4 The Role of Mitochondrial Quality Imbalance in Multiple Organ Dysfunction Syndrome Following Severe Trauma, Shock, and Sepsis

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Abstract

Multiple organ dysfunction syndrome (MODS) is a life-threatening condition with high morbidity and mortality. Mitochondria are multifunctional organelles, whose failure triggers multiple organ dysfunction and is directly associated with patient's vicious outcome. Physiologically, mitochondria undergo continuous fission, fusion, biogenesis, and mitophagy (selective mitochondrial autophagy) to maintain homeostasis, whose disruption may heavily impact the mitochondrial quality and result in damaged cell and organ functions under pathological conditions such as severe trauma, shock, and sepsis. Mitochondrial quality imbalance is a key step in MODS process, and rebalancing the mitochondrial quality may be a promising approach in the treatment of MODS following severe trauma, shock, and sepsis.

Keywords

MODS · Mitochondrial quality · Intensive care medicine · Severe trauma · Mitochondrial dynamics · Mitophagy

4.1 Introduction

As medical techniques greatly develop, some diseases have been effectively controlled or got better care; however, severe trauma, shock, sepsis, severe pancreatitis, etc. which induced multiple organ dysfunction syndrome (MODS) have not been controlled well yet. It is reported that approximately 50% of patients in ICU can develop MODS, and their mortality is up to 30–100%. Patients with two organ

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dysfunction have more than 70% mortality rate [1]. However, such high mortality has not changed much since the 1980s.

Several mechanisms have been put forward to explain the process of MODS, such as immunosuppression and hypometabolism, ischemia and hypoxia induced by hypoperfusion, uncontrolled inflammation-induced extensive tissue damage, and so on. Some measures have been widely applied, such as anti-infection therapy, blood purification and immune adsorption, microcirculation modulation and hemodynamic support, etc., which made some contributions to the improvement of the outcome to these critical diseases. However, studies toward further understanding of MODS are still necessary. This review will focus on the mitochondrial quality imbalance and its role in MODS following severe trauma, shock, and sepsis; this might help to provide the better prevention and management of MODS.

4.2 Role of Mitochondrial Quality Imbalance in Diseases

Mitochondria are power houses of cells and responsible for aerobic respiration. Mitochondria not only produce ATP through oxidative phosphorylation but also participate in the regulation of metabolism, calcium homeostasis [2], oxidative signaling [3], steroid synthesis [4], etc. In pathologic conditions, mitochondria also induce oxidative injury and calcium overload, initiate cell apoptosis, etc. Mitochondria undergo continuous fission, fusion, biogenesis, and mitophagy to maintain the good quality and function of mitochondrial population. More and more studies revealed that mitochondrial quality imbalance plays important role in various pathological conditions.

4.2.1 Role of Mitochondria Dysfunction in Various Diseases

Mitochondrial dysfunction is involved in a wide range of clinical diseases, ranging from heart and brain diseases and diabetes to acute illnesses such as sepsis, traumatic injuries, and poisoning. As mitochondria are the center of cellular function and energy production, it is not surprising that these disease processes result in bioenergetic dysfunction [5]. Oxidative injury is considered as another major source of cell damage in various organ systems. Oxidative stress initiates diverse pathological shifts, such as mitochondrial DNA (mtDNA) mutation and apoptosis [6], and eventually boosts cell injuries. Since ROS generates in mitochondria, mitochondria are easily attacked by ROS. ROS-induced mitochondrial DNA (mtDNA) mutation and depletion would result in more downstream mitochondrial stresses [6].

Oxidative stress is one of the important pathological factors of chronic diseases including cardiovascular diseases (i.e., atherosclerosis, hypertension, cardiomyopathy, and congestive heart failure), neurodegeneration diseases (i.e., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), asthma and chronic obstructive pulmonary disease (COPD), and renal failure. In acute pathologies such

as trauma, stroke, and acute myocardial infarction, oxidative stress is also an important inducing factor of secondary injury of organs and tissues.

Besides, mitochondria store calcium and sustain calcium hemostasis, which are the important cytosolic buffer for calcium. In pathological conditions, mitochondrial permeability transition pore (mPTP) and mitochondrial calcium uniporter (MCU) complex might mediate excessive calcium inflow toward mitochondria and provoke calcium overload, which induces apoptosis afterward [7–9]. Intensive long-lasting excitatory stimuli eventually cause a persistent mitochondrial calcium accumulation and cytotoxicity; this is a mechanism that has been implicated in the pathogenesis of neurological disorders such as Alzheimer's and Huntington's disease and schizophrenia [10]. Mitochondria-derived cell injury can finally initiate intrinsic apoptosis, which has been widely studied in many cell types (as reviewed by Wu et al.) [11], including immune cells, cardiomyocytes, hepatocytes, hemotocytes, etc. Damaged mitochondria can be fixed or cleared to avoid the final detrimental effect. This process relies on mitochondrial quality control. However, the underlying mechanism for mitochondrial quality control is not fully understood yet.

4.2.2 Mitochondrial Quality Balance Is a Dynamic Process to Regulate Mitochondrial Function

Continuous fission, fusion, mitophagy, and biogenesis sustain mitochondrial quality balance, including adequate mitochondrial mass and function, which is indispensable for normal cell function. In mitochondria fission, parental mitochondrion divides into at least two mitochondria to achieve cell mitogen or meet energy demand; in mitochondria fusion, mitochondria merge to achieve self-renewal and promote mitochondrial function; in mitophagy, damaged mitochondria are segregated and degraded by selective autophagy process to diminish detrimental effects; in mitochondria biogenesis, mitochondrial functional or structural proteins are synthesized to replenish mitochondrial pool.

Basic studies indicated that mitochondrial characteristics vary from one kind of cell to another. Mitochondria account for ~40% of cardiomyocytes cell volume while 10–20% in vascular smooth muscle cells or vascular endothelia cells; cardiomyocyte completes rejuvenation in 2–3 days while vascular endothelial cells or intestinal epithelial cells in 2–3 h. Despite such heterogeneity, mitochondria share almost common fission, fusion, mitophagy, and biogenesis mechanisms (Fig. 4.1).

4.2.2.1 Mitochondrial Fission

Mitochondrial fission is essential for stabilizing mitochondrial genome, regulating energy production, and modulating oxidative signaling [12–15]. The mechanism of mitochondrial fission is complex and has attracted much attention recently. Dynamin-related protein (DRP1) is recruited from cytoplasm to bind receptors (e.g., FIS1, MFF, Mid49/51) on mitochondria outer membrane [16]. Then, DRP1 oligomerizes and hydrolizes GTP to mediate constriction of the fission site [17, 18]. DRP1 possesses an N-terminal GTPase domain thought to provide mechanical

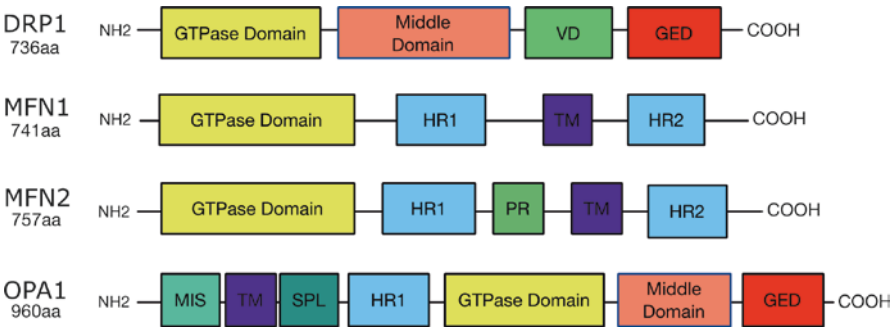

Fig. 4.1 Schematics of functional domains of the mitochondrial dynamic proteins. *HR* heptad repeat domain, *TM* transmembrane domain, *PR* proline-rich domain, *MIS* mitochondrial import sequence, *GED* GTPase effector domain, *VD* variable domain

force, a dynamin-like middle domain, and a GTPase effector domain (GED) located in the C-terminal region domain. DRP1 is predicted to exist as a T-shaped dimer or tetramer that contains a head (containing GTPase domain), leg (VD), and stalk (middle and GED domains). GTP induces the rearrangement of the head and stalk, which generates a force ultimately resulting in membrane constriction [19].

Phosphorylation, ubiquitination, S-nitrosylation, SUMOylation, and O-GlcNAcylation of DRP1 regulate mitochondrial fission. The phosphorylation of DRP1 is the most studied. Generally, the phosphorylation of DRP1 Ser616 activates DRP1, while DRP1 Ser637/600/716/656 phosphorylation inhibits it [19]. CaMKII [20], calcineurin [21, 22], PINK1 [23], Parkin [24], RhoA/ROCK pathway [25, 26], ERK [27, 28], cyclins [29], and Cdk5 [30] are proven to be responsible for the phosphorylation or dephosphorylation of DRP1. March5 (also known as MITOL) may ubiquitinate DRP1 or MiD49 on the MOM and reduces mitochondrial fragmentation [31–33]. S-nitrosylation of DRP1 at Cys-644 may enhance GTPase activity and DRP1 oligomerization and results in excessive mitochondrial fission in neurons and neuronal damage [34]. In addition, increased DRP1 SUMOylation by MAPL overexpression may upregulate mitochondrial fission [35], and decreased DRP1 SUMOylation (i.e., deSUMOylation) by SENP5 may rescue the mitochondrial fission [36]; O-GlcNAcylation at Thr-585 and Thr-586 may reduce the mitochondrial fragmentation [37].

4.2.2.2 Mitochondrial Fusion

The most important function of mitochondrial fusion is to facilitate the heterogeneous mitochondria to mix and exchange content. Mitochondrial fusion participates in the quality control of mtDNA [12] and energy metabolism regulation, e.g., ameliorating oxidative stress, cell differentiation, stress adaption and steroidogenesis, and so on [38–40].

Since mitochondria are double-membrane bound organelles, the complete fusion calls for merging of both the outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM), either process possesses different mechanisms,

respectively. MFN1 and MFN2 form homo-oligomers or hetero-oligomers (i.e., MFN1/MFN1, MFN2/MFN2, or MFN1/MFN2) to mediate OMM fusion [41]. OPA1 is responsible for IMM fusion and cristae morphology formation [42, 43]. Mitofusin harbors a GTPase domain close to the N-terminus that is involved in the GTP hydrolysis. Two hydrophobic heptad repeat (HR) domains are localized in the middle (HR1) and C-terminal (HR2) regions and provide the basis for most coiled-coil interactions. The HR2 domain was shown to be of great importance for mitochondrial fusion activity; formation of HR2 dimers promotes the generation of a mitochondrial tether before mitochondrial fusion. OPA1 contains an N-terminal mitochondrial localization sequence, responsible for import of the protein into the mitochondrial inner membrane. This region also has three putative cleavage sites for the mitochondrial processing peptidase. Other structural motifs include a transmembrane domain that anchors OPA1 in the mitochondrial inner membrane; the first coiled-coil domain, involved in protein-protein interactions; a GTPase domain crucial for protein activity; the middle domain, which participates in tetramerization and higher-order assembly of OPA1; and a second coiled-coil domain in the C-terminus that mediates the interaction between OPA1 and MFN1/2 [44], but the exact mechanism in which OPA1 drives IMM fusion is far from being elucidated. Expression level of MFNs or OPA1 influences mitochondrial fusion. Mitochondrial fusion is also regulated by ubiquitination, deacetylation of MFNs, or protease-dependent cleavage of OPA1 by OMA1, YME1L. MFN1/MFN2 are generally regulated at transcriptional and post-transcriptional levels. Upregulation of MFN1/MFN2 may result in the increased fusion [40, 45, 46], and downregulation of MFN1 or MFN2 may result in the decreased fusion [47, 48]. Deacetylation of MFN1 by HDAC6 may increase the fusion in fasting mice skeletal cells so as to produce more energy [49]. Ubiquitination of MFNs by USP30 or Parkin may result in the reduced fusion, which contributes to selectively isolate damaged mitochondria [50, 51]. Parra et al. found OPA1 upregulation induced by insulin in cardiomyocytes resulted in the increased mitochondrial fusion, along with the increase of the intracellular ATP levels and oxygen consumption [52]. Exercise pretreatment is protective in nervous system ischemia/reperfusion injury via upregulation of OPA1 and mitochondrial fusion [53]. Besides, protease-dependent cleavage seems to conduct the functional shift of OPA1. OPA1 could be processed into long form (L-OPA1) and short form (S-OPA1) possessing different functions, respectively. Mitochondrial fusion regulation is thought to depend on the coordination of L- and S-OPA1 [54]. Two key players for OPA1 proteolysis are the IMM peptidase OMA1 and the i-AAA protease YME1L. Loss function study of YME1L suggests that it is responsible for constitutive processing of OPA1 [54, 55], while OMA1 regulates stress-induced OPA1 cleavage [56]. But the role of OMA1 and YME1L in mitochondrial morphology remains controversial. Anand et al. found that long OPA1 forms were sufficient to mediate mitochondrial fusion in these cells and expression of short OPA1 forms promoted mitochondrial fragmentation, demonstrating a dispensable role of OPA1 processing in mitochondrial fusion and a stimulatory role of S-OPA1 [57]. Detailed studies into mitochondrial fusion mechanism are eagerly needed to facilitate the adequate manipulation of mitochondrial dynamics, which may further contribute to mitochondrial function management.

4.2.2.3 Mitophagy

Mitophagy is a selective autophagic process conserved in eukaryotes and plays an essential role in mitochondrial quality and quantity control. It is involved in myogenic differentiation, cardiomyocyte mitochondrial plasticity and metabolic transitioning of perinatal hearts [58], and metabolism regulation in the liver [59] and β cells [60]. Mitophagy can be classified into ubiquitin-dependent and receptor-dependent pathways. A ubiquitin/PINK1/Parkin-dependent mitophagy pathway was unraveled and was extensively characterized, in short: (1) damaged mitochondria are isolated by fission mechanisms and PINK1 is preserved on OMM; (2) ubiquitin chain is connected to OMM proteins (e.g., MFNs, DRP1, FIS1) of damaged mitochondria by the E3 ubiquitin ligase Parkin, which is activated by PINK1; (3) adaptors (p62/SQSTM1, optineurin/OPTN, NBR1, etc.) associate ubiquitin with membrane protein LC3 through their LC3-interacting region (LIR); and (4) damaged mitochondria are encapsulated by autophagosome and degraded in autophagolysosome. Besides, the consistent mitochondrial outer membrane receptors FUNDC1, NIX/BNIP3L, BNIP3, and Bcl2L13 mediate receptor-dependent mitophagy; they interact with LC3 directly through LIR and promote encapsulation and latter processes [61, 62].

PINK1 serves as the sensor for the mitochondrial polarization state. Mitochondrial depolarization inactivates its import and proteasomal degradation, leading to PINK1 accumulation on the OMM, then PINK1 phosphorylates MFN2 (at serine 442, threonine 111, etc.), and phosphorylated MFN2 can act as a receptor to recruit Parkin, an E3 ubiquitin ligase. PINK1 also phosphorylates ubiquitin at serine 65 and the ubiquitin-like domain of Parkin at serine 65, which recruit more Parkin to OMM and activate its E3 ligase activity. As for adaptors, p62 and NBR1 were found to be dispensable, and primary but redundant autophagy receptor functions were defined for OPTN and NDP52. USP8 deubiquitylation of auto-ubiquitylated Parkin is required for its localization to depolarized mitochondria and thereby for efficient activation of mitophagy. On the other hand, the ubiquitin-specific proteases USP30, which localizes at the OMM via a transmembrane domain, and USP15, which can fractionally localize to mitochondria, remove Parkin-ligated ubiquitin from OMM proteins and reduce mitophagy. In addition, mitophagy receptors upon expression, constitutively localize at the OMM via transmembrane domains, are transcriptionally regulated, and engagement of mitophagy receptor activity is controlled through the phosphorylation status of their LIR. Phosphorylation of serine residues 17 and 24 flanking the Bnip3 LIR specifically promotes binding to LC3B and GATE-16, but to date it remains undetermined which kinases and phosphatases are responsible for controlling the phosphorylation state of the Bnip3. In response to hypoxia or mitochondrial uncoupling, PGAM5 dephosphorylates CK2-phosphorylated serine 13 of FUNDC1 to activate LC3 binding. In addition, ULK1 phosphorylates serine 17 of the FUNDC1 LIR motif, resulting in increased LC3 binding [63].

4.2.2.4 Mitochondrial Biogenesis

Mitochondrial biogenesis includes synthesis of mtDNA-encoded protein, synthesis and import of nuclear-encoded proteins, assembly of the dual genetic origin-derived proteins and mtDNA replication, and finally formation of new organelle structures

[64]. Nuclear-encoded mitochondrial proteins are synthesized in cytoplasm and are then imported into mitochondria. mtDNA-encoded proteins are synthesized within the organelle itself.

The regulation of mitochondrial biogenesis includes a set of nuclear transcription factors. The nuclear transcription factor, NRF1, governs the expression of nuclear OXPHOS genes as well as the expression of nuclear-encoded factors involved in mitochondrial transcription, protein import, and protein assembly. NRF2 binding sites have been also identified in several other mitochondrial genes including the OXPHOS subunits, mitochondrial protein import machinery, and mitochondrial translation factors. Additional transcription factors such as the estrogen-related receptor α (ERRα), cAMP response element-binding protein (CREB), and Yin Yang 1 (YY1) are also involved. A higher level of regulation is achieved by the family of coactivators of the peroxisome proliferator-activated receptors (PPARs). The best studied member of this family is the PPAR coactivator 1α (PGC-1α), which is termed the master regulator of mitochondrial biogenesis. PGC-1α expression is upregulated by PPARs, CREB, and YY1/mTOR and is downregulated by RIP140, 160MYB, DNMT3b, p53, etc. Besides, PGC-1α can be phosphorylated by p38, MAPK, and AMPK and inhibited by Akt. Activation of Sirt1 and the deacetylation of PGC-1α can also activate PGC-1α [65].

Mitochondrial biogenesis and mitochondrial mass can be modulated through several stimuli and cellular pathways, including but not limited to hormones such as thyroid hormone [66] and estrogen [67], inflammatory signaling [68], as well as calcium signaling [69]. As a result, mitochondrial biogenesis plays vital role in cell differentiation [70–72], immune response [73–75], and inflammation response in the liver, kidney, heart, and lung [76–79].

4.2.3 Role of Mitochondrial Quality Imbalance in Various Diseases

Diversified stimuli disrupt such dynamics by hindering any of the above four processes and results in mitochondrial quality imbalance, which induces functional impairment or structural damage in mitochondria and strongly insults organ function [80].

Mitochondrial quality imbalance is largely seen in neurodegeneration [81, 82]. Downregulation of MFN2 may cause mitochondrial dysfunction, alter calcium homeostasis, and enhance Bax translocation to mitochondria, resulting in delayed neuronal death in in vitro and in vivo models of excitotoxicity [48]. Defect in mitophagy may result in damaged mitochondria accumulation and neurodegeneration [83]. Loss of PINK1 function is associated with early-onset recessive Parkinson's disease, in vitro studies showed that cells lacking Pink1 had lower DRP1 and MFN2 expression, and mitochondrial morphology was fragmented [84]. Impaired mitochondrial biogenesis contributed to mitochondrial dysfunction in Alzheimer's disease [85]. TNF-α may activate NF-κB signaling and increase OPA1 expression, while IL-6 may upregulate fission inducer FIS1 and downregulate

MFN2, both signal axes contributed to islet cell apoptosis and type 2 diabetes [86]. Disturbances in mitochondrial biogenesis and PGC-1α levels are involved in type 2 diabetes, neurodegenerative disease, and many age-related pathologies [87, 88].

Mitochondrial quality imbalance also participates in infection and inflammatory diseases. *S. mansoni* infection may change hepatocyte mitochondrial morphology and affect mitochondrial function, in which mitochondrial biogenesis and fission were also upregulated [89]. The toxic bile salt glycochenodeoxycholate-induced mitochondrial fragmentation was associated with an increase in ROS levels and hepatic cell death [90]. Induction of mitochondrial fission by cathepsin E in lung epithelial contributed to increased caspase activation/apoptosis, and lung epithelial-targeted transgenic cathepsin E mice developed emphysema similarly [91].

Mitochondrial quality balance is also studied in the cardiovascular system. Rat cardiac arrest model showed excessive autophagy and mitophagy, along with increased apoptosis in cardiomyocytes [92]. Genetic ablation of both MFN1 and MFN2 in the adult murine heart resulted in mitochondrial fragmentation, impairment in mitochondrial respiration, and a severe lethal cardiomyopathy after 7–8 weeks [93, 94]. Upregulation of miR-140 and downregulation of MFN1 were found in right ventricles of pulmonary arterial hypertension rats, which correlated with increased right ventricular systolic pressure and hypertrophy [95].

4.3 Role of Mitochondrial Quality Imbalance in MODS Following Severe Trauma, Shock, and Sepsis

4.3.1 Role of Mitochondrial Dysfunction in MODS Following Severe Trauma, Shock, and Sepsis

Studies revealed pivotal role of mitochondria dysfunction in MODS, and mitochondrial status is directly associated with patient outcome [96]. Decreased mitochondrial complex I activity was associated with the degree of nitric oxide (NO) production in the skeletal muscle of patients admitted to intensive care unit with septic shock [97]. Respiratory protein subunits and transcripts were depleted in critically ill patients [98]. In rat sepsis models induced by cecal ligation and puncture (CLP), Karlsson et al. found a mismatch between reduced oxygen delivery and increased oxygen demand which impaired mitochondria and vital organs including the brain and liver [99]. Besides, adenosine diphosphate (ADP)-stimulated respiratory rates of cardiac fibers were reduced in septic mice due to reduced Ser-58 phosphorylation of cytochrome c oxidase subunit IV-1, resulted in cardiac dysfunction [100]. LPS reduced ATP content in HepG2 cell and primary human hepatocytes, partly by modulating complex II respiration [101]. LPS significantly induced heart oxidative stress and abnormal oxidative phosphorylation, which further impair cardiac contractile and bioenergetic function [25]. In addition, Herminghaus A et al. investigated the varying degrees of sepsis on hepatic mitochondrial function and related varied respiratory control ratio (RCR) to the severity of sepsis [102]. Joseph L et al. found the increased cardiac oxidative stress and decreased systolic function

were accompanied with mitochondrial calcium overload and depolarization of the mitochondrial inner membrane potential in a mouse model of endotoxemia [103]. Besides, studies also showed increased renal tubular cell [104] and endothelial cell [105] apoptosis by LPS stimulus. In addition, in experimental models of hemorrhagic shock and resuscitation in murine and porcine, mitochondrial injury was observed, as well as cell injury and organ dysfunction [106]. These studies remind us of the fact that mitochondrial respiration is impaired and decreased mitochondria function is closely related to organ function in sepsis and other critical illness.

4.3.2 Possible Role of Mitochondrial Quality Imbalance in MODS Following Severe Trauma, Shock, and Sepsis

As above discussed, mitochondrial quality imbalance has been studied in chronic pathologies, such as neurodegeneration, diabetes, and inflammatory diseases. However, mitochondria are highly dynamic organelles, and acute stresses including trauma, shock- and sepsis-induced ischemia, hypoxia, endotoxemia, and cytokines could induce rapid changes in mitochondrial morphology and function in multiple organs (Fig. 4.2).

Dysregulated fission and fusion are widely reported. In a traumatic rat model, the number of heart mitochondria was increased, while smaller-sized mitochondria were extensively observed. Translocation of DRP1 and phosphorylation of its Ser-616 were significantly increased. Inhibition of mitochondrial fission with melatonin pretreatment significantly reduced cardiac function impairment [107]. Rat sepsis model induced by CLP showed significant decrease of MFN2 mRNA and increase of DRP1 mRNA, while there was MFN2 mRNA decrease in the endotoxemia model. Both models showed mitochondrial fragmentation in the heart [108]. Besides, serum from burn rats significantly increased mitochondrial fission in murine myoblast C2C12 cells, consistent with the decreased mitochondrial membrane potential and increased cell apoptosis. Treatment with IL-6 antibody prevented mitochondrial fragmentation and cell death, suggesting cytokine-induced mitochondrial fission plays an important role in second-hit tissue damage [109]. These studies suggest that abnormal fission-fusion balance may contribute to the progression of trauma-, burn-, and sepsis-induced organ function.

Mitochondrial biogenesis is also impaired in these acute pathologies. In LPS-treated hepatocytes [76], the septic heart [78], sepsis- or I/R-induced kidney injury [77, 110], etc., mitochondria mass was reduced, accompanied with deceased ATP production, decreased mitochondrial membrane potential, and increased oxidative injury and apoptosis. Decreased mitochondrial biogenesis and mitophagy caused by inhibition of SIRT1, PINK1, and Parkin are associated with higher risk of lung injury in sepsis [111]. Suppression of mitochondrial biogenesis through Toll-like receptor 4-dependent MAPK kinase increased endotoxin-induced acute kidney injury [112].

The behavior of mitophagy is complex. A sublethal dose of *E. coli* lipopolysaccharide (LPS) was injected to mouse; mitochondrial function was decreased temporarily and gets fully recovered later, but Parkin-deficient mice exhibited

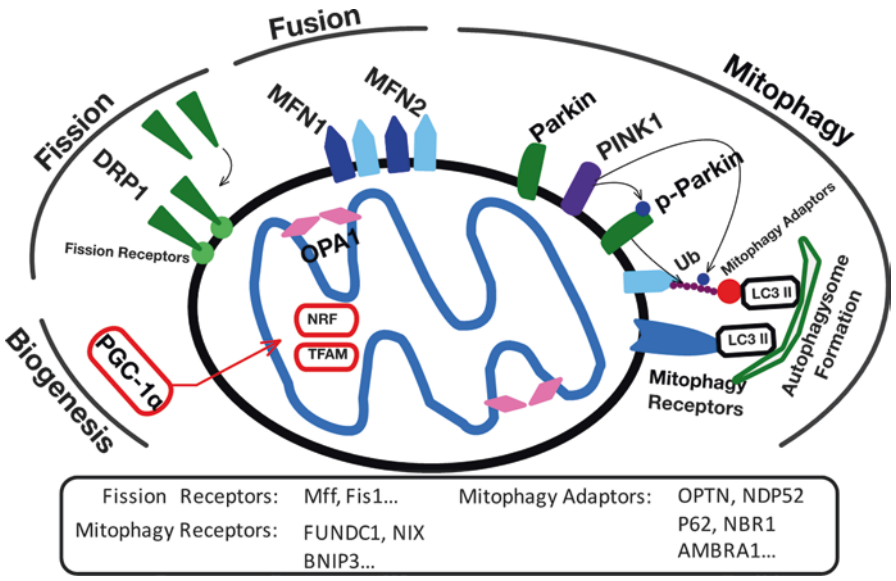

Fig. 4.2 Schematics for mitochondrial quality balance maintenance. Biogenesis: PGC-1α is the master of mitochondrial biogenesis, which activates NRF and TFAM in mitochondrial plasma to mediate mitochondrial protein synthesis. Fission: DRP1 is recruited from cytoplasm to bind receptors (e.g., MFF, FIS1) on mitochondrial outer membrane and hydrolyze GTP to drive mitochondrial fission. Fusion: MFN1 and MFN2 on mitochondrial outer membrane form homo-oligomers or hetero-oligomers and hydrolyze GTP to drive adjacent mitochondrial outer membrane fusion; OPA1 is responsible for inner membrane fusion and cristae morphology. Mitophagy: PINK1 is preserved on mitochondrial outer membrane and activates Parkin by phosphorylation, and then Parkin ubiquitin OMM proteins (e.g., MFN1, MFN2) and adaptors (e.g., OPTN, NDP52, p62, NBR1, etc.) are recruited, and then adaptors are connected to LC3 on autophagosome membrane; mitophagy receptors (e.g., FUNDC1, BNIP3, BNIP3L/NIX, etc.) on mitochondrial outer membrane interact with LC3 directly to mediate mitophagy

impaired recovery of cardiac contractility and constant degradation of mitochondrial metabolic functions, suggesting a protective role of mitophagy [113]. Ischemia/reperfusion injury is common in liver resection, hemorrhagic shock, and resuscitation. Due to nutrition and ATP depletion, calcium overload, and oxidative injury during ischemia, autophagy-related protein BECN1 and ATG7 are degraded, causing defective autophagy and mitochondrial clearance; more ROS production and CytC release were induced during fluid reperfusion and resulted in a severer liver injury, suggesting a harmful role of inadequate mitophagy [114]. By enhancing mitophagy, ischemic hepatocytes were protected from apoptosis [115], VSMC was prevented from LDL-induced injury [116], and lung epithelial cells were prevented from hypoxic injury [117]. However, the cross talk between autophagy and apoptosis makes the situation complex. A mouse model of cardiac myocyte ischemia/reperfusion injury showed increased autophagic flux, inhibiting autophagy

attenuated I/R-induced increase in oxidative stress, along with decrease in myocardial infarction size, suggesting that autophagy mediated myocardial injury during I/R [118]. However, whether mitophagy is a double-edged sword remains to be investigated.

4.3.3 Cross Talk of Fission, Fusion, Mitophagy, and Biogenesis Regulates Organ Function

Mitochondrial fission and fusion, mitophagy, and biogenesis are the dynamic process for maintaining the mitochondrial function. After fission, healthy mitochondria participate in normal function maintaining of cell, while slightly injured mitochondria can be restored with the help of fusion, severely damaged mitochondria with decreased membrane potential are degraded by mitophagy, and mitochondrial biogenesis counteracts the mitochondrial mass loss caused by mitochondrial clearance [119].

Studies showed that mitochondrial fission protein DRP1 may regulate mitochondrial fusion and mitophagy. The differential binding of MFN2 and DRP1 regulates mitochondrial fusion. DRP1 may act as a regulatory factor for both mitochondrial fusion and fission [120]. Studies found ablating DRP1 in myocytes not only interrupted the mitochondrial fission but also provoking mitophagy by regulating parkin [121], indicating a contrary role of fission and mitophagy.

The cross talk between fusion and mitophagy was also discovered. PINK1 may phosphorylate MFN2 at Thr-111 and Ser-442 and promote its Parkin-mediated ubiquitination and mitophagy [122]; ablation of either DRP1 or mitofusins (Mfn) in cardiomyocytes showed abnormal mitochondrial morphology; MFN null cells showed increased damaged mitochondria, while DRP1 null cells showed increased loss of mitochondria [123].

Mitochondrial biogenesis and mitophagy may cooperate to realize mitochondrial modification. Skeletal myoblasts may specifically shift from a highly glycolytic state to relying predominantly on oxidative phosphorylation (OXPHOS) upon differentiation; this phenomenon requires both mitochondrial clearance and biogenesis. During early myogenic differentiation, autophagy is robustly upregulated, and this coincides with mitophagy. Mitochondria are then repopulated via PPARGC1A/PGC-1alpha-mediated biogenesis; inhibiting autophagy may result in reduced mitochondrial biogenesis [58].

We may safely draw the conclusion that the regulation of mitochondrial fission, fusion, biogenesis, and mitophagy network has important influences on cell status and organ function. MODS is a consequence of various factors action, including infection, endotoxemia, hypoxia or ischemia, cytokines, etc. These factors may contribute to the impairment of one of the four processes (i.e., fission, fusion, biogenesis, and mitophagy). Multifactor-induced imbalance of mitochondrial quality may expand cell injury and participates in the occurrence of MODS (Fig. 4.3).

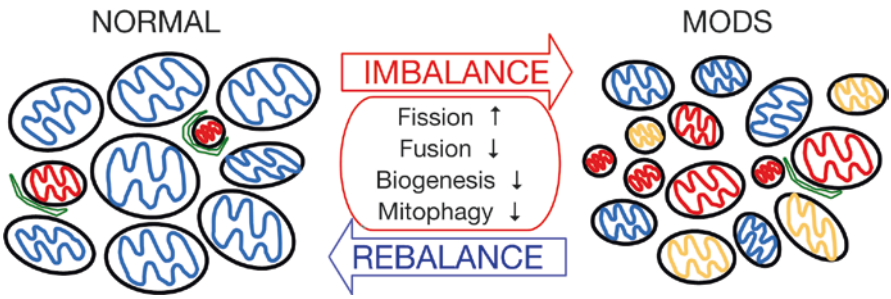

Fig. 4.3 Schematic for mitochondrial quality imbalance in MODS Mitochondria in normal cells undergo continuous fission, fusion, biogenesis, and mitophagy to maintain mitochondrial quality balance. Under stress conditions (e.g., severe trauma, shock, sepsis, MODS), the mitochondrial dynamics, biogenesis, and clearance are dysregulated and appear to be quality imbalance. Imbalanced mitochondrial quality may appear as mitochondrial fragmentation, decreased mitochondrial membrane potential and calcium overload, increased ROS and decreased ATP generation, etc. Restoring mitochondrial quality balance might be a therapeutic target to manage MODS. The blue inner mitochondrial membrane indicates a healthy status, the orange indicates unhealthy, and the red indicates damaged.

4.4 Restoring Mitochondrial Quality Balance Preserves Cellular and Organ Function

Some treatments have been applied to restore mitochondrial function such as vitamin C, vitamin E, β-carotene, coenzyme Q and resveratrol, and so on [124, 125]. Some novel antioxidants such as MitoQ, SS-31, MitoGSH, and MitoTEMPO have been developed and used to improve mitochondrial function. MitoQ, a mitochondria-targeted antioxidant, which is designed to protect against oxidative damage within mitochondria, has been proven to be beneficial for ischemic renal damage [126], intestinal inflammation [127], and sepsis [128]. SS-31 has gained benefits in neurodegeneration [129, 130] and hypoxic renal tubular cell injury [131] by decreasing free radical production and oxidative damage. MitoGSH may directly restore GSH levels and preserve mitochondrial redox buffering and signaling capacity [132]. Modifying mitochondrial respiration by manipulating substrate or electron transport chain enzyme activity are the other ways to improve mitochondrial function. A newly developed synthetic antimicrobial peptide 19-2.5 (Pep2.5) was found to prevent mitochondrial dysfunction in murine cardiomyocytes stimulated with serum from septic shock patients by enhancing the mitochondrial respiratory function and increasing cellular ATP levels [133]. In addition, other efforts aiming at decreasing calcium overload and apoptosis have also been made.

Large amount of studies observed the beneficial effect of modification of mitochondrial dynamics. Research showed inhibition of ROCK pathway with Fasudil significantly reduced the mitochondrial fragmentation in endotoxemic cardiomyocytes and improved the cardiac function [25]. Inhibition of the excessive

mitochondrial fission by blocking DRP1 with P110 at the onset of reperfusion significantly raised the long-term benefits of acute myocardial infarction [134]. Inhibition of mitochondrial fission with mdivi-1, the inhibitor of DRP1, significantly reduced Aβ-induced microglial apoptosis, exerting neuroprotective effect [135]. Mdivi-1 inhibition of mitochondrial fission may help to attenuate TBI-induced cell death through maintaining normal mitochondrial morphology and inhibiting activation of apoptosis [136]. In cardiomyocyte cell model of ischemia, overexpression of mitofusin proteins, MFN1 or MFN2, was found to be mitochondrial and cytoprotective [137].

Regulating mitochondrial biogenesis and PGC-1α expression was also found beneficial in some diseases including muscular, neurodegenerative disorders and renal and cardiac dysfunction [76, 110, 112, 138–141]. For example, overexpression of PINK1 and parkin could increase mitophagy of VSMC and decrease oxidized LDL-induced apoptosis [116].

4.5 Perspective

Mitochondrial quality imbalance might play a critical role in the occurrence and development of MODS. Severe trauma, shock, hypoxia, infection, and overproduction of inflammatory mediators and cytokines are the most common damage factors for mitochondrial quality and organ function. These factors can regulate or interrupt the balance of mitochondrial quality by regulating mitochondrial fission-, fusion-, mitophagy-, and biogenesis-related proteins such as DRP1, MFN1/MFN2, FIS1, OPA1, PGC1α, etc. [142–144].

p53 has been extensively studied in cancer and apoptosis; recent studies found p53 made a great contribution to directly modulating mitochondrial fission and fusion [145]. By attenuating the impairment of mitochondrial fission/fusion, biogenesis, and mitophagy, melatonin was found to be effective in restoring mitochondrial function in liver fibrosis induced by chronic carbon tetrachloride exposure [146]. Overexpression of heme oxygenase-1 (HO-1) may inhibit fission; promote fusion, biogenesis, and basal mitophagy; and thus play a protective role in heart oxidative injury [147]. Phospholipids in mitochondria are associated with dynamin-related GTPase (i.e., MFN1/MFN2, OPA1, DRP1), which regulate not only mitochondria fission and fusion but also mitophagy [148]. These studies suggested that manipulating mitochondrial fission and fusion, biogenesis, and mitophagy simultaneously seems to be more effective in correcting mitochondrial quality imbalance in some complicated situations.

Endoplasmic reticulum (ER) and mitochondria contact were considered a transport platform for calcium, the lipid between mitochondria and ER. Recent study found mitochondrial fission occurred at the mito-ER contact site. This contact may regulate mitochondrial fission, fusion, and mitophagy [149]. Studies are called to examine the exact role of such contact, which may inspire new therapeutic measures for mitochondrial imbalance and organ function protection.

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