Mechanism of Mitochondrial Damage in Cardiac Dysfunction Induced by Sepsis

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Abstract—**Sepsis is a syndrome with a high fatality rate, which is the dysfunction of multiple organs in the whole body caused by the host's inflammation response caused by infection. The cardiac insufficiency caused by sepsis is called Septic-Induced Myocardial Dysfunction (SIMD), which is mainly characterized by bilateral systolic and diastolic dysfunction of the heart, which is one of the most serious complications of sepsis. Normal mitochondrial structure and function are essential for maintaining mitochondrial homeostasis. Mitochondrial homeostasis plays a central role in the pathophysiology of SIMD, and its structural changes, oxidative stress, inflammation, endoplasmic reticulum stress and autophagy are directly or indirectly related to the occurrence and development of SIMD, which has a promising future as a targeted therapy for SIMD. Therefore, this paper focuses on the molecular mechanism and signaling pathway of mitochondrial homeostasis in the pathogenesis of SIMD, and provides implications for the search for therapeutic targets and biomarkers of SIMD. In addition, many traditional Chinese medicine components play a protective role in maintaining mitochondrial homeostasis in sepsis, and have the potential to be developed as novel therapeutics for SIMD.**

Keywords—**septic cardiomyopathy, mitochondrial homeostasis, mitochondrial dysfunction, autophagy**

I. INTRODUCTION

Sepsis is a life-threatening systemic multi-organ dysfunction caused by the host's dysfunctional response to infection. This definition emphasizes that the pathogenesis of sepsis is organ dysfunction caused by infection [1]. According to statistics, tens of millions of patients with sepsis die every year due to multi-organ complications and poor prognostic effects, and Sepsis Induced Myocardial Dysfunction (SIMD) is one of the most serious complications. SIMD is defined as the reversible systolic and diastolic dysfunction of the left and right ventricles induced by sepsis. Early observation showed that the cardiac output of patients with sepsis could still maintain a high level, so it was considered that the cardiac systolic function of patients was normal. It

was not until 1984 that Parker *et al.* [2], using radionuclide angiography, found that the Left Ventricular Ejection Fraction (LVEF) of patients with sepsis decreased significantly. The patient's "normal" stroke output is maintained by compensatory fluid replenishment and compensatory LV dilation.

Studies have shown that the pathogenesis of SIMD involves multiple pathways, these include the release of circulating myocardial inhibitory substances, Pathogen-Associated Molecular Pattern (PAMP) and Damage-Associated Molecular Pattern activation (DAMP), downregulation of adrenaline pathways, release of Nitric Oxide (NO) and Reactive Oxygen Species (ROS), dysregulation of calcium, mitochondrial dysfunction, alterations in coronary microvascular structure and function, and genes encoding sarcomere and mitochondrial protein-related genes downward adjustment, etc. [3, 4]. The systolic and diastolic functions of the heart require large amounts of Adenosine Triphosphate (ATP), and the heart does not have the capacity to store ATP that keeps the heart beating, so the heart is rich in mitochondria. The volume of mitochondria in mammalian cardiomyocytes accounts for 22%–37% of that in the middle cardiomyocytes. At the same time, mitochondrial dysfunction not only affects the abnormal energy metabolism of cardiomyocytes, but also causes oxidative stress, inflammation and cell death of cardiomyocytes. Studies have shown that SIMD is related to mitochondrial homeostasis (Fig. 1). In this paper, the molecular mechanisms, signaling pathways and potential therapeutic targets of mitochondrial morphology and dysfunction in SIMD are analyzed and discussed.

II. SIMD AND MITOCHONDRIAL HOMEOSTASIS

Structural abnormalities of myocardial mitochondria during sepsis have been demonstrated in animals and patients. Vanasco *et al.* [5] pointed out that after LPS treatment for 6h and 18h, mitochondrial swelling, formation of internal vesicles, loss or rupture of ridge, matrix clearance, destruction of inner and outer membranes and other abnormalities occurred in rat cardiomyocytes, and mitochondrial remodeling process still existed 24h later. Similarly, mitochondrial edema and

mitochondrial crest structure changes (vacuoles and collapse) have been found in the hearts of patients with

sepsis, so there is great potential to study the mechanisms related to mitochondrial structure changes [5, 6].
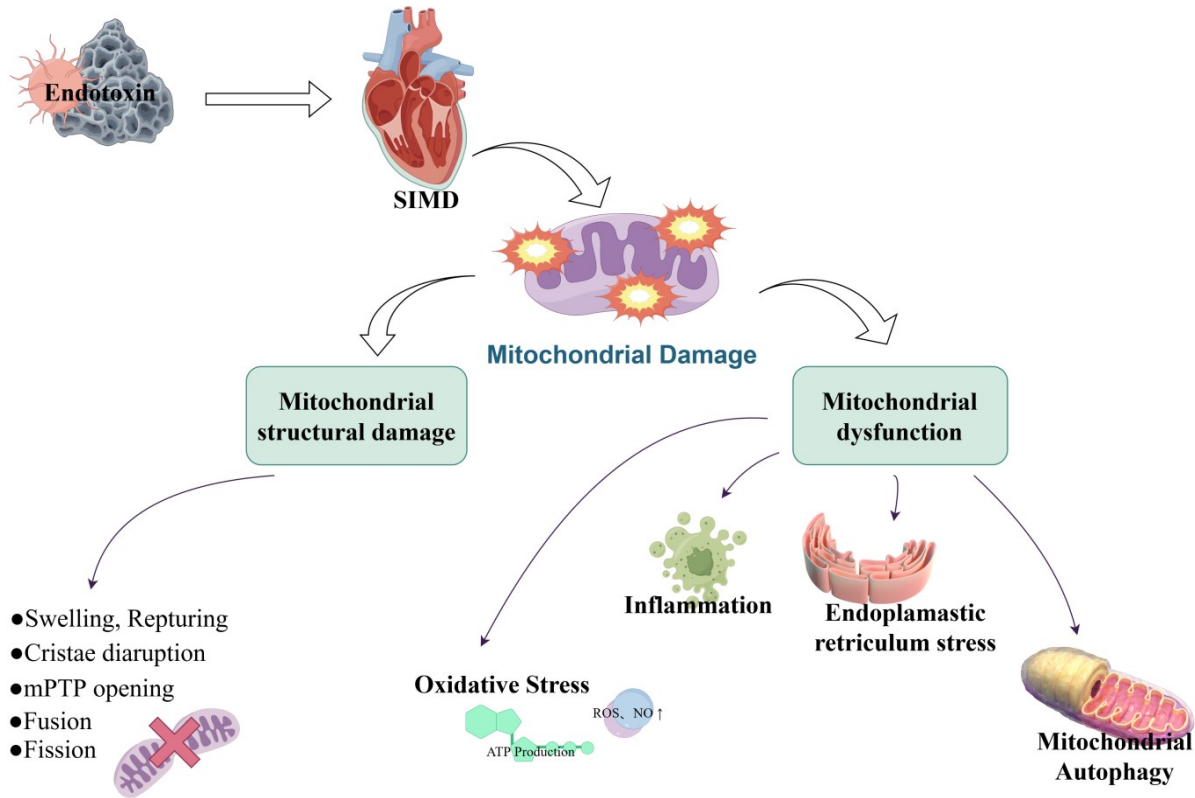

Fig. 1. Mechanism of mitochondrial damage in cardiac dysfunction induced by sepsis.

A. Structure and Function of Mitochondria

Mitochondria are highly dynamic and autonomous organelles that provide ATP for life activities. With a bilayer membrane structure, the Outer Membrane (OMM) is both a perfect barrier and an exchange platform. The Inner Membrane (IMM) consists of three structures: the inner membrane boundary (IBM), the ridge junction, and the ridge. The ridge increases the area of the inner membrane of mitochondria and is the main site of cell respiration and metabolism. The dynamic nature of mitochondria is reflected in continuous fusion and cyclic division. Cytoplasmic environment is the decisive factor for mitochondrial fusion. Mitochondrial fusion can promote the communication between mitochondria and host cells, and can realize the exchange of mtDNA, proteins, lipids, and metabolites. Mfn1 and Mitofusin 2 (Mfn2) are effector molecules of mammalian mitochondrial outer membrane fusion, while the mitochondrial fusion protein OPA1 is the mediator of IMM fusion. The maximum effect of mitochondrial fusion is to maintain a healthy mitochondrial population, for example by diluting toxic superoxides through fusion. The second way mitochondria respond to the cytoplasmic environment is division, which involves three key steps: (1) labeling the division site; (2) assembling the DRP1 (Dynamin-related Protein 1) dimer and oligomer into a superhelical structure around the labeled division site; (3) GTP hydrolysis and DRP1 spiral contraction cut mitochondria. DRP1, the only mitochondrial division

protein currently found in mammals, is present in the cytoplasm, where a continuous increase in Ca^{2+} levels activated DRP1 translocation to the mitochondria, leading to its division. In short, both division and fusion are responses to the intracellular environment.

At the same time, the integrity of mitochondrial structure and function is also important for the homeostasis of the intracellular environment. Mitochondria regulate energy production and control biosynthesis precursors, regulate intracellular Ca^{2+} levels, regulate REDOX states, ROS production, and initiate apoptosis by activating mitochondrial permeability transition pore (mtPTP). Mitochondrial permeability transition is mediated by the non-specific highly conductive channel mPTP located in the inner mitochondrial membrane. The opening of mPTP is triggered by overload of Ca^{2+}, but its sensitivity depends on various conditions, including oxidative and nitrification stress, adenine nucleotide depletion, and mitochondrial membrane potential dissipation. The main result of mPTP opening is the dissipation of proton prime modems (breakdown of mitochondrial membrane potential), which leads to uncoupling of oxidative phosphorylation and abnormal depletion of ATP. In sepsis, mitochondrial dysfunction has two serious consequences: inducing oxidative stress and generating energy crisis, which will directly or indirectly cause apoptosis or necrosis of cardiomyocytes, leading to myocardial dysfunction.

B. Mitochondrial Structure Changes in SIMD

The characteristics of sepsis induced cardiomyocyte inhibition include decreased mitochondrial membrane potential, mitochondrial ROS overload, and activation of cardiomyocyte apoptosis. These changes lead to decreased myocardial contractility and elevated markers of myocardial damage. Studies have shown that in addition to functional impairment, LPS-induced sepsis also disrupts the structure of cardiomyocyte mitochondria. Damaged mitochondria recover their function through adaptive responses such as fission, fusion, phagocytosis, mitochondrial unfolded protein response (UPRmt), and mitochondrial biogenesis. Among them, UPRmt and mitochondrial phagocytosis can be considered as unique mitochondrial repair pathways, with the former altering mitochondrial proteomics and the latter altering mitochondrial number. In sepsis, when UPRmt fails to fully repair mitochondrial damage, it induces mitochondrial division to isolate the damaged area from healthy mitochondria, and then mitochondrial phagocytosis is activated. At present, studies have shown that FUNDC1 (FUN14 domain containing 1, FUNDC1) can also activate mitochondrial phagocytosis, protecting the heart from damage caused by LPS by preserving mitochondrial function and structure. This study identified an association between FUNDC1 dependent mitochondrial phagocytosis and UPRmt, but did not elucidate the regulatory mechanism between FUNDC1 and UPRmt [7]. In addition, other studies have demonstrated that irisin mediates FundC1-related mitochondrial phagocytosis and improves mitochondrial function and survival number of cardiomyocytes after LPS stimulation [8].

In addition, mitochondrial division is the upstream regulatory signal of mitochondrial homeostasis, and the increase of mitochondrial division can induce the aggravation of mitochondrial damage. Mitochondrial division has received extensive attention in the study of mitochondrial dysfunction and cardiomyocyte death. At present, studies have used LPS-induced SIMD cell models to prove that treatment with P110, a selective inhibitor of DRP1/Fis1 (Fission 1, Fis1) interaction, can reduce mitochondrial pathological division, improve cell respiration and maintain ATP production [9]. Mukherjee [10] showed that DRP1 can mediate p53 mitochondrial localization, and by blocking the activation of DRP1 and reducing the interaction between DRP1-p53, mitochondrial dysfunction can be improved. At the same time, it was found that drug blocking DRP1/p53 interaction and inhibiting p53 mitochondrial binding could significantly restore the contractile function of cardiomyocytes in mouse LPS model. Tan *et al.* [11] showed that LPS can mediate the activation of DRP1-related mitochondrial division through the JNK-LATS2 pathway and participate in the pathogenesis of SIMD, while irisin can inhibit DRP1-related mitochondrial division and normalize the JNK-LATS2 signaling pathway. Irisin, as a newly discovered hormone in recent years, plays an important role in regulating human metabolism and oxidative stress, and is expected to be a therapeutic drug for SIMD.

III. SIMD AND MITOCHONDRIAL DYSFUNCTION

The disruption of mitochondrial homeostasis is not only related to mitochondrial structural homeostasis, but also closely related to mitochondrial dysfunction, which is mainly caused by oxidative stress, inflammation, endoplasmic reticulum stress, etc. The imbalance of these pathways promotes mitochondrial dysfunction and may also lead to SIMD In addition, interventions through these pathways may also become a novel and promising strategy for the treatment of SIMD.

A. Mitochondrial Dysfunction and Oxidative Stress

Oxidative stress refers to the excessive production or reduced removal of free radicals (superoxide anion, hydrogen peroxide, and hydroxyl free radicals) in the body under exogenous or endogenous stimulation, resulting in the imbalance of oxidation-antioxidant homeostasis and the oxidative damage of tissue cells. Mitochondria are the main source of ROS and support the metabolic activity of cardiomyocytes through Oxidative Phosphorylation (OXPHOS). Mitochondria can use O_2 in the electron transport chain to produce ATP, but during energy processing, they sometimes leak 1–2% of electrons resulting in the production of Reactive Oxygen Species (ROS), superoxide anions, and hydrogen peroxide [12]. In healthy physiological conditions, ROS plays an important signal transduction function. Most ROS in mitochondria are released in the mitochondrial matrix. While hydrogen peroxide permeates freely and diffuses rapidly into the cellular cytosol, superoxide diffuses more slowly and tends to be processed by the mitochondrial antioxidant system. Manganese superoxide dismutase converts superoxide to hydrogen peroxide, which is then processed into water via the glutathione/thioredoxin system. The imbalance between the production of ROS and the antioxidant defense capacity of mitochondria can lead to the progressive accumulation of ROS and oxidative stress [13]. During SIMD, mitochondrial homeostasis is unbalanced, resulting in excessive production of ROS and NO, calcium overload, cAMP-PKA signal transduction changes, and depletion of antioxidants in mitochondria [14]. Excessive ROS and NO will cause mitochondrial membrane protein and DNA damage, resulting in mitochondrial dysfunction and myocardial damage.

Due to the low storage capacity of ATP, under normal conditions, 95% of the energy ATP in the heart comes from oxidative phosphorylation of mitochondria, and 60-90% of this is through fatty acid oxidation. The production of ATP is related to a variety of substrates, including Fatty Acids (FA), glucose, Ketone Bodies (KB), and Amino Acids (AA), and this process will change the type and quantity of substrates used according to the change of working load, internal environment, and substrate content [15, 16]. In general, mitochondrial oxidative phosphorylation is regulated by associated

enzymes and transcription factors, with peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) or PGC-1β binding to peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α). PGC-1α interacts with estrogen-like receptor α (ERRα), and also activates nuclear receptor factors 1 and 2 (NRF 1/2) [16, 17], including AMPK81, which senses the AMP/ATP ratio, and co-regulates mitochondrial oxidative phosphorylation.

Starting from mitochondrial oxidative phosphorylation, some studies have demonstrated that β-hydroxybutyric acid (β-OHB) can maintain pyruvate/malate cycle, improve mitochondrial respiration, and ensure ATP production in sepsis. β-OHB also reduced overall carbonylation protein and lipid oxidation levels and increased superoxide dismutase 2 (SOD2) activity, confirming that β-OHB prevents the overproduction of ROS to protect mitochondrial structure and function. This mechanism suggests that β-OHB inhibits histone deacetylase (HDAC) and activates the antioxidant FoxO3a/MT2 pathway, alleviating myocardial oxidative stress and maintaining mitochondrial respiratory function, and ultimately improving the cardiac performance of SIMD [18]. This study provides direct evidence to support the protective role of β-OHB in SIMD. Its main regulatory mechanism is to regulate mitochondrial homeostasis by improving mitochondrial oxidative stress, but the study has yet to prove whether there is a sex difference. Inspired by traditional Chinese medicine, Chen *et al.* [19] studied the mechanism of rhodiola rosea in SIMD and proved that rhodiola Rosea side can effectively inhibit the ROS-mediated PI3K/Akt/mTOR pathway to alleviate myocardial damage. Due to the important role of fatty acid oxidation in oxidizing phosphoric acid, a large amount of lipid accumulation was found in the heart of patients who died from sepsis cardiomyopathy, suggesting that fatty acid oxidation disorders occurred in the later stage of SIMD, which may be a new therapeutic target for SIMD research.

B. Mitochondrial Dysfunction and Inflammation

The development of septic cardiomyopathy is characterized by innate immune cell infiltration and release of pro-inflammatory cytokines, the main mechanism of which is inflammation and immune dysfunction [20]. Under the stimulation of LPS, macrophages, and neutrophils are recruited into the damaged myocardial tissue under the action of chemokines and release pro-inflammatory cytokines. Such as IL-1β, IL-6, TNF-a, and IL-8, these factors can cause abnormal calcium homeostasis, disturbance of energy metabolism, oxidative stress, and thus damage cardiomyocytes [21, 22]. Therefore, inhibition of over activation of immune cells and reduction of cytokine release have become another research direction in sepsis cardiomyopathy.

When sepsis is induced by infection, toll-like receptor signaling in response to PAMP and DAMP triggers multiple intracellular pathways, including the activation of NF-κB and mitogen-activated protein kinases. In monocytes and macrophages, toll-like receptor activation

promotes cytokine production and has a direct impact on myocardial contractile [23]. High Mobility Group Protein B1 (HMGB1), a pro-inflammatory DAMP, may also play a role in mediating the pathophysiology of sepsis induced cardiomyopathy, including advanced myocardial dysfunction [3].

Apoptosis is a way of programmed cell death, which is mainly mediated by casepase-3/8/9 and ends in a non-inflammatory way. This process can be observed in the formation of apoptotic bodies. In SIMD, LPS stimulation causes the imbalance of mitochondrial homeostasis, and eventually leads to the apoptosis of a large number of cardiomyocytes, which is unable to perform normal cardiac function. The release of inflammatory factors plays a key role in SIMD. Numerous studies have been conducted to reduce apoptosis and maintain myocardial function by inhibiting the expression of inflammatory factors. For example, the use of deoxyadrenergy (PE) can reduce the contents of TNF-α, IL-6, ICAM-1, VCAM-1, and myeloperoxidase in myocardial tissue of sepsis rats, and increase the expression of mitochondrial fusion protein, the mechanism of which is to inhibit inflammation and slow down mitochondrial damage through the PI3K/Akt signaling pathway [24]. In addition, Interferon Regulatory factor-2 Binding Protein 2 (IRF2BP2) has been shown to be an effective anti-inflammatory factor by inhibiting the activation of NF-κB signaling pathway. Decrease the production of proinflammatory cytokines; IRF2BP2 also activated AMPK pathway, which effectively inhibited inflammation and apoptosis. It is suggested that activating the IRF2BP2-AMPK axis has potential application prospects in the treatment of SIMD [25]. C1q/tumor necrosis factor related protein (CTRP1), a circulating adipokine, inhibits the nuclear translocation of NF-κB by activating Sirt1, increases the expression of Nrf 2, and inhibits systemic inflammatory response and oxidative stress. To achieve cardioprotective effect on SIMD [26]; other studies have shown that the combined use of melatonin/irisin can significantly inhibit the LPS-induced activation of Mst1-JNK pathway, thus proving that LPS mainly activates mitochondria-related apoptosis pathways [27], which may open up new ways for the clinical treatment of sepsis cardiomyopathy. In recent years, with the improvement of technology and in-depth research, researchers have proposed another way of programmed cell death – cytopyrosis, which also participates in the innate immune response and can activate immune cells to engulf and kill pathogens. Cell pyrodeath is a pro-inflammatory programmed death mediated by casepase1/4/5/11, resulting in swelling and rupture of cell morphology, resulting in inflammatory cell death [28–30]. There are two ways of pyrodeath: classical and atypical. The classical pathway refers to the activation of cytoplasmic Pattern Recognition Receptors (PRRs), including NLRP3, NLRC4, and NLRP 1B in the NOD-Like Receptor (NLR) family, stimulated by Pathogen-Associated Molecular Patterns (PAMP), and Damage-Associated Molecular Patterns (DAMP). The apoptoses-related spot-like protein (APSP) containing

CARD binds to the precursor of Casepase 1 to form an inflammatory complex, cleaves the GSDMD protein and releases GSDMD-NT, which forms a small hole in the cell membrane, leading to cytoplasmic leakage and cell pyrosis [30, 31]. The non-classical pathway is that LPS directly binds and activates Casepase11, induces ATP release, causes large loss of K+, stimulates the activation of NLRP3 inflammasome and secretion of IL-1β, and enhances the inflammatory response. NLRP3 in the NOD-Like Receptor (NLR) family may be an important bridge between the typical and SARS-type pyrogenic pathways.

Therefore, researchers are trying to find new targets for the treatment of SIMD by starting with pyrodeath. Studies have shown that in SIMD mouse models, GSDMD not only mediates the release of inflammatory factors and the cascade amplification of inflammatory response, but also leads to mitochondrial damage, overproduction of ROS, and activation of NLRP3 inflammasome [32]. Apelin, a peptide hormone recently shown to be an endogenous ligand of G protein-coupled receptors, was used in SIMD rats and found to inhibit myocardial pyrodeath by inhibiting TLR4 and NLRP3 signaling pathways, reducing plasma levels of IL-6, TNF-α and IL-1β [33]. It has also been found that irisin can maintain mitochondrial homeostasis and inhibit the decomposition of NLRP3/GSDMD by activating mitochondrial ubiquitin ligase (MARCH 5, also known as MITOL), thereby regulating myocardial pyroptosis and alleviating cardiac dysfunction in patients with septic cardiomyopathy [34]. At the same time, after activating MITOL, irisin can also inhibit endoplasmic reticulum stress, ROS, and malondialdehyde levels, and alleviate myocardial ischemia-reperfusion injury. These findings highlight the clinical relevance and therapeutic potential of Apelin, irisin, and MITOL in the treatment of cardiac dysfunction caused by concentration disorders.

At present, the rise of photogenetic technology provides new ideas and means for SIMD and other cardiovascular diseases research. Two light-gated cAMP cyclases, bPAC and biPAC, have been transfected into macrophages, and the inflammatory activity of macrophages can be regulated by light irradiation. Subsequently, LPS was injected into mice to establish a SIMD model, and the assembled Gelma-(3) GES-LED system was implanted into mice to fine-tune cardiac inflammation by light ejaculation in vitro. The results showed that SIMD mice significantly inhibited leukocyte infiltration, especially macrophages and neutrophils, inhibited the release of proinflammatory cytokines, and alleviated the cardiac dysfunction caused by sepsis. The advantage of this study is that it achieves in situ anti-inflammatory therapy of the heart without affecting the antibacterial function of systemic inflammation and without damaging cardiomyocytes [35]. In addition, although this approach is a great breakthrough compared with traditional therapy, the clinical application and ethical review of modified macrophage transfusions are still difficult.

C. *Mitochondiral Dysfunction and Endoplasmic Reticulum Stress*

In recent years, a new research field, contactology, is emerging, which uses multidisciplinary interactions to analyze the mode and function of interactions between organelles, and the mitochondria-endoplasmic reticulum has been identified in biosynthesis, signal transduction, cell support, and mitochondrial dynamics. At present, the mitochondria-endoplasmic reticulum contact mode and the role of structure in Ca^{2+} and ROS signal transduction have been widely concerned.

There is evidence that mitochondrial oxidative stress and Endoplasmic Reticulum (ER) stress play key roles in the pathogenesis of septic injury. LPS disrupt ER homeostasis, resulting in pathologic protein unfolded response (UPR), Ca^{2+} disorder, and cell death. Studies have shown that protein kinase 3 (Ripk3) interacts with the degradation of mitochondria, endoplasmic reticulum and cytoskeleton of cardiomyocytes, and the activation of Ripk3 leads to increased inflammation. Ripk3 has been found to promote mitochondrial dysfunction through up-regulation of NADPH oxidase-4 (NOX4) and inhibition of mitochondrial complex I and III. However, in a mouse model with Ripk3 gene knock-down, the degree of organ damage induced by sepsis was somewhat alleviated [36]. In addition, Zhu *et al.* [37] found that upregulation of Ripk3 caused ER stress, which was accompanied by increased intracellular Ca^{2+} level and Xanthine Oxidase (XO) expression. Activated XOs increase ROS production and mediate mitochondrial Permeability Transition Pore (mPTP) opening and necrotic apoptosis of cardiomyocytes. However, the expression of Ripk3 in mouse heart tissues increased after LPS stimulation [38], suggesting that Ripk3 is a common upstream signal of mitochondrial damage and ER stress.

Melatonin, a transformation product of tryptophan, plays a role in regulating inflammation, oxidative stress and apoptosis. Studies have shown that melatonin alleviates septic myocardial injury by inhibiting Ripk3, improving mitochondrial and endoplasmic reticulum stress [38]. Mitochondrial aldehyde dehydrogenase (ALDH2) plays an important role in cardiometabolic diseases, mediating inflammation, oxidative stress and other cardiovascular reactions. Pang [39] demonstrated that ALDH2 protects LPS-induced cardiac abnormalities by inhibiting ER stress and autophagy in a CAMKKβ/AMPK/mTOR dependent manner. The ALDH2 activator Alda-1 eliminated LPS-induced Ca^{2+} – ATPase (SERCA) oxidation, autophagy, and cardiac dysfunction in the myocardium sarcoplasmic reticulum, while the AMPK activator AICAR or rapamycin counteracts the beneficial effects of Alda-1 on LPS. In addition, it was found that Qiangxin 1, a traditional Chinese medicine compound, can reduce the expression of ER and the key regulatory factors of apoptosis induced by mitochondrial stress in sepsis, such as CHOP, GRP 78, Cyt-c, Bcl-2, Bcl-XL and Bax, and this drug has been applied in clinic as a complementary drug [40].

Abnormal intracellular calcium flow is another factor in mitochondrial dysfunction. The endoplasmic reticulum

serves as the intracellular calcium reservoir and supports the diastolic and systolic functions of cardiomyocytes by regulating the concentration of cytoplasmic calcium. However, in the SIMD model, the concentration of calcium in rat cardiomyocytes was too high, the expression of calmodulin was significantly up-regulated, and the heart function was damaged. In the hearts of septic rats, due to the opening of mPTP, mitochondrial dysfunction was observed, and increased calmodulin, collagen staining, necrosis, and structural damage were observed in the left ventricular intercardial tissue and the whole heart. The use of Pyrvinium, a Wnt/ beta-catenin antagonist, can alleviate sepsis induced serum and tissue biochemical changes as well as changes in cardiac function and structure [41]. It has been observed that in LPS-stimulated cardiomyocytes, accumulated ROS can induce the formation of calcium release activated calcium channels (CRAC), mediating Ca^{2+} inflow in cardiomyocytes. In addition, paragalaconitine may reduce the damage of cardiomyocytes induced by LPS by activating Nrf2/ARE and NRF1 signaling pathways [42]. In addition, LPS stimulation has also been shown to impair Sirt3 activity, affecting calpin-mediated ATP synthesis and thereby causing cardiac dysfunction, suggesting that maintaining Sirt3 activity may also be a potential strategy for the treatment of SIMD [43]. In the complement system, C5a acts as a strong pro-inflammatory mediator, and in sepsis, its receptors C5aR1 and C5aR2 interact with cardiomyocytes to cause dysfunction and release pro-inflammatory factors. In recent years, it has been found that C5a can affect intracellular Ca^{2+} homeostasis and electrophysiological function of cardiomyocytes. The mechanism may be that LPS activates the complement system, induces the activation of Mitogen-Activated Protein Kinases (MAPKs), and thus activates the NLRP3 inflammasome and triggers the emergence of extracellular histones. All these events can lead to decreased concentrations of key Ca^{2+} regulatory proteins (SERCA2 and NCX) and Na+/K+ – ATPase in cardiomyocytes, resulting in failure of timely removal of cytoplasmic Ca^{2+} after contraction of cardiomyocytes, abnormal action potential of cardiomyocytes, ROS redundancy and release of inflammatory factors [44, 45]. Inhibiting the expression of C5a and its downstream proteins can slow down the progression of SIMD.

IV. Mitochondrial Autophagy

Autophagy is a highly conserved biological process that maintains protein quality and organelle function by degrading damaged or dysfunctional cell components, enabling cells to adapt to changes in internal environment and mild stress. However, in SIMD, dysautophagy will cause a large quantity of toxic substances to accumulate and eventually lead to cell dysfunction and death [46]. In cellular and animal sepsis models, a significant increase in autophagosomes in the bilayer-membrane structure enclosing suborganelles was observed using electron microscopy, and excessive autophagy flow in cells was detected by transfection of mRFP-GFP-LC3 adeno-

associated virus, as well as significant changes in autophagy specific markers LC3 and P62. These results indicate activation of autophagy in SIMD models [47–50]. Mitochondrial autophagy is considered to be the main mechanism of mitochondrial quality control and plays an important role in maintaining mitochondrial homeostasis. Therefore, studies on mechanisms related to mitochondrial autophagy may contribute to the recovery of mitochondrial function and reduce the incidence of septic cardiomyopathy.

In China, with the deepening of the research and application of traditional Chinese medicine, the inspiration of healing has been found in ancient prescriptions (Table I). Puerarin is the main living substance extracted from puerarin, which is usually used in the adjuvant treatment of coronary heart disease and angina pectoris. In 2014, Peng *et al.* [51] found that puerarin can resist hypoxia/reoxygenation injury by reducing ROS production, loss of mitochondrial membrane potential, and necrosis and apoptosis of H9C2 cells through PKCε pathway. Thus, they further found that the expression of 14-3-3γ can be upregulated by the expression of karyolin, which interacts with PKCε, phosphorylates PKCε, promotes its migration to mitochondria, activates adaptive autophagy, inhibits the release of inflammatory cytokines and excessive oxidative stress, maintains mitochondrial function, and ultimately protects cardiomyocytes from LPS damage [52]. Luteolin, a flavonoid polyphenolic compound with antioxidant activity that can be isolated from many vegetables, fruits and herbs [53], has anti-inflammatory and antioxidant activities; studies have shown that luteolin may exert a protective effect on the heart by activating AMPK/ULK1 signaling pathway to increase autophagy and reduce apoptosis in a mouse model of sepsis [54]. Resveratrol glycoside (PD) is a single crystal compound isolated from the rhizome of knotstalk and can be used as both medicine and food. Studies have shown that resveratrol can play a protective role in lung injury in mice with sepsis by upregating heme oxygenase-1 (HO-1) [55]. Later studies have shown that resveratrol glycosides can alleviate myocardial damage in sepsis by promoting SIRT6-mediated autophagy, and have potential therapeutic effects of SIMD [56]. Neferine is an alkaloid with anti-inflammatory, anti-arrhythmic, anti-platelet aggregation and anti-hypertensive cardiovascular disease protective effects. Pharmacological mechanisms suggest that it can clear ROS, prevent NF-kB nuclear translocation, and alleviate hypoxia-induced oxidative stress [57, 58]. The protective effect of liensinine on LPS-induced myocardial dysfunction may be realized through the regulation of PI3K/AKT/mTOR pathway to achieve anti-apoptosis and anti-oxidative stress [59].

With the spread of sequencing technology and proteomics, which provide more accurate targets for clinical treatment, researchers analyzed autophagy related genes that are differentially expressed during SIMD based on the transcriptome of human sepsis heart, and identified 8 key autophagy genes (CCL2, MYC, TP53, SOD2, HIF1A, etc.) by constructing protein interaction

networks. CTNNB1, CAT, and ADIPOQ), these genes may be used as targets and biomarkers for later research [60]; In the study of non-coding RNA, LncRNA SOX2OT plays an important role in regulating SOX2 transcription, while SOX2 can maintain mitochondrial homeostasis and increase autophagy level, so as to improve mitochondrial dysfunction during sepsis and alleviate cardiac inflammation [61, 62]. The specific mechanism may be binding to the regulatory region of mTOR promoter to inhibit its transcription and thus increase mitochondrial autophagy [63], but further experimental proof is needed. miR-22 may be another potential gene target. Studies have shown that miR-22 KO mice have reduced myocardial dysfunction, decreased apoptosis, and increased autophagy in the sepsis cardiomyopathy model, and the results in vivo and in vitro models are consistent, which may be related to the activation of Sirt1 signaling pathway [64].

TABLE I. THE THERAPEUTIC EFFECT OF CHINESE HERBAL MEDICINE ON MITOCHONDRIAL AUTOPHAGY IN MYOCARDIAL DYSFUNCTION CAUSED BY SEPSIS

Traditional Chinese medicine	Animal/Cell	Sepsis induction	Target	Effect	[Ref.]
Puerarin	Mouse/Primary cultured neonatal rat cardiomyocytes	LPS	14-3-3γ/PKCε	Activate adaptive autophagy and protect the myocardium	[52]
Luteolin	Mice	LPS	AMPK	Attenuated LPS-induced myocardial injury	[54]
Polydatin	Rat/H9C2 cell	LPS/CLP	Sirt6	Suppressed apoptosis and expression of inflammatory factor	[56]
Neferine	Mouse/H9C2 cell	LPS	PI3K/AKT/mTOR	Ameliorated cardiac dysfunction	[59]

Abbreviations: LPS = Lipopolysaccharide; CLP = cecal ligation and puncture.

V. PROSPECTS AND PROSPECTS

Due to the complex condition, rapid progression, high mortality, and poor clinical management of sepsis induced cardiomyopathy, a good treatment strategy has been urgently needed. In many studies, it can be found that the destruction of mitochondrial homeostasis, mitochondrial number reduction, structural abnormalities, dysfunction, and autophagy are common during SIMD. Therefore, the therapy targeting mitochondrial homeostasis is a promising emerging SIMD treatment strategy. In this review, sequencing technology and multi-omics analysis were combined to explore the signaling pathways and molecular targets related to SIMD from the perspective of the mechanism of mitochondrial homeostasis, in order to provide suggestions for SIMD therapy. In addition, there is no unified clinical definition of SIMD, which is usually defined through imaging and other auxiliary methods, so the discussion of the mechanism of SIMD may also provide help for the search for biomarkers. At present, although antibiotics are recommended to treat patients with early sepsis clinically, there is also potential harm of antibiotic abuse. Seeking useful ingredients from traditional Chinese medicine is also a good inspiration for the treatment of septic cardiomyopathy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Sihui Zheng and Xueting Yu conceived the review and wrote the original manuscript; Sihui Zheng edited and supplemented the final manuscript; all authors had approved the final version.

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