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Ferroptosisand Its Role in the Treatment of Sepsis-Related Organ Injury: Mechanisms and Potential Therapeutic Approaches

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Abstract: Sepsis is a complicated clinical disease caused by a defective host response to infection, leading to elevated morbidity and fatality globally. Sepsis patients have a significant risk of life-threatening organ damage, including hearts, brains, lungs, kidneys, and livers. Nevertheless, the molecular pathways driving organ injury in sepsis are not well known. Ferroptosis, a non-apoptotic cell death, occurs due to iron metabolism disturbance and lipid peroxide buildup. Multiple studies indicate that ferroptosis has a significant role in decreasing inflammation and lipid peroxidation during sepsis. Ferroptosis inhibitors and medications, aimed at the most studied ferroptosis process, including Xc−system, Nrf2/GPX4 axis, and NCOA4-FTH1-mediated ferritinophagy, alleviating sepsis effectively. However, few clinical trials demonstrated ferroptosis-targeted drugs's effectiveness in sepsis. Our study examines ferroptosis-targeted medicinal agents and their potential benefits for treating sepsis-associated organ impairment. This review indicates that ferroptosis suppression by pharmaceutical means may be a useful therapy for sepsis-associated organ injury.

Keywords: sepsis, ferroptosis, sepsis-associated organ injury, ferroptosis inhibitor, medications

Introduction

Sepsis is a deadly illness that is the consequence of an inappropriate host response to infection.[1] This complicated illness causes abrupt organ malfunction and has a substantial risk of mortality.[2] Sepsis is the primary cause of mortality globally, resulting in almost 31.5 million fatalities annually.[3] Furthermore, it can result in several organ injuries, including sepsis-induced cardiomyopathy (SIC), sepsis-associated kidney injury (SAKI), sepsis-associated lung injury (SALI), and sepsis-induced liver injury (SiLI), sepsis-associated encephalopathy (SAE). Despite progress in understanding sepsis etiology and organ failure, there are no authorized sepsis-specific treatments.[4] To enhance patient outcomes, researchers should focus on particular molecular pathways underlying sepsis and its associated organ damage.

Ferroptosis, initially introduced by Brent R. Stockwell, is defined by the buildup of lipid peroxidation that relies on iron.[5] Ferroptosis differs from other types of programmed cell death regarding morphology and biochemistry.[6] In morphology, the mitochondria undergo notable alterations, including reduction in size, decrease or loss of mitochondrial ridges, increase in mitochondrial membrane density, and damage to the outer membrane. In biochemistry, iron metabolism, lipid peroxidation, and ferroptosis defense systems are key elements contributing to its occurrence (Supplementary Figure 1).[7,8]

Ferroptosis acts on the progression of sepsis and sepsis-associated organ injury.[9,10] Sepsis disrupts iron metabolism by causing an iron absorption, retention, and efflux imbalance. Elevated intracellular iron levels facilitate the initiation of ferroptosis, inflammatory cascade reactions, and eventual harm to tissues.[11] Furthermore, the link between ferroptosis and inflammation is presented from three perspectives: iron accumulation and GPX4 inhibition accelerate inflammation, lipid peroxidation (LPO) enhances inflammation, and ferropotic cells secrete damage-associated molecular patterns

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(DAMPs).[12] Overall, ferroptosis leads to an increase in inflammation and worsens organ damage. Hence, substances that hinder ferroptosis can potentially target sepsis-related organ injury (Supplementary Table 1).

This paper initially outlines the fundamental process of ferroptosis and its correlation with sepsis. We also outline the benefits of targets and drugs aiming at ferroptosis for sepsis treatment. In summary, this study seeks to outline effective ways to alleviate sepsis-related organ injury.

The Mechanism of Ferroptosis

Iron Metabolism

Iron metabolism involves the mechanisms of iron uptake, retention, and release. Iron is mostly present in its Fe^{3+} state within the human circulation, where it combines with transferrin (Tf) to form a complex and is absorbed by transferrin receptor 1 (TFR1) by endocytosis.[13] Upon entering the cell, Fe^{3+} undergoes reduction to Fe^{2+} by epithelial antigen of prostate 3 (STEAP3), and subsequently, Fe^{2+} is transported from the endosome to the cytosol by divalent metal-ion transporter-1 (DMT1).[14] Fe^{2+} is either used to synthesize ferritin or stored in the labile iron pool (LIP). If Fe^{2+} is over, unbound Fe^{2+} in the LIP can engage in Fenton reactions with H_2O_2, producing hydroxyl radicals and ROS that cause oxidative harm.[15] Hence, it is vital to maintain optimal amounts of Fe^{2+} in the LIP to ensure the balance of iron metabolism.

Nuclear receptor coactivator 4 (NCOA4) promotes ferritin to reach lysosomes, where ferritin is degraded, resulting in elevated iron concentration and the triggering of ferroptosis.[16] GAO et al found that knocking down the NCOA4 gene in cancer cells could hinder ferroptosis.[17] Additionally, it was found that cigarette smoke (CS)-induced ferroptosis via NCOA4-mediated ferritin breakdown increased LIP, 4-HNE, and lipid peroxidation levels in lung epithelial cells.[18] Overall, these studies indicate that ferritinophagy is the crucial factor triggering ferroptosis. Finally, during iron exportation, internal Fe^{2+} was converted to Fe^{3+} and exported to the extracellular by ferroportin (FPN).

Additionally, iron regulatory proteins (IRP) attach to iron response elements (IRE) in the untranslated regions (UTR) of mRNA-encoding proteins important in iron homeostasis.[19,20] If cellular iron levels are inadequate, IRP's active core binds to the IRE's stem-loop structure at the 3-UTR region of TfR1 and DMT1 mRNAs, therefore stabilizing TfR1 and DMT1 mRNAs and boosting their cellular expression and iron absorption. Furthermore, IRP binds to the IRE at the 5-UTR region of FPN1 or ferritin mRNAs, slowing their translation and lowering protein expression. When there is an excess of intracellular iron, this mechanism is inhibited. Fe-S occupied IRP's active core, preventing binding to TfR1 or DMT1's IRE, reducing translation levels and iron uptake. Overall, IRE and IRP control iron at the transcriptional level, which upholds cellular iron homeostasis.

Lipid Peroxidation

Polyunsaturated fatty acids (PUFAs) are crucial constituents of membrane bilayers and vitally modulate cell membrane fluidity. Lipid peroxidation is concentrated in phosphatidyl ethanolamine, which consists of either arachidonic acid (AA) or adrenaline (ADA), which is more likely to induce ferroptosis.[21] PUFAS-PE's peroxidation serves as the signal for ferroptosis, and its creation and oxidation processes may be described as follows: The enzyme acyl-CoA synthetase long-chain family member 4 (ACSL4) binds PUFAs with CoA to generate PUFA-CoA. LPCAT3 esterifies acyl-CoA derivatives to PUFA-PL. PUFA-PL undergoes oxidation to produce lipid hydrogen peroxide (PL-OOH) by the LOXs or POR's action.[22] The generation of PL-OOH and other secondary products such as 4-HNE and MDA, together with chain reactions, can lead to more severe cellular harm.[23]

In all, lipid peroxidation of PUFAS-PE damages the structure of the membrane and makes it less effective through several mechanisms. Hence, to mitigate ferroptosis, further research into the process of lipid peroxidation is required.

Ferroptosis Defense Systems

Xc-/GPX4 Axis

The Xc- system consists of a dimer of solute carrier family 7 member 11 (SLC7A11) and SLC3A2, linked by disulfide bonds in the cell membrane.[24] Xc- transfers glutamate extracellularly with cystine intracellularly in a 1:1 proportion. Cystine that is consumed is converted to cysteine.[25] GSH is generated by cysteine under the effect of glutamate-cysteine

ligase and glutathione synthase. Hence, Xc- plays a role in GSH production. GPX4 functions as an antioxidant by using GSH as a coenzyme, exhibiting a key enzyme in removing LOOH and avoiding ferroptosis.[26] Research has demonstrated that GPX4 elimination under specific conditions triggered the deterioration and death of motor neurons in mice.[27] Erastin and RSL3 are both ferroptosis inhibitors, but their mechanisms of operation differ. Erastin decreases cystine absorption by reducing the function of SLC7A11, causing lower expression of GSH and GPX4.[28] Nevertheless, RSL3 establishes a direct covalent linkage with GPX4, causing the buildup of ROS and inducing ferroptosis.[29] Overall, it is evident that the Xc-/GPX4 axis is an essential regulator of ferroptosis.

FSP1-CoQH2 Axis

GPX4 has been the primary inhibitor of ferroptosis from its description, although additional research showed that blocking GPX4 did not necessarily cause ferroptosis. Bersuker and Doll et al discovered that ferroptosis-suppressor-protein 1 (FSP1) effectively blocked ferroptosis through complementing GPX4 inactivation in osteosarcoma cells.[30,31] FSP1 on the cellular membrane could inhibit lipid peroxidation via converting CoQ10 to CoQ10-H2 with NADPH as a cofactor. Therefore, FSP1 reduces the sensitivity of ferroptosis independently of GSH and GPX4. Jo et al found that FSP1 inhibitors, plasma-activated medium (PAM), lowered FSP1 levels and stimulated lung cancer ferroptosis.[32] Furthermore, small molecule NPD4928 could directly decrease FSP1 function and accelerate ferroptosis.[33] Overall, the FSP1-CoQH2 axis showed that GPX4 does not exclusively prevent ferroptosis, and FSP1 is also a novel target for ferroptosis inhibition.

DHODH-CoQH2 Axis

Dihydroorotic dehydrogenase (DHODH), located in the inner mitochondrial membrane, converts dihydroorotate acid to orotate, reduces CoQ to CoQH2, and removes PL-LOOH.[34] Mao et al found that DHODH did not control ferroptosis-associated enzymes like GPX4 and FSP1 but interacted with GPX4 to prevent mitochondria-associated ferroptosis, independent of FSP1.[35] DHODH even elevated its quantity to compensate for GPX4 inactivation. Recent research indicated that DHODH inhibitors SA771726 and Brequinar sodium effectively treated several cancers, including melanoma, osteosarcoma, and breast cancer.[36,37] Additional investigation is required to evaluate whether DHODH inhibitors in conjunction with GPX4 antagonists or other stimulants will improve treatment outcomes. This is a promising area of ferroptosis research.

GCH1-BH4 Axis

Tetrahydrobiopterin (BH4), known for maintaining cellular redox stability, is a novel target for ferroptosis suppression. The enzyme GTP cyclic hydrolase 1 (GCH1), controlling BH4 production, was found to be a prospective ferroptosis suppressor. Following investigations, the GCH1-BH4 axis prevented ferroptosis by regulating BH4 production, decreasing intracellular PL-OOH and ROS.[38] In addition, Hu et al discovered that GCH1/BH4 reduced erastin-induced ferroptosis in colon cancer by specifically suppressing NCOA4-ferritin mediating ferritinophagy.[39] Ultimately, the GCH1-BH4 pathway may be a potent inhibitor separate from the Xc-/GPX4 and FSP1/CoQH2 axis. The modulators of this axis should be investigated in various pathological conditions.

The Role of Ferroptosis in Sepsis

The Correlation Between Ferroptosis and Sepsis

Dysregulation of Iron Metabolism in Sepsis

Iron metabolism changes during sepsis, with cells taking in and storing more iron and exporting less iron. Therefore, iron in the cytoplasm was upregulated, whereas serum iron was decreased. Sepsis patients and sepsis models have lower serum iron levels than healthy controls.[40–44] Decreased serum iron makes it less available to pathogens in the blood, which is a defensive approach against pathogens.[45,46] However, excess iron within the cytoplasm might trigger oxidative harm and ferroptosis, and finally damage many organs. On the other hand, downregulated serum iron could cause anemia and a poorer outcome. Following is a presentation of iron metabolism abnormalities linked to sepsis, based on iron absorption, storage, exportation, and a dual factor HO-1.

Iron metabolism in sepsis begins with increased iron uptake. Sepsis-induced inflammatory cytokine storm could stimulate TfR levels in cells, further absorbing Tf and its associated iron.[47] Moreover, ZIP14 was elevated, suggesting intracellular non-transferrin-bound iron (NTBI) transport.[48] Secondly, iron storage is affected by NCOA4-ferritin. Mechanistically, LPS enhanced NCOA4 levels, which directly degraded ferritin via ferritinophagy, releasing excess ferro. Cytoplasmic Fe^{2+} triggered mitochondrial membrane siderofexin (SFXN1), carrying Fe^{2+} into mitochondria, causing mitochondrial ROS and ferroptosis.[49] Low iron efflux is the final stage of sepsis. The transcriptional downregulation of FPN occurs when the bacterial lipopeptide FSL1 binds to TLRs 2 and 6, or when LPS binds to TLR4.[50,51] In addition, elevated levels of IL-1β, IL-6, IL-22, and activin B significantly increased hepcidin expression. Meanwhile, Hepcidin interacts with FPN, causing FPN to undergo ubiquitination and degradation, hence lowering FPN expression.[52] Therefore, the study revealed that Hepcidin ablation in the sepsis model might improve the condition of anemia in the ICU.[53]

Moreover, HO-1 modulating iron metabolism exhibits two sides in sepsis. HO-1 alleviates septic damage by catalyzing labile heme. HO-1 transforms labile heme to biliverdin, carbon monoxide, and ferro, decreasing sepsis-induced hemoglobin release that damages liver integrity and microcirculation.[54] However, HO-1 upregulation raised the fatality rate in sepsis. HO-1 activation could lead to ferroptosis by elevating LIP levels and increasing iron toxicity through degrading heme.[55–57] Therefore, HO-1 has a dual role in controlling iron metabolism during sepsis development.

Ferroptosis and Inflammation in Sepsis

The link between ferroptosis and inflammation is introduced from three perspectives: iron buildup and GPX4 inhibition accelerate inflammation, lipid peroxidation increases inflammation, and ferropotic cells release inflammatory factors.

Iron, which regulates ferroptosis, also regulates the immune system. The study revealed that intracellular iron excess polarizes M1 macrophages.[58] Handa et al found that iron excess activated hepatic macrophage M1, fibrogenesis, and steatohepatitis in mice.[59] DIBI, a new iron-chelator, reduced inflammatory mediators and restored intestinal muscle layer capillary density for sepsis therapy.[60,61] Furthermore, GPX4 expression is reduced in sepsis animal models and patients. GPX4 disruption increases LOX and COX expression, which could metabolize AA to produce active inflammatory compounds like leukotrienes and prostaglandins, causing enlarged inflammation.[62,63] Therefore, iron-chelating agents and GPX4 upregulation have been well targeted for treating sepsis by inhibiting ferroptosis and alleviating inflammatory response.

Lipid peroxidation and inflammation are connected, and their vicious cycle may be seen from two perspectives. On the one hand, redundant ROS stimulated transcription factors like Nrf2, NF-κB, and TNF-α, causing elevated inflammatory molecules, and accelerating inflammation.[64,65] On the other hand, increased inflammatory factor levels in the sepsis model disrupted the mitochondrial oxidative respiratory chain, leading to ROS buildup and ferroptosis. Thus, LPO engaged in a harmful cycle of ferroptosis and inflammation in sepsis.

Ferropotic cells releasing inflammatory factors are still little known at present.[66] Ferroptotic cells can cause sterile inflammation and inflammatory disorders by activating NF-κB through the advanced glycation end-product receptor (AGER).[67,68] Additionally, ferroptotic cells can generate DAMPs, such as high mobility group box 1 (HMGB1), 4-hydroxynonenal (4-HNE), and prostaglandin E2, worsening inflammation. Wen et al discovered that HMGB1 binds to AGER, not TLR4, starting signaling cascades further and causing inflammation.[12] Overall, ferroptotic cells generate inflammatory factors, which amplify cascade reactions, and heighten the inflammatory process.

Comparison of Ferroptosis with Necroptosis, Apoptosis in Sepsis

Necroptosis is mediated by RIPK1 and RIPK3, which produce necrosomes in response to stimuli and caspase-8 inhibition. Phosphorylation of MLKL by the necrosome leads to membrane hole formation.[7,69] Early alterations in necroptosis include ATP consumption, ROS production, Ca^{2+} overload, and mitochondrial permeability loss, which can lead to immunological responses. Duprez et al found that RIPK3 deletion decreased the release of DAMPs, preventing deadly sepsis induced by CLP.[70] Furthermore, RIPK-targeted medicines, like Necrostatin-1 (Nec-1), reduced sepsis-related damage and enhanced mice survival.[71] Overall, RIPK3 and MLKL deficiencies are the clear criteria for necroptosis.

Apoptosis, a natural cell death mechanism, occurs through the extrinsic and intrinsic pathways.[72] The extrinsic pathway involves death receptors, such as Fas, TNFR, and Trail, leading to cell apoptosis by recruiting FADD and procaspase-8, forming a death-inducing signaling complex, and activating caspase-3. The intrinsic pathway is regulated

by anti-apoptotic and apoptotic members of the Bcl-2 family. It is also influenced by cytokine/chemokine/growth factor signaling, including PI3K/Akt, and NF-κB.[72] Improper immune cell apoptosis regulation may lead to multiple organ failure in sepsis. Apoptosis occurs in immune cells such as neutrophils, macrophages, and lymphocytes. Lymphocytes are most affected by dysregulated apoptosis. The study revealed that blocking lymphocyte apoptosis with selective Bcl-2 overexpression reduced mice mortality in the CLP model.[73]

Ferroptosis has more biomarkers than necroptosis in sepsis treatment. Additionally, ferroptosis indicators may change due to apoptosis-related intrinsic processes, hence analyzing them may help explain the upstream mechanism. Numerous studies related ferroptosis, apoptosis, and sepsis to the P13K/AKT pathway. They revealed that PI3K/AKT pathway activation lowered Bax and boosted anti-apoptotic protein.[74,75] The PI3K/AKT pathway regulated GPX4 and Bax/Bcl2 expression, controlling ferroptosis and apoptosis.[76,77] The direct relationship between ferroptosis and apoptosis in medications-reduced sepsis is unknown. Future research is needed to determine the mechanism of action.

Ferroptosis and Sepsis-Related Organ Damage

Ferroptosis and Sepsis-Induced Cardiomyopathy

Severe sepsis and septic shock can cause sepsis-induced cardiomyopathy (SIC), which reduces left ventricular dilatation and ejection fraction and increases mortality.[78] Currently, ferroptosis has been investigated extensively, and the following have been identified to target ferroptosis in SIC. Transmembrane protein 43 (TMEM43) (1), malonylate voltage-dependent anion channel 2 (VDAC2) (2), Bmal-1 (3), ICA69 (4), neutrophil-derived lipocalin-2 (LCN2) (5). 1, TMEM43, reduced P53 expression and activated SLC7A11 and GPX4, controlling the P53/SLC7A11 pathway to exert ferroptosis inhibition in SIC.[79] 2, VDAC2 malonylation modulation caused mitochondrial malfunction, decreased mitochondrial membrane potential, and increased Fe^{2+} and ROS levels.[80] Targeting VDAC2 malonylation, TPP-AAV nanomaterial substantially reduced cardiac damage by inhibiting cardiomyocyte ferroptosis. This provided a link between VDAC2 malonylation and ferroptosis for the first time. 3, Bmal-1, a key circadian clock component, is directly related to the severity of sepsis in clinical trials. It suppressed cardiomyocyte ferroptosis via the AKT/p53 pathway. AKT activation to lower p53 raised GPX4 and SLC7A11 levels while reducing ROS and MDA levels, improving cell viability and dramatically inhibiting H9c2 cell ferroptosis.[81] 4, ICA69 levels are highly expressed in septic patients, whereas ICA69 deficiency decreased serum inflammatory cytokines and ferroptotic marker levels like Fe, PTGS2, MDA, 4-HNE, and ROS, but not Xc- dependently.[82] 5, LCN2 increased the labile iron pool to induce H9C2 cell ferroptosis, while its depletion decreased cardiac failure and ferroptosis.[83]

Numerous drugs have also shown promise in treating SIC by inhibiting ferroptosis. The following is a summary of these compounds. Resveratrol (1), Dexmedetomidine (2), Puerarin (3), Matrine (4), CeO2 nanozyme cooperation with Curcumin (5), Quercetin (6), Tectorigenin (7), NaHS (8), DEF (9). 1, Resveratrol hindered ferroptosis by triggering the SIRT1/Nrf2 axis in SIC, hence elevating Nrf2 expression and decreasing MDA, 4-HNE, and Fe^{2+} levels.[84] 2, Dexmedetomidine increased GPX4 expression while lowering HO-1, heme, iron, and inflammatory factors levels.[85] It focused on HO-1's downstream iron toxicity, unlike prior studies on HO-1's antioxidant advantages. 3, Puerarin activated AMPK to prevent ferroptosis, which reduced ROS and ACSL4 and enhanced GPX4 expression, exhibiting cardioprotective effects in SIC.[86] 4, Matrine activated the PI3K/AKT axis to suppress ferroptosis in SIC, which ultimately lowered MDA and ACSL4 levels and increased SOD and GPX4 expression.[77] 5, CeO2 nanozyme cooperation with Curcumin exhibited SOD-like and CAT-like activities, suppressed ROS and cytokine production, and increased M2 macrophage polarization, showing anti-ferroptosis and anti-inflammatory effects to cure SIC.[87] 6, Quercetin triggered the SIRT1/p53/SLC7A11 axis in vivo *and* in vitro, lowering Fe^{2+}, MDA, and PTGS2 levels while increasing GSH, GPX4, and ferritin expression.[88] 7, Tectorigenin suppressed Smad3 to inhibit ferroptosis in the LPS group, which decreased MDA and ACSL4 expression and upregulated SOD and GPX4 levels.[89] 8, NaHS decreased p-BECN1 and elevated SLC7A11 and GPX4 protein expression. It reversed LPS-induced BECN1 phosphorylation and BECN1 bound with SLC7A11, further reducing system Xc− activity and promoting ferroptosis.[90] 9, DEF, mitochondrial iron chelation, suppressed mitochondrial iron and ROS generation to alleviate heart dysfunction and inflammation in SIC.[49] Overall, targeting ferroptosis in cardiomyocytes would be beneficial to avoid SIC going forward. These findings highlighted potential therapy approaches for SIC management.

Ferroptosis and Sepsis-Associated Kidney Injury

Sepsis is typically followed by severe kidney failure. In critical care units, there is a strong correlation between the morbidity of SAKI and the patient's death.[91–93] Studies on ferroptosis in SAKI have been conducted, and related targets are described below. Maresin conjugates in tissue regeneration-1 (MCTR1) increased Nrf2 to inhibit ferroptosis in septic mice. The Nrf2 inhibitor ML-385 reversed MCTR1's action, suggesting that Nrf2 is vital for MCTR1's ferroptosis inhibition.[94] Similarly, Klotho, a family of aging-associated proteins, found its overexpression activated Nrf2 to suppress ferroptosis.[95] In addition, NADPH oxidase produces most ROS in sepsis.[96] NADPH oxidase's inhibition reduced ROS generation or oxidative stress, suppressing ferroptosis and improving renal function.[97]

Numerous medications that target ferroptosis have demonstrated promise in alleviating SAKI (Supplementary Figure 2). This article's description of these substances may be found below. Irisin (1), Ginsenoside Rg1 (2), Melatonin (3), GYY4137 (4), Melittin (5). 1, irisin activated SIRT1/Nrf2 signaling to decrease ROS and iron levels and improve mitochondrial function. Furthermore, Irisin's benefits were reduced by SIRT1 inhibitor EX527 in vivo and SIRT1 siRNA in vitro, suggesting that SIRT1/Nrf2 axis was key for irisin's ferroptotic inhibition.[98] 2, Ginsenoside Rg1 hindered ferroptosis through decreasing iron, FTL, FTH, and MDA and elevating GSH, GPX4, and FSP1. Nevertheless, ginsenoside Rg1's actions were reversed by FSP1 suppression, indicating that it might target FSP1 to reduce renal tubular epithelial cell ferroptosis.[99] Similar to the above mechanism, Ginsenoside Rg1 was supplementary discovered to activate the FSP1-CoQ10-NAD(P)H axis to block ferroptosis.[100] 3, Melatonin stimulated the Nrf2/HO-1 axis and enhanced GPX4 expression to lower lipid peroxidation and inhibit ferroptosis.[101] 4, H2S donor GYY4137 treated SAKI by suppressing ferroptosis caused by mitochondrial oxidative stress.[102] 5, Melittin increased Nrf2 nuclear translocation and GPX4 expression, effectively blocking ferroptosis through the Nrf2/GPX4 pathway.[103] These treatments for SAKI may lead to new concepts for clinical research and medication development.

Ferroptosis and Sepsis-Associated Lung Injury

Sepsis, a fatal systemic infection, causes most acute lung injury (ALI), including acute respiratory distress syndrome (ARDS). ALI and ARDS create extensive injury to alveolar and microvascular endothelial cells, alveolar damage and edema, and increased lung tissue inflammatory cell aggregation.[104] Currently, research on ferroptosis in SALI is extensive. AU-rich element-binding factor 1 (AUF1) (1), circEXOC5 (2), MUC1 (3), Protectin conjugates in tissue regeneration 1 (PCTR1) (4), neutrophil extracellular traps (NETs) (5), and Yes-associated protein 1 (YAP1) (6) have been shown to modulate ferroptosis in alveolar epithelial cells. 1, AUF1, an mRNA-binding protein, regulated ferroptosis via positively controlling Nrf2 and adversely influencing ATF3. AUF1 upregulation alleviated SALI injury and extended mice's life.[105] 2, CircEXOC5 modulated the IGF2BP2/ATF3 axis to promote ferroptosis and worsen SALI by recruiting IGF2BP2 to enhance ATF3 mRNA degradation and reduce GPX4 levels.[106] 2, CircEXOC5 has new additions. CircEXOC5 modulated the PTBP1/ACSL4 axis to worsen ferroptosis by combining with RNA-binding protein PTBP1 and upregulating ACSL4's expression.[107] The above two experiments discovered a novel gene and mechanism for targeting SALI. 3, MUC1, a polymeric transmembrane glycoprotein, modulated the GSK3β/KEAP1-Nrf2-GPX4 axis to prevent ferroptosis. It decreased Keap1 expression, increased GSK3β phosphorylation, promoted Nrf2 nucleus entrance, elevated GPX4 levels, prevented lipid peroxidation, blocked ferroptosis, and lowered pulmonary damage.[108]

Like MUC1, PCTR1 is also a negative factor of ferroptosis in SALI. 4, PCTR1 blocked ferroptosis through the ALX/PKA/CREB axis. It interacted with the extracellular regions of its receptor ALX, a G-protein-coupled receptor, to activate the downstream protein PKA. PKA phosphorylated CREB at Ser-133, which improved GPX4 transcription.[109] 5, NETs level was linked to disease severity in SALI patients and mice models. NETs induced dynamic m6A alteration on GPX4 by METTL3 alteration, accelerating alveolar epithelial cell ferroptosis.[110] 6, YAP1 blocked the NCOA4-FTH1 association, preventing ferritin degradation to Fe^{2+}, ROS generation, ferritinophagy, and ferroptosis. SALI is worsened by YAP1 loss, whereas its overexpression reduces ferritinophagy-mediated ferroptosis in pulmonary epithelial cells.[111]

Many medications that target ferroptosis have shown potential in the treatment of SALI. Ferulic acid (1), rmMANF (2), GYY4137 (3), Puerarin (4). 1, Ferulic acid stimulated the Nrf2/HO-1 axis to suppress ferroptosis and alleviate SALI.[112] 2, rmMANF pretreatment blocked the PERK/ATF4 axis to enhance the downstream gene of ATF4, GPX4,

hence reducing sepsis-related pulmonary damage.[113] 3, GYY4137, a novel H2S donor, inhibited ferroptosis in SALI by reducing COX-2 and NOX1 expression while enhancing SLC7A11 and GPX4 expression.[114] 4, Puerarin treatment increased SLC7A11, GPX4, and FTH1 levels, whereas decreased iron, MDA, and ROS expression in A549 cells.[115]

In the above, there are contradictory points about ATF3. AUF1 inhibited ATF3 to alleviate SALI damage, while CircEXOC5 inhibited ATF3 levels to aggravate SALI damage. The former suggested that ATF3 negatively regulated SLC7A11 levels, so inhibiting AUF1 increased SLC7A11 levels and promoted GPX4 expression. The latter indicated that ATF3 mRNA's downstream target was GPX4, so inhibiting AUF1 reduced GPX4 expression. This may stem from our limited knowledge of ATF3, making it challenging to understand its contradictions clearly. In summary, these targets and medications aiming at ferroptosis inhibition showed potential for ameliorating SALI.

Ferroptosis and Sepsis-Induced Liver Injury

In early sepsis, liver impairment occurs and is a separate risk factor for an adverse prognosis.[116] The research found that sepsis patients' serum irisin expression was low and adversely connected with disease severity. In the experiment, RGD peptide and Echistain, irisin receptor inhibitors, greatly decreased GPX4, mitochondrial activity, and ATP levels in the LPS group. Thus, irisin protected against SiLI impairment by inhibiting ferroptosis.[117] Additionally, Wang et al observed that SLC7A11 and GPX4 were decreased at 24 and 48 h after CLP, whereas GPR116 protein levels rapidly rose at 48 h.[118] GPR116, a member of the adhesion GPCRs, reduced system Xc− and GPX4 expression to promote ferroptosis in septic circumstances. Thus, blocking GPR116 might be an effective target for SiLI. Unlike ferroptosis-positive regulators GPR116, YAP1 prevented ferritinophagy-mediated ferroptosis in hepatocytes by blocking the NCOA4-FTH1 association.[119] Additionally, Xie et al found that WenQingYin blocked hepatocyte ferroptosis by increasing Nrf2 translocation into the nucleus, which stimulated the target genes' transcription such as GPX4, SLC7A11, HO-1, and FSP1.[120] Meanwhile, proinflammatory factor levels like IL-6, IL-1β, and TNF-α were decreased in the LPS group. Like WenQingYin, Nobiletin (NOB), plant-based polymethoxyflavone, activated Nrf2/GPX4 signaling and reduced ferroptosis in the gut microbiota.[121] Overall, these findings revealed that agents inhibiting hepatocyte ferroptosis offered innovative sepsis treatments.

Ferroptosis and Sepsis-Associated Encephalopathy

SAE is a widespread CNS illness without a visible sign and causes consciousness disturbances, neuroinflammation, aberrant BBB permeability, and neurological abnormalities.[122] In SAE, Hippocampal ROS, MDA, ALOX12, and ASCL4 levels rose significantly. Compared to CLP mice, Fer-1 treatment increased GPX4, SLC7A11, Nrf2, HO-1, and GSH expression, to enhance mice survival and cognitive performance.[123] Comparable to Fer-1's role, Acetaminophen (APAP) decreased hippocampus dysfunction and improved cognitive deficits in CLP mice by decreasing iron, ROS, and 4-HNE but enhancing GPX4 expression.[124] Additionally, research revealed that exosome-packaged NEAT1 modulated the miR-9-5p/TFRC/GOT1 axis to trigger ferroptosis. NEAT1, a long non-coding RNA, functioned as a ceRNA for miR-9-5p to enhance TFRC and GOT1 production, which accelerated brain microvascular endothelial cell iron absorption and promoted ferroptosis.[125] Unlike positive-ferroptosis controllers NEAT1, Irisin blocked ferroptosis by activating the Nrf2/GPX4 axis. Meanwhile, Irisin reduced neurologic severity score, hippocampal ferroptosis, and improved microglial activity in SAE mice.[126] Taken together, drugs targeting ferroptosis would hinder the progression of SAE (Supplementary Figure 3).

Summary on Ferroptosis in Sepsis

Summarizing multiple experimental articles, ferroptosis was addressed to cure sepsis-related organ damage from two medications and target perspectives. Firstly, most research focused on the Xc− system, such as the P53/SLC7A11/GPX4 and Nrf2/GPX4 axis. That's because LPS raised BECN1 phosphorylation and BECN1 bound with SLC7A11, hence reducing system Xc− activity and promoting ferroptosis. P53 is also an important target for SLC7A11, so extensive research on sepsis has focused on the P53/SLC7A11 axis. Nrf2/GPX4 axis has been widely researched since Nrf2 translocation into the nucleus increased the transcription of target genes such as GPX4, HO-1, and FSP1. Additionally, NCOA4-FTH1-mediated ferritinophagy has been found in sepsis-related heart and liver organ damage, indicating

a viable avenue for further research on sepsis. Thirdly, related research discovered inflammatory factors and ferroptosis-related molecules concurrently to evaluate their curative effect. Finally, sepsis-related liver, kidney, and brain investigations are scarcer than sepsis-related heart and lung studies, and further studies are needed in the future.

Furthermore, few sepsis treatments targeting ferroptosis have been tested in clinical trials, and their effects are inconsistent. L-carnitine medication decreased NADPH oxidase and ROS levels to alleviate oxidative stress in sepsis from surgery/anesthesia trauma.[127] N-acetyl-cysteine (NAC) is commonly used to treat oxidative stress and GSH deficiency. Ortolani et al confirmed that high-dose GSH and NAC reduced lipoperoxidative damage in early septic shock patients.[128] His department's pilot experiment found it beneficial in septic shock at 150 mg/kg/d without negative effects. However, Najafi et al found that high doses of NAC worsened sepsis patient outcomes, exacerbated inflammation, and raised serum creatinine in a clinical trial.[129] Although GSH levels in the NAC group were slightly higher, NAC and control groups had similar ICU stays, SOFA scores, and systemic oxygenation. This suggests that sepsis medications targeting ferroptosis are still contradictory in clinical trials and need further research in the future.

Last but not least, medications targeting ferroptosis have both advantages and disadvantages in complementing conventional sepsis therapy. Previous sepsis treatments involve two categories. The initial treatment, antibiotics, vasoactive drug dopamine, and glucocorticoids were used to fight pathogens, control arterial tone to stabilize cardiac function, maintain hemodynamic stability, and treat sepsis fast.[130] The second treatment, herbal injection with Xuebijing, diminished HMGB1 and inflammatory factor mediators, effectively curing sepsis.[131] Medications targeting ferroptosis have the same anti-inflammatory and antioxidant impact as established drugs. Additionally, novel ferroptosis-targeting medications could be utilized alongside established drugs to improve therapeutic efficacy and prevent drug resistance. It could also personalize treatment programs and offer additional sepsis treatment choices for patients. However, it has limits, as most of the research is basic, and clinical experiment research is few.

Conclusion

Sepsis represents a significant disease due to its elevated fatality and morbidity rates. The primary sepsis of infection is dysregulation of the host response, leading to damage and dysfunction across several organs. Although treatment and care recommendations are regularly revised, outcomes remain dismal. To effectively treat sepsis, it is crucial to understand its underlying processes and create medications that target those systems. Ferroptosis, a kind of cell death linked to ferro, lipid, and amino acid metabolism, has received significant interest in the context of sepsis. This review explores signaling pathways, targets, and medications that aim at ferroptosis. It concentrates on the relationships between ferroptosis and sepsis, targets for treating sepsis-related organ diseases, and the efficacy of ferroptosis-targeted medications.

Nevertheless, this study does have several drawbacks. Although we attempted to compile and evaluate pertinent research, the linkages and processes of specific mechanisms remain unclear. The paper mainly concentrates on the pharmacological effects of medications targeting ferroptosis in sepsis-associated organ injury, rather than delving into the precise mechanism behind it. Additionally, related drugs' insights are in the laboratory stage, and their efficacy has been preliminarily shown. Still, they must grow through pharmacokinetics, toxicology, drug dosage forms, and formulations before being used in clinical practice. Basic research generally lacks human medication efficacy and safety data, which might stimulate great endeavors in future research. Ferroptosis's involvement in the pathophysiology and therapy of sepsis is still being explored. Future research in sepsis therapy might focus on addressing ferroptosis through various pharmacological and targeted interventions.

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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Disclosure

The authors report no conflicts of interest in this work.

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