Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/843291jljiwm

Research progress on ferroptosis in the pathogenesis of sepsis

Yu Xiang, Jiameng Liu, Huan Li, Kecheng Zhai, Xingchen Yue, Shangping Fang

Anesthesia Laboratory and Training Center, School of Anesthesiology, Wannan Medical College, Wuhu 241002, Anhui Province, China.

Corresponding author: Shangping Fang.

Acknowledgement: This work was supported by Anhui Province College Student Innovation and Entrepreneurship Project (S202310368027 and S202410368031).

Declaration of conflict of interest: None.

Received December 12, 2024; Accepted February 14, 2025; Published September 30, 2025

Highlights

- Lipid metabolism and iron metabolism pathways are key biological pathways involved in ferroptosis.
- Ferroptosis exhibits complex crosstalk with other cell death forms in sepsis, with significant implications for disease pathogenesis and therapy.
- Ferroptosis plays a critical role in sepsis-related organ damage and prognosis.
- This review suggests directions and perspectives for treating ferroptosis and sepsis in the perioperative period.

Abstract

Ferroptosis is a newly identified form of cell death that has garnered attention in recent years. Current research has clarified several key mechanisms of ferroptosis, with reactive oxygen species, oxidative stress, and iron metabolism emerging as central factors. Additionally, various signaling pathways, molecules, and organelles also contribute to the regulation and progression of ferroptosis. Activation of ferroptosis has significant implications for sepsis-related inflammation, providing both a valuable area for scientific investigation and a potential target for therapeutic interventions. This article reviews the biological processes and molecular mechanisms of ferroptosis, as well as the small molecules and signaling pathways that regulate it. Additionally, we discuss the role of ferroptosis in the progression of sepsis and its contribution to organ damage.

Keywords: Ferroptosis, sepsis, inflammation, GPX4

I Introduction

Sepsis is a systemic inflammatory response syndrome caused by the invasion of pathogenic microorganisms into the body [1, 2]. Based on global research data, it is estimated that sepsis incidence exceeds 48.9 million new cases annually, with approximately 11 million sepsis-related deaths, accounting for 19.7% of all global mortalities [3]. This imposes a substantial burden on healthcare systems and represents a significant threat to human health. Recent global estimates derived from data on hospitalized adults in seven high-income countries report an annual incidence of 19.4 million sepsis cases (formerly severe sepsis) and 5.3 million sepsis-related deaths [3]. These figures suggest that sepsis may be more prevalent and lethal than currently estimated, warranting further research and attention [4].

However, therapeutic advances in sepsis remain largely limited to supportive care, including organ support and fluid resuscitation [5, 6]. There remains a gap in the development of effective medications for sepsis, making it crucial to explore new therapeutic directions and pathophysiological mechanisms [7].

Address correspondence to: Shangping Fang, Anesthesia Laboratory and Training Center, School of Anesthesiology, Wannan Medical College, No.22, Wenchang West Road, Lugang Street, Yijiang District, Wuhu 241002, Anhui Province, China. Tel: +86-19855362767; E-mail: 20180041@wnmc.edc.cn.

Recently, ferroptosis, a novel form of regulated cell death, has been implicated in sepsis, although its precise relationship remains incompletely understood. Sepsis has been described as a failed starvation response, where the body undergoes an intense starvation reaction, involving the production of high-energy metabolites such as lactate and free fatty acids [8]. Investigating the mechanisms of oxidative stress, ferroptosis, and other metabolic abnormalities in sepsis, particularly those related to lipid peroxidation and cellular ion metabolism, may provide new insights and potential targets for sepsis management.

II Ferroptosis: A novel form of regulated cell death

In 2012, Professor Stockwell identified a molecule, Erastin, that activates iron-dependent cell death, which was subsequently named ferroptosis [9]. Ferroptosis represents a novel regulatory form of cell death distinct from other forms, such as apoptosis, due to its unique morphological, biochemical, or genetic characteristics. Morphologically, ferroptosis is typically characterized by a reduction in mitochondrial volume, increased mitochondrial membrane density, and a loss or disappearance of mitochondrial cristae, while the cell membrane, nucleus, and chromatin remain largely unaffected [10]. Biochemically, ferroptosis involves the depletion of intracellular nicotinamide adenine dinucleotide hydride and glutathione (GSH), a reduction in the activity of glutathione peroxidase 4 (GPX4), and an accumulation of reactive oxygen species (ROS), all of which promote ferroptosis. Genetically, various cancer-related genes have been shown to influence cellular sensitivity to ferroptosis [11].

Biological processes associated with ferroptosis

Ferroptosis is characterized by iron ion-mediated oxidative damage. An increase in iron-dependent ROS within cells, inhibition of GPX4, or depletion of GSH can all trigger ferroptosis. Recent research has identified three distinct pathways involved in ferroptosis: the classical GPX4 regulatory pathway, the lipid metabolism pathway, and the iron metabolism pathway [12].

The classical GPX4 regulatory pathway

Erastin, a small molecule compound, selectively induces cell death in tumor cells expressing Small T oncoprotein (ST) and RAS by activating ferroptosis. It operates through various molecular mechanisms, including the cystine-glutamate transporter (system Xc^-), voltage-dependent anion channels, and p53. Erastin inhibits the cystine-glutamate antiporter system, leading to a depletion of intracellular cystine in the cell, which in turn disrupts the normal synthesis of GSH and inactivates intracellular GPX4. Both GPX4 and GSH are essential for cellular antioxidant defense, and their inactivation leads to the accumulation of lipid ROS and other peroxides, damaging proteins or membranes, ultimately inducing ferroptosis [13, 14].

Lipid metabolism pathways

Lipid peroxidation is a hallmark of ferroptosis, with lipid peroxides playing a crucial role in this process [15]. Polyunsaturated fatty acids increase membrane fluidity, which are crucial for cellular adaptation, but also serve as substrates for lipoxygenases, which catalyze the formation of pro-ferroptotic lipid peroxides [16]. Arachidonic acid and adrenic acid are two primary polyunsaturated fatty acids involved in lipid peroxidation during ferroptosis. Synthetase long chain family member 4 (Acyl-CoA) synthetase long-chain family member 4 (ACSL4) facilitates the conjugation of unsaturated fatty acids with coenzyme A, forming acyl-CoA [17, 18]. Subsequently, acyl-CoA can undergo re-acylation through various lysolipid phosphatidylcholine acyltransferases, with ACSL4 and lysolipid phosphatidylcholine acyltransferases 3 playing an essential role in the biosynthesis and remodeling of arachidonic acid/adrenic acid derivatives. Lipid peroxides themselves generate phospholipid hydroperoxides, which degrade into malondialdehyde (MDA) and 4-hydroxynonenal. These products induce cytotoxicity, destabilizing cell membranes and leading to cell death [19, 20].

Iron metabolism pathway

Although iron is a trace element, it plays a vital role in cellular metabolism. It is absorbed as non-heme iron in the small intestine, binds to transferrin in the serum, and is subsequently recognized by the transferrin receptor on the cell membrane. Once internalized by the transferrin receptor, STEAP3 metalloreductase reduces trivalent iron ions to divalent iron ions, which are then stored in the labile iron pool and ferritin [21]. Ferritin, composed of the ferritin light chain and ferritin heavy chain 1, can be degraded by lysosomes to increase free iron [22]. Under normal circumstances, excess divalent iron is oxidized to trivalent iron to iron homeostasis [23]. However, when iron homeostasis is disrupted, excess iron can act as a

cofactor in oxidative stress, promoting erastin-induced ferroptosis by depleting cysteine desulfurase (NFS1), thereby inhibiting iron-sulfur cluster biosynthesis [24].

Signaling pathways related to ferroptosis

The modulation of ferroptosis-associated processes, such as molecular regulation, lipid metabolism, oxidative stress, and iron metabolism, can influence ferroptosis. Research has shown that the oxidative stress transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) can stimulate the expression of multiple target genes to mitigate ferroptosis [25]. Furthermore, accumulating evidence suggests that several signaling pathways determine a cell's susceptibility to ferroptosis within specific biological contexts. These signaling pathways can be broadly categorized into GPX4-dependent pathways (for instance, the classical system Xc^-: GSH-GPX4 axis) and GPX4-independent pathways [26].

The system Xc^-, specifically the GSH–GPX4 axis, is an amino acid antiporter composed of two essential subunits: solute carrier family 7 member 11 (SLC7A11/xCT) and SLC3A2 [27]. This system typically facilitates the exchange of extracellular cystine and intracellular glutamate across the plasma membrane. The expression or activity of SLC7A11 can be finely tuned through protein-protein interactions (e.g., BECN1), gene transcription (e.g., *NFE2L2* or *TP53*), or protein degradation (e.g., via OTU deubiquitinating enzymes like OTUB1). Once cystine enters the cell, it is reduced to cysteine, which is subsequently utilized for the synthesis of GSH. Glutathione, also known as L- γ -Glutamyl-L-cysteinyl-glycine, is a tripeptide composed of glutamate, cysteine, and glycine, and plays a critical role in cellular antioxidant defense [28]. The reactive thiol group (-SH) of GSH is readily oxidizable. During glutathione synthesis, γ -glutamylcysteine synthetase (γ -GCS) catalyzes the reaction between glutamate and cysteine to produce gamma-glutamylcysteine [29]. As a potent reducing agent, glutathione effectively converts harmful lipid hydroperoxides generated during cellular metabolism into harmless lipid alcohols, a process that is crucial for determining cellular susceptibility to ferroptosis [30].

GPX4, a selenium-dependent protein, functions as a phospholipid hydroperoxidase, reducing phospholipid hydroperoxides (arachidonic acid/adrenic acid-PE-OOH) to their corresponding phospholipids [12, 31]. The primary role of GPX4 is to utilize the tripeptide GSH as a cofactor to detoxify lipid hydroperoxides formed during oxidative stress, thereby preserving membrane integrity.

A significant number of ferroptosis-inducing agents are regulated by the NRF2 pathway, which is maintained at low levels by three E3 ubiquitin ligases: Kelch-like ECH-associated protein 1-CUL3-RBX1, $SCF^{\beta TrCP}$, and synoviolin/Hrd1. Under normal conditions, the protein level of the nuclear transcription factor NFE2L2 is maintained at a low level due to its binding with Kelch-like ECH-associated protein 1, leading to its ubiquitination and degradation [32]. As an E3 ubiquitin ligase, HECT and RCC1-like domain containing protein 2 (HERC2) plays a critical role in iron homeostasis by targeting nuclear receptor coactivator 4 (NCOA4), a ferritin receptor that mediates ferritin autophagy, and F-box and leucine-rich repeat protein 5 (FBXL5),a regulator of iron regulatory proteins IRP1/2 that mediates ferritin synthesis, for degradation, thereby downregulating iron levels. NRF2 upregulates HERC2 to counteract ferroptosis [33]. Moreover, NRF2 positively regulates xCT (SLC7A11, a subunit of system Xc^-), which facilitates the exchange of extracellular cystine for intracellular glutamate. NRF2 also transcriptionally regulates thioredoxin and thioredoxin reductase 1, both of which facilitate the reduction of cystine to cysteine. Furthermore, NRF2 enhances the expression of solute carrier family A1 member 5, a critical transporter for glutamine uptake, thereby contributing to the biosynthesis of GSH (**Figure 1**).

Potential crosstalk between ferroptosis and other forms of cell death in sepsis

A complex interplay exists between ferroptosis and other forms of cell death, including apoptosis, necrosis, and pyroptosis, during sepsis, influencing both disease pathogenesis and therapeutic strategies.

• Ferroptosis and Apoptosis: Apoptosis, a programmed cell death modality orchestrated by caspase family proteases, involves key processes such as cytochrome C release, caspase-3 and caspase-7 activation, nuclear condensation, and membrane blebbing [34]. In sepsis, ferroptosis and apoptosis may reciprocally influence each other. Lipid peroxidation products generated during ferroptosis, such as MDA and ROS can activate apoptotic signaling pathways, including the mitochondrial pathway [35]. For instance, in sepsis-associated myocardial injury, upregulation of ferroptosis markers, such as cyclooxygenase-2, is closely associated with increased cardiomyocyte apoptosis. Conversely, the loss of cell membrane integrity during apop-

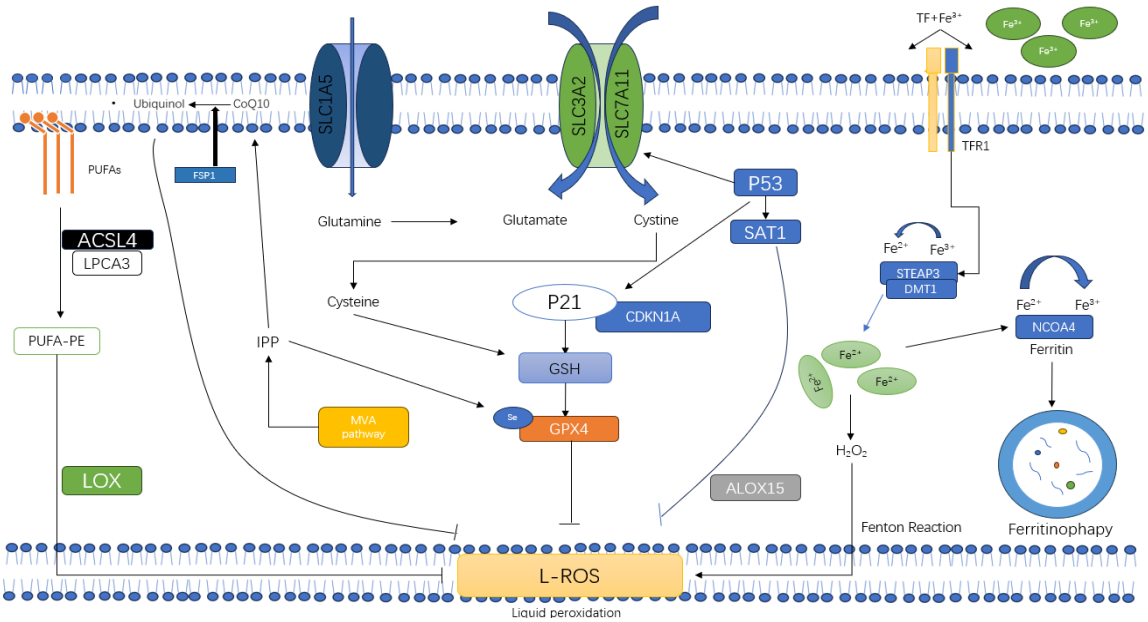

Figure 1. Ferroptosis-related signaling pathways. GSH, glutathione; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; SLC1A5, solute carrier family 1 member 5; TF, transferrin; TFR1, the transferrin receptor 1; NCOA4, nuclear receptor coactivator 4; DMT1, divalent metal transporter 1; P53, a tumor suppressor protein; SAT1, spermine N^1-acetyltransferase 1; CDKN1A, Cyclin-dependent kinase inhibitor 1A; ALOX15, 15-lipoxygenase; PUFA-PE, oxidation of polyunsaturated phosphatidylethanolamines; LOX, lectin-like oxidized low-density lipoprotein receptor; ACSL4, acyl-CoA, synthetase long chain family member 4; PUFAs, polyunsaturated fatty acids.

tosis may also promote the release of iron ions, thereby exacerbating ferroptosis [36].

• Ferroptosis and Necrosis: Ferroptosis and necrosis may also interact in sepsis. Necrosis, a more drastic form of cell death than ferroptosis, is typically characterized by the loss of cell membrane integrity, cellular swelling, and leakage of cellular contents [21, 37]. In ferroptosis, the intracellular accumulation of iron ions promotes lipid peroxidation, leading to damage and dysfunction of the cell membrane. Necrosis, however, is more often triggered by severe changes in the cellular environment (e.g., ischemia, hypoxia, infection), resulting in the disruption of cellular structures [38]. Concurrently, lipid peroxidation products (e.g., MDA) and ROS generated during ferroptosis can further damage the cell membrane, leading to the loss of membrane integrity and necrosis. The release of cellular contents during necrosis can exacerbate local inflammatory responses, which in turn may promote the occurrence of ferroptosis.

• Ferroptosis and Pyroptosis: Pyroptosis is a form of programmed cell death triggered by inflammasome activation. The central mechanisms involve the activation of caspase-1, cleavage of Gasdermin D, and the formation of membrane pores, resulting in the release of cellular contents and inflammatory responses [39]. In the context of ferroptosis, the generation of ROS and lipid peroxidation products exacerbates intracellular oxidative stress [40]. This increased stress may activate inflammasomes, subsequently triggering pyroptosis. Concurrently, the release of cellular contents during pyroptosis further amplifies the localized inflammatory response, which could, in turn, promote ferroptosis through various pathways [41].

Ferroptosis in sepsis

Sepsis is a life-threatening condition triggered by an uncontrolled immune response, leading to organ dysfunction and often causing mortality in critically ill patients, particularly in Intensive Care Units [42]. It is defined as a clinical syndrome characterized by a systemic inflammatory response to infection. The immune response in sepsis is multifactorial, typically described as comprising two components [43]. The first component is a state of excessive inflammation, driven by the systemic inflammatory response to infection [44]. Damage-associated molecular patterns interact with pattern recognition receptors expressed on the surface of immune cells, resulting in the release of pro-inflammatory cytokines and chemokines, as well as the mobilization of immune cells to the site of inflammation, thereby exacerbating inflammation and organ dysfunction. The second component is an immunosuppressive phase,

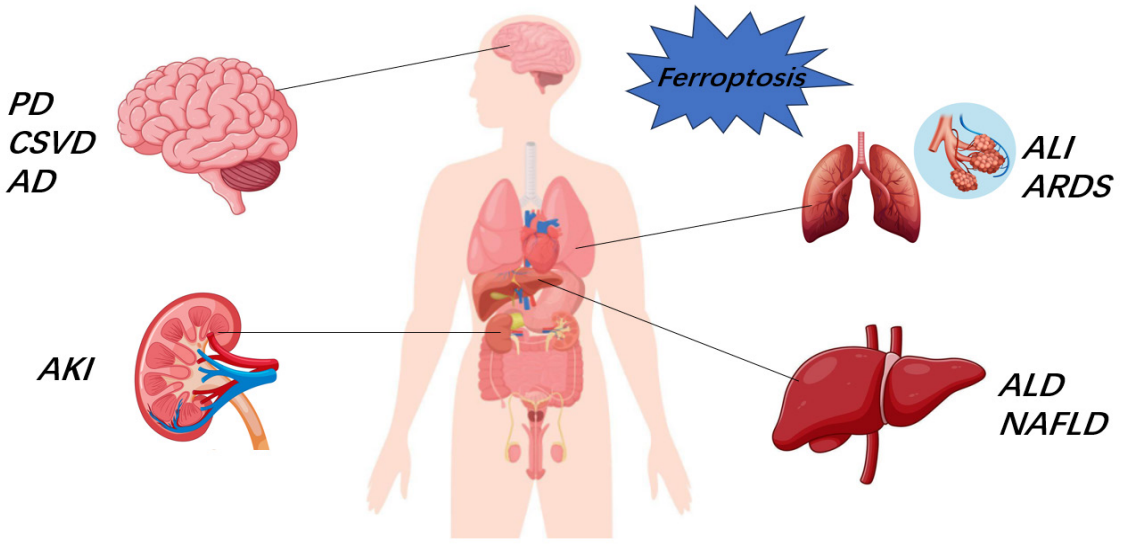

Figure 2. Diseases associated with ferroptosis. PD, Parkinson's disease; CSVD, cerebral small vessel disease; AD, Alzheimer's disease; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease.

which increases susceptibility to secondary infections [45]. Various forms of cell death play a critical role in both the excessive inflammation and the immunosuppressive state in sepsis, regardless of whether they involve immune or non-immune cells. Ferroptosis alters the immune response in both immune and non-immune cells and significantly contributes to disease progression.

Iron overload and its role in bacterial infection-induced sepsis

Iron plays a crucial role in the metabolic processes of pathogenic microorganisms during sepsis. Certain bacteria, such as Escherichia coli and Klebsiella pneumoniae, are highly dependent on iron for virulence [46-48]. In the early stages of infection, iron-induced cell death in intestinal epithelial cells compromises the intestinal barrier, facilitating the entry of harmful gut bacteria and toxins into the bloodstream and extravascular tissues [49]. To mitigate iron uptake and alleviate infection, the body employs a defensive strategy that involves reducing serum iron levels, increasing tissue iron sequestration, and sequestering iron from bacteria through cytoplasmic mechanisms [50]. However, excessive intracellular free iron not only exacerbates the inflammatory response but also induces cell death through oxidative reactions. During sepsis, macrophages, essential immune cells, are activated via Toll-like receptors, thereby activating the immune response. Iron-induced cell death can impair macrophage autophagy via the PI3K/AKT/mTOR signaling pathway, disrupting the clearance of inflammatory mediators and promoting the release of damage-associated molecular patterns, ultimately intensifying the inflammatory response [51]. Lipid peroxidation in sepsis arises during the immune response to infection, leading to elevated levels of ROS and reactive oxygen intermediates, which interact with lipids in cell membranes and trigger lipid peroxidation. The byproducts of this process, such as MDA and 4-hydroxy-2-nonenal (HNE), further exacerbate sepsis [52]. Notably, HNE can inhibit ATP-triggered cell death by suppressing GPX4, while promoting ferroptosis-related responses [53]. In macrophages, ferroptosis is characterized by substantial increases in both intracellular iron and lipid peroxidation. Ferroptosis inducers, such as RSL3, sulfasalazine, and acetaminophen, enhance the bactericidal activity of macrophages [54]. However, the inhibition of GPX4 caused by lipid peroxidation can disrupt the binding of T cell receptor (TCR) to T cells, affecting the homeostatic survival of CD8 T cells and the proliferation of $CD4^+$ and $CD8^+$ T cells in response to infection, thereby diminishing the body's immune response to infections. Thus, ferroptosis acts as a double-edged sword: while it facilitates bacterial entry into the body and contributes to the initiation of sepsis, it can also help immune cells eliminate pathogens [55].

Ferroptosis in organ damage during sepsis

Recent studies have highlighted the significant role of ferroptosis in the pathogenesis of sepsis [56, 57]. Given that sepsis affects multiple organ systems, ferroptosis contributes notably to organ damage across various sites (**Figure 2**) [58].

The role of ferroptosis in sepsis-related brain injury

Ferroptosis is crucial in the context of sepsis-related brain injury. The systemic inflammatory response triggered by sepsis can alter the brain's microenvironment, disrupting the iron metabolism balance in brain cells. During septic encephalopathy, the abnormal accumulation of iron ions can generate substantial amounts of hydroxyl radicals through the Fenton reaction, resulting in lipid peroxidation, membrane damage, and ultimately neuronal injury and cognitive dysfunction [59]. Studies have shown that the levels of iron ions in the brain tissue of sepsis patients are significantly elevated and positively correlate with the severity of neurological injury [60, 61]. As a catalyst in the Fenton reaction, the excessive accumulation of iron ions can exacerbate oxidative stress, further promoting neuronal damage. One key factor in sepsis-related brain injury is the disruption of the blood-brain barrier [2]. The abnormal translocation of iron ions across the blood-brain barrier intensifies oxidative stress in the brain, promoting ferroptosis and exacerbating brain tissue damage.

The role of ferroptosis in sepsis-related lung injury

Acute lung injury and acute respiratory distress syndrome are common complications in sepsis, with ferroptosis playing a significant role in their progression [62]. The accumulation of iron ions in alveolar epithelial cells and endothelial cells promotes lipid peroxidation, leading to cell membrane rupture and the disruption of the alveolar-capillary barrier. This causes pulmonary edema and impaired gas exchange. Excessive accumulation of iron ions in these cells increases the permeability of the alveolar-capillary barrier by activating lipid peroxidation pathways, representing a critical mechanism in the development of acute lung injury/acute respiratory distress syndrome. Additionally, iron ions can influence the progression of sepsis-related lung injury by modulating pulmonary inflammatory responses [63]. Iron-induced oxidative stress activates the release of inflammatory mediators such as tumor necrosis factor-alpha and interleukin-6, exacerbating lung inflammation.

The role of ferroptosis in sepsis-related liver injury

The liver, as the primary organ involved in iron metabolism, is highly susceptible to damage during sepsis. Ferroptosis significantly impacts liver function, primarily through direct damage to hepatocytes. Extensive hepatocyte death disrupts the liver's metabolic, detoxification, and synthetic functions, further exacerbating the pathological progression of sepsis. Additionally, the inflammatory response triggered by ferroptosis recruits immune cells, leading to disturbances in the hepatic microenvironment and impairing liver function [64, 65]. The accumulation of iron ions within hepatocytes promotes oxidative stress and lipid peroxidation, resulting in hepatocyte injury and liver dysfunction [66]. Furthermore, iron ions modulate the liver's inflammatory response, with iron-induced oxidative stress enhancing the release of inflammatory cytokines, intensifying liver inflammation and damage.

The role of ferroptosis in sepsis-related kidney injury

The kidneys are another organ vulnerable to damage during sepsis. Renal tubular epithelial cells are particularly sensitive to iron overload in the septic state [67]. During the septic state, the body's inflammatory response leads to an increased release of iron ions, especially within the renal tubular cells. The accumulation of iron ions in these cells promotes lipid peroxidation, resulting in cellular dysfunction and tubular necrosis, which impairs the kidneys' filtration and excretion capabilities. Iron overload within renal tubular epithelial cells contributes to cellular damage and dysfunction through the activation of oxidative stress pathways, representing a critical mechanism underlying sepsis-associated acute kidney injury [67]. Additionally, iron ions can influence the progression of sepsis-related kidney injury by modulating the renal inflammatory response. Iron-induced oxidative stress triggers the release of inflammatory mediators, exacerbating renal inflammation and damage.

Targeting ferroptosis for sepsis treatment

Targeted therapies for ferroptosis

Targeting ferroptosis in sepsis involves modulating key mechanisms such as iron ion accumulation, lipid peroxidation, and the inhibition of GPX4 activity [68]. Potential therapeutic targets include:

• ACSL4 and lysolipid phosphatidylcholine acyltransferases 3: these enzymes are important drivers of ferroptosis. They promote lipid peroxidation by catalyzing the esterification and oxidation of polyunsaturated fatty acids. Studies have found that inhibiting the activity of ACSL4

can reduce tissue damage associated with ferroptosis [69-71].

• SLC7A11: As a key subunit of the system Xc^-, SLC7A11 affects intracellular glutathione levels by regulating the uptake of cystine, thereby regulating the sensitivity of ferroptosis.

• Ferroptosis suppressor protein 1: Ferroptosis suppressor protein 1 protects cells from ferroptosis by regulating ubiquinone levels) [38, 72, 73]. Targeting ferroptosis suppressor protein 1 has been shown to enhance the sensitivity of lung cancer cells to radiation.

Ferroptosis therapies in clinical settings include ferroptosis agonists and inhibitors (e.g., Fer-1). Ferroptosis agonists induce cell ferroptosis by promoting iron ion accumulation, lipid peroxidation, or inhibiting antioxidant systems. For example, arginine has been identified as a ferroptosis promoter, which regulates ferroptosis through polyamine metabolism, making cancer cells more susceptible to radiotherapy and chemotherapy [74]. Ferroptosis inhibitors protect cells from damage by blocking key ferroptotic pathways. For example, preserving GPX4 or regulating iron metabolism-related proteins (e.g., SLC7A11) can reduce intracellular lipid peroxidation and iron ion accumulation. In sepsis research, the ferroptosis inhibitor Fer-1 has been shown to significantly restore pericyte viability, reduce lipid ROS content, lower inflammatory cytokine levels, and ameliorate pulmonary vascular barrier dysfunction [75].

Other factors influencing ferroptosis susceptibility and therapeutic response

• Genetic factors: Studies have revealed that genetic variations play a significant role in determining cellular sensitivity to ferroptosis [76-78]. For instance, p53 tumor suppressor can sensitize cells to ferroptosis by inhibiting the transcription of the *SLC7A11* gene [79]. Conversely, NRF2 can protect cells from ferroptosis by upregulating *SLC7A11*.

• Polyamine metabolism: Studies from Fudan University have discovered that iron overload activates ornithine decarboxylase 1 through the WNT/MYC signaling pathway, promoting polyamine synthesis, which forms a positive feedback loop that amplifies ferroptosis. Interestingly, cancer cells with polyamine overload are not only more susceptible to ferroptosis but can also transmit this sensitivity to surrounding cells via extracellular vesicles [74].

Comorbidities influencing ferroptosis susceptibility

• Depression: Increased iron deposition in the brain of patients with depression has been linked to increased susceptibility to ferroptosis. Iron catalyzes the generation of harmful hydroxyl radicals through the Fenton reaction, leading to DNA oxidation and lipid damage, which in turn compromise neurotransmitter synthesis and the function of nerve cells [80].

• Diabetes: In type 1 diabetes, pancreatic β-cells are extremely sensitive to oxidative stress. Stimuli such as hyperglycemia and hyperlipidemia significantly increase oxidative stress in β-cells, thereby amplifying their susceptibility to ferroptosis [81]. In patients with hereditary hemochromatosis, the accumulation of iron in β-cells can induce cell death, leading to the development of diabetes.

• Cardiovascular Diseases: Cardiovascular diseases are closely associated with ferroptosis, oxidative stress, and inflammatory responses. Research indicates that ferroptosis may exacerbate the pathological processes of cardiovascular diseases by augmenting oxidative stress and inflammatory responses [82, 83].

• Tumors: In the tumor microenvironment, dysregulation of iron metabolism and increased oxidative stress in tumor cells render them more susceptible to ferroptosis. Studies have shown that targeting ferroptosis pathways can enhance the sensitivity of tumor cells to chemotherapy and radiotherapy [84, 85].

The response to ferroptosis inhibitors or inducers varies among individuals. For instance, neonatal hypoxic-ischemic encephalopathy can be mitigated by Fer-1, but this therapeutic effect is influenced by genetic factors and the severity of the disease. Combining ferroptosis inhibitors with other therapeutic modalities, such as chemotherapy or radiotherapy, has shown promise in improving therapeutic outcomes. For example, in the treatment of gliomas, combined use of ferroptosis inhibitors and radiotherapy can enhance therapeutic efficacy [86].

Controversies and unresolved issues in the study of ferroptosis in sepsis

While many studies suggest ferroptosis plays a significant role in the development and progression of sepsis, there remains a debate regarding whether ferroptosis is a primary cause of sepsis or merely a secondary event in the disease's pathophysiology. For instance, some studies have found that iron chelators can re-

duce iron ion concentrations, inhibit the occurrence of cellular ferroptosis, and thus improve the survival rate of sepsis patients [87, 88]. However, other studies propose that ferroptosis may be a consequence of systemic inflammatory response syndrome and multiple organ dysfunction syndrome, rather than a direct initiator of sepsis pathology [89, 90].

Currently, the detection methods for ferroptosis are not fully standardized, and there are differences in the detection indicators and methods used across studies. For example, some studies assess the occurrence of ferroptosis by detecting intracellular iron content and lipid peroxidation products (e.g., MDA levels), while other studies rely on specific cellular morphological changes, such as loss of cell membrane integrity or mitochondrial shrinkage [62]. This lack of uniformity complicates the interpretation of ferroptosis' role in sepsis and hinders the development of reliable biomarkers for clinical application [59].

The precise molecular mechanisms underlying ferroptosis, particularly in the context of sepsis, remain incompletely elucidated. While iron metabolism and lipid peroxidation are well-established triggers, the roles of key regulatory proteins, such as ACSL4 and GPX4, as well as the intricate signaling pathways involved (e.g., Nrf2/ARE pathway, ferroptosis-related autophagy), require further investigation [74].

Sepsis can induce multi-organ dysfunction, yet the roles and mechanisms of ferroptosis in different organs remain unclear. For example, whether ferroptosis plays a consistent role in sepsis-associated complications like myocardial injury and acute kidney injury, as well as the specific mechanisms and targets in different organs, warrants further study.

Although some studies have explored the potential therapeutic value of ferroptosis inhibitors in sepsis treatment, effective clinical strategies and drugs are currently lacking [91, 92]. For example, while iron chelators have demonstrated therapeutic potential in experimental studies, their clinical application faces challenges, including drug toxicity, administration routes, and dosage issues. Moreover, formulating personalized ferroptosis intervention strategies based on individual differences, such as genetic background and disease severity, is a critical issue that needs to be addressed.

III Summary

This review summarizes the mechanisms of ferroptosis, its primary biological responses, and its role in the pathogenesis of sepsis. Ferroptosis plays a significant role in the inflammatory processes of sepsis, contributing not only to direct cell damage but also to the amplification and persistence of the inflammatory response. However, the molecular mechanisms and regulatory networks governing ferroptosis in sepsis remain insufficiently understood. Further research is essential to unravel these processes, which could lead to novel therapeutic approaches for more effective clinical treatment. Additionally, the identification and validation of biomarkers related to ferroptosis hold promise for early diagnosis and precision treatment of sepsis. As our understanding of the mechanisms of ferroptosis continues to evolve, there is potential for it to bring new hope and direction in the clinical treatment of sepsis.

Author contributions: Yu Xiang: research design, data analysis, and drafting of the manuscript; Jiameng Liu: data collection and partial data analysis; Huan Li: conceptualization and theoretical support; Kecheng Zhai: software operation; Xingchen Yue: figure generation; Corresponding Author (Shangping Fang): overall planning and coordination of the research, as well as the final review of the manuscript.

References

[1] Wang M, Gao Q, Guo S. Diagnostic and prognostic significance of apelin-13, APJ for sepsis in the emergency department: A prospective study. Heliyon 2024;10(7):e28620.

[2] Pan S, Lv Z, Wang R, et al. Sepsis-Induced Brain Dysfunction: Pathogenesis, Diagnosis, and Treatment. Oxid Med Cell Longev 2022;2022:1328729.

[3] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200-211.

[4] Gańczak M, Miazgowski T, Kożybska M, et al. Changes in disease burden in Poland between 1990-2017 in comparison with other Central European countries: A systematic analysis for the Global Burden of Disease Study 2017. PLoS One 2020;15(3):e0226766.

[5] Xu J, Tao L, Jiang L, et al. Moderate Hypothermia Alleviates Sepsis-Associated Acute Lung Injury by Suppressing Ferroptosis Induced by Excessive Inflammation and Oxidative Stress via the Keap1/GSK3β/Nrf2/GPX4 Signaling Pathway. J Inflamm Res 2024;17(0):7687-7704.

[6] Evans L, Rhodes A, Alhazzani W, et al.

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181-1247.
[7] Oczkowski S, Alshamsi F, Belley-Cote E, et al. Surviving Sepsis Campaign Guidelines 2021: highlights for the practicing clinician. Pol Arch Intern Med 2022;132(7-8):16290.
[8] Vandewalle J, Libert C. Sepsis: a failing starvation response. Trends Endocrinol Metab 2022;33(4):292-304.
[9] Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 2022;185(14):2401-2421.
[10] Chen T, Liang L, Wang Y, et al. Ferroptosis and cuproptposis in kidney Diseases: dysfunction of cell metabolism. Apoptosis: an international journal on programmed cell death 2024;29(3-4):289-302.
[11] Gan B. ACSL4, PUFA, and ferroptosis: new arsenal in anti-tumor immunity. Signal transduction and targeted therapy 2022;7(1):128.
[12] Gao M, Yi J, Zhu J, et al. Role of Mitochondria in Ferroptosis. Mol Cell 2019;73(2):354-363. e353.
[13] Liu J, Kang R, Tang D. Signaling pathways and defense mechanisms of ferroptosis. Febs j 2022;289(22):7038-7050.
[14] Wang L, Liu Y, Du T, et al. ATF3 promotes erastin-induced ferroptosis by suppressing system Xc(). Cell Death Differ 2020;27(2):662-675.
[15] Liang D, Feng Y, Zandkarimi F, et al. Ferroptosis surveillance independent of GPX4 and differentially regulated by sex hormones. Cell 2023;186(13):2748-2764.e2722.
[16] Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell 2017;171(2):273-285.
[17] Sun Y, Chen P, Zhai B, et al. The emerging role of ferroptosis in inflammation. Biomed Pharmacother 2020;127:110108.
[18] Liang D, Minikes AM, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell 2022;82(12):2215-2227.
[19] Battaglia AM, Chirillo R, Aversa I, et al. Ferroptosis and Cancer: Mitochondria Meet the "Iron Maiden" Cell Death. Cells 2020;9(6):1505.
[20] Mortensen MS, Ruiz J, Watts JL. Polyunsaturated Fatty Acids Drive Lipid Peroxidation during Ferroptosis. Cells 2023;12(5):804.
[21] Li J, Cao F, Yin HL, et al. Ferroptosis: past, present and future. Cell Death Dis 2020;11(2):88.
[22] Tang D, Chen X, Kang R, et al. Ferroptosis: molecular mechanisms and health implications. Cell Res 2021;31(2):107-125.
[23] Bogdan AR, Miyazawa M, Hashimoto K, et al. Regulators of Iron Homeostasis: New Players in Metabolism, Cell Death, and Disease. Trends Biochem Sci 2016;41(3):274-286.
[24] Outten FW, Theil EC. Iron-based redox switches in biology. Antioxid Redox Signal 2009;11(5):1029-1046.
[25] Kerins MJ, Ooi A. The Roles of NRF2 in Modulating Cellular Iron Homeostasis. Antioxid Redox Signal 2018;29(17):1756-1773.
[26] Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol 2021;22(4):266-282.
[27] Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012;149(5):1060-1072.
[28] Kennedy L, Sandhu JK, Harper ME, et al. Role of Glutathione in Cancer: From Mechanisms to Therapies. Biomolecules 2020;10(10):1429.
[29] Yao J, Li J, Xiong D, et al. Development of a highly efficient and specific L-theanine synthase. Appl Microbiol Biotechnol 2020;104(8):3417-3431.
[30] He F, Zhang P, Liu J, et al. ATF4 suppresses hepatocarcinogenesis by inducing SLC7A11 (xCT) to block stress-related ferroptosis. J Hepatol 2023;79(2):362-377.
[31] Ursini F, Maiorino M. Lipid peroxidation and ferroptosis: The role of GSH and GPx4. Free Radic Biol Med 2020;152:175-185.
[32] Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the Hallmarks of Cancer. Cancer Cell 2018;34(1):21-43.
[33] Anandhan A, Dodson M, Shakya A, et al. NRF2 controls iron homeostasis and ferroptosis through HERC2 and VAMP8. Sci Adv 2023;9(5):eade9585.
[34] Ai Y, Meng Y, Yan B, et al. The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death. Mol Cell 2024;84(1):170-179.
[35] Li J, Jia YC, Ding YX, et al. The crosstalk between ferroptosis and mitochondrial dynamic regulatory networks. Int J Biol Sci 2023;19(9):2756-2771.
[36] Dai E, Chen X, Linkermann A, et al. A guideline on the molecular ecosystem regulating ferroptosis. Nat Cell Biol 2024;26(9):1447-1457.
[37] Hassannia B, Van Coillie S, Vanden Berghe T. Ferroptosis: Biological Rust of Lipid Membranes. Antioxid Redox Signal 2021;35(6):487-509.
[38] Feng H, Yu J, Xu Z, et al. SLC7A9 suppression increases chemosensitivity by inducing

ferroptosis via the inhibition of cystine transport in gastric cancer. EBioMedicine 2024;109:105375.
[39] Tan Y, Chen Q, Li X, et al. Pyroptosis: a new paradigm of cell death for fighting against cancer. J Exp Clin Cancer Res 2021;40(1):153.
[40] Jin X, Tang J, Qiu X, et al. Ferroptosis: Emerging mechanisms, biological function, and therapeutic potential in cancer and inflammation. Cell Death Discov 2024;10(1):45.
[41] Newton K, Strasser A, Kayagaki N, et al. Cell death. Cell 2024;187(2):235-256.
[42] Srzić I, Nesek Adam V, Tunjić Pejak D. SEPSIS DEFINITION: WHAT'S NEW IN THE TREATMENT GUIDELINES. Acta Clin Croat 2022;61(Suppl 1):67-72.
[43] Shimizu J, Murao A, Nofi C, et al. Extracellular CIRP Promotes GPX4-Mediated Ferroptosis in Sepsis. Front Immunol 2022;13:903859.
[44] Aziz M, Jacob A, Yang WL, et al. Current trends in inflammatory and immunomodulatory mediators in sepsis. J Leukoc Biol 2013;93(3):329-342.
[45] Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 2013;13(3):260-268.
[46] Snyder CC, Barton JR, Habli M, et al. Severe sepsis and septic shock in pregnancy: indications for delivery and maternal and perinatal outcomes. J Matern Fetal Neonatal Med 2013;26(5):503-506.
[47] Barton JR, Sibai BM. Severe sepsis and septic shock in pregnancy. Obstet Gynecol 2012;120(3):689-706.
[48] Postelnicu R, Evans L. Monitoring of the physical exam in sepsis. Curr Opin Crit Care 2017;23(3):232-236.
[49] Yang T, Feng X, Zhao Y, et al. Dexmedetomidine Enhances Autophagy via α2-AR/AMPK/mTOR Pathway to Inhibit the Activation of NLRP3 Inflammasome and Subsequently Alleviates Lipopolysaccharide-Induced Acute Kidney Injury. Front Pharmacol 2020;11:790.
[50] Ma D, Jiang P, Jiang Y, et al. Effects of Lipid Peroxidation-Mediated Ferroptosis on Severe Acute Pancreatitis-Induced Intestinal Barrier Injury and Bacterial Translocation. Oxid Med Cell Longev 2021;2021:6644576.
[51] Wang J, Zhu Q, Wang Y, et al. Irisin protects against sepsis-associated encephalopathy by suppressing ferroptosis via activation of the Nrf2/GPX4 signal axis. Free Radic Biol Med 2022;187:171-184.
[52] Huang Q, Ding Y, Fang C, et al. The Emerging Role of Ferroptosis in Sepsis, Opportunity or Challenge? Infect Drug Resist 2023;16:5551-5562.
[53] Li F, Wang S, Zhou Y, et al. [Signal transducer and activator of transcription 6 mediates skeletal muscle cell injury in septic mice by regulating ferroptosis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2023;35(8):813-817.
[54] Ma R, Fang L, Chen L, et al. Ferroptotic stress promotes macrophages against intracellular bacteria. Theranostics 2022;12(5):2266-2289.
[55] Matsushita M, Freigang S, Schneider C, et al. T cell lipid peroxidation induces ferroptosis and prevents immunity to infection. J Exp Med 2015;212(4):555-568.
[56] Lai K, Song C, Gao M, et al. Uridine Alleviates Sepsis-Induced Acute Lung Injury by Inhibiting Ferroptosis of Macrophage. Int J Mol Sci 2023;24(6):5093.
[57] Zhang H, Liu J, Zhou Y, et al. Neutrophil extracellular traps mediate m(6)A modification and regulates sepsis-associated acute lung injury by activating ferroptosis in alveolar epithelial cells. Int J Biol Sci 2022;18(8):3337-3357.
[58] Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, et al. Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection. Cell 2020;181(5):969-977.
[59] Zeng F, Nijiati S, Tang L, et al. Ferroptosis Detection: From Approaches to Applications. Angew Chem Int Ed Engl 2023;62(35):e202300379.
[60] Du L, Wu Y, Fan Z, et al. The Role of Ferroptosis in Nervous System Disorders. J Integr Neurosci 2023;22(1):19.
[61] David S, Jhelum P, Ryan F, et al. Dysregulation of Iron Homeostasis in the Central Nervous System and the Role of Ferroptosis in Neurodegenerative Disorders. Antioxid Redox Signal 2022;37(1-3):150-170.
[62] Wu D, Spencer CB, Ortoga L, et al. Histone lactylation-regulated METTL3 promotes ferroptosis via m6A-modification on ACSL4 in sepsis-associated lung injury. Redox Biol 2024;74:103194.
[63] Xu F, Xie J, Mou W, et al. The VDR/FFAR2 axis mitigates sepsis-induced lung injury by suppressing macrophage lipid peroxidation. Int Immunopharmacol 2024;143(Pt 2):113328.
[64] Valenti L, Corradini E, Adams LA, et al. Consensus Statement on the definition and classification of metabolic hyperferritinaemia. Nat Rev Endocrinol 2023;19(5):299-310.
[65] Valenti L, Corradini E, Adams LA, et al. Author Correction: Consensus Statement on the definition and classification of metabolic hyperferritinaemia. Nat Rev Endocrinol

2024;20(3):185.
[66] Zhu Z, Chambers S, Bhatia M. Suppressing the Substance P-NK1R Signalling Protects Mice against Sepsis-Associated Acute Inflammatory Injury and Ferroptosis in the Liver and Lungs. Antioxidants (Basel) 2024;13(3):300.
[67] Vlahakos D, Arkadopoulos N, Kostopanagiotou G, et al. Deferoxamine attenuates lipid peroxidation, blocks interleukin-6 production, ameliorates sepsis inflammatory response syndrome, and confers renoprotection after acute hepatic ischemia in pigs. Artif Organs 2012;36(4):400-408.
[68] Meng Y, Sun H, Li Y, et al. Targeting Ferroptosis by Ubiquitin System Enzymes: A Potential Therapeutic Strategy in Cancer. Int J Biol Sci 2022;18(14):5475-5488.
[69] Cui Y, Zhang Y, Zhao X, et al. ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. Brain Behav Immun 2021;93:312-321.
[70] Wang Y, Zhang M, Bi R, et al. ACSL4 deficiency confers protection against ferroptosis-mediated acute kidney injury. Redox Biol 2022;51:102262.
[71] Liao P, Wang W, Wang W, et al. CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. Cancer Cell 2022;40(4):365-378.e366.
[72] Koppula P, Lei G, Zhang Y, et al. A targetable CoQ-FSP1 axis drives ferroptosis- and radiation-resistance in KEAP1 inactive lung cancers. Nat Commun 2022;13(1):2206.
[73] Bersuker K, Hendricks JM, Li Z, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature 2019;575(7784):688-692.
[74] Bi G, Liang J, Bian Y, et al. Polyamine-mediated ferroptosis amplification acts as a targetable vulnerability in cancer. Nat Commun 2024;15(1):2461.
[75] Liu Y, Bao D, She H, et al. Role of Hippo/ACSL4 axis in ferroptosis-induced pericyte loss and vascular dysfunction in sepsis. Redox Biol 2024;78:103353.
[76] Huang B, Wang H, Liu S, et al. Palmitoylation-dependent regulation of GPX4 suppresses ferroptosis. Nat Commun 2025;16(1):867.
[77] Wang G, Qin S, Chen L, et al. Butyrate dictates ferroptosis sensitivity through FFAR2-mTOR signaling. Cell Death Dis 2023;14(4):292.
[78] Dixon SJ, Olzmann JA. The cell biology of ferroptosis. Nat Rev Mol Cell Biol 2024;25(6):424-442.
[79] Jiang L, Kon N, Li T, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015;520(7545):57-62.
[80] Zhang Y, Wang M, Chang W. Iron dyshomeostasis and ferroptosis in Alzheimer's disease: Molecular mechanisms of cell death and novel therapeutic drugs and targets for AD. Front Pharmacol 2022;13:983623.
[81] Dai L, Wang Q. Targeting ferroptosis: opportunities and challenges of mesenchymal stem cell therapy for type 1 diabetes mellitus. Stem Cell Res Ther 2025;16(1):47.
[82] Li N, Jiang W, Wang W, et al. Ferroptosis and its emerging roles in cardiovascular diseases. Pharmacol Res 2021;166:105466.
[83] Fang X, Ardehali H, Min J, et al. The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nat Rev Cardiol 2023;20(1):7-23.
[84] Wang Y, Wang W, Zhang Y, et al. Targeting ferroptosis offers therapy choice in sepsis-associated acute lung injury. Eur J Med Chem 2025;283:117152.
[85] Sun S, Shen J, Jiang J, et al. Targeting ferroptosis opens new avenues for the development of novel therapeutics. Signal Transduct Target Ther 2023;8(1):372.
[86] Wan S, Zhang G, Liu R, et al. Pyroptosis, ferroptosis, and autophagy cross-talk in glioblastoma opens up new avenues for glioblastoma treatment. Cell Commun Signal 2023;21(1):115.
[87] Tao L, Yang X, Ge C, et al. Integrative clinical and preclinical studies identify FerroTerminator1 as a potent therapeutic drug for MASH. Cell Metab 2024;36(10):2190-2206.e2195.
[88] Chen Y, Li X, Wang S, et al. Targeting Iron Metabolism and Ferroptosis as Novel Therapeutic Approaches in Cardiovascular Diseases. Nutrients 2023;15(3):591.
[89] Li H, Wu D, Zhang H, et al. New insights into regulatory cell death and acute pancreatitis. Heliyon 2023;9(7):e18036.
[90] Van Coillie S, Van San E, Goetschalckx I, et al. Targeting ferroptosis protects against experimental (multi)organ dysfunction and death. Nat Commun 2022;13(1):1046.
[91] Xl L, Gy Z, R G, et al. Ferroptosis in sepsis: The mechanism, the role and the therapeutic potential. Front Immunol 2022;13:956361.
[92] Huo L, Liu C, Yuan Y, et al. Pharmacological inhibition of ferroptosis as a therapeutic target for sepsis-associated organ damage. Eur J Med Chem 2023;257:115438.