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Mitochondrial dysfunction in AMI: mechanisms and therapeutic perspectives

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Abstract
Acute myocardial infarction (AMI) and the myocardial ischemia-reperfusion injury (MI/RI) that typically ensues represent a significant global health burden, accounting for a considerable number of deaths and disabilities. In the context of AMI, percutaneous coronary intervention (PCI) is the preferred treatment option for reducing acute ischemic damage to the heart. Despite the modernity of PCI therapy, pathological damage to cardiomyocytes due to MI/RI remains an important target for intervention that affects the long-term prognosis of patients. In recent years, mitochondrial dysfunction during AMI has been increasingly recognized as a critical factor in cardiomyocyte death. Damaged mitochondria play an active role in the formation of an inflammatory environment by triggering key signaling pathways, including those mediated by cyclic GMP-AMP synthase, NOD-like receptors and Toll-like receptors. This review emphasizes the dual role of mitochondria as both contributors to and regulators of inflammation. The aim is to explore the complex mechanisms of mitochondrial dysfunction in AMI and its profound impact on immune dysregulation. Specific interventions including mitochondrial-targeted antioxidants, membrane-stabilizing peptides, and mitochondrial transplantation therapies have demonstrated efficacy in preclinical AMI models.

Keywords Acute myocardial infarction, Myocardial ischemia-reperfusion injury, Mitochondrial damage, Inflammatory response, Cell death, Therapeutic strategy

Introduction

Acute myocardial infarction (AMI) represents a significant and severe form of cardiovascular disease, accounting for a considerable proportion of global morbidity and mortality. The pathophysiology of myocardial infarction (MI) is based on the sudden occlusion of a coronary artery, which results in myocardial ischemia and subsequent necrosis of cardiac tissue. This event initiates a cascade of ischemia, necrosis and an inflammatory response, which exacerbates tissue damage and impairs cardiac function. The current clinical approach to therapy is focused on reperfusion strategies and pharmacological interventions with the objective of limiting infarct size and improving prognosis. In the context of MI, a rapid and robust inflammatory response is essential for the processes of tissue remodeling and repair. However, an excessive inflammatory response can lead to pathological consequences, including cardiac remodeling, fibrosis and ultimately heart failure (HF) [1].

Mitochondria are a primary source of cellular energy and are involved in a number of essential processes, including the maintenance of redox homeostasis, Ca^{2+}

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homeostasis and a range of other key functions that are crucial for cell survival. Mitochondrial homeostasis is achieved by maintaining a balance between the processes of mitochondrial fission, fusion, biogenesis and mitophagy [2]. Mitochondria are involved in the immune response not only as cellular powerhouses but also as centers of innate immune signals against viruses and bacteria. Additionally, mitochondria serve as hubs for pro-inflammatory responses, exerting a pivotal influence on the inflammatory cascade in AMI [3].

Accumulating evidence demonstrates that mitochondria serve as critical mediators in AMI pathogenesis. Both experimental and clinical studies have established significant mitochondrial damage during AMI progression. Beyond their fundamental role in energy production, mitochondria regulate cellular metabolism and numerous cellular processes. During AMI, dysfunctional mitochondria initiate inflammatory cascades through diverse signaling pathways. Recent investigations have elucidated the essential role of mitochondria in orchestrating the inflammatory response during MI. Mitochondrial dysfunction and the release of mitochondrial DNA (mtDNA) into the cytoplasm have been demonstrated to activate a number of inflammatory pathways, including the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, the NLR pyrin domain containing 3 (NLRP3) inflammasome and the Toll-like receptor 9 (TLR9) pathway [4]. These pathways contribute to the perpetuation of an inflammatory environment within the infarcted myocardium, which in turn results in further tissue damage and adverse outcomes. By elucidating the mechanisms of activation of these pathways and their downstream effects, we aim to identify potential therapeutic targets that may be employed to reduce inflammation and improve the prognosis of patients with MI.

The objective of this paper is to examine the intricate mechanisms of mitochondrial dysfunction in MI and its profound impact on immune dysregulation. Furthermore, we present promising interventions targeting mitochondria that have demonstrated therapeutic efficacy in preclinical MI models. By gaining a comprehensive understanding of the interplay between mitochondrial integrity and the immune response, we aim to pave the way for the development of novel and effective therapeutic approaches to protect myocardial function and limit myocardial fibrosis after MI/RI. This highlights the potential of this approach as a therapeutic agent for MI.

Mitochondrial structure and function

Mitochondria, double membrane-bound organelles fundamental to eukaryotic cells, orchestrate cellular energy production and metabolic homeostasis. Their distinctive architectural organization enables the spatial segregation of diverse biochemical pathways critical for cellular processes. Contemporary research has revealed that mitochondria extend beyond their canonical role in ATP generation, serving as central regulators of cellular signaling networks, programmed cell death, and oxidative stress responses.

Mitochondria are often referred to as the "powerhouses" of the cell due to their central role in oxidative phosphorylation (OXPHOS), a process that generates ATP through the electron transport chain (ETC). This process is not only critical for energy metabolism but also influences various cellular signaling pathways. For instance, mitochondrial dysfunction has been linked to a range of diseases, including neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes, highlighting the importance of maintaining mitochondrial health for overall cellular homeostasis [5, 6].

Basic structure of mitochondria

The mitochondria are dynamic double-membrane organelles, with an inner and outer membrane separated by a membrane gap. The outer mitochondrial membrane (OMM) is smooth and permeable to small molecules and ions. The inner mitochondrial membrane (IMM) is characterized by a high degree of folding into structures known as cristae, which serve to significantly enhance the surface area available for biochemical reactions. mtDNA, the citric acid cycle and ribosomes are found in the mitochondrial matrix within the inner membrane. This unique structure allows mitochondria to perform their roles in energy production and metabolic regulation effectively [7]. The majority of the ATP consumed by the heart comes from mitochondria, which are present in one-third of cardiomyocytes in the adult heart, and are therefore often considered the 'powerhouse of the cell' [8]. Mitochondria produce ATP via two major processes: (1) oxidation of NADH and FADH2 produced during the tricarboxylic acid (TCA) cycle or glycolysis and (2) OXPHOS to produce ATP. Mitochondrial fission, fusion, mitophagy and biogenesis mechanisms maintain mitochondrial homeostasis when the cells experience metabolic or environmental stress, which is referred to as mitochondrial dynamics. Other mitochondrial functions include maintenance of calcium homeostasis, production of reactive oxygen species (ROS), maintenance of the redox balance, protein modification, cell proliferation and apoptosis, iron-sulfur cluster biosynthesis, fatty acid oxidation and innate immune signaling [9–11]. Recent studies have demonstrated that alterations in cristae morphology impact the efficiency of ATP synthesis and organelle response to stress, underscoring the significance of mitochondrial structure in the context of health and disease [12].

Role of mitochondria in energy metabolism

Mitochondria are often referred to as the powerhouses of the cell due to their central role in ATP production through OXPHOS. The process begins with *the Krebs cycle*, where substrates derived from carbohydrates, fats, and proteins are oxidized, generating electron carriers NADH and FADH2. Subsequently, the ETC facilitates the transfer of electrons from the nutrients to the membrane gap, thereby pumping protons into the membrane. This results in the formation of a proton gradient, which in turn facilitates the synthesis of ATP via the action of ATP synthase. They also play a crucial role in regulating metabolic flexibility, enabling cells to adapt to varying energy demands. Dysregulation of mitochondrial energy metabolism is implicated in various conditions, including obesity, diabetes, and cancer, where altered mitochondrial function can lead to metabolic disorders [13].

Fatty acid oxidation

Mitochondria are pivotal in the process of fatty acid oxidation, a critical metabolic pathway for energy production. This process involves the breakdown of fatty acids into acetyl coenzyme A units, which subsequently enter the citric acid cycle for ATP generation. The enzymes responsible for fatty acid oxidation, such as acyl-CoA dehydrogenases, are localized in the mitochondrial matrix and are essential for the proper functioning of this pathway. Disruptions in fatty acid oxidation can lead to metabolic disorders, including fatty acid oxidation disorders, characterized by the accumulation of fatty acids and their derivatives in tissues, which can cause damage and dysfunction. Furthermore, the regulation of this pathway is influenced by various factors, including hormonal signals and substrate availability. For instance, increased levels of malonyl-CoA, a product of fatty acid synthesis, can inhibit carnitine palmitoyl transferase 1, thereby preventing the entry of fatty acids into the mitochondria for oxidation [14]. Research has also shown that certain dietary components, such as omega-3 fatty acids, can enhance mitochondrial fatty acid oxidation, suggesting that nutrition plays a significant role in modulating this metabolic pathway [15]. Overall, the efficiency of fatty acid oxidation in mitochondria is crucial for maintaining energy homeostasis and preventing metabolic diseases.

Amino acid metabolism

Mitochondria are integral to amino acid metabolism, serving as sites for various biochemical reactions that convert amino acids into energy substrates. Amino acids can be catabolized through transamination and deamination processes, resulting in the formation of intermediates that enter the TCA cycle. For instance, glutamate can be deaminated to produce α-ketoglutarate, which is a key TCA cycle intermediate [16]. Additionally, the metabolism of branched-chain amino acids occurs predominantly in the mitochondria, where they are converted into acetyl coenzyme A and succinyl-CoA, further linking amino acid metabolism to energy production [17]. The interplay between amino acid metabolism and mitochondrial function is particularly significant in conditions such as cancer, where altered amino acid metabolism can promote tumor growth and survival. Moreover, mitochondrial dysfunction can lead to impaired amino acid catabolism, contributing to metabolic dysregulation and disease states.

Glycolysis

The relationship between glycolysis and mitochondrial function is a fundamental aspect of cellular energy metabolism. Glycolysis, which occurs in the cytoplasm, breaks down glucose into pyruvate, producing a small amount of ATP in the process. The pyruvate generated is then transported into the mitochondria, where it is converted into acetyl coenzyme A, linking glycolysis to the TCA cycle and OXPHOS [18]. This connection is crucial for maximizing ATP yield, as the complete oxidation of glucose through aerobic respiration in mitochondria results in significantly more ATP compared to glycolysis alone. Additionally, the regulation of glycolysis is influenced by mitochondrial activity; for instance, an increase in mitochondrial ATP production can lead to a decrease in glycolytic flux through feedback mechanisms. Furthermore, under conditions of hypoxia or mitochondrial dysfunction, cells may rely more heavily on glycolysis for energy production, a phenomenon known as *the Warburg effect* [19]. This shift highlights the adaptability of cellular metabolism in response to energetic demands and environmental changes.

Mitochondrial stress and damage during AMI

Mitochondrial-Associated inflammation

The innate immune system is the host's first line of defense against pathogenic microorganisms. Innate immune sensors include pattern recognition receptors (PRRs), which monitor the extracellular and intracellular environment by detecting pathogen-associated molecular patterns (PAMPs), microbial structures in the form of host-derived danger signals called danger-associated molecular patterns (DAMPs). There are several subgroups of PRRs, toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors, retinoic acid-inducible gene I like receptors (RLRs). It has been demonstrated that each PRR permits the secretion of type I interferons (IFN-I) and pro-inflammatory cytokines via nuclear factor kappa B (NF-κB). The NLR pathway plays a role in the mechanisms of resistance to infection and cellular damage. It is a fallacy to assume that only pathogenic infectious diseases cause inflammation. In

fact, tissue damage activates a variety of inflammatory mechanisms via DAMPs [20]. Mitochondria contain several DAMPs, including mtDNA, cardiolipin, N-formyl peptides, ROS, and some metabolites (e.g., ATP and succinate).

Mitochondria as sources of inflammatory signals

Mitochondria play a pivotal role in cellular metabolism, but they also function as critical sources of inflammatory signals. When cells are subjected to stressors such as infection, injury, or metabolic disturbances, mitochondria can release various DAMPs that trigger inflammatory responses. One of the most studied DAMPs is mtDNA, which, when released into the cytosol or extracellular space, can activate innate immune pathways, particularly through the cGAS-STING signaling pathway. This pathway leads to the production of IFN-I and pro-inflammatory cytokines, exacerbating the inflammatory response. Furthermore, mitochondrial dysfunction can lead to the generation of ROS, which also serve as signaling molecules that amplify inflammation by activating NF-κB and other inflammatory transcription factors [21]. The interplay between mitochondrial function and inflammation is thus bidirectional; while inflammation can induce mitochondrial dysfunction, the release of mitochondrial signals can also initiate and sustain inflammatory processes, indicating that mitochondria are indispensable players in the orchestration of inflammatory responses [3].

Release of mitochondrial DNA and inflammatory response

mtDNA is a circular, double-stranded genome distinct from nuclear DNA, encoding essential proteins required for mitochondrial function. Located in the mitochondrial matrix of the inner mitochondrial membrane, mtDNA is more prone to mutations due to its proximity to ROS generated during ATP production. Unlike nuclear DNA, mtDNA is maternally inherited. Upon release into the cytoplasm, mtDNA activates various PRRs and innate immune responses, including cGAS, TLR9, and inflammasomes. Mutations in mtDNA can lead to a range of mitochondrial disorders, impairing energy metabolism and contributing to age-related diseases. Recent advancements in sequencing technologies have significantly enhanced our understanding of mtDNA variations and their impact on health and disease [22, 23]. For instance, high-throughput sequencing has enabled the detection of low-frequency heteroplasmic mutations, which are often associated with mitochondrial diseases such as coronary artery disease [24]. Single-cell sequencing has revealed cell-to-cell heterogeneity in mtDNA mutations, providing insights into the mosaic distribution of mitochondrial dysfunction in tissues, which is particularly relevant in aging and cancer [25].

The release of mtDNA from damaged mitochondria is a key event in the initiation of inflammatory responses. Under pathological conditions, such as ischemia or trauma, mtDNA can leak into the cytosol or extracellular environment, where it can be recognized by PRRs like TLR9. This recognition triggers a cascade of inflammatory signaling, leading to the production of pro-inflammatory cytokines and chemokines [26, 27]. Studies have shown that mtDNA can amplify inflammatory responses in various contexts, including age-related cardiovascular diseases and neuroinflammation [28]. Moreover, the presence of oxidized mtDNA can further enhance its pro-inflammatory potential, contributing to chronic inflammation seen in diseases such as Alzheimer's and autoimmune disorders [29]. Therefore, the release of mtDNA serves not only as a marker of mitochondrial damage but also as an active mediator of inflammation, underscoring its role in disease pathogenesis and potential therapeutic targets [30].

Mitochondrial damage

Mitochondrial dysfunction in the setting of AMI is characterized by alterations in mitochondrial morphology, bioenergetics, and the regulation of apoptotic pathways. Notably, the opening of the mitochondrial permeability transition pore (mPTP) has been implicated in the initiation of cell death processes during ischemia/reperfusion injury (IRI). The mPTP opening leads to a loss of mitochondrial membrane permeabilization (MMP), swelling, and ultimately, necrosis or apoptosis of cardiomyocytes, which is a hallmark of MI [31]. Oxidative stress arises from an imbalance between the production of ROS and the body's ability to eliminate these harmful compounds. The sources of oxidative stress can be both endogenous and exogenous. Endogenous sources primarily include mitochondrial respiration, where the ETC can leak electrons, leading to the formation of superoxide radicals. Additionally, various enzymatic reactions, such as those involving xanthine oxidase and nitric oxide synthase, contribute to ROS generation. Exogenous factors include environmental pollutants, ultraviolet radiation, and certain drugs, which can exacerbate oxidative stress by increasing ROS levels or depleting antioxidant defenses. Lifestyle factors such as diet, smoking, and physical inactivity also play a crucial role in modulating oxidative stress levels.

Mitochondrial damage and ROS generated by mitochondrial oxidative stress can serve as substrates to induce mitophagy. The upregulation of mitophagy during ischemia is thought to be beneficial. For instance, a study demonstrated that mice with a knockout of the Parkin gene exhibited increased sensitivity to myocardial infarction, characterized by reduced autophagy and swollen, dysfunctional mitochondria in cardiomyocytes

following the infarction. A study has demonstrated that the ablation of the mitofusin 1 (MFN1) and mitofusin 2 (MFN2) genes exerts a protective effect against MI. This is achieved through mechanisms that are related to the inhibition of mPTP opening, a reduction in oxidative stress, and an attenuation of mitochondria0l Ca^{2+} overload [32]. In patients with ST-elevation myocardial infarction, the presence of excess ROS, B-cell lymphoma-2 (Bcl-2) proteins and dysregulated calcium promote mitochondrial membrane permeabilization during perfusion, leading to translocation of apoptotic factors such as cytochrome c (cyt c) and high-temperature requirement serine peptidase 2 from the mitochondria to the cytoplasmic lysate [33]. In animal models, Liao et al. [34] observed that attenuation of hypoxia/re-oxygenation-induced malondialdehyde levels, the elevation of ATP levels, and the suppression of autophagy-related Dynamic Protein-Related Protein 1 (DRP1) expression in H9C2 cells were achieved through the activation of the AMP-activated protein kinase (AMPK) signaling pathway. Liang et al. [35] effectively alleviated apoptosis, oxidative stress injury and fibrosis caused by myocardial ischemia by down-regulating the transforming growth factor-β1 signaling pathway.

Mitochondrial damage mechanism

ROS/RNS burst

The mitochondria, as the powerhouse of the cell, are central to ATP production via OXPHOS, but they also serve as a primary source of ROS. In healthy myocardium, ROS are highly reactive molecules that are by-products of various metabolic processes, especially mitochondrial respiration, and their concentration is tightly controlled by superoxide dismutase at low steady-state levels. Under normal physiological conditions, ROS play a role in cell signaling and homeostasis; however, excessive ROS production can lead to oxidative stress, which is implicated in various pathological conditions, including cardiovascular diseases. Oxidative stress is typically linked to elevated levels of ROS or reactive nitrogen species (RNS) at the cellular and subcellular levels. Studies have shown that mitochondrial dysfunction, characterized by impaired ETC activity, can exacerbate ROS generation, leading to cellular damage and apoptosis [36]. Furthermore, the accumulation of ROS can damage mitochondrial components, including lipids, proteins, and DNA, thereby compromising mitochondrial integrity and function [37]. This damage can create a vicious cycle, as dysfunctional mitochondria may produce even more ROS, contributing to the progression of diseases such as HF and IRI [38].

RNS, including nitric oxide (NO) and peroxynitrite, play significant roles in cellular signaling and the regulation of various physiological functions. One of the most extensively studied triggers of mitochondrial damage is NO, an RNS produced by inducible nitric oxide synthase (iNOS) [39]. It is possible to convert NO into other RNS, including nitrite and NO_2. Under pathological conditions, the excessive production of RNS can lead to nitrosative stress, which is detrimental to myocardial health. RNS are known to interact with ROS, leading to the formation of more reactive and damaging species, such as peroxynitrite, which can modify proteins and lipids, resulting in cellular dysfunction and apoptosis [40]. In the context of myocardial injury, RNS have been implicated in various mechanisms, including inflammation, endothelial dysfunction, and impaired myocardial contractility. For instance, increased levels of NO can lead to vasodilation and reduced myocardial oxygen consumption in healthy hearts; however, in the setting of HF or myocardial ischemia, this can result in detrimental effects due to altered hemodynamics and increased oxidative stress [41]. Moreover, studies have indicated that RNS can exacerbate oxidative stress by promoting mitochondrial dysfunction and apoptosis in cardiac myocytes, thus contributing to the progression of MI/RI [42].

Mitochondrial dynamics

The regulation of mitochondrial fusion and fission is mediated by a network of proteins that include mitofusins and optic atrophy 1 (OPA1) for fusion, and DRP1 for fission (Fig. 1.a and 1.b). The interplay between these proteins is essential for maintaining mitochondrial morphology and function. In AMI, these dynamics regulators exhibit disease-specific alterations: MFN2 expression is markedly reduced in ischemic myocardium, impairing mitochondrial fusion capacity and exacerbating mitochondrial fragmentation [43]. Concurrently, OPA1 undergoes proteolytic cleavage during AMI, resulting in cristae instability and cytochrome c release, a critical step in apoptosis initiation [44]. Conversely, elevated oxidative stress during AMI predominantly increases Drp1 expression and promotes mitochondrial fission. This process is associated with mitochondrial dysfunction and cardiomyocyte apoptosis [45].

Therapeutic interventions targeting these proteins show AMI-specific effects: MFN2 overexpression preserves mitochondrial networks and reduces infarct area in murine models [46], while the DRP1 inhibitor Mdivi-1 attenuates mitochondrial fission and improves left ventricular ejection fraction [47]. The mitochondria-targeted peptide SS-31 stabilizes OPA1 oligomers, preventing cristae disassembly and mPTP opening. In ex vivo rat hearts, SS-31 reduces lactate dehydrogenase release during reperfusion injury [48]. These findings underscore the central role of mitochondrial dynamics proteins in AMI pathophysiology and their potential as therapeutic targets.

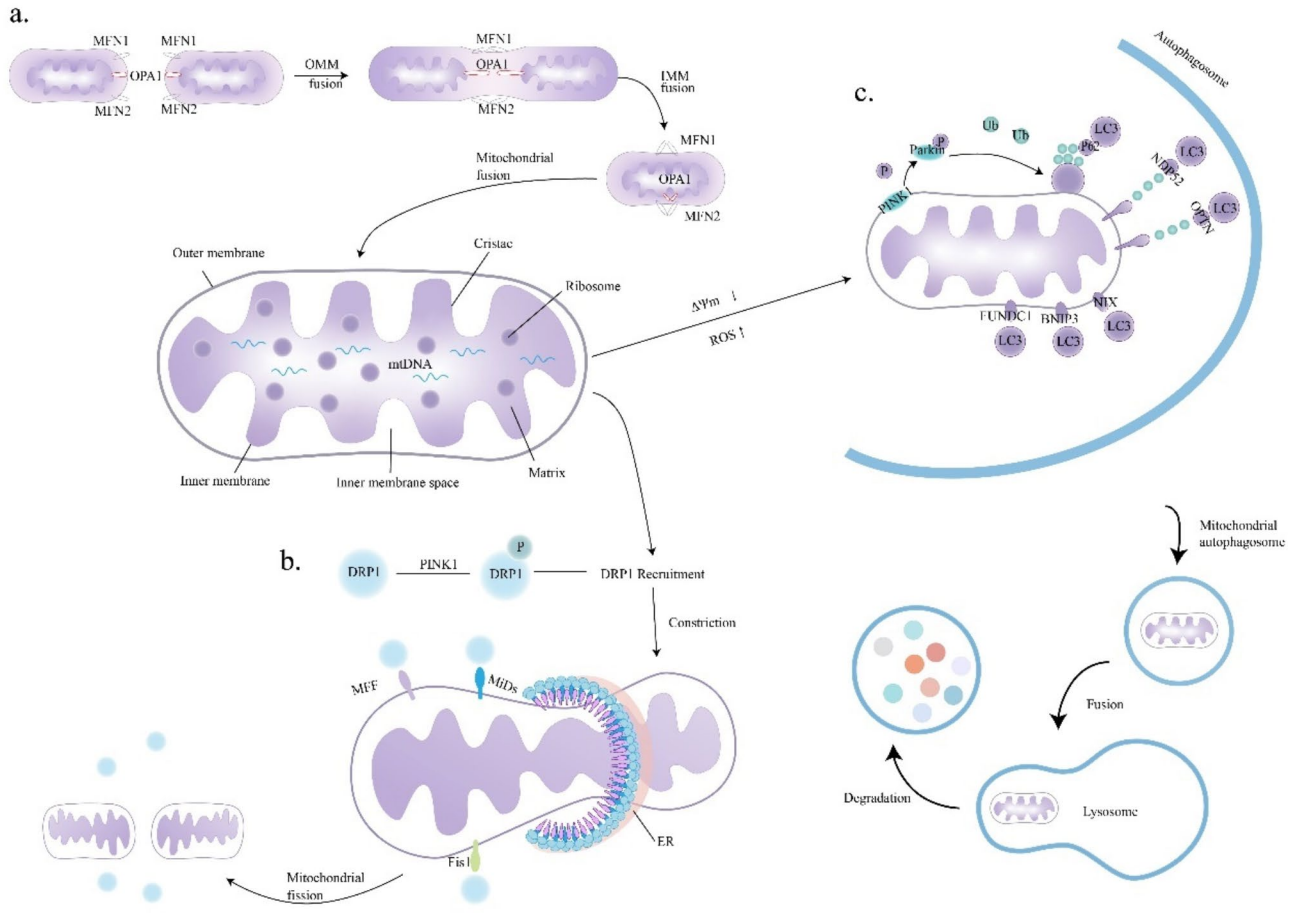

Fig. 1 Mitochondrial dynamics and the mitophagy pathway

Mitophagy

Mitophagy represents a specialized form of autophagy, whereby damaged mitochondria are selectively degraded (Fig. 1.c). Autophagy is a vital cellular process responsible for the degradation and recycling of cellular components, allowing cells to maintain homeostasis and adapt to stress. The basic mechanism of autophagy involves the formation of double-membrane structures known as autophagosomes, which engulf damaged organelles, proteins, and other cellular debris. These autophagosomes then fuse with lysosomes, where their contents are degraded by lysosomal enzymes. This process is regulated by various signaling pathways, including the mammalian target of rapamycin (mTOR) pathway, which senses nutrient availability and energy status, and the AMPK pathway, which responds to low energy levels. In the context of mitophagy, a selective form of autophagy, the degradation of dysfunctional mitochondria is critical for maintaining mitochondrial quality and function. Recent studies have highlighted the role of specific proteins such as PTEN-induced kinase 1 (PINK1) and Parkin in mitophagy, where PINK1 accumulates on damaged mitochondria, recruiting Parkin to initiate the autophagic process [49]. PINK1 protein is highly expressed in the myocardium [50] and plays a pivotal role in initiating mitochondrial quality control. Under physiological conditions, PINK1 is continuously imported into healthy mitochondria and degraded by PARL protease. However, during mitochondrial depolarization, PINK1 accumulates on the outer mitochondrial membrane, creating binding sites for Parkin recruitment [51]. This PINK1/Parkin signaling axis promotes ubiquitination of mitochondrial outer membrane proteins, ultimately triggering selective autophagic clearance of damaged mitochondria through interaction with autophagy receptors like OPTN and NDP52. This selective degradation is crucial not only for cellular health but also for preventing the accumulation of damaged mitochondria that can lead to cell death and various diseases, including neurodegenerative disorders and cancer [52].

Mitophagy plays a significant role in cardiac protection, particularly in the context of IRI, in which the heart is temporarily deprived of blood supply and then restored, leading to oxidative stress and mitochondrial dysfunction. Mitophagy helps to mitigate these effects by selectively removing damaged mitochondria, thereby

preventing the release of pro-apoptotic factors that can trigger cell death. It was demonstrated that the early inhibition of mitophagy may result in the accumulation of dysfunctional mitochondria and an enhancement of bacterial defense mechanisms [53]. Conversely, the late activation of mitophagy represents a cellular response aimed at attenuating inflammation and restoring host homeostasis. Augmented autophagy markedly enhanced cardiac function and diminished infarct size following ischemic events. For instance, the activation of pathways involving Bcl-2 interacting protein 3 (BNIP3) and Hypoxia-inducible factor 1-alpha has been demonstrated to promote mitophagy and protect against MI/RI [54]. AMPK functions as a regulator of autophagy, positively influencing mitochondrial clearance through the activation of UNC-51-like autophagy-activated kinase 1 [55]. It has been demonstrated that toll-like receptor 9 signaling can impede the activation of AMPK in neutrophils and macrophages. It can thus be postulated that a lack of AMPK activation may be a contributory factor in the accumulation of damaged mitochondria in AMI. The interplay between mitophagy and other cellular processes, such as inflammation and apoptosis, further underscores its importance in maintaining cardiac health [56]. Thus, targeting mitophagy may represent a promising strategy for developing novel therapies aimed at improving outcomes in various cardiovascular diseases.

(a) The process of mitochondrial fusion is divided into the fusion of OMM and the fusion of IMM. Fusion of OMM is mediated by MFN1/2 and fusion of IMM is mediated by OPA1. Mitochondrial fusion allows contents to be exchanged between different mitochondria. (b) There are three main steps in mitochondrial division: (1) Drp1 undergoes phosphorylation; (2) Drp1 is recruited from the cytoplasm to the OMM by interacting with Drp1 receptors including fission protein 1 (Fis1), mitochondrial fission factor (Mff) and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51); (3) Drp1 assembles into a ring-like structure that surrounds and compresses the mitochondria, consuming GTP and generating two separate organelles, a process mediated by the ER. c. One of the most well-defined mechanisms of mitochondrial autophagy is the PINK1/Parkin pathway, which is a ubiquitin-dependent pathway. c. One of the most well-defined mechanisms of mitophagy is the PINK1/Parkin pathway, which is a ubiquitin-dependent pathway. In the event of a loss of $\Delta\Psi m$ or an increase in ROS, PINK1 is targeted to the OMM, where it recruits and activates Parkin. Parkin then proceeds to ubiquitinate mitochondrial surface proteins, thereby signaling to the autophagosome for junctional proteins, including P62, Optineurin (OPTN), calcium-binding and coiled-coil domain-containing protein 2 (NDP52), and others. Reattachment of the ubiquitin chain to microtubule-associated protein 1 light chain 3 (LC3) on phagophores plays a role. Alternatively, damaged mitochondria can be eliminated through other autophagic pathways, specifically those that are non-ubiquitin-dependent. Some mitochondrial receptor proteins (or lipids), such as FUN14 domain containing 1 (FUNDC1), BCL2-interacting protein 3 (BNIP3), and Nip3-like protein X (NIX), have the capacity to recruit phagocytic membranes independently of ubiquitin. Mitochondria are wrapped by autophagosomes to form mitochondrial autophagosomes, which eventually fuse with lysosomes to degrade and recycle mitochondria.

Mitochondrial membrane permeabilization

MMP is a critical event in cellular apoptosis and is characterized by the disruption of the mitochondrial membrane integrity, leading to the release of pro-apoptotic factors such as cyt c into the cytosol. The mechanisms underlying MMP are complex and involve various proteins and pathways. Three principal mechanisms involved in pore formation during AMI are mitochondrial permeability transition (MPT), mitochondrial outer membrane permeabilization (MOMP), and more recently characterized gasdermins-mediated mitochondrial membrane opening. (Fig. 2)

A pivotal regulatory event during cell necrosis is the opening of the mPTP, a protein complex hypothesized to span both the inner and outer mitochondrial membranes, thereby promoting loss of endosomal potential, swelling and eventual rupture of the organelle. Permeability transition pore (PTP) is formed by the interaction of several mitochondrial proteins, including the voltage-dependent anion channel (VDAC), adenine nucleotide translocator (ANT), and cyclophilin D. These proteins facilitate the opening of the PTP in response to various stress signals, such as increased calcium levels and oxidative stress, ultimately resulting in mitochondrial depolarization and loss of ATP production [57, 58]. The results of preliminary studies indicate that calcium and ROS are potent activators of PTP. The pharmacological inhibition of MPT by cyclosporin A (CsA) has been demonstrated to significantly attenuate the release of mtDNA and mitochondrial dysfunction. A number of studies have demonstrated that CsA is effective in reducing infarct size following I/R, even when the drug infusion is initiated after the onset of an ischemic episode [59, 60]. In a mouse model, Zhang et al. [61] demonstrated that the up-regulation of microRNA-325-3p resulted in the inhibition of the Receptor-interacting protein kinase 3 (RIPK3)- calcium/calmodulin-dependent protein kinase II-mPTP signaling pathway, preventing the subsequent necrosis and progression of AMI.

The classical function of the pro-cell death Bcl-2 family proteins Bcl-2-associated X protein (BAX) and Bcl-2

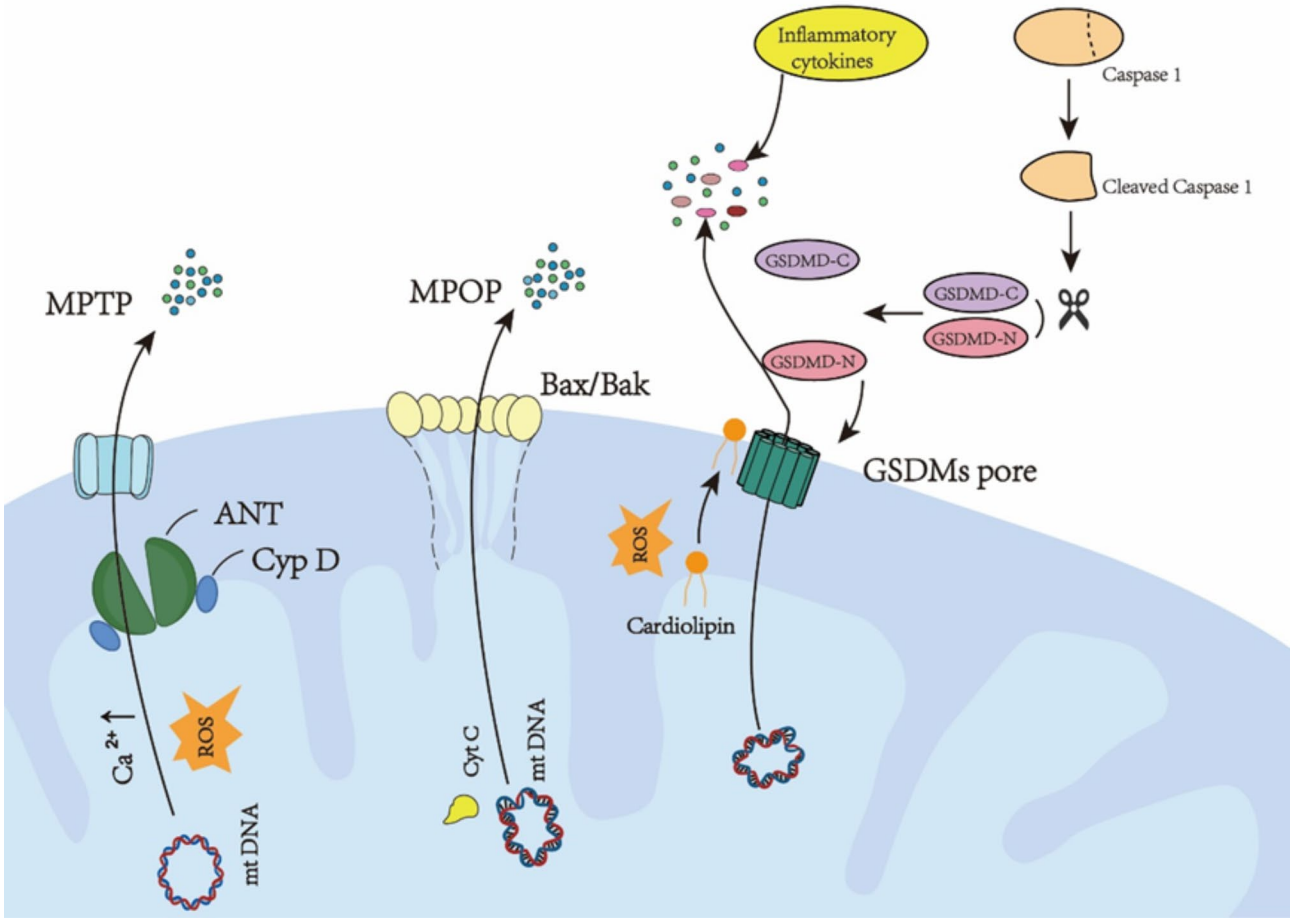

Fig. 2 Mechanisms of mitochondrial membrane permeabilization in AMI

homologous antagonist/killer (BAK) is to mediate the permeabilization of the outer mitochondrial membrane during apoptosis, resulting in the release of apoptogens. The Bax/Bak proteins facilitate the formation of extensive pores, which permit the release of cyt c and the subsequent activation of the caspase cascade [62]. The role of pro-apoptotic proteins like Bax and Bak has been extensively studied, as their oligomerization on the outer mitochondrial membrane is crucial for pore formation and subsequent membrane permeabilization [63]. The findings of Hochhauser et al. that Bax knockout mouse hearts exhibit reduced infarct size and improved myocardial function after permanent coronary artery occlusion provide further evidence that inhibition of BAX-induced apoptosis leads to an improved prognosis in MI. Ishikita et al. [64] demonstrated that nanoparticle-mediated delivery of mitochondrial division inhibitor 1 to the myocardium protects the heart from IRI by inhibiting mitochondrial outer membrane permeability.

Gasdermin D (GSDMD), a key participant in the immune response, is a cytoplasmic protein that contains the cleavage site for inflammatory caspases and acts as a substrate for caspase-1, which plays a very important role in the process of cellular pyroptosis [65]. Subsequently, GSDMD, releasing the active N-terminal fragment. It rapidly disrupt the mitochondrial IMM and OMM, resulting in a reduction in mitochondrial population, mitophagy, ROS, loss of transmembrane potential, attenuated OXPHOS and the release of mitochondrial proteins and DNA from the matrix and intermembrane space [66, 67]. Recent findings indicate that GSDMD targets the mitochondrial membrane, representing a novel pathway for mitochondrial permeabilization [68]. GSDMD has been demonstrated to cause rapid, cardiolipin-dependent mitochondrial disruption. This is due to the fact that ROS facilitate the externalization of cardiolipin from the IMM to the OMM, which provides an explanation for the accumulation of GSDMD-N on the OMM, given that under normal conditions, cardiolipin is predominantly located in the IMM [69].

The formation of the mitochondrial membrane pore in AMI is a complex process that involves three main mechanisms. The opening of the MPTP represents a pivotal regulatory event during the process of cell necrosis. MPTP is a protein conformer that spans the inner and outer mitochondrial membranes. The PTP is comprised

of multiple mitochondrial proteins, including the VDAC, ANT, and cyclophilin D(Cyp D). These proteins facilitate the opening of the PTP in response to a multitude of stress signals, such as elevated calcium levels and ROS. These proteins facilitate the activation of PTP in response to a variety of stress signals, including elevated calcium levels and ROS. MOMP is mediated by the Bcl-2 family Bax/Bak. The formation of larger pores by Bax/Bak permits the IMM to protrude into the cytoplasmic lysate, thereby facilitating the release of cyt c and the escape of other mitochondrial matrix contents. GSDMD is a cytoplasmic protein that is cleaved by activated caspase1 to release the active N-terminal fragment of GSDMD, The resulting GSDMD-N rapidly disrupts both the inner and outer mitochondrial membranes, representing a novel pathway for mitochondrial membrane permeabilization. In addition, ROS promote the externalization of cardiolipin from IMM to OMM, mediating the formation of mitochondrial pores.

Epigenetic regulation of mitochondrial homeostasis

During AMI, epigenetic mechanisms dynamically regulate mitochondrial homeostasis through a three-dimensional regulatory network, and their role runs through the entire process of mitochondrial dynamics, remodeling, quality control, and inflammatory response. DNMT3A-mediated hypermethylation of the MFN2 promoter suppresses mitochondrial fusion by reducing MFN2 expression, while simultaneously promoting DRP1-dependent fission, a process reversible through DNA methyltransferase inhibition with decitabine [70].

The binding of BRD4 to the DRP1 enhancer region of H3K27 acetylation has been demonstrated to enhance transcriptional activity. Meanwhile, SIRT2-mediated deacetylation of H3K18 has been shown to directly inhibit Parkin promoter activity, leading to the accumulation of the mitochondrial autophagy receptor protein PINK1 and the impediment of damaged mitochondrial clearance [71]. This epigenetic coordination extends to the non-coding RNA network, where multiple long-stranded non-coding RNAs regulate myocardial infarction pathological processes through a competitive endogenous RNA mechanism. PVT1 attenuates cellular charring by inhibiting the TLR4/NF-κB/NLRP3 inflammatory pathway through adsorption of miR-181a [72], XIST promotes apoptosis and inflammatory factor release by targeting miR-340-5p, and regulates the Bax/Bcl-2/caspase-3 pathway to promote apoptosis and inflammatory factor release [73].

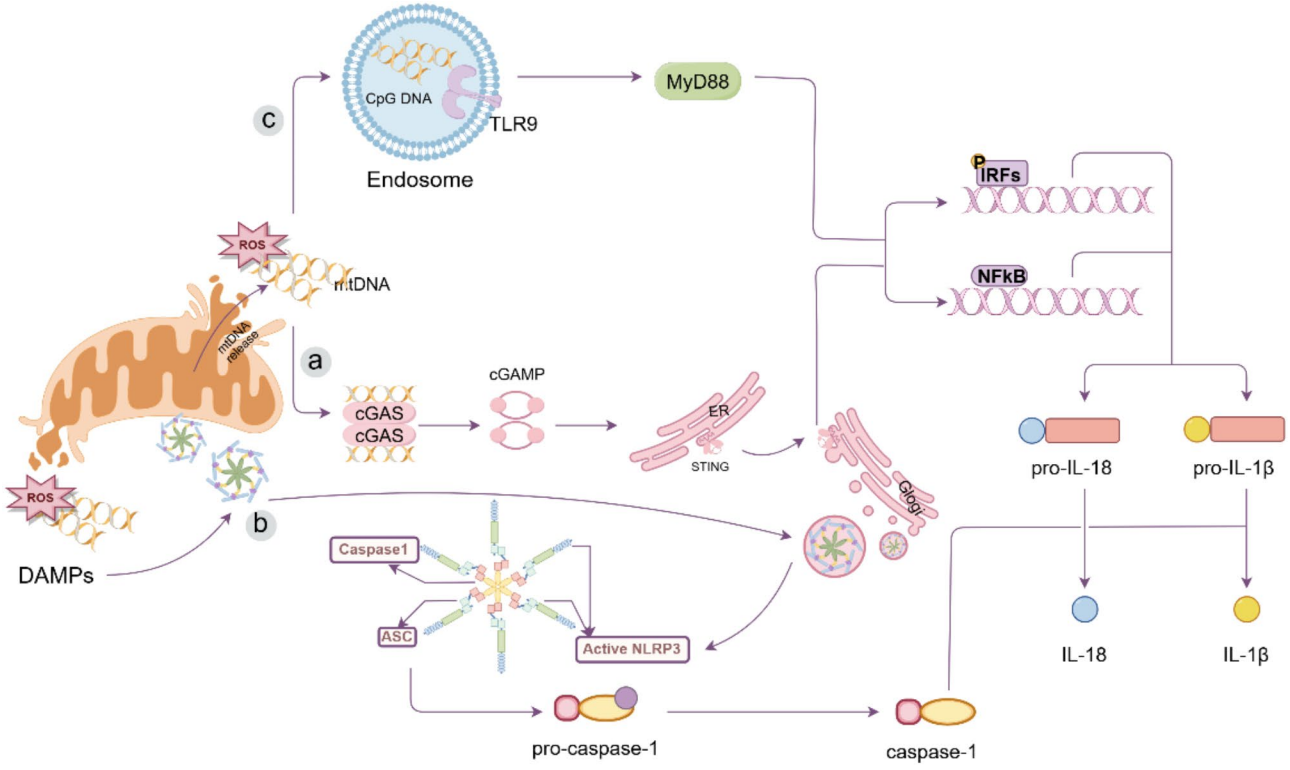

Fig. 3 Mitochondria regulate inflammatory pathways during AMI

Damaged mitochondria are potent triggers of immune respons

Mitochondrial-mediated inflammatory pathways

cGAS-STING pathway activation

The cGAS-STING pathway is mitochondria-regulated inflammatory pathway (Fig. 3.a). cGAS is a cellular DNA monitor that activates the innate immune response by detecting double-stranded DNA (dsDNA) and forming dimers [74]. Subsequently, cGAS utilizes ATP and GTP to facilitate the synthesis of the second messenger cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) [75]. The innate immune macromolecule STING is expressed predominantly in the heart, spleen, peripheral leukocytes and kidney, where it functions as an articulator. STING is an endoplasmic reticulum (ER) membrane protein. In the resting state, STING neither directly performs its biological function nor directly recognizes DNA; instead, cGAMP in mammalian cells binds to activate its biological effects [76]. ER-resident STING proteins form a complex with cGAMP, which induces a conformational change in the C-terminal tail. TANK-binding kinase 1 (TBK1) is recruited into STING, where it is phosphorylated by the transcription factor interferon regulatory factor 3 (IRF3), triggering transcription of IFN-I and other pro-inflammatory cytokines [77]. STING also upregulates inflammatory cytokines and chemokines through activation of inhibitor of kappa B kinase, which phosphorylates and inactivates the inhibitor of kappa B kinase family of inhibitors of the transcription factor NF-kB [78]. Huang et al. [79] determined that pore-forming GSDMD releases mtDNA into the cytoplasmic lysate and activates the DNA-sensing cGAS-STING pathway during inflammatory injury. This pathway not only enhances the inflammatory response but also impedes the supplementary functions of endothelial cell proliferation and vascular repair. King et al. [80] demonstrated that mice lacking IRF3 or the type I interferon receptor exhibited a higher survival rate following MI compared to control subjects. This finding suggests that this signaling pathway may be a suitable target for therapeutic intervention in MI patients.

During programmed cell death, the pro-apoptotic proteins BAX and BAK are activated, leading to OMM permeabilization. This allows pro-apoptotic molecules to move from the inner membrane space into the cytoplasmic lysate, where they can initiate the caspase cascade reaction leading to rapid cell death [81]. White et al. and Rongvaux et al. [82] showed that Bak- and Bax-mediated mitochondrial damage results in the release of mtDNA, which triggers the cGAS/STING-mediated cytoplasmic DNA sensing pathway. It was shown that in the absence of apoptotic caspase activation, mtDNA activates cGAS, leading to slightly elevated levels of IFN-β protein in the blood. This supports the idea that caspases inhibit immune response during cell death. Activation of the cGAS-STING pathway results in the activation of numerous downstream signaling cascades. The principal pathways encompass the activation of NF-κB and IRF3, which facilitate the production of type I interferons and other pro-inflammatory cytokines, thereby ensuring an efficacious immune response to pathogens.

During MI, mitochondrial damage and the release of mtDNA into the cytoplasm serve as potent activators of the cGAS-STING pathway. The hypoxic and oxidative stress conditions in the infarcted myocardium lead to mPTP opening and the release of mtDNA. This mtDNA is recognized by cGAS, triggering the activation of the cGAS-STING pathway. In addition to mediating inflammatory responses, this signaling pathway has been linked to a number of other pathological processes, including cardiac remodeling, insulin resistance, left ventricular dysfunction and ageing. Therefore, identifying the chronic activation of downstream STING signaling and targeting the cGAS-STING pathway can effectively control the persistent damage of inflammation on cardiomyocytes after AMI.

The persistent activation of the cGAS-STING pathway can lead to detrimental effects, including prolonged inflammation and cardiac dysfunction. Studies have found that excessive production of IFN-I and pro-inflammatory cytokines post-MI correlates with worse cardiac remodeling, increased risk of HF, and poor long-term survival outcomes. The chronic inflammatory state induced by cGAS-STING might ultimately lead to cardiomyocyte death and fibrosis, which compromises heart function.

NLRP3 inflammasome pathway

An alternative pathway for mitochondrial regulation of the innate immune system is the NLRP3 inflammasome signaling (Fig. 3.b). As a signaling cascade reaction, it can be separated and defined by three typical components: sensor, adaptor and effector [83]. These roles are played by NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the effector protein caspase-1, respectively. NLRP3 contains an N-terminal pyrin structural domain (PYD), a central nucleotide binding or oligomerization domain, and a C-terminal leucine-rich repeat (LRR) motif. NLRP3, a member of the NLR family, is activated by a diverse range of stimuli, including PAMPs and DAMPs [84]. Upon recognition of these signals, NLRP3 undergoes a conformational change that facilitates its oligomerization and the recruitment of ASC, which subsequently activates pro-caspase-1. Active caspase-1 is the prototypical inflammatory caspase, formed by cleavage of pro-caspase-1, which breaks down pro-IL-1β and pro-IL-18 into their

active forms, leading to the secretion of these potent pro-inflammatory cytokines.

It is widely believed that NLRP3 inflammasome activation requires two signals: (1) priming the NLRP3 inflammasome: signal I activates the transcription factor NF-κB, followed by up-regulation of NLRP3 and pro-IL-1β in response to activation of transcription-modulating PRRs, such as TLRs, or of proinflammatory cytokine receptors; (2) activating the NLRP3 inflammasome: signal II triggers the assembly and activation of the NLRP3 inflammasome [85]. For example, ethanol (Signal I) activates the NLRP3 inflammasome in glial cells by inducing increased NLRP3 expression and TLR4-dependent pro-IL-1β production, as well as mitochondrial ROS formation (Signal II) to trigger caspase-1 maturation and IL-1β secretion [86].

Activation of NLRP3 is induced by a wide variety of stimuli, including ATP, K^+ ionophores, nigericin, heme, monosodium urate, bacterial, fungal toxins and viruses [87–89]. It appears that NLRP3 is capable of sensing common cellular events that are triggered by activating stimuli. These cell signaling events include K^+ efflux (decrease in intracellular K^+ concentration), increase in intracellular Ca^{2+}, Na^+ influx and Cl^- efflux, lysosomal damage, and ROS production [90, 91]. For instance, mtDNA released into the cytosol can directly activate NLRP3, linking metabolic disturbances to inflammatory responses [92]. Additionally, the role of specific proteins, such as NIMA related kinase 7, has been identified as critical for the assembly of the NLRP3 inflammasome, indicating that the interaction between NLRP3 and other cellular components is essential for its activation [93]. Furthermore, the involvement of G protein subunits has been highlighted, where the β1 subunit negatively regulates NLRP3 activation, suggesting a delicate balance in the regulation of inflammasome activity [94].

NLRP3 has multiple roles in the immune response. By activating inflammasome, NLRP3 promotes the production of IL-1β and IL-18, cytokines important in the regulation of innate and adaptive immunity. For example, deletion of NLRP3 was found to attenuate metabolic disturbances induced by a high-fat diet, suggesting a potential role for NLRP3 in metabolic diseases [95]. In addition, NLRP3 is involved in the inflammatory response in neurodegenerative diseases, and its activation is closely linked to the development of the disease [96]. In the tumor microenvironment, NLRP3 is also known to be a key factor in immune escape, influencing the immune response of tumors by regulating the expression of immune checkpoints [97]. Therefore, targeting the regulation of NLRP3 inflammasome not only helps to understand its role in pathophysiology, but also provides new targets for the treatment of related diseases [98].

Its activation is particularly significant during the processes of MI/RI, where the restoration of blood flow can paradoxically lead to further myocardial injury. The mechanism of NLRP3 activation during MI/RI involves several steps, primarily triggered by the release of DAMPs and the production of ROS. The inflammatory response mediated by NLRP3 is exacerbated by mitochondrial dysfunction, where mtDNA released into the cytosol acts as a potent activator of the inflammasome, thereby enhancing the inflammatory cascade and contributing to myocardial damage [99]. The formation of the NLRP3 inflammasome in cardiomyocytes results in the processing and release of IL-1β and IL-18, prominent pro-inflammatory cytokines involved in the inflammatory cascade. The subsequent reperfusion phase often results in a surge of inflammatory mediators that can further enhance NLRP3 activation. Recent studies have shown that pharmacological agents targeting NLRP3 can significantly reduce infarct size and improve cardiac function after reperfusion [100].

Cytokines and danger signals are pivotal in modulating NLRP3 inflammasome activation duringMI. Pro-inflammatory cytokines such as IL-1β and IL-18, which are released upon NLRP3 activation, not only propagate inflammation but also create a feedback loop that enhances NLRP3 activation itself [101]. Furthermore, the presence of danger signals, including mtDNA and heat shock proteins, can prime the NLRP3 inflammasome, making it more responsive to subsequent stimuli. For instance, insulin has been shown to reduce pyroptosis and inflammation by downregulating NLRP3 activation, indicating that metabolic signals can influence inflammasome activity [102].

Activation of NLRP3 leads to the maturation and release of pro-inflammatory cytokines such as IL-1β and IL-18, which can induce apoptotic pathways in cardiomyocytes. For instance, studies have shown that NLRP3 inflammasome activation contributes to doxorubicin-induced cardiomyocyte senescence and apoptosis, highlighting its role in drug-induced cardiac toxicity [103]. Moreover, the inflammatory signaling mediated by NLRP3 can exacerbate ischemic conditions, leading to increased apoptosis during MI/RI [104]. The interplay between NLRP3 activation and apoptosis is further evidenced by findings that inhibiting NLRP3 can significantly reduce apoptotic cell death in models of cardiac stress. Thus, targeting the NLRP3 inflammasome may provide a therapeutic avenue to mitigate cardiomyocyte apoptosis and improve cardiac outcomes in various pathological settings.

TLR9 pathway activation

In recent years, the role of TLR9 in MI has garnered increasing attention (Fig. 3.c). TLR9 not only plays a critical role in the immune system but also mediates inflammatory responses through mitochondria, impacting the

survival and function of cardiomyocytes. TLR9 is also involved in the recognition of mtDNA. TLR9 is expressed predominantly in immune cells and recognizes unmethylated CpG motifs (consisting of a central cytosine-guanine dinucleotide and flanking regions) in bacterial and viral DNA, whereas unmethylated CpG DNA is usually released in response to cellular injury, including MI [105].

Structurally, TLR9 is a type I transmembrane protein characterized by an extracellular domain rich in LRRs that facilitate the binding of its ligands, primarily unmethylated CpG DNA motifs found in bacterial and viral genomes. The LRRs are crucial for the TLR9's ability to distinguish between self and non-self nucleic acids, a function that is essential in preventing autoimmunity while mounting an effective immune response against pathogens [106]. Upon ligand binding, TLR9 undergoes a conformational change that initiates intracellular signaling cascades, primarily through the myeloid differentiation primary response gene 88 (MyD88)-dependent pathway, leading to the activation of various transcription factors, including NF-κB and IRF7, which are pivotal in the expression of pro-inflammatory cytokines and IFN-I [107]. Furthermore, TLR9's intracellular localization within endosomal compartments is critical for its activation, as it needs to encounter its ligand in a specific environment conducive to signaling [108]. This unique structural and functional configuration underscores TLR9's role as a key sensor of microbial DNA, linking innate and adaptive immunity.

TLR9 plays a multifaceted role in orchestrating the immune response, particularly in recognizing and responding to DNA from pathogens. Upon activation by its ligands, TLR9 triggers a cascade of signaling events that culminate in the production of cytokines and chemokines, which are essential for recruiting and activating immune cells such as dendritic cells, B cells, and macrophages [109]. TLR9-mediated signaling enhances antigen presentation and promotes B cell differentiation into antibody-secreting plasma cells [110]. In addition, TLR9's involvement in autoimmune disorders highlights its dual role, where excessive activation can lead to tissue damage and chronic inflammation [111]. Recent research also suggests that TLR9 may interact with other immune modulators, such as chemokines, to regulate immune tolerance and response [111]. Thus, TLR9 serves as a critical bridge between innate and adaptive immunity, with its precise regulation being vital for maintaining immune homeostasis and preventing disease.

In the endolysosomes, TLR9 recognizes and binds to CpG DNA motifs, leading to the recruitment of the adaptor protein MyD88. This activates downstream signaling pathways, including activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways and the production of pro-inflammatory cytokines such as IL-1β and tumor necrosis factor-α (TNF-α). Recent studies have highlighted the involvement of TLR9 in the activation of the NLRP3 inflammasome, which is crucial for the maturation and secretion of IL-1β in response to mtDNA released during cellular stress or injury. For instance, monosodium urate-induced mtDNA has been shown to activate TLR9, resulting in NLRP3 inflammasome activation and subsequent IL-1β production, underscoring the critical link between TLR9 signaling and mitochondrial stress responses. Recent research has indicated that TLR9 activation can significantly impact mitochondrial function. Upon activation, TLR9 can stimulate the release of mtDNA into the cytosol, which can further activate inflammatory pathways, including the NLRP3 inflammasome [112]. This interaction not only highlights the role of mtDNA as a signaling molecule but also suggests that TLR9 serves as a bridge between immune signaling and mitochondrial dynamics. Additionally, TLR9 activation has been associated with mitochondrial dysfunction, characterized by altered MMP and increased ROS production, which can exacerbate cellular damage and apoptosis [113].

TLR9 plays a critical role in the immune response following MI. In the setting of MI, TLR9 can be activated by necrotic cell debris, including dsDNA released from dying cardiomyocytes and damaged mitochondria. These DAMPs can trigger TLR9 signaling pathways in various immune cells, such as macrophages. This recognition leads to a pro-inflammatory response that can either exacerbate myocardial damage or promote tissue repair, depending on the circumstances. In the context of diseases such as MI/RI, TLR9 ablation has been shown to reduce mitochondrial damage and improve cell survival, indicating that TLR9 activation might contribute to mitochondrial dysfunction during pathological conditions [114]. Once activated, TLR9 signaling leads to the induction of NF-κB and IRF pathways, resulting in the transcription of various inflammatory mediators, including cytokines, chemokines, and other factors that facilitate an immune response. This activation not only recruits more immune cells to the site but also amplifies the inflammatory response, promoting further myocardial injury and dysfunction.

PRRs recognize PAMPs and DAMPs in microorganisms and regulate inflammatory signaling through three pathways.

a. Mitochondria regulate the cGAS-STING signaling pathway. cGAS is activated by and binds to mtDNA, leading to the synthesis of cGAMP. cGAMP induces conformational changes in STING proteins, which are activated on the ER. Once activated, STING translocates to the Golgi apparatus, which in turn regulates the activity of IRF3 and NF-κB. This

then initiates the production of proinflammatory cytokines, which are essential for mounting an effective immune response to the pathogen.

b. Mitochondrial activation of NLRP3 inflammasome. The release of DAMPs such as ROS and mtDNA from injured mitochondria promotes the activation of NLRP3 inflammasome. the NLRP3 protein is first translocated to the mitochondria, where it is redistributed to the Golgi in the form of an oligomeric cage. Subsequently, NLRP3 is translocated to the microtubule-organizing center (MTOC) and reorganized, acquiring the designation of NLRP3 inflammasome. NLRP3 is then separated and defined by three typical components: the NLRP3, ASC, and caspase-1. Activation of NLRP3 inflammasome results in the activation of pro-caspase-1. Active caspase-1 is the prototypical inflammatory caspase, formed by the cleavage of pro-caspase-1, which then catabolizes pro-IL-1β and pro-IL-18 into their active forms.

c. Mitochondrial activation of inflammatory pathways via TLR9. mtDNA exhibits structural similarities to bacterial DNA, which enables its recognition by TLR9. TLR9 is capable of recognizing unmethylated CpG motifs present in both bacterial and viral DNA, subsequently binding within the endosome. Upon ligand binding, TLR9 undergoes a constitutive change that initiates an intracellular signaling cascade, primarily through a MyD88-dependent pathway. This leads to the activation of various transcription factors (including IRF3 and NF-κB), which regulate the inflammatory response.

Mechanisms of myocardial cell death involving mitochondria

Mitochondrial dysfunction is intricately linked to various cell death pathways in cardiomyocytes during MI/RI. The primary forms of cell death observed include pyroptosis, apoptosis, autophagy, necroptosis, ferroptosis and cuproptosis, each characterized by distinct biochemical pathways. Mitochondria serve as central regulators of apoptosis through the release of cyt c and activation of caspases, which lead to programmed cell death [115]. In contrast, necrosis is often associated with severe mitochondrial damage and loss of membrane integrity, resulting in cell lysis and inflammation. Recent studies have highlighted the role of ferroptosis, a form of regulated necrosis driven by iron-dependent lipid peroxidation, in exacerbating myocardial injury during I/R [116]. Understanding these mechanisms is crucial for developing targeted therapies aimed at mitigating mitochondrial dysfunction and preventing cardiomyocyte death, thereby improving outcomes in patients with AMI.

Pyroptosis

Pyroptotic death occurs in a relatively limited number of endothelial cells, yet it is still sufficient to mediate tissue and vascular damage. Indeed, it is the predominant mode of cell death following AMI. Pyroptosis is a form of programmed cell death that is characterized by the formation of pores in the cell membrane, leading to cell lysis and the release of pro-inflammatory cytokines. This process is mediated by gasdermin proteins, particularly GSDMD, which are activated by caspases in response to inflammatory signals [117]. Morphologically, pyroptosis differs from apoptosis in that it is characterized by the activation of inflammasome, cell swelling, rupture of the plasma membrane and subsequent loss of cytoplasmic content [118]. The most critical role of pyroptosis is to induce a robust inflammatory response to defend against intracellular pathogens. However, excessive cellular pyroptosis has been linked to a number of inflammatory diseases, including autoimmune disorders [66]. Pyroptosis is closely associated with the NLRP3 inflammasome-driven caspase-1 activation pathway [119].

Following AMI, the formation of ASC patches was observed in endothelial cells of the mouse heart, indicating that endothelial NLRP3 inflammasome may be involved [120]. NLRP3 inflammasome act as an upstream trigger for the activation of caspase 1, which in turn leads to the production of inflammatory cytokines and GSDMD-mediated cellular pyroptosis [121]. Moreover, GSDMD has been demonstrated to activate cGAS in endothelial cells through the release of mtDNA following LPS treatment [66]. The activation of the NLRP3 inflammasome in response to mitochondrial stress has been shown to facilitate pyroptosis in cardiomyocytes, thereby amplifying the inflammatory cascade and worsening myocardial injury [122]. Ventricular remodeling represents a pivotal step in the progression of MI to HF. Emerging evidence suggests that NLRP3 inflammasome also exert a significant influence on ventricular remodeling following MI [123].

Apoptosis

Apoptosis, or programmed cell death, is a crucial process that regulates cellular turnover and homeostasis, particularly in response to stressors such as MI. In the context of MI, endothelial cell apoptosis is particularly significant due to its role in vascular integrity and function. Endothelial cells are integral to maintaining vascular homeostasis, and their loss can result in impaired angiogenesis, increased vascular permeability, and exacerbation of ischemic damage. The apoptosis of these cells contributes to the inflammatory response observed post-MI, as dying cells release pro-inflammatory signals that can further damage surrounding tissues. The mechanisms underlying endothelial cell apoptosis in MI include

intrinsic and extrinsic pathways. The intrinsic pathway is primarily mediated by mitochondrial dysfunction, leading to the release of cyt c and subsequent activation of caspases, particularly caspase-9 and −3. This pathway is often triggered by oxidative stress and hypoxia, conditions prevalent during MI [124]. Conversely, the extrinsic pathway involves death receptors, such as TNF receptors, which upon ligand binding activate caspase-8, leading to apoptosis [125]. Recent studies have identified additional modulators of apoptosis, such as microRNA and long non-coding RNAs, which can either promote or inhibit apoptotic signaling in endothelial cells, highlighting the complexity of apoptotic regulation in the context of MI [126].

Several signaling pathways are implicated in the regulation of endothelial cell apoptosis during MI. The phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) pathway is one of the key survival pathways that counteracts apoptosis by promoting cell survival and growth. Activation of this pathway has been associated with reduced endothelial cell apoptosis and improved angiogenesis in the aftermath of MI [127]. Conversely, the MAPK pathway has been implicated in promoting apoptosis under stress conditions, including ischemia. Additionally, the role of ROS in mediating apoptosis through the activation of pro-apoptotic factors has been well-documented, emphasizing the need for oxidative stress management in MI [128]. Furthermore, recent findings suggest that exosome signaling may play a role in modulating apoptosis and promoting endothelial cell survival, indicating a potential therapeutic avenue for future research [129]. Understanding these signaling pathways will be crucial for developing targeted therapies aimed at mitigating endothelial cell apoptosis and improving outcomes in MI patients.

Autophagy

Autophagy is a crucial cellular process that facilitates the degradation and recycling of cytoplasmic components, thereby maintaining cellular homeostasis. It plays a significant role in various physiological and pathological processes, including development, immunity, and response to stress. Various factors influence endothelial autophagy, including shear stress, inflammatory cytokines, and growth factors. For example, shear stress has been shown to induce autophagy in endothelial cells, promoting their survival and function during ischemic conditions [130]. In the context of MI, autophagy is particularly important as it helps to remove damaged organelles and proteins, thus preventing cellular apoptosis and promoting cell survival. The dysregulation of autophagy has been implicated in the pathogenesis of various cardiovascular diseases. Recent studies have highlighted that upregulation of autophagy can protect cardiac cells from IRI, suggesting that therapeutic strategies aimed at modulating autophagic pathways may offer new avenues for MI treatment [131].

The relationship between autophagy and MI is complex and multifaceted. On one hand, autophagy can exert protective effects by removing damaged cellular components and promoting cell survival during ischemic events. For instance, studies have demonstrated that enhancing autophagy can improve cardiac function and reduce infarct size following myocardial ischemia [132]. Conversely, excessive autophagy may lead to cell death, indicating that a balanced autophagic response is crucial for cardiac health. Recent research has highlighted the role of specific signaling pathways in modulating autophagy during MI. For example, the PI3K/Akt pathway has been implicated in the regulation of autophagy and its protective effects against IRI [133]. Additionally, microRNAs have emerged as essential regulators of autophagy in endothelial cells; for instance, miR-204-5p facilitates atheroprotective communication between endothelial and smooth muscle cells through autophagy modulation [134].

Necroptosis

Necroptosis represents a form of programmed cell death that is activated when apoptosis is inhibited. It is characterized by cell swelling, loss of membrane integrity and, ultimately, the release of cellular contents into the extracellular space, which leads to the onset of inflammation. This process is typically mediated by the receptor-interacting protein kinases (RIPK1 and RIPK3), which form a necrosome complex that activates the mixed lineage kinase domain-like (MLKL) protein. Upon phosphorylation, it translocate to the plasma membrane, causing its rupture and subsequent necrotic cell death resulting in membrane rupture and subsequent necrotic cell death. This process promotes the release of DAMPs, which trigger the inflammatory response and the activation of cellular pyroptosis [79]. Additionally, the efflux of PAMPs triggers the inflammatory response in the context of cellular infection [135]. A number of innate immune signaling pathways, including those mediated by the activation of TLRs, death receptors and RLRs, have been demonstrated to induce necroptosis.

In the aftermath of an MI, necroptotic cell death can amplify the inflammatory response, leading to further cardiomyocyte loss and worsening ischemia. Studies have demonstrated that necroptosis is upregulated in the heart following IRI, suggesting that it plays a role in the pathophysiology of MI [136]. Moreover, the presence of necroptotic cells in the infarcted myocardium can trigger an immune response that may be detrimental, as the resulting inflammation can lead to adverse cardiac remodeling and HF. Necroptosis not only affects

cardiomyocytes but also significantly impacts endothelial cells. Research indicates that necroptosis in endothelial cells can lead to increased vascular permeability and inflammation, contributing to the progression of ischemia and subsequent reperfusion injury [137]. The release of pro-inflammatory cytokines and DAMPs from necrotic endothelial cells can further exacerbate the inflammatory response, worsening myocardial injury. For instance, studies have shown that necroptosis can induce endothelial dysfunction, which is characterized by impaired vasodilation and increased thrombosis risk [138].

Ferroptosis

Ferroptosis is a regulated form of cell death characterized by the accumulation of lipid peroxides to lethal levels, distinct from apoptosis and necrosis. Iron is involved in the mitochondrial OXPHOS process and its production of ROS and ATP [139]. When oxidation due to iron deposition exceeds the antioxidant capacity of the cell, intracellular oxidative stress occurs, causing direct or indirect damage to macromolecular proteins, nucleic acids and lipids, leading to cell damage and death. The key players in ferroptosis include the enzyme glutathione peroxidase 4 (GPX4), which protects cells from lipid peroxidation [140]. When GPX4 is inhibited or its expression is decreased, cells become susceptible to ferroptosis due to the inability to detoxify lipid peroxides effectively. The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is a key regulator of cellular antioxidant responses and plays a critical role in the 'NRF2-lipid peroxidation-iron death' axis implicated in iron death in a variety of diseases [141]. NRF2 has been demonstrated to downregulate heme oxygenase 1 (HO-1) by inhibiting iron death. HO-1 is responsible for the breakdown of heme into ferrous ions and certain inducible enzymes that promote lipid peroxidation [141].

Recent studies have highlighted that ferroptosis is particularly relevant in the context of MI, where oxidative stress is markedly elevated due to ischemia and reperfusion injury. For instance, the activation of the NRF2 signaling pathway has been shown to suppress ferroptosis in cardiomyocytes post-MI, indicating potential therapeutic avenues to mitigate heart damage by targeting this pathway [142]. The role of ferroptosis in MI has garnered significant attention due to its implications for cardiac tissue damage and recovery. Evidence suggests that ferroptosis occurs predominantly during the reperfusion phase rather than during ischemia itself, highlighting a critical window for therapeutic intervention [143]. Inhibition of ferroptosis has been shown to alleviate myocardial injury, with studies indicating that ferroptosis inhibitors can significantly reduce cell death and improve cardiac function post-infarction [144].

Cuproptosis

In 2022, Peter Tsvetkov and colleagues discovered a new type of Cu-induced cell death, distinct from apoptosis, necroptosis, pyroptosis and ferroptosis, and named it "Cu cell death". Normally, intracellular copper concentrations are relatively low. When cellular copper levels are elevated, excess copper ions bind to mitochondrial proteins, leading to protein lipoylation, membrane permeability, cell destruction and cell death [145]. It is primarily induced by the accumulation of copper ions within the cell, which leads to the binding of copper to lipoylated components of the TCA cycle, disrupting mitochondrial function and triggering cell death pathways. The mechanism involves the dysregulation of cellular copper homeostasis, which can result from both exogenous sources, such as environmental exposure, and endogenous factors, including metabolic disorders.

The role of cuproptosis in MI is an emerging area of research that highlights the potential impact of copper homeostasis on cardiac health. Elevated serum copper levels have been observed in patients with AMI, suggesting a link between copper metabolism and cardiac events [146]. The mechanisms underlying this association may involve copper's influence on mitochondrial function and its ability to induce cell death in cardiomyocytes, leading to increased myocardial injury during ischemic events. Recent studies have identified cuproptosis-related genes as potential biomarkers for ischemic cardiomyopathy, indicating that alterations in copper metabolism could serve as therapeutic targets for improving outcomes in MI patients [147]. However, how myocardial oxidative stress affects elevated copper ion levels during myocardial ischemia and the key targets remain to be demonstrated in further studies.

Mitochondrial targeting therapeutic strategies

As outlined in the critique, mitochondria serve an essential function in MI/RI. The significance of mitochondria in these biological mechanisms renders this organelle a compelling and promising candidate for the formulation of therapeutic strategies. Indeed, numerous studies have explored mitochondrial-targeted therapeutic approaches, emphasizing the utilization of antioxidants, mitochondrial-driven inhibitors of inflammation, and beyond (Table 1).

Application of antioxidants

Mitochondria are primary sites for ROS generation during cellular respiration, and excessive ROS can lead to mitochondrial dysfunction, contributing to various diseases, including neurodegenerative disorders and cancer. The role of antioxidants in mitigating mitochondrial oxidative stress has garnered significant attention in therapeutic strategies. Recent studies have highlighted

Table 1 Mitochondria-targeted therapeutic drugs and action targets

Compound	Target/Mechanism	Position of action
MitoQ	Targeted mitochondrial ROS clearance (Targeting the inner mitochondrial membrane, combined with CoQ10)	IMM
CoQ10	Antioxidant, supports ETC complex function	IMM
MitoVitE	Targeting mitochondrial lipid peroxidation (vitamin E derivatives)	IMM (lipid bilayer)
MitoTempol	Scavenging mitochondrial superoxide radicals (SOD mimetics)	mitochondrial matrix
NAD precursors	Promote the efficient operation of respiratory chain complexes and increase ATP production.	Cytoplasmic →mitochondrial association
MCC950	Inhibits NLRP3 inflammatory body assembly (blocks ATPase activity)	Cytoplasmic → mitochondrial association
OLT1177	Inhibition of caspase-1 activation and IL-1β release	Cytoplasmic → mitochondrial association
VX-765 (Belnacasan)	Inhibition of caspase-1 activation and IL-1β release	Cytoplasmic → mitochondrial association
Emricasan	Inhibition of caspase-1 and caspase-4 activation	Cytoplasmic → mitochondrial association
16673-34-0	Inhibition of caspase-1 activation	Cytoplasmic → mitochondrial association
Nitrofuran derivatives (C-176)	Inhibits STING palmitoylation, thereby inhibiting the activity of STING	Cytoplasm
H-151	Inhibit STING palmitoylation and block cGAS-STING signaling pathway	Cytoplasm
RU.521	Competitive inhibition of cGAS enzyme activity, reducing cGAMP synthesis	Cytoplasm
Amlexanox	Block TBK1-induced STING serine 366 check point phosphorylation and inhibit STING activation	Cytoplasm
antimalarials	Inhibits the TLR9 type I interferon pathway, reducing IL-6 release	Cytoplasm
Necrostatin	Inhibit RIPK1 and block necrotic apoptosis	Cytoplasmic → mitochondrial membrane permeability
Cyclosporine A	Inhibit mPTP opening and reduce mitochondrial swelling	IMM
SS-31	Stabilize the inner mitochondrial membrane structure (bind cardiolipin, inhibit cy c release)	Mitochondrial intima (cardiolipin binding)
Urolithin A	Activates mitochondrial autophagy (via the PINK1/Parkin pathway)	mitochondrial autophagosome
Metformin	Activate AMPK pathway, inhibit mTOR, and promote mitochondrial autophagy	Cytoplasmic → mitochondrial autophagy regulation

the potential of antioxidant therapies in preserving mitochondrial integrity and function.

Mitoquinol mesylate (MitoQ)

MitoquinoL mesylate (MitoQ) is a mitochondria-targeted antioxidant that exhibits selective activity towards species. It comprises a lipophilic triphenyl phosphonium cation linked to the ubiquinone antioxidant portion of Coenzyme Q_{10} (CoQ_{10}). MitoQ has been demonstrated to reduce mitochondrial oxidative stress by promoting autophagy and mitochondrial biogenesis, preventing impaired mitochondrial dynamics and increasing mitochondrial turnover. This ultimately leads to the attenuation of metabolic syndrome disorders, including obesity, insulin resistance, hypertension and cardiovascular disease [148]. MitoQ exerts its regulatory influence over mitochondrial homeostasis through the mediation of AMPK and its downstream signaling pathways, including mTOR, sirtuin 1, Nrf2 and NF-κB.

Studies indicate that MitoQ enhances mitochondrial function and reduces ROS generation, ultimately protecting cardiac cells from ischemic damage. For instance, MitoQ has been demonstrated to maintain mitochondrial homeostasis and improve cardiac function in models of IRI [149]. Additionally, MitoQ's ability to activate the Nrf2 pathway has been linked to improved antioxidant defense mechanisms, providing further rationale for its application in clinical settings involving myocardial injury [150].

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ_{10}), which is also known as ubiquinone, is a vital antioxidant within the mitochondrial ETC, playing a crucial role in cellular energy production. CoQ_{10} is a vitamin-like, fat-soluble molecule that has been demonstrated to possess antioxidant, anti-inflammatory and neuroprotective properties [151]. A number of studies have demonstrated that CoQ_{10} treatment has the effect of supporting mitochondrial function by enhancing the activity of the ETC, the level of MMP, and the synthesis of ATP. Furthermore, it has been shown to maintain cellular redox balance by activating antioxidant enzymes and reducing the expression of NOS, thereby inhibiting the production of ROS and RNS [152].

Its supplementation has been associated with improved cardiac function post-MI, particularly in patients with heart failure. Research suggests that CoQ_{10} supplementation can enhance energy metabolism and reduce oxidative stress, thereby mitigating myocardial damage during ischemic episodes. Furthermore, its dual

role in modulating inflammatory responses highlights its potential as a multifaceted therapeutic agent in the context of MI [153]. Recent findings suggest that stem cell transplantation can significantly improve mitochondrial function, thereby enhancing overall cardiac health. Pretreatment strategies, including the administration of CoQ_{10}, have been explored with the objective of enhancing stem cell mitochondrial biogenesis, activating mitochondrial function, and further improving their therapeutic efficacy [154].

MitoVitE

MitoVitE is a mitochondria-targeted form of vitamin E, a modified derivative that binds to the triphenylphosphonium (TPP) to provide augmented protection against oxidative stress in cardiac tissue. Studies have shown that MitoVitE effectively reduces lipid peroxidation and improves mitochondrial function in ischemic conditions. This targeted approach not only protects against ROS but also contributes to the stabilization of mitochondrial membranes, thereby preserving cellular integrity during MI [155].

MitoTempol

MitoTempol is a mitochondria-targeted antioxidant that has been constructed by combining piperidinium nitrate with TPP. The latter has been demonstrated to improve oxidative stress and inflammation in the context of MI. By scavenging superoxide radicals and modulating mitochondrial function, MitoTempol has demonstrated cardioprotective effects in various experimental models. Its ability to enhance mitochondrial biogenesis and reduce apoptosis in cardiomyocytes positions it a valuable candidate for therapeutic intervention in acute and chronic myocardial ischemic conditions [156].

Nicotinamide adenine dinucleotide precursors (NAD precursors)

NAD precursors, such as nicotinamide riboside and nicotinamide mononucleotide, play a significant role in cellular metabolism and mitochondrial function [157]. Their supplementation has been linked to improved cardiac function and reduced oxidative stress in models of MI. By enhancing NAD levels, these precursors facilitate energy production and promote sirtuin activation, which is crucial for cellular repair and survival during ischemic events [158]. Furthermore, recent findings have indicated that the administration of NAD precursors may confer protection to the mitochondria of peripheral blood mononuclear cells, thereby reducing the inflammatory response observed in patients with HF [159]. This provides further evidence of the potential of NAD precursors in enhancing mitochondrial health, thereby offering a novel therapeutic strategy for the treatment of myocardial ischemia.

Mitochondria-driven inflammation inhibitors

NLRP3 inhibitors

In previous discussions, the pivotal function of the NLRP3 inflammasome in the inflammatory response following MI has been elucidated. MCC950 is a selective inhibitor of the NLRP3 inflammasome. MCC950 directly interacts with the ATP-hydrolysis motif within the structural domains of nucleotide binding or oligomerization domain, thereby blocking its ATP enzyme activity and the assembly of NLRP3 inflammasome. Consequently, it is the most potent and widely used NLRP3 inhibitor. Gao et al. [160] demonstrated that MCC950 attenuates fibrosis and improves cardiac function in a mouse model by inhibiting the early inflammatory response following MI. By inhibiting NLRP3 activation, MCC950 has been shown to reduce myocardial injury and improve cardiac function in clinical models of IRI. This anti-inflammatory action not only mitigates cell death but also promotes healing in damaged myocardial tissue, highlighting the therapeutic potential of targeting the inflammasome pathway in MI treatment [161].

OLT1177 (Dapansutrile), another NLRP3 inflammasome inhibitor, has demonstrated efficacy in reducing inflammation and preserving cardiac function following MI. OLT1177 is a β-sulfonyl nitrile synthetic compound that has been demonstrated to inhibit downstream caspase-1 activation and the maturation of IL-1β, IL-18, and IL-6. This is achieved by inhibiting the ATPase activity of NLRP3 and preventing the formation of NLRP3 inflammasome [162]. Its ability to attenuate the inflammatory response associated with ischemic injury suggests that it could be a valuable addition to current MI therapies [163]. The results of several studies have demonstrated that OLT1177 is an effective agent for reducing infarct size and improving HF that occurs after ischemia [164]. These findings provide a compelling rationale for its clinical use.

The VX-740 (Pralnacasan) and its analogue VX-765 (Belnacasan) are caspase-1 inhibitors that inhibit caspase-1 activity and the release of the pro-inflammatory cytokine IL-1β [163]. The potential of this compound to reduce inflammation and cell death in MI has been the subject of investigation. It has been demonstrated that the combination of VX-765 and a $P2Y_{12}$ antagonist inhibits Caspase-1, resulting in a sustained reduction in myocardial infarct size and the preservation of ventricular function [165]. By inhibiting the activation of caspase-1, VX-765 can effectively diminish the release of pro-inflammatory cytokines, thereby limiting myocardial damage during ischemic episodes. Experimental evidence supports its cardioprotective effects, making it

a promising candidate for further investigation in clinical settings [166].

Emricasan is a pan-caspase antagonist that inhibits the subsequent inflammatory response by blocking caspase-1 and caspase-4. The results demonstrated that emricasan administration 10 min prior to reperfusion resulted in a notable cardioprotective effect [167]. The study by Yang et al. demonstrates the cardioprotective effects of emricasan in mice subjected to ischemia and two hours of reperfusion. The cardioprotective effect was observed to be significant even in the presence of caspase-1 or caspase-4 deficiency [168]. By inhibiting caspase activation, emricasan has been demonstrated to reduce myocardial injury and improve cardiac prognosis. Consequently, it may be considered a candidate for further clinical exploration [169].

Therapeutic targets of the cGAS-STING pathway

Nitrofuran derivatives (C-176, C-178, C-170, and C-171) are selective and irreversible STING antagonists that exert their inhibitory effects by covalently binding to STING at the Cys91 site. The STING inhibitor C-176 has been demonstrated to reverse hyperglycaemic activation of the cGAS-STING system-dependent IRF3/NF-κB pathway in mouse aortic endothelial cells, thereby inhibiting inflammation and apoptosis [170]. Its derivatives, C-170 and C-171, demonstrated a positive inhibitory effect on hSTING palmitoylation. Furthermore, the 3-acylaminoindole derivative H-151 has been demonstrated to possess the same target as the nitrofuran derivative. In a mouse model of MI, H-151 was observed to reduce infarct enlargement and scar formation, increase left ventricular systolic function to near normal values, and reduce myocardial hypertrophy [171]. The study demonstrated that H-151 protects cardiac tissue from ischemic injury by inhibiting the STING pathway, thereby reducing the inflammatory response and limiting myocardial fibrosis. This highlights the potential of H-151 as a therapeutic agent for MI [172].

The RU family of small molecule compounds includes RU.521 and RU.365. The most extensively researched cardiovascular RU compound is RU.521, which competes with ATP and GTP for the active site of cGAS, thereby inhibiting cGAS expression. Xu et al. [173] demonstrated that RU.521 protects the heart by increasing SIRT3 expression in the hearts of septic mice and attenuates inflammatory responses, oxidative stress and apoptosis. A prospective study revealed that elevated 2'3'-cGAMP, IL-1β and IL-18 in cardiomyocytes from patients with atrial fibrillation and HF were activated by mitochondrial dysfunction. In contrast, the use of RU.521, a specific cGAS inhibitor, effectively reversed the mitochondrial dysfunction-induced upregulation of 2'3'-cGAMP and phosphorylation of STING, while inhibiting the secretion of NLRP3 inflammasome, IL-1β, and IL-18 [174]. Furthermore, RU.521 was demonstrated to exert a pivotal influence on the attenuation of age-related endothelial dysfunction, endothelial focal death-induced atherosclerosis [175], and I/R-induced myocardial apoptosis and cardiac insufficiency [175, 176].

Amlexanox inhibits the full activation of STING by preventing TBK1-induced phosphorylation of STING at the Ser366 site. This is due to the high affinity and specificity of Amlexanox for TBK [177]. In a study conducted by Mo et al., amlexanox was demonstrated to enhance cardiac functionality, diminish ventricular remodeling, and reduce inflammatory cell infiltration, consequently attenuating myocardial apoptosis following AMI in rats [178]. Furthermore, recent studies have demonstrated that amlexanox markedly attenuates chronic pressure overload-induced cardiac hypertrophy and myocardial fibrosis, ameliorates obesity-associated metabolic dysfunction, ameliorates dyslipidemia and prevents atherosclerosis in mice [177, 179].

TL9 pathway inhibitors

Recent studies have demonstrated that certain classical antimalarials, including quinoline (e.g., chloroquine [CQ] and hydroxychloroquine [HCQ]) and acridine (QC), have been repurposed for the treatment of MI due to their anti-inflammatory properties. HCQ has been demonstrated to mitigate myocardial ischemia and reperfusion injury by inhibiting the TLR9 type I interferon pathway [180]. In a multicenter, double-blind, placebo-controlled trial, it was observed that HCQ treatment reduced the IL-6 levels in patients with non-rheumatic disease following MI. However, the onset of its anti-inflammatory effects was gradual, typically requiring 4 to 6 weeks to manifest. Notably, six months after discontinuation of HCQ treatment, IL-6 levels in the placebo group showed a slight decline, while levels in the HCQ group experienced a modest increase, ultimately leading to comparable levels between the two groups. This finding suggests that as long as the medication is administered, the impact of HCQ on IL-6 levels is sustained [181]. In a retrospective study conducted by Chen and colleagues, HCQ was identified as a protective factor against the onset of cardiovascular diseases (CVDs) in patients with established risk factors, with a particularly pronounced effect observed in elderly patients [182].

Non-Antioxidants

Necrostatin

Necrostatin is a compound that has been demonstrated to inhibit RIPK1 with a high degree of specificity. It is postulated that this inhibition may contribute to a reduction in cell death that is induced by ischemia-reperfusion. The study by Koudstaal et al. demonstrated that

necrostatin administered prior to post-ischemic reperfusion significantly reduced myocardial infarct size, decreased oxidative stress, and reduced neutrophil infiltration in the infarct zone. Furthermore, necrostatin was observed to enhance left ventricular functionality, which lends credence to its potential as a cardioprotective pharmaceutical agent [183]. The administration of necrostatin has been demonstrated to attenuate programmed necrosis in cardiomyocytes by blocking the programmed necrosis signaling pathway. Liu et al. demonstrated that Necrostatin markedly reduced the incidence of MI and diminished the expression level and phosphorylation of RIPK1 and RIPK3 in myocardial tissues. These findings suggest that necrostatin not only inhibits apoptosis but also effectively reduces necrosis of cardiomyocytes.

Cyclosporine A

CsA is primarily recognized for its immunosuppressive properties, which are employed to prevent immune responses to organs that are the subject of inhibition [184]. The opening of the mPTP represents a pivotal mechanism underlying reperfusion injury and cardiomyocyte death [185]. The opening of mitochondrial pores may be triggered by the accumulation of calcium ions beyond a certain threshold, which may subsequently result in cellular damage. In the presence of calcium ions, inorganic phosphate and oxidative stress, cyclosporine, a potent pore inhibitor, was observed to effectively inhibit sucrose entry. In the MI/RI study, CsA was effectively delivered to ischemic cardiomyocytes by binding to apoferritin [186]. The mechanism of action of CsA included restoration of the MMP and reduction of ROS levels, which attenuated cardiomyocyte injury and apoptosis. In this process, apoferritin serves not only as a delivery vehicle, but also as an inhibitor of ferroptosis in ischemic cardiomyocytes. This is achieved by increasing the protein expression of GPX4 and decreasing the levels of unstable ferric ion and lipid peroxides. Nevertheless, the utilization of CsA for the management of MI/RI is constrained by its immunosuppressive impact on other normal organs and tissues. Consequently, CsA exerts a protective effect against MI/RI solely when delivered to the IMM of ischemic cardiomyocytes. In contrast, SS-31 represents a novel mitochondria-targeting peptide that directs the accumulation of drugs into mitochondria.

SS-31

SS-31 is a mitochondria-targeting peptide that has been demonstrated to offer considerable promise in the protection of mitochondrial function during myocardial ischemia. Cardiolipin is a distinctive phospholipid, exclusively expressed on the IMM, which plays a pivotal structural role in the formation of cristae and the organization of respiratory complexes into supercomplexes for optimal OXPHOS. By interacting with cardiolipin, SS-31 inhibits the conversion of cyt c to peroxidase by cardiolipin while preserving its electron-carrying function. Consequently, SS-31 safeguards the structural integrity of mitochondrial cristae and facilitates OXPHOS, which replenishes cellular energy reserves and restores bioenergy [48]. Furthermore, it enhances the stability of the IMM and prevents the collapse of the membrane potential, thereby ensuring the optimal functioning of the mitochondria [187]. The administration of SS-31 has been demonstrated to enhance mitochondrial biogenesis and reduce oxidative stress, thereby improving cardiac prognosis in an IRI model [188]. Furthermore, SS-31 has been demonstrated to safeguard mitochondrial integrity, mitigate cardiomyocyte apoptosis and myocardial enlargement zone, and exert substantial cardioprotective effects in a rat cardiac MI/RI model [189]. These effects are attributed to the inhibition of mPTP opening and ROS production. Its distinctive mechanism of action renders it a crucial therapeutic agent for myocardial protection.

Urolithin A

Urolithin A (UA) is an active and potent intestinal metabolite produced by the gut microbiota from ellagitannins and ellagic acid, a complex polyphenol found mainly in strawberries, pomegranates, walnuts, and raspberries. Prior research has substantiated the anti-inflammatory, tumor proliferation-inhibiting and anti-ageing properties of UA in diverse disease models, as well as its capacity to enhance cellular mitochondrial function [190]. From a mechanistic perspective, UA has been demonstrated to upregulate antioxidant levels and attenuate iron-induced cell death in lung tissue through the activation of the Nrf2/HO-1 pathway [191]. In vitro experiments conducted by Chen and colleagues demonstrated that UA upregulated Nrf2 expression and ameliorated myocardial injury and myocardial fibrosis induced by MI [192]. Furthermore, UA facilitated Nrf2 nuclear translocation and triggered the activation of downstream antioxidant defenses, thereby attenuating iron-induced cell death and safeguarding the heart from IRI [193].

Metformin

Metformin is a widely used antidiabetic drug with a paucity of clinical experience and experimental data that raise concerns regarding its safety [194]. Prior research has demonstrated that metformin exerts its protective effects against I/R injury through the modulation of multiple signaling pathways in various organs, including the kidney, heart and brain [195]. In a mouse model of AMI, Qin et al. observed that metformin administration resulted in a reduction in infarct size, attenuation of macrophage autophagy, and a decrease in NLRP3 expression [196]. The anti-diabetic drug metformin has been

demonstrated to effectively inhibit the up-regulation of myocardial inflammatory cytokines, including IL-1β, IL-18 and TNF-α, through the AMPK/NLRP3 inflammatory vesicle pathway. This has been shown to prevent MI/RI and pyroptosis [197]. Following a 14-day reperfusion period, metformin treatment was observed to significantly reduce TNF-α and IL-6 levels, thereby attenuating inflammatory remodeling and the area of myocardial fibrosis. In a study conducted by Loi and colleagues, it was demonstrated that metformin exerts a protective effect on the heart, preventing hypertrophy and remodeling following a MI. This is achieved by inhibiting cardiomyocyte apoptosis through the inhibition of the forkhead box O1 pathway [198]. The available evidence suggests that metformin exerts cardioprotective effects following MI, with the underlying mechanism involving multiple pathways. However, the efficacy of metformin in improving outcomes in patients with MIremains a topic of debate. A Mendelian randomization study found no evidence that metformin treatment affects the risk of MI [199]. Nevertheless, in cases of MI, old myocardial infarction, AMI and lower wall acute transmural myocardial infarction, metformin may potentially act as a risk factor for patients. Consequently, additional assessment of the efficacy and safety of metformin in patients with MI will enhance our comprehension of the clinical viability of metformin as a therapeutic option.

Limitations and translational challenges

While preclinical studies highlight the potential of mitochondrial-targeted therapies, critical challenges remain. First, animal models of AMI often fail to fully recapitulate human comorbidities (e.g., diabetes, aging), which may alter mitochondrial dynamics and drug responses. Second, achieving mitochondrial-specific drug delivery in humans remains technically challenging; for instance, SS-31 requires cardiolipin binding for IMM localization, which may vary between species. Furthermore, it has been demonstrated that the long-term utilisation of antioxidants such as MitoQ has the potential to disrupt redox homeostasis in non-cardiac tissues.The present study investigates the effects of MitoQ on liver metabolism and steatosis in rats [200]. Finally, the issue of biomarker gaps remains unresolved. The prevailing models are currently incapable of monitoring mitochondrial repair in real time due to an absence of real-time biomarkers. Although serum mtDNA levels have been shown to correlate with injury, they are unable to distinguish between necrosis and mitochondria-driven release.

Public health implications and preventive strategies

This review emphasizes mitochondrial dysfunction as a key therapeutic target that has the potential to transform the management of AMI beyond traditional reperfusion strategies. Public health programs that focus on mitochondrial health have the potential to reduce the incidence of AMI. These programs may include the promotion of diets rich in antioxidants (e.g., coenzyme Q10, polyphenols), regular exercise to enhance mitochondrial biogenesis, and smoking cessation to reduce oxidative stress. Furthermore, the early detection of biomarkers of mitochondrial damage (e.g. circulating mtDNA) can enable preemptive intervention in at-risk populations. It is also recommended that dietary interventions be considered in order to promote a diet rich in antioxidants (e.g. coenzyme Q10, rosin tannins) with a view to reducing baseline oxidative stress. By linking laboratory-to-bedside innovation with population-level prevention, this study highlights the potential to transform global cardiovascular care.

Conclusion and future perspectives

Mitochondria-mediated inflammatory responses are of pivotal importance in the pathophysiology of MI. A number of factors contribute to mitochondrial damage during AMI, including mechanisms such as the production of RNS/ROS, impaired mitochondrial autophagy, changes in mitochondrial dynamics, and mitochondrial membrane permeabilization. Damaged mitochondria have been observed to promote immune responses through the cGAS-STING pathway, the NLRP3 inflammasome, and the TLR9 signaling pathway. Each pathway contributes to the production of pro-inflammatory cytokines and the recruitment of immune cells, resulting in heightened inflammation, myocardial injury, and a poor clinical prognosis. Targeting different pathways of damage to mitochondria, preclinical studies have identified a number of promising agents targeting mitochondria that have been shown to be effective in reducing inflammation and mortality in AMI models.

Future research directions should focus on metal ion homeostasis and elucidate the interaction mechanism of copper/iron metabolism imbalance in mitochondrial injury, and validate the clinical potential of disulfiram to inhibit copper death and inflammation through the FDX1/HSP70 dual pathway [201]. Recent studies have introduced precision engineering of exosome to optimize exosomal cargo (e.g. microRNAs, metabolic modulators) and surface modifications to enhance cardiac-specific targeting [202]. In addition, develop robust in vitro models, such as mitochondrial systems that simulate ischemia-reperfusion, and introduce high-throughput screening methods to rapidly evaluate succinate

oxidation inhibitors, reactive oxygen scavengers, and mitochondrial protectors [203]. Promote combination therapy centered on SGLT2i (such as MitoQ synergistic intervention), and simultaneously correct energy metabolism disorders, oxidative stress and programmed cell death pathways.

Abbreviations

AMI	Acute myocardial infarction
MI/RI	Myocardial ischemia-reperfusion injury
PCI	Percutaneous coronary intervention
MI	Myocardial infarction
HF	Heart failure
mtDNA	Mitochondrial DNA
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
NLRP3	NLR pyrin domain containing 3
TLR9	Toll-like receptor 9
OXPHOS	Oxidative phosphorylation
ETC	Electron transport chain
OMM	Outer mitochondrial membrane
IMM	Inner mitochondrial membrane
TCA	Tricarboxylic acid
ROS	Reactive oxygen species
PRRs	Pattern recognition receptors
PAMPs	Pathogen-associated molecular patterns
DAMPs	Danger-associated molecular patterns
TLRs	Toll-like receptors
NLRs	NOD-like receptors
RLRs	Retinoic acid-inducible gene I like receptors
IFN-I	Type I interferons
NF-κB	Nuclear factor kappa B
mPTP	Mitochondrial permeability transition pore
IRI	Ischemia/reperfusion injury
MMP	Mitochondrial membrane permeabilization
MFN1	Mitofusin 1
MFN2	Mitofusin 2
Bcl-2	B-cell lymphoma-2
cyt c	Cytochrome c
DRP1	Dynamin-related protein 1
AMPK	AMP-activated protein kinase
RNS	Reactive nitrogen species
NO	Nitric oxide
iNOS	inducible nitric oxide synthase
OPA1	Optic atrophy 1
mTOR	Mammalian target of rapamycin
PINK1	PTEN-induced kinase 1
BNIP3	Bcl-2 interacting protein 3
Fis1	Fission protein 1
Mff	Mitochondrial fission factor
MiD	Mitochondrial dynamics proteins
OPTN	Optineurin
NDP52	Calcium-binding and coiled-coil domain-containing protein 2
LC3	Light chain 3
FUNDC1	FUN14 domain containing 1
NIX	Nip3-like protein X
MPT	Mitochondrial permeability transition
MOMP	Outer membrane permeabilization
PTP	Permeability transition pore
VDAC	Voltage-dependent anion channel
ANT	Adenine nucleotide translocator
CsA	Cyclosporin A
RIPK	Receptor-interacting protein kinases
BAX	Bcl-2-associated X protein
BAK	Bcl-2 homologous antagonist/killer
GSDMD	Gasdermin D
Cyp D	Cyclophilin D
dsDNA	Double-stranded DNA
cGAMP	Cyclic guanosine monophosphate-adenosine monophosphate
ER	Endoplasmic reticulum
TBK1	TANK-binding kinase 1
IRF3	Interferon regulatory factor 3
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
PYD	Pyrin structural domain
LRR	leucine-rich repeat
MyD88	Myeloid differentiation primary response gene 88
MAPK	Mitogen-activated protein kinase
TNF-α	Tumor necrosis factor-α
MTOC	Microtubule-organizing center
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
GPX4	glutathione peroxidase 4
NRF2	Nuclear factor erythroid 2-related factor 2
HO-1	Heme oxygenase 1
MitoQ	MitoquinoL mesylate
CoQ10	Coenzyme Q10
TPP	Triphenylphosphonium
NAD	Nicotinamide adenine dinucleotide
AF	Atrial fibrillation
CVDs	Cardiovascular diseases
UA	Urolithin A

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Data availability
All data generated by this systematic search are included in this published article.

Declarations

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