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The role and research progress of ferroptosis in myocardial injury in sepsis

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Highlights

- A comprehensive review of the role of ferroptosis in sepsis-induced myocardial injury is presented.
- The mechanisms of ferroptosis and recent advancements in its involvement in sepsis-induced myocardial injury are discussed.
- Perioperative whole-process risks may induce sepsis, activate ferroptosis and raise myocardial injury risk, while integrating ferroptosis into management can reduce this risk.

Abstract

Sepsis is triggered by the body's dysregulated response to infection, often accompanied by acute organ dysfunction and a high risk of mortality. The incidence of myocardial injury in sepsis patients ranges from 40% to 70%, with complex pathophysiological mechanisms. In recent years, ferroptosis, a novel form of programmed cell death, has attracted widespread attention. Studies suggest that it may play a key role in sepsis-related myocardial injury; however, research in this field is still in the preliminary stage, with some controversial findings and unclear underlying mechanisms. Notably, risks throughout the perioperative period (preoperative stage, intraoperative trauma/infection, and postoperative recovery) can induce sepsis, which further activates the ferroptosis pathway and leads to myocardial injury. Based on this, integrating ferroptosis into the perioperative management system—optimizing risk stratification through marker screening and implementing targeted interventions—holds great significance for reducing the risk of perioperative sepsis-related myocardial injury. This article systematically summarizes the latest research progress on ferroptosis in sepsis-related myocardial injury, explores its potential mechanisms, and screens for potential therapeutic targets by combining the characteristics of perioperative risks, thereby providing references for subsequent clinical research and practice.

Keywords: Sepsis, myocardial injury, ferroptosis, perioperative period, research progress

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Introduction

Sepsis is a severe clinical syndrome, which can also be induced by perioperative infections, trauma, and other factors. Typically caused by infection, it leads to an uncontrolled immune response in the body, thereby triggering a systemic inflammatory response and multi-organ damage [1]. In recent years, ferroptosis, as a form of iron-dependent programmed cell death, has attracted increasing attention. Studies have shown that ferroptosis is closely related to oxidative stress and plays an important role in the pathological process of sepsis [2]. However, the specific role of ferroptosis in sepsis-induced myocardial injury and its molecular mechanism remain to be further explored.

The mechanism of ferroptosis mainly involves the dysregulation of intracellular iron metabolism and the accumulation of lipid peroxides. Studies have found that ferroptosis plays an important role in multiple-organ damage caused by sepsis, including injury to the heart, liver, lung and kidney [3]. Specifically, ferroptosis aggravates myocardial injury in sepsis by promoting the accumulation of intracellular lipid peroxides, leading to cardiomyocyte death [4]. Several studies have shown that inhibiting ferroptosis can improve the survival rates in septic mice and reduce heart damage, providing novel therapeutic avenues for clinical treatment [5].

Multiple signaling pathways regulate ferroptosis in sepsis-induced myocardial injury. For example, p53 is an important regulator of ferroptosis, which helps cells resist external stimuli by modulating the expression of downstream genes [6]. In addition, the Nrf2/GPX4 axis and NCOA4-FTh1-mediated ferritin autophagy are also important mechanisms in the regulation of ferroptosis [7]. These mechanisms not only deepen our understanding of the role of ferroptosis in sepsis-induced myocardial injury, but also provide potential targets for developing targeted therapeutic strategies.

In terms of treatment, the application of iron chelators and ferroptosis inhibitors has shown promising results. For example, Fer-1, a ferroptosis inhibitor, not only significantly improves cardiac function and reduces the cardiac inflammatory response in septic mice, but also can reduce the risk of perioperative septic myocardial injury when used for preoperative pretreatment [8]. Studies have also shown that inhibition of ferroptosis can reduce myocardial injury caused by sepsis and enhance both the structure and function of the heart, providing a new direction for the treatment of sepsis-induced myocardial injury [9].

This article summarizes the research progress of ferroptosis in sepsis-induced myocardial injury, focuses on the regulatory characteristics and mechanisms of ferroptosis during the perioperative period, identifies therapeutic targets, and provides insights for the precise prevention and treatment of perioperative sepsis-induced myocardial injury.

Pathophysiological mechanisms of sepsis

Infection and systemic inflammatory response

Sepsis is a systemic inflammatory response syndrome caused by infection, often accompanied by multiple organ dysfunction. Pathogens (such as bacteria, viruses, or fungi) activate the host immune system by releasing endotoxins or other pathogenic substances, leading to a series of complex physiological reactions. These reactions include the release of cytokines, activation of white blood cells, and increased vascular permeability, all of which trigger a systemic inflammatory response. Although this response serves as the body's defense mechanism against infection, excessive inflammatory response can lead to tissue damage and organ dysfunction, and further aggravate the condition of sepsis [10, 11]. Studies have shown that inflammatory mediators such as tumor necrosis factor (TNF-α) and interleukins (IL-1, IL-6) play a key role in the occurrence and development of sepsis, especially in the process of myocardial injury, which promotes the apoptosis and dysfunction of myocardial cells [12].

Mechanisms of myocardial injury in sepsis

Sepsis-induced myocardial injury is multifactorial. First, the release of inflammatory mediators directly affects cardiomyocyte function, leading to a decreases myocardial contractility. Second, oxidative stress in sepsis aggravates cardiomyocyte damage and increases the generation of reactive oxygen species (ROS), which in turn triggers intracellular lipid peroxidation and leads to the death of cardiomyocytes [14].

In addition, disturbances in iron metabolism play an important role in sepsis-induced myocardial injury. Excessive iron accumulation promotes iron-dependent cell death (ferroptosis), a form of cell death closely related to cardiomyocyte dysfunction [13]. Additionally, specific signaling pathways, such as activation of the NLRP3 inflammasome, are closely related to myocardial injury in sepsis, and inhibiting these pathways may offer protective effects [15, 16].

Effects of iron metabolism disorders on myocardium

Proper functioning of iron metabolism is essential for heart muscle health. Patients with sepsis often experience excessive iron accumulation, which not only triggers oxidative stress but also leads to ferroptosis in cardiomyocytes [17]. Ferroptosis is a novel form of programmed cell death primarily mediated by lipid peroxidation. Studies have shown that during sepsis, the content of iron in myocardial tissue increases significantly, leading to cardiomyocyte dysfunction and death [18]. In addition, iron metabolism disorders may aggravate myocardial injury by disrupting mitochondrial function in myocardial cells [19, 20]. Regulating iron uptake, storage and excretion offers potential new ideas and strategies for the treatment of septic myocardial injury.

The basic mechanism of ferroptosis

Intracellular iron homeostasis

Iron, an essential trace element for cellular proliferation and one of the most abundant metal elements in the human body, is tightly regulated under physiological conditions through uptake, metabolism, and storage processes to maintain homeostasis. Ferritin, the primary iron storage protein, effectively sequesters iron ions, preventing their participation in harmful free radical reactions [21]. Dysregulation of iron homeostasis, particularly iron overload, is a critical trigger for ferroptosis, a regulated form of cell death characterized by lethal lipid peroxidation. Iron overload promotes lipid peroxide accumulation and exacerbates oxidative stress, resulting in cellular injury [4]. During ferroptosis, depletion of intracellular glutathione (GSH) and reduced activity of glutathione peroxidase 4 (GPX4) impair the detoxification of lipid peroxides, allowing ferrous iron (Fe^{2+}) to catalyze Fenton-like reactions that generate excessive ROS, ultimately inducing cell death [22]. Morphologically, ferroptotic cells exhibit distinct mitochondrial abnormalities, including mitochondrial shrinkage, decreased or absent cristae, and increased membrane density [23]. Iron accumulation and lipid peroxidation are key initiating events in membrane oxidative damage during ferroptosis, underscoring the importance of maintaining intracellular iron homeostasis for cell survival.

Ferroptosis and amino acid metabolism

Ferroptosis is an iron-dependent, lipid peroxidation-driven form of programmed cell death, primarily mediated by excessive intracellular iron accumulation, GSH depletion, and impaired GPX4 function [24]. Its sensitivity is closely linked to the dynamic balance of amino acid metabolism [25]. Among these, the cystine/cysteine metabolic axis plays a central role. The system Xc^- antiporter, composed of SLC7A11 and SLC3A2, exports glutamate in exchange for cystine, which is subsequently reduced to cysteine—an essential precursor for intracellular GSH synthesis [26, 27]. GSH serves as a cofactor for GPX4, facilitating the reduction of lipid hydroperoxides. GSH depletion leads to GPX4 inactivation and triggers ferroptosis [28]. Moreover, glutamate accumulation may exacerbate oxidative stress through excitotoxicity, forming a positive feedback loop between metabolism and cell death.

Additional amino acid pathways are also play a role in regulating ferroptosis. Arginine metabolism, through nitric oxide synthase (NOS) or polyamine biosynthesis pathways, modulates the cellular redox state; branched-chain amino acids, such as leucine, can activate the mTOR pathway, thereby suppressing ATF4-mediated antioxidant responses [28-30]. Furthermore, NCOA4-FTH1 phase separation-mediated ferritinophagy regulates iron metabolism and ferroptosis sensitivity, representing a promising therapeutic target [31]. Recent studies have also highlighted the aberrant expression of amino acid transporters, such as LAT1 (SLC7A5), in promoting ferroptosis resistance in tumor cells, suggesting that reprogrammed amino acid metabolism may be a critical mechanism by which cells evade ferroptosis in disease con-

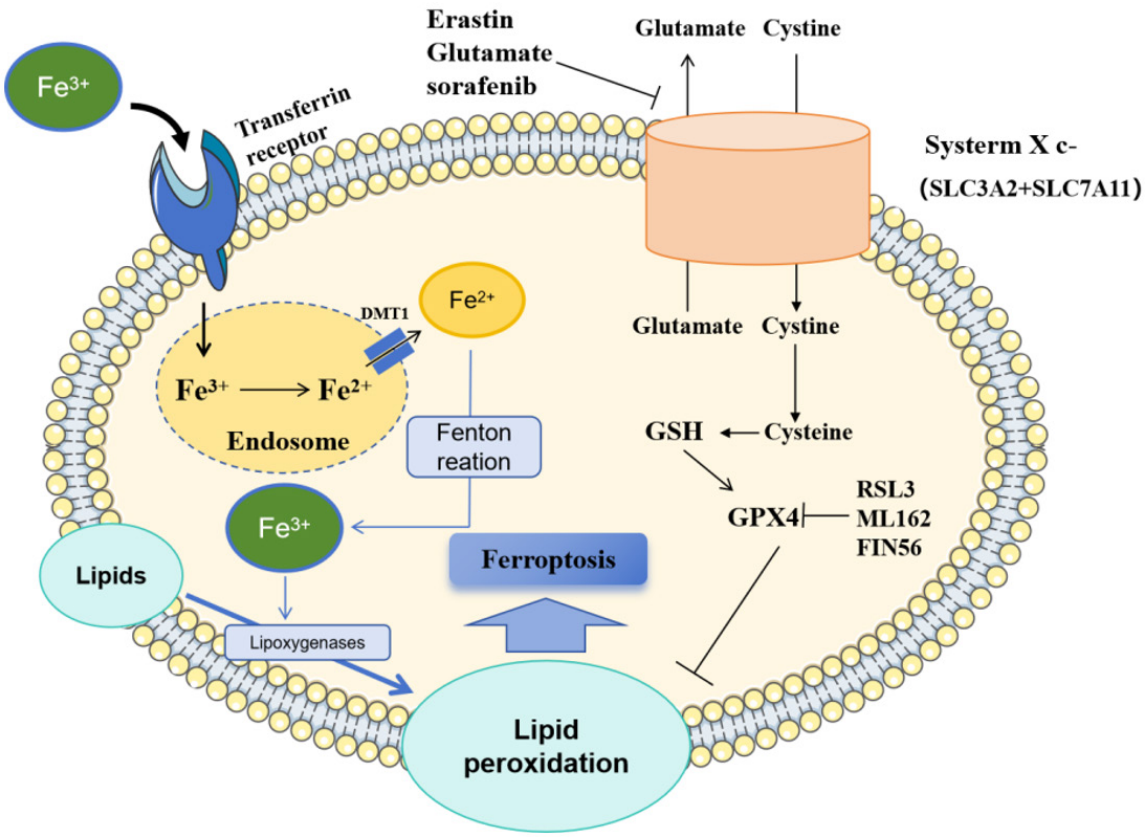

Figure 1. Schematic diagram of the ferroptosis-lipid peroxidation signaling pathway.

texts [32]. A deeper understanding of the crosstalk between ferroptosis and amino acid metabolism may shed light on the metabolic foundations of various diseases and offer novel therapeutic strategies for ferroptosis-associated conditions, including cancer and neurodegenerative disorders.

The link between ferroptosis and lipid peroxidation

Ferroptosis, an important regulatory cell death outcome, is essentially triggered by the dysregulation of lipid peroxidation products. Inflammatory responses induced by bacterial infections lead to the production of large amounts of reactive oxygen species (ROS) [5]. Studies have shown that in the intrinsic association between ferroptosis and lipid peroxidation, ROS act as a core signaling molecule, permeating the entire "oxidative damage-death execution" cascade and forming a triangular regulatory network of iron-ROS-lipid peroxidation [8]. This network can be intuitively understood by combining the **Figure 1**: In the initiation phase, extracellular Fe^{3+} enters the endosome via the transferrin receptor and is reduced to free ferrous ions (Fe^{2+}), which then participate in the Fenton reaction. Fe^{2+} synergizes with ROS to attack the double bonds of polyunsaturated fatty acids (PUFAs) in the cell membrane: ROS (such as •OH) directly participate in hydrogen atom abstraction reactions to generate lipid radicals (L•), while Fe^{2+} accelerates the decomposition of hydrogen peroxide (H_2O_2), amplifying ROS generation efficiency [33]. In the propagation phase, lipid radicals (L•) combine with oxygen to form lipid peroxyl radicals (LOO•), which further drives the vicious cycle of oxidative damage. This process not only consumes PUFAs within the membrane but also continuously generates new ROS (such as singlet oxygen $^1O_2$), forming a "ROS-lipid peroxidation" positive feedback loop that amplifies oxidative damage exponentially.

Under normal physiological conditions, cells eliminate lipid hydroperoxides (LOOH) through the glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis [34]. As shown in **Figure 1**, System Xc^- mediates the entry of cystine into the cell and its conversion to cysteine, which provides

the raw material for GSH synthesis. GSH, as a cofactor of GPX4, helps it scavenge lipid peroxides. Meanwhile, antioxidant enzyme systems such as superoxide dismutase (SOD) and catalase (CAT) can neutralize ROS and maintain redox balance. However, when ferroptosis occurs, it is often accompanied by the depletion of GSH and inhibition of GPX4 activity, which can be caused by inhibitors like Erastin blocking System Xc^- and RSL3 inhibiting GPX4, leading to the dysregulation of lipid peroxidation.

As the "core messenger" in the ferroptosis and lipid peroxidation network, the dynamic regulation of ROS not only determines cell fate but also provides multi-dimensional targets for intervening in oxidative damage-related diseases [35].

Other regulatory mechanisms of ferroptosis

In addition to the aforementioned pathways, ferroptosis is finely regulated by various signaling molecules. For instance, studies have shown that downregulation of nuclear receptor coactivator 4 (NCOA4) inhibits ferritinophagy, thereby reducing intracellular iron accumulation and lipid peroxidation, and ultimately suppressing ferroptosis [36]. Moreover, ferroptosis suppressor protein 1 (FSP1) has been found to reduce Coenzyme Q10 (CoQ10) and inhibit lipid peroxidation, exerting an anti-ferroptotic effect independently of the GPX4 pathway [37]. Jiang et al. demonstrated that nuclear p53 regulates ferroptosis through both transcriptional and post-translational mechanisms, while also exerting antioxidant effects [38]. Conversely, overactivation of heme oxygenase-1 (HO-1) can lead to excessive intracellular ferrous iron accumulation and increased ROS production, thereby promoting ferroptosis [39]. The mevalonate pathway also plays an essential role in ferroptosis regulation: its metabolites, including CoQ10 and isopentenyl pyrophosphate, are involved in modulating ferroptotic sensitivity. Isopentenyl pyrophosphate, derived from decarboxylated mevalonate, affects the maturation of selenocysteine tRNA, thus regulating the synthesis of GPX4 [40]. These signaling molecules act on diverse nodes within the networks of iron metabolism, oxidative stress, and lipid peroxidation, highlighting the multifactorial complexity and versatility of ferroptosis regulation [6].

Mechanisms and research progress of ferroptosis in sepsis-induced myocardial injury

Oxidative stress and inflammatory response

Sepsis is a life-threatening condition resulting from a dysregulated host response to infection [41]. It induces systemic inflammatory responses and oxidative stress, increasing intracellular ROS levels in cardiomyocytes, which disrupt cellular structures and impair cardiac function. Evidence suggests that oxidative stress and inflammation are key inducers of ferroptosis [45]. The mechanism involves three core factors: elevated oxidative stress, iron metabolism dysregulation, and impaired antioxidant defenses [43]. In septic myocardial injury, systemic inflammatory cascades elevate ROS levels, damaging biological membranes and initiating lipid peroxidation, which promotes ferroptosis. Iron overload, frequently observed in sepsis, provides excess free Fe^{2+} that fuels ROS generation via Fenton chemistry, exacerbating myocardial damage [44]. Inflammatory mediators can also modulate iron-related proteins, such as transferrin receptor 1 (TfR1), promoting iron uptake and facilitating ferroptosis [45]. Ferroptosis leads to lipid peroxide accumulation and loss of membrane integrity in cardiomyocytes, further intensifying myocardial injury in sepsis [21, 44]. Dysfunction of the antioxidant system, particularly the system Xc^-–GSH–GPX4 axis, impairs lipid hydroperoxide clearance, accelerating ROS accumulation. Regulatory molecules like acyl-CoA synthetase long-chain family member 4 (ACSL4) and GPX4 exhibit aberrant expression in myocardial injury and are closely associated with cardiac dysfunction severity [46]. Inhibiting ferroptosis has been shown to mitigate septic myocardial injury and improve cardiac function, offering a promising therapeutic strategy [42, 47].

Mitochondrial dysfunction

Sepsis-induced mitochondrial dysfunction significantly contributes to myocardial injury. Most cellular ROS originate from mitochondrial oxidative phosphorylation. Ferroptosis and mitochondrial dysfunction are mutually reinforcing: lipid peroxides generated during ferroptosis attack mitochondrial membranes, causing swelling, cristae disappearance, and outer membrane rupture, impairing mitochondrial function [48]. Ferroptosis disrupts intracellular iron homeostasis, and excess Fe^{2+} catalyzes ROS produc-

tion, damaging mitochondrial respiratory chain complexes, decreasing ATP synthesis, and impairing cardiomyocyte energy metabolism. Moreover, ferroptosis leads to GSH depletion and GPX4 inactivation, preventing the effective clearance of lipid peroxides and ROS, resulting in persistent mitochondrial oxidative stress. Conversely, mitochondrial dysfunction promotes ferroptosis by destabilizing ferritin, facilitating ferritinophagy, and increasing intracellular free iron. As mitochondria are the primary site of ROS generation, their dysfunction amplifies ROS production, creating a vicious cycle of lipid peroxidation and ferroptosis. This bidirectional interaction exacerbates septic myocardial injury and may contribute to organ failure and mortality.

Amino acid metabolism

Ferroptosis alters amino acid metabolism in septic myocardial injury and induces autophagic responses. GPX4 regulates ferroptosis and oxidative stress by converting reduced GSH into oxidized glutathione (GSSG), thereby preventing ferroptosis [49]. In sepsis, oxidative stress decreases GPX4 activity, increasing susceptibility to ferroptosis and worsening myocardial injury [50]. ACSL4, a key enzyme in lipid peroxidation, is upregulated during ferroptosis and correlates with myocardial damage [51]. NCOA4, the selective receptor for ferritin, mediates ferritin degradation and elevates intracellular Fe^{2+} levels during ferroptosis [52]. Inflammatory factors in sepsis upregulate NCOA4 expression, promoting ferritinophagy and iron release, thereby enhancing ferroptosis. Lipocalin-2 (Lcn2) binds iron-loaded siderophores, restricting iron uptake and inhibiting ferroptosis. Lcn2 deficiency increases iron uptake and ferroptosis risk, while Lcn2 upregulation may protect the myocardium by mitigating ferroptosis-induced injury [53]. Elevated myocardial iron levels have been observed in sepsis patients and are positively correlated with myocardial damage severity, highlighting iron dysregulation as a therapeutic target in septic cardiomyopathy [42, 47].

Research progress on ferroptosis in sepsis-induced myocardial injury

Findings from animal model studies

In recent years, animal models have played a pivotal role in elucidating the relationship between ferroptosis and sepsis-induced myocardial injury. Studies have demonstrated that sepsis can induce ferroptosis in cardiomyocytes, a process closely linked to iron metabolism dysregulation and lipid peroxide accumulation [54]. By establishing the cecal ligation and puncture (CLP) model in mice, researchers found that administration of ferroptosis inhibitors significantly reduced myocardial injury and improved cardiac function in septic animals [55]. Additionally, iron chelators such as deferoxamine have been shown to mitigate cardiac damage in septic mice, suggesting that ferroptosis may be a critical mechanism in sepsis-induced cardiomyopathy [5]. These findings deepen our understanding of the pathophysiological mechanisms underlying sepsis-related cardiac injury and provide potential therapeutic targets for intervention.

Preliminary results from clinical studies

In clinical research, the role of ferroptosis in sepsis patients has garnered increasing attention. One study revealed a positive correlation between dysregulated iron metabolism and the severity of myocardial injury in sepsis patients, indicating that ferroptosis may play a key role in this context [9]. Among the regulatory factors, the p53 transcription factor family has been implicated in ferroptosis [56]. Specifically, tetracycline-induced p53 promoter activation and ROS-induced cellular stress responses were shown to promote ferroptosis by suppressing the expression of SLC7A11 [59]. Furthermore, Li et al. reported that ferritinophagy-mediated ferroptosis constitutes a critical mechanism in sepsis-induced cardiac damage. In a lipopolysaccharide (LPS)-induced sepsis model, LPS was shown to upregulate the expression of nuclear receptor coactivator 4 (NCOA4), which promotes ferritin degradation and the release of free iron [60]. This, in turn, activates mitochondrial membrane-associated iron-binding proteins, exacerbating oxidative injury. Clinical data have suggested that ferroptosis inhibitors may be beneficial in improving cardiac function and reducing inflammatory responses in sepsis patients [8]. However, current clinical trials targeting ferroptosis are still limited, and further research is needed to verify the efficacy and safety of such therapies in sepsis-induced myocardial injury.

Therapeutic prospects of targeting ferroptosis

Recent research indicates that ferroptosis plays a significant role in sepsis-related organ dam-

age, including myocardial injury [57]. Targeted therapeutic strategies against ferroptosis mainly include iron chelators, antioxidants, and specific ferroptosis inhibitors [58]. For example, deferoxamine has been shown to effectively prevent iron accumulation, thereby alleviating cardiac injury in sepsis models [5]. Moreover, ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 have demonstrated the ability to reduce myocardial damage and improve cardiac function in septic animals [7]. Combining ferroptosis inhibitors with other treatments, such as anti-inflammatory agents or antioxidants, may further enhance therapeutic efficacy [61]. Despite these encouraging findings, several challenges remain, including optimizing dosage, determining appropriate routes of administration, and ensuring long-term safety. Future research should focus on refining ferroptosis-targeted treatment strategies to provide more effective solutions for sepsis-induced myocardial injury. These emerging therapeutic approaches offer new insights and directions for the management of septic cardiomyopathy.

Effects of combination therapy on sepsis-induced myocardial injury

Combination therapy is gaining increasing attention in the treatment of sepsis, particularly in strategies targeting ferroptosis. Studies have shown that the co-administration of certain drugs can significantly enhance therapeutic efficacy. For instance, combining antioxidants with ferroptosis inhibitors has been demonstrated to alleviate oxidative stress and inflammatory responses in sepsis patients, thereby reducing oxidative damage in cardiomyocytes and mitigating myocardial injury [8]. Additionally, certain compounds derived from traditional Chinese medicine, such as ginsenoside Re, have been reported to ameliorate sepsis-induced cardiac injury by modulating ferroptosis pathways and enhancing antioxidant defenses [44]. This combination therapy approach not only improves treatment effectiveness but also provides new possibilities for the clinical management of sepsis-related myocardial injury.

Conclusion

Ferroptosis, as a newly identified form of regulated cell death, is gaining growing attention for its role in sepsis-induced myocardial injury. Studies have shown that ferroptosis is closely associated with cardiomyocyte damage and may play a pivotal role in the pathophysiological processes of sepsis. Although current research has uncovered potential mechanisms and implications of ferroptosis in septic cardiomyopathy, many questions remain unresolved and warrant further investigation.

Discrepancies among studies—stemming from variations in experimental design, model selection, and evaluation criteria—highlight the need for standardized protocols in future research. Establishing uniform methodological frameworks and fostering multicenter collaborations and interdisciplinary communication will be essential for a more comprehensive understanding of ferroptosis in sepsis-induced myocardial injury.

Looking forward, therapeutic interventions targeting ferroptosis hold great promise for improving cardiac function and overall outcomes in sepsis patients. The development of novel drugs or treatment strategies that modulate ferroptosis-related pathways could offer new clinical options. However, the efficacy and safety of these interventions must be rigorously validated through clinical trials to ensure tangible benefits for patients.

In summary, an in-depth exploration of ferroptosis not only broadens our understanding of the mechanisms underlying sepsis-induced myocardial injury but also opens new avenues for clinical intervention. Continued research in this area may ultimately lead to the development of more effective therapeutic strategies, thereby reducing the incidence of cardiac complications in sepsis and improving patient quality of life.

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