

REVIEW ARTICLE

The role of copper and core gene network controlling cuproptosis in infection immunity, diagnosis, and treatment

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Abstract

Copper is an essential trace element in living organisms and is involved in a variety of biochemical processes, including cellular respiration, iron metabolism, and nerve function. In recent years, research has shown that copper is not only essential for fundamental physiological functions but also plays an important role in immune response and pathological states. In particular, copper death (cuproptosis), a recently discovered cell death pathway that is strongly associated with copper overload, is emerging as an appealing area of immune research. Excess copper can induce cell death as a result of copper ions directly binding to sulfide proteins in the tricarboxylic acid cycle. In-depth studies of copper metabolism and its related mechanisms will contribute to developing new diagnostic tools and therapeutic strategies and providing new ideas and approaches for tackling infections and other related diseases. This review summarizes the newest understanding of copper death and the latest advancements in disease diagnosis and treatment, providing a valuable reference for the follow-up research on tuberculosis-related vaccines and copper in immunity.

Keywords: Copper toxicity; Cuproptosis; Tricarboxylic acid cycle

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1. Introduction

Bacterial infections can lead to serious health issues, including pneumonia, tuberculosis, diarrhea, hepatitis, and meningitis.¹ They can be transmitted through food, water, air, or contact, and may result in severe diseases, death, or other serious consequences. At present, antibiotics are the most effective means to inhibit bacterial growth, but the problem of antibiotic resistance is a significant concern.² Apart from antibiotics, metallic elements possess antibacterial properties that can effectively inhibit bacterial growth and reproduction, thereby preventing deleterious impacts attributed to infections in the human body.³ Among these metallic elements, copper exhibits antioxidative properties that can deter bacterial toxins from causing harm to the human body.⁴

Copper is an essential nutrient that plays a role in various biological processes involving bacteria, such as redox reactions, protein synthesis, and cell signaling.⁵ In addition, copper can promote bacterial growth and development.⁶ However, for bacteria, copper is a double-edged sword; while trace amounts of copper can stimulate bacterial growth, an excess of copper can lead to bacterial death.⁷ Compared to other forms of programmed cell death, copper-induced cell death, known as cuproptosis, represents a novel mechanism of cell death.⁸ Studies have shown that copper ions can induce cell death through mitochondrial sulfurtransferase A. When copper ions bind to the sulfurtransferase A protein in the mitochondria, they inhibit the protein's activity, leading to protein toxicity stress response and ultimately resulting in cell death.⁹ Moreover, copper can induce cell death through oxidative stress mediated by lipid acylation proteins.¹⁰ Bacteria experience copper-related cell death when exposed to copper. Copper death, as a type of programmed cell death, may allow bacteria to program a response when faced with pressure from copper ions. Using this mechanism, it is possible to leverage cuproptosis to initiate bacterial cell death under specific therapeutic conditions, to clear the infection. At the same time, appropriate concentrations of copper enhance the response of the host immune system and strengthen the function of macrophages and other immune cells, thereby contributing to infection control. This review primarily summarizes the mechanisms underlying bacterial cuproptosis, aiming to provide novel application insights.

2. Cuproptosis and copper metabolism

Copper-mediated bacterial cell death, also known as cuproptosis, refers to the process of bacterial demise triggered by the toxic effects of copper ions. This unique mechanism of bacterial cell death heavily relies on the toxicity of copper ions to eradicate bacteria.¹¹ Several studies have elucidated the potential mechanisms underlying copper toxicity observed across various microbial genera. Among these, the most recognized mechanism involves copper ions mediating the Fenton reaction, leading to the generation of oxygen atoms and hydroxyl radicals (reactive oxygen species [ROS]) that inflict oxidative damage on macromolecules such as proteins, lipids, and DNA.¹² While low concentrations of copper ions are essential for bacteria and participate in various biological processes such as cell growth and differentiation, high concentrations can induce cuproptosis in bacteria.¹³

An increase in copper (II) ion concentration results in a sharp rise in ROS levels, leading to decreased survival of mycobacteria.¹⁴ Furthermore, copper has been shown to deplete glutathione, a crucial antioxidant that protects

against heavy metal toxicity.¹⁵ It has been suggested that glutathione may bind to copper, disrupting the activity of Fe-S cluster enzymes.¹⁶ In the absence of oxygen atoms, copper replaces iron in Fe-S clusters, forming sulfur bridges with copper instead. Fe-S clusters are organic metal components of iron and sulfur responsible for biological electron transfer, serving as storage reservoirs for iron and sulfur, and playing roles in genome stability and nucleic acid metabolism.¹⁷ Their inactivation leads to the downregulation of several key metabolic enzymes, driving cells into a toxic stress state and ultimately resulting in their demise.

Copper is primarily absorbed in the small intestine, where it is taken up by intestinal cells and transported into the bloodstream.¹⁸ This process relies on specific transporters, such as copper transporter 1 (CTR1).¹⁹ Once in the bloodstream, copper is predominantly carried by proteins such as albumin and ceruloplasmin (plasma ceruloplasmin) to various tissues throughout the body.²⁰ Within cells, copper is directed to different organelles, including the mitochondria and the endoplasmic reticulum.²¹ The liver plays a crucial role in copper storage;²² liver cells can store copper and release it into the bloodstream as needed. This regulation involves several proteins, such as metallothionein.²³ Excess copper is excreted from the body through bile, and the mechanisms governing copper excretion are influenced by the physiological state and copper levels in the body.²⁴

3. Effects of copper metabolism disorders on human

Following the normal physiological processes of copper absorption, transportation, and distribution within the body as described above, any disruption in these finely tuned mechanisms can lead to the onset of copper metabolism disorders. Copper is an essential trace element involved in a variety of physiological functions, including enzyme activity, antioxidant defense, iron metabolism, and nerve conduction.²⁵ However, an excess or deficiency of copper in the body can cause serious health problems (Table 1). Wilson's disease and Mendelian diseases characterized by copper deficiency can be grouped under the umbrella of copper metabolism disorders. The proper regulation of copper levels is thus of utmost importance for maintaining overall health and homeostasis.

Wilson's disease is a genetic disorder primarily caused by mutations in the *ATP7B* gene, leading to a deficiency in a copper-transporting protein crucial for copper excretion in the liver. This deficiency results in copper accumulation and damage in various tissues, including the liver, brain, kidneys, and eyes.²⁶ Symptoms of Wilson's disease can be diverse,

encompassing liver problems such as hepatitis, cirrhosis, and liver failure;²⁷ neurological issues such as movement disorders, cognitive impairments, and behavioral changes;²⁸ and ocular manifestations, notably the Kayser–Fleischer ring – a green or brown deposit at the corneal edge. Additional complications associated with Wilson’s disease include kidney injury, anemia, and joint pain.²⁹

Menkes disease is a rare X-linked genetic disorder primarily caused by mutations in the *ATP7A* gene, causing disruption to the absorption and transport of copper in the body.³⁰ This leads to a cellular deficiency of copper, with symptoms often appearing within a few months of birth.³¹ Affected individuals may experience growth retardation, neurological issues such as mental retardation, seizures, and poor motor coordination, as well as distinct hair abnormalities characterized by thinning and copper coloration.³² Additional complications may include abnormal bone development and low immune function.^{33,34} Menkes disease is diagnosed by a combination of clinical evaluation, biochemical tests for measuring blood levels of copper and related proteins (such as ceruloplasmin), and genetic testing to confirm *ATP7A* mutations.³⁵ Current treatment strategies mainly involve copper supplementation, particularly with copper-amino acid complexes, alongside symptomatic management to address neurological symptoms, though the effectiveness of these interventions is limited.³⁶

In addition to Wilson’s disease and Menkes disease, abnormal copper metabolism can be linked to other conditions. Copper deficiency may arise from malnutrition or absorption disorders, such as Crohn’s disease, and can manifest as anemia, immune dysfunction, and osteoporosis.³⁷ Conversely, while relatively rare, copper overload can occur due to certain liver and kidney diseases or prolonged use of specific medications, such as oral contraceptives, leading to copper accumulation and potential toxicity.³⁸

4. The role of copper and cuproptosis in *Mycobacterium tuberculosis* and their broader implications

Copper plays a crucial role in cellular function, but its dysregulation can lead to toxicological effects, particularly in the context of infections such as *M. tuberculosis*. The mechanisms underlying copper-induced cell death primarily involve oxidative stress, mitochondrial damage, and inflammatory responses.⁵⁰ A comprehensive understanding of these processes is essential, especially in the context of developing therapeutic strategies targeting copper metabolism disorders, such as Wilson’s disease, which is characterized by excessive copper accumulation in the body. Within the copper-related network, several key genes significantly influence cellular responses to varying copper levels. Genes such as *ATP7A* and *ATP7B* are pivotal for maintaining copper homeostasis, they facilitate copper transport and excretion, thereby preventing toxicity.⁴⁰ In addition to these transport mechanisms, antioxidant genes such as superoxide dismutase 1 and glutathione peroxidase are critical in mitigating oxidative stress associated with elevated copper levels.^{51,52} The regulation of cell fate in response to copper stress is also governed by apoptosis-related genes. For instance, genes such as *Bcl-2* and *Bax* play vital roles in the apoptotic pathways that determine whether a cell survives or undergoes programmed cell death under conditions of copper-induced stress.⁵¹ In addition, inflammatory-related genes involved in the nuclear factor kappa B signaling pathway further complicate the interplay between cell survival and death in environments rich in copper.⁵³ The activation of this pathway is often linked to the inflammatory response associated with infection and stress, influencing the overall cellular outcome. Recent research has shed light on the protective role of the cuproptosis regulatory factor ferredoxin 1 (FDX1) in clear cell renal cell carcinoma.⁵⁴ The

Table 1. Cuproptosis-related immune markers for the diagnosis and treatment of diseases

Disease	Copper-related immune markers	References
Wilson’s disease	Plasma ceruloplasmin, non-ceruloplasmin-bound copper	26,39
Menkes disease	Activity and expression level of copper transporter ATP7A	40
Rheumatoid arthritis, etc.	Serum copper level, copper/zinc ratio	41
Breast cancer, lung cancer, etc.	Copper content in tumor tissue and serum ceruloplasmin level	42,43
Primary biliary cholangitis	Serum copper, ceruloplasmin	44
Alzheimer’s disease	Urinary copper excretion and hepatic copper content	45
Amyotrophic lateral sclerosis	Copper content in the brain and copper concentration in cerebrospinal fluid	46
Multiple sclerosis	Ceruloplasmin fragments of cerebrospinal fluid	47
Hemochromatosis	Copper/iron ratio	48
Inflammatory bowel disease	Intestinal mucosal copper content, serum copper-related protein	49

expression levels of FDX1 have been correlated with tumor malignancy, suggesting that it may function as a potential therapeutic target.⁵⁵ Notably, FDX1 appears to enhance antitumor immune responses, indicating its dual role in both cancer progression and immune modulation.⁵⁶ The differential expression and mutation of cuproptosis-related genes across various cancers underscore their potential role in tumor prognosis, immune evasion, and the dynamics of the tumor microenvironment, suggesting that cuproptosis may be instrumental in cancer initiation and progression.⁵⁷

Several cuproptosis-related proteins, such as DBT and SLC31A1, have been shown to correlate significantly with immune cell functions, including those of macrophages, neutrophils, and regulatory T cells.⁵⁸ This relationship indicates that cuproptosis may play a dual role in modulating immune responses and influencing the pathological mechanisms underlying diverse conditions, including metabolic disorders such as diabetes. Furthermore, copper exposure has profound implications on mitochondrial function. Elevated copper levels can result in the release of mitochondrial DNA into the cytoplasm, a phenomenon often triggered by deficiencies in transcription factor A.⁵⁹ This release activates the cGAS-STING signaling pathway, which is a critical trigger for innate immune responses, particularly in liver cells.

Copper, while an essential trace element, can become toxic at elevated concentrations, necessitating the development of sophisticated detoxification mechanisms to ensure bacterial stability. This is particularly significant for *M. tuberculosis*, which exhibits a complex repertoire of copper resistance genes to mitigate the harmful effects of excess copper (Figure 1). Key genes involved in copper resistance include *copA*, *copB*, *copC*, and *copD*, which contribute directly to the bacteria's ability to withstand copper-induced stress.⁶⁰ The copper-inducible transcriptional regulatory factor CopR plays a vital role in orchestrating the expression of these resistance genes, ensuring a coordinated response to copper exposure.⁶¹ In addition, the copper-resistance system comprises essential components such as CopT, a copper-translocating P-type ATPase critical for efficient copper transport, and CopZ, a copper-binding protein that sequesters free copper ions. Another key player is CopY, which functions as a copper tolerance protein, mitigating copper's toxic effects.⁶² The interplay among these genes underlies a signaling pathway centered around the regulatory functions of CopR, the transport capabilities of CopT, the binding affinities of CopZ, and the protective roles of CopY.

5. The role of cuproptosis in *M. tuberculosis* immunoevasion

M. tuberculosis has developed intricate strategies to survive and replicate within host macrophages, a feat closely linked

to its sophisticated copper homeostasis system. Following the phagocytosis of *M. tuberculosis* by macrophages, the host's immune response actively deploys copper ions as a means to limit bacterial growth. Despite this hostile environment, *M. tuberculosis* has evolved complex regulatory mechanisms to manage copper levels effectively, which enhances its survival and pathogenicity.

A key component of the bacterial response to copper stress is the global regulator sigma factor C (SigC). Acting as a transcriptional activator, SigC facilitates copper acquisition and helps *M. tuberculosis* adapt to conditions of copper scarcity, thus underscoring its vital role in the bacterium's pathogenic strategies during episodes of copper deficiency. This regulatory pathway encapsulates the dual nature of copper, which serves as an essential nutrient for bacterial growth but can also act as a toxin under conditions of excess, particularly through the generation of harmful hydroxyl free radicals. Several copper-related proteins are integral to maintaining copper balance within *M. tuberculosis*. Among these, copper efflux proteins CptV (Rv0969) and MctB (Rv1698) play critical roles in conferring copper resistance by actively transporting surplus copper ions out of the bacterial cytoplasm. In addition, the copper-binding protein MymT (Rv0186A) is involved in sequestering copper, thereby mitigating its toxic effects. The interplay among these proteins is particularly crucial in the host environment, where elevated copper concentrations arise during the immune response against infection.

The dynamics of copper metabolism are further complicated by the action of interferon-gamma (IFN- γ), a cytokine produced by CD4+ T cells, which enhances macrophage activation and boosts their capacity to contain pathogens. IFN- γ upregulates various copper transport mechanisms, including the high-affinity copper uptake protein CTR1. This protein, along with partner proteins such as ATOX1 and ATP7A, is instrumental in facilitating copper transport into phagosomes, thereby amplifying the host's antimicrobial strategies. Notably, the hypoxic conditions associated with granuloma formation during *M. tuberculosis* infection promote the expression of CTR1, highlighting the nuanced relationship between copper metabolism and immune responses.

While copper is essential for bacterial growth, the high concentrations introduced by macrophages can be detrimental, catalyzing the production of reactive hydroxyl radicals. In response, *M. tuberculosis* employs various resistance mechanisms, such as the chelation of copper by MymT and the efflux of copper ions mediated by CptV and MctB. The cooperative action of CptV and MctB is particularly significant, as MctB has been shown to be essential for the virulence of *M. tuberculosis*. In the

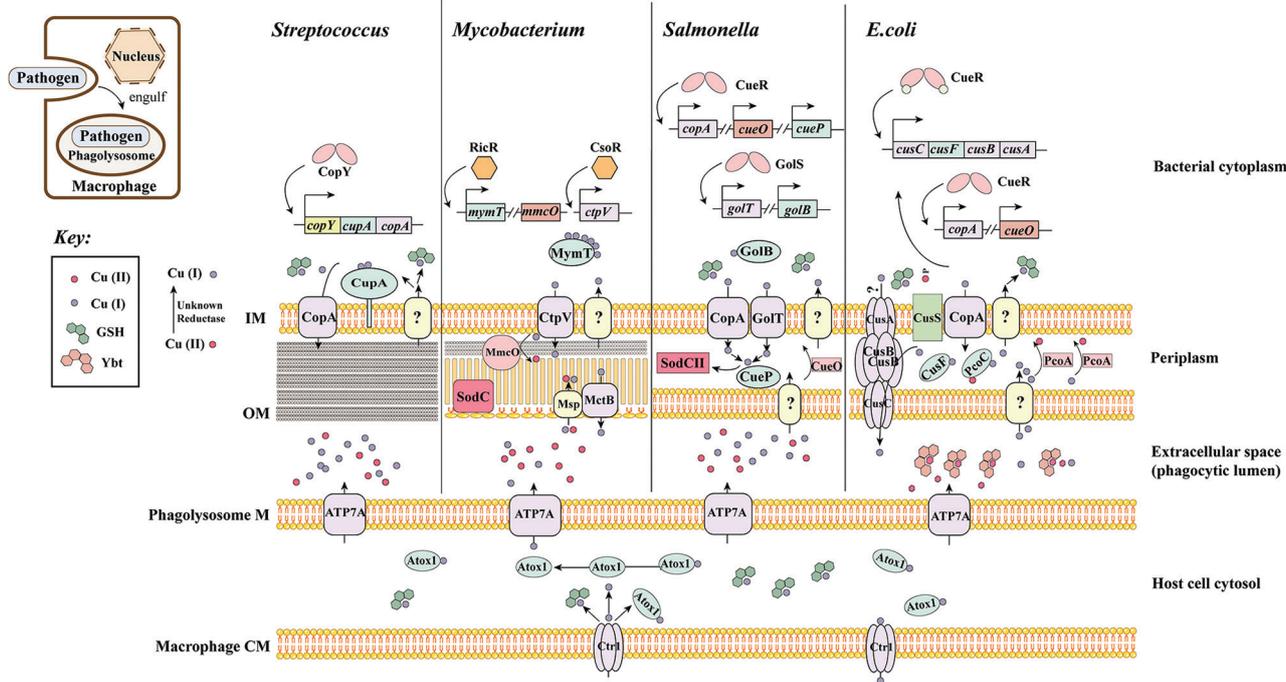


Figure 1. Schematic representation of bacterial pathogens in the context of host-pathogen interaction. This figure illustrates the copper transport, efflux, induction, and resistance pathways within selected bacterial pathogens, namely the Gram-positive *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, as well as the Gram-negative *Escherichia coli* and *Salmonella*. Notably, whereas the Gram-negative bacteria are characterized by a more prominent periplasmic space, which is integral to their copper handling and other physiological processes, the Gram-positive bacteria, despite having a relatively less conspicuous periplasmic region (as indicated by shading and annotated in the legend), also partake in these mechanisms.

absence of MctB, the bacterium becomes vulnerable to copper overload, which jeopardizes its survival.

The coordination of copper homeostasis in *M. tuberculosis* is further regulated by copper-inducible proteins, including CosR, which modulate intracellular copper concentrations. Under conditions of excess copper, *M. tuberculosis* initiates the expression of MymT to sequester the surplus copper, followed by expulsion through the action of CptV and MctB.⁶³ This finely tuned regulation of copper ions not only contributes to bacterial resilience against host defenses but also reinforces the pathogen’s overall virulence.

6. Similarities and differences in cuproptosis and related gene networks: Infection immunity versus other diseases

The metal’s involvement in immune responses is characterized by its ability to modulate the function of immune cells, particularly white blood cells, thereby promoting antimicrobial effects (Figure 2). For instance, copper enhances the bactericidal capacity of macrophages, bolstering the host’s defenses against pathogens. However, the relationship between copper, cell death mechanisms, and infection immunity is complex, demonstrating both

similarities and distinct differences when compared to other diseases. One of the primary roles of copper in immune function is its influence on antimicrobial activities. During infection, elevated copper levels can stimulate immune responses, aiding in pathogen resistance. This heightened copper concentration is integral to the innate immune response, as it acts as a signaling molecule that regulates the kinase activity of α -kinase 1, enhancing the host’s ability to respond to bacterial infections.⁶⁴ In addition, copper mediates various cell death pathways that can influence the fate of immune cells, particularly under conditions of infection. For example, copper-induced cell death, referred to as cuproptosis, can lead to immune cell apoptosis in certain contexts, thereby shaping the overall inflammation and immune response.⁶⁵

The metabolic abnormalities associated with copper can lead to the accumulation of ROS, which are critical mediators in many pathological conditions, including infections, cancer, and neurodegenerative diseases. ROS not only influences immune responses but also modulates cellular signaling pathways and gene expression. Notably, the generation of ROS can differ vastly between infectious and non-infectious conditions, impacting cellular outcomes of stress and damage. Despite its essential role in enhancing

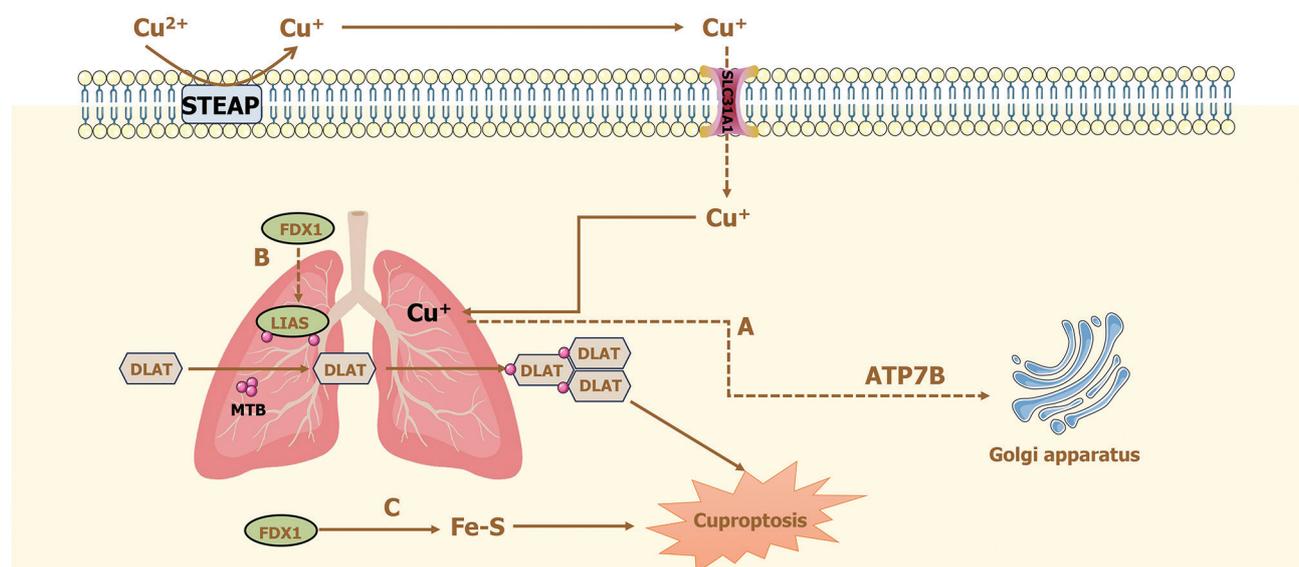


Figure 2. Schematic of copper death-immune network. (A) Copper entry and homeostasis: Cu^{2+} enters cells. ATP7B, under low intracellular copper, transports Cu^{2+} to the Golgi apparatus for ceruloplasmin maturation. (A) Disruption of copper balance, such as excessive intake or expulsion failure, triggers abnormal intracellular copper ion concentration changes, which act as a signal to initiate copper death. (B) Protein lipidation, and copper redox reaction: FDX1 and LIAS regulate protein lipidation. FDX1 reduces Cu^{2+} to Cu^+ , which then affects the TCA cycle through DLAT. (C) TCA cycle impact and apoptosis: Cu^+ interaction with TCA cycle components leads to protein aggregation and Fe-S cluster protein destabilization, causing proteotoxic stress and apoptosis. *Mycobacterium tuberculosis* or pathological conditions can alter copper dynamics through proteins such as ATP7B, influencing this network. Abbreviations: DLAT: Dihydrolipoamide S-acetyltransferase; FDX1: Ferredoxin 1; LIAS: Lipoic acid synthase; MTB: *Mycobacterium tuberculosis*; STEAP: Six-Transmembrane Epithelial Antigen of the Prostate family; TCA: Tricarboxylic acid.

immune responses, copper exhibits divergent biological activities depending on the context. While increased copper levels are typically beneficial in pathogen resistance during infections, excessive copper accumulation can be detrimental, promoting cell apoptosis and inflammation in cancer and neurodegenerative diseases.⁶⁶ For instance, the copper-dependent transcription factor Mac1 enables the endogenous fungal pathogen *Histoplasma capsulatum* to sense low copper environments within macrophage phagosomes. This adaptation allows the pathogen to modulate its copper acquisition mechanisms and other strategies to counteract the elevated antimicrobial defenses activated by post-immune response.

7. Copper’s role in cell death, with analysis and prospects for diagnosis and drug targets

The conservation analysis of copper and the core gene network controlling cuproptosis, involving the conservation and regulatory networks of genes, in different organisms holds huge significance. Across various organisms, copper-related genes and their regulatory factors exhibit high sequence and functional similarities, indicating a crucial role of copper metabolism in the evolutionary process. Copper plays a vital role in cellular signaling, as it induces the expression of alpha-fetoprotein and interacts with C-C chemokine

receptor type 5, leading to leukocyte death and subsequent immune suppression, which may explain the phenomenon of recurrent or chronic infections in some patients with mitochondrial disease.⁶⁷ These genes and signaling pathways are typically associated with processes such as cellular energy metabolism, redox status, and cell cycle regulation, highlighting the importance of their physiological functions.

In the diagnostic realm, abnormal copper metabolism and cuproptosis-related genes can serve as potential biomarkers for early diagnosis and disease monitoring. For instance, alterations in copper levels and related gene expression in serum or tissues may provide information on pathological conditions such as cancer, neurodegenerative diseases, and others. The potential value of 16 long non-coding RNAs (lncRNAs) associated with cuproptosis in predicting prognosis for lung adenocarcinoma suggests that high-risk patients not only have shorter survival but also face greater risks of immune evasion, indicating that these lncRNAs could become new targets for clinical application and immunotherapy.⁶⁸ Cuproptosis also plays a role in Crohn’s disease and inflammatory bowel disease, where genes associated with cuproptosis impact immune cell infiltration and metabolic activities in the pathological processes. This suggests that cuproptosis may promote the progression of CD by inducing immune responses and metabolic dysfunction, offering new insights into the disease mechanisms and potential therapeutic

targets.^{69,70} The detection of these biomarkers altogether can aid in further understanding disease mechanisms and developing personalized treatment strategies.

Copper-related genes and key molecules in the cuproptosis pathway can serve as targets for novel drug development, where inhibitors or activators targeting specific genes or signaling pathways can modulate copper metabolism. For example, inhibiting certain copper transport proteins may help restrict tumor growth. Research has established a cuproptosis-related gene signature that can effectively predict the prognosis of hepatocellular carcinoma patients, revealing that upregulation of pyridoxal kinase promotes the proliferation and metastasis of liver cancer, whereas PDXK deficiency enhances the sensitivity of liver cancer cells to cuproptosis inducers, indicating that PDXK may be a potential diagnostic and therapeutic target for liver cancer.⁷¹ Bioinformatics analysis has identified the significant role of copper metabolism-related genes (CMRGs) in osteosarcoma patient prognosis, immune microenvironment, and drug sensitivity, shedding light on the potential relationship between copper metabolism and osteosarcoma and suggesting that CMRGs could serve as novel prognostic markers and therapeutic targets.⁷² Furthermore, therapeutic approaches based on copper-based drugs or copper supplementation have shown potential in anticancer strategies and immunomodulation. These studies present new opportunities for the clinical application of copper-related biology.

Utilizing bacterial cuproptosis mechanisms can lead to the development of novel antibacterial measures. A nano-drug, nitrite-oxidizing nanoparticles embedded in electrodeposited copper (NP@ESCu), combined with copper and elesclomol, has been designed to induce cuproptosis in cancer cells while boosting anti-tumor immune responses, offering a new strategy for future cancer therapies.⁷³ In bacteria, copper activates the response regulator CopR, which regulates the rearrangement of lipid proteins and the expression of copper resistance genes, thereby reducing the immunostimulatory properties of lipid proteins from high to low. This mechanism may be commonly present in other Firmicutes as well.⁷⁴ The following strategies are proposed to combat bacterial copper-related resistance mechanisms: (i) developing inhibitors that specifically target copper resistance genes to disrupt the copper tolerance mechanisms of bacteria. This approach aims to prevent bacteria from effectively handling high copper environments, thereby weakening their survival and growth capabilities; (ii) designing inhibitors against the copper sensor CopR. By blocking CopR, the bacteria's ability to sense changes in copper levels is impaired, which, in turn, disrupts the downstream regulatory pathways related to copper response; (iii) developing inhibitors directed at the copper transport protein CopT. These inhibitors are intended to

hinder the process of bacterial copper transport, restricting the uptake or efflux of copper ions and thus disturbing the normal copper homeostasis within the bacteria; (iv) creating inhibitors that target the copper-binding protein CopZ. By disrupting the interaction between CopZ and copper, the bacteria's ability to bind and sequester copper is compromised, leading to abnormal copper metabolism; (v) developing inhibitors against the copper-resistance protein CopY. This can impede the bacteria's overall copper resistance function, making them more vulnerable to the toxic effects of copper in the environment. The importance of copper in human physiological and pathological processes—especially in maintaining immune function, lipid balance, and related diseases such as ischemic heart disease and non-alcoholic fatty liver disease⁷⁵—necessitates further exploration of biomarkers for copper deficiency, dietary recommendations, and its potential impacts on health.

8. Summary and future direction

Copper homeostasis and cuproptosis are correlated with tuberculosis. The cellular metabolic process of cuproptosis mainly disrupts the tricarboxylic acid cycle and may play a regulatory role in the progression of tuberculosis. Cuproptosis is a newly discovered form of regulatory cell death that is closely related to other forms of regulated cell death, suggesting a potential relationship between cuproptosis and tuberculosis. Many researchers are now investigating this relationship with various major diseases. At present, despite existing clinical options, there are no effective treatments for tuberculosis. Treatment efficacy varies among patients due to different factors. Researchers are beginning to explore the link between copper dysregulation and tuberculosis. Studies of tuberculosis have analyzed the connections between specific genes and various aspects of the disease. Some researchers have identified a potentially important role for these genes in the association between cuproptosis and tuberculosis. However, due to insufficient biological evidence and experimental validation, these studies have only indirectly demonstrated a link between cuproptosis and tuberculosis. Whether cuproptosis directly contributes to the pathogenesis of tuberculosis or impacts its progression remains unclear.

The discovery of cuproptosis enhances our understanding of tuberculosis and its underlying molecular mechanisms. Cuproptosis may also hold potential value in drug screening for treating this disease. Future research could focus on developing strategies to lower intracellular copper levels or inhibit copper transport proteins, leveraging the chelating effects of copper chelators. This opens up new avenues for intervention in the treatment of tuberculosis. In addition, copper can be transported into cells using copper ion carriers to increase intracellular copper levels. However,

thorough studies of cuproptosis and its associated genes necessitate well-designed pre-clinical experiments and clinical trials, which present significant implementation challenges. Nonetheless, this is a promising research area, and we look forward to future advancements.

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Conflict of interest

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