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REVIEW

The Emerging Role of Ferroptosis in Sepsis, Opportunity or Challenge?

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Abstract: Sepsis is a syndrome in multi-organ dysfunction triggered by a deleterious immunological reaction of the body to a condition caused by infection, surgery, or trauma. Currently, sepsis is thought to be primarily associated with abnormal immune responses resulting in organ microcirculatory disturbances, cellular mitochondrial dysfunction, and induced cell death, although the exact pathogenesis of sepsis is still inconclusive. In recent years, the role of abnormal metabolism of trace nutrients in the pathogenesis of sepsis has been investigated. Ferroptosis is a type of cell death that relies on iron and is characterized by unique morphological, biochemical, and genetic features. Unlike other forms of cell death, such as autophagy, apoptosis, necrosis, and pyroptosis, ferroptosis is primarily driven by lipid peroxidation. Ferroptosis cells may be immunogenic, amplify inflammatory responses, cause more cell death, and ultimately induce multi-organ failure. An increasing number of studies have indicated the significance of ferroptosis in sepsis and its role in reducing inflammation. The effectiveness of sepsis treatment has been demonstrated by the use of drugs that specifically target molecules associated with the ferroptosis pathway, including ferroptosis inhibitors. Nevertheless, there is a scarcity of studies investigating the multi-organ dysfunction caused by ferroptosis in sepsis. This article presents a summary and evaluation of recent progress in the role of ferroptosis through molecularly regulated mechanisms and its potential mechanisms of action in the multi-organ dysfunction associated with sepsis. It also discusses the current challenges and prospects in understanding the connection between sepsis and ferroptosis, and proposes innovative ideas and strategies for the treatment of sepsis.

Keywords: sepsis, ferroptosis, organ damage, lipid peroxidation, treatment

Introduction

Sepsis, a frequently encountered clinical disorder, is a severe and potentially fatal condition characterized by the malfunctioning of multiple organs. It arises due to the disruption of the body's response to infection and poses a significant threat to acutely and critically ill individuals.[1] The occurrence of sepsis among patients admitted to the hospital is approximately 52.8%, accompanied by morbidity and mortality rates ranging from 34.9% to 66.7%. This presents a substantial danger to human well-being and has a profound impact on the steady progress of the global economy and society.[2] For a long time, sepsis has been a primary worldwide clinically challenging issue.[3] However, advances in sepsis treatment have been limited to symptomatic therapies, including organ support and fluid resuscitation. There is still a void in sepsis research on effective drug development for therapy, and exploring new therapeutic directions and pathophysiology is essential. Recently, a novel type of cell death called ferroptosis has been strongly associated with the severity of sepsis, but its exact molecular biological mechanism has not been fully elucidated.[4] Exploring mechanisms and finding potential targets related to oxidative stress, ferroptosis, and other circulatory and metabolic abnormalities in sepsis, tightly correlated with lipid peroxidation and cellular ion metabolism, may provide new perspectives in sepsis treatment and management. To further clarify the role of ferroptosis in sepsis, we review the definition of ferroptosis, related mechanisms, and advances in research on ferroptosis leading to sepsis injury and identify new ideas for sepsis treatment and prevention.

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Ferroptosis is a specific type of cell death known to be suppressed by antioxidants identified in a high-throughput small-molecule screening study and iron chelators (deferrioxamine methyl sulfonate).[5] Ferroptosis was officially named in 2012 since the morphological, biochemical, and genetic characteristics are categorized in programmed cell death.[6] Intracellular iron-dependent lethal lipid peroxidation involves mechanisms such as iron overload, reactive oxygen species (ROS) generation,[7] and increased phospholipid polyunsaturated fatty acids, resulting in loss of cell membrane integrity,[8] interference with normal cell membrane function through lipid cross-linking, and oxidative damage to macromolecules and cell structures, ultimately leading to cell death.[9] Morphologically, ferroptosis is characterized by the typical phenomena of mitochondrial consolidation and loss of mitochondrial cristae.[10] Genetically, genes that regulate ferroptosis include cytochrome c oxidase-2 (COX2), acyl coenzyme a synthase long-chain family member 4 (ACSL4), glutathione peroxidase 4 (GPX4), ferritin heavy chain 1 (FTH1), nuclear factor erythroid 2-related factor 2 (Nrf2), ferroptosis-related solute carrier family 7 member 11 (SLC7A11), and arachidonate 12-oxidoreductase (ALOX12).[11–13] Biochemically, the most important is the increase in free iron (Fe^{2+}), which binds polyunsaturated fatty acids (PUFA) in the cell membrane to promote Fenton reactions[14] and induces lipid peroxidation via providing free electrons to generate lipid hydroperoxides (LOOHs).[15] When the antioxidant system is compromised, these LOOHs accumulate in excess, triggering cellular ferroptosis.[13] Typically, a dynamic balance exists between the antioxidant system, including the Xc system, glutathione, GPX4, and several newly discovered pathways, and the oxidative system, including Fe^{2+}, Fenton reaction, and ROS.[16,17] When infections and inflammation occur, this balance is disrupted and promotes the development of ferroptosis, which can lead to or exacerbate the adverse effects of the disease.[4] Iron homeostasis and disorders.[18] In sepsis, when bacteria infect the organism, iron is required for bacterial growth in vivo, and the shedding of intracellular iron releases excess intracellular iron for use by the bacteria.[19] Thus, shedding intracellular iron can become a feast for the infected bacteria.[20] At the same time, bacterial infection provides several materials for lipid peroxides, including reactive oxygen species and fatty acids,[21] which can become a vicious cycle, exacerbating the infections and consequently leading to sepsis, which can trigger multi-organ dysfunction.[22] In conclusion, there is no doubt that ferroptosis exacerbates infections by bringing in multiple sources for bacterial growth, an essential cascade in sepsis.

Whether the role of ferroptosis can be fully elucidated and whether exploring ferroptosis as a direction for intervention can bring a breakthrough in treating and diagnosing sepsis still require intensive study. The role of ferroptosis may vary depending on the etiology of sepsis.

This review explores the pathophysiological processes that contribute to ferroptosis during sepsis, along with the present state of research in this area. Our objective is to investigate the correlation between ferroptosis and sepsis and analyze the significant influence of ferroptosis on sepsis. This will offer valuable perspectives for future research on diagnosing and treating sepsis by regulating ferroptosis.

Regulatory Processes in the Development of Ferroptosis

Ferroptosis is an intracellular iron-dependent lethal lipid peroxidation reaction involving iron overload, ROS production, and increased phospholipid polyunsaturated fatty acids, leading to loss of cell membrane integrity, lipid cross-linking that disrupts normal cell membrane function, and oxidative damage to macromolecules and cell structures, ultimately resulting in cell death.[23–25] Two pathways regulate ferroptosis: a conventional pathway that depends on GPX4 and a GPX4-independent pathway. The former is the systemic Xc-glutathione (GSH)-GPX4 pathway.[26] This pathway takes up extracellular cystine via cystine-glutamate reverse transfer protein, catalyzes thioredoxin reductase 1 to produce cysteine, synthesizes GSH, and participates in GPX4-mediated reduction of intracellular PLOOH to attenuate lipid peroxidation.[27] GPX4-independent pathways include the ferroptosis suppressor protein 1 (FSP1)-ubiquinone, squalene, and tetrahydrobiopterin-mediated lipid peroxidation suppression systems, which mainly exert antioxidant effects and suppress lipid peroxidation through corresponding reduction reactions and trapping of endogenous free radicals.[28–30]

Mechanism of Ferroptosis

Abnormalities in Iron Metabolism

Iron, an important trace element, is an essential cofactor for several iron-containing enzymes.[31] Iron plays a role in multiple biochemical and physiological reactions, such as DNA synthesis, energy production, and especially redox reactions.[32]

Pathological excess of tissue iron triggers the generation of reactive oxygen species and induces oxidative stress, ferroptosis, and other toxic reactions.[33] Iron circulates and flows as Fe^{2+} and Fe^{3+} form.[34] Iron in food is primarily Fe^{3+}, which cannot be absorbed directly and is assisted by transferrin (TF), a factor involved in iron transport.[35] The primary sources of intracellular iron are Extracellular iron (Fe^{3+}) binding to transferrin receptor 1 (TFR1) via endocytosis to form endosomes and is transported into the cell via TFs.[36] Once inside the cell, Fe^{3+} in acidic endocytic vesicles is reduced to Fe^{2+} by prostate six membrane epithelial antigen (STEAP3), and Fe^{3+} transportation to the cytoplasm is induced via a divalent metal transporter 1 (DMT1)[37] Fe^{2+} has oxidative activity, and excess Fe^{2+} reacts with hydrogen peroxide to form Fe^{3+} with a robust oxidative capacity and forming hydroxyl radicals.[38] The presence of hydroxyl radicals makes the Fenton reaction a strong oxidative force and promotes the generation of ROS toxic to cells, and Fe^{2+} plays a driving role in the function of ferroptosis.[39]

On the other hand, ferroportin (Fpn) is the only iron transport protein that can attenuate ferroptosis via decreasing levels of intracellular iron;[40] overexpression of TFR1 or Fpn knockdown induces intracellular ferroptosis, while ferrostatin-1 (Fer-1) upregulated Fpn and can reduce intracellular iron levels, ameliorate lipid peroxidation, and mitigate the occurrence of ferroptosis, as confirmed by some studies.[41] Under physiological conditions, excess intracellular Fe^{2+} is oxidized to Fe^{3+} and stored in ferritin.[42] FTH1 is an essential component of transferrin and reduces intracellular free iron by performing an iron storage function.[43]

Disorders of Lipid Metabolism

Lipid peroxidation is an essential feature and step of ferroptosis development. Driven primarily by lipoxygenase, free polyunsaturated fatty acids (PUFA) are peroxidized via ROS. Essentially, it is a process in which biological membranes are oxidized by ROS, resulting in changes in cell structure and function; PUFAs have active chemistry and are most susceptible to free radicals-induced oxidation, and PUFAs on cell membranes are the main targets of ROS attack.[44] The substrates of lipid peroxidation are phospholipids, including PUFAs.[45] Studies have shown that lysophosphatidylcholine acyltransferase (LPCAT3) and ACSL4 function for phospholipid synthesis.[13] First, PUFAs, including adrenergic acyl (AdA) and arachidonic acid (AA), are produced into lipids and integrated into phospholipids consisting of plasma membrane catalyzed by ACSL4 and LPCAT3 to form the PUFAs-PL complex.[46] Then, lipid hydroperoxides are oxidized by peroxidase (LOX), at which point ferroptosis is initiated.[10] The described lipid metabolism enzymes can be a target to suppress the onset of ferroptosis, developing a new strategy for treating various disorders.[23] Patients with sepsis have been shown to have markedly elevated ROS levels due to the Fenton reaction.[47] According to this hypothesis, ROS reacts with PUFA to form toxic lipid peroxides, causing ferroptosis. At the structural level, the accumulation of ROS forms membrane pores, disrupting barrier function and altering membrane permeability.[48] At the molecular mechanics level, ROS increases the curvature of biological membranes, leading to membrane destabilization and micelle formation, and these changes induce osmotic pressure, affecting cell survival.[49] Antioxidants can terminate the above reactions by suppressing autoxidation and enzymatic destruction of PUFAs, thus preventing the occurrence of ferroptosis.[10] It is clear that lipid peroxidation and mitochondria, the leading production site of intracellular ROS, play an essential role in ferroptosis development.[27,50] The development of ferroptosis has been found to be accompanied by morphological and functional disturbances of mitochondria.[51] Thus, peroxidation of lipids is a complex and dynamic process, and by implicating it in the storage and synthesis of oxidized substrates or by affecting the critical enzyme activities, the development of ferroptosis can be further controlled, offering future promise for the therapy of various disorders such as infection and immunity.[52]

Xc-System

Xc-system is a transmembrane cystine-glutamate inversion transporter composed of a non-glycosylated light-chain subunit and an N-terminal glycosylated heavy-chain subunit.[27] Xc-system functions for cystine uptake in intracellular glutamate exchange. Cysteine, the precursor of glutathione (GSH) synthesis, is generated via intracellular degradation of cystine, so enough cysteine supply is the rate-limiting step in GSH generation.[53] GSH, the sole GPX4 substrate, functions as an in vivo endogenous antioxidant, which cleans up lipid peroxides and ROS from the cells, reducing iron-dependent cell death.[54] The principal reduction systems in the human body are glutathione and glutathione peroxidase; the intracellular concentration of GSH is regulated by the amino acid retro transport Xc-system, which, when inhibited, limits GSH synthesis and significantly increases ferroptosis.[51] GPX4 is a membrane lipid peroxide. Its

ability to reduce lipids has been determined to play a significant role in ferroptosis prevention.[55] When GPX4-mediated detoxification of lipid peroxidation is reduced to levels insufficient to inhibit membrane PUFA oxidation, ferroptosis occurs, accumulating harmful ROS for up-regulation of the GPX4 expression level significantly reduces ferroptosis.[23]

GPX4-Dependent Regulatory Pathway

GSH plays an essential role in mitigating lipid peroxidation,[56] acting as an electron donor in reactions catalyzed by GPX4, reducing toxic PLOOH to non-toxic phospholipid alcohol GPX4 acts as an antioxidant with lipid damage repair activity GPX4, the selenoprotein family, is a critical molecule to reduce peroxides (eg, R-OOH) to the corresponding alcohol (R-OH) as a primary role.[57] This antioxidant system can be utilized to counteract the ferroptotic pathway by cysteine transportation to GSH via the Xc-system, as GPX4 reduces peroxides. GPX4 also contains selenocysteine. Selenocysteine is similar in structure to cysteine, with the difference that it contains selenium instead of sulfur. Selenium is an essential element for animal living; the selenocysteine utilization by GPX4 provides excellent resistance to irreversible peroxidation, but cells expressing the cysteine mutant are susceptible to peroxide-induced ferroptosis. Selenocysteine acts as a catalytic component that ensures rapid reduction by GPX4, which also prevents ferroptosis. GPX4 prevents iron-dependent cell death by removing lipid ROS and peroxides.[58] Nrf2 serves as an essential controller of the GSH antioxidant mechanism, which has a vital function in averting ferroptosis. The induction of xCT and GPX4 expression by Nrf2 can directly inhibit ferroptosis by reducing lipid peroxides and maintaining GSH levels.[59]

GPX4-Independent Regulatory Pathways

Current research on ferroptosis focuses on oncology, where sensitivity to GPX4 inhibitors varies widely among cancer cell lines, suggesting that other factors may regulate an organism's susceptibility to ferroptosis. Apoptosis-inducing mitochondria-associated factor 2 (AIMF2) is a target gene of p53 and promotes p53-dependent apoptosis of cells.[60] AIMF2 was found to prevent cells from ferroptotic cell death, and Bersuke et al renamed FSP1.[61] FSP1 is a potent ferroptosis resistance factor, and the FSP1 over-expression reduced ferroptosis. However, when treated with apoptosis-inducing agents, FSP1 did not prevent ferroptosis.[62]

On the other hand, FSP1 can act in the cytoplasm as a redox enzyme that reduces ubiquinone. The reduction in ubiquinone produces ubiquinol, an antioxidant that scavenges lipophilic free radicals and blocks lipid peroxide accumulation.[63] It has also been shown that FSP1 protects against ferroptosis caused by GPX4 deficiency, and this protection is mediated by ubiquinone. Ubiquinone traps free radicals generated by lipid peroxidation, and FSP1 catalyzes ubiquinone regeneration via NAD(P)H. FSP1-ubiquinone-NAD(P)H functions alone with GSH-GPX4 as a system that inhibits lipid peroxidation of phospholipids and suppresses ferroptosis.[13] Thus, FSP1 functions independently of the activity of GPX4 without affecting other iron attachment pathways.

P53 in Ferroptosis Regulation

P53, a well-known protein, acts as a tumor suppressor by controlling the progression of cell cycle and apoptosis. Nevertheless, recent research indicates that p53 also has a vital function in controlling ferroptosis, an emerging type of controlled cellular demise propelled by iron-induced lipid peroxidation.[64] P53 has been demonstrated to regulate both ferroptosis pathways that rely on GPX4 and those that do not depend on GPX4. Through the GPX4-dependent route, p53 has the ability to increase the GPX4 expression,[65] which in turn decreases lipid peroxidation and safeguards against ferroptosis. Through the GPX4-independent route,[66] p53 has the ability to enhance levels of reactive oxygen species (ROS) and consequent lipid peroxidation. In addition, p53 also suppressed the expression of key components of the Xc-system, sensitizing cells to ferroptosis by inhibiting cystine uptake and inducing cell ferroptosis in response to ROS-induced stress.[67]

Ferroptosis in Sepsis

Sepsis Pathogenesis

Sepsis is a lethal disease triggered by a dysregulation of the infection-mediated immune response in the body, resulting in a life-threatening organ dysfunction syndrome.[68] Numerous studies have shown that ferroptosis alters the immune reaction of the organism in both immune and non-immune cells and functions in the progression and development of sepsis.[69]

Iron Overloaded in Sepsis

Iron is involved in critical bio-metabolic processes of pathogenic microorganisms in sepsis; for example, the virulence of certain bacteria, such as Escherichia coli and Klebsiella pneumoniae, depends on iron, which can increase the virulence of bacteria and accelerate their growth.[70] To control infection and limit the organism's access to iron, the organism must reduce serum iron, increase intracellular unstable iron, and sequester iron from bacteria through the cytoplasm, which is a defense mechanism.[71] However, excess intracellular free iron exacerbates the inflammatory response and induces cell death due to solid oxidative reactions.[72] A typical process in sepsis caused by different pathogens is that the invading pathogen triggers an innate immune response in the body.[73] Pathogen-associated molecular patterns are recognized by pattern recognition receptors on macrophages, which activate immune cells, releasing inflammatory cytokines, causing a storm of intracellular inflammatory factors and an excessive inflammatory response that ultimately leads to the immunosuppression of the organism.[74] Iron dysregulation is a notable feature that is strongly linked to the severity of sepsis,[75,76] underscoring the potential value of iron as a promising diagnostic biomarker for evaluating disease progression and predicting clinical outcomes.

In sepsis, infection stimulates increased expression of nuclear receptor coactivator 4 (NCOA4) and FTH1 associated with NCOA4. It initiates iron autophagy, degrading ferritin and releasing large amounts of iron, raising intracytoplasmic Fe^{2+}, and activating expression of mitochondrial membrane permeability protein and transporting Fe^{2+} into mitochondria, resulting in mitochondrial lipid peroxidation and death.[77–79] Knockdown of NCOA4 reduced iron autophagy and made cells more resistant to lipid peroxidation and ferroptosis.[80] Then, the application of iron chelators, which reduce iron ion concentrations, suppressed ferroptosis and improved survival of septic patients, suggesting that the development of ferroptosis requires abnormal iron metabolism as a critical step.

Lipids Peroxidized in Sepsis

During sepsis, the body's immune response to an infection can become uncontrolled, leading to widespread inflammation and organ damage. Inflammation and harm can lead to a rise in the generation of reactive oxygen species (ROS) and reactive oxygen intermediates (ROI), which can interact with lipids in cellular membranes and initiate lipid peroxidation. Consequently, the development of sepsis is facilitated by the production of lipid peroxidation byproducts such as MDA and 4-HNE. Elevated concentrations of MDA and 4-HNE have been detected in individuals with sepsis,[81,82] indicating that oxidative damage to lipids is a crucial factor in the advancement and evolution of septic conditions. In mouse models of sepsis, HNE was discovered to hinder ATP-triggered cell demise and restrain glutathione peroxidase 4, leading to decreased inflammasome activation by boosting endogenous HNE levels.[83]

Induction of lipid peroxidation by reactive oxygen species severely damages mitochondrial function. Research has shown that the lipid peroxidation product MDA can disrupt the integrity of mitochondrial membranes in septic mice.[84] Meanwhile, the initiation of STING prompts a signaling cascade that results in cell death from sepsis,[85] which includes the production of reactive oxygen species and the activation of pro-death signaling pathways.

Overall, there is a clear connection between lipid metabolism disorders, ferroptosis, and the progression of sepsis. To address the challenges posed by ferroptosis and sepsis, future research could investigate approaches for regulating lipid metabolism to promote cell membrane integrity, suppress inflammation, and improve patient outcomes.

Ferroptosis-Related Pathways in Sepsis

Wang et al,[86] it was discovered that sepsis-related encephalopathy triggered ferroptosis in the hippocampus. This was supported by increased levels of ferroptosis-associated proteins, such as GPX4, ACSL4, and SLC7A11. The lack of GPX4 results in a rise in the quantities of lipid peroxidation byproducts, which can harm cellular membranes and initiate

the creation of compounds with proteins like albumin. This process promotes the progression of sepsis.[87] Upon receiving intracellular or extracellular stimulation and pressure, p53 functions as a transcription factor that controls the expression of downstream genes, which contribute to the cellular and organismal ability to resist stimuli.[88] The Nrf2/HIF-1/TF signaling pathway is responsible for the protective impact of p53 inhibitors against sepsis induced by LPS.

Ferroptosis-Mediated Dysfunction of Multiple Organs in Sepsis

Recently, several investigations have demonstrated that ferroptosis functions for sepsis pathogenesis.[89] The severity of tissue damage and multi-organ dysfunction syndrome after sepsis is directly proportional to the degree of iron accumulation.[90] Inhibitors of ferroptosis also down-regulate the inflammation response and thus reduce the impairment of dysfunction of multi-organs resulting from sepsis.[91] Intracellular iron overload, which causes lipid peroxidation and ferroptosis, exhibits different phenotypes in the corresponding organs, and many studies on the mechanisms have been conducted in recent years.[92] In contrast, the effects of inhibitors on ferroptosis have only been investigated by non-human experimental approaches, and thus future clinical confirmation is needed.

Ferroptosis and Septic Cardiomyopathy

Septic cardiomyopathy is a common underlying sepsis complication and reversible left ventricular systolic dysfunction.[93] When sepsis is complicated by septic cardiomyopathy, the prognosis for patients tends to be poor, with significantly higher morbidity and mortality.[94] Apoptosis, autophagy, pyroptosis, and necrosis have been demonstrated to be involved in sepsis-related myocardial damage, but the exact mechanisms have not been elucidated. Recently, in LPS-induced septic cardiomyopathy mice and H9c2 myofibroblasts, the expression levels of ferroptosis markers such as prostaglandin-endoperoxide synthase 2, also known as COX2, MDA, and ROS are significantly increased which have been shown to be upregulated.[95] The changes in mitochondrial morphology were consistent with morphological changes in cells undergoing ferroptosis. This may be due to the activation of transferrin expression on mitochondrial membranes in cardiomyocytes during septicemia, which transports iron ions into the mitochondria and inhibits iron ion metabolism, resulting in ferroptosis. In in vivo and in vitro experiments, the ferroptosis inhibitor Fer-1 was found to reduce mitochondrial damage, improve cardiac function, and increase survival in septic mice, indicating that ferroptosis may function for septic cardiomyopathy as the pathogenesis.[96] It has also been shown that inhibition of ferroptosis suppresses myocardial damage, which may be related to the suppression of endoplasmic reticulum stress.[97] Therefore, it is hoped that a deeper exploration of the mechanism of ferroptosis in septic cardiomyocytes will direct the proposal of a novel approach for the prevention and treatment of septic cardiomyopathy in the future.

Ferroptosis and Sepsis-Related Lung Injury

Acute lung injury (ALI) is another common sepsis-related complication and can even cause acute respiratory distress syndrome (ARDS).[98] Increased iron ion concentrations in alveolar epithelial cells due to sepsis are another mechanism of injury. Iron overload promotes lipid peroxidation of alveolar epithelial cells, migration of neutrophils, and increased proliferation of fibroblasts, exacerbating the inflammatory response and initiating pulmonary fibrosis.[99] Ferroptosis continues to be shown to play an essential role in lung injury induced by sepsis, and researchers have developed sevoflurane (Sev) as a protective molecule against acute lung injury induced by LPS-.[100] This effect is similar to Fer-1 involved in an inhibitor of ferroptosis; Fer-1 and Sev can upregulate the expression of GPX4 and suppress expression levels of inflammation-related factors in LPS-induced acute lung injury, with similar conclusions from in vitro experiments.[101] Similarly, inhibition of ferroptosis has been shown to reduce lung injury and improve lung function. Thus, modulation of ferroptosis is thought to be a novel target for treating sepsis-associated lung injury.

Ferroptosis and Liver Injury Associated with Sepsis

The liver also plays an essential role in sepsis pathogenesis. Liver dysfunction is often seen early in the onset of sepsis and is often an independent risk factor affecting the inferior sepsis prognosis.[102] Irisin is actively secreted during exercise and restores mitochondrial dysfunction under various conditions. The pathway of ferroptosis also regulates mitochondrial function. It has been shown that GPX4 expression is significantly increased in the liver of cecal ligation and puncture (CLP) mice following irisin administration;[26] GPX4 expression, glutathione levels, mitochondrial morphology, iron

accumulation, lipid peroxidation are critical indicators to characterize ferroptosis. In septic mice, hepatic GSH levels were markedly reduced, Fe^{2+} and MDA levels were markedly upregulated, mitochondria were atrophic, and bilayer density increased.[103] Irisin treatment reversed the levels of these indices and morphologically attenuated mitochondrial damage.[104] These results demonstrate that ferroptosis is involved in liver injury in septic mice and that irisin administration can significantly reduce liver injury by decreasing liver ferroptosis and restoring mitochondrial function in septic mice, thus offering new possibilities for sepsis treatment.

Ferroptosis and Sepsis-Related Kidney Damage

Acute kidney injury occurs early in the course of sepsis, with clinical manifestations of rapid and persistent loss of renal function over a short period, leading rapidly to acute renal failure and even death.[105] Many patients with septic shock develop acute renal failure early in life. ROS-induced acute kidney injury is considered the most critical mechanism for inducing or exacerbating acute renal failure, with concurrent involvement of ferroptosis.[106] This is thought to be because iron ions are filtered by the glomerulus and reabsorbed in the renal tubules, and when the sepsis-related renal injury occurs, intravascular hemolysis, proinflammatory factors, and hemoglobin release increase renal iron ion levels and induce renal ferroptosis, the occurrence of which positively correlates with the incidence, morbidity, and mortality of sepsis-related renal injury, which correlates positively with the incidence of sepsis-related renal injury, morbidity, and mortality.[107] Ferroptosis is now considered a critical therapeutic target in acute renal failure.[108] Studies using GPX4-deficient mice have found that these mice die within 2 weeks due to massive tubular necrosis and acute renal failure and that removal of lipid peroxidation products prolongs survival.[103] Similarly, ferroptosis inhibitors in various acute kidney injury models have been found to alleviate acute kidney injury and protect the kidneys. Thus, the targeted development of ferroptosis inhibitors could more effectively treat sepsis-related renal injury.[109]

Ferroptosis and Sepsis-Related Encephalopathy

Sepsis-associated encephalopathy, a typical neurodegenerative lesion in sepsis, occurs in about 70% of patients with sepsis, and its pathogenesis involves neuroinflammation, altered neuronal function, and signaling, cerebral hyperperfusion due to microcirculatory disturbances, oxidative stress, and altered blood–brain barrier.[110] Pathogenesis is illustrated secondary to diffuse dysfunction of the brain to initiate infections in the body, without apparent infections to CNS. Its clinical manifestations range from mild discomfort and attention deficit to deep coma, with high morbidity and mortality and poor prognosis.[111] Recent studies have confirmed the role of pathogenesis for ferroptosis in sepsis-associated encephalopathy (SAE) and its protective effect through resistance to ferroptosis while examining neuroinflammation, blood–brain barrier integrity, neurological deficits, and cognitive function.[86] Extracellular NEAT1 functioned as a miR-9-5p absorber, resulting in elevated TFRC and GOT1 levels, thereby triggering ferroptosis in cerebral microvascular endothelial cells.[112]

On the other hand, Fer-1 inhibited the attenuation of ferroptosis.[113] Fer −1 decreased neurological severity scores, learning and memory deficits, and Fluoro-Jade C (FJC) staining after SAE. Acetaminophen has also been found to attenuate sepsis-induced cognitive dysfunction by inhibiting ferroptosis via the GPX4 signaling pathway.

Taken together, inhibition of ferroptosis can potentially ameliorate SAE and may represent a new target in treating SAE.

Summary and Perspectives

This article reviews recent research findings regarding the mechanisms of ferroptosis, its major regulatory pathways, and its mechanisms of action in sepsis-related organ damage. While research on ferroptosis has been fruitful in elucidating the pathogenesis of tumors and neurological diseases, many questions remain unanswered in the field of sepsis-related research. With the continuous updating of sepsis management guidelines, improvements in management and treatment are underway, but outcomes are far from satisfactory. Studying sepsis mechanisms and developing a targeting therapy is the most beneficial approach to treating sepsis and remains a challenge for the future. Although the function and direction for potential therapy targeting ferroptosis in sepsis and the resultant damage of multi-organs and their failure are increasingly being revealed, the field of ferroptosis is still new, and the role of ferroptosis in sepsis physiology, pathogenesis, and treatment is still underway. Studies for developing anti-ferroptosis via new drugs and understanding

the mechanisms unquestionably represent a novel implication in further research for sepsis therapy, and future therapeutic application is promising.

Data Sharing Statement

No data were available for this review.

Compliance with Ethical Standards

This article does not contain any studies with 430 animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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