Mitochondrial quality control as a therapeutic target in cardiovascular disease: Mechanistic insights and future directions

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ABSTRACT

Mitochondrial dysfunction is increasingly recognized as a critical driver in the pathogenesis of cardiovascular diseases. Mitochondrial quality control (MQC) is an ensemble of adaptive mechanisms aimed at maintaining mitochondrial integrity and functionality and is essential for cardiomyocyte viability and optimal cardiac performance under the stress of cardiovascular pathology. The key MQC components include mitochondrial fission, fusion, mitophagy, and mitochondria-dependent cell death, each contributing uniquely to cellular homeostasis. The dynamic interplay among these processes is intricately linked to pathological phenomena, such as redox imbalance, calcium overload, dysregulated energy metabolism, impaired signal transduction, mitochondrial unfolded protein response, and endoplasmic reticulum stress. Aberrant mitochondrial fission is an early marker of mitochondrial injury and cardiomyocyte apoptosis, whereas reduced mitochondrial fusion is frequently observed in stressed cardiomyocytes and is associated with mitochondrial dysfunction and cardiac impairment. Mitophagy is a protective, selective autophagic degradation process that eliminates structurally compromised mitochondria, preserving mitochondrial network integrity. However, dysregulated mitophagy can exacerbate cellular injury, promoting cell death. Beyond their role as the primary energy source of the cell, mitochondria are also central regulators of cardiomyocyte survival, mediating apoptosis and necroptosis in reperfused myocardium. Consequently, MQC impairment may be a determining factor in cardiomyocyte fate. This review consolidates current insights into the regulatory mechanisms and pathological significance of MQC across diverse cardiovascular conditions, highlighting potential therapeutic avenues for the clinical management of heart diseases.

Key words: mitochondrial quality control; mitochondrial fission; fusion; mitophagy; mitochondrial death

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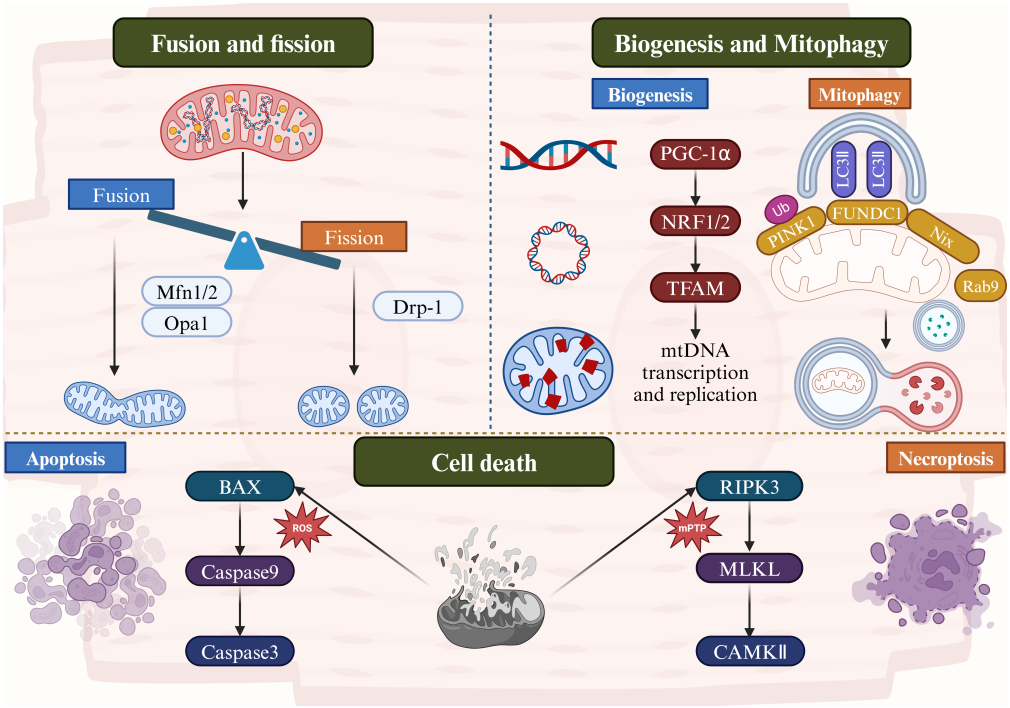
Graphical Abstract



Healthy cardiomyocytes feature a precise balance between mitochondrial fusion (mediated by MFN1/2 and Opa1) and division (mediated by Drp1). Fusion contributes to mitochondrial network stability and functional restoration, while division ensures mitochondrial renewal and the removal of damaged parts. PGC-1α, NRF1/2 and TFAM regulate mitochondrial biogenesis to ensure mtDNA transcription and replication and maintain mitochondrial quantity and quality. Mitochondrial autophagy selectively removes damaged mitochondria through LC3II, FUNDC1, PINK1-Parkin, and other molecular pathways to prevent the accumulation of cell damage. The cell begins to undergo a series of stress responses when the balance between mitochondrial fusion and division is disrupted or biogenesis and autophagy are impaired. Initially, BAX activates caspase-9, initiating the apoptosis pathway, leading to the activation of caspase-3 and cell death. If mitochondrial damage is aggravated, RIPK3 activates MLKL, which triggers necroptosis through CAMKII mediation, leading to cell structure destruction and loss of function. The interactions between mitochondrial fusion and division, biogenesis and autophagy were demonstrated, and the specific mechanisms of how these processes progressively affect cardiomyocyte survival are described. MFN1/2: mitofusin 1 and 2; Opa1: optic atrophy protein 1; Drp1: dynamin related protein 1; FUNDC1: Fun14 domain-containing protein 1; PINK1: PTEN induced putative kinase 1; RIPK3: receptor-interacting protein kinase 3; MLKL: mixed lineage kinase domain-like protein; CAMKII: Ca2+-calmodulin-dependent protein kinase II.

INTRODUCTION

The mitochondria are maternally inherited and originally derived from ancient bacterial ancestors, and are essential double-membraned organelles present in nearly all eukaryotic cells and even certain prokaryotes.[1] Traditionally regarded as the primary source of cellular adenosine 5'-triphosphate (ATP) *via* oxidative phosphorylation, the mitochondria are pivotal in energy production through glucose and lipid metabolism. However, detection technology advancements have revealed that mitochondrial function extends far beyond energy metabolism. The mitochondria are central hubs for cellular signaling, integration, and amplification, regulating oxidative stress, calcium homeostasis, and apoptosis processes.[2,3] Mitochondrial dysfunction leads to energetic stress and also disrupts these critical signaling networks, contributing to the pathogenesis of numerous human diseases, including cardiovascular disorders, chronic obstructive pulmonary disease, acute kidney injury,[4] metabolic syndrome,[5] and cancer.[6]

Mitochondrial impairments, such as genetic mutations, compromised membrane integrity, metabolic inactivity, and pro-apoptotic signaling activation, act as independent pathological drivers and also synergize with other molecular mechanisms, aggravating disease processes.[6] Consequently, understanding and targeting mitochondrial damage has become a promising avenue for developing therapeutic strategies that aim to restore mitochondrial health and treat a broad spectrum of human diseases.

In cardiovascular diseases, such as myocardial ischemia-reperfusion (I/R) injury, hypertension, coronary atherosclerosis, diabetic cardiomyopathy (DCM), and azithromycin-induced cardiomyopathy, mitochondrial quality control (MQC) is critical in maintaining cardiomyocyte resilience against stress.[7,8] MQC refers to

a suite of adaptive responses that regulate mitochondrial morphology, ATP synthesis, genomic stability, protein homeostasis, and intracellular signaling.[9] In response to mild stresses, such as hypoxia, mitochondrial dynamics, primarily fission, are upregulated to increase mitochondrial mass and match cellular energy demands. During this phase, mild increases in mitochondrial calcium enhance metabolic enzyme activity, adapting mitochondria to shifting energy requirements.[10]

Moderate stressors, such as oxidative stress or inflammation, compromise mitochondrial membrane integrity, leading to outer mitochondrial membrane (OMM) hyperpermeability.[11] This disruption releases mitochondrial signaling molecules into the cytoplasm, potentially initiating inflammatory responses, and also promotes water influx, leading to mitochondrial swelling.[12] Damaged mitochondria can undergo fusion with healthier counterparts, mitigating the accumulation of dysfunctional components within the mitochondrial network. When damage becomes irreversible, the structurally compromised mitochondria are removed through mitophagy, a selective form of autophagy. This recycling process is facilitated by key mitophagy regulators, such as B-cell lymphoma-2 (BCL2)/adenovirus E1B 19 kDa protein-interacting protein 3 (Bnip3), Parkin, and Fun14 domain-containing protein 1 (Fundc1), while mitochondrial biogenesis simultaneously compensates for mitochondrial loss, enabling the generation of a rejuvenated mitochondrial network.[13]

However, the mitochondria initiate the cell death pathways when stress overwhelms these protective mechanisms, including apoptosis, necrosis, and necroptosis. Mitochondrial-mediated cell death represents a crucial cellular decision point: while apoptosis and necroptosis offer potentially reversible outcomes, mitochondrial-driven necrosis is terminal and non-reversible.[14] Therefore, the mitochondria serve as the energy centers of the cell and are also the critical arbiters of cell fate, particularly in the face of severe cardiovascular stressors.

This review consolidates insights into the diverse roles of MQC across various cardiovascular diseases, examining the complex interactions among mitochondrial dynamics, mitophagy, biogenesis, and cell death regulation. Cells respond to fluctuating energy demands, redox imbalance, and calcium dysregulation through mitochondrial fission and fusion, while mitophagy and biogenesis ensure the removal and replenishment of damaged mitochondrial units. Additionally, cell death pathways are explored with a focus on the transition from reversible to irreversible cell death in conditions such as DCM and drug-induced cardiomyopathy. By advancing our understanding of these MQC mechanisms, we aim to highlight potential therapeutic targets that could mitigate mitochondrial dysfunction and enhance cardiomyocyte survival across a range of cardiovascular disorders (Figure 1).

MITOCHONDRIAL FISSION

Initially perceived as static structures, the mitochondria are now well recognized as dynamic organelles constantly reshaped by fusion and fission processes. Mitochondrial fission is essential for the targeted removal of dysfunctional mitochondria in cardiomyocytes (Figure 2), with fission activity finely tuned according to the cell metabolic demands. Properly regulated fission generates new mitochondria, supporting the oxidative phosphorylation essential for myocardial development and function.[15] Moreover, fission enables the mitochondria to segregate damaged regions from the mitochondrial network, a crucial process for maintaining mitochondrial homeostasis in cardiomyocytes.[16]

Mitochondrial fission is primarily controlled by dynamin-related protein 1 (Drp1) and its receptors anchored in the OMM, including mitochondrial fission factor (Mff), mitochondrial fission 1 protein (Fis1), and mitochondrial dynamics proteins of 49 kDa (Mid49) and 51 kDa (Mid51).[17] Under physiological conditions, Drp1 predominantly resides in the cytoplasm in an inactive form that lacks binding affinity for OMM receptors, maintaining basal fission activity. However, Drp1 undergoes post-translational modifications (ubiquitination, acetylation, phosphorylation) under stress, which induce conformational changes.[18] These modifications expose the Drp1 binding sites, facilitating its translocation to the mitochondrial surface and enhancing its interaction with OMM receptors, which increases fission activity.

Notably, Drp1 transcription levels alone are unreliable indicators of its fission activity,[19] as mass spectrometry-based proteomics (PhosphoSitePlus) have revealed various post-translational modification sites.[20,21] For example, Drp1 phosphorylation at Ser616 promotes its oligomerization around the OMM, a crucial step in forming the mitochondrial fission ring.[22] Conversely, phosphorylation at Ser637 inhibits Drp1 oligomerization, downregulating fission.[23] Post-translational modifications also affect Drp1 receptors: for example, Mff demonstrates enhanced Drp1 affinity when phosphorylated at Ser146, a modification associated with cardiac microvascular I/R injury.[24] The Fis1 N-terminal arm normally acts in an auto-inhibitory manner to limit Drp1 binding, but phosphorylation at this region enhances Drp1 interaction.[25] Although Mid49 and Mid51 modifications have been less studied, their roles in modulating Drp1-

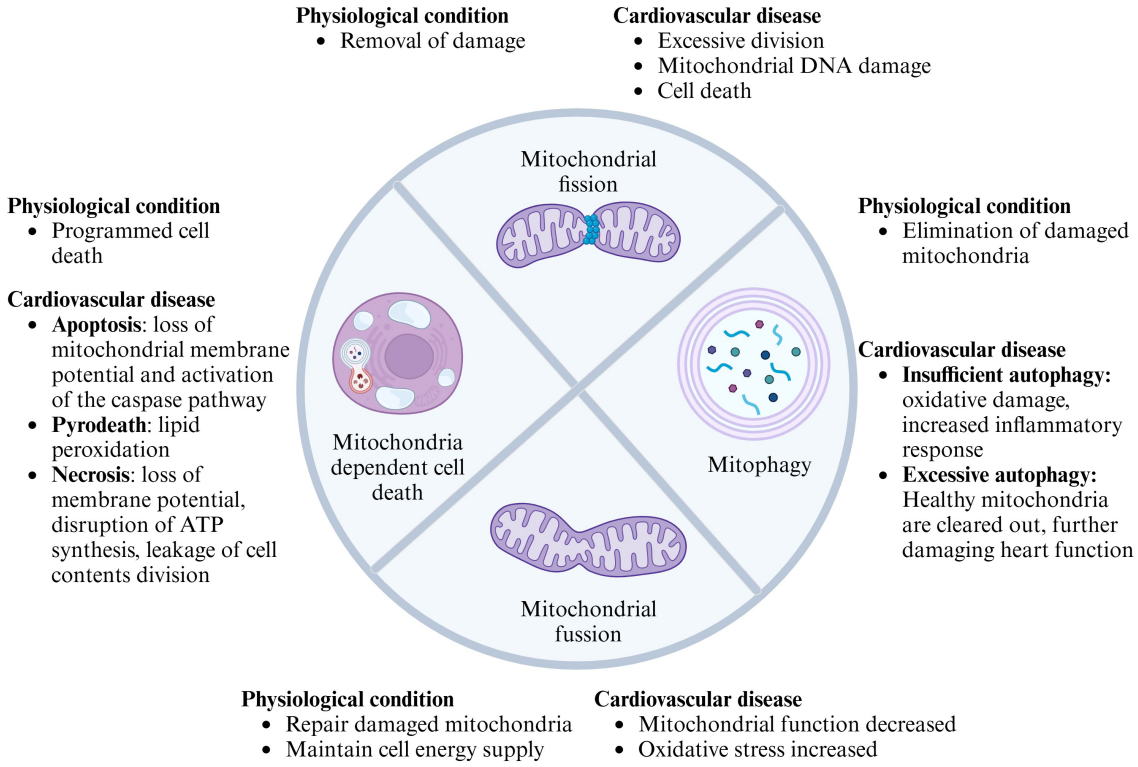


Figure 1: Review of MQC in physiological conditions and cardiovascular diseases. MQC coordinates fission, fusion, mitochondrial autophagy, and mitochondria-controlled cell death to ensure cell homeostasis. Mitochondrial dysfunction is thought to be a major mechanism in cardiovascular disease development, and failure of quality control processes can exacerbate mitochondrial dysfunction. Several potential MQC targets could treat cardiovascular disease by inhibiting mitochondrial division, promoting mitochondrial fusion, moderately activating mitochondrial autophagy, and inhibiting mitochondria-dependent cell death. MQC: mitochondrial quality control; ATP: adenosine 5'-triphosphate.

dependent fission merit further exploration.

Role of mitochondrial fission in cardiac I/R injury

Mitochondrial fission is closely linked to mitochondrial damage and cardiomyocyte death in cardiac I/R injury (Figure 2). Mechanistically, reduced phosphorylation of Drp1 at Ser637 leads to its mitochondrial localization, triggering excessive fission, calcium overload, and myocardial contractile dysfunction.[23] Conversely, Drp1 Ser616 phosphorylation is increased after I/R injury, elevating reactive oxygen species (ROS) production and oxidative stress in cardiomyocytes.[26] Enhanced expression and phosphorylation of Mff further promote fission in cardiac microvascular I/R injury, while Mff deletion preserves mitochondrial DNA (mtDNA) integrity and mitochondrial respiration, benefiting endothelial cell viability.[24,27]

Excessive fission contributes to ATP depletion, cytochrome c (cyt-c) release, mitochondrial permeability transition pore (mPTP) opening, and cardiomyocyte apoptosis.[28] Mitochondrial fission also impairs antioxidant defenses, reducing superoxide dismutase 2 (SOD2) and heme oxygenase 1 (HO-1) levels, and suppresses autophagy, indicated by the lower expression of the LC3-phosphatidylethanolamine (LC3) II/I ratio, Beclin-1, and autophagy related 5/7 gene (ATG5/7).[29] Notably, the extent of the fission correlates with the myocardial infarction size and inversely with cardiac performance, highlighting its role in I/R injury.[29,30] Pharmacological or genetic inhibition of mitochondrial fission has cardioprotective effects. The Drp1 inhibitor Mdivi-1 reduces Drp1 translocation to the mitochondria,[31] stabilizes membrane potential, prevents mPTP opening,[32,33] and attenuates mitochondrial apoptosis pathways.[27] Additionally, Mdivi-1 modulates antioxidant activity, increasing manganese superoxide dismutase (SOD) and reducing malondialdehyde (MDA) levels, suggesting the role of fission in redox regulation.[31] Furthermore, fission affects key cardioprotective signaling pathways, including the protein kinase B (PKB), extracellular regulated protein kinases (ERK), adenosine 5'-monophosphate-activated protein kinase (AMPK), and nitric oxide (NO) pathways, which are upstream regulators of Drp1.[34-36]

However, timing and specificity are critical considerations.

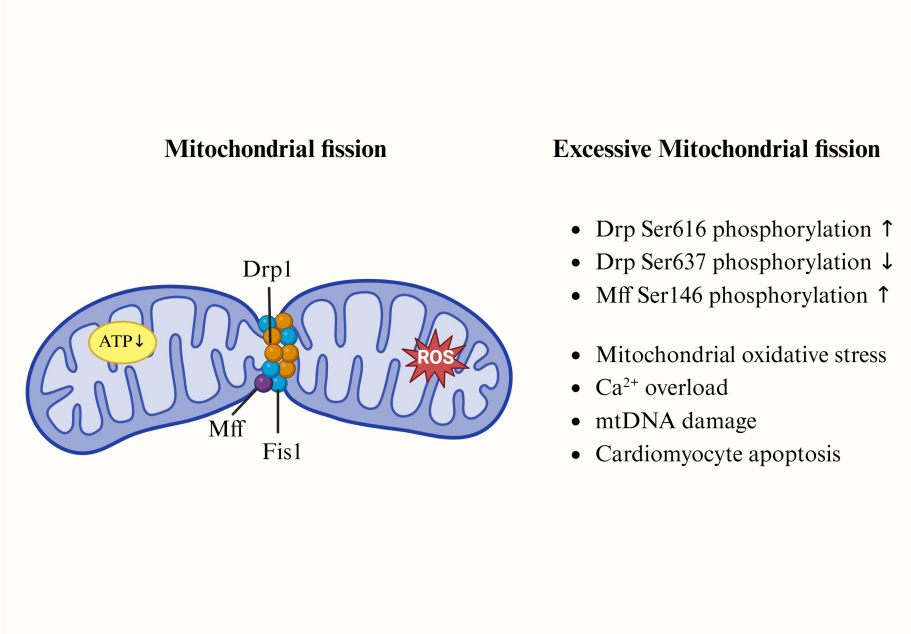


Figure 2: DRP1 and its receptors, including MFF and FIS1, regulate mitochondrial fission. Increased mitochondrial fission is associated with oxidative stress, Ca^{2+} overload, mtDNA damage, and mitochondrial apoptosis activation. DRP1: dynamin-related protein 1; MFF: mitochondrial fission factor; FIS1: mitochondrial fission 1 protein; ROS: reactive oxygen species; ATP: adenosine 5′-triphosphate.

Pre-ischemic administration of Mdivi-1 is more effective than later interventions, as physiological fission may benefit cardiac function during ischemia, while pathological fission predominates post-ischemia.[37] Moreover, while inhibiting fission reduces apoptosis, it may inadvertently increase necroptosis, as seen in Mdivi-1-treated models.[27,38] These insights indicate the need for careful interpretation of the effects of Mdivi-1 and suggest broader implications for targeted mitochondrial fission modulation in cardiac I/R injury.

Role of mitochondrial fission in myocardial infarction

Mitochondrial fission is markedly increased following myocardial infarction (MI) and is driven by hypoxia and oxidative stress. Hypoxia induces profound intracellular environmental changes, activating numerous signaling pathways that alter the expression and activity of key proteins in mitochondrial division and enhancing fission.[39] Elevated mitochondrial division often disrupts mitochondrial function, aggravating cardiomyocyte injury. Excessive fission fragments the mitochondrial network, impairing essential functions such as energy metabolism and molecular transport, which results in cellular energy deficits, metabolite accumulation, and accelerated cardiomyocyte damage and death.[40]

Drp1 is a pivotal mediator of mitochondrial fission, where its expression and activity are frequently upregulated during MI. Increased Drp1 promotes mitochondrial fragmentation, contributing to mitochondrial dysfunction. Drp1 activity in the ischemic myocardium is modulated by hypoxia, oxidative stress, and intracellular calcium fluctuations. For example, hypoxia activates specific signaling pathways that phosphorylate Drp1, increasing its affinity for mitochondrial membrane receptors and facilitating fission.[41,42] The oxidative stress induced by MI exacerbates mitochondrial dysfunction, with hypoxia-driven redox imbalances generating ROS. ROS directly impair the mitochondrial structure and function and also activate additional signaling cascades that compromise mitochondrial homeostasis, upregulating Drp1 and accelerating fission.[43,44] Additionally, Drp1 is key in mitochondrial calcium regulation; activated Drp1 translocates to the mitochondria, intensifying fission and ROS production in cardiomyocytes.

Apoptosis is also closely linked to mitochondrial fission, exacerbating cardiomyocyte damage. As central regulators of apoptosis, the mitochondria undergo morphological and functional alterations during apoptotic processes. Certain pro-apoptotic proteins, such as Bax, influence mitochondrial membrane permeability and may increase Drp1 activity, promoting mitochondrial fission and exacerbating cellular damage.[45]

Drp1 inhibitors, such as Mdivi-1, have been explored as therapeutic agents in MI. These inhibitors mitigate cardiomyocyte injury by inhibiting Drp1 activity and reducing mitochondrial division. Mdivi-1 binds to Drp1,

preventing it from forming functional fission complexes, reducing mitochondrial fragmentation. Furthermore, Mdivi-1 reduced myocardial injury and improved cardiac function in MI models.[46,47]

Antioxidants such as vitamins C and E have been investigated as treatments for MI, with evidence suggesting that they support cardiomyocyte function by reducing oxidative stress and improving mitochondrial health. These antioxidants scavenge intracellular ROS, alleviating oxidative damage to the mitochondria and preserving mitochondrial function.[48] Additionally, natural compounds such as ginsenosides and tanshinones have been studied for their protective effects in MI, with results indicating that they improve cardiomyocyte function by reducing oxidative stress, suppressing inflammation, and enhancing mitochondrial function.[49-52]

Role of mitochondrial fission in hypertension

Hypertension is a complex disease commonly accompanied by severe complications affecting the vascular systems of the heart, brain, and kidneys, presenting a significant threat to human health. Endothelial damage and vascular wall thickening are key contributors to hypertension onset and progression.[53]

Mitochondrial fission is essential to cellular homeostasis and is primarily regulated by a set of specialized proteins. Drp1 is a central fission regulator that exists in the cytosol in inactive form under physiological conditions. Upon receiving activation signals, Drp1 translocates to the OMM, where it oligomerizes into a helical structure that constricts the mitochondria, leading to their division.[54] Fis1 is located on the OMM and facilitates this process by recruiting Drp1.[55]

Abnormal mitochondrial fission has been observed within endothelial cells in hypertensive conditions, contributing to mitochondrial dysfunction and reduced NO production. NO is a crucial vasodilator, and its diminished availability under hypertensive conditions contributes to increased vascular tone. Drp1 upregulation in hypertensive endothelial cells may be triggered by oxidative stress and inflammatory signals, which disrupt normal mitochondrial structure and function.[56] In spontaneously hypertensive rats (SHR), Drp1 expression was markedly elevated in vascular endothelial cells, accompanied by thickening of the thoracic aorta medial layer and increased inflammatory factor expression.[53]

Mitochondrial fission is also intensified in vascular smooth muscle cells (VSMCs) during hypertension, increasing fragmented mitochondria. These fragmented mitochondria exhibit altered calcium handling and elevated ROS production. The increased ROS activates signaling pathways that drive VSMC contraction and proliferation, promoting vascular wall thickening and elevating blood pressure.[57] Angiotensin II (AngII) stimulation enhances Drp1 phosphorylation at Ser616, prompting its translocation to the mitochondria and initiating mitochondrial fission. This shift transforms VSMCs from a contractile phenotype to a synthetic, proliferative, and migratory state, actively participating in the vascular remodeling associated with hypertension. The mitochondrial morphology in VSMCs was notably fragmented after AngII treatment, with reduced branch length and an increase in mitochondrial count.[58]

Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor implicated in hypertension pathogenesis and induces ROS-dependent activation of Rho-associated protein kinase (ROCK) signaling.[59] ROCK activation promotes mitochondrial fission, and the ROCK inhibitor Y-27632 alleviated ET-1-induced vasoconstriction and inhibited ET-1-induced mitochondrial fragmentation in rat aortic smooth muscle cells.[60]

Pharmacological agents targeting mitochondrial fission-related proteins hold therapeutic potential in hypertension. Compounds such as Mdivi-1 (a Drp1 inhibitor) and Y-27632 (a ROCK inhibitor) may counteract excessive Drp1 activation, restoring mitochondrial function in vascular and renal cells and supporting blood pressure regulation.[31,58,60]

Role of mitochondrial fission in DCM

Mitochondrial fission is markedly dysregulated in DCM. Mitochondrial fission becomes excessive in high glucose-induced H9c2 cardiomyoblasts, accompanied by lipid accumulation, oxidative stress, and apoptosis.[61] These results suggest that abnormal mitochondrial fission is closely associated with myocardial cell injury and may be central in DCM pathogenesis. Diabetic mouse models exhibit similar disruptions in mitochondrial structure and function, including increased fission, decreased fusion, reduced membrane potential, elevated ROS levels, increased apoptosis, and impaired cardiac function.[62]

Enhanced mitochondrial fission critically affects cardiomyocyte function by promoting mitochondrial fragmentation, which disrupts energy metabolism as the mitochondria are the primary source of ATP through oxidative phosphorylation. Additionally, excessive mitochondrial fission is linked to increased apoptosis, characterized by the upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins.[35,61] Drp1 is a key mediator of mitochondrial fission whose expression and phosphorylation in DCM are altered

under high-glucose conditions, exacerbating mitochondrial fragmentation. Inhibiting Drp1, such as through the inhibitor Mdivi-1, reduces fission and mitigates myocardial cell damage. Other fission-related proteins, such as Mff and Fis1, may also contribute, with signaling pathways such as protein kinase B-mammalian target of rapamycin (Akt-mTOR) and glycogen synthase kinase-3β (GSK-3β) playing regulatory roles. For example, nimbolide activates the Akt-mTOR pathway, inhibiting mitochondrial fission and ameliorating DCM, while perillaldehyde modulates fission by upregulating miR-133a-3p to inhibit GSK-3β expression.[62,63]

Pharmacological studies have highlighted promising therapeutic avenues. Curcumin-conjugated gold nanoclusters (AuCur) demonstrated potential in reducing lipid accumulation, ROS levels, and mitochondrial fission under hyperlipidemic conditions, possibly through peroxisome proliferators-activated receptors α (PPARα) regulation.[64] Other compounds, such as nimbolide and perillaldehyde, exhibit protective effects in animal models and cellular assays.[63] Molecular mechanistic research has also identified novel targets, such as m6A-mediated phase separation affecting Notch1 expression, which inhibited mitochondrial fission and provided a new therapeutic strategy for diabetic cardiac fibrosis.[65]

Role of mitochondrial fission in drug-induced cardiomyopathy

The heart is an energy-intensive organ reliant on the mitochondria to sustain its function through ATP production *via* oxidative phosphorylation. The mitochondria are dynamic organelles that continually undergo fusion and fission to preserve their morphology, size, and functionality. However, this balance is often disrupted in drug-induced cardiotoxicity, leading to mitochondrial dysfunction and subsequent cardiomyocyte injury. Under physiological conditions, mitochondrial fission is crucial in MQC by facilitating the removal of damaged or dysfunctional mitochondria *via* mitophagy, thereby maintaining the overall health of the mitochondrial network. Controlled fission also contributes to key cellular signaling pathways associated with metabolic adaptation and survival, allowing cardiomyocytes to respond to fluctuating energy demands and environmental stressors.[66]

Doxorubicin is a widely used and potent chemotherapeutic agent limited by its severe cardiotoxic effects, which manifest as progressive cardiomyopathy. Evidence indicates that doxorubicin-induced cardiotoxicity is closely associated with increased ROS production, leading to oxidative stress and mitochondrial damage. This damage is frequently characterized by excessive mitochondrial fragmentation, a process tightly linked to mitochondrial fission. Abnormal fission in doxorubicin-treated cardiomyocytes appears to be mediated by Drp1, whose phosphorylation at specific sites promotes its translocation to the mitochondria and drives fission. This dysregulated mitochondrial fragmentation facilitates cyt-c release and caspase activation, culminating in cardiomyocyte apoptosis.[67-69]

Beyond doxorubicin, other chemotherapeutic agents have been similarly implicated in mitochondrial fission-mediated cardiotoxicity. For example, cisplatin disrupts mitochondrial dynamics, enhancing fission and compromising mitochondrial function, which contributes to cardiomyocyte injury and potentially to heart failure. Similarly, 5-fluorouracil is associated with mitochondrial dysfunction and oxidative stress, potentially mediated by alterations in mitochondrial fission and fusion.[70-72]

Notably, mitochondrial fission-induced cardiotoxicity is not confined to chemotherapeutics. Certain non-chemotherapeutic agents, including specific antipsychotic drugs, have also been linked to increased risk of cardiomyopathy, potentially through mechanisms involving disrupted mitochondrial fission and altered mitochondrial morphology.[73]

MITOCHONDRIAL FUSION

Mitochondrial fusion is the converse of fission and is a dynamic process involving the sequential merging of the outer and inner membranes of individual mitochondria to form elongated, interconnected networks.[74,75] This structural integration facilitates mitochondrial communication and resource sharing, allowing damaged or smaller mitochondrial fragments to merge with healthier mitochondria, supporting mitochondrial repair and functional resilience. Fusion is a protective mechanism that aids in maintaining mitochondrial homeostasis, particularly under stress conditions.[76]

Mechanistically, fusion is regulated by two key guanosine triphosphate hydrolases (GTPases): mitofusin 1 and 2 (MFN1/2), localized on the OMM, and optic atrophy protein 1 (Opa1), which governs inner mitochondrial membrane (IMM) fusion.[77] Fusion begins with MFN1/2 dimerization on adjacent mitochondria, which facilitates tethering with the assistance of ATP and F-actin. Subsequent OMM fusion is promoted by the hydrolysis of cardiolipin, a critical phospholipid within the mitochondrial membrane bilayer.[78] IMM fusion, regulated by Opa1, completes the process, although understanding of this step remains incomplete at the mechanistic level (Figure 3).

Mitochondrial fusion confers cytoprotective benefits by counterbalancing fission and mitigating fission-induced

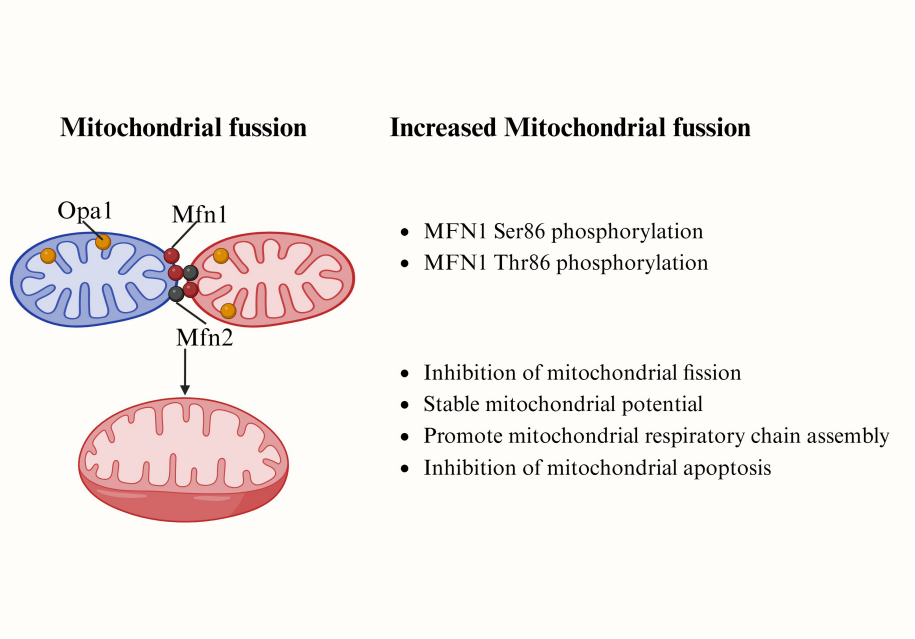


Figure 3: Mitochondrial fusion is orchestrated by MFN2, which resides in the OMM, and OPA1, found in the IMM. These proteins are crucial for increasing mitochondrial fusion, inhibiting mitochondrial fission, maintaining mitochondrial membrane potential, promoting mitochondrial bioenergetics, and preventing mitochondrial apoptosis, collectively preserving mitochondrial integrity and function. MFN2: mitofusin 2; OPA1: optic atrophy protein 1; OMM: outer mitochondrial membrane; IMM: inner mitochondrial membrane.

apoptosis. Mitochondrial fusion supports a continuous electrochemical gradient across the mitochondrial network, enhancing the ability of the mitochondrial pool to identify and respond to localized damage.[79] Additionally, fusion ensures the even distribution of mitochondrial components, including proteins, lipids, metabolites, and mtDNA, which collectively aid in alleviating localized stress responses and restoring mitochondrial equilibrium.[80]

Pathological conditions, such as myocardial I/R, disrupt mitochondrial fusion. MFN1, MFN2, and Opa1 levels are significantly downregulated in reperfusion models, correlating with reduced mitochondrial integrity, a shortened replicative lifespan, and increased apoptotic rates in endothelial cells.[81] The loss of fusion capacity in such contexts exacerbates mitochondrial fragmentation, ATP depletion, and oxidative stress, further impairing cardiomyocyte viability. Therapeutic strategies aimed at preserving or enhancing mitochondrial fusion may therefore potentially restore mitochondrial homeostasis and protect against mitochondrial-driven cellular damage in cardiovascular disease.

Role of mitochondrial fusion in cardiac I/R injury

While mitochondrial fusion is generally considered protective under physiological conditions, its role in cardiac I/R injury remains debated. MFN1 and Mfn2 are key OMM fusion regulators that appear to have distinct functions in cardiomyocytes. MFN1 deficiency in mice influences cardiac function minimally,[82,83] whereas mtDNA damage and fragmentation were increased in Mfn2-null hearts.[84] Cardiomyocyte-specific MFN1 knockout (MFN1-KO) models retain respiratory function and demonstrate enhanced resistance to mitochondrial depolarization and oxidative stress, suggesting a protective effect against fission-induced cell injury.[85] Conversely, Mfn2 loss promotes mPTP opening, elevates ROS production, and sensitizes cardiomyocytes to apoptosis.[86,87] In hypoxia-reoxygenation models, Mfn2 silencing exacerbates apoptosis, which caspase-9 inhibition or Bcl-x (L) overexpression reversed, underscoring its distinct regulatory role.[88] Additionally, MFN1/Mfn2 double knockout leads to the accumulation of defective mitochondria, hinting at an unexplored role of Mfn2 in MQC.[89,90]

Unlike MFN1/2, the role of Opa1 in cardioprotection is well documented. Opa1 knockdown increases mitochondrial heterogeneity and promotes ventricular dilation with impaired contractile function.[91] Opa1 expression is decreased in myocardial I/R, and its genetic activation suppresses mitochondrial fission and apoptosis.[92] Mechanistically, overlapping activity with m-AAA protease-1 (OMA1)-mediated cleavage of Opa1 during reperfusion leads to fragmentation, cyt-c release, and apoptosis.[93,94] Furthermore, dysregulating Opa1 impairs mitochondrial bioenergetics and exacerbated oxidative stress, further compromising cardiomyocyte survival.[95]

Additionally, Opa1 promotes fatty acid oxidation, reducing ROS generation and preserving mitochondrial structure in heart failure, although this has not been confirmed in I/R models.[96,97]

MFN1/2 and Opa1 undergo post-translational modifications that modulate fusion activity. The phosphorylation of MFN1 at Ser86 by protein kinase C beta II (βIIPKC) impairs fusion and leads to mitochondrial fragmentation,[98] while other kinases, including mitogen-activated protein kinase (MAPK) and ERK, phosphorylate MFN1 at Tyr562, reducing its oligomerization efficiency and increasing susceptibility to apoptosis.[99] Mfn2 phosphorylation by PINK1 facilitates mitophagy, while stress-induced phosphorylation and degradation by c-Jun N-terminal kinase (JNK) hinder fusion and promote cell death.[100] Although the post-translational regulation of MFN1/2 in I/R is not fully elucidated, MFN1/2 protein levels are both significantly downregulated. Opa1 stability is predominantly controlled by the redox-sensitive proteases OMA1 and ATP-dependent zinc metalloprotease (Yme1L), which are activated under stress to degrade Opa1 during I/R.[96] ROS scavenging extends Opa1 stability,[101] while signal transducer and activator of transcription 3 (STAT3) and RelA transcriptional regulation may influence Opa1 expression, although this has not been fully validated in I/R.[102] Furthermore, Opa1 is subject to acetylation and O-linked-β-N-acetylglucosamine (O-GlcNAcylation) in response to stress, impairing its GTPase activity and contributing to mitochondrial dysfunction and cell death.[103,104]

Therapeutic strategies to restore mitochondrial fusion have been promising. Sevoflurane postconditioning reduces cardiac I/R injury by upregulating Opa1 and Mfn2, while vagal nerve stimulation improves mitochondrial dynamics in ischemic myocardium.[81] Epigallocatechin gallate stabilizes Opa1 by inhibiting OMA1 degradation, and melatonin enhances Opa1 expression *via* the AMPK pathway, increasing mitochondrial resistance to I/R injury.[94] These findings underscore the therapeutic potential of targeting Mfn2 and Opa1 to preserve mitochondrial fusion and protect cardiomyocytes during I/R injury.

Role of mitochondrial fusion in MI

During MI, mitochondrial morphology shifts dramatically from an elongated, networked structure to a fragmented form, likely due to an imbalance between mitochondrial fusion and fission. Impaired fusion reduces the mitochondrial capacity to maintain structural and functional connectivity, which is evident in ischemic cardiomyocyte models where mitochondrial fragmentation correlates with cellular damage severity.[97] Dysfunctional fusion disrupts mitochondrial functions, impairing energy metabolism, increasing ROS production, and leading to calcium imbalance. Normal fusion preserves mitochondrial membrane potential stability, supports respiratory chain complex assembly, and maintains the ATP generation essential for the high energy demands of cardiomyocytes. However, disrupted fusion during MI impairs oxidative phosphorylation, leading to ATP deficiency, while excessive ROS production further damages the mitochondria and cardiomyocytes.[105]

Recent studies have suggested that Notch1 signaling influences mitochondrial fusion by modulating Mfn2 expression, enhancing cardiomyocyte resilience to ischemic injury. Activation of the Notch1 intracellular domain (NICD) translocates it to the nucleus, where it binds transcription factors to regulate downstream genes, potentially including *Mfn2*.[106] Furthermore, Notch1 and MAPK signaling exhibit mutual regulation, with MAPK-linked phosphorylation of mitochondrial fusion proteins affecting fusion capacity.[107] AMPK is activated under MI-induced energy stress and also regulates fusion by phosphorylating Mfn2, enhancing mitochondrial fusion and preserving mitochondrial morphology.[108] Silent mating type information regulation 2 homolog-1 (SIRT1) and SIRT3 modulate mitochondrial fusion through acetylation status, with SIRT3 deacetylating OPA1 to promote its GTPase activity, facilitating fusion and maintaining mitochondrial structure and function.[109]

Several pharmacological interventions have demonstrated promise in modulating mitochondrial fusion to improve MI outcomes. The mitochondrial fission inhibitor Mdivi-1 indirectly promotes fusion by inhibiting Drp1 GTPase activity, reducing infarct size and enhancing cardiac function in myocardial I/R models. However, Mdivi-1 specificity and clinical viability are uncertain, with concerns about off-target effects and unknown human pharmacokinetics.[106] Melatonin has multi-target effects and activates the Notch1-Mfn2 pathway, promoting mitochondrial fusion and NICD and Mfn2 expression, and has antioxidant properties by scavenging free radicals, inhibiting lipid peroxidation, and supporting mitochondrial biogenesis.[57] Resveratrol activates the SIRT1-SIRT3-Mfn2-Parkin-peroxisome proliferators-activated receptor γ coactivator α (PGC1α) pathway, promoting fusion, autophagy, and biogenesis, thereby reducing infarct size in myocardial I/R models. However, its limited bioavailability presents a challenge.[110] Isosteviol sodium supports fusion by inhibiting fission protein activity, preserving membrane potential, reducing ROS production, and preventing apoptosis in cellular and animal models, although its efficacy and safety should be confirmed with clinical data.[111] Targeted mitochondrial antioxidants such as MitoQ, which accumulate within the mitochondria to clear ROS and protect fusion proteins,

remain in the early clinical stages.[112]

Despite advances in targeting mitochondrial fusion for cardioprotection, significant challenges remain in developing clinically viable therapies, necessitating further research into specificity, dosing, safety, and efficacy for optimal therapeutic outcomes.

Role of mitochondrial fusion in hypertension

Mitochondrial fusion is a finely regulated process essential for cellular homeostasis.[113] In mammalian cells, fusion is primarily mediated by OPA1 and MFN1/2.[114] These proteins enable dynamic mitochondrial fusion and division, maintaining a balanced mitochondrial network. OPA1 is localized to the IMM and is central in fusion, regulating cristae integrity and energy efficiency. OPA1 promotes IMM fusion through polymeric complex formation, and its expression and functional status directly influence fusion efficiency.[115] MFN1 and MFN2 are embedded in the OMM and facilitate membrane tethering by forming homotypic or heterotypic dimers essential for mitochondrial material exchange.[116] MFN1/2 activity is further modulated by post-translational modifications: acetylation at specific sites on MFN1 (K222, K491) reduces its GTPase activity, while phosphorylation by the MEK-ERK pathway at T562 impairs oligomerization.[99] Additionally, stress-related truncation at Ser27 reduces MFN2 degradation, promoting elongation and preventing apoptosis.[117]

Efficient mitochondrial fusion supports intracellular energy transfer and metabolic stability, crucial for cell function. Hypertension disrupts this balance, leading to mitochondrial dysfunction, as shown in animal models and clinical studies. Significant mitochondrial abnormalities in SHR, such as swelling, disrupted cristae, and reduced matrix density, indicate impaired mitochondrial function.[118] Hypertension also alters fusion-related protein expression; specifically, reductions in OPA1 and MFN2 lead to fragmented mitochondrial networks, hindering normal metabolic exchange. Clinical studies in hypertensive patients have revealed similar mitochondrial dysfunctions in vascular smooth muscle and cardiomyocytes. Genetic variations in the fusion-related genes may contribute to hypertension pathogenesis by affecting mitochondrial dynamics, intracellular calcium signaling, and ROS production. For example, the OPA1 single-nucleotide polymorphism (SNP) rs7646250 may alter Forkhead Box A2 (FOXA2) transcription factor binding, enhancing mitochondrial fusion and conferring increased resilience against hypertension.[119] Similarly, the PARK2 SNP rs6902041 has been associated with blood pressure regulation.[120]

Therapeutically, several drugs targeting mitochondrial fusion show potential for hypertension management. O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime (BGP-15) enhances fusion, inhibits fission, and promotes mitochondrial biogenesis. BGP-15 improved mitochondrial morphology and cardiac function in hypertension-induced heart failure models by upregulating fusion proteins (OPA1, MFN2) and downregulating fission proteins (DRP1, MFF).[121] Acacetin similarly augments mitochondrial fusion *via* phosphatidylinositol 3-kinase (PI3K)-Akt signaling, elevating MFN2 levels and suppressing DRP1 and MFF expression, protecting against hypertension-induced cardiac damage.[122]

In summary, mitochondrial fusion integrity is critical in hypertension pathophysiology, influencing cellular energy balance, oxidative stress, and apoptosis, and ultimately affecting organ health. Targeting mitochondrial fusion offers a promising therapeutic strategy for hypertension. However, further studies are needed to elucidate the precise regulatory pathways, optimize fusion-targeting therapies, and establish the long-term safety of these interventions. Continued research may unveil effective, fusion-focused treatment strategies, providing novel options for hypertension management and prevention.

Role of mitochondrial fusion in DCM

Mitochondrial fusion is a critical repair process for mildly damaged mitochondria and consists of two key stages: OMM fusion and IMM fusion, which are facilitated by MFN1/2 and Opa1, respectively. During fusion initiation, MFN1/2 on the OMM of adjacent mitochondria interact to stimulate OMM fusion in a GTP-dependent process.[123] Subsequently, Opa1 promotes IMM fusion, with long (L-Opa1) and short (S-Opa1) isoforms working synergistically.[124,125] The loss of Opa1 impairs fusion capacity and also induces mitochondrial fragmentation and disrupts cristae structure, underscoring its role in mitochondrial integrity. Increased S-Opa1 and reduced L-Opa1 were observed as early as week 5 in diabetic mouse cardiomyocytes, indicating enhanced fission and reduced fusion, which correlated with vacuolar mitochondria and suggested the importance of early intervention.[126]

Mfn2 is pivotal in endoplasmic reticulum (ER)-mitochondrial interactions, which are essential for Ca^{2+} signaling. Hyperglycemia reduces Mfn2 expression, disrupting ER-mitochondria communication and resulting in mitochondrial Ca^{2+} overload, ROS accumulation, mPTP opening, and the activation of caspase-dependent apoptotic pathways, leading to myocardial dysfunction.[127] Increased fission and reduced Opa1 expression, coupled with elevated O-GlcNAc glycosylation, drive mitochondrial dysfunction in type 1 DCM.[126]

Several therapeutic agents have demonstrated potential in modulating mitochondrial fusion to counteract DCM. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, inhibited excessive fission and upregulate MFN1 and Opa1 in diabetic mouse cardiomyocytes, improving mitochondrial morphology, reducing myocardial fibrosis, and attenuating cardiac hypertrophy. AMPK activation may mediate this effect by suppressing division-related proteins and promoting fusion.[123,128] Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, enhanced mitochondrial fusion and autophagy in diabetic models by activating the mTOR-UNC-51-like kinase 1 (ULK1) and AMPK pathways, improving cardiac function and slowing DCM progression.[129,130]

Melatonin is a natural antioxidant that promotes mitochondrial fusion, biogenesis, and autophagy in diabetic rat cardiomyocytes through the SIRT6-AMPK-PGC1α-Akt pathway, maintaining MQC and alleviating DCM.[131,132] Paeonol enhanced mitochondrial fusion under hyperglycemic conditions *via* the casein kinase 2α (CK2α)-Stat3-Opa1 pathway, preventing mitochondrial oxidative stress and preserving respiratory and cardiac function by sustaining Opa1 expression and promoting mitochondrial integrity.[133]

In summary, mitochondrial fusion is essential in cellular homeostasis, and its dysregulation in conditions such as hypertension and DCM highlights its therapeutic potential. Targeting fusion through pharmacological modulation offers a promising approach to managing these cardiovascular diseases, although further studies are needed to elucidate the precise mechanisms, optimize fusion-targeting therapies, and assess their clinical viability for long-term management of DCM and related pathologies.

Role of mitochondrial fusion in drug-induced cardiomyopathy

Doxorubicin (DOX) is a widely used chemotherapeutic agent associated with significant cardiotoxicity, which is largely attributed to mitochondrial fusion disruptions. This cardiotoxicity manifests at both cellular and subcellular levels, exacerbating cardiac dysfunction. Under normal conditions, cardiomyocyte mitochondria form an interconnected tubular or reticular network, supporting efficient energy exchange and material transport essential for cellular homeostasis. However, DOX exposure induces mitochondrial fragmentation, characterized by shortened, dispersed mitochondria that disrupt network integrity, impairing cellular energy metabolism and material transport.[134]

Impaired fusion compromises mitochondrial function at the subcellular level. Following DOX treatment, decreased mitochondrial membrane potential hinders oxidative phosphorylation, reducing ATP production. Furthermore, inhibited fusion elevates ROS levels and disrupts calcium homeostasis, collectively impairing cardiomyocyte contractility and promoting cardiac dysfunction.[135] Trastuzumab is another cardiotoxic drug that similarly downregulates MFN1/2, reducing mitochondrial fusion and contributing to cardiotoxicity in treated patients.[136,137] Mitochondrial fusion proteins are central in this cardiotoxicity. Mfn2 is essential for both mitochondrial fusion and ER-mitochondria interactions and is downregulated by DOX, disrupting calcium and lipid homeostasis and exacerbating cardiomyocyte injury.[138] Opa1 is responsible for IMM fusion and cristae maintenance, undergoes altered proteolytic processing and post-translational modification in response to DOX, further compromising mitochondrial structure and energy metabolism.[139]

Signaling pathways such as PI3K-Akt and p53 also modulate mitochondrial fusion during cardiotoxicity. DOX inhibits PI3K-Akt, reducing phosphorylation of the downstream GSK-3β, which promotes mPTP opening, decreases membrane potential, and induces cyt-c release and apoptosis.[50] Additionally, DOX activates the p53 pathway, which transcriptionally regulates fusion and fission proteins; p53 activation inhibits Mfn2 and upregulates Drp1, driving excessive fission, apoptosis, and cardiac dysfunction.[140]

Therapeutic interventions targeting mitochondrial fusion demonstrate potential for mitigating DOX-induced cardiotoxicity. Shenmai injection is used clinically for cardiovascular support and alleviates DOX-induced toxicity by activating the PI3K-Akt and AMPK pathways, increasing Mfn2 expression, and promoting fusion. Studies on DOX-treated models demonstrated that Shenmai injection reduced apoptosis, oxidative stress, and mitochondrial fragmentation, ultimately preserving cardiac function.[50] Mitochondria-targeted antioxidants, such as MitoQ, directly scavenge mitochondrial ROS, mitigating oxidative damage and preserving mitochondrial fusion and structural integrity, although their efficacy should be verified in further clinical studies.[112] Exosomes derived from human trophoblast stem cells (TSC-Exos) have emerged as promising therapeutic agents. TSC-Exos increase Mfn2 expression, reduce DOX-induced fission, and decrease cardiomyocyte apoptosis rates, as shown by improved cardiac function and reduced fibrosis in DOX-treated mouse models.[141]

In summary, mitochondrial fusion disruptions are critical drivers of cardiotoxicity. Comprehensive understanding of the mechanisms governing mitochondrial fusion and

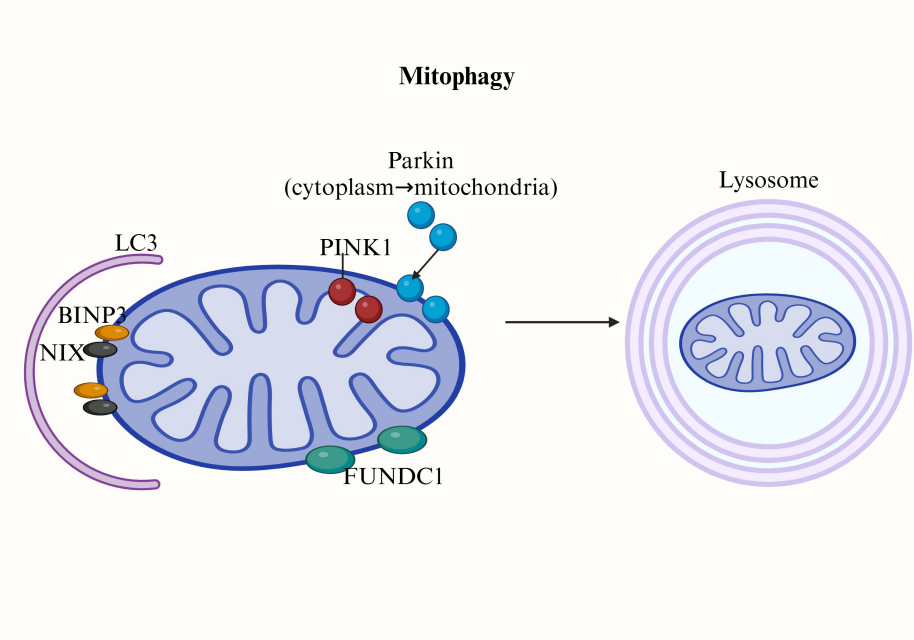


Figure 4: Mitophagy is facilitated through receptor-independent pathways, with key roles played by PARKIN and FUNDC1. Mechanistically, targeted mitochondria are engulfed by autophagy precursors, leading to autophagosome. Thereafter, LC3 conjugates with phosphatidylethanolamine to form LC3II. Ultimately, lysosomes mediate the hydrolytic degradation of autophagosomal contents, including proteins, nucleic acids, carbohydrates, and lipids, which are recycled by the cell to reinstate cellular homeostasis. FUNDC1: Fun14 domain-containing protein 1; BINP3: B-cell lymphoma-2 (BCL2)/adenovirus E1B 19 kDa protein-interacting protein 3; PINK1: PTEN induced putative kinase 1; LC3: microtubule-associated protein 1A/1b-light chain 3.

its dysregulation in drug-induced cardiotoxicity can aid in developing targeted therapeutic strategies. Currently, specific drugs aimed at restoring mitochondrial fusion in cardiomyocytes are lacking, and further exploration is required to optimize combinatory use with cardiotoxic treatments.

MITOPHAGY

Mitophagy is a selective autophagic process targeting damaged mitochondria for degradation and is crucial for maintaining cellular homeostasis, especially in cardiac I/R injury. As with mitochondrial fission and fusion, mitophagy initiation and completion depend on specific adaptor proteins, including Parkin, Bnip3, Fundc1, and Nix (Figure 4). These adaptors operate *via* receptor-dependent or-independent pathways depending on their cellular localization. For example, Bnip3, Fundc1, and Nix are anchored on the OMM and facilitate receptor-dependent mitophagy, whereas Parkin, residing in the cytoplasm, translocates to the mitochondria upon activation, initiating receptor-independent mitophagy.[142,143]

Mechanistically, receptor-dependent mitophagy relies on direct interactions between these adaptors and LC3, a key autophagic protein. The N-terminal regions of Bnip3, Fundc1, and Nix contain LC3-interacting regions (LIRs), which enable binding to LC3. This interaction converts LC3I into its phosphatidylethanolamine-conjugated form, LC3II, a critical step in autophagosome formation.[144] Contrastingly, Parkin-mediated mitophagy operates *via* the PINK1-Parkin pathway. Upon mitochondrial depolarization, PINK1 stabilizes on the OMM, phosphorylating Parkin at Ser65, which triggers Parkin translocation to the mitochondria. Parkin subsequently ubiquitylates numerous OMM proteins, creating ubiquitin chains that recruit LC3 receptors such as prohibitin2 (PHB2), promoting autophagosome formation around damaged mitochondria.[145]

Post-translational modifications, such as phosphorylation, tightly regulate these adaptor-LC3 interactions, ensuring controlled mitophagy activation. For example, Fundc1 phosphorylation at Ser13 by CK2 enhances its binding affinity to LC3, facilitating mitophagy under stress conditions.[146] Similarly, Bnip3 phosphorylation at Ser17 by JNK promotes LC3 interaction,[147] while PINK1-induced phosphorylation of Parkin at Ser65 is essential for its mitochondrial binding and mitophagy initiation.[148]

While mitophagy is generally protective, excessive or dysregulated mitophagy can be maladaptive, leading to cellular energy depletion and cardiomyocyte death. Research has identified three primary mechanisms through which mitophagy may drive cell death. First, selective removal of damaged mitochondria under mild stress supports

cell survival. However, severe stress induces widespread mitochondrial damage that overwhelms the mitophagic capacity, resulting in cell death as mitophagy fails to restore mitochondrial homeostasis. Second, excessive mitophagy can deplete mitochondrial mass, impairing ATP production and predisposing cells to necroptosis rather than ATP-dependent apoptosis. Finally, adaptors such as Bnip3 and Nix, which initiate mitophagy by linking LC3 to damaged mitochondria, are also involved in the apoptosis pathways. For example, Bnip3 overexpression sensitizes cells to intrinsic apoptosis, highlighting the fact that the role of mitophagy in cell survival or death often depends on adaptor activity and cell type.[148]

Therapeutic strategies targeting mitophagy regulation demonstrate potential for mitigating cardiac injury. For example, modulating Fundc1 or Bnip3 phosphorylation enhanced controlled mitophagy under ischemic conditions, balancing mitochondrial turnover without tipping towards excessive degradation.[149,150] Furthermore, understanding cell type-specific mitophagy responses could enable more targeted cardioprotective interventions tailored to optimize MQC without compromising cellular energy reserves.

Role of mitophagy in cardiac I/R injury

Extensive studies have sought to clarify the role of mitophagy in maintaining myocardial function and cardiomyocyte survival in cardiac I/R injury (Figure 4). Current evidence suggests that the influence of mitophagy, whether protective or deleterious, depends largely on the specific adaptor proteins involved. For example, Opa1-mediated mitophagy exacerbates reperfusion-induced cardiomyocyte death due to calcium overload, whereas pharmacological activation of Opa1-induced mitophagy protects against I/R injury. Similarly, ablating Opa1 impaired mitophagy and increased I/R-mediated myocardial damage, underscoring its role in cardioprotection.[93] In contrast, Parkin-mediated mitophagy is harmful in reperfused hearts as it promotes cyclophilin D (CypD)-dependent mPTP opening, a hallmark of necroptosis.[151] Cardiac microvascular I/R injury studies have confirmed that Parkin-mediated mitophagy triggers excessive mitochondrial clearance and ATP depletion, signaling cell death in cardiac microvascular endothelial cells.[152] Bnip3-related mitophagy also exerts lethal effects, as functional abrogation of Bnip3 prevents mitophagy activation and mitigates necrotic cell death in cardiomyocytes.[153]

Conversely, cardiolipin-induced mitophagy appears cardioprotective, attenuating oxidative stress, reducing calcium overload, and enhancing cardiomyocyte survival during I/R injury.[154,155] Similarly, Fundc1 (an OMM protein regulated *via* post-transcriptional modifications) promotes protective mitophagy. Dephosphorylated Fundc1 facilitates mitophagy during ischemia, reversing mitochondrial membrane potential, reducing ROS overproduction, and inhibiting apoptosis in reperfused myocardium.[156,157] The E3 ubiquitin ligase tumor necrosis factor receptor associated factor-2 (TRAF2) also initiates protective mitophagy, mitigating mitochondrial fragmentation in reperfused hearts.[158,159]

Despite these advances, little is known about the molecular crosstalk among mitophagy adaptors in cardiac I/R injury, which complicates the assessment of the net effects of mitophagy. While some studies have indicated mitophagy activation during I/R,[151,160] others have reported its inhibition.[93,161] This discrepancy may stem from different reperfusion time points, as ischemia/hypoxia triggers autophagy (mitophagy) initially.[162,163] During reperfusion, autophagic flux declines within the early phase (0-24 h post-I/R) but increases during the later recovery stages (1-3 days post-I/R).[164,165] Recent work using autophagy receptor reporter mice (CAG-RFP-EGFP-LC3) subjected to renal I/R injury observed minimal autophagy at 4 h post-reperfusion, followed by autophagosome-lysosome fusion from 1 to 3 days post-reperfusion.[166] These observations suggest that early suppression and later activation of mitophagy may constitute an adaptive protective response. In early reperfusion, when ROS surge and calcium overload precipitate significant cell death, cardiomyocytes may suppress mitophagy to avoid the potential activation of mitophagic cell death, which could exacerbate myocardial damage. In contrast, later-stage mitophagy may aid mitochondrial repair and enhance cardiomyocyte recovery.

Notably, mitophagy adaptors exhibit varied dynamics during reperfusion. For example, Parkin is upregulated,[152] whereas Fundc1 is rapidly inactivated in early reperfusion.[156] This suggests that the net mitophagy response involves complex interplay among adaptors, each with unique timing and roles. Furthermore, the mitophagy regulatory landscape is intricate, with multiple adaptors compensating for each other's function. For example, germline deletion of Parkin did not eliminate mitophagy entirely, as mitochondrial E3 ubiquitin protein ligase 1 (Mul1) can substitute for Parkin-mediated mitophagy under physiological conditions.[167] Similarly, BCL2L13, the mammalian homologue of yeast Atg32, partially compensated for basal mitophagy in Atg32-deficient yeast,[168] and Mfn2 knockout-induced mitophagy deficiency was mitigated by nonselective autophagy activation.[169]

These compensatory mechanisms ensure sustained mitophagy across diverse cellular contexts, highlighting the complexity of MQC. Research should focus on elucidating the interactive networks and compensatory pathways among mitophagy adaptors in cardiac I/R injury, as

understanding these interactions may present new avenues for therapeutic intervention.

Role of mitophagy in MI

Mitochondrial autophagy (mitophagy) undergoes complex dynamic changes following MI, which are initially activated in response to ischemia and hypoxia to remove damaged mitochondria and reduce cellular stress. Autophagy-related proteins such as LC3-II increase rapidly immediately post-infarction, indicating elevated mitophagy flux.[170] However, prolonged ischemia and hypoxia may lead to overactive mitophagy, overwhelming autophagic capacity and causing autophagosome accumulation and mitochondrial damage. This impairs MQC and exacerbates cell death.

MI induces marked alterations in mitochondrial morphology and function, characterized by fragmentation, swelling, and functional decline (reduced membrane potential, ATP depletion, increased ROS production). Dysfunctional mitochondria impair cellular energy homeostasis and also release pro-apoptotic factors, such as cyt-c, further driving cardiomyocyte apoptosis.[171] These mitochondrial changes are intricately linked to mitophagy: damaged mitochondria serve as mitophagy substrates, while excessive ROS from dysfunctional mitochondria can hinder autophagic processes, such as autophagosome-lysosome fusion, reducing autophagy efficiency.

The PINK1-Parkin pathway is pivotal in mitophagy regulation. Under normal conditions, PINK1 is imported into the mitochondria, cleaved by the presenilin associated rhomboid like Gene (PARL) protease, and degraded in the cytosol. During MI, mitochondrial depolarization inhibits PINK1 degradation, allowing its accumulation on the OMM. Activated PINK1 recruits Parkin, which ubiquitinates OMM proteins (voltage dependent anion channel 1 Gene [VDAC1], Mfn2), marking them for recognition by autophagy receptors (p62, optineurin, nuclear dot protein 52 [NDP52]) that mediate autophagosome formation.[172,173] FUNDC1 is another key mitophagy receptor activated under hypoxia and is regulated by phosphorylation at Tyr18, Ser13, and Ser17. Hypoxic stress dephosphorylates FUNDC1, enhancing its LC3-binding affinity and promoting mitophagy.[174] Similarly, BNIP3 and BNIP3L/NIX are upregulated in hypoxia and ischemic conditions, where they interact with LC3 to drive mitophagy and influence mitochondrial membrane potential and calcium homeostasis.[175]

Beyond the PINK1-Parkin pathway, other mitophagy mechanisms are essential in the myocardial stress response. ULK1 is a central kinase in autophagy initiation that is activated post-infarction *via* AMPK-mediated phosphorylation independent of mTORC1 inhibition. ULK1 regulates mitophagy receptors, such as phosphorylating FUNDC1 to enhance LC3 interaction, and initiates autophagosome formation.[13,176] Rab9 is a small GTPase that mediates an alternative mitophagy pathway by forming complexes with ULK1 and DRP1 under pathological conditions. Rab9 is involved in mitochondrial transport and localization, facilitating the delivery of damaged mitochondria to autophagosome assembly sites, which may open avenues for therapeutic intervention.[177,178]

Several therapeutic strategies have demonstrated potential in targeting mitophagy for MI treatment. For example, melatonin inhibits excessive PINK1-Parkin-mediated mitophagy following ischemic injury, preserving cardiac function.[152] Natural compounds, such as berberine, modulate mitophagy *via* the hypoxia-inducible factor (HIF)-1α-BNIP3 pathway, attenuating myocardial I/R injury.[179] Gene therapy also presents opportunities: overexpressing mitophagy-promoting genes, such as Parkin and FUNDC1, improved mitochondrial clearance and enhanced cardiac recovery in animal models. However, challenges remain in optimizing gene delivery and ensuring safety.[180]

Mitochondrial autophagy in MI involves complex regulatory networks, balancing protective and potentially deleterious effects. While mitophagy-targeted therapies are promising, further research is necessary to elucidate the mechanistic nuances and optimize strategies for enhanced myocardial recovery.

Role of mitophagy in hypertension

Mitophagy undergoes substantial alterations during the progression of hypertension. Factors such as platelet-derived growth factor (PDGF) induce aberrant mitophagy in VSMCs, which drives VSMC proliferation and migration, ultimately affecting vascular structure and function. PDGF triggers mitochondrial calcium influx and activates Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII), increasing mitochondrial motility and fission while reducing the expression of Mfn2, a protein integral to mitochondrial fusion. These changes collectively promote VSMC proliferation and migration, key features of vascular remodeling in hypertension.[181-183] In renal cells, hypertension-induced mitophagy dysfunction contributes to pathological processes such as tubulointerstitial fibrosis, although the precise mechanisms remain under investigation.[184] Fine-tuning mitophagy may be neuroprotective in neurons with hypertension-related injury, underscoring tissue-specific mitophagy roles in hypertension.[185]

The PINK1-Parkin pathway is a molecular-level primary mechanism of mitophagy regulation. Under physiological

conditions, PINK1 is rapidly degraded within the mitochondria, but accumulates on the OMM upon mitochondrial damage, where it recruits and activates Parkin. Parkin then ubiquitinates several OMM proteins, marking damaged mitochondria for degradation by recruiting autophagy receptors *via* LC3-interacting region (LIR) motifs, which facilitate autophagosome assembly.[184,186] Other receptor-dependent mitophagy pathways involve the BNIP3, NIX, and FUNDC1 proteins, which bind LC3 through LIR motifs. BNIP3 is upregulated in hypoxia and promotes mitophagy while regulating ROS production.[175] Similarly, FUNDC1 undergoes dephosphorylation in response to hypoxia or mitochondrial depolarization, enhancing its interaction with LC3 to induce mitophagy.[150]

Signaling pathways are also crucial in mitophagy regulation within hypertensive contexts. The ras homolog family member A-Rho kinase (RhoA-ROCK) pathway is activated by agents such as apatinib and leads to VSMC dysfunction, characterized by heightened proliferation, migration, and anti-apoptotic capacity. Inhibition by ROCK inhibitors, such as Y27632, mitigates these effects, highlighting the significance of the pathway in hypertension-related VSMC behavior.[187] AngII, PDGF, hypoxia, and hyperglycemia influence mitochondrial dynamics and autophagy, affecting VSMC proliferation and migration. For example, AngII activates DRP1 to promote mitochondrial fission, facilitating VSMC proliferation and migration.[182]

Therapeutic strategies targeting mitophagy in hypertension have yielded promising results. The deubiquitinating enzyme inhibitor PR-619 enhanced Parkin-mediated mitophagy in experimental glaucoma models, protecting retinal ganglion cells by reducing ubiquitin-specific protease 15 (USP15) expression, which otherwise inhibits Parkin-dependent mitophagy.[188] In hypertensive rat models, resveratrol and regular exercise improved systolic blood pressure and cardiac function by modulating stress responses, *i.e.*, oxidative stress, ER stress, nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome activation, and mitophagy. These interventions promoted mitochondrial function by upregulating antioxidative genes, relieving ER stress, inhibiting NLRP3 inflammasome activation, and increasing PINK1 and Parkin expression.[189] Furthermore, the ROCK inhibitor Y27632 and RhoA-ROCK pathway gene silencing (*e.g.*, leukemia-associated Rho guanine nucleotide exchange factor [LARG] knockdown) have demonstrated potential in counteracting apatinib-induced VSMC dysfunction, offering a target for mitigating vascular injury associated with ROCK pathway dysregulation.[187]

Drug development targeting mitochondrial dynamics and mitophagy-related molecules also demonstrates therapeutic promise. The DRP1 inhibitor Mdivi-1 suppresses VSMC proliferation and migration, while upregulating Mfn2 or inhibiting miR-93 (which downregulates Mfn2) similarly limits VSMC proliferation and migration. Bioactive compounds, such as liraglutide and tanshinone IIA, modulate mitochondrial dynamics and mitophagy, providing a basis for potential therapeutic options for cardiovascular diseases linked to mitochondrial dysfunction.[182]

Role of mitophagy in DCM

The role of mitochondrial autophagy in DCM remains contentious. While some studies have reported that cardiac and mitochondrial autophagy are activated in DCM, others have suggested the opposite. These discrepancies may be due to differences in research methodologies, animal models, or diabetes progression stages. Cardiac autophagy in type 2 diabetes mellitus (T2DM)-associated DCM undergoes dynamic shifts: cardiac autophagy in a high-fat diet (HFD)-induced diabetic mouse model was initially activated (within 6 weeks) and subsequently declined, whereas mitochondrial autophagy persisted for approximately 2 months post-activation.[10]

The PINK1-Parkin pathway is essential for mitochondrial autophagy and is notably altered in DCM. Several studies have reported downregulation of PINK1 and Parkin downregulation in diabetic hearts, leading to impaired mitophagy. For example, PINK1 and Parkin expression in type 1 diabetes (T1DM) mouse model cardiomyocytes was reduced, decreasing mitophagic flux. Conversely, some studies have indicated that the PINK1-Parkin pathway may be activated in certain contexts, although its precise role in DCM warrants further investigation.[190] FUNDC1 is another mitophagy regulator that has a complex role in DCM progression: FUNDC1 dysfunction inhibits mitophagy, exacerbating cardiac impairment. However, other studies have suggested that reducing FUNDC1 expression alleviates mitochondrial calcium overload and may confer protection in diabetic heart disease, indicating a nuanced role for FUNDC1 in DCM.[174] Research on BNIP3 and NIX in DCM is limited, although increased mitochondrial ROS and inhibited BNIP3 expression have been reported in prediabetic models, implying a potential role for BNIP3 in DCM pathogenesis. Additionally, changes in SIRT3 expression and activity in DCM may alter the acetylation status of mitophagy-related proteins, modulating mitophagy. For example, SIRT3 deacetylates and regulates Parkin, affecting mitophagy and potentially influencing DCM progression.[191]

Several therapeutic agents have demonstrated promise in modulating mitophagy for DCM treatment. Canagliflozin is an SGLT2 inhibitor that traditionally lowers blood glucose by inhibiting renal glucose reabsorption. Canagliflozin

treatment significantly improved cardiac function in T2DM mouse models, evidenced by increased left ventricular ejection fraction (LVEF) and shortening fraction (LVFS) and decreased left ventricular end-diastolic and end-systolic diameters (left ventricular internal diameter at end-diastole [LVIDd], LVID at end-systole [LVIDs], respectively). Mechanistically, canagliflozin enhances PINK1-Parkin-dependent mitophagy, increasing PINK1 and Parkin expression, LC3II levels, and mitochondrial respiratory capacity while reducing p62 accumulation and oxidative stress, preserving mitochondrial structure and function.[192] Empagliflozin is another SGLT2 inhibitor that normalizes mitochondrial size and density in diabetic hearts by activating the AMPKα1-ULK1-FUNDC1-mitophagy pathway.[193,194] Metformin is a classic antidiabetic drug that enhanced cardiac autophagy and improved cardiac function in diabetic OVE26 mice with long-term use.[195] Additionally, coenzyme Q10 is a potent antioxidant that may aid in stabilizing mitochondrial function and mitigating oxidative stress-related mitochondrial damage in DCM treatment.[196]

Despite these advances, challenges remain in optimizing drug therapies targeting mitophagy for DCM. Key issues, such as determining optimal dosing, defining therapeutic windows, and assessing long-term safety, still require clarification through further research.

Role of mitophagy in drug-induced cardiomyopathy

DOX is a well-studied chemotherapeutic agent widely recognized for its potent anti-cancer efficacy and cardiotoxic effects. DOX-induced cardiotoxicity is attributed to mitochondrial damage, dysfunction, disrupted dynamics, excessive autophagy, and both the apoptosis and necrosis of cardiomyocytes, impairing cardiac function. DOX treatment downregulated Parkin expression in mouse hearts and H9c2 cardiomyoblasts, while Parkin overexpression activated mitophagy, reduced apoptosis, and mitigated DOX-induced cardiotoxicity.[197]

Yes-associated protein (YAP) influences Parkin transcriptional regulation. DOX treatment decreases YAP expression; conversely, exogenous YAP inhibits DOX-induced mitochondrial fragmentation and apoptosis, promotes autophagic flux, and upregulates Parkin expression by interacting with TEA domain transcription factor 1 (TEAD1), alleviating DOX-induced cardiotoxicity.[198] Additionally, DOX reduces TANK-binding kinase 1 (TBK1) phosphorylation levels, impairing cardiac function, increasing mortality, and promoting interstitial fibrosis. TBK1 mediates mitochondrial protection through SQSTM1/p62-dependent mitophagy, and its overexpression mitigates DOX-induced mitochondrial damage and cardiotoxicity. Conversely, knocking down TBK1 or inhibiting its phosphorylation exacerbates these deleterious effects.[199]

DOX also activates p53, which interacts with Parkin to inhibit its mitochondrial translocation, blocking mitophagy. This inhibition results in the accumulation of damaged mitochondria and consequent cardiotoxicity. Harpagoside (HAR) inhibits p53-Parkin binding, facilitates Parkin translocation to mitochondria, and restores mitophagy, alleviating DOX-induced cardiotoxicity without compromising the anti-cancer efficacy of DOX.[200]

Furthermore, DOX reduces plasma SIRT6 expression while elevating lactate levels. *In vitro*, SIRT6 overexpression reduces DOX toxicity in cardiomyocytes and enhances its anti-cancer effects. *In vivo*, SIRT6 overexpression ameliorates DOX-induced cardiac dysfunction and potentiates its tumor-suppressive activity. SIRT6 enhances mitochondrial biogenesis and mitophagy by inhibiting serum/glucocorticoid-regulated kinase 1 (SGK1), coordinating metabolic remodeling to protect cardiomyocytes from DOX-induced energy depletion.[201]

MITOCHONDRIA-DEPENDENT CELL DEATH

Heart injury is characterized by the rapid loss of functional cardiomyocytes through programmed cell death (PCD), a terminal mechanism of MQC. As a central determinant of cell fate, the mitochondria mediate cardiomyocyte death *via* two primary routes (Figure 5). The first pathway involves OMM hyperpermeabilization, facilitating cyt-c release into the cytoplasm. Cyt-c subsequently activates caspase-9, which cleaves and activates caspase-3, initiating classical mitochondria-dependent apoptosis.[202,203] This apoptotic pathway is marked by mitochondrial membrane potential decline, excessive ROS generation, upregulated Bax, and downregulated Bcl-2.[204,205]

The second route of cell death involves sustained mPTP opening driven by VDAC multimerization, CypD phosphorylation, and upregulation of the adenine nucleotide translocator (ANT), although the exact composition of the mPTP complex remains contentious.[206,207] mPTP opening induces IMM permeability, leading to mitochondrial swelling, electron transport chain dysfunction, and disruption of the tricarboxylic acid (TCA) cycle.[208,209] These mitochondrial disturbances lead to ATP depletion, cytoplasmic swelling, membrane rupture, and organelle breakdown, culminating in necroptotic cell death.[210] Unlike apoptosis, necroptosis is non-energy-dependent and characterized by cellular and organelle swelling, extensive mitochondrial disruption, blebbing, and eventual

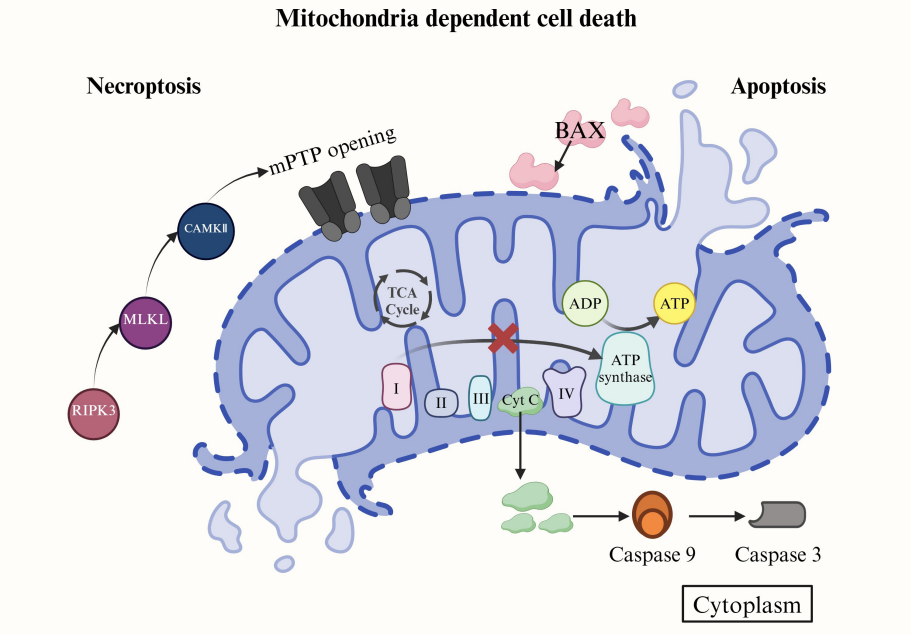


Figure 5: Mitochondrial cell death encompasses apoptosis and necrosis. Apoptosis is regulated by OMM permeabilization, mitochondrial membrane potential reduction, BAX activation, and caspase-9. Necrosis is triggered by RIPK3-MLKL-CAMKII pathway activation and mPTP opening. Subsequently, dysfunction of the mitochondrial electron transport chain and termination of the TCA cycle lead to ATP depletion, cytosolic swelling, and membrane rupture. OMM: outer mitochondrial membrane; RIPK3: receptor-interacting protein kinase 3; MLKL: mixed lineage kinase domain-like protein; mPTP: mitochondrial permeability transition pore; CaMKII: Ca^{2+}-calmodulin-dependent protein kinase II; TCA: tricarboxylic acid; ATP: adenosine 5′-triphosphate.

irreversible plasma membrane rupture.[211,212]

At the molecular level, key regulators of mitochondrial apoptosis and necroptosis are critical for understanding the signal transduction pathways underlying mitochondria-dependent cell death in myocardial injury. Bax is a primary inducer of OMM permeabilization in the apoptotic pathway, whereas Bcl-2 acts as a protective antagonist. Under normal conditions, Bcl-2 binds Bax, forming a heterodimer that neutralizes the pro-apoptotic potential of Bax. Bax expression is upregulated upon stimulation, and cytoplasmic Bax forms homodimers, which migrate to and integrate into the OMM, initiating permeabilization.[213,214] Consequently, Bcl-2 and Bax levels, and mitochondrial membrane potential reduction, are reliable mitochondrial apoptosis markers.

The critical signaling molecules in necroptosis include receptor-interacting protein kinase 3 (RIPK3), phosphoglycerate mutase 5 (Pgam5), and mixed lineage kinase domain-like protein (Mlkl). During reperfusion, oxidative stress and calcium overload directly or indirectly activate RIPK3, leading to Pgam5 and Mlkl phosphorylation and Mlkl oligomerization at the cell membrane, where Mlkl forms pores that mediate lytic cell death.[215] Recent studies have implicated mPTP opening as a downstream effect of RIPK3 activation in cardiac I/R injury. First, RIPK3 activates CaMKII, which promotes mPTP opening.[216] Additionally, RIPK3 upregulation enhances Pgam5 expression, which phosphorylates CypD, increasing mPTP opening frequency.[217] Together, RIPK3 expression, Mlkl phosphorylation, and mPTP opening present promising targets for modulating mitochondria-driven necroptosis in cardiac injury contexts.

Role of mitochondria-dependent cell death in cardiac I/R injury

Apoptosis has long been considered the principal mechanism of cardiomyocyte death in cardiac I/R injury, contributing significantly to myocyte loss during and post-I/R. However, recent studies have challenged this notion, indicating that the pan-caspase inhibitor Z-Val-Ala-DL-Asp-fluoromethylketone (zVAD) rescues only 30% of cell death in I/R injury, whereas deletion of the necroptosis-related genes, such as RIPK3, reduces cardiomyocyte death by nearly 50%. These results suggest that necroptosis, rather than apoptosis, may be the dominant form of PCD in cardiac I/R injury.[218] This shift in understanding is supported by observations of infarct composition, where the infarct core ("umbra") exhibits predominantly necroptotic cell death, while the surrounding ischemic penumbra is marked by apoptotic cells.[219,220]

Despite advances in characterizing the regulatory mechanisms of apoptosis and necroptosis, their interplay remains incompletely understood. Studies have indicated

that RIPK3, a key necroptotic effector, is also an upstream activator of caspase-8-dependent apoptosis in MI.[221,222] Conversely, caspase-8 activation degrades RIPK3, inhibiting necroptosis. Mitochondrial apoptosis inhibitors such as cellular inhibitors of apoptosis 1 and 2 (c-IAP1 and c-IAP2) further influence this crosstalk by promoting RIPK3 ubiquitination and preventing necroptosis activation.[223,224]

Additional evidence from cellular reperfusion models suggests that RIPK3 may engage in mitochondrial dynamics by activating Drp1, contributing to mitochondrial potential loss and potentially promoting mitochondrial apoptosis. Interestingly, deleting RIPK3 reversed Fundc1-induced mitophagy, generating an anti-apoptotic signal in reperfused hearts.[218] Conversely, inhibiting autophagy flux triggers necroptotic cardiomyocyte death, underscoring a reciprocal relationship between necroptosis and MQC mechanisms.[225]

Together, these results reveal an intricate overlap between apoptosis and necroptosis, especially in their downstream effects, despite being regulated by distinct upstream pathways. Consequently, cardioprotective strategies aimed at mitigating myocardial I/R injury should consider both anti-apoptotic and anti-necroptotic interventions for comprehensive efficacy.

Role of mitochondria-dependent cell death in MI

Cardiomyocytes receive ischemic and hypoxic damage during MI, which activates the mitochondrial apoptotic pathway. Proapoptotic proteins, such as Bax, translocate from the cytoplasm to the mitochondria, initiating mitochondrial release of cyt-c. This release triggers apoptotic protease activator 1 (Apaf-1) to form apoptosomes, which activate caspase-9 and subsequently the effector caspase-3, leading to apoptosis. Studies using Bax knockout mice have demonstrated reduced cardiomyocyte apoptosis, decreased infarct size, and improved cardiac function, underscoring Bax-mediated mitochondrial apoptosis as a pivotal mechanism in MI pathology.[226,227]

MI impairs mitochondrial respiratory chain complex activity, decreases ATP production, reduces mitochondrial membrane potential, and increases mitochondrial permeability, facilitating the release of cyt-c and other pro-apoptotic factors. Concurrently, mitochondrial ROS accumulation induces oxidative stress, damaging cell membranes, proteins, and DNA, further compromising cell structure and promoting apoptosis. For example, cardiomyocytes in the infarcted region in MI rat models exhibited significant mitochondrial morphological changes, such as swelling and disrupted cristae, and elevated expression of the apoptosis-related proteins Bax and caspase-3, linking mitochondrial dysfunction closely to apoptosis.[228,229] Atorvastatin modulated WW domain-containing E3 ubiquitin protein ligase 2 (WWP2) expression and stabilized the Bcl-2-Bax axis within the mitochondrial apoptosis pathway, reducing apoptosis, enhancing cardiac function, and alleviating vascular wall thickening and fibrosis in MI rat models.[230]

Key proteins such as RIPK1, RIPK3, and MLKL are critical in mitochondrial necroptosis. The RIPK3-CaMKII-mPTP signaling axis is activated in MI, with RIPK3-mediated phosphorylation of CaMKII promoting mPTP opening. This causes mitochondrial membrane potential collapse, leading to necroptotic cell death. Treatment with the necroptosis inhibitor necrostatin-1 reduced infarct size and improved cardiac function in MI models, highlighting necroptosis as a significant contributor to MI pathology.[231]

Lipid peroxidation has emerged as a crucial driver of myocardial damage in MI, suggesting a role for ferroptosis in MI pathology. Ferroptosis inhibitors have demonstrated promising cardioprotective effects. For example, the iron chelator deferoxamine (DFO) binds excess iron ions to reduce iron overload and inhibit ferroptosis. DFO treatment reduced myocardial iron levels in MI animal models, mitigated tissue damage, and improved cardiac function.[230] Antioxidants such as vitamin E, which scavenges ROS and inhibits lipid peroxidation, aid in maintaining mitochondrial membrane integrity and provide additional cardioprotection. Post-intervention studies have indicated that vitamin E reduced oxidative stress, limited ferroptotic cell death in cardiomyocytes, and partially restored cardiac function in MI models.[231]

Role of mitochondria-dependent cell death in hypertension

Oxidative stress levels are elevated in hypertension, increasing ROS production. ROS-induced mitochondrial dysfunction in vascular endothelial cells disrupts mitochondrial respiratory chain complex activity, reduces ATP synthesis, and decreases the mitochondrial membrane potential. These disruptions can trigger the mPTP opening, releasing pro-apoptotic factors such as cyt-c, which activates the apoptosis signaling cascade and induces cell death. Studies on SHR models have reported significantly elevated ROS levels in vascular tissues, accompanied by mitochondrial morphological and functional abnormalities, such as swelling and cristae disruption, suggesting that oxidative stress-induced mitochondrial dysfunction is pivotal in hypertension pathogenesis.[232]

AngII is a critical hypertension mediator that exerts its effects by activating the type 1 receptor (AT1R), which activates Ras-MAPK-ERK signaling within the rostral ventrolateral medulla (RVLM) of the brainstem.[233] This

pathway increases the expression of the mitochondrial pro-apoptotic proteins Bax and Bad, decreases anti-apoptotic Bcl-2 levels, and activates caspase-3 *via* the mitochondrial apoptotic pathway, leading to neuronal apoptosis. In the SHR model, heightened Ras, p38 MAPK, and ERK activity in the RVLM are accompanied by increased Bax and Bad expression and enhanced caspase-3 activity, implicating the Ras-MAPK-ERK pathway as a key driver of mitochondrial apoptosis in hypertension-induced sympathetic overactivation.[234]

Emerging studies suggest that ferroptosis (a form of iron-dependent cell death) may also contribute to hypertension pathogenesis. Iron metabolism imbalance in hypertensive states may cause mitochondrial iron overload, amplifying ROS production *via* the Fenton reaction, thereby exacerbating oxidative stress, compromising mitochondrial membrane integrity, and promoting cell death. Lipid peroxidation is an important facet of ferroptosis, wherein polyunsaturated fatty acids are oxidized under ROS attack, undermining cellular membrane integrity and culminating in cell death. Despite its potential significance, the precise role and regulatory mechanisms of mitochondrial ferroptosis in hypertension remain unclear and warrant further investigation.

Atorvastatin is a commonly prescribed lipid-lowering agent that has demonstrated vascular protective effects relevant to hypertension management. Atorvastatin reduced AngII-induced vascular endothelial injury and apoptosis in cellular models by upregulating the E3 ubiquitin ligase WWP2, which mediates ATP synthase F1 subunit alpha (ATP5A) degradation through the ubiquitin-proteasome pathway. This regulation aids in stabilizing the Bcl-2-Bax axis within the mitochondrial apoptosis pathway, mitigating cell death. Atorvastatin improved endothelial function in hypertensive animal models, lowered blood pressure, and reduced vascular wall thickening and fibrosis, suggesting that its protective effects on endothelial cells are closely linked to enhanced mitochondrial function.[233,235] Additionally, traditional Chinese medicine (TCM) compounds, such as icariside II, have demonstrated protective effects against hypertension-related damage. Icariside II lowered blood pressure in SHR models, improved left ventricular function, and reduced cardiomyocyte apoptosis and fibrosis potentially by inhibiting the apoptosis signal-regulating kinase 1 (ASK1)-c-Jun N-terminal kinases (JNK)-p38 pathway, thereby reducing oxidative stress and preserving mitochondrial function in cardiomyocytes.[235]

While advances have been made in elucidating the relationship between mitochondrial death and hypertension, significant limitations remain. Mechanistic studies often focus on a limited number of signaling pathways, leaving the broader regulatory network underlying mitochondrial death in hypertension incompletely understood. For example, the specific role of mitochondrial ferroptosis in hypertension and mitochondrial death heterogeneity across different cell types requires further exploration to fully characterize the effects on disease pathology.

Role of mitochondria-dependent cell death in DCM

DCM is closely linked to ferroptosis, which is critical in DCM pathogenesis and progression. Iron overload is a hallmark of diabetes; for example, transferrin receptor 1 (TFR1) upregulation increases cellular iron uptake, while ferroportin (FPN) downregulation reduces iron export and enhances mitochondrial iron accumulation.[236] Excess iron catalyzes ROS production *via* the Fenton reaction, precipitating mitochondrial dysfunction, as evidenced by decreased respiratory chain complex activity, ATP depletion, reduced mitochondrial membrane potential, and enhanced mPTP opening.[237] These mitochondrial disruptions further elevate ROS levels, creating a vicious cycle that exacerbates cardiomyocyte damage.

Lipid peroxidation is significantly increased in DCM. Hyperglycemia-induced accumulation of advanced glycation end-products (AGEs), heightened oxidative stress, and mitochondrial ROS attack polyunsaturated fatty acids (PUFAs) in cellular membranes, initiating lipid peroxidation. Peroxidation products such as MDA and 4-hydroxynonenal (4-HNE) compromise membrane integrity, alter permeability, and disrupt ion homeostasis, driving ferroptotic cell death. This process further activates inflammatory responses and recruits immune cells, aggravating myocardial tissue damage.[238]

Antioxidant defense system dysfunction also contributes to ferroptosis in DCM. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of antioxidant responses and normally sequestered by Keap1 in the cytoplasm. Under oxidative stress, Nrf2 dissociates from Keap1, translocates to the nucleus, and activates antioxidant gene expression. However, the stability of Keap1 and subsequent Nrf2 activation are impaired in DCM, reducing the expression of downstream antioxidants such as glutathione peroxidase 4 (GPX4) and diminishing cellular defenses against oxidative stress and ferroptosis.[239]

Several pharmacological interventions have demonstrated potential in modulating ferroptosis in DCM. For example, canagliflozin is a SGLT2 inhibitor that attenuates ferroptosis in animal and cell models by restoring cardiac iron homeostasis, enhancing the glutathione (GSH)-GPX4 axis, and activating AMPK signaling, thereby ameliorating oxidative stress and cardiac function.[240] While metformin

Table 1: Compounds or drugs that target MQC in cardiovascular disease

Name	Mechanism	Target	Disease	Reference
Mdivi-1	Mitochondrial fission	Drp1	Myocardial I/R injury	31
Mdivi-1	Mitochondrial fission	Drp1	MI	46, 47
Mdivi-1	Mitochondrial fission	Drp1	Hypertension	58
Y-27632 (ROCK inhibitor)	Mitochondrial fission	Drp1	Hypertension	60
Nimbolide	Mitochondrial fission	Akt/mTOR	DCM	62
Perillaldehyde	Mitochondrial fission	miR-133a-3p	DCM	63
AuCur	Mitochondrial fission	PPARα	DCM	64
Sevoflurane	Mitochondrial fusion	OPA1/MFN2	Myocardial I/R injury	81
Epigallocatechin gallate	Mitochondrial fusion	OPA1	Myocardial I/R injury	94
Melatonin	Mitochondrial fusion	Notch1/Mfn2	MI	57
Resveratrol	Mitochondrial fusion	Sirt1/Sirt3-Mfn2-Parkin-PGC1α	MI	110
BGP-15	Mitochondrial fusion	OPA1/MFN2	Hypertension	121
Acacetin	Mitochondrial fusion	MFN2	Hypertension	122
Liraglutide	Mitochondrial fusion	AMPK/OPA1	DCM	129
Shenmai injection	Mitochondrial fusion	AMPK/Mfn2	Drug cardiomyotoxicity	50
Melatonin	Mitophagy	PINK1/Parkin	MI	153
Berberine	Mitophagy	HIF-1α/BNIP3	MI	180
Resveratrol	Mitophagy	PINK1/Parkin	Hypertension	190
Y27632	Mitophagy	RhoA/ROCK	Hypertension	188
Canagliflozin	Mitophagy	PINK1/Parkin	DCM	193
Empagliflozin	Mitophagy	AMPKα1/ULK1/FUNDC1	DCM	194
Harpagoside	Mitophagy	p53/Parkin	Drug cardiomyotoxicity	201
Atorvastatin	Apoptosis	Bcl-2/Bax	MI	231
Atorvastatin	Apoptosis	WWP2/Bcl-2/Bax	Hypertension	234
Icariside II	Apoptosis	ASK1-JNK/p38	Hypertension	236
H_2	Ferroptosis	Nrf2/GPx4/GSH	DCM	243
MCC950	Pyroptosis	NLRP3	Drug cardiomyotoxicity	251

DRP1: dynamin-related protein 1; I/R: ischemia-reperfusion; MI: myocardial infarction; ROCK: Rho-associated protein kinase; Akt/mTOR: protein kinase B/mammalian target of rapamycin; DCM: diabetic cardiomyopathy; AuCur: Curcumin-AuNCs; PPARα: peroxisome proliferators-activated receptors α; OPA1: optic atrophy protein 1; MFN2: mitofusin 2; SIRT1: silent mating type information regulation 2 homolog-1; PGC1α: peroxisome proliferators-activated receptor γ coactivator α; AMPK: adenosine 5′-monophosphate-activated protein kinase; PINK1: PTEN induced putative kinase 1. HIF-1α: hypoxia-inducible factor-1 alpha; Bcl-2: B-cell lymphoma-2; BNIP3: BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; ULK1: UNC-51-like kinase 1. FUNDC1: Fun14 domain-containing protein 1; WWP2: WW domain-containing E3 ubiquitin protein ligase 2; ASK1: apoptosis signal-regulating kinase 1; JNK: c-Jun N-terminal kinases; Nrf2: Nuclear factor erythroid 2-related factor 2; GPx4: glutathione peroxidase 4; GSH: glutathione; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3.

has demonstrated cardioprotective effects in diabetes-related myocardial injury, its direct role in ferroptosis inhibition within DCM requires further investigation.[241] Additionally, molecular hydrogen (H_2) has demonstrated promise in mitigating ferroptosis and mitochondrial apoptosis by promoting SYNV1-Kelch-like ECH-associated protein 1 (Keap1) interaction and regulating the Nrf2-GPx4-GSH pathway, exerting protective effects on diabetic myocardium.[242] Nevertheless, most results have been derived from animal or *in vitro* studies, underscoring the need for clinical validation and mechanistic elucidation to optimize therapeutic approaches targeting ferroptosis in DCM.

Necroptosis is also markedly elevated in DCM, with increased expression and activity of key necroptotic molecules observed in streptozotocin (STZ)-induced and db/db diabetic mouse models. Elevated RIPK3 expression promotes necrosome formation through RIPK1 binding and MLKL phosphorylation. MLKL oligomerizes and translocates to the cell membrane, disrupting membrane integrity and leading to necroptotic cell death.[243-246]

Mitochondrial dysfunction, including reduced membrane potential and increased oxidative stress, forms a feedback loop with necroptosis in DCM. Mitochondrial impairment amplifies ROS production, which activates necroptotic signaling, while necroptosis-associated mPTP opening and ion imbalance further compromise mitochondrial integrity, perpetuating myocardial injury.[243,244]

Upregulated RIPK3 in DCM also activates CaMKII *via* phosphorylation and oxidation, promoting mitochondrial fragmentation and dysfunction, exacerbating cardiomyocyte injury and necroptosis.[216,243] Additionally, RIPK1 and RIPK3 activate the NLRP3 inflammasome, which recruits and cleaves pro-caspase-1 into active caspase-1, leading to interleukin-1β (IL-1β) maturation and release, amplifying the inflammatory responses.[244,245]

Therapeutic strategies targeting necroptosis have demonstrated promise. Hydrogen sulfide (H_2S) donors, such as sodium hydrosulfide (NaHS), improved cardiac function in db/db and STZ-induced diabetic mice by inhibiting oxidative stress and reducing RIPK1, RIPK3, and MLKL phosphorylation, attenuating necroptosis. H_2S also suppresses NLRP3 inflammasome activation, reducing IL-1β release and subsequent inflammatory damage to cardiomyocytes. Furthermore, H_2S promotes the transcription of retinoic acid receptor-related orphan receptor α (RORα), which attenuates oxidative stress and necroptosis through an RORα-dependent pathway, conferring cardioprotection in DCM.[245,246] Other promising strategies include modulating CaMKIIδ splice variants and activity by targeting protein phosphatase 1 inhibitor 1 (I1PP1), which has demonstrated potential in improving cardiac function and reducing necroptotic myocardial injury in diabetic models. These results suggest that targeting CaMKII activity could be a viable therapeutic avenue for DCM, although further investigation is necessary for drug development and clinical application.[243]

Role of mitochondria-dependent cell death in drug-induced cardiomyopathy

Drug-induced cardiotoxicity studies have described multifaceted mechanisms of mitochondrial death, which encompass various forms of regulated cell death, including mitochondrial apoptosis, necroptosis, ferroptosis, and pyroptosis. For example, the widely used chemotherapeutic agent DOX induces cardiomyocyte apoptosis, impairing cardiac function. Atorvastatin improved cardiac function and reduced vascular wall thickening and fibrosis in DOX-treated models, underscoring its protective role in mitigating drug-induced cardiac damage.[233,247]

In necroptosis, critical mediators such as RIPK1, RIPK3, and MLKL contribute significantly to mitochondrial necroptotic signaling in drug-induced cardiotoxicity. Treating DOX-induced cardiotoxicity in mice with necrostatin-1, a necroptosis inhibitor, reduced infarct size and improved cardiac function, indicating the pivotal role of necroptosis in drug-related cardiac injury.[243]

Ferroptosis is another pathway implicated in cardiotoxicity and closely associated with dysregulated iron metabolism. The iron chelator DFO binds excess iron ions, reducing iron overload and inhibiting ferroptosis. DFO treatment decreased myocardial iron levels in animal models of DOX-induced cardiotoxicity, alleviated cardiac damage, and improved cardiac function. Similarly, ferristatin-1 was efficacious in inhibiting ferroptosis and mitigating myocardial injury in DOX-treated models.

Pyroptosis in drug-induced cardiotoxicity is intricately linked to inflammasome activation. DOX triggers NLRP3 inflammasome activation, promoting pro-caspase-1 cleavage into active caspase-1 and leading to the maturation and release of inflammatory cytokines such as IL-1β and IL-18.[248] Concurrently, gasdermin D (GSDMD) cleavage facilitates membrane pore formation, a hallmark of pyroptosis, which results in cell swelling, blistering, and eventual lysis.[249] DOX-treated cardiomyocytes exhibited increased expression and activation of NLRP3, caspase-1, and GSDMD, coupled with distinct morphological changes typical of pyroptosis.

Therapeutic interventions targeting these pathways have demonstrated potential. For example, the NLRP3 inflammasome inhibitor MCC950 significantly reduced DOX-induced myocardial injury by inhibiting NLRP3 assembly and activation, curtailing pyroptotic cell death and reducing inflammatory cytokine release.[250] Arbuscular mycorrhiza fungi (AMF) is a mitochondrial function regulator that attenuates DOX-induced pyroptosis and inflammation by suppressing the stimulator of interferon genes-nucleotide-binding domain (NBD), leucine-rich repeat (LRR), and pyrin domain (PYD)-containing protein 3 (STING-NLRP3) signaling pathway, effectively mitigating cardiotoxicity.[251] MitoTEMPO is a mitochondria-targeted antioxidant that has demonstrated cardioprotective effects by reducing mitochondrial damage and indirectly inhibiting pyroptosis.[252] Additionally, SIRT3 overexpression alleviates DOX-induced cardiotoxicity by suppressing NLRP3-mediated pyroptosis, restoring autophagic balance, and dampening inflammatory responses.[244]

Despite these advances, challenges remain in achieving target-specific modulation of mitochondrial death pathways in drug-induced cardiotoxicity. Many agents lack specificity, affecting unrelated physiological pathways and potentially causing adverse effects. For example, some

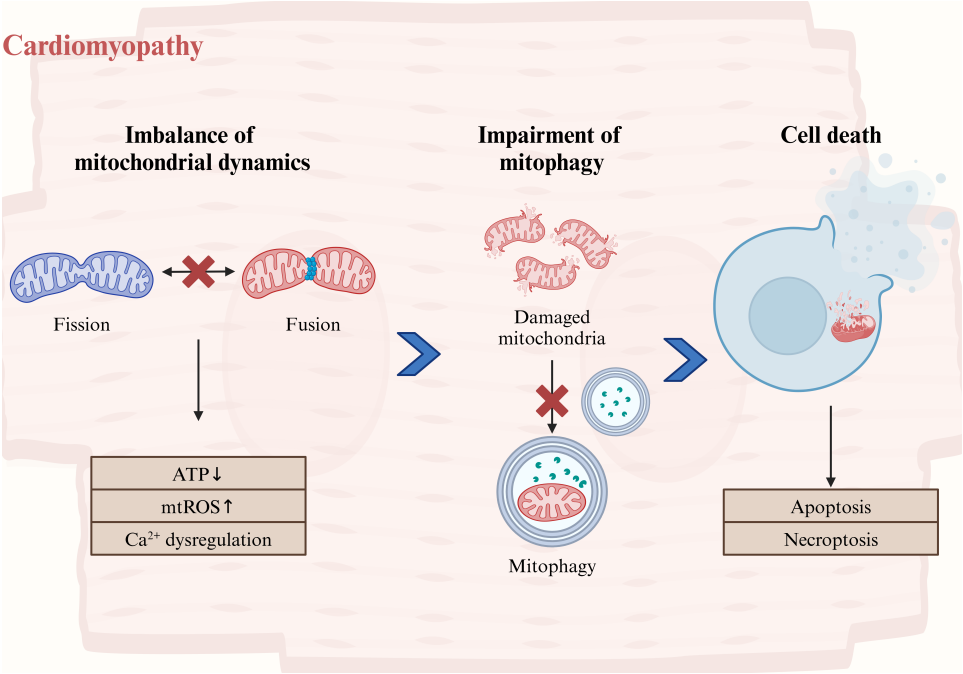


Figure 6: Role of mitochondrial dynamic imbalance, impaired mitochondrial autophagy, and cell death in cardiomyopathy. The balance between mitochondrial division and fusion is disrupted, impairing the mitochondrial network structure and function. Increased division and decreased fusion lead to mitochondrial fragmentation, which decreases ATP energy production, elevates mitochondrial ROS levels, and causes imbalanced calcium ion regulation. The increased damaged mitochondria cannot be effectively cleared by mitochondrial autophagy, which aggravates mitochondrial dysfunction and cell stress. Cardiomyocyte survival is threatened and they may die by apoptosis or necroptosis. The apoptotic pathway involves key proteins such as BAX, caspase-9, and caspase-3, while necrotic apoptosis is closely related to molecules such as RIPK3, MLKL, and CAMKII. ATP: adenosine 5′-triphosphate; mtROS: mitochondrial reactive oxygen species; RIPK3: receptor-interacting protein kinase 3; MLKL: mixed lineage kinase domain-like protein; CaMKII: Ca^{2+}-calmodulin-dependent protein kinase II.

ferroptosis inhibitors may inadvertently disrupt normal iron homeostasis. Furthermore, the complex pharmacokinetics and multi-target effects of these drugs complicate therapeutic outcome stability and reliability, underscoring the need for more precise, targeted approaches in managing mitochondrial dysfunction-associated cardiotoxicity.

CONCLUSION AND FUTURE PERSPECTIVES

MQC represents a critical adaptive system that mitigates cellular damage across various cardiovascular diseases, including MI, DCM, drug-induced cardiomyopathy, and hypertension. MQC preserves mitochondrial integrity, balances energy supply, and maintains cellular homeostasis under physiological and pathophysiological stress through mitochondrial fission, fusion, mitophagy, and regulated cell death pathways. The balance between mitochondrial fission and fusion determines the overall outcome of the mitochondrial network, and is achieved through various mechanisms. For example, mitochondrial fission promotes the isolation and elimination of damaged mitochondria, while fusion allows functional complementarity and mixing of contents, buffering the effects of damaged proteins and maintaining mitochondrial function.[253] Mitochondrial fission and fusion imbalances can lead to mitochondrial dysfunction in different disease states, which affects cell health and survival. For example, increased mitochondrial fission in myocardial I/R injury is strongly associated with mitochondrial damage and cardiomyocyte death.[8] In hypertension, increased mitochondrial fission leads to VSMC proliferation and migration, which affects vascular structure and function.[58] This suggests that regulating mitochondrial fission and fusion is essential for maintaining energy metabolism and cellular stress responses. Mitochondrial division and fusion imbalances lead to mitochondrial dysfunction, which can be partially compensated by autophagy. However, damaged mitochondria can accumulate if autophagy is inhibited, exacerbating mitochondrial dysfunction. Biogenetic processes can replenish mitochondria reduced by autophagy, but the inhibiting these process will result in a further decline in mitochondrial numbers and function. Eventually, an imbalance in these processes can lead to mitochondrial dysfunction, activating the cell death pathway and leading to cardiomyocyte apoptosis and necrosis (Figure 6).

The rapid activation of MQC mechanisms in MI and I/R injury can remove damaged mitochondrial fragments, while timely fusion and mitophagy aid in restoring mitochondrial network function, protecting cardiomyocytes from

oxidative and ischemic damage. Similarly, MQC is critical in DCM in addressing mitochondrial iron overload, elevated ROS, and the metabolic imbalances that drive disease progression. In drug-induced cardiomyopathy, such as that caused by DOX, dysregulated MQC contributes to excessive mitochondrial fission, increased ROS production, and cardiomyocyte apoptosis, leading to cardiac dysfunction. Protective strategies targeting specific MQC pathways, such as inhibiting fission or enhancing mitophagy, have therapeutic potential for mitigating the cardiotoxic effects of chemotherapy agents. Furthermore, MQC mechanisms are essential for preserving endothelial and VSMC function in hypertensive cardiovascular disease, where mitochondrial dynamics and autophagy imbalances exacerbate oxidative stress, endothelial dysfunction, and inflammation, contributing to vascular remodeling and hypertension progression (Table 1).

Future research should focus on precisely modulating these MQC pathways to enhance their cardioprotective effects while minimizing the detrimental outcomes associated with prolonged or excessive activation. Fine-tuning mitophagy, fission, and fusion responses to specific stressors could enhance resilience to injury and improve outcomes across various cardiomyopathies. Furthermore, an integrated therapeutic approach targeting both apoptosis and necroptosis in combination with MQC modulation may present a synergistic strategy for conditions such as MI and DCM. Emerging pharmacological and genetic interventions directed at specific MQC proteins, such as those involved in the PINK1-Parkin pathway, Drp1-mediated fission, and antioxidant responses, are promising. However, translating these promising preclinical findings into effective clinical therapies presents several challenges. One major challenge is the complexity of mitochondrial biology and the specificity of targeting the MQC pathway without causing adverse off-target effects. Developing drugs that can selectively regulate MQC components, such as Drp1 inhibitors or mitosis enhancers, requires a deep understanding of the molecular mechanisms involved and their effects on human physiology. Patient population heterogeneity and disease progression variability complicate the treatment response prediction and treatment strategy optimization.

Another challenge is delivering the therapeutic agent to the mitochondria inside the heart muscle cells. Ensuring that the drug achieves its intended goal while minimizing systemic adverse effects is a key aspect of developing effective MQC targeted therapies. Additionally, the long-term safety and efficacy of these treatments must be rigorously evaluated in clinical trials to determine their usefulness in routine clinical practice. Current clinical trials have reported that ABI-009 (rapamycin derivative, nanoparticle albumin-binding sirolimus) treats Leigh or Leigh-like syndrome by targeting mitochondrial autophagy (NCT03747328). A phase Ia/Ib trial of KL1333 (NCT03888716), a cellular nicotinamide adenine dinucleotide (NAD^+) level modulator, is being conducted in people with primary mitochondrial diseases.[254]

Mitochondrial transplantation is an emerging approach for treating mitochondrial diseases by using isolated functional mitochondria to restore dysfunctional mitochondria in defective cells. Baharvand *et al.*'s study of platelet-derived mitochondrial transplantation in 30 patients with acute ST-elevation myocardial infarction (STEMI) observed a slightly larger improvement in the LVEF over 40 days in the intervention group compared to the control group.[255] Coupled with technological innovations in drug delivery and precision medicine, advances in understanding the molecular basis of MQC are poised to facilitate the transition from the laboratory to the bedside. While a large body of relevant data currently supports an association between MQC and cardiovascular disease, relying primarily on relevant data to establish causality is subject to limitations. While these data can reveal associations between changes in MQC and cardiovascular disease phenotypes, they do not fully prove causation. Future research can overcome these limitations by relying more on genetic models, mechanism studies, and clinical trials to directly manipulate the MQC process and validate these findings in human samples. This approach will contribute to a more accurate understanding of the role of MQC in cardiovascular disease and provide a solid foundation for developing new treatment strategies.

In conclusion, while the road to clinical application is challenging, the preclinical and emerging clinical data on MQC modulation offer a glimpse into a future where targeted therapies could significantly affect the treatment landscape of cardiovascular diseases. Additionally, advancements in biomarker-based diagnostics to monitor mitochondrial health in real-time could enable more personalized MQC-targeted therapies. Understanding the interplay of these pathways within different cellular environments, such as cardiomyocytes, endothelial cells, and smooth muscle cells, will be critical for developing highly specific and safe treatments. Innovative therapeutic avenues will likely emerge as the complex dynamics of MQC are decoded further, with the potential to significantly improve outcomes in a broad spectrum of cardiovascular diseases, from acute ischemic events to chronic metabolic and hypertensive heart disease.

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Author Contributions

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Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

Authors state no conflict of interest.

Use of Large Language Models, AI and Machine Learning Tools

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No additional data.

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