Mitochondrial Ca\textsuperscript{2+} regulation in the etiology of heart failure: physiological and pathophysiological implications

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Heart failure (HF) represents one of the leading causes of cardiovascular diseases with high rates of hospitalization, morbidity and mortality worldwide. Ample evidence has consolidated a crucial role for mitochondrial injury in the progression of HF. It is well established that mitochondrial Ca\textsuperscript{2+} participates in the regulation of a wide variety of biological processes, including oxidative phosphorylation, ATP synthesis, reactive oxygen species (ROS) generation, mitochondrial dynamics and mitophagy. Nonetheless, mitochondrial Ca\textsuperscript{2+} overload stimulates mitochondrial permeability transition pore (mPTP) opening and mitochondrial swelling, resulting in mitochondrial injury, apoptosis, cardiac remodeling, and ultimately development of HF. Moreover, mitochondria possess a series of Ca\textsuperscript{2+} transport influx and efflux channels, to buffer Ca\textsuperscript{2+} in the cytoplasm. Interaction at mitochondria-associated endoplasmic reticulum membranes (MAMs) may also participate in the regulation of mitochondrial Ca\textsuperscript{2+} homeostasis and plays an essential role in the progression of HF. Here, we provide an overview of regulation of mitochondrial Ca\textsuperscript{2+} homeostasis in maintenance of cardiac function, in an effort to identify novel therapeutic strategies for the management of HF.

Keywords: heart failure; mitochondrial Ca\textsuperscript{2+} homeostasis; mitochondrial Ca\textsuperscript{2+} transport; MAMs; ATP synthesis, ROS production; myocardial apoptosis

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INTRODUCTION
Heart failure (HF) is common in many end-stage cardiovascular diseases with high morbidity and mortality [1–3]. HF is believed to be responsible for most hospitalizations throughout the world, and its prevalence continues to rise with the aging population [4–7]. Despite substantial advances in the recent clinical management of HF, the survival rate of patients afflicted with HF remains dismal. The ESC-HF pilot study revealed that the one-year hospitalization rates for patients with acute and chronic HF were 43.9% and 31.9%, respectively [8]. The 5-year survival rate of patients with HF is only 50% [4]. In this context, it is pertinent to elaborate the precise mechanisms underlying HF in an effort to identify novel therapeutic regimens to retard or reverse the pathological progression of HF, ultimately improving quality of life and reducing mortality [3, 9–13].

The rhythmicity, automaticity and contraction of the heart demand profound energy, which is driven by oxidative phosphorylation within mitochondria [14–18]. Not surprisingly, mitochondria play a crucial role in the etiology of HF [19–21]. Mitochondrial dysfunction has been shown to contribute to defects in bioenergetics, Ca\textsuperscript{2+} transport, redox balance, mitochondrial membrane potential (ΔΨ\text{m}), metabolic signaling, and apoptosis and other forms of cell death [10, 14, 22–24]. Numerous findings have shown that mitochondrial disorders are detrimental to cardiac function, resulting in cardiac hypertrophy and ultimately HF [1, 14, 19, 25–28]. In the early phase of cardiac hypertrophy, the increased energy demand triggers complementary regulation of mitochondrial oxidative phosphorylation through Ca\textsuperscript{2+} and ADP. These maladaptive processes are closely associated with disrupted mitochondrial Ca\textsuperscript{2+} homeostasis in the myocardium.

Ca\textsuperscript{2+} acts as a ubiquitous second messenger that translates information delivered by an array of cell signals [29, 30]. Ca\textsuperscript{2+} dynamics play critical roles in the excitation-contraction coupling (ECC) of cardiomyocytes [18, 31, 32]. Transient increases in cytoplasmic Ca\textsuperscript{2+} levels activate the formation of cross bridges to engage myocardial contraction [32]. Mitochondria accumulate Ca\textsuperscript{2+} during systole and participate in the process of mitochondrial oxidative phosphorylation and the ATP synthesis electron transport chain (ETC) function [33]. On the other hand, excessive mitochondrial Ca\textsuperscript{2+} uptake stimulates the production of reactive oxygen species (ROS), opening of the mitochondrial permeability transition pore (mPTP) and initiation of apoptosis, resulting in mitochondrial injury, cardiac remodeling and ultimately HF [34]. In this review, we present a brief update on recent progress in understanding the vital role of mitochondrial Ca\textsuperscript{2+} homeostasis in the maintenance of cardiac function and how mitochondrial Ca\textsuperscript{2+} perturbation may contribute to the onset and development of HF.
MAINTENANCE OF MITOCHONDRIAL Ca^{2+} HOMEOSTASIS

Cytoplasmic Ca^{2+} and ER Ca^{2+}

Intracellular Ca^{2+} controls nearly all cellular biological processes encompassing muscle contraction, secretion and gene transcription [35]. The level of intracellular Ca^{2+} needs to be maintained at a range of ~100–1000 nmol/L, an ~10,000-fold difference than the extracellular Ca^{2+} concentration (1.5 nmol/L) maintained through consumption of considerable amounts of energy [35, 36]. Due to the significant electrochemical gradient between the extracellular space and cytoplasm, increases in intracellular Ca^{2+} can be elicited by both Ca^{2+} entry from the extracellular pool through ion channels in plasma membranes and Ca^{2+} release from intracellular stores, including the ER. In addition, Ca^{2+} may enter the intracellular domains from the extracellular space through voltage-gated Ca^{2+} channels (VGCCs) and transient receptor potential ion channels (TRPCs) located in the plasma membrane [37, 38].

The sarcoplasmic reticulum (SR) represents a specialized form of the endoplasmic reticulum (ER) in cardiomyocytes [39]. Both SR and ER are enriched with Ca^{2+} channels – inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs) – in the ER and SR, respectively [40]. Both channels mainly release Ca^{2+} from the ER or SR to the cytoplasm when intracellular Ca^{2+} levels are low. There are three isoforms of RyRs, of which, RyR2 is mainly localized in the myocardium, although the RyR1 isoform may also be found in cardiac mitochondria [40–42].

In addition, relaxation of cardiomyocytes depends on a decrease in intracellular Ca^{2+} levels that allows myofilament cross-bridge uncoupling [15, 56]. The cyclical decrease in cytosolic Ca^{2+} occurs mainly through Ca^{2+} re-uptake by the SR, which is mediated by Ca^{2+}-ATPase 2 (SERCA2) in the SR and, to some extent, sarclemma Ca^{2+} ATPase, an Na^{+}/Ca^{2+} exchanger, and mitochondrial uptake machinery [43].

Mitochondrial Ca^{2+} influx

Mitochondria are important intracellular organelles in regulating Ca^{2+} dynamic oscillation due to their high Ca^{2+}-buffering capacity [44]. Mitochondria possess a series of Ca^{2+} transport channels to maintain tight regulation of Ca^{2+} influx and efflux, which prevents drastic intracellular Ca^{2+} oscillations [31]. Mitochondria are structurally segregated into 4 distinct compartments by two membranes, the outer mitochondrial membrane (OMM), the intermembrane space, the inner mitochondrial membrane (IMM), and the mitochondrial matrix. Because of the high permeability of Ca^{2+} in the OMM, the Ca^{2+} levels in the intermembrane space are comparable to the Ca^{2+} levels in the cytoplasm [45]. In cells at rest, the Ca^{2+} levels in the mitochondrial matrix are comparable to those found in the cytoplasm (~100 nmol/L). When cells are excited, cytoplasmic Ca^{2+} levels can be in concentrations as low as ~2–3 μmol/L, and Ca^{2+} levels can rise to 10 μmol/L or even higher (500 μmol/L) in the mitochondrial matrix [44].

Mitochondrial voltage-dependent anion channels (VDACs).

The accumulation of mitochondrial Ca^{2+} requires Ca^{2+} to pass through the OMM and IMM. In living cells, the high conductance protein VDAC, located on the OMM, governs the transport of Ca^{2+} into the intermembrane space of a mitochondrion. There are three identified isoforms of the VDAC protein: VDAC1, VDAC2, and VDAC3 [46]. The most abundant isoform, VDAC1, is deemed the main Ca^{2+}-transport channel [47]. Ca^{2+} ions move across the IMM driven by an electrical gradient controlled through the mitochondrial Ca^{2+}-uniporter (MCU) complex and reach the mitochondrial matrix. The Ca^{2+} levels in the mitochondrial matrix can reach a level of approximately one or two orders of magnitude greater than that in the cytoplasm. VDAC1 levels were reported to be increased in the left ventricular tissues of patients suffering from hypertrophic cardiomyopathy [48]. During hypoxia-reoxygenation of cardiomyocytes, the VDAC1-mediated Ca^{2+} channeling complex is increased concomitantly with mitochondrial Ca^{2+} content. The inhibition of VDAC1 channels dramatically suppressed mitochondrial Ca^{2+} overload and thus protected cells from hypoxia-reoxygenation stress [49].

The mitochondrial Ca^{2+} uniporter (MCU) complex. The MCU complex is a highly selective ion channel located on the IMM and transports Ca^{2+} into the mitochondrial matrix [50, 51]. MCU is critical for the mitochondrial energetic adaptation initiated by mitochondrial Ca^{2+} uptake. A fundamental property of MCU is the low activity of resting cytosolic Ca^{2+} levels, which prevent mitochondrial Ca^{2+} overload.

Several proteins were recently indicated to participate in mitochondrial Ca^{2+} uptake, including MCUa, MCEB1, and its regulators MICU1/2, mitochondrial Ca^{2+} uniporter regulator 1 (MCUR1) and the essential MCU regulator (EMRE). The pore-forming subunit molecule MCUa is a 35 kDa protein with a highly conserved DIME motif that is composed of two coiled-coil domains and two transmembrane helices. The DIME motif of MCU are sides at the pore entrance and accounts for selective Ca^{2+} uptake, while the other transmembrane domain constitutes a hydrophilic pore, with the coiled-coil domains stabilizing the overall architecture [52]. MCUB shares 50% homology with MCUa but the DIME motifs are considerably different, which inhibits mitochondrial Ca^{2+} uptake. MCUB is considered a dominant-negative form of MCUa, physically binding to MCUa and modulating Ca^{2+} permeation. MICU1 binds to the D-ring domain of MCU through the DIME motif to regulate both the Ca^{2+} transport current and ruthenium red sensitivity of the MCU complex [53]. The high-affinity interaction of the MICU1/2 complex appears to serve as an on-off switch in direct response to cytosolic Ca^{2+} signals [54–56]. At low Ca^{2+} levels, MICU2 shuts down MCU function, whereas MICU1 allows mitochondria to promptly respond to elevated cytoplasmic Ca^{2+} [57]. Moreover, EMRE is reported to act as a scaffold protein to mediate the interaction between MCU and the MICU1/2 complex. In the absence of EMRE, MCU complex-mediated mitochondrial Ca^{2+} conductance is abolished in a manner similar to MCU silencing [58].

The precise pathophysiological effect of the MCU complex in HF needs further exploration. Regarding the role of MCU-mediated mitochondrial Ca^{2+} uptake in HF, conflicting results from previous studies have led to an ongoing debate [59]. It has been suggested that the level of mitochondrial MCU protein was significantly increased in mouse hearts in cases of pressure overload-induced cardiac hypertrophy, while this level was markedly downregulated in type 1 diabetic mouse hearts [50, 60, 61]. However, the probability of MCU being open was significantly decreased in failing human hearts, as determined by patch clamping of the inner membrane of mitochondria [62]. During acute ischemic injuries, MCU may mediate acute mitochondrial Ca^{2+} overload, trigger the permeability transition and ultimately induce cardiomyocyte death [63]. In addition, the MCU complex is necessary for increases in heart rate under stress challenge, while MCU inhibitors can lower the inappropriate tachycardia without affecting resting heart rhythm [64]. A compensatory rise in MCU was noted in cardiomyocytes during an energy shortage during the initial phase of transverse aortic constriction (TAC)-induced cardiac hypertrophy. In cardiac-selective MCU-knockout mice, cytosolic Ca^{2+} elevation was mainly the result of impaired mitochondrial Ca^{2+}-dependent oxidative phosphorylation and ATP generation in the mitochondrial matrix [65]. In the context of elevated MCU levels, mitochondrial Ca^{2+} uptake is elevated to best facilitate mitochondrial ATP synthesis [50]. These findings have prompted the speculation of a potential role for MCU complex-mediated mitochondrial Ca^{2+} uptake in therapeutic targeting against HF.
Mitochondrial Na\(^+\) uptake during Ca\(^2+\) oscillations [68]. Further exploration is required to investigate the mechanism of RyR1 in the progression of HF.

Mitochondrial Ca\(^{2+}\) efflux

To accommodate mitochondrial Ca\(^{2+}\) in response to changes in cytosolic Ca\(^{2+}\) levels, an Ca\(^{2+}\) ions are extruded from the mitochondrial matrix. Two major pathways are identified to counter the MCU complex and trigger Ca\(^{2+}\) efflux from mitochondria, namely, the Na\(^+\)/Ca\(^{2+}\)/Li\(^+\) permeable exchanger (NCLX) [69, 70] and the H\(^+\)/Ca\(^{2+}\) exchanger (HCX) [71].

Mitochondrial Na\(^+\)/Ca\(^{2+}\)/Li\(^+\) permeable exchanger (NCLX). NCLX is the primary mechanism of Ca\(^{2+}\) extrusion from the mitochondrial matrix [72]. NCLX is located on the IMM and appears to be the predominant antipporter in the heart and brain. NCLX exchanges 3 or 4 Na\(^+\) for 1 Ca\(^{2+}\). The kinetics of mitochondrial Ca\(^{2+}\) efflux are much slower than those of Ca\(^{2+}\) influx, which accounts for mitochondrial Ca\(^{2+}\) accumulation and sequentially contributes to the activation of the Krebs cycle following \(\beta\)-adrenergic stimulation [73]. The electrochemical gradient for Na\(^+\) influx into the mitochondrial matrix is the main driving force for NCLX. Given the intracellular Na\(^+\) levels of 4–8 mmol/L in cardiomyocytes, elevated intracellular Na\(^+\) in HF accelerates NCLX-mediated Ca\(^{2+}\) efflux and thereby reduce intramitochondrial Ca\(^{2+}\) levels [74].

Mitochondrial H\(^+\)/Ca\(^{2+}\) exchanger (HCX). HCX, another protein participating in mitochondrial Ca\(^{2+}\) extrusion, is also known as leucine zipper EF-hand-containing transmembrane protein 1 (LETM1) [79]. This protein mainly mediates Ca\(^{2+}\) release from mitochondria in the liver and kidney with the exchange of 2 H\(^+\) for 1 Ca\(^{2+}\). The LETM1 motif contains only a single transmembrane helix and might oligomerize into a hexameric structure to function as a transport route [80]. However, electroneutral transport of Ca\(^{2+}\) and insensitivity to ruthenium red and CGP-37157 were noted in highly purified LETM1-containing liposomes, confirming a role for LETM1 as a candidate for HCX function [81]. However, conflicting findings were also found for mitochondrial Ca\(^{2+}\) in LETM1-null cells; more supporting evidence is required to clarify the vital role of LETM1 in mitochondrial Ca\(^{2+}\) efflux [80]. LETM1 was reported to

Other channels of mitochondrial Ca\(^{2+}\) influx. More channels have been identified to shuffle Ca\(^{2+}\) into mitochondria. "Rapid-mode" uptake(RaM) allows fast intramitochondrial Ca\(^{2+}\) changes to mirror cytosolic Ca\(^{2+}\) changes in the time frame of milliseconds to turn on the mitochondrial metabolic reaction [66, 67]. Ryanodine receptor isoform (RyR)1 is another channel located in the IMM and plays an important role in the dynamic uptake of Ca\(^{2+}\) into mitochondria during Ca\(^{2+}\) oscillations [68]. Further exploration is required to investigate the mechanism of RyR1 in the progression of HF.

It was noted that both the mRNA and protein levels of NCLX were decreased in myocardial infarction-induced HF [75]. NCLX overexpression contributes to contractile dysfunction and arrhythmogenesis, probably through compensatory Ca\(^{2+}\) transport [76, 77]. Moreover, tamoxifen-induced cardiac-specific NCLX-knockout mice displayed severe myocardial dysfunction, and less than 13% of these mice survived beyond two weeks. This impressive lethality of the mouse models underscores a critical role of NCLX as the primary mitochondrial Ca\(^{2+}\) efflux mechanism. In addition, ROS production and mPTP opening in cardiomyocytes were significantly increased in the NCLX-knockout mice compared with the control mice [78]. However, cardiac dysfunction from acute myocardial infarction (MI) was rescued in NCLX-knockout mice crossed with cyclophilin D-null mice, indicating that cardiomyocyte apoptosis and cardiac fibrosis may be attributed to Ca\(^{2+}\)-induced mPTP opening in the NCLX-knockout mice [78]. Together, these findings suggest that NCLX may have potent therapeutic potential in the management of heart diseases.

Fig. 1 Cartoon depicting various representative molecules in the Ca\(^{2+}\) channel complex that regulate Ca\(^{2+}\) transfer at mitochondria-associated ER membranes (MAMs). ER endoplasmic reticulum, IMM inner mitochondrial membrane, OMM outer mitochondrial membrane, MFN1/2 mitofusin 1/2, MCU mitochondrial calcium uniporter, NCLX Na\(^+\)/Ca\(^{2+}\)/Li\(^+\) permeable exchanger, VDAC1 voltage-dependent anion channel, IP3R inositol 1,4,5-triphosphate receptor, GRP75 chaperone 75 kDa glucose-regulated protein, FUNDC1 FUN14 domain containing 1, Sig-1R the sigma-1 receptor, PTPIP51 protein tyrosine phosphatase-interacting protein 51, and VAPB vesicle-associated membrane protein-associated protein B.
Mitochondrial Ca$^{2+}$ in heart failure

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Mitochondria-associated ER membranes (MAMs)
Mitochondrial Ca$^{2+}$ homeostasis is closely associated with the communication between mitochondria and the ER, which mainly assists in Ca$^{2+}$ transfer, signal transduction, mitochondrial metabolism, and mitochondrial dynamics [87, 88]. Mitochondria and ER possess contact sites, which account for ~20% of the total mitochondrial network with the distance between two organelles ranging from 10 nm–60 nm, structures commonly termed mitochondria-associated endoplasmic reticulum membranes (MAMs) [89]. At MAMs, Ca$^{2+}$ directly transfers from the ER to mitochondria and promotes the Krebs cycle to synthesize ATP in the mitochondrial matrix [90]. In cardiomyocytes, SR-mitochondria coupling also serves as an important regulator of biological events, including Ca$^{2+}$ signaling, lipid metabolism, inflammation, autophagy, and apoptosis [88, 91, 92]. MAMs maintain mitochondrial Ca$^{2+}$ homeostasis through MAM-related protein bridges. MAMs provide a microenvironment with a high level of Ca$^{2+}$, which is necessary for mitochondria internalization of Ca$^{2+}$ [88]. How do MAM-related proteins affect mitochondrial Ca$^{2+}$ ions? Recent evidence has confirmed that several molecules work as Ca$^{2+}$ transport complexes to regulate Ca$^{2+}$ transfer at MAMs (Fig. 1).

IP3R1-GRP75-VDAC1. Multiprotein complexes participate in regulating Ca$^{2+}$ transfer from the ER to mitochondria. Inositol 1,4,5-trisphosphate receptor type 1 (IP3R1), the major channel in the ER that releases Ca$^{2+}$, allows the formation of microdomains highly enriched with Ca$^{2+}$ in the vicinity of the ER [87]. Conversely, VDAC1 in the OMM acts as a Ca$^{2+}$-uptake channel with high conductance. As the third element of this complex, a 75 kDa chaperone, glucose-regulated protein (GRP75), a member of the Hsp70 family, tethers cytosolic portions of IP3R1 and VDAC1 [93]. Thus, Ca$^{2+}$ is directly transferred from the ER to the cytosol and then moves across the OMM into the intermembrane space of a mitochondrion. Finally, Ca$^{2+}$ ions enter the mitochondrial matrix through the MCU complex.

The increased expression of IP3R1 has been demonstrated in heart tissues from HF patients and experimental animals [94]. In addition, genetic or pharmacological inhibition of cyclophilin D, a chaperone of the IP3R1-GRP75-VDAC1 complex, may mitigate Ca$^{2+}$ transfer from the ER to mitochondria through IP3R1 in adult cardiomyocytes and thus attenuate mitochondrial Ca$^{2+}$ overload, ultimately protecting cells from hypoxia-reoxygenation [49, 95].

MFN1–MFN2. In addition to the IP3R1-GRP75-VDAC1 complex, mitochondrial fusion also forms bridges that enjoin the ER and mitochondria. Mitochondrial fusion is traditionally realized through the function of mitofusin (MFN)2, a GTPase that resides at the OMM as tethers to juxtaposed mitochondria. MFN2 resides on ER membranes and forms dimers with MFN1 or MFN2 located on the OMM [96]. Mitochondrial Ca$^{2+}$ uptake is inhibited due to the disassociation of the ER and mitochondria in MFN2-knockout cells, which does not affect the Ca$^{2+}$ release capacity of the ER [97].

Furthermore, these results not only reflect the distance between these subcellular organelles but also show the coordinated regulation of the mitochondrial network and ER dynamics. It was reported that the levels of MFN1 were increased in mitochondria during HF, yet its GTPase activity was significantly compromised, revealed by an accumulation of defective MFN1 in HF [98]. Several reports have suggested that MFN2 is downregulated in myocardial hypertrophy and doxorubicin-induced cardiotoxicity [99, 100], while MFN2-knockout cells displayed overtly reduced junctional SR–mitochondria contact sites and developed dilated cardiomyopathy in mice. In addition, MFN1/MFN2 cardiac-knockout induces resistance to mPTP opening due to a reduction in SR–mitochondria contacts, mitochondrial Ca$^{2+}$ overload, and ROS generation during cardiac ischemia/reperfusion (I/R) injury [101, 102].

**FUNDC1-IP3R2.** FUN14 domain containing 1 (FUNDC1) is a highly conserved OMM molecule that mediates independent mitophagy [103]. A recent study suggested that FUNDC1 localized at MAMs and interacted with IP3R2 to mediate Ca$^{2+}$ release from SR into both mitochondrial and cytoplasmic cardiomyocytes. Although deletion of IP3R2 did not influence the progression of HF in diabetes-related cardiac disease or pressure overload-induced HF [104], FUNDC1 deletion led to cardiac dysfunction characterized by disrupted MAMs and impaired Ca$^{2+}$ transfer from the SR to mitochondria [105]. In FUNDC1-knockout cells, both intracellular and mitochondrial Ca$^{2+}$ levels were reduced, and Ca$^{2+}$-sensitive CREB-mediated Fis1 expression was suppressed, causing mitochondrial dysregulation, cardiac dysfunction and HF [105].

**VAPB-PTPIP51.** In addition to the aforementioned molecules, vesicle-associated membrane protein-associated protein B (VAPB), located on the ER surface, is coupled to an OMM called protein tyrosine phosphatase interacting protein 51 (PTPIP51) [106]. Previous work has revealed that modifying the expression of VAPB and PTPIP51 affects the transfer of Ca$^{2+}$ between the two subcellular organelles. Recently, studies suggested that VAPB-PTPIP51 regulates Ca$^{2+}$ transfer by influencing the function of IP3R-VDAC1 to regulate autophagy [107]. Further studies are required to elucidate the likely role and mechanism of action of VAPB-PTPIP51 in HF.

**Other.** Recent findings have also identified several molecular chaperones, including calnexin [108], syntaxin-17 and sigma-1 receptor (Sig-1R) at MAMs, which are involved in the regulation of information exchange, such as Ca$^{2+}$ ions between the ER and mitochondria. Sig-1R is a chaperone located in MAMs that regulates Ca$^{2+}$ transfer between mitochondria and ER by binding with IP3R3 [109]. Upon the induction of ER stress, Sig-1R is separated from BIP, and IP3R3 is stabilized to accelerate Ca$^{2+}$ influx from the ER into mitochondria to increase the production of ATP. It has been suggested that Sig-1R knockout leads to mitochondrial dysfunction and HF [109]. In addition, it has been suggested that syntaxin-17 interacts with Drp1 and regulates the calcium concentration in the ER and cytoplasm [110]. Under various stress conditions, mitochondrial Ca$^{2+}$ homeostasis is affected by the influence of MAM-related proteins. RyR2 was found to interact with VDAC2 in HL-1 cells and mediate calcium transfer between the SR and mitochondria [111].

**DISRUPTION OF MITOCHONDRIAL CA$^{2+}$ HOMEOSTASIS IN HF**
Mitochondrial Ca$^{2+}$ and ATP generation
Mitochondria constitute ~30% of the cellular volume in cardiomyocytes, where they supply ATP to meet the heightened energy demand for cardiac function. Ca$^{2+}$ plays a crucial role in ATP production for communicating cellular energy demands to mitochondria [112, 113]. Oxidative phosphorylation is tightly regulated by mitochondrial Ca$^{2+}$ as Ca$^{2+}$ activates tricarboxylic acid dehydrogenases to produce equivalents (NADH/NADPH) for electron transport [114]. Mitochondria constitute a vital buffer...
Mitochondrial Ca\(^{2+}\) and ROS production

Mitochondria are major sources of ROS due to their oxidative reactions. Thus, mitochondria are more prone to oxidative damage than other organelles [116]. Oxidative stress may damage mitochondrial DNA, leading to protein oxidative damage and impaired mitochondria and myocardial energetics in HF. In animal models, ROS generation in mitochondria is causally linked to the onset and progression of cardiac dysfunction triggered by various pathological stimuli, including angiotensin II, pressure overload, and cardiac ischemia, and lead to an increased risk of arrhythmia [14, 117].

In failing hearts, O$_2$ anions form at mitochondrial complex I and are then converted to hydroxyl radicals, the major mitochondrial ROS in the heart. ROS induce injuries to the mitochondrial respiratory chain and slow electron transfer through complex I, thereby causing a reduction in NADH [118]. Furthermore, mitochondria may potentiate ROS through ROS-induced ROS release, which involves ROS-induced activation of anion channels in the IMM, mPTP, and ATP-sensitive K\(^+\)-channels [20, 119]. Activation of these channels dissipates the \(\Delta\Psi\) and consumes NADH and NADPH, resulting in the emission of H$_2$O$_2$. Finally, hyper acetylation of mitochondrial proteins was found to be significantly increased in the hearts of patients with HF, which may be attributed to increased myocardial levels of acetyl-CoA and acetylation of various proteins [120, 121].

One of the common triggers for ROS-induced ROS release is angiotensin II stimulation or pressure overload, resulting in damage to the ECC through the negative effects of RyR2s, SERCA2, and NCLX [20]. Mitochondrial Ca\(^{2+}\) overload is induced by mitochondrial ROS, which favor Ca\(^{2+}\) efflux via NCLX, thereby eliciting nonspecific Ca\(^{2+}\) flux that reverses the polarization of \(\Delta\Psi\). In addition, ROS activate Ca\(^{2+}\)-/calmodulin-dependent protein kinase II (CaMKII), an essential regulator involved in both Ca\(^{2+}\) and Na\(^{+}\) processes, including those involved with RyR2s, phospholamban, L-type Ca\(^{2+}\) channels, and late Na\(^{+}\) current, ultimately contributing to cardiac dysfunction and arrhythmias in HF. CaMKII also induces cardiac remodeling and cardiac hypertrophy through the phosphorylation of histone deacetylase (HDAC), potentially leading to elevated ROS generation. Therefore, ROS and mitochondrial Ca\(^{2+}\) overload contribute to HF through several mechanisms, prompting a vicious cycle resulting in cardiac hypertrophy, interstitial fibrosis, contractile dysfunction and sudden death [20].

Mitochondrial Ca\(^{2+}\) and mitochondrial dynamics in HF

Ample evidence has suggested that mitochondrial architecture is constantly modified by highly dynamic organelle transformations [30, 122–124]. Mitochondria undergo continuous fusion and fission to maintain mitochondrial integrity and remove damaged mitochondria [125, 126]. Dynamin-related protein 1 (DRP1) is recruited to mitochondria and forms a constricted ring that drives mitochondrial fragmentation. In contrast, mitochondrial fusion is regulated by MFN1, MFN2, and optic atrophy protein 1 (OPA1) [125–127]. MFN1/MFN2 are located on the membrane of two adjacent mitochondria that interact with each other to mediate OMM fusion. OPA1, on the other hand, resides on the IMM and is critical for the for maintenance of crist structures and IMM fusion.

The precise interplay between Ca\(^{2+}\) and mitochondrial dynamics is poorly understood in the context of cardiac hypertrophy. Recent studies indicated that Ca\(^{2+}\) inhibits mitochondrial motility to retain mitochondrial Ca\(^{2+}\) signaling and energy supply levels [128]. It was also indicated that calcineurin, as a Ca\(^{2+}\)-dependent phosphatase, is overtly activated by elevated Ca\(^{2+}\) levels to phosphorylate Drp1 at Ser\(^{297}\) and promote Drp1 recruitment to mitochondria, resulting in mitochondrial fission [129, 130]. In addition, it has been noted that the treatment of cardiomyocytes with norepinephrine promotes extensive mitochondrial fission and mitochondrial injury through the activation of the \(\alpha\)-adrenergic-receptor-Ca\(^{2+}\)-calcineurin-Drp1 signaling axis [131]. These findings suggest a key role for mitochondrial Ca\(^{2+}\) in mitochondrial dynamics and pathological cardiac remodeling [132].

Mitochondrial Ca\(^{2+}\) and mitophagy in HF

Mitochondria account for ~20%–30% of cardiac mass, and their degradation is crucial for mitochondrial quality control. Interfering with mitochondrial quality control results in the accumulation of dysfunctional mitochondria and, ultimately, cardiac dysfunction [26]. Mitophagy is an essential process of selective autophagy, which results in the removal of irreversibly damaged mitochondria [125, 126]. Emerging evidence supports the protective role of mitophagy in the progression of HF [125, 126, 133]. Mitophagy is mainly mediated by the PINK1/Parkin pathway. PINK1-deficient hearts are more susceptible to I/R injury and transition more rapidly to failure in response to pressure overload [134]. Moreover, PRKN-knockout mice showed dysfunctional mitochondrial accumulation following MI and were susceptible to doxorubicin-induced cardiotoxicity and cardiac dysfunction [135–137]. These observations revealed a cardioprotective role for mitophagy in HF progression and highlight the utility of promoting mitophagy in therapeutics targeted to HF [138–140].

Recent studies revealed an important role for mitochondrial Ca\(^{2+}\) content in mitochondrial autophagy (mitophagy) regulation. In particular, mitochondrial Ca\(^{2+}\) uptake regulates AMP kinase (AMPK) activity and activates autophagy via the AMPK-mammalian target of rapamycin-UNC-51-like kinase 1 (AMPK/mTORULK1) signaling pathway [141]. However, mitochondrial Ca\(^{2+}\) overload perturb mitochondrial physiology, leading to ROS production, mPTP opening and mitophagy initiation [142]. These findings suggested that aberrant levels of Ca\(^{2+}\) may have opposite effects on autophagy. Moreover, mitochondrial Rho-GTPase (RHO1) is an OMM protein and a Ca\(^{2+}\)-sensitive regulator because of its two EF-hand Ca\(^{2+}\) binding domains [143]. PINK1 may phosphorylate RHO1 and trigger Parkin-mediated mitophagy [144]. In addition, the accumulation of

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**Fig. 2** Mitochondrial Ca\(^{2+}\) dysregulation in the progression of cardiac remodeling and heart failure. mPTP mitochondrial permeability transition pore, ROS reactive oxygen species.
α-synuclein (SNCA) was found to increase mitochondrial Ca\(^{2+}\) levels and promote oxidative damage, whereas SNCA loss impaired mitochondrial Ca\(^{2+}\) and enhanced autophagy [145, 146]. Future work is warranted to elucidate how mitochondrial Ca\(^{2+}\) participates in the modulation of mitophagy in cardiomyocytes.

Mitochondrial Ca\(^{2+}\) overload, mPTP opening, mitochondrial apoptosis and necrosis

Excess uptake of mitochondrial Ca\(^{2+}\) and mitochondrial ROS production may both result in the depolarization of the ΔΨm, the opening of the mPTP, and a decreased proton gradient. Ca\(^{2+}\) and cytochrome c efflux from mitochondria results in mitochondrial swelling, loss of ΔΨm and apoptosis [147, 148]. The mPTP appears to be a crucial, but still incompletely understood, target of Ca\(^{2+}\)-dependent CaMKII. Cardiomyocytes from transgenic mice overexpressing CaMKII inhibitory protein sustained higher Ca\(^{2+}\) levels in mitochondria prior to mPTP opening and were more resistant to apoptosis induced by I/R or MI injury, suggesting that Ca\(^{2+}\) levels promote mPTP opening and myocardial apoptosis partly through the activation of CaMKII [149].

Apoptosis refers to programmed cell death to maintain the stability of the internal environment of cells. Three main branches of signaling pathways are currently proposed, including the death receptor, endoplasmic reticulum (ER) and mitochondrial pathways [150]. The mitochondrial pathway is the most common and core mechanism regulated by mitochondrial Ca\(^{2+}\) [151]. Under apoptosis-inducing stimuli, such as toxins, hypoxia, viral infections, radiation, high cytosolic Ca\(^{2+}\) levels, and oxidative damage by ROS, mitochondria show increased permeability and Ca\(^{2+}\) overload, depolarized transmembrane potential, and cytochrome c and pro-apoptotic mediator release [152].

Mitochondria Ca\(^{2+}\) overload is a key element in the processes that control cellular death and survival through convergence at MAMs [153]. Bcl-2-like protein 1, an antiapoptotic protein, is localized to MAMs and promotes Ca\(^{2+}\) transfer from the ER to mitochondria as an adaptive response to promote mitochondrial bioenergetics and prevent cytosolic Ca\(^{2+}\) overload under stress conditions [154]. The phosphatase PTEN has been identified as another protective component of MAMs. PTEN is commonly referred to as a canonical tumor suppressor due to its inhibition of Akt on plasma membranes. PTEN also resides at MAMs, where it antagonizes the PI3K–Akt signaling pathway. PTEN overexpression can enhance autophagy [145, 146].

In cardiomyocytes, aldosterone accelerates the mitochondrial apoptotic pathway through the dephosphorylation of the pro-apoptotic molecule Bad, enhancement of mitochondrial permeability, release of cytochrome c and concomitant activation of caspase 3, directly contributing to the progression of HF [156]. However, the effects of aldosterone were suppressed by inhibitors of the Ca\(^{2+}\)-dependent phosphatase calcineurin and FK506 [157]. Furthermore, cytochrome c is released from mitochondria and is translocated to the ER, where it selectively binds to InP3Rs, resulting in mitochondrial Ca\(^{2+}\) overload and the induction of additional cytochrome c release, which amplifies the apoptotic signaling response to ischemia stress [158]. These findings revealed a feed-forward modality in which early cytochrome c release facilitates IP3R function, leading to mitochondrial-induced apoptosis [155].

Notably, the dysregulation of mitochondrial Ca\(^{2+}\) is also a potent trigger of cellular necrosis [156, 159, 160]. With the simultaneous opening of the mPTP pores in mitochondria, ATP is depleted, with the level becoming insufficient to aggregate apoptosomes. The obviously increased cytosolic Ca\(^{2+}\) may activate a number of hydrolytic enzymes, resulting in organelle swelling, structural degeneration and necrotic death. This sequence of events leads to cardiomyocyte necrosis with the leakage of intracellular contents, including troponins, which serve as danger signals to the innate immune system. Later, inflammatory cells and myofibroblasts are recruited to the site of necrosis, resulting in reparative fibrosis, cardiac remodeling, and, not surprisingly, HF [159].

PERSPECTIVES AND CONCLUSION

The mitochondrion is an intracellular organelle governing energy supply, cell signaling and cell survival. Much attention has been paid to understanding the role of mitochondrial Ca\(^{2+}\) in the etiology of HF. Mitochondrial function is determined by the amplitude and kinetics of Ca\(^{2+}\) cycling and a number of key molecules governing various mitochondrial Ca\(^{2+}\) transport machineries. Much progress has been made in understanding these mitochondrial Ca\(^{2+}\) transport processes, including ion specificity, activation, inhibition, kinetics, electrical conductivity and other characteristics. With the development of recent cutting-edge technical methodologies, such as molecular biology and bioinformatics, more molecular mechanisms of these Ca\(^{2+}\) transport pathways are being revealed. In addition, due to the identification of mitochondrial Ca\(^{2+}\) transport machineries, including MCU, MICU1, and NCLX, the study of mitochondrial Ca\(^{2+}\) transport will shift from the classical cellular level to the molecular level to generate a better understanding of the physiological functions of mitochondrial Ca\(^{2+}\) transport. In animal models, mitochondrial Ca\(^{2+}\) transport inhibitors have been used to discern the physiological function of mitochondrial Ca\(^{2+}\) transport. However, the use of inhibitors such as ruthenium red, ruthenium 360, diltiazem, clonazepam, and CGP37157 often yield disparate and inconsistent results [161]. Therefore, drug development targeting mitochondrial Ca\(^{2+}\) transfer is pertinent for the advance of the field.

Several studies have suggested alterations in mitochondrial function and ER disorders are related to cardiomyopathies, cardiac hypertrophy and HF progression [21, 105]. However, the field of ER–mitochondria communication has received much less attention. Several pieces of evidence have indicated that interactions at MAMs may serve as critical factors in the pathophysiology of HF. The maintenance of mitochondrial Ca\(^{2+}\) homeostasis and mitochondrial function is essential for cardiomyocyte survival and cardiac function. The acquisition of novel technical tools necessary to regulate MAMs is an important objective for future research and therapeutic approaches. The in-depth understanding of mechanisms involved in mitochondrial Ca\(^{2+}\) regulation will contribute to the development of therapeutic strategies towards improving mitochondrial dysfunction in the heart and ultimately HF.

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ADDITIONAL INFORMATION

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