Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(8): 47390
https://doi.org/10.31083/FBL47390

Review

Septic Cardiomyopathy and Mitochondrial Quality Control

Xiangyi Pu[1], Zhaoqi Yan[1], Zhiming Liu[1], Xing Chang[1,*], Ruxiu Liu[1,*]

[1]Internal Medicine of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 100053 Beijing, China
*Correspondence: xingchang_tcm@outlook.com (Xing Chang); liuruxiu1@163.com (Ruxiu Liu)
Academic Editor: Paramjit S. Tappia
Submitted: 15 October 2025 Revised: 17 January 2026 Accepted: 26 January 2026 Published: 31 July 2026

Abstract

Septic cardiomyopathy (SCM) is a prevalent and serious cardiac complication arising from sepsis-induced multiple organ dysfunction syndrome (MODS). The pathogenesis of SCM is complex and primarily involves immune-inflammatory responses, oxidative stress, programmed cell death, and mitochondrial dysfunction. In recent years, mitochondrial quality control (MQC) has attracted growing interest as a central mechanism for maintaining cellular homeostasis and myocardial energy metabolism in SCM. This review systematically summarizes recent advances in four key MQC mechanisms involved in SCM: (1) phosphatase and tensin homolog-induced putative kinase 1 (PINK1)/Parkin-mediated mitophagy; (2) mitochondrial dynamics, including dynamin-related protein 1 (Drp1)/fission protein 1 (FIS1)-driven fission and optic atrophy protein 1 (OPA1)/mitofusin (MFN)-regulated fusion; (3) mitochondrial biogenesis under the regulatory control of the peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)/nuclear respiratory factor 1 (NRF1)/mitochondrial transcription factor A (TFAM) axis; and (4) the mitochondrial unfolded protein response (UPRmt), which maintains mitochondrial proteostasis through mediators such as C/EBP homologous protein (CHOP), YME1-like protease (YME1L), and Overlapping activity with m-AAA protease 1 (OMA1). These mechanisms have been shown to work synergistically to regulate mitochondrial clearance, renewal, and functional maintenance. Any imbalance among them can exacerbate myocardial injury. This review also emphasizes the redox crosstalk between oxidative stress and immune inflammation, with an emphasis on the pivotal contributions of NADPH oxidase 2 (NOX2), high mobility group box 1 (HMGB1), and the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in vascular endothelial dysfunction and cardiac depression. In conclusion, preserving the dynamic equilibrium of MQC is crucial for preventing or reversing SCM and may present novel molecular targets and therapeutic strategies.

Keywords: sepsis; cardiomyopathies; mitochondrial dysfunction; mitophagy; mitochondrial dynamics; oxidative stress; inflammation

1. Introduction

Myocardial dysfunction caused by sepsis is marked by transient and reversible cardiac abnormalities that can progress to left ventricular dilation accompanied by loss of contractile function. In severe cases, it can result in multiple organ failure or even death. Sepsis is a critical clinical syndrome defined by life-threatening organ dysfunction caused by an aberrant and dysregulated host response to infection [1]. The contemporary definition of sepsis highlights organ dysfunction as a core component, with cardiac impairment—driven by systemic inflammation and altered blood volume distribution—serving as a critical factor and further intensified by the reduced efficiency of tissue oxygen utilization [2]. Emerging evidence suggests that septic myocardial dysfunction is predominantly mediated by two principal mechanisms: the direct impact of invading pathogens, and activation of the immune system triggered within the host [3,4]. Pathophysiologically, myocardial injury arises from a multifaceted interplay between reduced myocardial perfusion, intrinsic myocardial depression, and mitochondrial dysfunction [4]. These processes are highly interconnected, and although each is recognized as a key contributor, growing evidence points to mitochondrial dysfunction as a central factor in the initiation and maintenance of sepsis-induced cardiac abnormalities (Fig. 1).

This review aims to elucidate the mechanisms underlying sepsis-induced myocardial dysfunction and explore potential therapeutic targets, with a particular focus on mitochondrial dysfunction.

This schematic summarizes the integrated mechanisms linking inflammation, oxidative stress, and mitochondrial quality control (MQC) dysfunction in septic cardiomyopathy. Under septic conditions, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) such as lipopolysaccharide (LPS) and mitochondrial DNA (mtDNA) can activate Toll-like receptor 4 (TLR4)–nuclear factor kappa B (NF-κB) signaling. This leads to excessive production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as the release of high-mobility group box 1 (HMGB1).

Inflammatory signaling is tightly coupled to oxidative stress through enhanced generation of mitochondrial reactive oxygen species (mtROS) and activation of NADPH oxidase 2 (NOX2). This forms a self-amplifying redox–inflammatory loop that overwhelms antioxidant de-

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

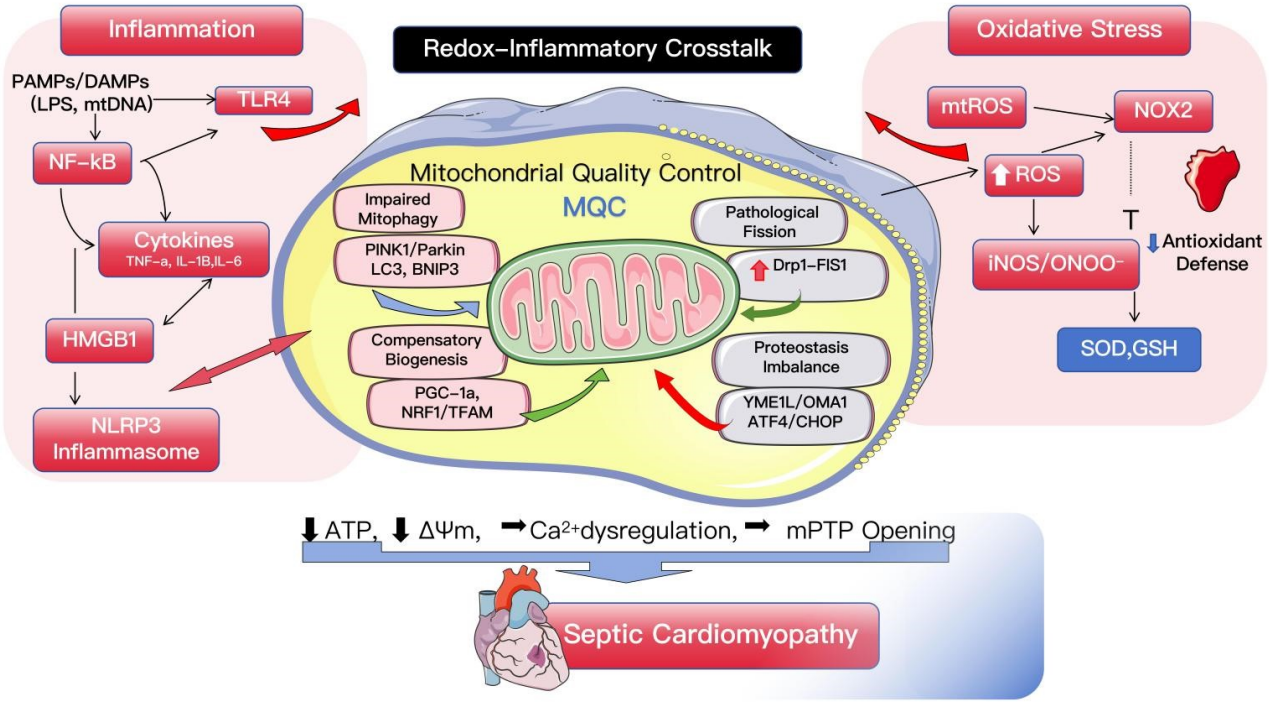


Fig. 1. Redox–inflammatory crosstalk–driven mitochondrial quality control failure in septic cardiomyopathy. TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; HMGB1, high mobility group box 1; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; PINK1, phosphatase and tensin homolog-induced putative kinase 1; BNIP3, B-cell lymphoma2 Interacting Protein 3; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; NRF1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A; Drp1, dynamin-related protein 1; FIS1, fission protein 1; YME1L, YME1-like protease; OMA1, Overlapping activity with m-AAA protease 1; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; ATP, adenosine triphosphate; mPTP, mitochondrial permeability transition pore; mtROS, mitochondrial reactive oxygen species; ROS, reactive oxygen species; NOX2, NADPH oxidase 2; iNOS, inducible nitric oxide synthase; $ONOO^-$, peroxynitrite; SOD, superoxide dismutase; GSH, glutathione; ΔΨm, mitochondrial membrane potential.

fenses, including superoxide dismutase (SOD) and glutathione (GSH), and promotes inducible nitric oxide synthase (iNOS)–derived reactive nitrogen species.

These converging stress signals target MQC pathways, resulting in impaired phosphatase and tensin homolog-induced putative kinase 1 (PINK1)/Parkin-mediated mitophagy, pathological dynamin-related protein 1 (Drp1)–fission protein 1 (FIS1)-dependent mitochondrial fission, disruption of mitofusin 1/2 (MFN1/2)- and optic atrophy protein 1 (OPA1)-mediated mitochondrial fusion, and insufficient compensatory mitochondrial biogenesis governed by the peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)–nuclear respiratory factor 1 (NRF1)–mitochondrial transcription factor A (TFAM) axis. Concurrent dysregulation of mitochondrial proteostasis, involving YME1-like protease (YME1L), OMA1 zinc metallopeptidase (OMA1), activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP), further exacerbates mitochondrial dysfunction.

Collectively, MQC failure leads to impaired oxidative phosphorylation, decreased adenosine triphosphate (ATP) production, loss of mitochondrial membrane potential (ΔΨm), calcium (Ca^{2+}) dysregulation, opening of the mitochondrial permeability transition pore (mPTP), cardiomyocyte injury, and ultimately the development of septic cardiomyopathy.

2. Literature Search Strategy

This literature search was conducted primarily in the PubMed database to identify relevant studies addressing mitochondrial dysfunction and quality control mechanisms in sepsis-induced cardiomyopathy. The search focused on articles published within the three most recent years. If insufficient literature was retrieved for specific topics, the search time frame was progressively extended to five years, and when necessary, up to 10 years to ensure comprehensive coverage of foundational and mechanistic studies.

Eligible article types included review articles, systematic reviews, randomized controlled trials, clinical trials, and meta-analyses. Studies were restricted to those published in English. Case reports, conference abstracts, editorials, and non-peer-reviewed articles were excluded.

In addition, the reference lists of key articles were manually screened to identify additional relevant studies that may not have been captured through the initial database search. This stepwise and iterative search strategy was applied to enhance methodological transparency and reproducibility, while ensuring the inclusion of both recent advances and seminal contributions in the field.

3. Pathological Mechanisms of Septic Cardiomyopathy

3.1 Inflammatory Injury

Sepsis is a clinical condition marked by systemic physiological and biochemical disturbances caused by an abnormal host response to infection that may result in multi-organ injury and potentially fatal outcomes [5]. Bacterial toxins and inflammatory mediators initiate a systemic immune response, underpinning the complex interaction between pathogens and the host immune system that characterizes the pathophysiology of sepsis.

As depicted in Fig. 2, the host immune system identifies invading pathogens by detecting PAMPs, including LPS, lipoteichoic acid, flagellin, bacterial DNA, as well as mannans from fungi and single- or double-stranded viral RNA. These mediators engage pattern recognition receptors (PRRs) expressed on host cells, such as TLRs. PRRs can also recognize DAMPs, which serve as endogenous danger signals, thus activating the innate immune response [3,6,7]. To date, ten TLR isoforms have been identified in the human genome [8]. Upon binding with PAMPs, these receptors activate intracellular signaling cascades that ultimately lead to the translocation of NF-κB into the nucleus, thereby promoting the transcription of pro-inflammatory mediators [9,10]. The onset of inflammation is attributed to an imbalance between pro-inflammatory and anti-inflammatory cytokines [11]. Within the spectrum of pro-inflammatory mediators, the excessive elaboration of interleukins (e.g., IL-6) and TNF-α represents a pivotal driver of myocardial cellular injury and apoptosis. In this pathogenic cascade, TNF-α and IL-1β exert synergistic effects to induce myocardial depression [12]. Both cytokines can also stimulate nitric oxide (NO) production—a process that perturbs normal cardiac physiological function [5,13]. HMGB1, another critical pro-inflammatory mediator, not only exacerbates endotoxin-induced mortality but also serves as a pivotal regulator in sepsis-associated cardiac dysfunction. Zhang et al. [14] identified at least one mechanistic pathway through which HMGB1 elicits cardiac dysfunction: upon interaction with TLR4, HMGB1 promotes the generation of intracellular reactive oxygen species (ROS), thereby initiating oxidative stress. This signaling cascade activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which subsequently mediates phosphorylation of the ryanodine receptor 2 (RyR2). Furthermore, HMGB1 induces Ca^{2+} spark-mediated Ca^{2+} leakage from the sarcoplasmic reticulum (SR) via TLR4 and ROS-dependent signaling. This leads to depletion of SR Ca^{2+} stores, impairment of excitation-contraction (EC) coupling, and ultimately a reduction in myocardial contractility [9].

3.2 Oxidative Stress and Inflammation

An imbalance between the generation and degradation of ROS is a hallmark of most cardiovascular disorders [15,16,17]. In the setting of sepsis, oxidative stress can promote adaptive responses under hypoxic conditions, facilitate bacterial clearance, and support endothelial repair. However, sepsis also disrupts the balance between ROS, reactive nitrogen species (RNS), and antioxidant defense systems. Endothelial cells continuously produce superoxide anions (O_2^-), which are converted by SOD into hydrogen peroxide (H_2O_2). H_2O_2 is subsequently detoxified into water by catalase and peroxidases. To counteract oxidative insults, mammals possess robust enzymatic systems such as glutathione peroxidase, glutathione reductase, and non-enzymatic antioxidants like vitamins A, C, and E. The balance between oxidants and antioxidants constitutes the redox homeostasis. During inflammation, oxidative stress is characterized by excess ROS and RNS, decreased activity of antioxidant enzymes such as SOD and catalase, reduced GSH levels, and potential vitamin deficiencies, leading to impaired antioxidant defenses [18]. The inflammatory process has been clearly linked to vascular dysfunction and a range of cardiovascular diseases, including hypertension, hypercholesterolemia, and coronary atherosclerosis [19,20]. These non-septic disease models provide well-established illustrative paradigms for understanding fundamental redox–immune interactions. Mechanistically, mitochondrial superoxide/H_2O_2 activates immune cells through redox signaling, leading to activation of phagocytic NOX2 [21,22]. Following infusion of angiotensin II (AT-II) in mice, T cells isolated from the spleen showed increased mitochondrial superoxide/H_2O_2 production, elevated TNF-α levels, and enhanced energy metabolism via increased ATP generation. These changes could be reversed *in vitro* by treatment with mitochondria-targeted antioxidants, such as the SOD mimetic mitoTEMPO [23]. Mitochondrial ROS production is a major trigger for NOX2 activation through redox crosstalk [24,25], and NOX2 activation is essential for the activation, recruitment, and vascular infiltration of monocytes and T cells [26,27,28]. This was confirmed by Wenzel et al. [26] via monocyte transfer experiments: mice lacking myeloid monocytes were tolerant to AT-II infusion; this tolerance was abolished by transplanting wild-type monocytes, but not $gp91^{phox-/-}$ ($Nox2^{-/-}$) monocytes. Similarly, Guzik et al. [28] showed that transferring wild-type T cells (but not B cells) into $RAG1^{-/-}$ immunodeficient mice restored AT-II-induced hypertension, an effect not seen with $p47^{phox-/-}$ T cells. B cells also play a substantial role in the progression of AT-II–induced hypertension [29]. Conversely, blood pressure normalization in hu-

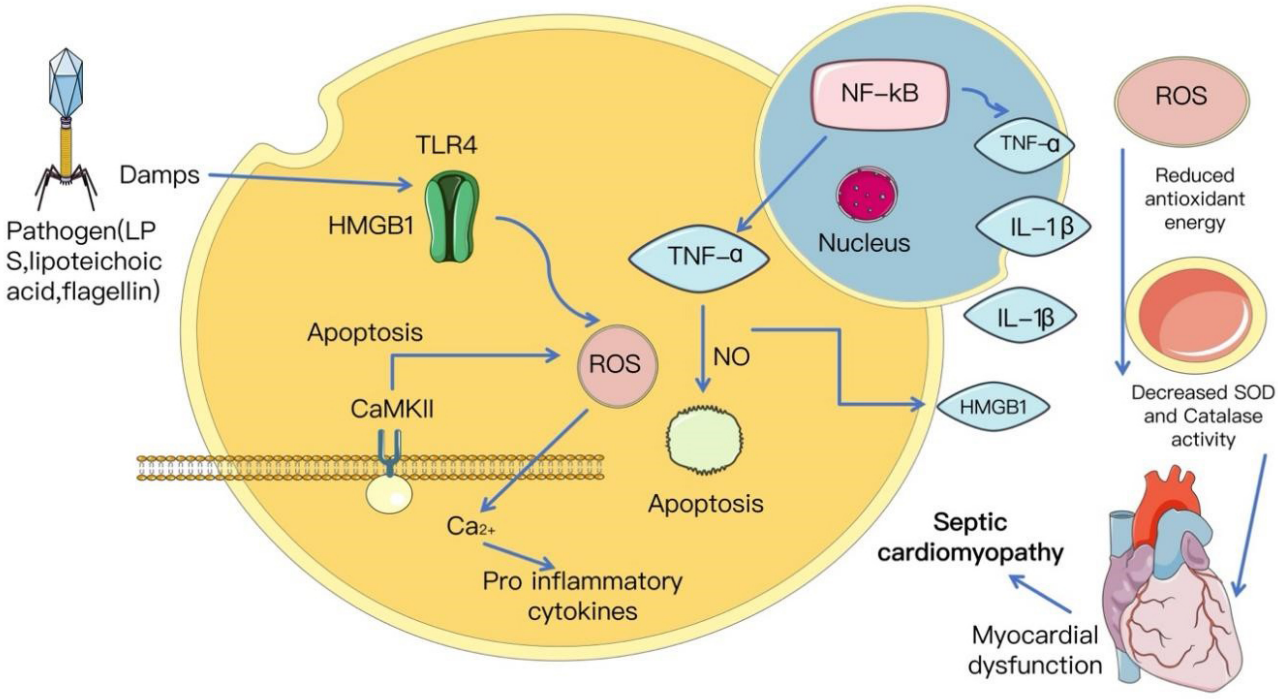


Fig. 2. Inflammatory and oxidative stress–mediated mechanisms contributing to sepsis-induced cardiomyopathy. LPS, lipopolysaccharide; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; Ca^{2+}, calcium; NO, nitric oxide.

manized hypertensive mouse models leads to reduced immune cell infiltration [30]. Although these findings arise primarily from hypertension models, they provide critical mechanistic insight into how mitochondrial ROS-NOX2 redox crosstalk drives immune activation. Importantly, in the setting of sepsis and septic cardiomyopathy (SCM), similar redox-sensitive immune mechanisms are engaged in a far more acute and systemic manner. In this context, PAMPs, DAMPs, and overwhelming cytokine release act as dominant upstream triggers, resulting in excessive NOX2 activation, amplification of mitochondrial oxidative stress, endothelial dysfunction, and profound myocardial depression.

Redox-dependent interactions between inflammation and coagulation have also been described in experimental hypertension, including elevated tissue factor (TF) expression, enhanced leukocyte-platelet interactions, immune cell infiltration, oxidative stress, endothelial dysfunction, and increased blood pressure. Targeting adhesion molecules and coagulation-related pathways such as Vascular Cell Adhesion Molecule-1 (VCAM-1), TF, thrombin, coagulation factor XI (FXI), platelet glycoprotein Ibα (GPIbα), and Mac-1 via pharmacological, genetic, or immunological approaches has been shown to reverse these pathological alterations [31]. Platelet function is therefore gaining increasing attention in cardiovascular risk assessment. Mean platelet volume (MPV) has been associated with hypertension and rheumatoid arthritis [32], although technical limitations currently hinder its widespread clinical application [33]. Notably, in sepsis, platelets actively participate in immunothrombosis and redox-sensitive inflammatory signaling, thereby contributing to microvascular dysfunction and myocardial injury. The complex interactions among immune cells (especially monocytes/macrophages), platelets, and vascular cells have been systematically reviewed, together with their regulation via redox mechanisms [34,35,36,37].

Oxidative stress also contributes to inflammation by promoting protein and DNA oxidation, generating oxidized nucleotides, activating protein kinases (e.g., ERK1/2, JNK), and inhibiting protein phosphatases. For instance, mtROS can enhance mitochondrial membrane permeability through opening the mPTP. This mechanism promotes the release of oxidized mtDNA, which functions as a DAMP to initiate sterile inflammatory responses [34,38]. ROS further modulate inflammatory signaling through multiple mechanisms: redox-sensitive protein complexes (e.g., p53–JNK, nuclear factor erythroid 2-related factor 2 (Nrf2)–Keap1); regulation of inflammatory mediators (e.g., HMGB1, S100 proteins, and DAMPs); oxidative modification of transcription factors, including Nrf2, activator protein 1 (AP-1), NF-κB, and hypoxia-inducible factor-1α (HIF-1α) [39,40,41]. Furthermore, highly reactive lipid-derived compounds termed isoketals have been implicated in hypertension by forming adducts with proteins, promoting immune cell infiltration into the vasculature, and contributing to elevated blood pressure [42]. The cellular redox status modulates monocyte migration and macrophage recruitment [43]. Additional mechanisms of redox regula-

tion include oxidative modification of Mitogen-Activated Protein Kinase (MAPK) phosphatase 1 [44], regulation of the Slingshot-1L interaction with binding protein 14-3-3ζ [45,46], and alterations in S-glutathionylation patterns [46]. Extensive evidence supports widespread crosstalk between oxidative stress and inflammatory signaling pathways. For example, activation of the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is redox-dependent [47,48,49,50,51,52], while HMGB1, a critical "redox hub", plays an essential role in orchestrating the inflammatory cascade [41,53,54]. Moreover, oxidative stress profoundly influences the formation of neutrophil extracellular traps (NETs) [55,56,57,58,59,60] as well as the regulation of numerous inflammatory transcription factors and mediators [35]. Notably, both NLRP3 and HMGB1—key regulators of the inflammatory response—are tightly controlled by cysteine redox modifications. The crystal structure of NLRP3 contains a conserved disulfide bond that links the pyrin (PYD) domain with the nucleotide-binding domain, rendering the inflammasome highly sensitive to changes in cellular redox status [52]. Similarly, HMGB1 exhibits distinct biological activities based on its redox state: in its fully reduced form, it acts as a chemokine; when a disulfide bond is formed between Cys23 and Cys45, it functions as a pro-inflammatory cytokine; and upon terminal oxidation of all cysteine residues, it becomes biologically inactive [54].

Direct molecular evidence for the interaction between oxidative stress and inflammation comes from genetically modified mouse models targeting antioxidant defenses or ROS-generating enzymes. These models exhibit pronounced inflammatory phenotypes. For example, GPx-1 knockout mice show age-related increases in the inflammatory marker CD68 and vascular ROS formation (detected via DHE staining), suggesting a link between mitochondrial ROS and chronic, low-grade inflammation in aging [61,62]. Additionally, SOD2 (MnSOD) heterozygous knockout mice exhibit increased NOX2 activity in leukocytes and worsened endothelial dysfunction, especially following exposure to AT-II [63]. Likewise, knockout of heme oxygenase-1 (HO-1) led to increased NOX2 levels, elevated vascular ROS, and worsened endothelial injury in the context of AT-II-induced hypertension [64]. HO-1 deficiency also promoted CCR2 (CD192) expression, leukocyte rolling and adhesion, and increased neutrophil and monocyte infiltration.

In sepsis-associated myocardial injury, the above inflammatory and oxidative stress signals do not operate in isolation, but instead form a persistently amplified pathogenic network through a highly coupled NOX2–HMGB1–NLRP3 signaling axis. Dysregulation of this axis can synergistically suppress mitochondrial biogenesis and disrupt the balance of mitochondrial autophagy and dynamics. Collectively, NOX2, HMGB1, and the NLRP3 inflammasome constitute a tightly interconnected pathogenic signaling axis that plays a central amplifying role in sepsis-induced myocardial injury. Aberrant activation of NOX2 markedly increases the generation of ROS in both the cytosol and mitochondria, leading to mitochondrial DNA damage, impairment of oxidative phosphorylation (OXPHOS), and the reduction of $\Delta\Psi m$ [65,66]. Sustained NOX2-derived ROS further suppresses mitochondrial biogenesis by inhibiting the PGC-1α–NRF1–TFAM signaling axis, thereby limiting the renewal and replacement of damaged mitochondria [67]. Concurrently, oxidative stress promotes Drp1-dependent mitochondrial fission while disrupting mitochondrial fusion dynamics, resulting in mitochondrial network fragmentation and functional decline. Under conditions of impaired autophagic flux, such dysfunctional mitochondria are prone to accumulation or excessive clearance [68].

As a prototypical DAMP, HMGB1 can be released from injured or stressed cardiomyocytes. It then amplifies inflammatory responses through TLR4- and RAGE-dependent signaling pathways, further exacerbating mitochondrial dysfunction and energetic failure [69]. Mechanistically, HMGB1 participates directly in regulating autophagy by modulating the interaction between Beclin-1 and Bcl-2. It exhibits a context-dependent "biphasic" effect: transient activation of autophagy facilitates clearance of damaged mitochondria, whereas sustained or excessive HMGB1 signaling induces excessive or non-selective autophagy, leading to mitochondrial depletion and aggravated cardiomyocyte injury [70]. Prolonged HMGB1-mediated inflammatory stimulation can also suppress mitochondrial biogenesis and trigger maladaptive endoplasmic reticulum stress responses, further disrupting mitochondrial proteostasis [14].

Mitochondrial damage driven by NOX2 and HMGB1 strongly activates the NLRP3 inflammasome through increased mitochondrial ROS production, mtDNA release, and externalization of cardiolipin [49,71]. Once activated, the NLRP3 inflammasome promotes caspase-1 activation and the release of pro-inflammatory cytokines, further amplifying mitochondrial dysfunction and energetic collapse and ultimately exacerbating cardiomyocyte injury [72]. Importantly, impaired mitophagy prevents the efficient removal of inflammasome-activating mitochondria, rendering NLRP3 signaling difficult to terminate and ultimately establishing a self-amplifying vicious cycle of "inflammation–mitochondrial damage" [73,74].

3.3 Programmed Cell Death

A large body of evidence has demonstrated that ROS and RNS serve as pivotal mediators in the triggering of programmed cell death [75,76]. For instance, H_2O_2, hydroxyl radicals (·OH), and peroxynitrite ($ONOO^-$) can induce oxidative modification of lipids, proteins, and DNA, as well as damage to various organelles, including mitochondria and the endoplasmic reticulum—ultimately resulting in exten-

sive biomolecular impairment [77,78,79]. These oxidative insults can trigger apoptotic pathways through the intrinsic mitochondrial pathway, as well as extrinsic pathways involving death receptors and the endoplasmic reticulum [80,81,82]. In particular, $ONOO^-$ has been shown to directly increase mitochondrial outer membrane permeability. This induces mPTP, disrupts the electron transport chain (ETC), and halts ATP synthesis, ultimately leading to irreversible cell death [77,83]. Moreover, both $ONOO^-$ and H_2O_2 rapidly activate the Fas death receptor pathway and downstream effectors caspases, including caspase-2, -7, and -9 [84]. It is important to note that ROS/RNS exert concentration-dependent effects on cells: low levels may activate pro-survival signaling pathways, moderate levels induce apoptosis, while high concentrations or prolonged exposure typically result in necrosis. Thus, the severity of redox imbalance dictates whether endothelial cells (ECs) undergo apoptosis or necroptosis, both of which contribute significantly to endothelial dysfunction. Mechanistically, apoptotic and necrotic ECs both exhibit procoagulant properties. For instance, in an apoptosis model induced by staurosporine, Bombeli et al. [85,86] observed rapid phosphatidylserine (PS) exposure and TF activation on the cell surface. This was accompanied by a marked reduction in anticoagulant factors, including thrombomodulin, tissue factor pathway inhibitor (TFPI), and heparan sulfate [85,86]. In contrast, necrotic cells release large quantities of DAMPs and PS-positive microparticles, which further amplify both local and systemic coagulation and inflammatory responses [63,87]. Ultimately, EC death leads to structural disruption and increased membrane permeability, exacerbating protein and fluid extravasation from capillaries under septic and oxidative stress conditions, and thereby aggravating organ damage [88].

PAMPs, including LPS, lipoteichoic acid, and flagellin, together with DAMPs such as HMGB1, activate TLR4 signaling in cardiomyocytes during sepsis.

Activation of TLR4 triggers downstream NF-κB signaling, promoting the production of proinflammatory cytokines, including TNF-α and IL-1β. Concurrently, excessive generation of ROS, Ca^{2+} overload mediated by CaMKII, and NO production contribute to mitochondrial dysfunction and cardiomyocyte apoptosis.

Sustained oxidative stress and inflammatory signaling impair antioxidant defense systems, characterized by reduced SOD and catalase activity, ultimately leading to myocardial dysfunction and the development of septic cardiomyopathy.

4. Physiological Regulation and Therapeutic Targets of Mitochondrial Quality Control

4.1 Mitophagy

Mitophagy, a selective form of autophagy, represents a fundamental mechanism for preserving mitochondrial quality and maintaining cellular homeostasis. By selectively degrading damaged or dysfunctional mitochondria, mitophagy ensures the proper functioning of cellular metabolism [89,90]. Currently, two major mitophagy pathways have been identified: the ubiquitin-dependent (non-receptor-mediated) pathway and the receptor-mediated pathway [91], as shown in Fig. 3. The ubiquitin-dependent mitophagy pathway is primarily regulated by PINK1 and its downstream E3 ubiquitin ligase Parkin. Under physiological conditions, PINK1 is imported into the mitochondrial intermembrane space and rapidly degraded by proteases [92]. In contrast, loss of $\Delta\Psi m$ results in the accumulation of PINK1 on the outer mitochondrial membrane (OMM) [93]. At this site, PINK1 phosphorylates itself, as well as ubiquitin molecules and Parkin at Ser65, thereby activating Parkin and recruiting it to the mitochondria [94,95]. Activated Parkin ubiquitinates several OMM proteins, including mitofusin 2 (Mfn2) [96], Tom20 [97], and voltage-dependent anion channel 1 (VDAC1). These ubiquitinated proteins are subsequently recognized by autophagic adaptors, including nuclear dot protein 52 (NDP52) and optineurin, which interact with microtubule-associated protein 1 light chain 3 (LC3). This interaction facilitates the recruitment of autophagic membranes to encapsulate the damaged mitochondria. The resulting autophagosome sequesters various mitochondrial components—proteins, nucleic acids, carbohydrates, and lipids—which are ultimately delivered to lysosomes for degradation [98,99].

The receptor-mediated mitophagy pathway functions independently of ubiquitin. Instead, specific mitochondrial membrane proteins bind directly to autophagy-related protein 8 (Atg8) family proteins via an LC3-interacting region (LIR) motif. BCL2-like protein 13 (BCL2L13), an OMM protein containing two LIR motifs, interacts with the Unc-51 like autophagy activating kinase 1 (ULK1) autophagy-initiating complex. Its phosphorylation enhances mitophagic activity, and it is considered a mammalian homolog of Atg32 [100,101].

B-cell lymphoma2 Interacting Protein 3 (BNIP3), which is monomeric in the cytoplasm under basal conditions, forms dimers upon stress and becomes anchored to the mitochondrial membrane. Phosphorylation of BNIP3 at Ser17 and Ser24 enhances its affinity for LC3 [102,103]. NIX, also known as BCL2 interacting protein 3 (BNIP3L), is structurally similar to BNIP3. Phosphorylation of NIX at Ser212 facilitates dimerization and membrane localization, while Ser34 and Ser35 phosphorylation increase its binding to Atg8 family proteins [104,105]. Additionally, FUN14 domain containing 1 (FUNDC1) is a hypoxia-sensitive mitochondrial receptor located on the OMM. Its N-terminal LIR motif is regulated by phosphorylation at three critical sites: Ser13, Ser16, and Tyr18. Phosphorylation at Ser16 activates FUNDC1-mediated mitophagy, whereas phosphorylation at Ser13 and Tyr18 exerts inhibitory effects [106,107,108,109,110]. Under physiological conditions, p-FUNDC1^{Ser13} and p-FUNDC1^{Tyr18} are highly expressed.

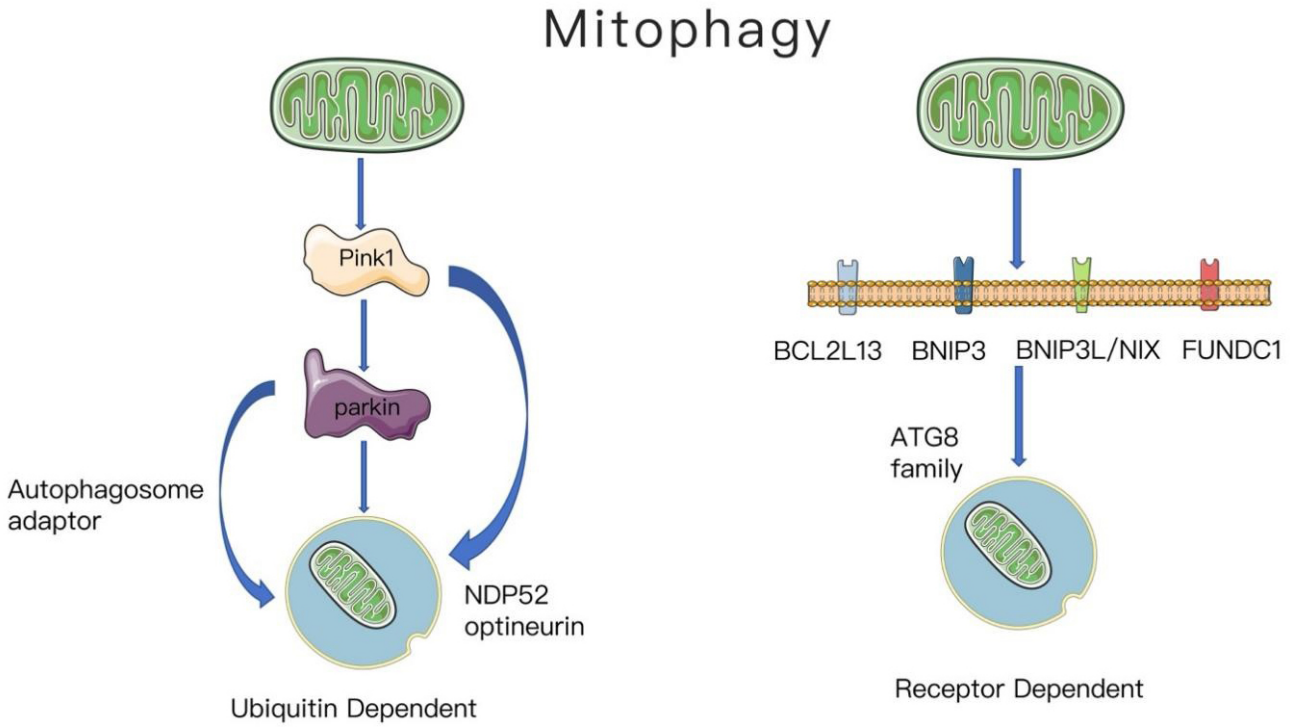


Fig. 3. Major pathways of mitophagy. BCL2L13, BCL2-like protein 13; BNIP3L/NIX, BCL2 interacting protein 3; FUNDC1, FUN14 domain containing 1; ATG8, Autophagy-related protein 8.

However, during acute hypoxia or cellular stress, their expression is downregulated, thereby enhancing FUNDC1-dependent mitophagic activity [108,109].

In summary, mitophagy operates via two complementary molecular pathways—ubiquitin-dependent and receptor-mediated—to enable the recognition, sequestration, and degradation of damaged mitochondria. This dual-system mechanism is essential for maintaining mitochondrial number and functional balance within the cell.

Ubiquitin-dependent mitophagy is characterized by the accumulation of PINK1 on damaged mitochondria, which recruits and activates Parkin, an E3 ubiquitin ligase. Parkin-mediated ubiquitination of OMM proteins promotes the recruitment of autophagy adaptor proteins, including NDP52 and optineurin, thereby facilitating autophagosome formation and mitochondrial sequestration.

Receptor-mediated mitophagy is initiated through direct interactions between LIR motifs present in OMM proteins—including BCL2L13, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), BNIP3L/NIX, and FUNDC1—and members of the Atg8/microtubule-associated protein 1 LC3 family. These interactions lead to the selective engulfment of mitochondria by autophagosomes.

4.2 Mitochondrial Dynamics

Mitochondrial dynamics occur primarily through three mechanisms: (1) transport of mitochondria along the cytoskeleton, (2) interactions with subcellular structures, and (3) morphological remodeling via fission and fusion, which together govern remodeling of both the outer and inner mitochondrial membranes. These dynamic processes are integral to mitochondrial biogenesis and mitophagy, as well as the maintenance of mitochondrial morphology. Moreover, the degradation of organelles occurs through autophagy [111]. Mitochondrial fission enables the generation of two or more daughter mitochondria [112,113], facilitating the autophagic clearance of damaged mitochondrial DNA. Fission plays an essential role in the asymmetric distribution of young and aged mitochondria, thus preserving stem cell characteristics and supporting mitochondrial DNA segregation during division [112,113,114]. In mammals, mitochondrial fission is mainly regulated by the GTPase Drp1, which is located in the cytosol alongside the dynein-dynactin retrograde motor complex [115]. Deletion of Drp1 leads to excessive mitochondrial elongation as a result of unopposed fusion activity, whereas dynamin 2 (DNM2) may contribute to the final scission between mitochondria and the endoplasmic reticulum, but its absence does not entirely inhibit fission [116,117,118]. Therefore, Drp1 is regarded as the master regulator of mitochondrial fission, capable of constricting mitochondrial membranes and functioning as the minimal machinery necessary for membrane scission [117].

Mitochondrial fusion proceeds through two sequential steps: fusion of the OMM, followed by fusion of the inner mitochondrial membrane (IMM). Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2) are dynamin-related GTPases abun-

dantly expressed in mammals. Both are central to OMM fusion [119]. Structurally, Mfn1 and Mfn2 each comprise four principal domains: (1) a conserved GTPase catalytic domain, (2) heptad repeat 1 (HR1), (3) heptad repeat 2 (HR2), and (4) a C-terminal transmembrane domain [120]. The HR1 and HR2 domains mediate Mfn1/2 dimerization, whereas the GTPase domain is critical for OMM recognition and the subsequent fusion of adjacent mitochondria.

During the fusion process, Mfn1 and Mfn2 located on distinct mitochondria first recognize and interact with one another, initiating OMM fusion through GTP hydrolysis. This is followed by IMM fusion, mediated by optic atrophy protein 1 (Opa1), completing the final stage of the fusion process. IMM fusion is pivotal for the formation of cristae structures that are indispensable for the efficiency of OXPHOS [121]. Opa1 contains four functional domains [122]: (1) an N-terminal mitochondrial targeting sequence (MTS), (2) a GTPase domain, (3) a GTPase effector domain (GED), and (4) an HR1 domain. Although the structure of Opa1 has been elucidated, the exact molecular mechanism underlying IMM fusion remains unclear. A recent study suggests that Opa1 can rapidly assemble in a head-to-tail configuration, promoting membrane curvature and forming unstable protrusions on opposing inner membranes [123].

Opa1 exists in two isoforms: long-form Opa1 (L-Opa1), which is primarily anchored to the IMM, and short-form Opa1 (S-Opa1), which is generated through cleavage of L-Opa1 by mitochondrial proteases, including OMA1 and ATP-dependent zinc metalloproteases [124]. The proteolytic conversion from L-Opa1 to S-Opa1 is typically associated with reduced fusion capacity, cristae remodeling, and the induction of mitochondrial fragmentation [125].

Mitochondrial fission—the division of a single mitochondrion into two or more daughter mitochondria—plays a critical role in regulating mitochondrial number, spatial distribution, and intracellular inheritance. In contrast to mitochondrial fusion, which involves both outer and inner membrane remodeling, fission is predominantly mediated by proteins associated with the OMM. As shown in Fig. 4, these include Drp1, mitochondrial fission factor (Mff), fission protein 1 (Fis1), and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51, respectively) [126,127].

Drp1 is a cytosolic, GTP-dependent dynamin-related protein composed of four functional domains: (1) the bundle signaling element (BSE), (2) the GTPase domain, (3) the GED, and (4) a variable region (B-insert) [128]. Upon interacting with its receptors on the OMM, Drp1 initiates fission by assembling into ring-like structures that constrict the mitochondrion through GTP hydrolysis, leading to division. The translocation of Drp1 from the cytosol to mitochondria is tightly regulated by multiple post-translational modifications, including phosphorylation, ubiquitination, SUMOylation, S-nitrosylation, O-GlcNAcylation, and acetylation [129]. These modifications enhance Drp1 oligomerization and receptor affinity, promoting fission. Similarly, the phosphorylation state of Drp1 receptors such as Fis1 and Mff also influences the efficiency of fission, with phosphorylated forms exhibiting higher Drp1-binding capacity [130].

While physiological fission contributes to mitochondrial homeostasis, pathological or excessive fission may result in mitochondrial damage or cell death. Overfragmentation can impair mitochondrial DNA integrity, reduce expression of ETC subunits, and compromise ATP production [131,132]. Furthermore, it promotes the generation of ROS and may induce dissociation of hexokinase 2 (HK2) from the OMM [133], thereby facilitating sustained opening of the mPTP. Mitochondrial fission disrupts the $\Delta\Psi m$, increases membrane permeability, and promotes the release of cytochrome c, which in turn initiates apoptotic signaling cascades [134]. Additionally, mitochondrial fission can induce necroptosis [135].

While the role of mitochondrial fission in metabolic regulation continues to be debated, Drp1-mediated mitochondrial fission is not a functionally homogeneous process. Instead, its downstream biological consequences largely depend on the specific OMM receptor proteins that are recruited [136]. Among the identified Drp1 receptors, Fis1 and MiD51 exhibit pronounced differences in the coupling between mitochondrial fission and mitophagy, and under certain stress conditions may even exert opposing regulatory effects [136,137,138]. Accumulating evidence indicates that Fis1 promotes the stable accumulation of PINK1 on the surface of depolarized mitochondria and enhances the recruitment of Parkin to the OMM, thereby activating the PINK1/Parkin-dependent mitophagy pathway and facilitating the selective clearance of damaged mitochondria [137]. However, Fis1 can also inhibit Parkin-independent mitophagy by restricting the recruitment of syntaxin 17 (STX17) to mitochondria. Given that STX17 is an essential SNARE protein required for autophagosome–lysosome fusion, Fis1 may bias MQC toward PINK1/Parkin-dependent mitophagy while concurrently suppressing the activation of alternative mitochondrial clearance mechanisms [138]. In contrast, MiD51 primarily functions as a high-affinity receptor for Drp1, driving the execution of mitochondrial fission events. However, fission mediated by MiD51 is inefficiently coupled to mitophagy signaling pathways. Under conditions of impaired or insufficient autophagic flux, sustained or excessive MiD51-dependent fission can lead to abnormal accumulation of fragmented mitochondria that are not promptly removed, ultimately exacerbating mitochondrial dysfunction [136,139]. Recent studies suggest that moderate fission supports mitochondrial metabolic homeostasis [140]. For example, in neonatal mouse hearts, Drp1 is highly expressed, and cardiomyocyte-specific knockout of Drp1 leads to impaired respiration, mitochondrial malformation, and myocardial hypertrophy. Conditional Drp1 deletion in

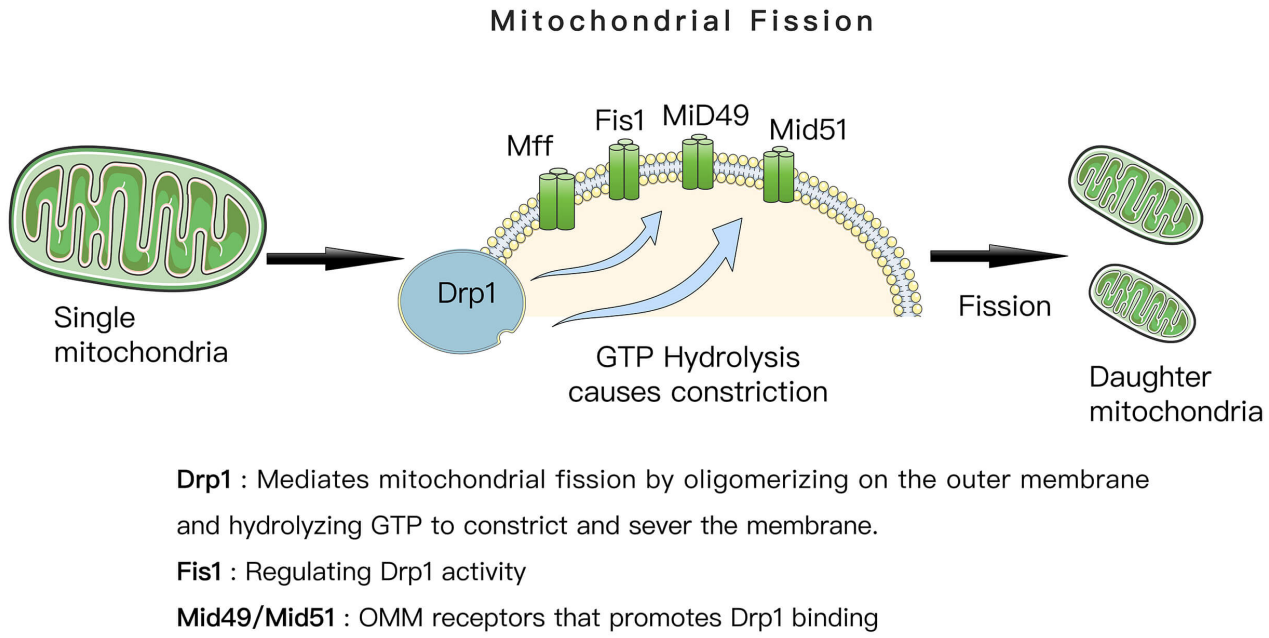


Fig. 4. Molecular mechanisms of mitochondrial fission. Mff, mitochondrial fission factor; Fis1, fission protein 1; MiD49, mitochondrial dynamics protein of 49; GTP, Guanosine Triphosphate; OMM, outer mitochondrial membrane.

cardiomyocytes results in swollen mitochondria and profound metabolic derangements [141].

Mitochondrial transport along the cytoskeleton is essential for cellular distribution and turnover [142]. In mammalian cells, mitochondria are primarily transported along microtubules, with kinesin motor proteins driving movement toward the plus end and dynein toward the minus end [143]. This association is coordinated by adaptor proteins such as Milton and the Rho GTPase Miro, which tether the mitochondria to kinesins [143]. Mfn1 and Mfn2 interact with Miro and Milton, and Mfn2 deletion results in defective mitochondrial trafficking in neurons [144]. Extracellular glucose also regulates mitochondrial motility in neurons. Most axonal mitochondria in mice are immobile, a state regulated by syntaphilin (SNPH), which anchors them to microtubules. Deletion of SNPH increases axonal mitochondrial mobility. In response to elevated Ca^{2+} levels, Miro releases kinesin-1, which then binds SNPH to suppress mitochondrial movement [145]. Additionally, Milton undergoes O-GlcNAcylation by O-linked N-Acetylglucosamine Transferase (OGT) in response to extracellular glucose, which inhibits mitochondrial motility [146,147].

The schematic illustrates the progression from an intact mitochondrion to two daughter mitochondria through a fission event. Drp1, a cytosolic GTPase, is recruited to mitochondrial fission sites on the OMM by multiple adaptor proteins, including Mff, Fis1, and MiD49 and MiD51. Upon recruitment, Drp1 oligomerizes into ring-like structures on the OMM and induces membrane constriction through GTP hydrolysis, ultimately resulting in mitochondrial division. The resulting daughter mitochondria maintain structural integrity and contribute to mitochondrial quality control, cellular metabolism, apoptosis regulation, and cell cycle progression.

4.3 Mitochondrial Biogenesis

Mitochondrial biogenesis is the cellular process by which mitochondrial number and mass are increased in response to elevated energy demands or specific intracellular signaling cues [148]. The majority of mitochondrial proteins are encoded by the nuclear genome, requiring tight coordination between nuclear transcription and translation and mitochondrial genome expression to ensure the efficient generation of new mitochondria [149]. Proper mitochondrial biogenesis relies on diverse signaling cascades and transcriptional networks, which are regulated by multiple classes of transcription factors and co-activators [150]. In addition to nuclear transcriptional regulators, mitochondrial biogenesis is also modulated by mitochondrial retrograde signals, such as ATP, ROS, and Ca^{2+} [151]. Disruption of $\Delta\Psi m$ impairs Ca^{2+} uptake by mitochondria, while increased cytosolic Ca^{2+} activates various Ca^{2+}-dependent kinases and initiates signaling cascades that regulate mitochondrial biogenesis [152], as shown in Fig. 5.

NRF1 and NRF2 were the first nuclear transcription factors identified to play pivotal roles in regulating mitochondrial biogenesis [153,154]. NRF1 regulates the expression of genes encoding respiratory chain complex subunits, enzymes involved in heme biosynthesis, components of the mtDNA transcription and replication machinery, as well as proteins essential for mitochondrial import and assembly [155]. NRF1 also activates multiple

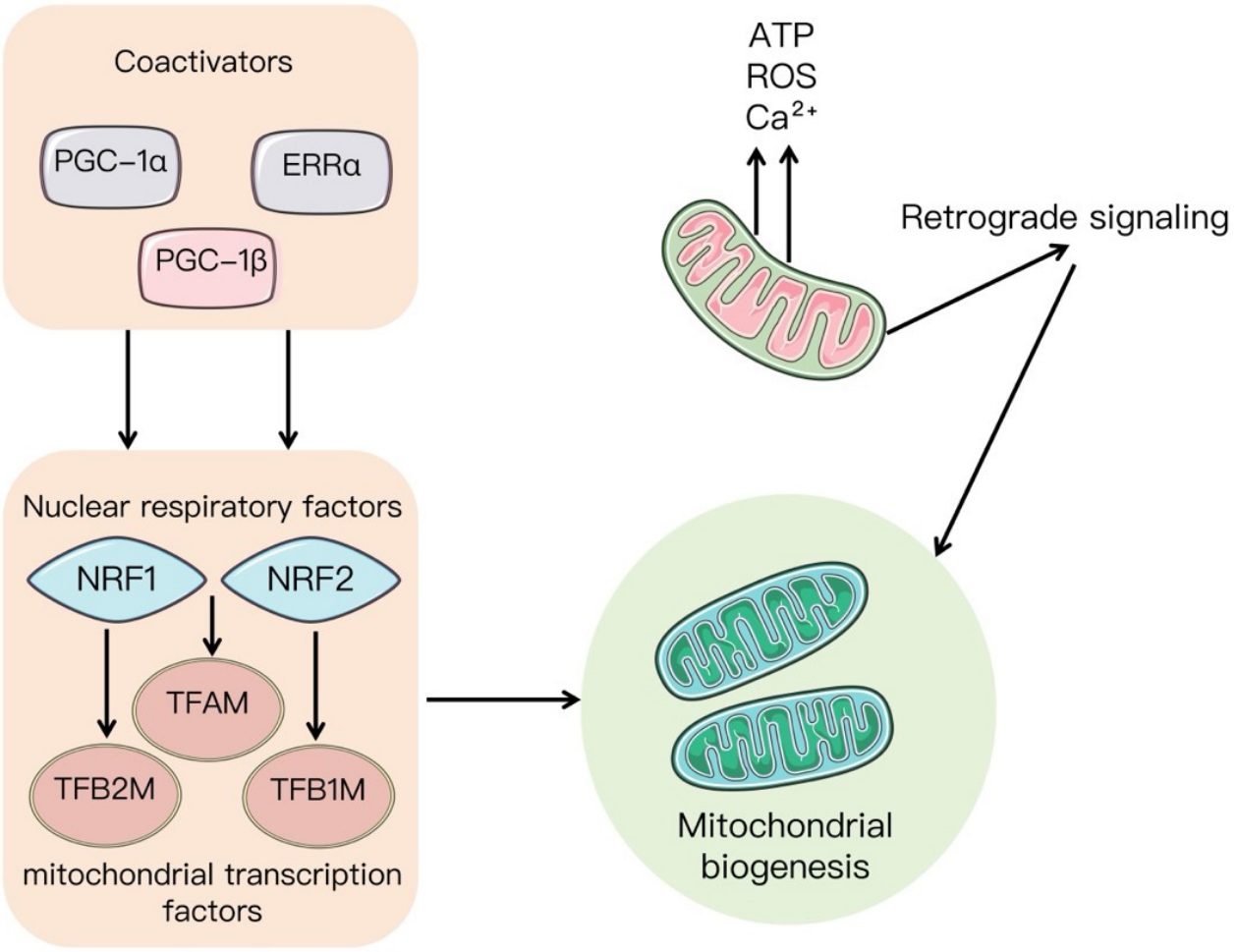


Fig. 5. Transcriptional regulation of mitochondrial biogenesis and retrograde signaling. PGC-1β, PGC-1 beta; ERRα, estrogen-related receptor alpha; TFB2M, mitochondrial transcription factor B2; TFB1M, mitochondrial transcription factor B1.

genes involved in the formation of the respiratory chain complex [154,156]. Furthermore, NRF1 directly induces transcription of TFAM, mitochondrial transcription factor B1 (TFB1M), and mitochondrial transcription factor B2 (TFB2M), all of which are key regulators of mitochondrial transcription and mtDNA maintenance [150,157]. NRF2, also known as GA-binding protein (GABP), is composed of two subunits—NRF2a and NRF2b—that assemble into a functional α2β2 heterotetrameric complex [158]. The DNA-binding domain (DBD) is located in NRF2a, while the transactivation domain (TAD) resides in NRF2b. Both subunits are essential for the transcriptional activity of the complex [159]. NRF2 plays a critical role in regulating genes involved in respiratory chain formation and mitochondrial transcription. Although NRF2 is a weaker activator of the TFAM promoter compared to NRF1, it can still bind to it [157]. The presence of both NRF1 and NRF2 binding sites within the TFAM promoter further supports a coordinated regulatory mechanism in mitochondrial biogenesis [152,155].

The estrogen-related receptor alpha (ERRα) also functions as a key regulator in mitochondrial biogenesis through its cooperation with PGC-1α and PGC-1 beta (PGC-1β). A large number of mitochondrial genes contain ERRα response elements, and knockout of ERRα significantly impairs PGC-1α/PGC-1β-induced mitochondrial biogenesis [160,161]. Importantly, NRF1 and NRF2 are downstream targets of the PGC-1α/ERRα axis, driving the expression of mitochondrial respiratory chain genes [162,163]. PGC-1α is widely regarded as the master regulator of mitochondrial biogenesis, functioning as a transcriptional coactivator that integrates the activities of multiple transcription factors, including NRF1, NRF2, and ERRα [155]. PGC-1α also enhances the transcriptional activity of NRF1, upregulates the expression of both NRF1 and NRF2, and promotes the transcription of TFAM as well as genes encoding components of the mitochondrial respiratory chain [164]. PGC-1β, a homolog of PGC-1α, also interacts with NRF1, NRRα, and NRRβ, indicating it has an equally critical role in regulating mitochondrial biogenesis [152].

This schematic illustrates the coordinated regulation of mitochondrial biogenesis through nuclear–mitochondrial communication. PGC-1α and PGC-1β function as central transcriptional coactivators that integrate metabolic and stress-related signals to activate downstream NRF1 and NRF2. These transcription factors induce the expression of mitochondrial transcriptional regulators, including TFAM, TFB1M, and TFB2M, thereby promoting mtDNA transcription and replication, and driving mitochondrial biogenesis. ERRα acts as an additional co-regulator within the PGC-1 signaling network, enhancing the transcription of genes involved in mitochondrial structure and oxidative metabolism.

In parallel, retrograde signals originating from mitochondria, such as ATP, ROS, and Ca^{2+}, feed back to the nucleus to modulate transcriptional programs, ensuring dynamic regulation of mitochondrial quantity and function.

4.4 Mitochondrial Unfolded Protein Response (UPRmt)

The mitochondrial UPRmt constitutes a highly conserved MQC mechanism that functions to preserve mitochondrial integrity and homeostasis under pathological conditions (Fig. 6). This adaptive response may be triggered by the accumulation of misfolded mitochondrial proteins, mitochondrial depolarization, or an imbalance in the expression levels between mitochondrial and nuclear-encoded proteomes. The UPRmt shares several common regulatory elements with the endoplasmic reticulum unfolded protein response (UPRER), particularly transcription factors such as CHOP, CCAAT/enhancer-binding protein β (C/EBPβ), and eukaryotic initiation factor 2α (eIF2α) [165,166]. The UPRmt involves a complex network of signaling molecules, transcription factors, mitochondrial proteases (e.g., OMI/HTRA2, LONP1, caseinolytic mitochondrial matrix peptidase proteolytic subunit (ClpP), paraplegin, YME1L, mitochondrial-processing peptidase [MPP], and OMA1), antioxidants (e.g., thioredoxin 2), endonucleases (e.g., endonuclease G), and molecular chaperones (e.g., mitochondrial 70-kDa heat shock protein [mtHsp70], Hsp60, Hsp10, and DnaJ homolog subfamily A member 3 [Hsp40]) [167,168,169,170]. Peptides generated by mitochondrial proteases are exported via half transporter, a member of the ATP-binding cassette subfamily B member 10 (ABCB10) in mammals. They subsequently activate the transcription factors CHOP, C/EBPβ, and ATF4 through the c-Jun/AP-1 pathway [165,166].

A key regulatory axis of UPRmt is governed by the reciprocal regulation between two mitochondrial proteases: YME1L and OMA1. YME1L, an ATP-dependent protease homologous to the yeast i-AAA, and OMA1, a zinc-dependent metalloprotease, can cleave and suppress each other under specific intracellular conditions [171]. Upregulation of YME1L results in OMA1 inactivation, and vice versa. Both enzymes can be induced under stress conditions. In the presence of sufficient ATP, persistently activated YME1L can be reactivated by mitochondrial depolarization. OMA1, which is inactive under non-stress conditions, becomes activated upon mitochondrial depolarization in the context of ATP depletion [171]. Notably, excessive oxidative stress can inactivate YME1L, resulting in cell death [172]. Although most studies suggest that OMA1 negatively affects mitochondrial and cellular function, Bohovych et al. [173] demonstrated that OMA1 deficiency compromises the stability of respiratory chain supercomplexes and mitochondrial biogenesis in mouse embryonic fibroblasts. When activated, YME1L promotes UPRmt by degrading mitochondrial proteins and disturbing mito-nuclear protein balance [174]. Loss of YME1L impairs normal mitochondrial fission and fusion, leading to excessive ROS production and increased sensitivity to oxidative stress, a phenomenon attributed to OMA1 upregulation and its cleavage of the pro-fusion protein OPA1 [175]. Additionally, YME1L deficiency reduces cell proliferation, diminishes anti-apoptotic capacity, and increases protein carbonylation [167].

UPRmt plays a critical protective role in maintaining mitochondrial function by sustaining ATP production, reducing excessive ROS, and inhibiting the activation and release of pro-apoptotic mitochondrial factors [176]. Under stress conditions, the UPRmt-associated transcription factor activating transcription factor associated with stress-1 (ATFS-1) promotes the assembly of oxidative phosphorylation complexes, ensuring continued energy metabolism [177]. Concurrently, UPRmt-related proteases such as YME1L [167] and ClpP [168] identify and eliminate dysfunctional respiratory chain components, facilitating repair and reconstruction of the electron transport chain. Through these mechanisms, the UPRmt helps to preserve OXPHOS in damaged mitochondria. It is important to note that hyperactivation of ClpP in tumor cells by agents such as ONC201 (imipridone) can paradoxically inhibit OXPHOS and induce apoptosis, reflecting a double-edged sword effect of UPRmt modulation [168,178].

This schematic illustrates activation of the UPRmt under conditions of mitochondrial stress. Accumulation of unfolded or misfolded proteins within mitochondria leads to increased ROS production, thereby triggering UPRmt signaling. Activation of the transcription factor ATFS-1 promotes the expression of mitochondrial proteases, including YME1L and ClpP. This facilitates the degradation of damaged respiratory chain subunits and maintenance of mitochondrial proteostasis.

In parallel, ATFS-1 translocates to the nucleus and induces the transcription of genes involved in OXPHOS assembly and function. Through these coordinated adaptive responses, UPRmt contributes to the stabilization of mitochondrial structure, restoration of OXPHOS complexes, increased ATP production, reduced ROS accumulation, and suppression of apoptosis.

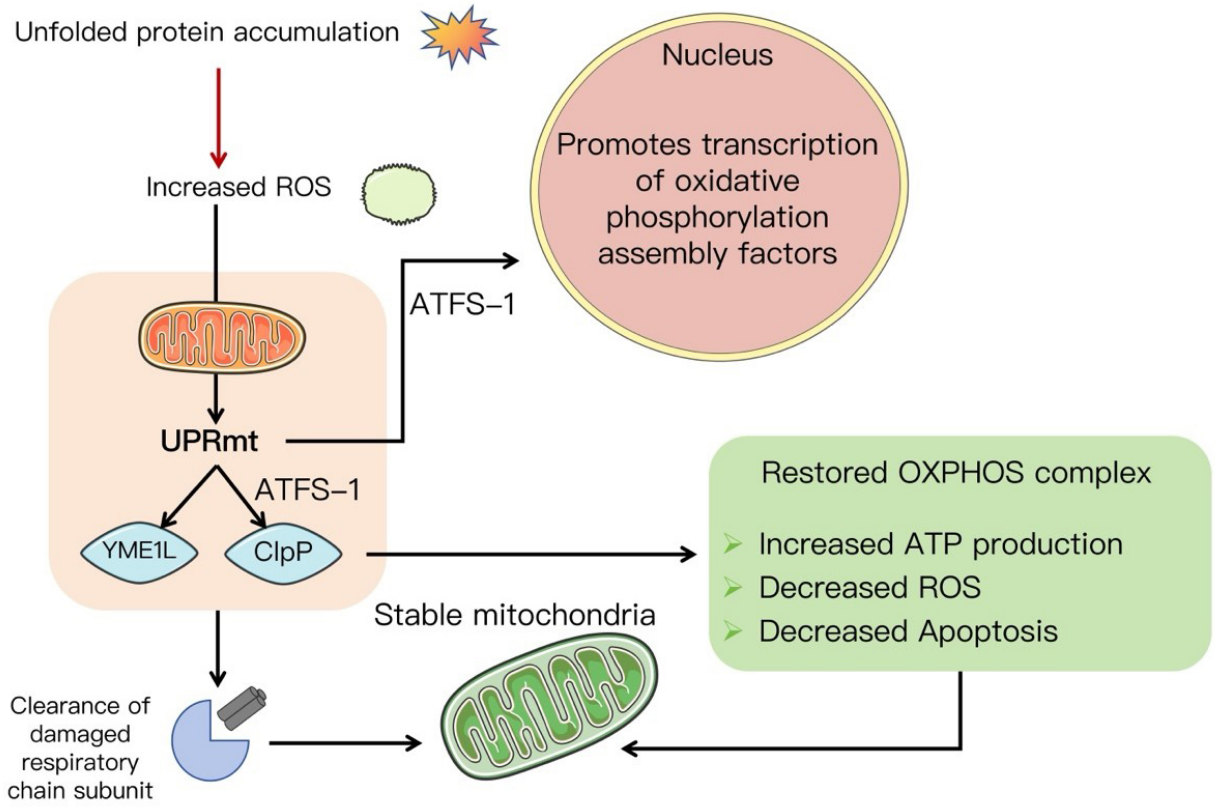


Fig. 6. Mitochondrial unfolded protein response (UPRmt) and restoration of mitochondrial proteostasis. ATFS-1, activating transcription factor associated with stress-1; ClpP, caseinolytic mitochondrial matrix peptidase proteolytic subunit; OXPHOS, oxidative phosphorylation.

4.5 Dynamic Decision-Making and Coordinated Mechanisms of Mitochondrial Quality Control

Based on the above mechanisms, MQC can be conceptualized as a highly coordinated and dynamic regulatory network. Mitochondrial biogenesis is primarily governed by the PGC-1α–NRF1–TFAM transcriptional axis, which precisely coordinates the expression of nuclear and mitochondrial-encoded genes to increase mitochondrial content and maintain functional integrity [179]. Importantly, mitochondrial biogenesis does not occur in isolation but is tightly coupled with other quality control processes, including mitochondrial dynamics, mitophagy, and the mtUPR, together forming a highly dynamic homeostatic network.

During the early phase of cellular stress or under conditions of mild mitochondrial damage, and when ΔΨm declines or protein import efficiency is compromised, cells typically initiate Drp1-mediated mitochondrial fission to segregate damaged regions from relatively healthy mitochondrial networks [139,180]. This process provides the structural and spatial basis for subsequent quality surveillance. If fission and the subsequent functional remodeling are sufficient to alleviate stress, cells preferentially activate mitochondrial fusion, allowing mixing of mitochondrial contents to dilute damage and promote functional recovery, thereby avoiding unnecessary mitochondrial elimination [179,181].

When mitochondrial damage persists or exceeds the cellular repair threshold, dysfunctional mitochondria generated by fission are selectively recognized and removed via PINK1/Parkin-dependent or independent mitophagy pathways [179,182]. It is worth noting that mitophagy is not a terminal event. Rather, its activation often feeds back to stimulate mitochondrial biogenesis in order to replenish mitochondrial numbers and sustain cellular energy homeostasis. This tight coupling between clearance and regeneration is considered a core operational principle of the MQC system [183]. In this context, mitochondrial dynamics function as a critical rheostat, whereby excessive fusion suppresses mitophagy. On the other hand, moderate mitochondrial fragmentation facilitates efficient recognition and removal of damaged mitochondria, thereby directly determining mitophagy efficiency and the rhythm of mitochondrial renewal [181].

Beyond dynamics and mitophagy, the mtUPR is another essential pillar of MQC that preserves mitochondrial proteostasis. When misfolded proteins accumulate within mitochondria or protein import is impaired, the mtUPR

is activated and induces the expression of mitochondrial chaperones (e.g., Hsp60) and proteases (e.g., ClpP and LonP1) via transcription factors such as ATFS-1, CHOP, and ATF5, thereby buffering proteotoxic stress and restoring protein homeostasis [184,185,186,187,188]. Importantly, the mtUPR is not merely a repair response. Under moderate stress, it often cooperates with mitochondrial fusion to promote functional recovery. However, under severe or sustained stress, if mtUPR activation fails to adequately compensate for damage, cells progressively shift toward a fission–mitophagy–biogenesis renewal program to achieve population-level mitochondrial remodeling [179].

4.6 Mitochondrial-Derived Vesicles (MDVs) as a Frontier Mechanism for Mitochondrial Quality Control

Within the classical framework of MQC, overall mitochondrial fate is collectively determined by mitochondrial fission, fusion, mitophagy, biogenesis, and the mtUPR. However, accumulating evidence indicates that when mitochondria sustain mild to moderate damage, cells do not invariably initiate mitophagy as an immediate response, but instead employ a more refined strategy of localized clearance. Within this context, MDVs have emerged as a novel and important compensatory mechanism within the MQC system [189].

MDVs are single- or double-membrane vesicles that bud from the OMM, IMM, and portions of the mitochondrial matrix, with a typical diameter of 70–150 nm. They can be generated under both basal and stress conditions, and their formation is independent of classical Drp1-mediated mitochondrial fission [190]. MDV generation is a physiological process in cardiomyocytes, but is markedly increased under oxidative stress, accompanied by selective alterations in cargo composition [191,192,193]. This suggests that MDVs represent a highly stress-responsive mode of MQC.

Under conditions of mild oxidative stress, mitochondrial membrane proteins undergo oxidative modifications, and ROS induce localized activation of PINK1 and Parkin. This promotes the budding and formation of MDVs that selectively package oxidized or damaged mitochondrial membrane proteins [191,194]. Consistent with observations in models of Parkinson's disease, impairment of PINK1/Parkin-mediated MDV formation leads to defective clearance of oxidized proteins, ultimately resulting in mitochondrial dysfunction [191]. In addition, the vacuolar protein sorting factor Vps35 has been identified as a critical regulator of MDV biogenesis, with mutations in Vps35 significantly compromising MDV formation [190].

Functionally, MDVs maintain mitochondrial functional integrity by selectively removing damaged mitochondrial components—including oxidized proteins, subunits of the respiratory chain complexes, and portions of mtDNA—without disrupting the overall mitochondrial structure [195,196,197,198]. This mechanism effectively prevents excessive reliance on mitophagy and the consequent wholesale degradation of mitochondria, and is therefore regarded as a "fine-tuning mode" of MQC. Beyond local quality control, MDVs also participate in inter-organelle communication, such as promoting peroxisome biogenesis, modulating immune responses, and conferring protection under pathological conditions, including hypoxia and myocardial ischemia [199].

Notably, mtDNA leakage has been recognized as a critical nexus linking mitochondrial dysfunction to innate immune activation [200]. As a prototypical DAMP, mtDNA activates multiple pattern recognition receptors, particularly the cyclic guanosine monophosphate-adenosine monophosphate synthase—stimulator of interferon genes—interferon regulatory factor 3 (cGAS–STING–IRF3) signaling axis, thereby initiating or amplifying inflammatory responses [199]. In this context, MDVs have been proposed as a key mechanism for maintaining immune homeostasis by limiting ectopic mtDNA exposure and preventing sustained immune activation triggered by mitochondrial rupture. Compared with mitophagy, MDV-mediated quality control represents a more moderate and precise mechanism that preserves mitochondrial function while restraining excessive amplification of inflammatory signaling [200].

However, the role of MDVs is not universally protective. Under certain pathological conditions, dysregulated MDV function or aberrant vesicle release may facilitate the intercellular transfer of mtDNA, thereby amplifying inflammatory signaling and accelerating disease progression. For example, in the setting of inflammasome activation, increased MDV secretion is considered an adaptive protective response, whereas prolonged or uncontrolled activation may exert unintended pro-inflammatory effects [200].

In summary, as a frontier component of the MQC system, MDVs fine-tune the selective removal of mitochondrial contents and play a critical role in preventing mtDNA leakage and suppressing aberrant activation of the cGAS–STING pathway. Dysregulation of MDV-mediated quality control may represent an important mechanism underlying the initiation and progression of inflammation-associated cardiovascular diseases, including sepsis-induced cardiomyopathy. This provides a theoretical basis for therapeutic strategies targeting the mitochondrial–immune axis.

5. Involvement of Mitochondrial Quality Control in Septic Cardiomyopathy

5.1 Mitophagy and Septic Cardiomyopathy

In sepsis, the recovery of organ function depends on the clearance of damaged mitochondria and the synthesis of new, functional ones [201]. These two processes, mitophagy and mitochondrial biogenesis, are essential for preserving mitochondrial homeostasis and sustaining cellular energy metabolism [202]. As a key quality control mecha-

nism, mitophagy selectively targets and eliminates dysfunctional mitochondria, thereby preventing the release of pro-apoptotic or pro-inflammatory factors that could exacerbate cellular injury. This process entails the engulfment of impaired mitochondria by autophagosomes, followed by their fusion with lysosomes, where the mitochondrial contents are degraded.

Multiple signaling pathways that regulate mitophagy have now been elucidated. The classical PINK1/Parkin (PARK2)-dependent pathway promotes ubiquitination of mitochondrial surface proteins. These are recognized by the autophagy adaptor p62, which subsequently interacts with LC3 to mediate mitophagic degradation. In addition, ubiquitin-independent mechanisms also exist, where autophagy-related proteins such as ATG8 directly bind to mitochondrial receptors like NIX, initiating mitophagic clearance [202,203].

Mitophagy not only aids in the early elimination of potentially hazardous mitochondria, but may also provide an alternative cytoprotective pathway when apoptotic mechanisms are limited. Studies have shown that septic conditions lead to significantly elevated levels of autophagy and mitophagy in multiple organs [204,205], including the heart. For instance, in LPS-induced endotoxemia models, the myocardial expression of key autophagy molecules (e.g., ATG3, ATG5, ATG7, LC3-II, and p62) is markedly upregulated, suggesting enhanced autophagic activity in cardiomyocytes [206,207]. Some studies have reported reduced numbers of mitochondria in cardiomyocytes following LPS treatment, implying accelerated degradation through mitophagy. However, others have reported no significant change in the total mitochondrial mass [208,209], indicating heterogeneity in this process across different models. A pivotal study by Piquereau et al. [210] highlighted the critical role of Parkin in mitochondrial functional recovery. These authors found that LPS exposure caused a dramatic decline in cardiac output and stroke volume in both wild-type and Parkin-deficient mice, but only wild-type mice fully recovered these parameters after 48 hours. Notably, the recovery of OXPHOS complex activity, mitochondrial oxygen consumption, and reduced mPTP sensitivity was observed only in wild-type mice, indicating that Parkin-dependent mitophagy is vital for the restoration of cardiac function. Interestingly, even in Parkin-deficient mice, mitophagy-related proteins such as Sequestosome 1 (SQSTM1), LC3-II, and BNIP3L/NIX were still recruited to mitochondria, suggesting the presence of compensatory mechanisms to facilitate mitochondrial clearance. Transmission electron microscopy (TEM) confirmed the presence of autophagosome-like structures [210]. These findings suggest that mitophagy activation during endotoxemia may serve a compensatory role by promoting the clearance of damaged mitochondria and preparing the ground for subsequent mitochondrial biogenesis. Some evidence indicates that mitophagy may promote mitochondrial regeneration through TLR9-dependent signaling pathways, although the underlying mechanism remains unclear [205]. It is also important to note that in certain contexts, autophagy may synergize with apoptosis, and the two processes share complex signaling interactions [211]. Taken together, the available evidence suggests that, in the context of sepsis, mitophagy predominantly represents an adaptive and cytoprotective response rather than a purely deleterious process. By its timely removal of dysfunctional mitochondria, mitophagy limits the release of mitochondria-derived pro-apoptotic and pro-inflammatory signals, thereby creating a favorable intracellular environment for subsequent mitochondrial biogenesis and functional recovery. Notably, studies using Parkin-deficient models have shown that impairment of mitophagy does not prevent the initial decline in cardiac function induced by sepsis, but markedly compromises myocardial recovery following injury. These findings indicate that mitophagy plays a critical role during the recovery phase of cardiac dysfunction, rather than during the acute injury phase.

However, the biological effects of mitophagy are highly context-dependent. In the absence of sufficient compensatory mitochondrial biogenesis, excessive or sustained mitochondrial clearance may lead to mitochondrial depletion and energetic failure, a phenomenon that is particularly pronounced in cardiomyocytes, which rely heavily on OXPHOS for ATP production. Moreover, extensive and complex crosstalk exists between autophagic and apoptotic signaling pathways, such that under specific pathological conditions, mitophagy may shift from a protective response to a pro-injury mechanism.

In sepsis-induced cardiomyopathy, mitophagy should therefore be regarded as a double-edged sword within the MQC system, since its beneficial effects are critically dependent on precise temporal regulation and coordinated balance with mitochondrial biogenesis. As such, the precise role of autophagy in sepsis—whether it be cytoprotective or part of programmed cell death—remains to be fully determined. Hence, further research is urgently needed to elucidate the exact role of mitophagy in SCM and to define its relationship with mitochondrial biogenesis [212].

5.2 Mitochondrial Biogenesis and Septic Cardiomyopathy

Mitochondrial biogenesis is the process by which mitochondria expand in both quantity and size through growth and division. This process relies on the coordinated regulation of multiple cellular mechanisms, including the synthesis and import of nuclear-encoded proteins, replication of mtDNA, translation of mitochondria-encoded proteins, and dynamic regulation of mitochondrial fusion and fission [148]. It is typically triggered by various cellular stress signals, such as elevated NO levels, enhanced oxidative stress, and increased AMP/ATP ratios, which induce the expression of peroxisome proliferator-activated receptor gamma coactivator family members, particularly PGC-

1α and PGC-1β [203,213]. PGC-1α acts as a coactivator that upregulates key transcription factors, such as ERRα/γ, NRF1, NRF2, and TFAM, thereby promoting the expression of both nuclear- and mitochondria-encoded subunits involved in OXPHOS. PGC-1α also regulates mtDNA transcription, replication, and various components of the protein import machinery [214]. Furthermore, by activating ERRα and PPARα, PGC-1α/β also enhances the expression of enzymes involved in fatty acid oxidation in the myocardium, helping to maintain the heart's primary energy supply pathway.

Research indicates that enhanced mitochondrial biogenesis is associated with improved survival in sepsis models, whereas the inhibition of mitochondrial biogenesis is frequently linked to worsening pathological outcomes [215,216]. This indicates that following the removal of damaged mitochondria in tissues, functional recovery is achieved through the activation of compensatory mitochondrial biogenesis. Vanasco et al. [206] reported that within 24 hours of LPS administration, the levels of PGC-1α and TFAM increased in myocardial tissue, accompanied by restored mtDNA content and increased mitochondrial number. However, despite the upregulation of biogenesis, ultrastructural analysis revealed significant mitochondrial damage, such as swelling, loss of cristae, matrix clearance, and intramitochondrial vacuole formation. Moreover, respiratory chain complexes I and II remained functionally impaired, suggesting that activation of mitochondrial biogenesis does not equate to functional recovery. Other studies have also observed upregulation of PGC-1α, NRF1, NRF2, TFAM, and mitochondrial DNA polymerase, alongside structural mitochondrial damage (e.g., swelling and cristae disruption) [209]. In neonatal cardiomyocytes, LPS stimulation increased TFAM expression, NRF1 nuclear translocation, and PGC-1α levels, but simultaneously led to mitochondrial dysfunction (e.g., decreased membrane potential and ATP content) and elevated autophagy markers [217]. Therefore, although mitochondrial biogenesis signaling is activated during endotoxemia, it remains unclear whether this is sufficient to reverse mitochondrial dysfunction. Russell et al. [218] further reported that although cardiomyocyte-specific overexpression of PGC-1α markedly enhanced mitochondrial biogenesis, it eventually resulted in the development of heart failure. This may be due to excessive activation disrupting the balance between gene expression and mitochondrial dynamics, leading to structural and functional mismatches and impaired mitochondrial functionality.

On the other hand, Schilling et al. [219] found that just 6 hours after LPS treatment, mRNA levels of PGC-1α and PGC-1β were significantly downregulated, accompanied by decreased expression of PPARα, ERRα, and NRF1, impaired cardiac function, reduced myocardial fatty acid oxidation, and increased lipid accumulation. During this period, mtDNA copy number and the mRNA levels of several key enzymes decreased, with reduced levels of respiratory chain complex I and IV proteins [209]. These results suggest that different experimental models and time points may show opposing trends in the signaling for mitochondrial biogenesis, and hence its adaptive value remains to be fully clarified. Notably, overexpression of PGC-1β can partially counteract the LPS-induced downregulation of PPARα, ERRα, and fatty acid oxidation enzymes. In PGC-1β transgenic mice, LPS treatment improved myocardial fatty acid oxidation and resulted in only mild cardiac dysfunction [219]. These findings further support the tight link between mitochondrial energy deficiency and cardiac dysfunction, and suggest that activation of mitochondrial biogenesis may confer protective effects under specific conditions. In a study on PPARα function, Drosatos et al. [212] found that LPS treatment downregulated the expression of PGC-1α/β, PPARα, and their metabolic targets. While evidence for the beneficial effects of PPARα agonists on cardiac function remains inconclusive, the PPARγ agonist rosiglitazone increased PGC-1 and TFAM expression and improved cardiac performance. In αMHC-PPARγ transgenic mice, LPS treatment resulted in better cardiac function and improved lipid metabolic status. However, whether the protective effects of PPARγ agonists during endotoxemia are directly mediated through mitochondrial biogenesis remains to be determined.

5.3 Mitochondrial Dynamics and Septic Cardiomyopathy

In recent years, increasing evidence has revealed that SCM is a critical component of sepsis-associated multiple organ dysfunction syndrome (MODS) [220], with mitochondrial dysfunction and dysregulated dynamics identified as central pathological mechanisms. Mitochondrial dynamics, particularly Drp1-mediated pathological fission (fragmentation), play a pivotal role in the onset and progression of SCM. Under physiological conditions, mitochondria maintain energy metabolism and quality control through a dynamic balance between fusion and fission. Fusion is regulated by OPA1, MFN1, and MFN2, while fission is coordinated by Drp1 and its OMM adaptors such as FIS1 and Mff [221].

Studies in SCM models have shown that LPS-induced inflammatory stimuli significantly enhance Drp1 activation (phosphorylation at serine 616 [Ser616]) and its interaction with FIS1, leading to excessive mitochondrial fission, loss of membrane potential, decreased ATP production, and increased ROS generation. This cascade causes marked mitochondrial morphological abnormalities in cardiomyocytes, ultimately contributing to cell death and cardiac dysfunction (Fig. 7). Using both cell and mouse models of LPS-induced SCM, Haileselassie et al. [222] identified the Drp1/FIS1 axis as a key mechanism mediating pathological fission, mitochondrial dysfunction, and cardiac suppression. Selective inhibition of Drp1/FIS1 by the peptide P110 demonstrated cardioprotective effects both *in*

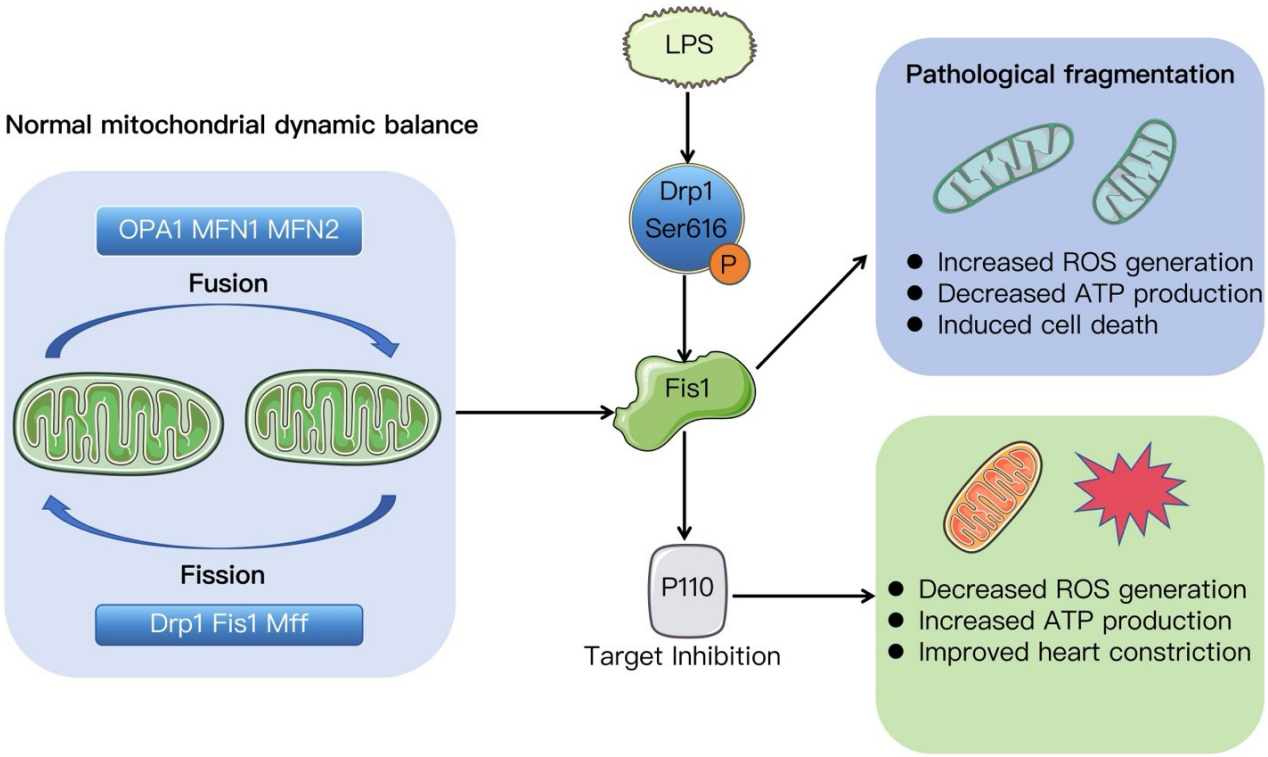


Fig. 7. Dysregulation of mitochondrial dynamics and therapeutic targeting of pathological fission. OPA1, optic atrophy protein 1; MFN1, mitofusin 1; MFN2, mitofusin 2; LPS, lipopolysaccharide; Ser616, serine 616.

vitro and *in vivo*, significantly improving ΔΨm, ROS levels, myocardial contractility, and overall survival in animal models. These findings are consistent with previous reports in ischemia/reperfusion (I/R) injury and heart failure (HF) models [223,224]. I/R injury has been shown to trigger Drp1 activation, which in turn enhances mitochondrial fission through FIS1, leading to cardiomyocyte death [200,225]. Inhibitors such as mdivi-1 [225] and P110 [224] can reduce fission and prevent myocardial cell death, highlighting their therapeutic potential. Notably, the overexpression of FIS1 has been associated with enhanced mitochondrial fission and increased cell death [223], whereas FUNDC1 deficiency, despite promoting a fusion phenotype, paradoxically resulted in mitochondrial dysfunction and heart failure in certain models [226]. These observations suggest that maintaining a proper balance between fission and fusion is vital for cardiac health.

The expression profiles of pro-fusion and pro-fission proteins show considerable heterogeneity among various types of HF. For example, Ahuja et al. [227] reported a decrease in OPA1 in ischemic cardiomyopathy, while Chen et al. [228] observed an increase in MFN2. However, these trends were inconsistent in dilated cardiomyopathy. Multiple animal HF models commonly exhibit increased Drp1 and FIS1, reduced OPA1 and MFN1, elevated mitochondrial fission, increased ROS generation, and reduced ATP production [229,230,231]. These findings resemble the mechanisms observed in SCM, further supporting the shared pathogenic role of Drp1-mediated fission across different cardiomyopathies. Importantly, while Drp1 serves as the key executor of pathological mitochondrial fission, it also plays an indispensable role in baseline fission and MQC. Inhibition of the interaction between Drp1 and other adaptors, such as Mff (e.g., using P259) can aggravate mitochondrial dysfunction [171]. Therapeutic strategies for SCM should therefore focus on selective inhibition of pathological Drp1/FIS1-mediated fission, while preserving physiological Drp1 functions.

In summary, Drp1/FIS1-mediated excessive mitochondrial fission represents a central mechanism of mitochondrial dysfunction and cardiac failure in SCM. Targeted intervention in this pathway—particularly with specific inhibitors like P110—offers a promising therapeutic avenue not only for SCM but also for broader forms of cardiomyopathy. These findings highlight the critical importance of maintaining mitochondrial dynamic equilibrium for safeguarding cardiac health [178].

This schematic illustrates the balance between mitochondrial fusion and fission under physiological and pathological conditions. Under normal conditions, mitochondrial dynamic homeostasis is maintained through coordinated fusion mediated by OPA1, MFN1, and MFN2, together with controlled fission regulated by Drp1, Fis1, and Mff.

Upon stimulation with LPS, Drp1 is phosphorylated at Ser616, promoting its recruitment to the mitochondrial outer membrane through Fis1 and triggering excessive mitochondrial fission. This pathological fragmentation results in increased generation of ROS, reduced ATP production, induction of cell death, and impaired myocardial contractile function.

Targeted inhibition of the Drp1–Fis1 interaction by the selective peptide inhibitor P110 attenuates excessive mitochondrial fission, restores mitochondrial morphology and function, reduces ROS production, enhances ATP generation, and improves myocardial contractility.

5.4 Novel Regulatory Factors in Septic Cardiomyopathy

5.4.1 Mitochondrial Ribosomal Proteins (MRPs) as Upstream Regulators of Mitochondrial Proteostasis

Recent studies have demonstrated that MRPs are not merely structural components of the mitochondrial translational machinery, but also serve as critical upstream regulators of mitochondrial protein quality control and homeostasis. MRPs play essential roles in transcription–translation coupling, mitochondrial ribosome biogenesis, and the maintenance of mitochondrial function [232]. As an integral regulatory layer within the MQC network, dysfunction of MRPs can impair the efficiency and fidelity of mitochondrial protein translation and assembly, triggering mitochondrial stress responses and indirectly amplifying inflammatory signaling.

Among the multiple differentially expressed MRPs identified in models of sepsis-induced myocardial injury, Han et al. [233] reported that MRPS16 and MRPL47 exhibited the most pronounced downregulation. Their biological functions were therefore investigated in further detail. Knockdown of MRPS16 or MRPL47 markedly exacerbated mitochondrial damage and cardiomyocyte dysfunction under septic conditions, as evidenced by further impairment of mitochondrial biogenesis (persistent reductions in COI and PGC-1α expression), decreased ATP production, elevated ROS levels, loss of $\Delta\Psi m$, and aggravated disturbances in Ca^{2+} homeostasis.

Concomitantly, suppression of MRPS16 and MRPL47 significantly increased the expression of key components of the non-canonical pyroptotic pathway, including IL-1β, caspase-4, and gasdermin D (GSDMD), thereby promoting cardiomyocyte pyroptosis and exacerbating myocardial injury [234,235,236]. From a mechanistic perspective, these findings suggest that MRP-mediated defects in mitochondrial protein translation not only compromise cellular energy metabolism but also induce mitochondrial functional imbalance, which in turn synergistically amplifies inflammatory responses and programmed cell death signaling.

In contrast, overexpression of MRPS16 or MRPL47 partially restored mitochondrial protein translation and quality control capacity, improved mitochondrial biogenesis and energy metabolism, and significantly attenuated cardiomyocyte pyroptosis and inflammatory responses. These observations are fully consistent with previous reports demonstrating the roles of MRPL12 and MRPL10 in the regulation of mitochondrial translation and respiratory function [237]. Together, they further establish MRPs as indispensable determinants of mitochondrial functional integrity and myocardial homeostasis.

5.4.2 Post-Translational Modification of Mitochondrial Proteins: The Role of MacroD1-Mediated MARylation

Beyond mitochondrial biogenesis, dynamics, and translational defects, increasing evidence indicates that post-translational modifications (PTMs) of mitochondrial proteins play an important regulatory role in mitochondrial dysfunction associated with SCM. Among these, mono-ADP-ribosylation (MARylation), a reversible post-translational modification, has emerged as a key molecular mechanism linking mitochondrial metabolic status to inflammatory signaling [238,239,240]. Macrodomain protein 1 (MacroD1) is a macrodomain-containing protein that is highly expressed in cardiomyocytes. It is localized to mitochondria, where it dynamically regulates mitochondrial protein MARylation and plays a critical role in maintaining mitochondrial respiratory function and metabolic homeostasis [241].

Studies have shown that MacroD1 expression is markedly upregulated in the cardiomyocytes of LPS-induced models of sepsis, and is closely associated with the development of SCM [242]. Mechanistic investigations further revealed that MacroD1-mediated MARylation predominantly targets proteins associated with mitochondrial respiratory chain complex I, thereby modulating their conformational stability and electron transfer efficiency [242,243]. Under septic conditions, mitochondrial Nicotinamide Adenine Dinucleotide (NAD^+)/ADP-ribose metabolic homeostasis is severely disrupted, despite increased MacroD1 expression, resulting in aberrant MARylation of complex I proteins. This in turn leads to impaired Reduced Nicotinamide Adenine Dinucleotide (NADH) oxidation, reduced ATP synthesis, and loss of $\Delta\Psi m$ [242,243,244].

These metabolic disturbances are frequently accompanied by excessive mitochondrial ROS generation, which serves as a critical trigger for the sustained activation of inflammation-related signaling pathways [244]. Accumulating *in vivo* and *in vitro* evidence further demonstrates that MacroD1 not only regulates mitochondrial metabolic function, but also participates in the functional coupling between mitochondrial dysfunction and inflammatory cell death programs. In models of sepsis, complex I dysfunction and excessive ROS production promote activation of the NLRP3 inflammasome, leading to caspase-1 activation, GSDMD cleavage, and release of IL-1β, thereby driving cardiomyocyte pyroptosis [245,246,247].

Table 1. Regulatory targets of mitochondrial quality control (MQC).

Regulatory mechanism	Key targets	Actions and regulatory mechanisms
Mitophagy	PINK1/Parkin pathway	PINK1: Upon loss of mitochondrial membrane potential, Parkin accumulates on the outer mitochondrial membrane and is activated by phosphorylation at the Ser65 site of ubiquitin and Parkin itself. Activated Parkin, an E3 ubiquitin ligase, ubiquitinates outer membrane proteins such as Mfn2, Tom20, and voltage-dependent anion channel 1 (VDAC1), recruiting adaptor proteins including nuclear dot protein 52 (NDP52) and optineurin, ultimately leading to autophagosome formation
	BNIP3/NIX	Under stress conditions, dimerization occurs with anchoring to the outer mitochondrial membrane, and phosphorylation at Ser17/Ser24 enhances binding to light chain 3 (LC3)
	FUNDC1	A hypoxia-sensitive receptor whose N-terminal LC3-interacting region (LIR) motif phosphorylation at Ser16 activates autophagy, while phosphorylation at Ser13 and Tyr18 inhibits autophagy
	BCL2L13	Contains an LIR motif, binds to the Unc-51-like kinase complex, and phosphorylation enhances autophagic activity
Mitochondrial Dynamics	Fission: Drp1/FIS1/Mff	Drp1: A cytosolic GTPase, whose phosphorylation at Ser616 promotes binding to receptors such as FIS1, Mff, and MiD49/51, mediating mitochondrial fission; FIS1 and Mff are outer mitochondrial membrane receptors, whose phosphorylation enhances their association with Drp1
	Fusion: Mfn1/Mfn2/OPA1	Mfn1/Mfn2: Outer membrane GTPase mediates outer membrane fusion through dimerization via heptad repeat 1 (HR1)/HR2 domains. OPA1, an inner membrane GTPase, maintains cristae structure in its long form (L-OPA1). The short form (S-OPA1), generated by cleavage through OMA1/YME1L, regulates the balance between mitochondrial fusion and fission
Mitochondrial Biogenesis	PGC-1α/β	A transcriptional coactivator that activates NRF1/2 and ERRα, promoting the expression of nuclear-encoded mitochondrial genes such as OXPHOS subunits and TFAM
	NRF1/2	A nuclear transcription factor that regulates the gene expression of respiratory chain complexes and mitochondrial DNA transcription factors (TFAM, TFB1M/TFB2M)
	TFAM	A mitochondrial transcription factor that directly regulates mtDNA replication and transcription
	ERRα	A nuclear receptor that cooperates with PGC-1α to induce mitochondrial gene expression
Mitochondrial Unfolded Protein Response (UPRmt)	CHOP/ATF4	A transcription factor activated via the c-Jun/AP-1 pathway that regulates the expression of chaperone proteins (e.g., Hsp60) and proteases (e.g., LonP1)
	YME1L/OMA1	YME1L: An ATP-dependent protease that cleaves and activates the mitochondrial unfolded protein response (UPRmt), maintaining balance through mutual degradation with OMA1. OMA1 is a zinc-dependent protease that cleaves OPA1 to regulate inner mitochondrial membrane fusion
	LonP1/ClpP	A mitochondrial matrix protease that eliminates misfolded or abnormal proteins and maintains respiratory chain function
	Hsp60/Hsp10	A chaperone protein that assists in mitochondrial protein folding
Redox Signaling Crosstalk in Inflammation	NOX2	NADPH oxidase mediates the crosstalk between mitochondrial ROS and inflammatory signaling, leading to the activation of the NLRP3 inflammasome
	HMGB1	A redox hub that induces mitochondrial Ca^{2+} leakage and oxidative stress via the TLR4 signaling pathway
	NLRP3 Inflammasome	Activated by mitochondrial ROS (mtROS), it promotes the release of pro-inflammatory cytokines such as IL-1β and exacerbates mitochondrial dysfunction
Mitochondrial protein translation and assembly	MRPS16/MRPL47	Core proteins of the small and large subunits of the mitochondrial ribosome that maintain the efficiency and fidelity of translation of mtDNA-encoded proteins (e.g., COI). Downregulation of MRPS16 or MRPL47 leads to insufficient synthesis of oxidative phosphorylation (OXPHOS) subunits and impaired respiratory chain assembly.

COI, cytochrome c oxidase subunit I.

Notably, cardiomyocyte-specific deletion of MacroD1 significantly attenuates activation of the complex I–ROS–NLRP3 signaling axis, reduces inflammatory cell death, and enhances myocardial tolerance to septic stress

Table 2. Targeted drugs for mitochondrial quality control.

Regulatory mechanism	Targeted drug	Therapeutic target	Functions and mechanisms
Mitochondrial Dynamics	P110 Peptide	Drp1/FIS1 interaction	Selective inhibition of the interaction between Drp1 and FIS1 reduces excessive mitochondrial fission, improves mitochondrial membrane potential and function, and in septic cardiomyopathy models, enhances animal survival and alleviates myocardial contractile dysfunction.
	mdivi-1	Drp1	Inhibition of Drp1 GTPase activity blocks mitochondrial fission and protects cardiomyocytes from ischemia/reperfusion injury.
	MitoTEMPO	Mitochondrial ROS	Mitochondria-targeted antioxidants scavenge mitochondrial superoxide radicals, correct TNF-α elevation induced by mitochondrial superoxide/hydrogen peroxide, and restore energy metabolism abnormalities.
Mitochondrial Biogenesis	Rosiglitazone	PPARγ	Activation of PPARγ enhances the expression of PGC-1α and TFAM, improves mitochondrial biogenesis and cardiac function, and maintains myocardial lipid metabolism and function.
Redox Signaling Crosstalk in Inflammation	HMGB1 Inhibitor	HMGB1/TLR4 pathway	Blocking the interaction between HMGB1 and TLR4 reduces intracellular reactive oxygen species generation and ameliorates Ca^{2+}-mediated myocardial contractile dysfunction.
	NLRP3 Inflammasome Inhibitor	NLRP3	Inhibition of NLRP3 inflammasome activation attenuates the release of pro-inflammatory cytokines such as IL-1β and mitigates mitochondrial dysfunction.
Mitochondrial Unfolded Protein Response (UPRmt)	ONC201 (Imipridone)	ClpP	Excessive activation of the mitochondrial matrix protease ClpP suppresses oxidative phosphorylation and induces apoptosis in tumor cells; however, it may compromise mitochondrial function in normal cells.

[242,245]. These findings suggest that in the context of sepsis, MacroD1 does not merely function as a protective compensatory factor, but also serves as a critical regulatory node that promotes pathological coupling between mitochondrial metabolic dysregulation and inflammatory cell death pathways.

MacroD1-mediated MARylation fine-tunes the function of mitochondrial complex I, thereby influencing mitochondrial redox homeostasis and amplifying inflammatory signaling. Aberrant activation of this pathway may exacerbate mitochondrial dysfunction and myocardial injury in SCM, highlighting mitochondrial MARylation dynamics and their downstream signaling axes as promising therapeutic targets for the treatment of sepsis-induced cardiomyopathy [242,245,246,247].

6. Conclusions

In summary, the pathophysiological progression of SCM is closely associated with an imbalance of MQC mechanisms. Inflammatory injury activates pro-inflammatory cytokines such as TNF-α and IL-6 via the NF-κB pathway. Alongside NOX2-mediated oxidative stress and HMGB1 release, this impairs the PINK1/Parkin-dependent mitophagy pathway, resulting in defective clearance of damaged mitochondria. Concurrently, excessive fission driven by Drp1/FIS1 and fusion disruption regulated by OPA1/MFNs exacerbate mitochondrial morphological abnormalities and dysfunction. Meanwhile, PGC-1α/NRF1/TFAM-mediated mitochondrial biogenesis is insufficient to fully restore energy metabolism. The protease imbalance between YME1L and OMA1 in the UPRmt pathway disrupts mitochondrial proteostasis, forming a pathological cycle of "damage–dysregulation–deterioration".

Importantly, emerging evidence extends the MQC framework beyond these classical pathways by identifying MRPs and mitochondrial protein PTMs as novel regulatory layers in SCM. Mitochondrial protein translation and respiratory chain integrity are compromised by the dysregulation of MRPs, including MRPS16, MRPL47, and MRPL12, thereby amplifying mitochondrial stress, inflammatory signaling, and cardiomyocyte pyroptosis. In parallel, aberrant MacroD1-mediated MARylation of mitochondrial proteins—particularly complex I components—links mitochondrial metabolic imbalance to excessive ROS generation, inflammasome activation, and inflammatory cell death. Together, these findings position MRPs and MacroD1 as promising upstream therapeutic targets for preserving mitochondrial function and myocardial homeostasis in SCM.

Future research is likely to include three major directions. (1) Mechanistic exploration. Further investigations should characterize the dynamic regulation of key MQC molecules within the septic microenvironment, such as Drp1 phosphorylation sites, OPA1 proteolytic process-

ing, MRP-dependent translational fidelity, and mitochondrial MARylation dynamics. Particular attention should be paid to redox-inflammatory crosstalk, including the interplay between mtROS, NLRP3 inflammasome activation, and mitochondrial PTM-mediated signaling within the broader MQC network. (2) Therapeutic strategies. Beyond conventional modulators of mitochondrial dynamics and biogenesis, future efforts should focus on the development of drugs targeting specific mitochondrial PTMs, such as selective regulators of MacroD1 activity or mitochondrial ADP-ribosylation, as well as interventions aimed at restoring MRP function and mitochondrial translation. These approaches may be combined with established agents—including the selective Drp1/FIS1 inhibitor P110 peptide, PGC-1α activators, and HMGB1/TLR4 pathway antagonists—to achieve synergistic mitochondrial protection and anti-inflammatory effects. Tables 1,2 summarize the key MQC-related molecular targets and corresponding therapeutic strategies discussed in this review. (3) Clinical application. Greater emphasis should be placed on the temporal evolution of MQC dysregulation in late-stage SCM, particularly in post-COVID-19 patients. Monitoring biomarkers of mitophagy (e.g., LC3-II/LC3-I ratio), mitochondrial biogenesis (e.g., TFAM expression), and emerging indicators of mitochondrial translation and PTM status may facilitate patient stratification and precision therapy. Moreover, mitochondria-targeted nano-delivery systems represent a frontier strategy to enhance drug specificity, improve mitochondrial bioavailability, and minimize off-target toxicity.

Targeting the dynamic and multilayered balance of MQC, including mitochondrial dynamics, mitophagy, biogenesis, translational control by MRPs, and PTM-mediated metabolic signaling, therefore holds great promise as a novel and integrative therapeutic strategy for the prevention and treatment of SCM.

Author Contributions

Conceptualization: XP, XC, ZL, RL; Literature search and data curation: XC, ZY, ZL, RL; Writing—original draft preparation: XP; Writing—review and editing: XP; Supervision: ZL, RL (corresponding author). All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank all colleagues who provided helpful discussions during the preparation of this manuscript.

Funding

This work was supported by grants from the Academic Inheritance and Communication Project of China Academy of Chinese Medical Sciences (CI2022E012XB); the Clinical Research Fund of Central High-Level Traditional Chinese Medicine Hospitals: Hospital Preparation Project Based on the Experience of Renowned Traditional Chinese Medicine Practitioners (HLCMHPP2023053); the Beijing Traditional Chinese Medicine Inheritance Project "New 3+3" – Zhimin Liu Three-Famous Inheritance Studio (2023-SZ-F-06); and the Beijing Traditional Chinese Medicine Inheritance Project "New 3+3" – Zhimin Liu's Disciple (Ruxiu Liu) Inheritance Studio (2023-SZ-G-02).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Angus DC, van der Poll T. Severe sepsis and septic shock. The New England Journal of Medicine. 2013; 369: 840–851. https://doi.org/10.1056/NEJMra1208623

[2] Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Medicine. 2007; 33: 1892–1899. https://doi.org/10.1007/s00134-007-0680-5

[3] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006; 124: 783–801. https://doi.org/10.1016/j.cell.2006.02.015

[4] Habimana R, Choi I, Cho HJ, Kim D, Lee K, Jeong I. Sepsis-induced cardiac dysfunction: a review of pathophysiology. Acute and Critical Care. 2020; 35: 57–66. https://doi.org/10.4266/acc.2020.00248

[5] Hiraiwa H, Kasugai D, Okumura T, Murohara T. Clinical implications of septic cardiomyopathy: A narrative review. Medicine. 2024; 103: e37940. https://doi.org/10.1097/MD.0000000000037940

[6] Russell JA, Boyd J, Nakada T, Thair S, Walley KR. Molecular mechanisms of sepsis. Contributions to Microbiology. 2011; 17: 48–85. https://doi.org/10.1159/000324009

[7] Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. Journal of Leukocyte Biology. 2007; 81: 1–5. https://doi.org/10.1189/jlb.0306164

[8] Akira S, Takeda K. Toll-like receptor signalling. Nature Reviews. Immunology. 2004; 4: 499–511. https://doi.org/10.1038/nri1391

[9] Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. Journal of Intensive Care. 2016; 4: 22. https://doi.org/10.1186/s40560-016-0148-1

[10] Thomas JA, Haudek SB, Koroglu T, Tsen MF, Bryant DD, White DJ, et al. IRAK1 deletion disrupts cardiac Toll/IL-1 signaling and protects against contractile dysfunction. American Journal of Physiology. Heart and Circulatory Physiology. 2003; 285: H597–H606. https://doi.org/10.1152/ajpheart.0655.2001

[11] Liu S, Chong W. Roles of LncRNAs in Regulating Mitochondrial Dysfunction in Septic Cardiomyopathy. Frontiers in Immunology. 2021; 12: 802085. https://doi.org/10.3389/fimmu.2021.802085

[12] Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock

serum. The Journal of Experimental Medicine. 1996; 183: 949–958. https://doi.org/10.1084/jem.183.3.949

[13] Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science (New York, N.Y.). 1992; 257: 387–389. https://doi.org/10.1126/science.1631560

[14] Zhang C, Mo M, Ding W, Liu W, Yan D, Deng J, et al. High-mobility group box 1 (HMGB1) impaired cardiac excitation-contraction coupling by enhancing the sarcoplasmic reticulum (SR) Ca(2+) leak through TLR4-ROS signaling in cardiomyocytes. Journal of Molecular and Cellular Cardiology. 2014; 74: 260–273. https://doi.org/10.1016/j.yjmcc.2014.06.003

[15] Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, et al. Vascular Inflammation and Oxidative Stress: Major Triggers for Cardiovascular Disease. Oxidative Medicine and Cellular Longevity. 2019; 2019: 7092151. https://doi.org/10.1155/2019/7092151

[16] Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part II: animal and human studies. Circulation. 2003; 108: 2034–2040. https://doi.org/10.1161/01.CIR.0000093661.90582.c4

[17] Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS. Circulation. 2003; 108: 1912–1916. https://doi.org/10.1161/01.CIR.0000093660.86242.BB

[18] Joffre J, Hellman J. Oxidative Stress and Endothelial Dysfunction in Sepsis and Acute Inflammation. Antioxidants & Redox Signaling. 2021; 35: 1291–1307. https://doi.org/10.1089/ars.2021.0027

[19] Karbach S, Wenzel P, Waisman A, Munzel T, Daiber A. eNOS uncoupling in cardiovascular diseases–the role of oxidative stress and inflammation. Current Pharmaceutical Design. 2014; 20: 3579–3594. https://doi.org/10.2174/13816128113196660748

[20] Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, et al. Inflammation, immunity, and hypertension. Hypertension (Dallas, Tex.: 1979). 2011; 57: 132–140. https://doi.org/10.1161/HYPERTENSIONAHA.110.163576

[21] Kröller-Schön S, Steven S, Kossmann S, Scholz A, Daub S, Oelze M, et al. Molecular mechanisms of the crosstalk between mitochondria and NADPH oxidase through reactive oxygen species-studies in white blood cells and in animal models. Antioxidants & Redox Signaling. 2014; 20: 247–266. https://doi.org/10.1089/ars.2012.4953

[22] Dikalov SI, Li W, Doughan AK, Blanco RR, Zafari AM. Mitochondrial reactive oxygen species and calcium uptake regulate activation of phagocytic NADPH oxidase. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2012; 302: R1134–R1142. https://doi.org/10.1152/ajpregu.00842.2010

[23] Nazarewicz RR, Dikalov SI. Mitochondrial ROS in the prohypertensive immune response. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2013; 305: R98–R100. https://doi.org/10.1152/ajpregu.00208.2013

[24] Schulz E, Wenzel P, Münzel T, Daiber A. Mitochondrial redox signaling: Interaction of mitochondrial reactive oxygen species with other sources of oxidative stress. Antioxidants & Redox Signaling. 2014; 20: 308–324. https://doi.org/10.1089/ars.2012.4609

[25] Daiber A, Di Lisa F, Oelze M, Kröller-Schön S, Steven S, Schulz E, et al. Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function. British Journal of Pharmacology. 2017; 174: 1670–1689. https://doi.org/10.1111/bph.13403

[26] Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, et al. Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. Circulation. 2011; 124: 1370–1381. https://doi.org/10.1161/CIRCULATIONAHA.111.034470

[27] Kossmann S, Schwenk M, Hausding M, Karbach SH, Schmidgen MI, Brandt M, et al. Angiotensin II-induced vascular dysfunction depends on interferon-γ-driven immune cell recruitment and mutual activation of monocytes and NK-cells. Arteriosclerosis, Thrombosis, and Vascular Biology. 2013; 33: 1313–1319. https://doi.org/10.1161/ATVBAHA.113.301437

[28] Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. The Journal of Experimental Medicine. 2007; 204: 2449–2460. https://doi.org/10.1084/jem.20070657

[29] Chan CT, Sobey CG, Lieu M, Ferens D, Kett MM, Diep H, et al. Obligatory Role for B Cells in the Development of Angiotensin II-Dependent Hypertension. Hypertension (Dallas, Tex.: 1979). 2015; 66: 1023–1033. https://doi.org/10.1161/HYPERTENSIONAHA.115.05779

[30] Itani HA, McMaster WG, Jr, Saleh MA, Nazarewicz RR, Mikolajczyk TP, Kaszuba AM, et al. Activation of Human T Cells in Hypertension: Studies of Humanized Mice and Hypertensive Humans. Hypertension (Dallas, Tex.: 1979). 2016; 68: 123–132. https://doi.org/10.1161/HYPERTENSIONAHA.116.07237

[31] Kossmann S, Lagrange J, Jäckel S, Jurk K, Ehlken M, Schönfelder T, et al. Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. Science Translational Medicine. 2017; 9: eaah4923. https://doi.org/10.1126/scitranslmed.aah4923

[32] Gasparyan AY, Stavropoulos-Kalinoglou A, Toms TE, Douglas KMJ, Kitas GD. Association of mean platelet volume with hypertension in rheumatoid arthritis. Inflammation & Allergy Drug Targets. 2010; 9: 45–50. https://doi.org/10.2174/187152810791292854

[33] Leader A, Pereg D, Lishner M. Are platelet volume indices of clinical use? A multidisciplinary review. Annals of Medicine. 2012; 44: 805–816. https://doi.org/10.3109/07853890.2011.653391

[34] Wenzel P, Kossmann S, Münzel T, Daiber A. Redox regulation of cardiovascular inflammation - Immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. Free Radical Biology & Medicine. 2017; 109: 48–60. https://doi.org/10.1016/j.freeradbiomed.2017.01.027

[35] Wenzel P. Monocytes as immune targets in arterial hypertension. British Journal of Pharmacology. 2019; 176: 1966–1977. https://doi.org/10.1111/bph.14389

[36] Knorr M, Münzel T, Wenzel P. Interplay of NK cells and monocytes in vascular inflammation and myocardial infarction. Frontiers in Physiology. 2014; 5: 295. https://doi.org/10.3389/fphys.2014.00295

[37] Karbach S, Lagrange J, Wenzel P. Thromboinflammation and Vascular Dysfunction. Hamostaseologie. 2019; 39: 180–187. https://doi.org/10.1055/s-0038-1676130

[38] Pittman K, Kubes P. Damage-associated molecular patterns control neutrophil recruitment. Journal of Innate Immunity. 2013; 5: 315–323. https://doi.org/10.1159/000347132

[39] Ortona E, Maselli A, Delunardo F, Colasanti T, Giovannetti A, Pierdominici M. Relationship between redox status and cell fate in immunity and autoimmunity. Antioxidants & Redox Signaling. 2014; 21: 103–122. https://doi.org/10.1089/ars.2013.5752

[40] Brüne B, Dehne N, Grossmann N, Jung M, Namgaladze D, Schmid T, et al. Redox control of inflammation in macrophages. Antioxidants & Redox Signaling. 2013; 19: 595–637. https://doi.org/10.1089/ars.2012.4785

[41] Janko C, Filipović M, Munoz LE, Schorn C, Schett G, Ivanović-

Burmazović I, et al. Redox modulation of HMGB1-related signaling. Antioxidants & Redox Signaling. 2014; 20: 1075–1085. https://doi.org/10.1089/ars.2013.5179
[42] Kirabo A, Fontana V, de Faria APC, Loperena R, Galindo CL, Wu J, et al. DC isoketal-modified proteins activate T cells and promote hypertension. The Journal of Clinical Investigation. 2014; 124: 4642–4656. https://doi.org/10.1172/JCI74084
[43] Qiao M, Zhao Q, Lee CF, Tannock LR, Smart EJ, LeBaron RG, et al. Thiol oxidative stress induced by metabolic disorders amplifies macrophage chemotactic responses and accelerates atherogenesis and kidney injury in LDL receptor-deficient mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009; 29: 1779–1786. https://doi.org/10.1161/ATVBAHA.109.191759
[44] Kim HS, Ullevig SL, Zamora D, Lee CF, Asmis R. Redox regulation of MAPK phosphatase 1 controls monocyte migration and macrophage recruitment. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: E2803–E2812. https://doi.org/10.1073/pnas.1212596109
[45] Kim HS, Ullevig SL, Nguyen HN, Vanegas D, Asmis R. Redox regulation of 14-3-3ζ controls monocyte migration. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014; 34: 1514–1521. https://doi.org/10.1161/ATVBAHA.114.303746
[46] Ullevig S, Kim HS, Asmis R. S-glutathionylation in monocyte and macrophage (dys)function. International Journal of Molecular Sciences. 2013; 14: 15212–15232. https://doi.org/10.3390/ijms140815212
[47] Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, Kim KY, et al. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). The Journal of Experimental Medicine. 2011; 208: 519–533. https://doi.org/10.1084/jem.20102049
[48] West AP, Brodsky IE, Rahner C, Woo DK, Erdjument-Bromage H, Tempst P, et al. TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. Nature. 2011; 472: 476–480. https://doi.org/10.1038/nature09973
[49] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011; 469: 221–225. https://doi.org/10.1038/nature09663
[50] Boeck C, Koenig AM, Schury K, Geiger ML, Karabatsiakis A, Wilker S, et al. Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. Mitochondrion. 2016; 30: 197–207. https://doi.org/10.1016/j.mito.2016.08.006
[51] Abais JM, Xia M, Zhang Y, Boini KM, Li PL. Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxidants & Redox Signaling. 2015; 22: 1111–1129. https://doi.org/10.1089/ars.2014.5994
[52] Bae JY, Park HH. Crystal structure of NALP3 protein pyrin domain (PYD) and its implications in inflammasome assembly. The Journal of Biological Chemistry. 2011; 286: 39528–39536. https://doi.org/10.1074/jbc.M111.278812
[53] Maugeri N, Rovere-Querini P, Baldini M, Baldissera E, Sabbadini MG, Bianchi ME, et al. Oxidative stress elicits platelet/leukocyte inflammatory interactions via HMGB1: a candidate for microvessel injury in sytemic sclerosis. Antioxidants & Redox Signaling. 2014; 20: 1060–1074. https://doi.org/10.1089/ars.2013.5298
[54] Venereau E, Casalgrandi M, Schiraldi M, Antoine DJ, Cattaneo A, De Marchis F, et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. The Journal of Experimental Medicine. 2012; 209: 1519–1528. https://doi.org/10.1084/jem.20120189
[55] Azevedo EP, Rochael NC, Guimarães-Costa AB, de Souza-Vieira TS, Ganilho J, Saraiva EM, et al. A Metabolic Shift toward Pentose Phosphate Pathway Is Necessary for Amyloid Fibril- and Phorbol 12-Myristate 13-Acetate-induced Neutrophil Extracellular Trap (NET) Formation. The Journal of Biological Chemistry. 2015; 290: 22174–22183. https://doi.org/10.1074/jbc.M115.640094
[56] Dan Dunn J, Alvarez LA, Zhang X, Soldati T. Reactive oxygen species and mitochondria: A nexus of cellular homeostasis. Redox Biology. 2015; 6: 472–485. https://doi.org/10.1016/j.redox.2015.09.005
[57] Douda DN, Khan MA, Grasemann H, Palaniyar N. SK3 channel and mitochondrial ROS mediate NADPH oxidase-independent NETosis induced by calcium influx. Proceedings of the National Academy of Sciences of the United States of America. 2015; 112: 2817–2822. https://doi.org/10.1073/pnas.1414055112
[58] Lood C, Blanco LP, Purmalek MM, Carmona-Rivera C, De Ravin SS, Smith CK, et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. Nature Medicine. 2016; 22: 146–153. https://doi.org/10.1038/nm.4027
[59] Morshed M, Hlushchuk R, Simon D, Walls AF, Obata-Ninomiya K, Karasuyama H, et al. NADPH oxidase-independent formation of extracellular DNA traps by basophils. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 5314–5323. https://doi.org/10.4049/jimmunol.1303418
[60] Kirchner T, Möller S, Klinger M, Solbach W, Laskay T, Behnen M. The impact of various reactive oxygen species on the formation of neutrophil extracellular traps. Mediators of Inflammation. 2012; 2012: 849136. https://doi.org/10.1155/2012/849136
[61] Mikhed Y, Daiber A, Steven S. Mitochondrial Oxidative Stress, Mitochondrial DNA Damage and Their Role in Age-Related Vascular Dysfunction. International Journal of Molecular Sciences. 2015; 16: 15918–15953. https://doi.org/10.3390/ijms160715918
[62] Oelze M, Kröller-Schön S, Steven S, Lubos E, Doppler C, Hausding M, et al. Glutathione peroxidase-1 deficiency potentiates dysregulatory modifications of endothelial nitric oxide synthase and vascular dysfunction in aging. Hypertension (Dallas, Tex.: 1979). 2014; 63: 390–396. https://doi.org/10.1161/HYPERTENSIONAHA.113.01602
[63] Liu Y, Zhang R, Qu H, Wu J, Li L, Tang Y. Endothelial microparticles activate endothelial cells to facilitate the inflammatory response. Molecular Medicine Reports. 2017; 15: 1291–1296. https://doi.org/10.3892/mmr.2017.6113
[64] Wenzel P, Rossmann H, Müller C, Kossmann S, Oelze M, Schulz A, et al. Heme oxygenase-1 suppresses a pro-inflammatory phenotype in monocytes and determines endothelial function and arterial hypertension in mice and humans. European Heart Journal. 2015; 36: 3437–3446. https://doi.org/10.1093/eurheartj/ehv544
[65] Joseph LC, Kokkinaki D, Valenti MC, Kim GJ, Barca E, Tomar D, et al. Inhibition of NADPH oxidase 2 (NOX2) prevents sepsis-induced cardiomyopathy by improving calcium handling and mitochondrial function. JCI Insight. 2017; 2: e94248. https://doi.org/10.1172/jci.insight.94248
[66] Zhang M, Brewer AC, Schröder K, Santos CXC, Grieve DJ, Wang M, et al. NADPH oxidase-4 mediates protection against chronic load-induced stress in mouse hearts by enhancing angiogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 18121–18126. https://doi.org/10.1073/pnas.1009700107
[67] Chen Z, Tao S, Li X, Yao Q. Resistin destroys mitochondrial biogenesis by inhibiting the PGC-1α/ NRF1/TFAM signaling pathway. Biochemical and Biophysical Research Communications. 2018; 504: 13-18. https://doi.org/10.1016/j.bbrc.2018.08.027
[68] Givvimani S, Pushpakumar SB, Metreveli N, Veeranki S, Kundu S, Tyagi SC. Role of mitochondrial fission and fusion in cardiomyocyte contractility. International Journal of Cardiology.

2015; 187: 325–333. https://doi.org/10.1016/j.ijcard.2015.03.352
[69] Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science (New York, N.Y.). 1999; 285: 248–251. https://doi.org/10.1126/science.285.5425.248
[70] Tang D, Kang R, Livesey KM, Cheh CW, Farkas A, Loughran P, et al. Endogenous HMGB1 regulates autophagy. The Journal of Cell Biology. 2010; 190: 881–892. https://doi.org/10.1083/jcb.200911078
[71] Iyer SS, He Q, Janczy JR, Elliott EI, Zhong Z, Olivier AK, et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. Immunity. 2013; 39: 311–323. https://doi.org/10.1016/j.immuni.2013.08.001
[72] Toldo S, Mezzaroma E, Mauro AG, Salloum F, Van Tassell BW, Abbate A. The inflammasome in myocardial injury and cardiac remodeling. Antioxidants & Redox Signaling. 2015; 22: 1146–1161. https://doi.org/10.1089/ars.2014.5989
[73] Nakahira K, Haspel JA, Rathinam VAK, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nature Immunology. 2011; 12: 222–230. https://doi.org/10.1038/ni.1980
[74] Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, et al. NF-κB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. Cell. 2016; 164: 896–910. https://doi.org/10.1016/j.cell.2015.12.057
[75] Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochimica et Biophysica Acta. 2016; 1863: 2977–2992. https://doi.org/10.1016/j.bbamcr.2016.09.012
[76] Ryter SW, Kim HP, Hoetzel A, Park JW, Nakahira K, Wang X, et al. Mechanisms of cell death in oxidative stress. Antioxidants & Redox Signaling. 2007; 9: 49–89. https://doi.org/10.1089/ars.2007.9.49
[77] Borutaite V, Morkuniene R, Brown GC. Release of cytochrome c from heart mitochondria is induced by high Ca2+ and peroxynitrite and is responsible for Ca(2+)-induced inhibition of substrate oxidation. Biochimica et Biophysica Acta. 1999; 1453: 41–48. https://doi.org/10.1016/s0925-4439(98)00082-9
[78] Halliwell B. Free radicals and antioxidants - quo vadis? Trends in Pharmacological Sciences. 2011; 32: 125–130. https://doi.org/10.1016/j.tips.2010.12.002
[79] Radi R, Cassina A, Hodara R. Nitric oxide and peroxynitrite interactions with mitochondria. Biological Chemistry. 2002; 383: 401–409. https://doi.org/10.1515/BC.2002.044
[80] Elmore S. Apoptosis: a review of programmed cell death. Toxicologic Pathology. 2007; 35: 495–516. https://doi.org/10.1080/01926230701320337
[81] Mahmood Z, Shukla Y. Death receptors: targets for cancer therapy. Experimental Cell Research. 2010; 316: 887–899. https://doi.org/10.1016/j.yexcr.2009.12.011
[82] Peter ME. Programmed cell death: Apoptosis meets necrosis. Nature. 2011; 471: 310–312. https://doi.org/10.1038/471310a
[83] Huet O, Dupic L, Harrois A, Duranteau J. Oxidative stress and endothelial dysfunction during sepsis. Frontiers in Bioscience (Landmark Edition). 2011; 16: 1986–1995. https://doi.org/10.2741/3835
[84] Pallepati P, Averill-Bates DA. Mild thermotolerance induced at 40°C protects HeLa cells against activation of death receptor-mediated apoptosis by hydrogen peroxide. Free Radical Biology & Medicine. 2011; 50: 667–679. https://doi.org/10.1016/j.freeradbiomed.2010.11.022
[85] Bombeli T, Karsan A, Tait JF, Harlan JM. Apoptotic vascular endothelial cells become procoagulant. Blood. 1997; 89: 2429–2442.
[86] Bombeli T, Schwartz BR, Harlan JM. Endothelial cells undergoing apoptosis become proadhesive for nonactivated platelets. Blood. 1999; 93: 3831–3838.
[87] Baxter AA. Stoking the Fire: How Dying Cells Propagate Inflammatory Signalling through Extracellular Vesicle Trafficking. International Journal of Molecular Sciences. 2020; 21: 7256. https://doi.org/10.3390/ijms21197256
[88] Gill SE, Rohan M, Mehta S. Role of pulmonary microvascular endothelial cell apoptosis in murine sepsis-induced lung injury in vivo. Respiratory Research. 2015; 16: 109. https://doi.org/10.1186/s12931-015-0266-7
[89] Chang X, Zhang T, Wang J, Liu Y, Yan P, Meng Q, et al. SIRT5-Related Desuccinylation Modification Contributes to Quercetin-Induced Protection against Heart Failure and High-Glucose-Prompted Cardiomyocytes Injured through Regulation of Mitochondrial Quality Surveillance. Oxidative Medicine and Cellular Longevity. 2021; 2021: 5876841. https://doi.org/10.1155/2021/5876841
[90] Li A, Gao M, Liu B, Qin Y, Chen L, Liu H, et al. Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. Cell Death & Disease. 2022; 13: 444. https://doi.org/10.1038/s41419-022-04906-6
[91] Liu M, Wu Y. Role of Mitophagy in Coronary Heart Disease: Targeting the Mitochondrial Dysfunction and Inflammatory Regulation. Frontiers in Cardiovascular Medicine. 2022; 9: 819454. https://doi.org/10.3389/fcvm.2022.819454
[92] Greene AW, Grenier K, Aguileta MA, Muise S, Farazifard R, Haque ME, et al. Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. EMBO Reports. 2012; 13: 378–385. https://doi.org/10.1038/embor.2012.14
[93] Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. The Journal of Cell Biology. 2008; 183: 795–803. https://doi.org/10.1083/jcb.200809125
[94] Kondapalli C, Kazlauskaite A, Zhang N, Woodroof HI, Campbell DG, Gourlay R, et al. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. Open Biology. 2012; 2: 120080. https://doi.org/10.1098/rsob.120080
[95] Gersch M, Gladkova C, Schubert AF, Michel MA, Maslen S, Komander D. Mechanism and regulation of the Lys6-selective deubiquitinase USP30. Nature Structural & Molecular Biology. 2017; 24: 920–930. https://doi.org/10.1038/nsmb.3475
[96] Tanaka A, Cleland MM, Xu S, Narendra DP, Suen DF, Karbowski M, et al. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. The Journal of Cell Biology. 2010; 191: 1367–1380. https://doi.org/10.1083/jcb.201007013
[97] Yoshii SR, Kishi C, Ishihara N, Mizushima N. Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane. The Journal of Biological Chemistry. 2011; 286: 19630–19640. https://doi.org/10.1074/jbc.M110.209338
[98] Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature. 2015; 524: 309–314. https://doi.org/10.1038/nature14893
[99] Padman BS, Nguyen TN, Uoselis L, Skulsuppaisarn M, Nguyen LK, Lazarou M. LC3/GABARAPs drive ubiquitin-independent recruitment of Optineurin and NDP52 to amplify mitophagy. Nature Communications. 2019; 10: 408. https://doi.org/10.1038/s41467-019-08335-6
[100] Otsu K, Murakawa T, Yamaguchi O. BCL2L13 is a mammalian homolog of the yeast mitophagy receptor Atg32. Autophagy. 2015; 11: 1932–1933. https://doi.org/10.1080/15548627.2015.

1084459
[101] Murakawa T, Yamaguchi O, Hashimoto A, Hikoso S, Takeda T, Oka T, et al. Bcl-2-like protein 13 is a mammalian Atg32 homologue that mediates mitophagy and mitochondrial fragmentation. Nature Communications. 2015; 6: 7527. https://doi.org/10.1038/ncomms8527
[102] Chinnadurai G, Vijayalingam S, Gibson SB. BNIP3 subfamily BH3-only proteins: mitochondrial stress sensors in normal and pathological functions. Oncogene. 2008; 27: S114–S127. https://doi.org/10.1038/onc.2009.49
[103] Zhu Y, Massen S, Terenzio M, Lang V, Chen-Lindner S, Eils R, et al. Modulation of serines 17 and 24 in the LC3-interacting region of Bnip3 determines pro-survival mitophagy versus apoptosis. The Journal of Biological Chemistry. 2013; 288: 1099–1113. https://doi.org/10.1074/jbc.M112.399345
[104] Marinković M, Novak I. A brief overview of BNIP3L/NIX receptor-mediated mitophagy. FEBS Open Bio. 2021; 11: 3230–3236. https://doi.org/10.1002/2211-5463.13307
[105] Ney PA. Mitochondrial autophagy: Origins, significance, and role of BNIP3 and NIX. Biochimica et Biophysica Acta. 2015; 1853: 2775–2783. https://doi.org/10.1016/j.bbamcr.2015.02.022
[106] Zhou H, Zhu P, Wang J, Zhu H, Ren J, Chen Y. Pathogenesis of cardiac ischemia reperfusion injury is associated with CK2α-disturbed mitochondrial homeostasis via suppression of FUNDC1-related mitophagy. Cell Death and Differentiation. 2018; 25: 1080–1093. https://doi.org/10.1038/s41418-018-0086-7
[107] Zhou H, Zhu P, Wang J, Toan S, Ren J. DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. Signal Transduction and Targeted Therapy. 2019; 4: 56. https://doi.org/10.1038/s41392-019-0094-1
[108] Zhou H, Zhu P, Guo J, Hu N, Wang S, Li D, et al. Ripk3 induces mitochondrial apoptosis via inhibition of FUNDC1 mitophagy in cardiac IR injury. Redox Biology. 2017; 13: 498–507. https://doi.org/10.1016/j.redox.2017.07.007
[109] Wang J, Zhu P, Li R, Ren J, Zhou H. Fundc1-dependent mitophagy is obligatory to ischemic preconditioning-conferred renoprotection in ischemic AKI via suppression of Drp1-mediated mitochondrial fission. Redox Biology. 2020; 30: 101415. https://doi.org/10.1016/j.redox.2019.101415
[110] Wang Y, Jasper H, Toan S, Muid D, Chang X, Zhou H. Mitophagy coordinates the mitochondrial unfolded protein response to attenuate inflammation-mediated myocardial injury. Redox Biology. 2021; 45: 102049. https://doi.org/10.1016/j.redox.2021.102049
[111] Quintana-Cabrera R, Scorrano L. Determinants and outcomes of mitochondrial dynamics. Molecular Cell. 2023; 83: 857–876. https://doi.org/10.1016/j.molcel.2023.02.012
[112] Murley A, Lackner LL, Osman C, West M, Voeltz GK, Walter P, et al. ER-associated mitochondrial division links the distribution of mitochondria and mitochondrial DNA in yeast. elife. 2013; 2: e00422. https://doi.org/10.7554/eLife.00422
[113] Lewis SC, Uchiyama LF, Nunnari J. ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. Science (New York, N.Y.). 2016; 353: aaf5549. https://doi.org/10.1126/science.aaf5549
[114] Ban-Ishihara R, Ishihara T, Sasaki N, Mihara K, Ishihara N. Dynamics of nucleoid structure regulated by mitochondrial fission contributes to cristae reformation and release of cytochrome c. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110: 11863–11868. https://doi.org/10.1073/pnas.1301951110
[115] Varadi A, Johnson-Cadwell LI, Cirulli V, Yoon Y, Allan VJ, Rutter GA. Cytoplasmic dynein regulates the subcellular distribution of mitochondria by controlling the recruitment of the fission factor dynamin-related protein-1. Journal of Cell Science. 2004; 117: 4389–4400. https://doi.org/10.1242/jcs.01299
[116] Fonseca TB, Sánchez-Guerrero Á, Milosevic I, Raimundo N. Mitochondrial fission requires DRP1 but not dynamins. Nature. 2019; 570: E34–E42. https://doi.org/10.1038/s41586-019-1296-y
[117] Kamerkar SC, Kraus F, Sharpe AJ, Pucadyil TJ, Ryan MT. Dynamin-related protein 1 has membrane constricting and severing abilities sufficient for mitochondrial and peroxisomal fission. Nature Communications. 2018; 9: 5239. https://doi.org/10.1038/s41467-018-07543-w
[118] Nagashima S, Tábara LC, Tilokani L, Paupe V, Anand H, Pogson JH, et al. Golgi-derived PI(4)P-containing vesicles drive late steps of mitochondrial division. Science (New York, N.Y.). 2020; 367: 1366–1371. https://doi.org/10.1126/science.aax6089
[119] Song Z, Ghochani M, McCaffery JM, Frey TG, Chan DC. Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. Molecular Biology of the Cell. 2009; 20: 3525–3532. https://doi.org/10.1091/mbc.e09-03-0252
[120] Casellas-Díaz S, Larramona-Arcas R, Riqué-Pujol G, Tena-Morraja P, Müller-Sánchez C, Segarra-Mondejar M, et al. Mfn2 localization in the ER is necessary for its bioenergetic function and neuritic development. EMBO Reports. 2021; 22: e51954. https://doi.org/10.15252/embr.202051954
[121] Meeusen S, DeVay R, Block J, Cassidy-Stone A, Wayson S, McCaffery JM, et al. Mitochondrial inner-membrane fusion and crista maintenance requires the dynamin-related GTPase Mgm1. Cell. 2006; 127: 383–395. https://doi.org/10.1016/j.cell.2006.09.021
[122] Yu C, Zhao J, Yan L, Qi Y, Guo X, Lou Z, et al. Structural insights into G domain dimerization and pathogenic mutation of OPA1. The Journal of Cell Biology. 2020; 219: e201907098. https://doi.org/10.1083/jcb.201907098
[123] Yan L, Qi Y, Ricketson D, Li L, Subramanian K, Zhao J, et al. Structural analysis of a trimeric assembly of the mitochondrial dynamin-like GTPase Mgm1. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117: 4061–4070. https://doi.org/10.1073/pnas.1919116117
[124] Anand R, Wai T, Baker MJ, Kladt N, Schauss AC, Rugarli E, et al. The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. The Journal of Cell Biology. 2014; 204: 919–929. https://doi.org/10.1083/jcb.201308006
[125] Gilkerson R, De La Torre P, St Vallier S. Mitochondrial OMA1 and OPA1 as Gatekeepers of Organellar Structure/Function and Cellular Stress Response. Frontiers in Cell and Developmental Biology. 2021; 9: 626117. https://doi.org/10.3389/fcell.2021.626117
[126] Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK. ER tubules mark sites of mitochondrial division. Science (New York, N.Y.). 2011; 334: 358–362. https://doi.org/10.1126/science.1207385
[127] Yang Y, Lei W, Zhao L, Wen Y, Li Z. Insights Into Mitochondrial Dynamics in Chlamydial Infection. Frontiers in Cellular and Infection Microbiology. 2022; 12: 835181. https://doi.org/10.3389/fcimb.2022.835181
[128] Fröhlich C, Grabiger S, Schwefel D, Faelber K, Rosenbaum E, Mears J, et al. Structural insights into oligomerization and mitochondrial remodelling of dynamin 1-like protein. The EMBO Journal. 2013; 32: 1280–1292. https://doi.org/10.1038/emboj.2013.74
[129] Jin JY, Wei XX, Zhi XL, Wang XH, Meng D. Drp1-dependent mitochondrial fission in cardiovascular disease. Acta Pharmacologica Sinica. 2021; 42: 655–664. https://doi.org/10.1038/

s41401-020-00518-y
[130] Wang S, Zhu H, Li R, Mui D, Toan S, Chang X, et al. DNA-PKcs interacts with and phosphorylates Fis1 to induce mitochondrial fragmentation in tubular cells during acute kidney injury. Science Signaling. 2022; 15: eabh1121. https://doi.org/10.1126/scisignal.abh1121
[131] Li Y, Chen H, Yang Q, Wan L, Zhao J, Wu Y, et al. Increased Drp1 promotes autophagy and ESCC progression by mtDNA stress mediated cGAS-STING pathway. Journal of Experimental & Clinical Cancer Research: CR. 2022; 41: 76. https://doi.org/10.1186/s13046-022-02262-z
[132] Li S, Lin Q, Shao X, Zhu X, Wu J, Wu B, et al. Drp1-regulated PARK2-dependent mitophagy protects against renal fibrosis in unilateral ureteral obstruction. Free Radical Biology & Medicine. 2020; 152: 632–649. https://doi.org/10.1016/j.freeradbiomed.2019.12.005
[133] Zhou H, Zhang Y, Hu S, Shi C, Zhu P, Ma Q, et al. Melatonin protects cardiac microvasculature against ischemia/reperfusion injury via suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis. Journal of Pineal Research. 2017; 63: e12413. https://doi.org/10.1111/jpi.12413
[134] Pereira GC, Lee L, Rawlings N, Ouwendijk J, Parker JE, Andrienko TN, et al. Hexokinase II dissociation alone cannot account for changes in heart mitochondrial function, morphology and sensitivity to permeability transition pore opening following ischemia. PloS One. 2020; 15: e0234653. https://doi.org/10.1371/journal.pone.0234653
[135] Li CJ, Lin LT, Tsai HW, Wen ZH, Tsui KH. Phosphoglycerate mutase family member 5 maintains oocyte quality via mitochondrial dynamic rearrangement during aging. Aging Cell. 2022; 21: e13546. https://doi.org/10.1111/acel.13546
[136] Losón OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Molecular Biology of the Cell. 2013; 24: 659–667. https://doi.org/10.1091/mbc.E12-10-0721
[137] Twig G, Shirihai OS. The interplay between mitochondrial dynamics and mitophagy. Antioxidants & Redox Signaling. 2011; 14: 1939–1951. https://doi.org/10.1089/ars.2010.3779
[138] Yamashita SI, Jin X, Furukawa K, Hamasaki M, Nezu A, Otera H, et al. Mitochondrial division occurs concurrently with autophagosome formation but independently of Drp1 during mitophagy. The Journal of Cell Biology. 2016; 215: 649–665. https://doi.org/10.1083/jcb.201605093
[139] Pickles S, Vigié P, Youle RJ. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Current Biology: CB. 2018; 28: R170–R185. https://doi.org/10.1016/j.cub.2018.01.004
[140] Ishihara T, Ban-Ishihara R, Maeda M, Matsunaga Y, Ichimura A, Kyogoku S, et al. Dynamics of mitochondrial DNA nucleoids regulated by mitochondrial fission is essential for maintenance of homogeneously active mitochondria during neonatal heart development. Molecular and Cellular Biology. 2015; 35: 211–223. https://doi.org/10.1128/MCB.01054-14
[141] Song M, Mihara K, Chen Y, Scorrano L, Dorn GW, 2nd. Mitochondrial fission and fusion factors reciprocally orchestrate mitophagic culling in mouse hearts and cultured fibroblasts. Cell Metabolism. 2015; 21: 273–286. https://doi.org/10.1016/j.cmet.2014.12.011
[142] Mishra P, Chan DC. Mitochondrial dynamics and inheritance during cell division, development and disease. Nature Reviews. Molecular Cell Biology. 2014; 15: 634–646. https://doi.org/10.1038/nrm3877
[143] Saxton WM, Hollenbeck PJ. The axonal transport of mitochondria. Journal of Cell Science. 2012; 125: 2095–2104. https://doi.org/10.1242/jcs.053850
[144] Misko A, Jiang S, Wegorzewska I, Milbrandt J, Baloh RH. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2010; 30: 4232–4240. https://doi.org/10.1523/JNEUROSCI.6248-09.2010
[145] Chen Y, Sheng ZH. Kinesin-1-syntaphilin coupling mediates activity-dependent regulation of axonal mitochondrial transport. The Journal of Cell Biology. 2013; 202: 351–364. https://doi.org/10.1083/jcb.201302040
[146] Pekkurnaz G, Trinidad JC, Wang X, Kong D, Schwarz TL. Glucose regulates mitochondrial motility via Milton modification by O-GlcNAc transferase. Cell. 2014; 158: 54–68. https://doi.org/10.1016/j.cell.2014.06.007
[147] Ni HM, Williams JA, Ding WX. Mitochondrial dynamics and mitochondrial quality control. Redox Biology. 2015; 4: 6–13. https://doi.org/10.1016/j.redox.2014.11.006
[148] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays in Biochemistry. 2010; 47: 69–84. https://doi.org/10.1042/bse0470069
[149] Ploumi C, Daskalaki I, Tavernarakis N. Mitochondrial biogenesis and clearance: a balancing act. The FEBS Journal. 2017; 284: 183–195. https://doi.org/10.1111/febs.13820
[150] Scarpulla RC. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiological Reviews. 2008; 88: 611–638. https://doi.org/10.1152/physrev.00025.2007
[151] Granat L, Hunt RJ, Bateman JM. Mitochondrial retrograde signalling in neurological disease. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2020; 375: 20190415. https://doi.org/10.1098/rstb.2019.0415
[152] Liu L, Li Y, Chen G, Chen Q. Crosstalk between mitochondrial biogenesis and mitophagy to maintain mitochondrial homeostasis. Journal of Biomedical Science. 2023; 30: 86. https://doi.org/10.1186/s12929-023-00975-7
[153] Virbasius JV, Virbasius CA, Scarpulla RC. Identity of GABP with NRF-2, a multisubunit activator of cytochrome oxidase expression, reveals a cellular role for an ETS domain activator of viral promoters. Genes & Development. 1993; 7: 380–392. https://doi.org/10.1101/gad.7.3.380
[154] Evans MJ, Scarpulla RC. NRF-1: a trans-activator of nuclear-encoded respiratory genes in animal cells. Genes & Development. 1990; 4: 1023–1034. https://doi.org/10.1101/gad.4.6.1023
[155] Scarpulla RC. Nuclear activators and coactivators in mammalian mitochondrial biogenesis. Biochimica et Biophysica Acta. 2002; 1576: 1–14. https://doi.org/10.1016/s0167-4781(02)00343-3
[156] Chau CM, Evans MJ, Scarpulla RC. Nuclear respiratory factor 1 activation sites in genes encoding the gamma-subunit of ATP synthase, eukaryotic initiation factor 2 alpha, and tyrosine aminotransferase. Specific interaction of purified NRF-1 with multiple target genes. The Journal of Biological Chemistry. 1992; 267: 6999–7006.
[157] Virbasius JV, Scarpulla RC. Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. Proceedings of the National Academy of Sciences of the United States of America. 1994; 91: 1309–1313. https://doi.org/10.1073/pnas.91.4.1309
[158] Watanabe H, Imai T, Sharp PA, Handa H. Identification of two transcription factors that bind to specific elements in the promoter of the adenovirus early-region 4. Molecular and Cellular Biology. 1988; 8: 1290–1300. https://doi.org/10.1128/mcb.8.3.1290-1300.1988
[159] Rosmarin AG, Resendes KK, Yang Z, McMillan JN, Fleming SL. GA-binding protein transcription factor: a review of GABP

as an integrator of intracellular signaling and protein-protein interactions. Blood Cells, Molecules & Diseases. 2004; 32: 143–154. https://doi.org/10.1016/j.bcmd.2003.09.005

[160] Schreiber SN, Emter R, Hock MB, Knutti D, Cardenas J, Podvinec M, et al. The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 6472–6477. https://doi.org/10.1073/pnas.0308686101

[161] Shao D, Liu Y, Liu X, Zhu L, Cui Y, Cui A, et al. PGC-1 beta-regulated mitochondrial biogenesis and function in myotubes is mediated by NRF-1 and ERR alpha. Mitochondrion. 2010; 10: 516–527. https://doi.org/10.1016/j.mito.2010.05.012

[162] Mootha VK, Handschin C, Arlow D, Xie X, St Pierre J, Sihag S, et al. Erralpha and Gabpa/b specify PGC-1alpha-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 6570–6575. https://doi.org/10.1073/pnas.0401401101

[163] Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M, et al. Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERRalpha and gamma. Cell Metabolism. 2007; 5: 345–356. https://doi.org/10.1016/j.cmet.2007.03.007

[164] Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell. 1999; 98: 115–124. https://doi.org/10.1016/S0092-8674(00)80611-X

[165] Boström P, Mann N, Wu J, Quintero PA, Plovie ER, Panáková D, et al. C/EBPβ controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. Cell. 2010; 143: 1072–1083. https://doi.org/10.1016/j.cell.2010.11.036

[166] Yao Y, Lu Q, Hu Z, Yu Y, Chen Q, Wang QK. A non-canonical pathway regulates ER stress signaling and blocks ER stress-induced apoptosis and heart failure. Nature Communications. 2017; 8: 133. https://doi.org/10.1038/s41467-017-00171-w

[167] Stiburek L, Cesnekova J, Kostkova O, Fornuskova D, Vinsova K, Wenchich L, et al. YME1L controls the accumulation of respiratory chain subunits and is required for apoptotic resistance, cristae morphogenesis, and cell proliferation. Molecular Biology of the Cell. 2012; 23: 1010–1023. https://doi.org/10.1091/mbc.E11-08-0674

[168] Ishizawa J, Zarabi SF, Davis RE, Halgas O, Nii T, Jitkova Y, et al. Mitochondrial ClpP-Mediated Proteolysis Induces Selective Cancer Cell Lethality. Cancer Cell. 2019; 35: 721–737.e9. https://doi.org/10.1016/j.ccell.2019.03.014

[169] Venkatesh S, Li M, Saito T, Tong M, Rashed E, Mareedu S, et al. Mitochondrial LonP1 protects cardiomyocytes from ischemia/reperfusion injury in vivo. Journal of Molecular and Cellular Cardiology. 2019; 128: 38–50. https://doi.org/10.1016/j.yjmcc.2018.12.017

[170] Blasco N, Cámara Y, Núñez E, Beà A, Barés G, Forné C, et al. Cardiomyocyte hypertrophy induced by Endonuclease G deficiency requires reactive oxygen radicals accumulation and is inhibitable by the micropeptide humanin. Redox Biology. 2018; 16: 146–156. https://doi.org/10.1016/j.redox.2018.02.021

[171] Rainbolt TK, Lebeau J, Puchades C, Wiseman RL. Reciprocal Degradation of YME1L and OMA1 Adapts Mitochondrial Proteolytic Activity during Stress. Cell Reports. 2016; 14: 2041–2049. https://doi.org/10.1016/j.celrep.2016.02.011

[172] Rainbolt TK, Saunders JM, Wiseman RL. YME1L degradation reduces mitochondrial proteolytic capacity during oxidative stress. EMBO Reports. 2015; 16: 97–106. https://doi.org/10.15252/embr.201438976

[173] Bohovych I, Fernandez MR, Rahn JJ, Stackley KD, Bestman JE, Anandhan A, et al. Metalloprotease OMA1 Fine-tunes Mitochondrial Bioenergetic Function and Respiratory Supercomplex Stability. Scientific Reports. 2015; 5: 13989. https://doi.org/10.1038/srep13989

[174] Jensen MB, Jasper H. Mitochondrial proteostasis in the control of aging and longevity. Cell Metabolism. 2014; 20: 214–225. https://doi.org/10.1016/j.cmet.2014.05.006

[175] Wai T, Saita S, Nolte H, Müller S, König T, Richter-Dennerlein R, et al. The membrane scaffold SLP2 anchors a proteolytic hub in mitochondria containing PARL and the i-AAA protease YME1L. EMBO Reports. 2016; 17: 1844–1856. https://doi.org/10.15252/embr.201642698

[176] Houtkooper RH, Mouchiroud L, Ryu D, Moullan N, Katsyuba E, Knott G, et al. Mitonuclear protein imbalance as a conserved longevity mechanism. Nature. 2013; 497: 451–457. https://doi.org/10.1038/nature12188

[177] Nargund AM, Fiorese CJ, Pellegrino MW, Deng P, Haynes CM. Mitochondrial and nuclear accumulation of the transcription factor ATFS-1 promotes OXPHOS recovery during the UPR(mt). Molecular Cell. 2015; 58: 123–133. https://doi.org/10.1016/j.molcel.2015.02.008

[178] Svaguša T, Martinić M, Martinić M, Kovačević L, Šepac A, Miličić D, et al. Mitochondrial unfolded protein response, mitophagy and other mitochondrial quality control mechanisms in heart disease and aged heart. Croatian Medical Journal. 2020; 61: 126–138. https://doi.org/10.3325/cmj.2020.61.126

[179] Cilleros-Holgado P, Gómez-Fernández D, Piñero-Pérez R, Romero-Domínguez JM, Reche-López D, López-Cabrera A, et al. Mitochondrial Quality Control via Mitochondrial Unfolded Protein Response (mtUPR) in Ageing and Neurodegenerative Diseases. Biomolecules. 2023; 13: 1789. https://doi.org/10.3390/biom13121789

[180] Kleele T, Rey T, Winter J, Zaganelli S, Mahecic D, Perreten Lambert H, et al. Distinct fission signatures predict mitochondrial degradation or biogenesis. Nature. 2021; 593: 435–439. https://doi.org/10.1038/s41586-021-03510-6

[181] Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. Science (New York, N.Y.). 2012; 337: 1062–1065. https://doi.org/10.1126/science.1219855

[182] Youle RJ, Narendra DP. Mechanisms of mitophagy. Nature Reviews. Molecular Cell Biology. 2011; 12: 9–14. https://doi.org/10.1038/nrm3028

[183] Michel S, Wanet A, De Pauw A, Rommelaere G, Arnould T, Renard P. Crosstalk between mitochondrial (dys)function and mitochondrial abundance. Journal of Cellular Physiology. 2012; 227: 2297–2310. https://doi.org/10.1002/jcp.23021

[184] Martinus RD, Garth GP, Webster TL, Cartwright P, Naylor DJ, Høj PB, et al. Selective induction of mitochondrial chaperones in response to loss of the mitochondrial genome. European Journal of Biochemistry. 1996; 240: 98–103. https://doi.org/10.1111/j.1432-1033.1996.0098h.x

[185] Zhao Q, Wang J, Levichkin IV, Stasinopoulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. The EMBO Journal. 2002; 21: 4411–4419. https://doi.org/10.1093/emboj/cdf445

[186] Zhu L, Zhou Q, He L, Chen L. Mitochondrial unfolded protein response: An emerging pathway in human diseases. Free Radical Biology & Medicine. 2021; 163: 125–134. https://doi.org/10.1016/j.freeradbiomed.2020.12.013

[187] Haynes CM, Petrova K, Benedetti C, Yang Y, Ron D. ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans. Developmental Cell. 2007; 13: 467–480. https://doi.org/10.1016/j.devcel.2007.07.016

[188] Haynes CM, Yang Y, Blais SP, Neubert TA, Ron D. The matrix peptide exporter HAF-1 signals a mitochondrial UPR by activating the transcription factor ZC376.7 in C. elegans. Molecular

Cell. 2010; 37: 529–540. https://doi.org/10.1016/j.molcel.2010.01.015
[189] Sugiura A, McLelland GL, Fon EA, McBride HM. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. The EMBO Journal. 2014; 33: 2142–2156. https://doi.org/10.15252/embj.201488104
[190] Popov LD. Mitochondrial-derived vesicles: Recent insights. Journal of Cellular and Molecular Medicine. 2022; 26: 3323–3328. https://doi.org/10.1111/jcmm.17391
[191] Cadete VJJ, Deschênes S, Cuillerier A, Brisebois F, Sugiura A, Vincent A, et al. Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system. The Journal of Physiology. 2016; 594: 5343–5362. https://doi.org/10.1113/JP272703
[192] Soubannier V, Rippstein P, Kaufman BA, Shoubridge EA, McBride HM. Reconstitution of mitochondria derived vesicle formation demonstrates selective enrichment of oxidized cargo. PloS One. 2012; 7: e52830. https://doi.org/10.1371/journal.pone.0052830
[193] Vasam G, Nadeau R, Cadete VJJ, Lavallée-Adam M, Menzies KJ, Burelle Y. Proteomics characterization of mitochondrial-derived vesicles under oxidative stress. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2021; 35: e21278. https://doi.org/10.1096/fj.202002151R
[194] Matheoud D, Sugiura A, Bellemare-Pelletier A, Laplante A, Rondeau C, Chemali M, et al. Parkinson's Disease-Related Proteins PINK1 and Parkin Repress Mitochondrial Antigen Presentation. Cell. 2016; 166: 314–327. https://doi.org/10.1016/j.cell.2016.05.039
[195] McLelland GL, Soubannier V, Chen CX, McBride HM, Fon EA. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. The EMBO Journal. 2014; 33: 282–295. https://doi.org/10.1002/embj.201385902
[196] Soubannier V, McLelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, et al. A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Current Biology: CB. 2012; 22: 135–141. https://doi.org/10.1016/j.cub.2011.11.057
[197] Bozi LHM, Bechara LRG, Dos Santos AF, Campos JC. Mitochondrial-derived vesicles: a new player in cardiac mitochondrial quality control. The Journal of Physiology. 2016; 594: 6077–6078. https://doi.org/10.1113/JP273124
[198] Li B, Zhao H, Wu Y, Zhu Y, Zhang J, Yang G, et al. Mitochondrial-Derived Vesicles Protect Cardiomyocytes Against Hypoxic Damage. Frontiers in Cell and Developmental Biology. 2020; 8: 214. https://doi.org/10.3389/fcell.2020.00214
[199] Pan C, Cheng C, Zhong S, Li S, Tan W, Yao Y. In vitro study on the promotion of osteogenic differentiation by mitochondrial-derived vesicles through activation of inflammation and reprogramming of metabolic pathways. Journal of Orthopaedic Surgery and Research. 2025; 20: 388. https://doi.org/10.1186/s13018-025-05749-5
[200] Heyn J, Heuschkel MA, Goettsch C. Mitochondrial-Derived Vesicles-Link to Extracellular Vesicles and Implications in Cardiovascular Disease. International Journal of Molecular Sciences. 2023; 24: 2637. https://doi.org/10.3390/ijms24032637
[201] Cimolai MC, Alvarez S, Bode C, Bugger H. Mitochondrial Mechanisms in Septic Cardiomyopathy. International Journal of Molecular Sciences. 2015; 16: 17763–17778. https://doi.org/10.3390/ijms160817763
[202] Kubli DA, Gustafsson ÅB. Mitochondria and mitophagy: the yin and yang of cell death control. Circulation Research. 2012; 111: 1208–1221. https://doi.org/10.1161/CIRCRESAHA.112.265819
[203] Gottlieb RA, Gustafsson AB. Mitochondrial turnover in the heart. Biochimica et Biophysica Acta. 2011; 1813: 1295–1301. https://doi.org/10.1016/j.bbamcr.2010.11.017
[204] Carchman EH, Rao J, Loughran PA, Rosengart MR, Zuckerbraun BS. Heme oxygenase-1-mediated autophagy protects against hepatocyte cell death and hepatic injury from infection/sepsis in mice. Hepatology (Baltimore, Md.). 2011; 53: 2053–2062. https://doi.org/10.1002/hep.24324
[205] Carchman EH, Whelan S, Loughran P, Mollen K, Stratamirovic S, Shiva S, et al. Experimental sepsis-induced mitochondrial biogenesis is dependent on autophagy, TLR4, and TLR9 signaling in liver. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2013; 27: 4703–4711. https://doi.org/10.1096/fj.13-229476
[206] Vanasco V, Saez T, Magnani ND, Pereyra L, Marchini T, Corach A, et al. Cardiac mitochondrial biogenesis in endotoxemia is not accompanied by mitochondrial function recovery. Free Radical Biology & Medicine. 2014; 77: 1–9. https://doi.org/10.1016/j.freeradbiomed.2014.08.009
[207] Ceylan-Isik AF, Zhao P, Zhang B, Xiao X, Su G, Ren J. Cardiac overexpression of metallothionein rescues cardiac contractile dysfunction and endoplasmic reticulum stress but not autophagy in sepsis. Journal of Molecular and Cellular Cardiology. 2010; 48: 367–378. https://doi.org/10.1016/j.yjmcc.2009.11.003
[208] Suliman HB, Welty-Wolf KE, Carraway MS, Schwartz DA, Hollingsworth JW, Piantadosi CA. Toll-like receptor 4 mediates mitochondrial DNA damage and biogenic responses after heat-inactivated E. coli. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2005; 19: 1531–1533. https://doi.org/10.1096/fj.04-3500fje
[209] Suliman HB, Welty-Wolf KE, Carraway M, Tatro L, Piantadosi CA. Lipopolysaccharide induces oxidative cardiac mitochondrial damage and biogenesis. Cardiovascular Research. 2004; 64: 279–288. https://doi.org/10.1016/j.cardiores.2004.07.005
[210] Piquereau J, Godin R, Deschênes S, Bessi VL, Mofarrahi M, Hussain SN, et al. Protective role of PARK2/Parkin in sepsis-induced cardiac contractile and mitochondrial dysfunction. Autophagy. 2013; 9: 1837–1851. https://doi.org/10.4161/auto.26502
[211] Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. Biochimica et Biophysica Acta. 2013; 1833: 3448–3459. https://doi.org/10.1016/j.bbamcr.2013.06.001
[212] Drosatos K, Khan RS, Trent CM, Jiang H, Son NH, Blaner WS, et al. Peroxisome proliferator-activated receptor-γ activation prevents sepsis-related cardiac dysfunction and mortality in mice. Circulation. Heart Failure. 2013; 6: 550–562. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000177
[213] Wenz T. Regulation of mitochondrial biogenesis and PGC-1α under cellular stress. Mitochondrion. 2013; 13: 134–142. https://doi.org/10.1016/j.mito.2013.01.006
[214] Kelly DP, Scarpulla RC. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes & Development. 2004; 18: 357–368. https://doi.org/10.1101/gad.1177604
[215] Lancel S, Hassoun SM, Favory R, Decoster B, Motterlini R, Neviere R. Carbon monoxide rescues mice from lethal sepsis by supporting mitochondrial energetic metabolism and activating mitochondrial biogenesis. The Journal of Pharmacology and Experimental Therapeutics. 2009; 329: 641–648. https://doi.org/10.1124/jpet.108.148049
[216] Reynolds CM, Suliman HB, Hollingsworth JW, Welty-Wolf KE, Carraway MS, Piantadosi CA. Nitric oxide synthase-2 induction optimizes cardiac mitochondrial biogenesis after endotoxemia. Free Radical Biology & Medicine. 2009; 46: 564–572. https://doi.org/10.1016/j.freeradbiomed.2008.11.007
[217] Hickson-Bick DLM, Jones C, Buja LM. Stimulation of mi-

tochondrial biogenesis and autophagy by lipopolysaccharide in the neonatal rat cardiomyocyte protects against programmed cell death. Journal of Molecular and Cellular Cardiology. 2008; 44: 411–418. https://doi.org/10.1016/j.yjmcc.2007.10.013

[218] Russell LK, Mansfield CM, Lehman JJ, Kovacs A, Courtois M, Saffitz JE, et al. Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner. Circulation Research. 2004; 94: 525–533. https://doi.org/10.1161/01.RES.0000117088.36577.EB

[219] Schilling J, Lai L, Sambandam N, Dey CE, Leone TC, Kelly DP. Toll-like receptor-mediated inflammatory signaling reprograms cardiac energy metabolism by repressing peroxisome proliferator-activated receptor γ coactivator-1 signaling. Circulation. Heart Failure. 2011; 4: 474–482. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959833

[220] Court O, Kumar A, Parrillo JE, Kumar A. Clinical review: Myocardial depression in sepsis and septic shock. Critical Care (London, England). 2002; 6: 500–508. https://doi.org/10.1186/cc1822

[221] Kornfeld OS, Qvit N, Haileselassie B, Shamloo M, Bernardi P, Mochly-Rosen D. Interaction of mitochondrial fission factor with dynamin related protein 1 governs physiological mitochondrial function in vivo. Scientific Reports. 2018; 8: 14034. https://doi.org/10.1038/s41598-018-32228-1

[222] Haileselassie B, Mukherjee R, Joshi AU, Napier BA, Massis LM, Ostberg NP, et al. Drp1/Fis1 interaction mediates mitochondrial dysfunction in septic cardiomyopathy. Journal of Molecular and Cellular Cardiology. 2019; 130: 160–169. https://doi.org/10.1016/j.yjmcc.2019.04.006

[223] Ong SB, Subrayan S, Lim SY, Yellon DM, Davidson SM, Hausenloy DJ. Inhibiting mitochondrial fission protects the heart against ischemia/reperfusion injury. Circulation. 2010; 121: 2012–2022. https://doi.org/10.1161/CIRCULATIONAHA.109.906610

[224] Disatnik MH, Ferreira JCB, Campos JC, Gomes KS, Dourado PMM, Qi X, et al. Acute inhibition of excessive mitochondrial fission after myocardial infarction prevents long-term cardiac dysfunction. Journal of the American Heart Association. 2013; 2: e000461. https://doi.org/10.1161/JAHA.113.000461

[225] Zaja I, Bai X, Liu Y, Kikuchi C, Dosenovic S, Yan Y, et al. Cdk1, PKCδ and calcineurin-mediated Drp1 pathway contributes to mitochondrial fission-induced cardiomyocyte death. Biochemical and Biophysical Research Communications. 2014; 453: 710–721. https://doi.org/10.1016/j.bbrc.2014.09.144

[226] Wu S, Lu Q, Wang Q, Ding Y, Ma Z, Mao X, et al. Binding of FUN14 Domain Containing 1 With Inositol 1,4,5-Trisphosphate Receptor in Mitochondria-Associated Endoplasmic Reticulum Membranes Maintains Mitochondrial Dynamics and Function in Hearts in Vivo. Circulation. 2017; 136: 2248–2266. https://doi.org/10.1161/CIRCULATIONAHA.117.030235

[227] Ahuja P, Wanagat J, Wang Z, Wang Y, Liem DA, Ping P, et al. Divergent mitochondrial biogenesis responses in human cardiomyopathy. Circulation. 2013; 127: 1957–1967. https://doi.org/10.1161/CIRCULATIONAHA.112.001219

[228] Chen L, Gong Q, Stice JP, Knowlton AA. Mitochondrial OPA1, apoptosis, and heart failure. Cardiovascular Research. 2009; 84: 91–99. https://doi.org/10.1093/cvr/cvp181

[229] Thai PN, Seidlmayer LK, Miller C, Ferrero M, Dorn GW, II, Schaefer S, et al. Mitochondrial Quality Control in Aging and Heart Failure: Influence of Ketone Bodies and Mitofusin-Stabilizing Peptides. Frontiers in Physiology. 2019; 10: 382. https://doi.org/10.3389/fphys.2019.00382

[230] Zhang D, Ma J. Mitochondrial Dynamics in Rat Heart Induced by 5-Fluorouracil. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2018; 24: 6666–6672. https://doi.org/10.12659/MSM.910537

[231] Naruse G, Kanamori H, Yoshida A, Minatoguchi S, Kawaguchi T, Iwasa M, et al. The intestine responds to heart failure by enhanced mitochondrial fusion through glucagon-like peptide-1 signalling. Cardiovascular Research. 2019; 115: 1873–1885. https://doi.org/10.1093/cvr/cvz002

[232] Serre V, Rozanska A, Beinat M, Chretien D, Boddaert N, Munnich A, et al. Mutations in mitochondrial ribosomal protein MRPL12 leads to growth retardation, neurological deterioration and mitochondrial translation deficiency. Biochimica et Biophysica Acta. 2013; 1832: 1304–1312. https://doi.org/10.1016/j.bbadis.2013.04.014

[233] Han Y, Liu Y, Zhen J, Hou S, Zhang B, Cui Z, et al. P53 regulates mitochondrial biogenesis via transcriptionally induction of mitochondrial ribosomal protein L12. Experimental Cell Research. 2022; 418: 113249. https://doi.org/10.1016/j.yexcr.2022.113249

[234] Hagar JA, Powell DA, Aachoui Y, Ernst RK, Miao EA. Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock. Science (New York, N.Y.). 2013; 341: 1250–1253. https://doi.org/10.1126/science.1240988

[235] Song F, Hou J, Chen Z, Cheng B, Lei R, Cui P, et al. Sphingosine-1-phosphate Receptor 2 Signaling Promotes Caspase-11-dependent Macrophage Pyroptosis and Worsens Escherichia coli Sepsis Outcome. Anesthesiology. 2018; 129: 311–320. https://doi.org/10.1097/ALN.0000000000002196

[236] Deng M, Tang Y, Li W, Wang X, Zhang R, Zhang X, et al. The Endotoxin Delivery Protein HMGB1 Mediates Caspase-11-Dependent Lethality in Sepsis. Immunity. 2018; 49: 740–753.e7. https://doi.org/10.1016/j.immuni.2018.08.016

[237] Wu L, Huang J, Jia X, Mao X. Role and Mechanism of Mitochondrial Ribosomal Proteins in Septic Myocardial Injury. Journal of Inflammation Research. 2025; 18: 2677–2698. https://doi.org/10.2147/JIR.S495987

[238] Wagner GR, Payne RM. Widespread and enzyme-independent Nε-acetylation and Nε-succinylation of proteins in the chemical conditions of the mitochondrial matrix. The Journal of Biological Chemistry. 2013; 288: 29036–29045. https://doi.org/10.1074/jbc.M113.486753

[239] Haikarainen T, Maksimainen MM, Obaji E, Lehtiö L. Development of an Inhibitor Screening Assay for Mono-ADP-Ribosyl Hydrolyzing Macrodomains Using AlphaScreen Technology. SLAS Discovery: Advancing Life Sciences R & D. 2018; 23: 255–263. https://doi.org/10.1177/2472555217737006

[240] Mattila S, Merilahti P, Wazir S, Quirin T, Maksimainen MM, Zhang Y, et al. Macrodomain Binding Compound MRS 2578 Inhibits Alphavirus Replication. Antimicrobial Agents and Chemotherapy. 2021; 65: e0139821. https://doi.org/10.1128/AAC.01398-21

[241] Weis S, Carlos AR, Moita MR, Singh S, Blankenhaus B, Cardoso S, et al. Metabolic Adaptation Establishes Disease Tolerance to Sepsis. Cell. 2017; 169: 1263–1275.e14. https://doi.org/10.1016/j.cell.2017.05.031

[242] Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet (London, England). 2002; 360: 219–223. https://doi.org/10.1016/S0140-6736(02)09459-X

[243] Vico TA, Marchini T, Ginart S, Lorenzetti MA, Adán Areán JS, Calabró V, et al. Mitochondrial bioenergetics links inflammation and cardiac contractility in endotoxemia. Basic Research in Cardiology. 2019; 114: 38. https://doi.org/10.1007/s00395-019-0745-y

[244] Van Gool F, Gallí M, Gueydan C, Kruys V, Prevot PP, Bedalov A, et al. Intracellular NAD levels regulate tumor necrosis

factor protein synthesis in a sirtuin-dependent manner. Nature Medicine. 2009; 15: 206–210. https://doi.org/10.1038/nm.1906

[245] Gerner RR, Klepsch V, Macheiner S, Arnhard K, Adolph TE, Grander C, et al. NAD metabolism fuels human and mouse intestinal inflammation. Gut. 2018; 67: 1813–1823. https://doi.org/10.1136/gutjnl-2017-314241

[246] Ye M, Zhao Y, Wang Y, Xie R, Tong Y, Sauer JD, et al. NAD(H)-loaded nanoparticles for efficient sepsis therapy via modulating immune and vascular homeostasis. Nature Nanotechnology. 2022; 17: 880–890. https://doi.org/10.1038/s41565-022-01137-w

[247] Liu YT, Qiu HL, Xia HX, Feng YZ, Deng JY, Yuan Y, et al. Macrod1 suppresses diabetic cardiomyopathy via regulating PARP1-NAD^+-SIRT3 pathway. Acta Pharmacologica Sinica. 2024; 45: 1175–1188. https://doi.org/10.1038/s41401-024-01247-2