondrial Ca^{2+} channels was discussed. However, the group of András Spät subsequently convincingly demonstrated that siRNA mediated knock-down of p38MAPK efficiently and specifically increased mitochondrial Ca^{2+} uptake upon cell stimulation with an IP_3 generating agonist [89]. Form this study and their subsequent intriguing work [90,91], the authors concluded that p38MAPK, novel isoforms of the protein kinase C (PKC) family and protein kinase D play central roles in the regulation of mitochondrial Ca^{2+} channels to prevent mitochondrial Ca^{2+} overload by explosive IP_3 mediated ER Ca^{2+} mobilization and hence protect cells from cell death. Further studies also point to different PKC isoforms that putatively modulate mitochondrial Ca^{2+} uptake channels: overexpression of PKCβ in HeLa cells was shown to reduce mitochondrial Ca^{2+} uptake, whereas overexpression of PKCζ increased mitochondrial Ca^{2+} transients upon cell stimulation with an IP_3 generating agonist [92] (Fig. 1E).

3.2. Regulation of mitochondrial Ca^{2+} channels by Ca^{2+}

Early Ca^{2+} uptake studies with isolated mitochondria indicated that mitochondrial Ca^{2+} channels are activated by Ca^{2+} [93]. These experiments suggest a slow and allosteric activation of the mitochondrial Ca^{2+} uniport by Ca^{2+}. In contrast, whole mitoplast patch-clamp experiments exclude a role for Ca^{2+} in activating mitochondrial Ca^{2+} channels [45], as a Na^+ conductance in the absence of Ca^{2+} was recorded, indicating that Ca^{2+} is not essential for MiCa activity. The inconsistency of such datasets show that depending on how isolated mitochondria/mitoplasts have been prepared and depending on the overall experimental conditions an methods used to measure the functioning of mitochondrial Ca^{2+} channels, clearly different, even contradictory results can be obtained [94] vs. [43]. Moreover, the Ca^{2+} sensitivity of mitochondrial Ca^{2+} channels might be linked to signaling proteins such as calmodulin, which are fragilely or transiently associated with mitochondrial Ca^{2+} channels in intact cells. Accordingly, mitochondrial isolation might lead to a loss of these kind of interactions as such procedures are simply too invasive. This view is supported by findings that mitochondrial Ca^{2+} uniport is partially a Ca^{2+}-calmodulin-gated process using permeabilized RBL-1 cells [95]. This study describes that mitochondrial Ca^{2+} uniport is activated via a Ca^{2+}-calmodulin dependent mechanism, whereas cytosolic Ca^{2+} subsequently leads to an inactivation of mitochondrial Ca^{2+} channels, preventing further Ca^{2+} uptake by these organelles. The role of calmodulin in facilitating the activity of the mitochondrial Ca^{2+} uniport was further confirmed by Csordas and Hajnoczky [96]. However, a biphasic regulation of mitochondrial Ca^{2+} uptake channels points to complex mechanisms that tune the transit of Ca^{2+} across the IMM in order to avoid fatal mitochondrial Ca^{2+} overload during intracellular Ca^{2+} signaling. Moreover, Moreau and Parekh continued their intriguing studies and reported recently that the Ca^{2+}-dependent inactivation of the mitochondrial Ca^{2+} uniporter is linked to proton-fluxes through the ATP-synthase [97], providing not only a mechanism of autoregulation of ATP synthesis but also a reasonable feedback mechanism between mitochondrial Ca^{2+} up-take and the organelle's metabolic function.

In isolated liver and heart mitochondria a so-called rapid mode of mitochondrial Ca^{2+} upake (RaM) exists [98]. This process allows a fast pulsatile uptake of large amounts of Ca^{2+} but only for a short period of time, because RaM was shown to be quickly inactivated by Ca^{2+} via Ca^{2+} binding to an external site [99]. Notably, RaM is also sensitive to RR and Ru360, hence, it is possible that RaM is not a distinct mitochondrial Ca^{2+} channel but rather reflects a certain state of mitochondrial Ca^{2+} uniport channel(s) (Fig. 1E).

4. Conclusion

Recently promising progresses in the identification and characterization of mitochondrial Ca^{2+} transporters has been accomplished. Nevertheless, despite numerous studies convincingly characterize functional and structural aspects of mitochondrial Ca^{2+} uptake, our current picture on the actual proteins being involved remains rather vague. Intriguingly, the existence of various distinct mitochondrial Ca^{2+} channels that accomplish the transfer of Ca^{2+} across the IMM have been reported, and it is tempting to speculate that a species- and tissue-specific diversities of mitochondrial Ca^{2+} channels exists. Nevertheless, the experimental conditions and techniques used to characterize mitochondrial Ca^{2+} fluxes have to be taken into consideration if a general assertion is made. Thus, despite recent progresses, the identification of the molecular components of mitochondrial Ca^{2+} channels remains a challenging task in molecular physiology and awaits further intensive investigation.

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Abbreviations

ANT	adenine nucleotide translocase
ER	endoplasmic reticulum
grp75	glucose-regulated protein 75
IML2	inter membrane loop 2
IMM	inner mitochondrial membrane
IP_3R	inositol 1,4,5-trisphosphate receptor
MAM	mitochondrial-associated ER membrane
MAPK	mitogen-activated kinase
mCa/MiCa	mitochondrial Ca^{2+} channel
MCU	mitochondrial Ca^{2+} uniporter
MTP	mitochondrial transition pore
NCX_{mito}	mitochondrial Ca^{2+}/Na^{+} exchanger
OMM	outer mitochondrial membrane

PKC	protein kinase C
RaM	rapid mode of mitochondrial Ca^{2+} uptake
RR	ruthenium red
SOCE	store-operated Ca^{2+} entry
UCP	uncoupling protein
VDAC	voltage-dependent anion selective channels

References

[1]. Duchen MR. Mitochondria in health and disease: perspectives on a new mitochondrial biology. Mol. Aspects Med. 2004; 25:365–451. [PubMed: 15302203]

[2]. Graier WF, Frieden M, Malli R. Mitochondria and Ca^{2+} signaling: old guests, new functions. Pflugers Arch. 2007; 455:375–396. [PubMed: 17611770]

[3]. McBride HM, Neuspiel M, Wasiak S. Mitochondria: more than just a powerhouse. Curr. Biol. 2006; 16:R551–R560. [PubMed: 16860735]

[4]. Soubannier V, McBride H. Positioning mitochondrial plasticity within cellular signaling cascades. Biochim. Biophys. Acta. 2008; 1793:154–170. [PubMed: 18694785]

[5]. Nagai T, Sawano A, Park ES, Miyawaki A. Circularly permuted green fluorescent proteins engineered to sense Ca^{2+} Proc. Natl. Acad. Sci. USA. 2001; 98:3197–3202. [PubMed: 11248055]

[6]. Rizzuto R, Simpson AW, Brini M, Pozzan T. Rapid changes of mitochondrial Ca^{2+} revealed by specifically targeted recombinant aequorin. Nature. 1992; 358:325–327. [PubMed: 1322496]

[7]. Brini M. Ca^{2+} signalling in mitochondria: mechanism and role in physiology and pathology. Cell Calcium. 2003; 34:399–405. [PubMed: 12909084]

[8]. Campanella M, Pinton P, Rizzuto R. Mitochondrial Ca^{2+} homeostasis in health and disease. Biol. Res. 2004; 37:653–660. [PubMed: 15709694]

[9]. Szabadkai G, Duchen MR. Mitochondria: the hub of cellular Ca^{2+} signaling. Physiology. 2008; 23:84–94. [PubMed: 18400691]

[10]. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. J. Physiol. 2000; 529:57–68. [PubMed: 11080251]

[11]. Nicholls DG. The influence of respiration and ATP hydrolysis on the proton-electrochemical gradient across the inner membrane of rat-liver mitochondria as determined by ion distribution. Eur. J. Biochem. 1974; 50:305–315. [PubMed: 4452361]

[12]. Carafoli E. Historical review: mitochondria and calcium: ups and downs of an unusual relationship. Trends Biochem. Sci. 2003; 28:175–181. [PubMed: 12713900]

[13]. McCormack JG, Denton RM. The effects of calcium ions and adenine nucleotides on the activity of pig heart 2-oxoglutarate dehydrogenase complex. Biochem. J. 1979; 180:533–544. [PubMed: 39549]

[14]. McCormack JG, Denton RM. Role of Ca^{2+} ions in the regulation of intramitochondrial metabolism in rat heart. Evidence from studies with isolated mitochondria that adrenaline activates the pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase complexes by increasing the intramitochondrial concentration of Ca^{2+} Biochem. J. 1984; 218:235–247. [PubMed: 6424656]

[15]. McCormack JG, Halestrap AP, Denton RM. Role of calcium ions in regulation of mammalian intramitochondrial metabolism. Physiol. Rev. 1990; 70:391–425. [PubMed: 2157230]

[16]. Robb-Gaspers LD, Burnett P, Rutter GA, Denton RM, Rizzuto R, Thomas AP. Integrating cytosolic calcium signals into mitochondrial metabolic responses. EMBO J. 1998; 17:4987–5000. [PubMed: 9724635]

[17]. Jouaville LS, Pinton P, Bastianutto C, Rutter GA, Rizzuto R. Regulation of mitochondrial ATP synthesis by calcium: evidence for a long-term metabolic priming. Proc. Natl. Acad. Sci. USA. 1999; 96:13807–13812. [PubMed: 10570154]

[18]. Malli R, Frieden M, Osibow K, Graier WF. Mitochondria efficiently buffer subplasmalemmal Ca^{2+} elevation during agonist stimulation. J. Biol. Chem. 2003; 278:10807–10815. [PubMed: 12529366]

[19]. Mackenzie L, Roderick HL, Berridge MJ, Conway SJ, Bootman MD. The spatial pattern of atrial cardiomyocyte calcium signalling modulates contraction. J. Cell Sci. 2004; 117:6327–6337. [PubMed: 15561771]

[20]. Petersen OH, Tepikin AV. Polarized calcium signaling in exocrine gland cells. Annu. Rev. Physiol. 2008; 70:273–299. [PubMed: 17850212]

[21]. Arnaudeau S, Kelley WL, Walsh JV Jr. Demaurex N. Mitochondria recycle Ca^{2+} to the endoplasmic reticulum and prevent the depletion of neighboring endoplasmic reticulum regions. J. Biol. Chem. 2001; 276:29430–29439. [PubMed: 11358971]

[22]. Malli R, Frieden M, Trenker M, Graier WF. The role of mitochondria for Ca^{2+} refilling of the ER. J. Biol. Chem. 2005; 280:12114–12122. [PubMed: 15659398]

[23]. Michalak M, Groenendyk J, Szabo E, Gold LI, Opas M. Calreticulin, a multi-process calcium-buffering chaperone of the endoplasmic reticulum. Biochem. J. 2009; 417:651–666. [PubMed: 19133842]

[24]. Michalak M, Mariani P, Opas M. Calreticulin, a multifunctional Ca^{2+} binding chaperone of the endoplasmic reticulum. Biochem. Cell Biol. 1998; 76:779–785. [PubMed: 10353711]

[25]. Michalak M, Robert Parker JM, Opas M. Ca^{2+} signaling and calcium binding chaperones of the endoplasmic reticulum. Cell Calcium. 2002; 32:269–278. [PubMed: 12543089]

[26]. Osibow K, Frank S, Malli R, Zechner R, Graier WF. Mitochondria maintain maturation and secretion of lipoprotein lipase in the endoplasmic reticulum. Biochem. J. 2006; 396:173–182. [PubMed: 16466345]

[27]. Pinton P, Giorgi C, Siviero R, Zecchini E, Rizzuto R. Calcium and apoptosis: ER-mitochondria Ca^{2+} transfer in the control of apoptosis. Oncogene. 2008; 27:6407–6418. [PubMed: 18955969]

[28]. Roy SS, Hajnóczky G. Calcium, mitochondria and apoptosis studied by fluorescence measurements. Methods. 2008; 46:213–223. [PubMed: 18948203]

[29]. Giorgi C, Romagnoli A, Pinton P, Rizzuto R. Ca^{2+} signaling, mitochondria and cell death. Curr. Mol. Med. 2008; 8:119–130. [PubMed: 18336292]

[30]. Nicholls DG. The regulation of extramitochondrial free calcium ion concentration by rat liver mitochondria. Biochem. J. 1978; 176:463–474. [PubMed: 33670]

[31]. Nicholls DG. Mitochondria and calcium signaling. Cell Calcium. 2005; 38:311–317. [PubMed: 16087232]

[32]. Saris NE, Allshire A. Calcium ion transport in mitochondria. Methods Enzymol. 1989; 174:68–85. [PubMed: 2633033]

[33]. Saris NE, Carafoli E. A historical review of cellular calcium handling, with emphasis on mitochondria. Biochemistry. 2005; 70:187–194. [PubMed: 15807658]

[34]. Bathori G, Csordas G, Garcia-Perez C, Davies E, Hajnoczky G. Ca^{2+}-dependent control of the permeability properties of the mitochondrial outer membrane and voltage-dependent anion-selective channel (VDAC). J. Biol. Chem. 2006; 281:17347–17358. [PubMed: 16597621]

[35]. Gincel D, Zaid H, Shoshan-Barmatz V. Calcium binding and translocation by the voltage-dependent anion channel: a possible regulatory mechanism in mitochondrial function. Biochem. J. 2001; 358:147–155. [PubMed: 11485562]

[36]. Hajnoczky G, Csordas G, Yi M. Old players in a new role: mitochondria-associated membranes, VDAC, and ryanodine receptors as contributors to calcium signal propagation from endoplasmic reticulum to the mitochondria. Cell Calcium. 2002; 32:363–377. [PubMed: 12543096]

[37]. Cheng EH, Sheiko TV, Fisher JK, Craigen WJ, Korsmeyer SJ. VDAC2 inhibits BAK activation and mitochondrial apoptosis. Science. 2003; 301:513–517. [PubMed: 12881569]

[38]. Crompton M. The mitochondrial permeability transition pore and its role in cell death. Biochem. J. 1999; 341:233–249. [PubMed: 10393078]

[39]. Rostovtseva TK, Antonsson B, Suzuki M, Youle RJ, Colombini M, Bezrukov SM. Bid, but Not Bax, Regulates VDAC Channels. J. Biol. Chem. 2004; 279:13575–13583. [PubMed: 14729675]

[40]. Tsujimoto Y, Shimizu S. VDAC regulation by the Bcl-2 family of proteins. Cell Death Differ. 2000; 7:1174–1181.

[41]. Tsujimoto Y, Shimizu S. The voltage-dependent anion channel: an essential player in apoptosis. Biochimie. 2002; 84:187–193. [PubMed: 12022949]

[42]. Bernardi P. Mitochondrial transport of cations: channels, exchangers, and permeability transition. Physiol. Rev. 1999; 79:1127–1155. [PubMed: 10508231]

[43]. Trenker M, Fertschai I, Malli R, Graier WF. UCP2/3 - likely to be fundamental for mitochondrial Ca^{2+} uniport. Nat. Cell Biol. 2008; 10:1237–1240.

[44]. Gunter TE, Buntinas L, Sparagna G, Eliseev R, Gunter K. Mitochondrial calcium transport: mechanisms and functions. Cell Calcium. 2000; 28:285–296. [PubMed: 11115368]

[45]. Kirichok Y, Krapivinsky G, Clapham DE. The mitochondrial calcium uniporter is a highly selective ion channel. Nature. 2004; 427:360–364. [PubMed: 14737170]

[46]. Bernardi P, Paradisi V, Pozzan T, Azzone GF. Pathway for uncoupler-induced calcium efflux in rat liver mitochondria: inhibition by ruthenium red. Biochemistry. 1984; 23:1645–1651. [PubMed: 6202317]

[47]. Reed KC, Bygrave FL. The inhibition of mitochondrial calcium transport by lanthanides and ruthenium red. Biochem. J. 1974; 140:143–155. [PubMed: 4375957]

[48]. de Jesús García-Rivas G, Guerrero-Hernández A, Guerrero-Serna G, Rodríguez-Zavala JS, Zazueta C. Inhibition of the mitochondrial calcium uniporter by the oxo-bridged dinuclear ruthenium amine complex (Ru360) prevents from irreversible injury in postischemic rat heart. FEBS J. 2005; 272:3477–3488. [PubMed: 15978050]

[49]. Michels G, Khan IF, Endres-Becker J, Rottlaender D, Herzig S, Ruhparwar A, Wahlers T, Hoppe UC. Regulation of the human cardiac mitochondrial Ca^{2+} uptake by 2 different voltage-gated Ca^{2+} channels. Circulation. 2009; 119:2435–2443. [PubMed: 19398664]

[50]. Demaurex N, Poburko D, Frieden M. Regulation of plasma membrane calcium fluxes by mitochondria. Biochim. Biophys. Acta. 2009; 1787:1383–1394. [PubMed: 19161976]

[51]. Gunter TE, Yule DI, Gunter KK, Eliseev RA, Salter JD. Calcium and mitochondria. FEBS Lett. 2004; 567:96–102. [PubMed: 15165900]

[52]. Sottocasa G, Sandri G, Panfili E, De Bernard B, Gazzotti P, Vasington FD, Carafoli E. Isolation of a soluble Ca^{2+} binding glycoprotein from ox liver mitochondria. Biochem. Biophys. Res. Commun. 1972; 47:808–813. [PubMed: 4260315]

[53]. Panfili E, Sandri G, Sottocasa GL, Lunazzi G, Liut G, Graziosi G. Specific inhibition of mitochondrial Ca^{2+} transport by antibodies directed to the Ca^{2+}-binding glycoprotein. Nature. 1976; 264:185–186. [PubMed: 995204]

[54]. Duchen MR. Mitochondria and Ca^{2+} in cell physiology and pathophysiology. Cell Calcium. 2000; 28:339–348. [PubMed: 11115373]

[55]. Duchen MR, Verkhratsky A, Muallem S. Mitochondria and calcium in health and disease. Cell Calcium. 2008; 44:1–5. [PubMed: 18378306]

[56]. Mattson MP. Calcium and neurodegeneration. Aging Cell. 2007; 6:337–350. [PubMed: 17328689]

[57]. Vercesi AE, Kowaltowski AJ, Oliveira HCF, Castilho RF. Mitochondrial Ca^{2+} transport, permeability transition and oxidative stress in cell death: implications in cardiotoxicity, neurodegeneration and dyslipidemias. Front. Biosci. 2006; 11:2554–2564. [PubMed: 16720333]

[58]. Davidson SM, Duchen MR. Endothelial mitochondria: contributing to vascular function and disease. Circ. Res. 2007; 100:1128–1141. [PubMed: 17463328]

[59]. Liu T, O'Rourke B. Regulation of mitochondrial Ca^{2+} and its effects on energetics and redox balance in normal and failing heart. J. Bioenerg. Biomembr. 2009; 41:127–132. [PubMed: 19390955]

[60]. Ralph SJ, Low P, Dong L, Lawen A, Neuzil J. Mitocans: mitochondrial targeted anti-cancer drugs as improved therapies and related patent documents. Recent Pat. Anticancer Drug Discov. 2006; 1:327–346. [PubMed: 18221044]

[61]. Mironova GD, Sirota TV, Pronevich LA, Trofimenko NV, Mironov GP, Grigorjev PA, Kondrashova MN. Isolation and properties of Ca^{2+}-transporting glycoprotein and peptide from beef heart mitochondria. J. Bioenerg. Biomembr. 1982; 14:213–225. [PubMed: 7130161]

[62]. Zazueta C, Zafra G, Vera G, Sanchez C, Chavez E. Advances in the purification of the mitochondrial Ca^{2+} uniporter using the labeled inhibitor ^{103}Ru360. J. Bioenerg. Biomembr. 1998; 30:489–498. [PubMed: 9932651]

[63]. Argyropoulos G, Harper M-E. Uncoupling proteins and thermoregulation. J. Appl. Physiol. 2002; 92:2187–2198. [PubMed: 11960973]

[64]. Nicholls DG. The physiological regulation of uncoupling proteins. Biochim. Biophys. Acta. 2006; 1757:459–466. [PubMed: 16725104]

[65]. Affourtit C, Crichton PG, Parker N, Brand MD. Novel uncoupling proteins. Novartis Found Symp. 2007; 287:70–80. discussion 80–91. [PubMed: 18074632]

[66]. Boss O, Samec S, Paoloni-Giacobino A, Rossier C, Dulloo A, Seydoux J, Muzzin P, Giacobino JP. Uncoupling protein-3: a new member of the mitochondrial carrier family with tissue-specific expression. FEBS Lett. 1997; 408:39–42. [PubMed: 9180264]

[67]. Nedergaard J, Matthias A, Golozoubova V, Jacobsson A, Cannon B. UCP1: the original uncoupling protein–and perhaps the only one? New perspectives on UCP1, UCP2, and UCP3 in the light of the bioenergetics of the UCP1-ablated mice. J. Bioenerg. Biomembr. 1999; 31:475–491. [PubMed: 10653476]

[68]. Nedergaard J, Cannon B. The “novel” uncoupling proteins UCP2 and UCP3: what do they really do? Pros and cons for suggested functions. Exp. Physiol. 2003; 88:65–84. [PubMed: 12525856]

[69]. Trenker M, Malli R, Fertschai I, Levak-Frank S, Graier WF. Uncoupling proteins 2 and 3 are fundamental for mitochondrial Ca^{2+} uniport. Nat. Cell Biol. 2007; 9:445–452. [PubMed: 17351641]

[70]. Jiang D, Zhao L, Clapham DE. Genome-wide RNAi screen identifies Letm1 as a mitochondrial Ca^{2+}/H^{+} antiporter. Science. 2009; 326:144–147. [PubMed: 19797662]

[71]. Dimmer KS, Navoni F, Casarin A, Trevisson E, Endele S, Winterpacht A, Salviati L, Scorrano L. LETM1, deleted in Wolf-Hirschhorn syndrome is required for normal mitochondrial morphology and cellular viability. Hum. Mol. Genet. 2008; 17:201–214. [PubMed: 17925330]

[72]. Froschauer E, Nowikovsky K, Schweyen RJ. Electroneutral K+/H+ exchange in mitochondrial membrane vesicles involves Yol027/Letm1 proteins. Biochim. Biophys. Acta. 2005; 1711:41–48. [PubMed: 15904662]

[73]. Graier WF, Trenker M, Malli R. Mitochondrial Ca^{2+}, the secret behind the function of uncoupling proteins 2 and 3? Cell Calcium. 2008; 44:36–50. [PubMed: 18282596]

[74]. Parekh AB. Mitochondrial regulation of store-operated CRAC channels. Cell Calcium. 2008; 44:6–13. [PubMed: 18243304]

[75]. Lemasters JJ. The mitochondrial permeability transition and the calcium, oxygen and pH paradoxes: one paradox after another. Cardiovasc. Res. 1999; 44:470–473. [PubMed: 10690277]

[76]. Lemasters JJ, Theruvath TP, Zhong Z, Nieminen A-L. Mitochondrial calcium and the permeability transition in cell death. Biochim. Biophys. Acta. 2009; 1787:1395–1401. [PubMed: 19576166]

[77]. Baines CP. The molecular composition of the mitochondrial permeability transition pore. J. Mol. Cell Cardiol. 2009; 46:850–857. [PubMed: 19233198]

[78]. Wieckowski MR, Szabadkai G, Wasilewski M, Pinton P, Duszyński J, Rizzuto R. Overexpression of adenine nucleotide translocase reduces Ca^{2+} signal transmission between the ER and mitochondria. Biochem. Biophys. Res. Commun. 2006; 348:393–399. [PubMed: 16887100]

[79]. Gonçalves RP, Buzhysnskyy N, Scheuring S. Mini review on the structure and supramolecular assembly of VDAC. J. Bioenerg. Biomembr. 2008; 40:133–138. [PubMed: 18683037]

[80]. Rapizzi E, et al. Recombinant expression of the voltage-dependent anion channel enhances the transfer of Ca^{2+} microdomains to mitochondria. J. Cell Biol. 2002; 159:613–624. [PubMed: 12438411]

[81]. Szabadkai G, et al. Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca^{2+} channels. J. Cell Biol. 2006; 175:901–911. [PubMed: 17178908]

[82]. Rizzuto R, et al. Ca^{2+} transfer from the ER to mitochondria: when, how and why. Biochim. Biophys. Acta. 2009; 1787:1342–1351. [PubMed: 19341702]

[83]. Hayashi T, Rizzuto R, Hajnoczky G, Su TP. MAM: more than just a housekeeper. Trends Cell Biol. 2009; 19:81–88. [PubMed: 19144519]

[84]. de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature. 2008; 456:605–610. [PubMed: 19052620]

[85]. Csordas G, et al. Structural and functional features and significance of the physical linkage between ER and mitochondria. J. Cell Biol. 2006; 174:915–921. [PubMed: 16982799]

[86]. Montero M, Lobaton CD, Moreno A, Alvarez J. A novel regulatory mechanism of the mitochondrial Ca^{2+} uniporter revealed by the p38 mitogen-activated protein kinase inhibitor SB202190. FASEB J. 2002; 16:1955–1957. [PubMed: 12368236]

[87]. Montero M, Lobaton CD, Gutierrez-Fernandez S, Moreno A, Alvarez J. Modulation of histamine-induced Ca^{2+} release by protein kinase C: effects on cytosolic and mitochondrial [Ca^{2+}] peaks. J. Biol. Chem. 2003; 278:49972–49979. [PubMed: 14523015]

[88]. Montero M, Lobaton CD, Hernandez-Sanmiguel E, Santodomingo J, Vay L, Moreno A, Alvarez J. Direct activation of the mitochondrial calcium uniporter by natural plant flavonoids. Biochem. J. 2004; 384:19–24. [PubMed: 15324303]

[89]. Szanda G, Koncz P, Rajki A, Spät A. Participation of p38 MAPK and a novel-type protein kinase C in the control of mitochondrial Ca^{2+} uptake. Cell Calcium. 2008; 43:250–259. [PubMed: 17628663]

[90]. Koncz P, Szanda G, Fülöp L, Rajki A, Spät A. Mitochondrial Ca^{2+} uptake is inhibited by a concerted action of p38 MAPK and protein kinase D. Cell Calcium. 2009; 46:122–129. [PubMed: 19631981]

[91]. Spät A, Fülöp L, Koncz P, Szanda G. When is high-Ca^{2+} microdomain required for mitochondrial Ca+ uptake? Acta Physiol. 2009; 195:139–147.

[92]. Pinton P, Leo S, Wieckowski MR, Di Benedetto G, Rizzuto R. Long-term modulation of mitochondrial Ca^{2+} signals by protein kinase C isozymes. J. Cell Biol. 2004; 165:223–232. [PubMed: 15096525]

[93]. Kröner H. Ca^{2+} ions, an allosteric activator of calcium uptake in rat liver mitochondria. Arch. Biochem. Biophys. 1986; 251:525–535. [PubMed: 3800383]

[94]. Brookes PS, et al. UCPs – unlikely calcium porters. Nat. Cell Biol. 2008; 10:1235–1237. [PubMed: 18978830]

[95]. Moreau B, Nelson C, Parekh AB. Biphasic regulation of mitochondrial Ca^{2+} uptake by cytosolic Ca^{2+} concentration. Curr. Biol. 2006; 16:1672–1677. [PubMed: 16920631]

[96]. Csordas G, Hajnoczky G. Plasticity of mitochondrial calcium signaling. J. Biol. Chem. 2003; 278:42273–42282. [PubMed: 12907683]

[97]. Moreau B, Parekh AB. Ca^{2+}-dependent inactivation of the mitochondrial Ca^{2+} uniporter involves proton flux through the ATP synthase. Curr. Biol. 2008; 18:855–859. [PubMed: 18514515]

[98]. Buntinas L, Gunter KK, Sparagna GC, Gunter TE. The rapid mode of calcium uptake into heart mitochondria (RaM): comparison to RaM in liver mitochondria. Biochim. Biophys. Acta. 2001; 1504:248–261. [PubMed: 11245789]

[99]. Sparagna GC, Gunter KK, Sheu SS, Gunter TE. Mitochondrial calcium uptake from physiological-type pulses of calcium. A description of the rapid uptake mode. J. Biol. Chem. 1995; 270:27510–27515. [PubMed: 7499209]

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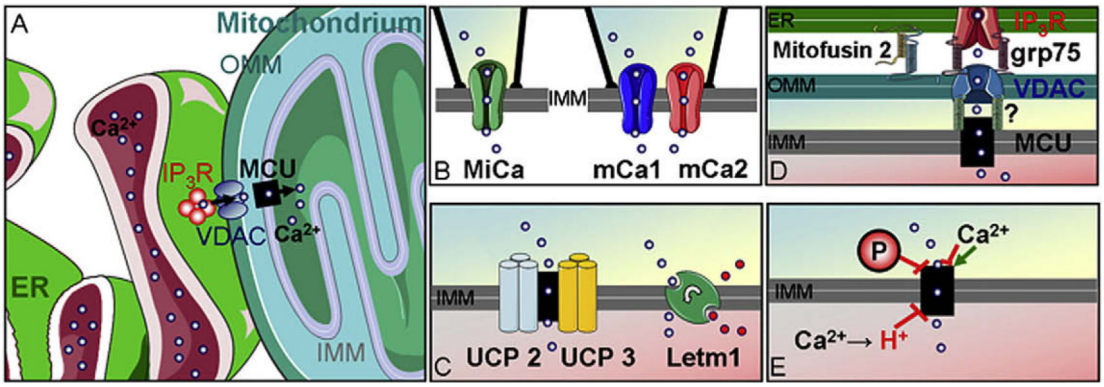

Fig. 1. Schematic illustration of mitochondrial Ca^{2+} uptake channels/carrier in the IMM, potential protagonists and the complexity if the mitochondrial environment.

(A) The complex environmental aspects of mitochondria in intact cells are illustrated. Local Ca^{2+} transfer from the ER via IP_3 mediated Ca^{2+} release. VDAC as porines in the OMM deliver Ca^{2+} ions to the MCU or Ca^{2+} exchanger at the IMM. (B) Electrophysiological characterizations revealed distinct mitochondrial Ca^{2+} channels: the MiCa in COS-7 cells and mCa1 as well as mCa2 in human ventricular myocytes. (C) Overexpression and siRNA mediated knock-down of UCP2/3 suggest a fundamental importance of these proteins for mitochondrial Ca^{2+} uniport. A genome-wide RNAi screen identified Letm1 as a mitochondrial Ca^{2+}/H^+ antiporter that significantly contributes to mitochondrial Ca^{2+} uptake in the physiological range of cytosolic Ca^{2+} elevation. (D) ER-mitochondria contact sites are stabilized by mitofusin 2 and probably other, so far unknown, proteins. The chaperon grp75 was shown to link the IP_3R to the VDAC in the OMM. Although proteins/factors that might link the VDAC to mitochondrial Ca^{2+} channels of the IMM have not been identified so far it is tempting to speculate that Ca^{2+} enters mitochondria via a Ca^{2+} tunnel spanning the OMM and IMM. (E) Evidence accumulated that kinases as well as Ca^{2+} and Ca^{2+}-calmodulin differentially modulate the activities of mitochondrial Ca^{2+} channels.

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