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REVIEW

Research Progress on Mechanisms and Treatment of Sepsis-Induced Myocardial Dysfunction

Yujie Hao, Runmin Liu, Hao Wang, Tao Rui, Junfang Guo

Division of Cardiology, Department of Medicine, the Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu, People's Republic of China

Correspondence: Junfang Guo, Email zjyyxngjf@163.com

Abstract: Sepsis is a syndrome of organ dysfunction caused by a dysregulated immune response to infection, with high morbidity and mortality. At present, there have been many advances in the study of its pathogenesis, especially the cardiac dysfunction caused by sepsis, namely sepsis-induced myocardial dysfunction, SIMD, which has received widespread attention. The mechanisms of SIMD mainly include excessive release of inflammatory mediators, impaired mitochondrial function, autophagy, apoptosis and myocardial dysfunction. This article reviews the pathogenesis of SIMD and elaborates on the progress in its treatment, aiming to improve the prognosis of patients with SIMD and sepsis.

Keywords: sepsis, sepsis-induced myocardial dysfunction, pathogenesis, treatment

Introduction

Sepsis is a systemic inflammatory response syndrome caused by infection. It is a fatal organ dysfunction caused by an imbalanced host response. And it is one of the most important causes of death to the patients in acute intensive care units.[1] The heart is one of the most likely damaged organs in sepsis. Sepsis can cause sepsis-induced myocardial dysfunction (SIMD). SIMD is related to the prognosis of patients with sepsis, and its mortality rate has reached more than 50%, which is much higher than that of patients with sepsis without cardiac injury.[2,3] The pathogenesis of SIMD is currently unclear, but it mainly includes excessive release of inflammatory mediators, impaired mitochondrial function, cell autophagy, apoptosis and myocardial dysfunction. There is still a lack of effective clinical treatment for SIMD. Further exploration about the pathogenesis of SIMD will help the development of targeted drugs.[4] Although the mortality rate of sepsis has declined in recent years with the timely application of broad-spectrum antibiotics, active resuscitation, improvement of tissue/cell oxygen supply, and the promotion of measures to protect organ function, it still remains at around 30%, which is one of the leading causes of death in critically ill patients.[5] This article reviews the pathogenic mechanism and treatment progress of SIMD, aiming to reduce the mortality rate of patients with septic cardiac dysfunction.

Clinical Manifestations of SIMD

SIMD manifests as ventricular dilation, ventricular systolic and/or diastolic dysfunction, hypoperfusion without ventricular systolic dysfunction, reduced ejection fraction, etc.[2] SIMD is divided into systolic and/or diastolic dysfunction of the left ventricular and/or right ventricular, which is a reversible functional change. Among them, septic myocardial injury (sepsis-induced myocardial injury, SIMI, a reversible cardiac dysfunction) is mainly manifested by weakened ventricular pumping function and poor effect on vasoactive drug therapy, but its diagnostic criteria have not yet been clearly defined.[6] The hemodynamic changes in SIMD are mainly divided into two stages: the first stage is the hyperdynamic stage, which is characterized by normal or slightly increased cardiac output and normal or low blood pressure. If the patient in this stage without active fluid resuscitation and effective myocardial protection, the patient will

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soon enter the second stage due to decreased myocardial contractility, and that is, the hypodynamic stage, which is manifested by decreased cardiac output and refractory hypotensive state.[7]

Pathogenesis of SIMD

Inflammatory Response and SIMD

SIMD is closely related to inflammatory response, and excessive release of inflammatory mediators through inflammatory signaling pathways is considered to be a key factor in sepsis-induced cardiac injury.[8] Toll-like receptors (TLRs) are type I transmembrane protein receptors. As pattern recognition receptors (PRRs), they can recognize different pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereupon then triggering multiple intracellular signaling pathways, including NF-κB and mitogen-activated protein kinases (MAPKs). The activation leads to the expression of inflammatory mediators and further mediates excessive inflammatory response in cardiomyocytes. The NF-κB signaling pathway is also involved in sepsis-induced myocardial oxidative damage.[9] Lipopolysaccharide (LPS) is a complex composed of lipids and polysaccharides. Studies have shown that lipopolysaccharide can increase the level of TLR4 and participate in the body's inflammatory activities and immune response through the Toll-like receptors (TLR) family, promoting the large-scale release of inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-α (tumor necrosis factor-α, TNF-α), and leading to cardiac dysfunction.[10] At the same time, sepsis can activate the MAPK/NF-κB pathway, causing myocardial cells to produce a large amount of TNF, thereby causing inflammatory damage to myocardial cells[11](Figure 1). In addition, LPS can activate multiple pathways such as JAK2/STAT3 and TLR4/JNK to induce the production of inflammatory mediators and aggravate cardiac damage.[12] Therefore, controlling the inflammatory response is one of the options to improve SIMD.

Mitochondria and SIMD

The heart is an organ rich in mitochondria, and the degree of mitochondrial dysfunction is closely related to the prognosis of sepsis.[13] Mitophagy (autophagy of damaged mitochondria) controls mitochondrial dynamics and function while also maintaining cellular homeostasis.[14] In sepsis, dysregulation of mitophagy and imbalance of mitochondrial dynamics aggravate heart damage. Some studies have found that activation of TLRs can stimulate cytokines to induce exosome-inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS). Excessive activation of iNOS to produce circulating NO can lead to damage to cardiovascular endothelial cells, mitochondrial damage, and cardiac dysfunction.[15] In sepsis, C5a can be upregulated to react with its receptor, causing inflammatory response and calcium overload in myocardial cells.[16] Studies have found that cardiomyocytes of septic mice can regulate the mitochondrial Na+ /Ca2+ exchanger (NCLX) by affecting PKA activity and cause mitochondrial damage.[17] Damaged mitochondria recognize

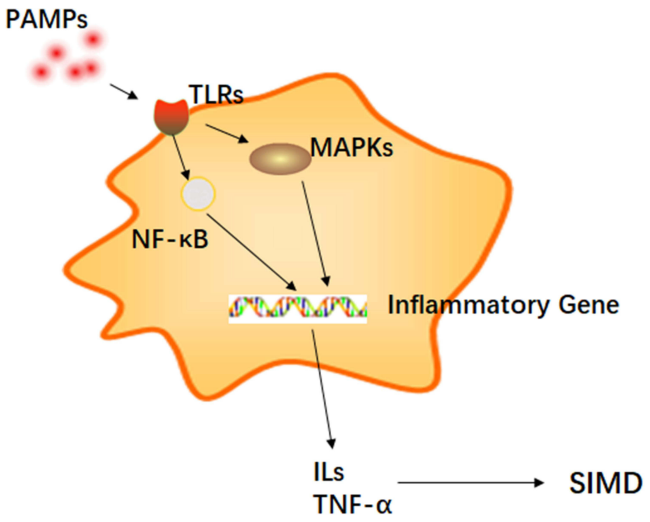

Figure 1 Inflammation influences the mechanisms of SIMD.

autophagy proteins through the PINK1/Parkin pathway, initiate mitophagy, accumulate and release toxic substances such as ROS in large quantities, which cause oxidative stress and induce excessive inflammatory response and programmed death of cardiomyocytes.[18] At the same time, Oxidative stress (OS) can lead to an increase in mitochondrial calcium and free fatty acid levels, which can cause mitochondrial damage, in turn aggravate OS, cytoplasmic calcium overload, and exacerbate cardiomyocyte damage.[19] Hence, improving mitochondrial function damage after sepsis is an effective means to the treatment of SIMD.

Cardiomyocyte Autophagy and SIMD

Autophagy refers to the double-layered membrane shed from the endoplasmic reticulum, which wraps part of the cytoplasm in the cell and the proteins that need to be broken down to form autophagosomes, and then fuse with lysosomes to form autophagic lysosomes. Lysosomes can break down the contents inside the membrane package and supply energy to the cell itself.[20] With the in-depth study of the role of autophagy in maintaining cellular homeostasis and protecting cardiomyocytes, its impact on septic myocardial injury has begun to be taken seriously.[21] Recent studies have found that excessive inflammatory mediators stimulated by LPS can cause significant changes in myocardial autophagy levels in mice.[22] Studies have shown that autophagy is an adaptive response of cells under stress, and increasing the amount of autophagy in cardiomyocytes can combat LPS-induced myocardial damage.[23] There are also studies showing that LPS-induced autophagy in cardiomyocytes is excessive autophagy and can damage cardiomyocytes. For example, Li et al believe that LPS-induced autophagy in cardiomyocytes is excessive. They discovered an important bioactive peptide, Alamandine, which can inhibit the increase of Atg3 mRNA levels in mouse hearts after LPS treatment, reduce the LPS-induced increase in Microtubule-associated Protein 1A/1B-light Chain 3 (MAPLC3), reduce the level of autophagy in mice and weaken the damage of LPS to the structure and function of the mouse heart to a certain extent.[24] Autophagy is a dynamic, complex process that requires a comprehensive assessment.

Myocardial Dysfunction and SIMD

Myocardial dysfunction generally refers to myocardial ischemia and hypoxia, which includes a variety of symptoms, such as chest tightness, chest pain, dyspnea, etc. During sepsis, microcirculatory disorders such as impaired capillary reactivity, lack of reactivity of arterioles, and changes in microvessel density limit the number of capillaries that can be "recruited", which leading to tissue hypoperfusion and shocking in patients with sepsis. And this finally results in myocardial ischemia, hypoxia, and myocardial dysfunction.[25] Severe sepsis endothelial cell dysfunction produces an excessive inflammatory response, and can dynamically regulate the microcirculation, through thrombin deposition form microthrombi, vascular permeability change and functional blood shunting, resulting in insufficient perfusion of myocardial tissue and affecting myocardium. Cells are hypoxic due to their uptake and utilization of oxygen, ultimately leading to cardiac dysfunction in sepsis.[26] In some septic patients with functional blood shunting caused by insufficient tissue oxygen uptake, even if myocardial function is suppressed, their mixed venous blood oxygen saturation is still elevated. This abnormal microcirculatory state may be irrelated to the systemic hemodynamic effects and deserve attention during clinical treatment.

Myocardial Cell Apoptosis and SIMD

Myocardial cell apoptosis plays an important role in SIMD. There are three main pathways of cardiomyocyte apoptosis: intrinsic apoptosis pathway (mitochondrial apoptosis pathway), exogenous apoptosis pathway, and endoplasmic reticulum stress apoptosis pathway. The mitochondrial apoptosis pathway during sepsis is mainly formed by regulating the imbalance between activated Bax and induction of the proapoptotic proteins release from the mitochondria, such as caspase-3 (caspase-3) precursor protein and anti-apoptotic proteins as Bcl-2.[27] The extrinsic apoptotic pathway and the mitochondria/cytochrome c-mediated intrinsic pathway cascade activate aspartate-specific caspase-3, which can directly degrade cellular DNA and lead to extensive apoptosis of cardiomyocytes.[28] It is currently believed that the MAPK and PI3K/AKT signaling pathways play a key role in the regulation of apoptosis in SIMD cardiomyocytes. The PI3K/AKT/mTOR signaling pathway can negatively regulate cardiomyocyte apoptosis. So, specifically inhibiting the activation of the

PI3K/AKT pathway can reduce cardiomyocyte apoptosis and alleviate SIMD.[29] Thus, inhibiting cardiomyocyte apoptosis pathway can be used as a key target to alleviate SIMD.

Exosomes and SIMD

Exosomes are extracellular vesicles with a diameter of 30 to 150 nm. They can transport a variety of biologically active substances including lipids, DNA, RNA, metabolites, cytoplasmic and cell surface proteins, etc., and they can mediate different signal communication in different types of cells in the body.[30] Stable exosomes exist in extracellular fluids (such as the body's blood, cerebrospinal fluid) and saliva, they have been recommended as biomarkers for the diagnosis of sepsis.[31] Factors related to SIMD such as pro-inflammatory factors, oxidants, endothelial cell dysfunction, calcium regulation, etc. are closely related to exosomes.[32] Among them, exosomes derived from different cell types play different roles in septic cardiomyopathy.

Exosomes are considered as carriers of myocardial inhibitory substances (excess proinflammatory factors in circulation).[33] Cytokines can activate Toll-like receptors through macrophages and other immune cells, which mainly activate the transcription factor NF-kB, control the expression of proinflammatory factors and play an important role in mediating cardiac dysfunction caused by sepsis.[34] Research by Es et al found that blocking the release of exosomes can reduce pro-inflammatory cytokines, alleviate cardiac dysfunction caused by sepsis, and reduce SIMD mortality.[35] Patients with sepsis can take up extracellular lactate through immune cells and rely on the p300/CBP (an important factor involved in cell differentiation and development) mechanism to promote high mobility group protein 1 (HMGB1, a nuclear protein) to complete lactation modification. Once HMGB1 is activated, it will aggravate the inflammatory response, and make sepsis and SIMD more serious.[36] Some studies have found that there is a correlation between plasma exosome levels and sequential organ failure assessment (SOFA) in patients with sepsis.[37] Some studies have also found that mesenchymal stem cell-derived exosomes can protect cardiomyocytes, inhibit their apoptosis, and reduce cardiac damage by releasing miR-223 and reducing calcium overload. Therefore, its specific clinical application prospects require further research.[38]

Treatment of SIMD

Since the pathogenesis of SIMD is still uncertain, there is currently no specific treatment.[39] The treatment strategy for SIMD is mainly to control the primary disease and prevent the occurrence of secondary SIMD, including infection control, vasoactive drugs and organ support therapy. However, the mortality rate is still at a high level, so research and development is aimed to the pathogenesis of SIMD. Targeted drugs aim to improve the prognosis and survival rate of SIMD patients.

Control Inflammatory Response

Inflammatory response plays an important role in the occurrence and development of sepsis. Consequently, effectively controlling excessive inflammatory response and reducing tissue cell damage can alleviate the symptoms of sepsis and delay the occurrence of septic cardiac dysfunction. The NF-κB signaling pathway is an important pathway in inducing cardiac damage in sepsis. Interrupting this pathway is also a therapeutic measure to alleviate sepsis. Losartan can regulate inflammatory cells through the NF-κB signaling pathway and reduce their infiltration into the myocardium, thereby reducing the inflammatory response and myocardial cell apoptosis, play a role in controlling sepsis and SIMD.[40] At the same time, various traditional Chinese medicines, such as *Tetrastigma hemsleyanum* and Astragalus polysaccharide have been proven to inhibit the activity of the TLR4/NF-κB pathway, reduce the inflammatory response of myocardial cells, which maintain myocardial cell vitality and improve sepsis and septic cardiac dysfunction.[41,42] Studies have found that *Ulinastatin*, a broad-spectrum protease inhibitor, can block the pathway between it and immune cells when infused intravenously, and quickly inhibits inflammatory reactions, thereby controlling the further development of sepsis.[43] Morelli et al found that in patients with severe sepsis and septic shock, the β-blocker esmolol can control heart failure in patients with septic shock and also has an impact on the clinical prognosis of patients.[44] Thus, inhibiting inflammatory mediators and blocking related inflammatory signaling pathways are important steps in the treatment of SIMD.

Maintain Mitochondrial Function

Mitochondrial dysfunction is an important mechanism in the pathogenesis of sepsis, and the use of drugs that affect mitochondrial function can regulate sepsis. Among them, Levosimendan, as a calcium ion sensitizer, can directly bind to troponin, change the configuration of troponin C, increase cardiac output, and treat SIMD.[45] In animal experiments, it was found that Levosimendan can target and mediate the PINK-1-Parkin pathway to activate mitophagy in mouse hearts, inhibit oxidative stress, and protect the heart function of mice.[46] Irisin (a hormone that can regulate body metabolism) can inhibit mitochondrial fission-related protein 1 (Drp 1) by regulating the JNK- LATS2 signaling pathway, inhibiting related mitochondrial fission, thereby maintaining mitochondrial function, reducing mitochondrial oxidative stress and cardiac dysfunction in patients with sepsis.[47] In short, improving mitochondrial function can reduce the occurrence and development of sepsis and SIMD, but its specific efficacy still requires further research.

Regulate Cardiomyocyte Status

During the development of sepsis, a series of microcirculation disorders lead to myocardial ischemia, hypoxia and even apoptosis, causing myocardial dysfunction. Correcting microcirculation disorders such as changes in microvascular function can improve sepsis.[25] Studies have shown that the mortality rate of sepsis patients who receive antiplatelet drugs (aspirin, etc.) is significantly lower than that of patients who do not receive this treatment.[48] Regulating the status of cardiomyocytes can also improve sepsis and SIMD. According to animal experiments, astaxanthin can inhibit cardiomyocyte apoptosis by adjusting the expression of Bax/Bcl-2, and alleviating cardiac dysfunction in septic mice.[29] Valproic acid can increase cardiomyocyte autophagy, reduce myocardial damage and cardiac dysfunction in septic rats by increasing the expression level of PTEN in cardiomyocytes and inhibiting the AKT/mTOR pathway.[49] In summary, correcting microvascular function and regulating myocardial cell status are important directions in the treatment of SIMD.

Other Drugs for SIMD

Oxidative stress is an important stress process that causes the progression of sepsis, so the application of oxygen free radical scavengers and antioxidants may improve the survival of sepsis patients. This possibility has been realized in sepsis animal models, but in clinical trials, the therapeutic effect of oxygen free radical scavengers and antioxidants on SIMD is uncertain, which provides us with new ideas.[50] For example, naturally occurring flavanone, quercetin, a naturally antioxidant may be protective against sepsis.[51] There is a complex relationship between exosomes and sepsis. It is undeniable that exosomes are also involved in myocardial protection. Among them, exosomal miRNA has certain value in the treatment of sepsis and SIMD. The present study reported that exosomal miRNA(miR-30d-5p) plays an important role in sepsis-related lung injury.[34] And exosomemiR-146a Cardiac dysfunction in septic mice can be reduced by targeting the regulation of TRAF6 and IRAK1 levels.[52]

Outlook

Sepsis is currently one of the main causes of death in patients in intensive care units. SIMD, as a fatal organ dysfunction caused by sepsis, has a high mortality rate, even with many treatments for sepsis and SIMD. Although some progresses have been made, many drug research and development are still in the basic research stage, and new clinical treatment drugs need to be developed based on the pathogenesis of SIMD.

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Disclosure

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