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REVIEW

Deciphering Cuproptosis in Sepsis: Mechanisms, Consequences, and Therapeutic Opportunities

Ruimin Tan[1,2], Kexin Wen[1,2], Tianyu Zhao[2,3], He Guo[2,4], Xumin Han[2,4], Jiakai Wang[2,4], Chen Ge[2], Quansheng Du[2]

[1]School of Clinical Medical, North China University of Science and Technology, Tangshan, Hebei, People's Republic of China; [2]Critical Care Department, Hebei General Hospital, Shijiazhuang, Hebei, People's Republic of China; [3]School of Graduate, Hebei North University, Zhangjiakou, Hebei, People's Republic of China; [4]School of Graduate, Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China

Correspondence: Quansheng Du, Critical Care Department, Hebei General Hospital, Shijiazhuang, Hebei, People's Republic of China, Email dqs888@126.com

Abstract: Cuproptosis is a form of programmed cell death triggered by the abnormal accumulation of intracellular copper ions, and its mechanism is closely associated with oxidative stress and mitochondrial dysfunction. Recent studies on sepsis have indicated a potential link between copper metabolism disorders and organ injury. Cuproptosis may be involved in the progression of multi-organ dysfunction in sepsis by disrupting immune homeostasis, promoting inflammatory responses, and altering energy metabolism. This review focuses on the potential role of cuproptosis in sepsis-related damage to major organs, including the heart, liver, lung, and kidney, and summarizes current findings regarding its molecular mechanisms. Potential therapeutic strategies, such as copper chelators and mitochondrial protectants, are also discussed. In addition, this review outlines key areas of ongoing debate and highlights future research directions, with the aim of informing further investigation into precision therapies for sepsis.

Keywords: cuproptosis, sepsis, oxidative stress, mitochondrial dysfunction, targeted therapy

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, and remains one of the leading causes of mortality in critically ill patients worldwide.[1] Despite advances in supportive care, effective targeted therapies for sepsis are still lacking, in part due to the complex and heterogeneous nature of its pathophysiological mechanisms.[2] Current understanding suggests that multiple factors—such as immune dysregulation, mitochondrial dysfunction, oxidative stress, and metabolic reprogramming—are involved in the development and progression of sepsis.[3] However, many of these mechanisms remain poorly understood or insufficiently targeted by existing interventions, underscoring the need for novel therapeutic strategies and molecular targets.

Recent studies have suggested that cuproptosis, a newly defined form of programmed cell death triggered by intracellular copper accumulation, may be critically involved in the pathogenesis of sepsis.[4,5] Copper levels in sepsis patients are frequently found to be abnormally elevated, which may be closely associated with disease severity and outcomes.[6] Excessive copper accumulation can induce cuproptosis and may also aggravate sepsis progression by promoting oxidative stress and pro-inflammatory responses.[4] Furthermore, certain copper ionophores and chelators have been proposed as potential therapeutic agents aimed at modulating copper homeostasis to mitigate sepsis-related tissue injury.[7]

In this review, we provide a comprehensive overview of the mechanistic basis of cuproptosis, summarize recent advances in its relevance to sepsis-related organ dysfunction, and discuss its emerging potential as a biomarker and therapeutic target for improving clinical management of sepsis.

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The Discovery Process of Cuproptosis

As early as in the 1980s, researchers found a unique cell death phenomenon induced by abnormal copper metabolism, but its mechanism has not yet been clarified.[8] In 2000, it was proposed that the copper ionophore elesclomol (ES), as a molecule soluble in lipids that binds copper ions reversibly, is capable of targeting copper ions for intracellular delivery, and this property has made it an important antitumor drug development direction for the development of antitumor drugs.[9] In 2012, a study confirmed that ES inhibits tumor cell proliferation by promoting copper ion transport to mitochondria, notably raising reactive oxygen species (ROS) and lowering iron-sulfur cluster protein levels, revealing for the first time the association between copper metabolism and mitochondrial dysfunction.[10,11] Subsequently, further studies demonstrated that copper ions, upon ES-mediated entry into cells, can generate hydroxyl radicals (·OH) by oxidizing ascorbic acid and catalyzing H_2O_2 decomposition, leading to DNA damage and collapse of mitochondrial membrane potential.[12] In 2016, ES was found to act on the mitochondrial respiratory chain and elevate intracellular reactive oxygen species levels through a ROS-mediated mechanism, ultimately inducing cell death.[9] In 2019, Tsvetkov et al identified the ferredoxin 1 (FDX1) gene as a core regulator of ES sensitivity through a genome-wide screen, which encodes a protein directly binds to the ES-Cu complex, inhibits iron-sulfur cluster biosynthesis and triggers aberrant aggregation of lipoylated proteins.[13] In 2022, the team further clarified the mechanism of copper-induced cell death and formalized the name "cuproptosis". The fundamental mechanism is the interplay between lipoylation, a conserved post-transcriptional protein modification pathway, and components of the tricarboxylic acid (TCA) cycle.[14]

Cuproptosis and Other Types of Cell Death

Cuproptosis is not just a method for cell death on its own; it may also interact with other mechanisms like autophagy and apoptosis. Copper ion overload can activate both apoptosis and cuproptosis death pathways, copper ions promote cross-activation of both forms of death by inhibiting glutathione (GSH) synthesis.[15,16] Furthermore, by activating the TLR4/NF-κB pathway, copper ion overload was observed to indirectly enhance localized death-related inflammatory responses.[15] This cascade impact was significant in an atherosclerosis model. Copper ions can enhance lipid peroxidation via the Fenton-like reaction, leading to the synergistic activation of ferroptosis and cuproptosis, a phenomenon that has been demonstrated in hepatocellular carcinoma cells.[17,18] Autophagy exhibits a dual role in cuproptosis: short-term copper stress activates protective autophagy to scavenge damaged mitochondria, but sustained copper overload leads to a blockage of autophagic flow and exacerbates proteotoxic stress.[19] Unlike autophagy-dependent death, the onset of cuproptosis does not depend on autophagy core genes such as ATG5/ATG7, but knockdown of p62/SQSTM1 enhances cuproptosis susceptibility through inhibition of aggregin degradation.[20] This intricate network relationship offers fresh insights into the function of cuproptosis in disease, which can interact with various death pathways during pathology despite having a molecular mechanism that is very different from recognized types of death. This complexity suggests the need to develop specific regulatory tools to precisely target cuproptosis in the future.

Regulatory Mechanisms of Cuproptosis

Cytotoxicity of Copper Ions

Copper, as an essential trace element, has intracellular concentrations that need to be tightly regulated to maintain normal physiological functions. Copper contributes to energy metabolism, antioxidant defense, and enzyme cofactoring under homeostatic settings.[21] However, cytotoxicity can be brought on by copper ion concentrations that are higher than the physiological range, which can result in oxidative stress and cellular damage. Excess copper ions have been demonstrated to bind to lipoylases and cause the aberrant aggregation of lipoylated proteins, which impairs cell activity and causes cuproptosis.[14] When copper ions attach to lipoylated proteins in the TCA cycle, iron-sulfur cluster proteins are lost, which causes protein aggregation and cytotoxic stress, which in turn causes cell death. This phenomenon is known as cuproptosis. In addition, copper ions can exacerbate cellular damage by inducing oxidative stress, endoplasmic reticulum stress, and other pathways, further affecting cell survival and function.[22,23]

Regulation of Cuproptosis

Cuproptosis is a new copper-dependent cell death mechanism that is brought on by an aberrant buildup of intracellular copper ions.[24] Its molecular mechanism involves the synergistic action of multiple signaling pathways involving copper metabolism, mitochondrial energy metabolism, and oxidative stress (Figure 1).

Copper Ion Transport and Homeostatic Regulation

When cellular copper homeostasis is out of balance, cuproptosis begins. Overexpression of copper transporter 1 (CTR1), which is in charge of the cellular uptake of copper ions, greatly increases vulnerability to cuproptosis.[25] Antioxidant 1 Copper Chaperone (ATOX1) transports copper ions to the Golgi apparatus upon cell entry. There, they are carried by the vesicular transport system mediated by ATPase copper transporting α (ATP7A) and ATPase copper transporting β (ATP7B) to achieve transmembrane transport and secretion.[26] It has been shown that loss-of-function mutations in ATP7B lead to aberrant accumulation of copper ions in the mitochondrial matrix and the formation of cytotoxic Cu^{2+}-thiol complex, which trigger mitochondrial membrane permeability transition and ultimately induce cuproptosis.[8] The copper chelator tetrathiomolybdate (TTM) inhibits cuproptosis by competitively binding free copper ions and blocking their interaction with thioctylated proteins.[27] In addition, depletion of metallothioneins (MTs) and GSH, which serve as important intracellular copper buffering systems, exacerbates copper homeostatic imbalance and promotes cuproptosis by decreasing the chelating capacity of copper ions.[28,29]

Mechanisms Associated with the Mitochondrial TCA Cycle

The TCA cycle's protein lipoic acid esterification in the mitochondrial respiratory chain is one of cuproptosis's primary characteristics. One significant lysine post-translational modification that is necessary for controlling major TCA cycle

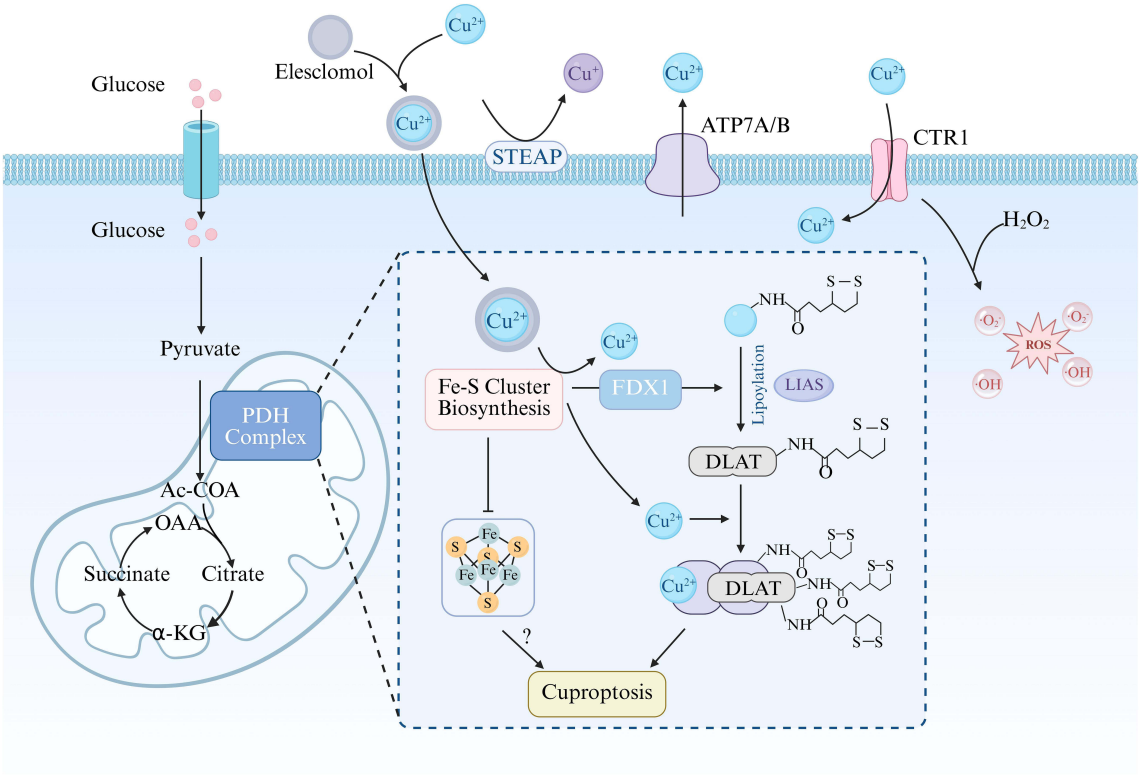

Figure 1 *Schematic of cuproptosis mechanism*. Cuproptosis is triggered by intracellular copper ion (Cu^{2+}/Cu^{+}) overload, which leads to accumulation via an imbalance between CTR1 uptake and ATP7A/B excretion. Excess Cu^{+} targets key nodes of mitochondrial metabolism (eg, PDH complex, DLAT, FDX1), inhibiting the TCA cycle and Fe-S cluster protein function, while triggering aberrant aggregation of thiol proteins and ROS bursts. Drug (Elesclomol) enhances cuproptosis, ultimately leading to energetic collapse and irreversible cell death.

Abbreviation: Ac-CoA, Acetyl-Coenzyme A; ATP7A/B, ATPase Copper Transporting α/β; α-KG, Alpha-Ketoglutarate; CTR1, Copper transporter 1; DLAT, Dihydrolipoamide S-Acetyltransferase; FDX1, Ferredoxin 1; LIAS, Lipoic acid synthetase; OAA, Oxaloacetic acid; PDH, Pyruvate dehydrogenase; ROS, Reactive oxygen species; STEAP, Six-transmembrane epithelial antigen of the prostate.

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enzymes is lipoic acid esterification. The metabolic function of mitochondria is inhibited when excess intracellular copper ions bind to lipoylated proteins, including related proteins like pyruvate, α-ketoglutarate, branched-chain cupric acid dehydrogenase, and glycine cleavage system.[30,31] This causes the lipoylated proteins to aggregate. This leads to disruption of the TCA cycle and insufficient cellular energy production, as well as triggering proteotoxic stress, which ultimately contributes to cellular cuproptosis.

FDX1 is an upstream regulator of cuproptosis, and its loss of function renders cells completely resistant to copper ion-induced death. It induces copper ions to interact with mitochondrial lipoylation-modified TCA cycle enzymes eg, dihydrolipoamide S-Succinyltransferase (DLST) and dihydrolipoamide S-Acetyltransferase (DLAT), undergo specific binding, which in turn promotes binding to lipoylated proteins.[32,33] It was found that knockdown of FDX1 or inhibition of enzymes related to lipoylation eg, lipoic acid synthetase (LIAS), lipoacyltransferase 1, prevented cuproptosis.[34] Therefore, biomarkers such as FDX1, LIAS, DLAT, lipoyltransferase 1, and dihydrolipoic acid dehydrogenase are important in the study of cuproptosis.

Disorders of Mitochondrial Respiratory Chain-Dependent Energy Metabolism

The mitochondrial respiratory chain's ability to operate properly is necessary for cuproptosis to develop. According to studies, copper ions disrupt the electron transport chain's ability to function by blocking either complex I (NADH dehydrogenase) or complex III (cytochrome bc1 complex).[29,35] This prevents the production of adenosine triphosphate (ATP), which lowers cellular sensitivity to cuproptosis.

A number of metabolic enzymes and the mitochondrial electron transport chain depend on iron-sulfur cluster proteins, whose breakdown impairs cellular energy metabolism and redox balance and ultimately results in cell death.[36] An overabundance of copper ions degrades iron-sulfur cluster proteins in mitochondria, disrupts iron-sulfur cluster biosynthesis, and reduces the stability of important respiratory chain components, all of which result in decreased ATP synthesis and disruption of mitochondrial ultrastructure.[33,34] Furthermore, copper ion accumulation aggravates the cellular energy crisis by blocking the mechanistic Target of Rapamycin Complex 1 (mTORC1)-mediated protein synthesis pathway, which in turn promotes the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway.[37] Preclinical studies have shown that the mitochondrial uncoupler carbonyl cyanide-p-trifluoromethoxy phenylhydrazone (FCCP) partially alleviates cuproptosis, possibly by modulating mitochondrial membrane potential, suggesting that mitochondrial respiratory function is closely associated with cuproptosis.[27]

Oxidation States of Copper in Regulating Cuproptosis

The redox states of copper, primarily Cu^{+} and Cu^{2+}, play a critical role in regulating its intracellular behavior and biological effects.[38] These oxidation states influence copper's capacity to participate in redox reactions, affect its transport and accumulation within the mitochondrial matrix, and modulate key processes such as protein lipoylation.[39] Such redox-dependent mechanisms are closely associated with the initiation of cuproptosis. In particular, the cycling between Cu^{+} and Cu^{2+} facilitates the generation of ROS, exacerbates oxidative stress, and contributes to mitochondrial damage, ultimately leading to regulated cell death.[40] Understanding these oxidation-dependent pathways provides a foundation for deciphering the molecular events involved in copper-induced cytotoxicity.

Oxidative Stress and DNA Damage Response

Copper ions catalyze the generation of hydroxyl radicals (·OH) from hydrogen peroxide via the Fenton-like reaction.[41] This sets off oxidative stress, resulting in lipid peroxidation, DNA damage, and rupture of the cell membrane. In vascular endothelial cells, exposure to copper oxide nanoparticles (CuONPs) leads to γH2AX focus formation and activation of the ATR/ATM-p53 signaling pathway, suggesting an important role of DNA damage in cuproptosis.[27] In the meantime, copper ions have the ability to suppress glutathione peroxidase 4 (GPX4) activity, which results in the buildup of lipid peroxides.[28,29] This alters the structure and function of cell membranes, increasing their permeability and allowing intracellular chemicals to seep out. Copper ions are also able to inhibit the ubiquitin-proteasome system, which in turn inhibits cellular protease activity, causing intracellular protein degradation and renewal to be blocked, and normal physiological cellular functions to be affected, ultimately inhibiting cell proliferation and contributing to the movement of cells toward cuproptosis.[42] Cuproptosis is triggered and ROS production is encouraged by the copper ionophore

NSC319726.[43] This results in deoxyribonucleotide depletion and DNA synthesis inhibition, which stops the cell in the G1 phase and causes death. Additionally, when dithiothreitol binds to copper ions, it suppresses the NF-κB signaling pathway, activates the p38 signaling pathway, and increases the creation of ROS, all of which cause cell death.[44] Notably, copper-specific induced oxidative stress is subcellular organelle-selective, with elevated mitochondrial ROS levels preceded by a cytoplasmic ROS burst, and antioxidants such as N-acetylcysteine (NAC) only partially alleviate cuproptosis.

Wnt/β-Catenin Signaling Pathway

Cuproptosis interacts with the signaling pathway of Wnt/β-catenin.[45] The Wnt/β-catenin pathway is activated when copper binds to 3-phosphoinositide-dependent protein kinase-1 (PDK1) and facilitates its interaction with protein kinase B (PKB).[46] Interestingly, cellular resistance to cuproptosis was enhanced by abnormal stimulation of Wnt/β-catenin signaling. Subsequent research revealed that the transcriptional complex β-catenin/transcription factor 4 (TCF4) directly binds to the promoter of ATP-binding cassette sub-family B member 1 (ATP7B) and triggers its production.[47] Copper ions are effluxed, intracellular copper concentration is decreased, and cuproptosis production is inhibited by ATP7B. Cuproptosis susceptibility is increased by TCF4 knockdown or pharmacological inhibition of the Wnt/β-catenin pathway.[48] These results indicate a connection between susceptibility to cuproptosis and copper homeostasis, which is controlled by the Wnt/β-catenin pathway. They also point to a precision medicine approach that uses cuproptosis to treat clinical illnesses.

Relationship Between Cuproptosis and Sepsis

Sepsis is a potentially fatal organ malfunction brought on by a dysregulated host response to infection. Its pathophysiology is intricate and includes several facets of cell death, inflammation, and immune response. Numerous studies have shown that cuproptosis occurs mainly under conditions of metabolic disorders, oxidative stress, and immune cell dysfunction in vivo, and thus it plays an important role in the development and progression of sepsis (Figure 2).[22,32]

Heart

Sepsis-induced myocardial depression is closely associated with cuproptosis. Copper ions may affect myocardial systolic and diastolic function by interfering with energy metabolic processes in cardiomyocytes. The mitochondrial respiratory chain complex in cardiomyocytes is inhibited when copper ions are overloaded, resulting in decreased ATP production and inadequate energy supply to cardiomyocytes. Meanwhile, excessive cuproptosis may also induce oxidative stress in cardiomyocytes, damaging cardiomyocyte membranes and intracellular biomolecules, leading to cardiomyocyte dysfunction and death. Animal experiments have shown that lipopolysaccharide (LPS) stimulation significantly up-regulates the expression of the key genes for cuproptosis, FDX1 and DLAT, in cardiomyocytes, resulting in decreased ATP production and the accumulation of mitochondrial thioctylated proteins.[49] According to clinical research, sepsis patients' higher cardiac troponin I levels and serum copper/zinc ratio are positively correlated, and the copper chelator TTM attenuated LPS-induced cardiomyocyte death.[50] In addition, alterations in the expression of genes linked to cuproptosis might also regulate septic heart damage, although the specific molecular mechanisms require further in-depth study.

Liver

In sepsis, the liver, as a major detoxification and metabolism organ, is susceptible to injury. Abnormal accumulation of copper ions in hepatocytes may lead to cuproptosis by inducing oxidative stress and mitochondrial dysfunction.[51] It has been shown that cuproptosis was found to be involved in the disease process in a mouse model of sepsis induced by cecal ligation and puncture, as well as in a lipopolysaccharide-stimulated cellular model of sepsis.[52] At the onset of sepsis, mice had considerably higher serum levels of aspartate aminotransferase and alanine aminotransferase, and their hepatocytes displayed noticeable swelling and necrosis. At the same time, liver tissues showed decreased expression of cuproptosis-related proteins, including FDX1, LIAS, and DLAT. It has also been found that when the copper chelator penicillamine or methanogens were used, mitochondrial structure and function were significantly improved and liver fibrosis was alleviated. In addition, cuproptosis may further exacerbate sepsis-induced liver injury by affecting the inflammatory response in the liver.

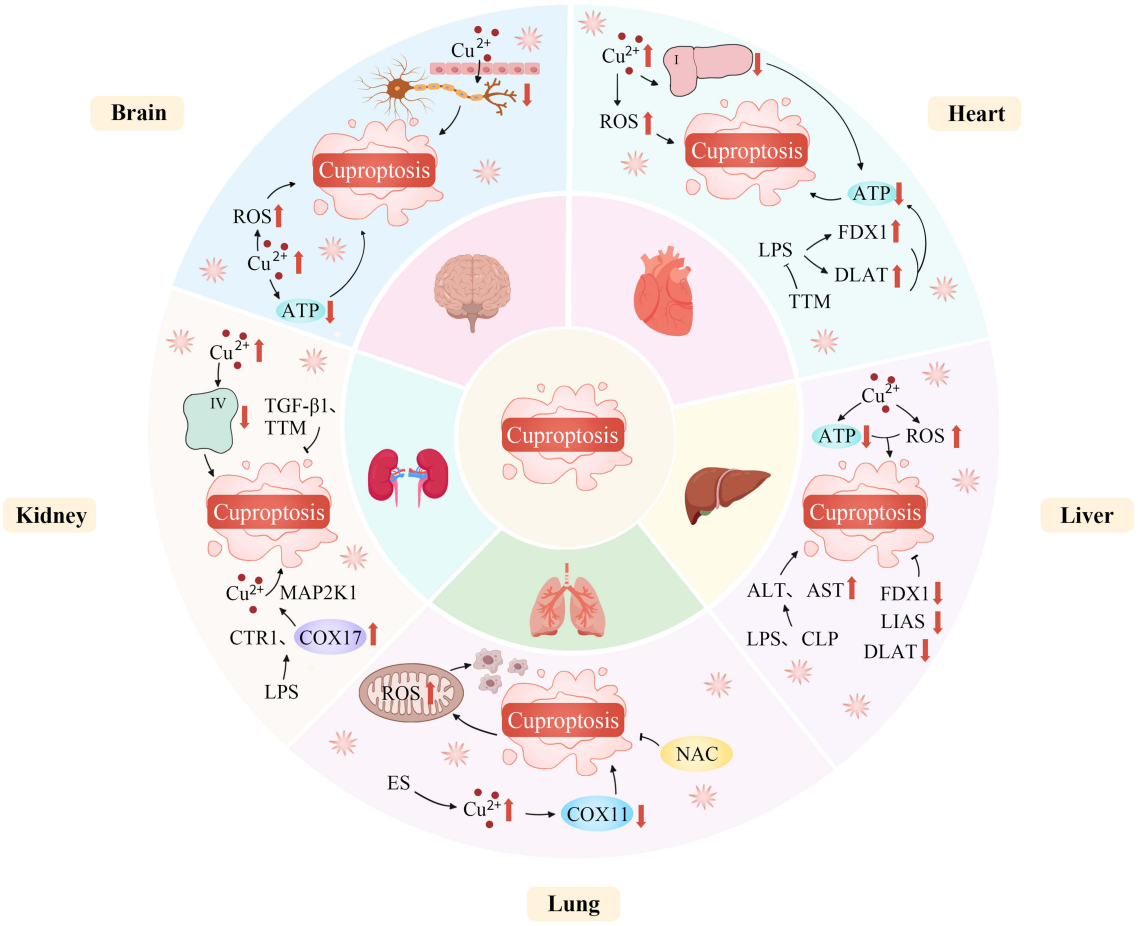

Figure 2 *Cuproptosis plays an important role in the occurrence and progression of sepsis*. Sepsis, triggered by a dysregulated host response to infection, is life-threatening and mechanistically complex. Recent studies have shown that cuproptosis is critical in the development of sepsis, leading to multiple organ damage. In sepsis, uncontrolled inflammation triggers disturbances in copper metabolism and large intracellular accumulation of copper ions, triggering cuproptosis. In the heart, cuproptosis interferes with energy metabolism, resulting in decreased myocardial contractility; in the liver, damage to hepatocytes affects liver function; in the lungs, disruption of the pulmonary vasculature and alveolar epithelium leads to impaired gas exchange; in the kidneys, damage to the tubular epithelium predisposes to the development of acute renal injury; and in the brain, the interference with neuronal cell function affects cognition and neuromodulation. In-depth study of the mechanism of cuproptosis injury is of great significance in finding new targets for sepsis treatment and improving the prognosis of patients.

Abbreviation: ATP, Adenosine triphosphate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CTR1, Copper transporter 1; CLP, Cecal ligation and puncture; COX11, Cytochrome c oxidase assembly protein 11; COX17, Cytochrome c oxidase assembly protein 17; DLAT, Dihydrolipoamide S-Acetyltransferase; ES, Elesclomol; FDX1, Ferredoxin 1; LIAS, Lipoic acid synthetase; LPS, Lipopolysaccharide; NAC, N-acetylcysteine; ROS, Reactive oxygen species; TGF-β1, Transforming growth factor-β1; TTM, Tetrathiomolybdate.

Lung

The lungs are among the most susceptible organs in sepsis, and cuproptosis may be a significant contributing factor. Cuproptosis causes pulmonary edema and lung injury by promoting mitochondrial ROS burst in alveolar epithelial cells, disrupting normal cellular function and structure, and increasing pulmonary vascular permeability. ES was found to enhance copper accumulation in lung tissue, leading to respiratory chain dysfunction and alveolar barrier disruption through inhibition of cytochrome c oxidase assembly protein 11 (COX11).[53] In addition, copper ions may affect the gas exchange function within the lungs, decreasing oxygenation capacity and aggravating respiratory failure. Notably, it has been demonstrated that the occurrence of moderate cellular cuproptosis may alleviate pulmonary fibrosis by inhibiting fibroblast activation.[54,55] The inhibitor of cuproptosis, NAC, also partially reversed lung histopathologic damage.

Kidney

In renal injury due to sepsis, cuproptosis may play an important role. The development of acute kidney injury is closely linked to the up-regulation of CTR1 and cytochrome c oxidase assembly protein 17 (COX17) in renal tubular epithelial

cells of sepsis patients. This up-regulation caused an aberrant build-up of copper ions in the mitochondrial matrix and caused renal tubular cell cuproptosis by activating the MAP2K1 signaling pathway and the release of inflammatory factors.[5] In sepsis, reduced renal perfusion and tissue hypoxia lead to metabolic disorders in renal cells, while copper ion accumulation further interferes with mitochondrial function and disrupts redox balance.[56] Additionally, copper ion buildup can directly impact mitochondrial respiratory chain complex IV activity, causing cellular damage and exacerbating renal fibrosis.[57] By preventing aberrant transforming growth factor-β1 (TGF-β1) from activating, selective divalent copper ion chelators have been shown to improve renal fibrosis.[58] TTM, on the other hand, improves fibrosis by lowering the amount of copper ions in renal tissue.

Brain

The investigation into how cuproptosis contributes to septic brain injury is still in its early phases. In sepsis, the blood-brain barrier permeability increases, and copper ions can enter the central nervous system through the damaged area of the blood-brain barrier, producing toxic effects on neurons and glial cells. On the one hand, copper ions interfere with the energy metabolism of neurons and inhibit the mitochondrial respiratory function, so that neurons lack energy supply and affect their normal physiological activities. On the other hand, oxidative stress resulting from the accumulation of cuproptosis-associated copper ions impairs cellular membranes and organelles in neuronal cells, thereby contributing to neuronal cell death. In addition, cuproptosis may also affect neurotransmitter metabolism and signaling in the brain, which in turn affects brain function and symptoms such as cognitive impairment and blurred consciousness. Nevertheless, additional investigation is required to identify the precise molecular processes and associated signaling pathways.

The Use of Cuproptosis in the Treatment of Sepsis

As research continues, it has been discovered that cuproptosis plays a significant regulatory role in sepsis, which offers fresh approaches to treating and preventing multi-organ dysfunction brought on by sepsis. The current research is still in the exploratory stage for therapeutic strategies against cuproptosis in sepsis. We explore the therapeutic potential of cuproptosis and sort out the present treatment options for cuproptosis in sepsis.

Application of Copper Chelating Agents

Copper chelators work by binding to copper ions and reducing their accumulation within cells, thereby potentially preventing or mitigating organ damage from cuproptosis. Penicillamine and triacetyltriamine are commonly used copper chelators that can reduce the intracellular concentration of free copper ions, thereby attenuating the toxic effects of copper ions on cells and inhibiting the occurrence of cuproptosis. It has been shown that in an animal model of sepsis, after administration of penicillamine treatment, a decrease in the copper ion content of tissues, an improvement in cell damage and death, and a recovery of related organ functions can be observed.[4] However, its specific efficacy and safety in sepsis still need further clinical validation.

Regulation of Copper Transporter Protein Expression

Regulation of the expression of copper transporter proteins can affect intracellular copper ion homeostasis, thereby preventing cuproptosis. Research has demonstrated that ATP7A/ATP7B and CTR1, two copper transporter proteins, are essential for preserving cellular copper homeostasis.[59] By controlling the production of these proteins, either genetically or by medication, cuproptosis may be less likely to occur and the excessive buildup of copper ions in cells may be avoided. In addition, it may also be possible to balance copper concentration and attenuate cuproptosis-mediated organ damage by targeting copper homeostasis-associated genes (eg, COX11).[60] However, the application of these strategies in sepsis therapy is still in the experimental stage.

Interventions Targeting Mitochondrial Function

Cuproptosis is strongly associated with mitochondrial dysfunction, and protection of mitochondrial function may help prevent cuproptosis. The use of mitochondria-targeted antioxidants or mitochondrial protective agents may have

a therapeutic role in treating cuproptosis in sepsis by mitigating the cellular damage caused by cuproptosis by maintaining the mitochondrial membrane potential and decreasing ROS production. The mitochondrial uncoupling agent FCCP may partially reverse the cuproptosis phenotype by restoring membrane potential.[61] In addition, some medications with antioxidant properties, including coenzyme Q10, can shield mitochondria from oxidative damage, preserve their regular operation, and lessen the harm that copper ions do to them, which helps to some degree to relieve cuproptosis.[62] In experimental studies of sepsis, improvement of mitochondrial structure and function, gradual normalization of cellular energy metabolism, and reduction of cellular damage and death associated with cuproptosis were observed after administration of these drugs.

Regulation of Related Genes and Signaling Pathways

Genes associated with cuproptosis, such as cluster of differentiation 274 (CD274), ceruloplasmin (CP), and vascular endothelial growth factor A (VEGFA), are significantly differentially expressed in sepsis-induced cardiotoxicity.[49] Using CD274 inhibitors to reduce LPS-induced myocardial damage has been demonstrated in animal studies, indicating that cuproptosis-related genes (CRGs) may be a potential therapeutic target. Likewise, m^6A methylation changes and genes linked to cuproptosis are significantly correlated, such as METTL3 and WTAP that may affect the expression of CRGs through epigenetic mechanisms.[63] Modulation of m^6A-modifying enzyme activities may provide new ways to attenuate cuproptosis.

AMPK, Wnt/β-catenin, and other signaling pathways are among those regulated in cuproptosis. While PKB/glycogen synthase kinase 3β (GSK-3β) is a crucial regulatory molecule, β-catenin is a multifunctional protein that plays a crucial role in the Wnt/β-catenin signaling pathway. Sepsis causes GSK-3β to become more phosphorylated, the β-catenin degradation complex to become less active, and β-catenin to accumulate and enter the cell's nucleus to bind with T cytokine/lymphoid enhancer factor transcription factors, increasing the transcription of downstream genes and performing a number of intricate physiological processes.[64] Research has demonstrated that administering the β-catenin inhibitor XAV-939 to septic mice lowers their levels of serum pro-inflammatory factors and lessens their inflammatory response.[65] In sepsis, memory γδ T17 cells in the small intestine are activated, which causes them to move to the lungs and release interleukin-17A (IL-17A), which intensifies acute lung injury and sets off excessive inflammatory responses. Because esketamine inhibits the lungs' Wnt/β-catenin signaling system and lowers the generation of chemokine (C-C motif) ligand 1 (CCL1), it can stop γδ T17 cell migration, thereby lightening sepsis-induced lung injury and inflammatory response.[66] It should be noted that inhibition of certain signaling pathways that promote cell survival makes cells more susceptible to the toxic effects of copper ions, which in turn induce cuproptosis, for the treatment of sepsis, and this approach may require more precise regulation to avoid excessive damage to normal cells.

Use of Antioxidants

Excess copper ions can trigger oxidative stress through ROS production, leading to cellular damage. Therefore, application of antioxidants may help to neutralize excess ROS and attenuate cellular damage triggered by cuproptosis. NAC has shown some protective effects in sepsis-related oxidative stress studies, but its specific effects and mechanisms still need to be further investigated.[67]

Development of Nanosystems

Recent studies have developed nanotechnology-based cuproptosis-inducing systems for enhanced cancer immunotherapy. For example, a nanosystem for inducing cuproptosis was constructed by encapsulating copper oxide nanoparticles with copper ionophores in a polymer.[53] This system causes cuproptosis, releases copper ions in tumor cells, and boosts the effectiveness of immune checkpoint inhibitors. Although this strategy is mainly targeted for tumor therapy, its role in regulating cuproptosis death may provide new ideas for sepsis treatment.

Future Research Directions

Modeling of Copper Disease

The establishment of animal models related to the mechanism of cuproptosis is a crucial step to deeply explore the specific mechanism of cuproptosis in sepsis. Cuproptosis has been implicated in the pathophysiologic process of sepsis in

recent years, particularly in the control of cell death and the inflammatory response. Researchers can monitor the dynamics of copper and its influence on the immune response by simulating various phases of sepsis in mice or rats. For example, the use of animal models of copper deficiency or excess can help study the biological functions of copper and its dual role in sepsis, which can either enhance antimicrobial effects or potentially lead to cytotoxicity. The development of suitable animal models can offer fundamental information and an experimental foundation for comprehending this intricate mechanism. Research has indicated that cuproptosis may influence prognosis during sepsis by encouraging oxidative stress and cell death. Furthermore, specialized knockout mice models of cuproptosis-related genes can be created utilizing gene editing methods like CRISPR-Cas9, which will aid in identifying the precise roles and modes of action of these genes in sepsis.

New Drug Development Strategies

The development of targeted drugs based on the mechanism of cuproptosis offers new therapeutic options for sepsis. Copper oxide nanoparticles have shown potential in attenuating sepsis-induced lung injury, and these nanoparticles work by scavenging ROS and inhibiting inflammatory responses. In addition, research is accelerating on copper ionophores and cuproptosis complexing agents that selectively increase intracellular copper concentrations, thereby inducing specific cell death pathways.[68,69]

By combining existing drug retargeting strategies, drugs like disulfiram have demonstrated antitumor effects against a wide range of cancers when combined with copper, which provides new ideas for the treatment of sepsis.[70,71] In order to increase sepsis patients' chances of survival and quality of life, future research could investigate the targeting of genes linked to cuproptosis in greater detail and create innovative copper-based medications. Overall, the study of the mechanism of cuproptosis not only provides a new direction for the treatment of sepsis, but also opens up a broad prospect for the treatment of other related diseases.

Discussion and Prospect

In recent years, cuproptosis has received increasing attention in sepsis research as a newly identified form of regulated cell death. Literature to date suggests that cuproptosis may not only be fundamental to cellular stress responses and mitochondrial dysfunction but may also offer novel insights into the pathogenesis and treatment of sepsis. The hallmark features of cuproptosis, including intracellular copper accumulation, oxidative stress, and metabolic disruption, may exacerbate immune dysregulation and tissue injury—both of which are central to the pathophysiology of sepsis. Notably, copper-induced oxidative stress has been shown to influence cytokine production and immune cell activity, indicating that cuproptosis may play a more active role in modulating inflammatory responses than previously recognized.

From a clinical perspective, targeting cuproptosis-related pathways—such as copper metabolism, mitochondrial stability, and redox balance—could offer promising avenues for therapeutic intervention in sepsis. Strategies including the use of copper chelators, mitochondrial protectants, or pathway-specific modulators may hold potential to attenuate organ dysfunction and improve patient outcomes. Furthermore, cuproptosis-related biomarkers may aid in early diagnosis or risk stratification, although these applications remain to be validated in clinical settings.

Nevertheless, substantial challenges remain. The molecular mechanisms of cuproptosis are not yet fully elucidated, and significant variability exists across studies in defining its regulatory network and interaction with other cell death pathways such as ferroptosis and apoptosis. Additionally, copper metabolism exhibits high interindividual variability depending on genetic, metabolic, and pathological states, which complicates translational efforts. These limitations underscore the need for further mechanistic studies and integrative models that incorporate cuproptosis into the broader immune and metabolic landscape of sepsis.

Future research should prioritize exploring how cuproptosis interacts with immune signaling and systemic inflammatory responses in sepsis. Multidisciplinary approaches integrating bioinformatics, metabolomics, and systems biology will be essential to map the regulatory network of cuproptosis and to evaluate its therapeutic potential in precision medicine.

In summary, while the study of cuproptosis offers an exciting new direction in sepsis research, its clinical relevance must be substantiated through mechanistic validation and translational exploration. A deeper understanding of its interplay with

inflammation, immune regulation, and metabolic stress will be key to transforming these insights into tangible clinical benefits.

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All data in this review are publicly available.

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References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801–810. doi:10.1001/jama.2016.0287
2. Yu SC, Betthauser KD, Gupta A, et al. Comparison of sepsis definitions as automated criteria. *Crit Care Med*. 2021;49:e433–43. doi:10.1097/CCM.0000000000004875
3. Huang W, Wang L, Huang Z, Sun Z, Zheng B. Peroxiredoxin 3 has a crucial role in the macrophage polarization by regulating mitochondrial homeostasis. *Respir Res*. 2024;25:110. doi:10.1186/s12931-024-02739-9
4. Huang Z, Cao L, Yan D. Inflammatory immunity and bacteriological perspectives: a new direction for copper treatment of sepsis. *J Trace Elem Med Biol*. 2024;84:127456. doi:10.1016/j.jtemb.2024.127456
5. Wang T, Fang X, Sheng X, et al. Identification of immune characteristic biomarkers and therapeutic targets in cuproptosis for sepsis by integrated bioinformatics analysis and single-cell RNA sequencing analysis. *Heliyon*. 2024;10:e27379. doi:10.1016/j.heliyon.2024.e27379
6. Li Y, Han Y, Shu Q, Kan Y, Wang Z. Cuproptosis and copper as potential mechanisms and intervention targets in alzheimer's disease. *Biomed Pharmacother*. 2025;183:117814. doi:10.1016/j.biopha.2025.117814
7. Lv X, Zhao L, Song Y, Chen W, Tuo Q. Deciphering the role of copper homeostasis in atherosclerosis: from molecular mechanisms to therapeutic targets. *Int J Mol Sci*. 2024;26:25. doi:10.3390/ijms252111462
8. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J, Chen X. Copper metabolism in cell death and autophagy. *Autophagy*. 2023;19:2175–2195. doi:10.1080/15548627.2023.2200554
9. Gao Y, Jin F, Zhang P, et al. Elesclomol-copper synergizes with imidazole ketone erastin by promoting cuproptosis and ferroptosis in myelodysplastic syndromes. *Biomed Pharmacother*. 2024;175:116727. doi:10.1016/j.biopha.2024.116727
10. Liu Y, Shen M, Zhu S, et al. Metallothionein rescues doxorubicin cardiomyopathy via mitigation of cuproptosis. *Life Sci*. 2025;363:123379. doi:10.1016/j.lfs.2025.123379
11. Huang X, Shi Z, Ming G, Xu D, Cheng S. S-Allyl-L-cysteine (SAC) inhibits copper-induced apoptosis and cuproptosis to alleviate cardiomyocyte injury. *Biochem Biophys Res Commun*. 2024;730:150341. doi:10.1016/j.bbrc.2024.150341
12. Bao J, Wang J, Chen S, et al. Coordination self-assembled AuTPyP-Cu metal-organic framework nanosheets with pH/ultrasound dual-responsiveness for synergistically triggering cuproptosis-augmented chemotherapy. *Acs Nano*. 2024;18:9100–9113. doi:10.1021/acsnano.3c13225
13. Tsvetkov P, Detappe A, Cai K, et al. Mitochondrial metabolism promotes adaptation to proteotoxic stress. *Nat Chem Biol*. 2019;15:681–689. doi:10.1038/s41589-019-0291-9
14. Tsvetkov P, Coy S, Petrova B, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science*. 2022;375:1254–1261. doi:10.1126/science.abf0529
15. Huang M, Zhang Y, Liu X. The mechanism of cuproptosis in parkinson's disease. *Ageing Res Rev*. 2024;95:102214. doi:10.1016/j.arr.2024.102214
16. Zhu Z, Song M, Ren J, Liang L, Mao G, Chen M. Copper homeostasis and cuproptosis in central nervous system diseases. *Cell Death Dis*. 2024;15:850. doi:10.1038/s41419-024-07206-3
17. Chen Z, Li Y, Liu X. Copper homeostasis and copper-induced cell death: novel targeting for intervention in the pathogenesis of vascular aging. *Biomed Pharmacother*. 2023;169:115839. doi:10.1016/j.biopha.2023.115839
18. Al-Omari S. Toward a molecular understanding of the photosensitizer-copper interaction for tumor destruction. *Biophys Rev*. 2013;5:305–311. doi:10.1007/s12551-013-0112-4
19. Ohno M, Narita T, Abe J, et al. Apoptosis in cerebrum of macular mutant mouse. *Acta Neuropathol*. 2002;103:356–362. doi:10.1007/s00401-001-0473-9
20. Gao L, Zhang A. Copper-instigated modulatory cell mortality mechanisms and progress in oncological treatment investigations. *Front Immunol*. 2023;14:1236063. doi:10.3389/fimmu.2023.1236063
21. Yu L, Liou IW, Biggins SW, et al. Copper deficiency in liver diseases: a case series and pathophysiological considerations. *Hepatol Commun*. 2019;3:1159–1165. doi:10.1002/hep4.1393
22. Ling W, Li S, Zhu Y, Wang X, Jiang D, Kang B. Inducers of autophagy and cell death: focus on copper metabolism. *Ecotoxicol Environ Saf*. 2025;290:117725. doi:10.1016/j.ecoenv.2025.117725

23. Pan C, Ji Z, Wang Q, et al. Cuproptosis: mechanisms, biological significance, and advances in disease treatment-A systematic review. *Cns Neurosci Ther*. 2024;30:e70039. doi:10.1111/cns.70039
24. Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease. *Signal Transduct Target Ther*. 2022;7:378. doi:10.1038/s41392-022-01229-y
25. Lonnerdal B. Intestinal regulation of copper homeostasis: a developmental perspective. *Am J Clin Nutr*. 2008;88:846S–850S. doi:10.1093/ajcn/88.3.846S
26. Kahra D, Mondol T, Niemiec MS, Wittung-Stafshede P. Human copper chaperone Atox1 translocates to the nucleus but does not bind DNA in vitro. *Protein Pept Lett*. 2015;22:532–538. doi:10.2174/0929866522666150506094546
27. He H, Zou Z, Wang B, et al. Copper oxide nanoparticles induce oxidative DNA damage and cell death via copper ion-mediated P38 MAPK activation in vascular endothelial cells. *Int J Nanomed*. 2020;15:3291–3302. doi:10.2147/IJN.S241157
28. Cao S, Wang Q, Sun Z, et al. Role of cuproptosis in understanding diseases. *Hum Cell*. 2023;36:1244–1252. doi:10.1007/s13577-023-00914-6
29. Maher P. Potentiation of glutathione loss and nerve cell death by the transition metals iron and copper: implications for age-related neurodegenerative diseases. *Free Radic Biol Med*. 2018;115:92–104. doi:10.1016/j.freeradbiomed.2017.11.015
30. Tang D, Chen X, Kroemer G. Cuproptosis: a copper-triggered modality of mitochondrial cell death. *Cell Res*. 2022;32:417–418. doi:10.1038/s41422-022-00653-7
31. Duan W, He R. Cuproptosis: copper-induced regulated cell death. *Sci China Life Sci*. 2022;65:1680–1682. doi:10.1007/s11427-022-2106-6
32. Feng Y, Yang Z, Wang J, Zhao H. Cuproptosis: unveiling a new frontier in cancer biology and therapeutics. *Cell Commun Signal*. 2024;22:249. doi:10.1186/s12964-024-01625-7
33. Lei G, Tang L, Yu Y, et al. The potential of targeting cuproptosis in the treatment of kidney renal clear cell carcinoma. *Biomed Pharmacother*. 2023;167:115522. doi:10.1016/j.biopha.2023.115522
34. Xie J, Yang Y, Gao Y, He J. Cuproptosis: mechanisms and links with cancers. *Mol Cancer*. 2023;22:46. doi:10.1186/s12943-023-01732-y
35. Wang X, Zhou M, Liu Y, Si Z. Cope with copper: from copper linked mechanisms to copper-based clinical cancer therapies. *Cancer Lett*. 2023;561:216157. doi:10.1016/j.canlet.2023.216157
36. Wu L, Huang F, Sun Z, et al. Downregulation of iron-sulfur cluster biogenesis may contribute to hyperglycemia-mediated diabetic peripheral neuropathy in murine models. *Antioxidants*. 2024;14:13. doi:10.3390/antiox13091036
37. Ramchandani D, Berisa M, Tavarez DA, et al. Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis. *Nat Commun*. 2021;12:7311. doi:10.1038/s41467-021-27559-z
38. Brose J, La Fontaine S, Wedd AG, Xiao Z. Redox sulfur chemistry of the copper chaperone Atox1 is regulated by the enzyme glutaredoxin 1, the reduction potential of the glutathione couple GSSG/2GSH and the availability of Cu(I). *Metallomics*. 2014;6:793–808. doi:10.1039/c4mt00020j
39. Lin C, Chin Y, Zhou M, Sobol RW, Hung M, Tan M. Protein lipoylation: mitochondria, cuproptosis, and beyond. *Trends Biochem Sci*. 2024;49:729–744. doi:10.1016/j.tibs.2024.04.002
40. Chen B, Pan Z, Feng W, Liu Q, Liu Y, He L. Synthesis, characterization and biological activity of novel copper complexes containing a beta-carboline derivative and amino acids. *Dalton Trans*. 2023;52:8040–8050. doi:10.1039/d3dt01088k
41. Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicity of metal ions. *Free Radic Biol Med*. 1995;18:321–336. doi:10.1016/0891-5849(94)00159-h
42. Oliveri V, Lanza V, Milardi D, et al. Amino- and chloro-8-hydroxyquinolines and their copper complexes as proteasome inhibitors and antiproliferative agents. *Metallomics*. 2017;9:1439–1446. doi:10.1039/c7mt00156h
43. Shimada K, Reznik E, Stokes ME, et al. Copper-binding small molecule induces oxidative stress and cell-cycle arrest in glioblastoma-patient-derived cells. *Cell Chem Biol*. 2018;25:585–594. doi:10.1016/j.chembiol.2018.02.010
44. Yip NC, Fombon IS, Liu P, et al. Disulfiram modulated ROS-MAPK and NFkappaB pathways and targeted breast cancer cells with cancer stem cell-like properties. *Br J Cancer*. 2011;104:1564–1574. doi:10.1038/bjc.2011.126
45. Liu Y, Chen L, Li S, et al. Dysregulated Wnt/beta-catenin signaling confers resistance to cuproptosis in cancer cells. *Cell Death Differ*. 2024;31:1452–1466. doi:10.1038/s41418-024-01341-2
46. Guo J, Cheng J, Zheng N, et al. Copper promotes tumorigenesis by activating the PDK1-AKT oncogenic pathway in a copper transporter 1 dependent manner. *Adv Sci*. 2021;8:e2004303. doi:10.1002/advs.202004303
47. Li L, Jensen RA. Understanding and overcoming immunosuppression shaped by cancer stem cells. *Cancer Res*. 2023;83:2096–2104. doi:10.1158/0008-5472.CAN-23-0230
48. Fang L, Zhu Q, Neuenschwander M, et al. A small-molecule antagonist of the beta-catenin/TCF4 interaction blocks the self-renewal of cancer stem cells and suppresses tumorigenesis. *Cancer Res*. 2016;76:891–901. doi:10.1158/0008-5472.CAN-15-1519
49. Yan J, Li Z, Li Y, Zhang Y. Sepsis induced cardiotoxicity by promoting cardiomyocyte cuproptosis. *Biochem Biophys Res Commun*. 2024;690:149245. doi:10.1016/j.bbrc.2023.149245
50. Xu X, Meng J, Fang Q. Prognostic value of serum trace elements copper and zinc levels in sepsis patients. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2020;32:1320–1323. doi:10.3760/cma.j.cn121430-20200313-00216
51. Li M, Tang S, Velkov T, Shen J, Dai C. Copper exposure induces mitochondrial dysfunction and hepatotoxicity via the induction of oxidative stress and PERK/ATF4 -mediated endoplasmic reticulum stress. *Environ Pollut*. 2024;352:124145. doi:10.1016/j.envpol.2024.124145
52. Wu Z, Qian Y, Suo J, Dai X, Peng Z. Effect of cuproptosis on sepsis-induced acute liver injury. *J Guizhou Med Univ*. 2023;48:901–907. doi:10.19367/j.cnki.2096-8388.2023.08.005
53. Li J, Zhang L, Pei S, et al. Copper-based nanoparticles for effective treatment against sepsis-induced lung injury in mice model. *Int J Nanomed*. 2024;19:13507–13524. doi:10.2147/IJN.S488357
54. Zhang B, Li S, Liu H. Immune infiltration in atherosclerosis is mediated by cuproptosis-associated ferroptosis genes. *Cardiovasc Innov Appl*. 2023;1. doi:10.15212/cvia20230003
55. Li G, Peng L, Wu M, Zhao Y, Cheng Z, Li G. Appropriate level of cuproptosis may be involved in alleviating pulmonary fibrosis. *Front Immunol*. 2022;13:1039510. doi:10.3389/fimmu.2022.1039510
56. Sondheimer JH, Mahajan SK, Rye DL, et al. Elevated plasma copper in chronic renal failure. *Am J Clin Nutr*. 1988;47:896–899. doi:10.1093/ajcn/47.5.896

57. Zhu S, Zhou W, Niu Y, et al. COX17 restricts renal fibrosis development by maintaining mitochondrial copper homeostasis and restoring complex IV activity. *Acta Pharmacol Sin*. 2023;44:2091–2102. doi:10.1038/s41401-023-01098-3
58. Gong D, Lu J, Chen X, et al. A copper(II)-selective chelator ameliorates diabetes-evoked renal fibrosis and albuminuria, and suppresses pathogenic TGF-beta activation in the kidneys of rats used as a model of diabetes. *Diabetologia*. 2008;51:1741–1751. doi:10.1007/s00125-008-1088-7
59. Ip V, Liu JJ, Mercer JFB, McKeage MJ. Differential expression of ATP7A, ATP7B and CTR1 in adult rat dorsal root ganglion tissue. *Mol Pain*. 2010;6:53. doi:10.1186/1744-8069-6-53
60. Radin I, Kost L, Gey U, Steinebrunner I, Rodel G. The mitochondrial copper chaperone COX11 has an additional role in cellular redox homeostasis. *PLoS One*. 2021;16:e261465. doi:10.1371/journal.pone.0261465
61. Bertholet AM, Natale AM, Bisignano P, et al. Mitochondrial uncouplers induce proton leak by activating AAC and UCP1. *Nature*. 2022;606:180–187. doi:10.1038/s41586-022-04747-5
62. Prasad panda S, Kesharwani A. Micronutrients/miRs/ATP networking in mitochondria: clinical intervention with ferroptosis, cuproptosis, and calcium burden. *Mitochondrion*. 2023;71:1–16. doi:10.1016/j.mito.2023.05.003
63. Sun L, Zhang Y, Yang B, et al. Lactylation of METTL16 promotes cuproptosis via m(6)A-modification on FDX1 mRNA in gastric cancer. *Nat Commun*. 2023;14:6523. doi:10.1038/s41467-023-42025-8
64. Nusse R, Clevers H. Wnt/beta-catenin signaling, disease, and emerging therapeutic modalities. *Cell*. 2017;169:985–999. doi:10.1016/j.cell.2017.05.016
65. Cheng X, Liu D, Ren X, et al. The beta-catenin/CBP signaling axis participates in sepsis-induced inflammatory lung injury. *Exp Biol Med*. 2022;247:1548–1557. doi:10.1177/15353702221097316
66. Xie B, Wang M, Zhang X, et al. Gut-derived memory gammadelta T17 cells exacerbate sepsis-induced acute lung injury in mice. *Nat Commun*. 2024;15:6737. doi:10.1038/s41467-024-51209-9
67. Ergin B, Guerci P, Zafrani L, et al. Effects of N-acetylcysteine (NAC) supplementation in resuscitation fluids on renal microcirculatory oxygenation, inflammation, and function in a rat model of endotoxemia. *Intensive Care Med Exp*. 2016;4:29. doi:10.1186/s40635-016-0106-1
68. Zhang C, Huang T, Li L. Targeting cuproptosis for cancer therapy: mechanistic insights and clinical perspectives. *J Hematol Oncol*. 2024;17:68. doi:10.1186/s13045-024-01589-8
69. Wang Y, Chen Y, Zhang J, et al. Cuproptosis: a novel therapeutic target for overcoming cancer drug resistance. *Drug Resist Updat*. 2024;72:101018. doi:10.1016/j.drup.2023.101018
70. Zeng M, Wu B, Wei W, et al. Disulfiram: a novel repurposed drug for cancer therapy. *Chin Med J*. 2024;137:1389–1398. doi:10.1097/CM9.0000000000002909
71. Xu X, Han Y, Deng J, et al. Repurposing disulfiram with CuET nanocrystals: enhancing anti-pyroptotic effect through NLRP3 inflammasome inhibition for treating inflammatory bowel diseases. *Acta Pharm Sin B*. 2024;14:2698–2715. doi:10.1016/j.apsb.2024.03.003