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Mechanisms of copper metabolism and cuproptosis: implications for liver diseases

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Copper is an essential trace element in the human body, involved in various biological processes, including cell metabolism, nerve development, and immune function. Its homeostasis is vital for maintaining normal cellular functions, and disruptions in copper homeostasis can lead to a wide range of diseases. Cuproptosis is a copper ion-dependent form of programmed cell death that leads to abnormal oligomerization of lipoylated proteins and dysfunction of iron-sulfur cluster proteins in the mitochondrial tricarboxylic acid (TCA) cycle, thereby triggering intracellular oxidative stress and proteotoxic stress. In this review, we have delved into the mechanisms of copper metabolism and cuproptosis, as well as their roles in several liver diseases, including Wilson disease (WD), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), acute liver injury (ALI), and hepatocellular carcinoma (HCC), as well as their therapeutic potential.

KEYWORDS

copper metabolism, cuproptosis, Wilson disease, alcoholic liver disease, non-alcoholic fatty liver disease, acute liver injury, hepatocellular carcinoma

1 Introduction

Copper is an essential trace element in the human body. Although its concentration in the body is relatively low, it plays a crucial role in many important biological functions, such as cell metabolism, nerve development, and immune function (1). In recent years, the crucial role of copper homeostasis in human health has increasingly drawn attention. The concentration of copper ions within cells must be maintained at a precise homeostatic level, which is vital for normal cellular physiological functions. Under physiological conditions, copper ion absorption, distribution, storage, and excretion are strictly controlled. However, if copper homeostasis is disturbed, cells may experience a cascade of metabolic disorders, leading to various diseases.

Programmed cell death (PCD) is an essential process for maintaining tissue stability and developmental equilibrium. Under normal physiological cycles or various pathological conditions, organisms initiate different mechanisms of PCD to maintain homeostasis. The abnormal regulation of these mechanisms can trigger the development of various diseases. To date, several PCDs have been identified, such as apoptosis, necroptosis and ferroptosis, etc (2). Each type of PCD follows its unique mechanisms, contributing to the regulation of cell fate, and thus playing crucial roles in maintaining tissue homeostasis, immune responses, and disease progression.

In 2022, Tsvetkov et al. reported that elesclomol, a CI, could trigger a novel copper-dependent PCD, leading to the demise of ABC1 cells (3). This type of PCD is unique and cannot be reversed by inhibiting caspase-3 (apoptosis), necroptosis-1 (necroptosis), or ferrostatin-1 (ferroptosis). Consequently, this new mechanism of PCD has been termed cuproptosis. Cells undergoing cuproptosis display a spectrum of unique morphological alterations characterized by the shrinkage of mitochondria, reduction of the inner mitochondrial membrane, and the formation of large vacuoles; the endoplasmic reticulum becomes loosely structured and disordered; and the cell membrane ruptures (4). The excessive accumulation of copper within cells severely disrupts a series of copper-dependent metabolic processes, including key stages in the tricarboxylic acid (TCA) cycle and mitochondrial electron transfer chain (mtETC) (5). The aberrant progression of these metabolic activities ultimately disrupts the cell membrane's integrity, causing the leakage of intracellular substances and resulting in cuproptosis. Cuproptosis plays a crucial role in various diseases, such as cancers, cardiovascular diseases, and pulmonary diseases (6–8). Moreover, as an immunogenic form of PCD, modulating cuproptotic regulators and cuproptosis is one of the key strategies to regulate immune cell infiltration and impact the prognosis of cancer patients (9–11).

Given the critical role of the liver in copper metabolism, research on copper homeostasis in various liver diseases has advanced significantly in recent years (12). However, the underlying mechanisms still require further exploration by scientific researchers to be fully elucidated. In this manuscript, we focus on the mechanisms of copper metabolism and cuproptosis, and explore their roles in various liver diseases, including Wilson disease (WD), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), acute liver injury (ALI), and hepatocellular carcinoma (HCC).

2 Copper metabolism

Copper is a vital trace element for the human body, typically acquired through diet. These food sources supply the body with the required copper levels to support essential functions, such as angiogenesis, neuroregulation, and energy metabolism, etc (1). Copper is primarily obtained from food as copper ions (Cu^+ and Cu^{2+}), and is absorbed by intestinal epithelial cells (IECs) (13). Here, Cu^{2+} is reduced by six transmembrane epithelial antigen of the prostate (STEAP) and duodenal cytochrome b (DCYTB), and subsequently, the absorption of Cu^+ is facilitated by copper

transport protein 1 (CTR1), which is situated on the surface of IECs (14–16). The absorption of copper is regulated by multiple factors. IECs secrete the intestinal mucus layer, which serves as a physical barrier for the small intestine and also regulates the absorption of nutrients (17). Mucins within the mucus layer are important regulators of copper absorption, modulating the solubility and diffusion rate of copper ions via their copper-binding sites (18). The trace element zinc also regulates copper absorption. Zinc can bind to mucins, and exhibiting a higher binding affinity than copper (19). Excessive zinc can competitively inhibit copper absorption. In addition, recent research has indicated that zinc transporter 1 (ZnT1) has the capability to directly transport Cu^{2+} (20). Conditional knockout of ZnT1 in IECs can lead to a decrease in intracellular Cu^{2+} levels.

Copper absorbed by IECs can serve as a cofactor for enzymes to modulate the intracellular redox state, thereby sustaining the cells' functionality and homeostasis. Additionally, it can be transported out of the cells via the ATP7A transporter (21). Copper in the bloodstream is transported by binding to companion proteins and delivered to target cells throughout the body (22). Similar to IECs, the process of copper entering target cells is also mediated by CTR1.

The liver is essential for copper metabolism. Copper that enters the bloodstream travels to the liver via the portal vein and subsequently enters hepatocytes through CTR1. In the liver, copper is incorporated into ceruloplasmin (CP), which is secreted by the liver and serves as the primary copper carrier protein. CP has a relatively short half-life, with fully copper-loaded CP (holo-CP) having a half-life of 4–5 days, while copper-free CP (apo-CP) has a half-life of approximately 5 hours. This dynamic regulation allows CP levels to fluctuate in response to changes in the hepatic copper pool, thereby maintaining systemic copper homeostasis. ATP7B is a transmembrane copper-transporting ATPase primarily expressed in the liver and is vital for maintaining overall copper balance in the body (23). ATP7B transports cytosolic copper ions to the Golgi apparatus, where they are loaded onto the precursor of CP to form functional CP, which is then secreted into the bloodstream (24). Additionally, when hepatic copper levels are elevated, ATP7B facilitates secrete excess copper into the bile for excretion, thereby maintaining copper homeostasis (Figure 1) (25).

In the bloodstream, copper ions transported to target cells by carrier proteins such as albumin and CP. At the surface of target cells, Cu^{2+} is reduced by STEAP and DCYTB (14, 15), and subsequently transported into the cell via CTR1 (26). Upon entering the cells, the storage, distribution, and efflux of copper ions are tightly regulated by various mechanisms. Metallothionein 1/2 (MT-1/2), which are rich in cysteine, can bind copper ions through their thiol groups (-SH), thereby mediating the storage of copper within cells (27). Moreover, copper ions can also be transported to specific target proteins via distinct chaperone proteins to exert their biological functions. For example, cytochrome c oxidase 17 (COX17) can transport copper to cytochrome c oxidase (CCO), participating in mitochondrial function and oxidative phosphorylation (28); copper chaperone for superoxide dismutase (CCS) can deliver copper ions to superoxide dismutase 1 (SOD1), thereby enhancing its

antioxidant activity against reactive oxygen species (ROS) (29); antioxidant 1 copper chaperone (ATOX1) can shuttle copper to ATP7A or ATP7B, thereby aiding in the synthesis of CP and other copper-requiring enzymes, or promoting copper efflux to preserve intracellular copper homeostasis (Figure 2) (30–32). These processes collectively form an intricate regulatory network of intracellular copper metabolism, ensuring the rational distribution and utilization of copper ions, thereby maintaining normal cellular physiological functions.

3 Cuproptosis

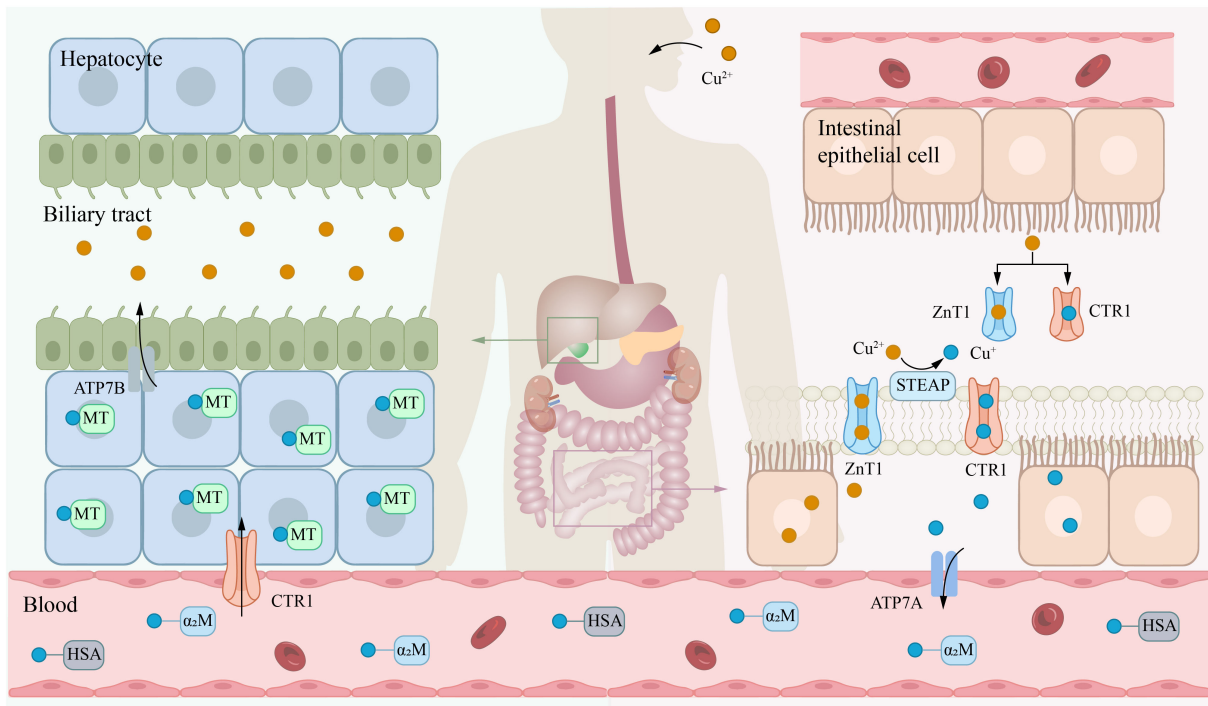
Intracellular copper ion levels must be meticulously controlled to remain within a precise homeostatic range (33). When these levels surpass the physiological threshold, copper ions can exert toxic effects. Over four decades ago, biologists found that excess copper could cause cell death (34). Patients with WD stand at the forefront of copper biology and have provided key insights into cell death (35). They accumulate excess copper, leading to extensive hepatocyte death (36). The link between copper dysregulation and cell death is crucial in rare diseases like WD and also has significant implications for more common conditions, including cancer. However, the exact molecular mechanisms remain to be fully understood. Copper ionophores (CIs) are lipophilic molecules capable of reversibly binding to copper. They can traverse the plasma and mitochondrial membranes, delivering copper ions to specific intracellular locations (37). CIs are widely used in the study of intracellular copper transport and the elucidation of related mechanisms. The most commonly used CIs are Disulfiram (DSF) and Elesclomol (ES). DSF was initially employed for alcohol abstinence therapy but was later discovered to function as a CI, inducing copper-dependent antitumor effects (38). ES, originally developed by Synta Pharmaceuticals, was initially believed to induce tumor cell apoptosis through oxidative stress (39). Subsequent research revealed that ES serves as a CI, transporting Cu^{2+} into the mitochondria. The reduction of Cu^{2+} within the mitochondria enhances the production of ROS, thereby contributing to its antitumor mechanisms (40). With the in-depth research on CIs, in 2019, Tsvetkov et al. reported that by replacing glucose with galactose to alter cellular metabolism and increase mitochondrial respiration (Hi-mito state), tumor cells could acquire resistance to proteasome inhibitors. Intriguingly, in this metabolic state, cells become more sensitive to ES (41, 42). Further analysis revealed that the mitochondrial reductase ferredoxin 1 (FDX1) is a direct target of ES, leading to a unique form of copper-dependent PCD (41, 42). Subsequently, in 2022, they further elucidated that this PCD results from copper binding to lipoylated components within the mitochondria. Specifically, within the cell, particularly in the mitochondria, excess copper leads to abnormal aggregation of lipoylated proteins, disrupts iron-sulfur (Fe-S) cluster proteins involved in mitochondrial respiration, triggers proteotoxic stress responses, and results in cell death (3). Notably, this cell death pathway is resistant to inhibition by established PCDs inhibitors, and it has been termed cuproptosis (3).

Mitochondria are a critical target for cuproptosis. Tsvetkov et al. reported that cells highly dependent on mitochondrial respiration exhibit significantly greater sensitivity to CIs than those primarily relying on glycolysis (3). In addition, mitochondrial antioxidants and mitochondrial function inhibitors can both reduce this sensitivity. Furthermore, inhibiting key enzymes in cellular aerobic glycolysis, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), can also increase the sensitivity to cuproptosis (43). Cuproptosis cells exhibit morphological features similar to apoptosis cells, including mitochondrial atrophy, plasma membrane rupture, and chromatin disruption (44). However, the underlying mechanisms are entirely different. Mechanistically, cuproptosis is initiated by the oligomerization of lipoylated components within the mitochondrial, rather than through the activation of caspase proteins.

Lipoylation is a conserved post-translational modification that regulates protein function by covalently attaching lipoic acid to lysine residues (45). To date, all known lipoylated proteins are key metabolic enzymes involved in the TCA cycle, such as dihydrolipoyl transacetylase (DLAT), dihydrolipoyllysine-residue succinyltransferase (DLST), pyruvate dehydrogenase complex component X (PDHX), and glycine cleavage system protein H (GCSH) (45). The lipoylated proteins are indispensable for the enzymatic activities of the energy metabolism complexes. However, the lipoic acid molecule contains two thiol groups (-SH), so proteins modified by lipoylation will also carry thiol groups, which endows them with a high affinity for copper ions (46, 47). Copper ions binding to thiol groups can induce thiol-dependent oligomerization of lipoylated proteins, leading to proteotoxic stress and culminating in cuproptosis (3, 48).

The primary regulators of protein lipoylation are lipoyltransferase 1/2 (LIPT1/2) and lipoic acid synthase (LIAS). LIPT2 can transfer the octanoyl group from acyl-carrier protein to GCSH, which serves as a precursor for lipoic acid synthesis (49). LIAS, which contains an Fe-S cluster, is a crucial enzyme in lipoic acid synthesis that inserts two sulfur atoms into carbons 6 and 8 of the octanoyl group to form complete lipoic acid (50). Subsequently, LIPT1 transfers lipoic acid from GCSH to the lysine residues of target proteins, completing the lipoylation modification (47, 51). In current studies, DLAT, LIPT1 and LIAS are implicated in positively regulating cuproptosis, with their expression levels being closely related to cuproptosis activity (3, 52–54). In contrast, the direct role of LIPT2 in cuproptosis is still unclear. However, given its essential function in lipoylation, LIPT2 may exert an indirect influence on cuproptosis by modulating the lipoylation pathway.

FDX1 is another pivotal regulator of cuproptosis. FDX1 is a small protein from the ferredoxin family and contains an Fe-S cluster (55). It serves as an electron donor and participates in the biosynthesis of steroids, heme, and Fe-S clusters. FDX1 can interact with ES-Cu to facilitate the reduction of Cu^{2+} and release Cu^+ into the mitochondrial matrix (41). This reduction reaction significantly amplifies the cytotoxicity of copper ions. Notably, copper overload can suppress FDX1 activity, leading to a decrease in the synthesis of Fe-S cluster proteins. Moreover, Cu^+ can directly bind to Fe-S clusters, which in turn disrupt their synthesis and function (3). In addition, FDX1 is an upstream regulator in the lipoylation pathway. Dreishpoon et al. reported that FDX1 can directly interact with

**FIGURE 1**

Systemic metabolism of copper. Copper is primarily absorbed in the small intestine, transported via the bloodstream to the liver for storage, and ultimately excreted into bile. The transporter CTR1 mainly facilitates the uptake of copper(I) (Cu^+), while ZnT1 can transport copper(II) (Cu^{2+}). Notably, zinc(II) ions (Zn^{2+}) and Cu^{2+} compete for binding to ZnT1. In the blood, Cu^+ is predominantly bound to HSA and $\alpha_2\text{M}$. Within the biliary system, copper ions are excreted primarily via the ATP7B. $\alpha_2\text{M}$, α_2 -macroglobulin; ATP7A, ATPase copper transporter 7A; CTR1, copper transport protein 1; HAS, human serum albumin; STEAP, six-transmembrane epithelial antigen of the prostate.

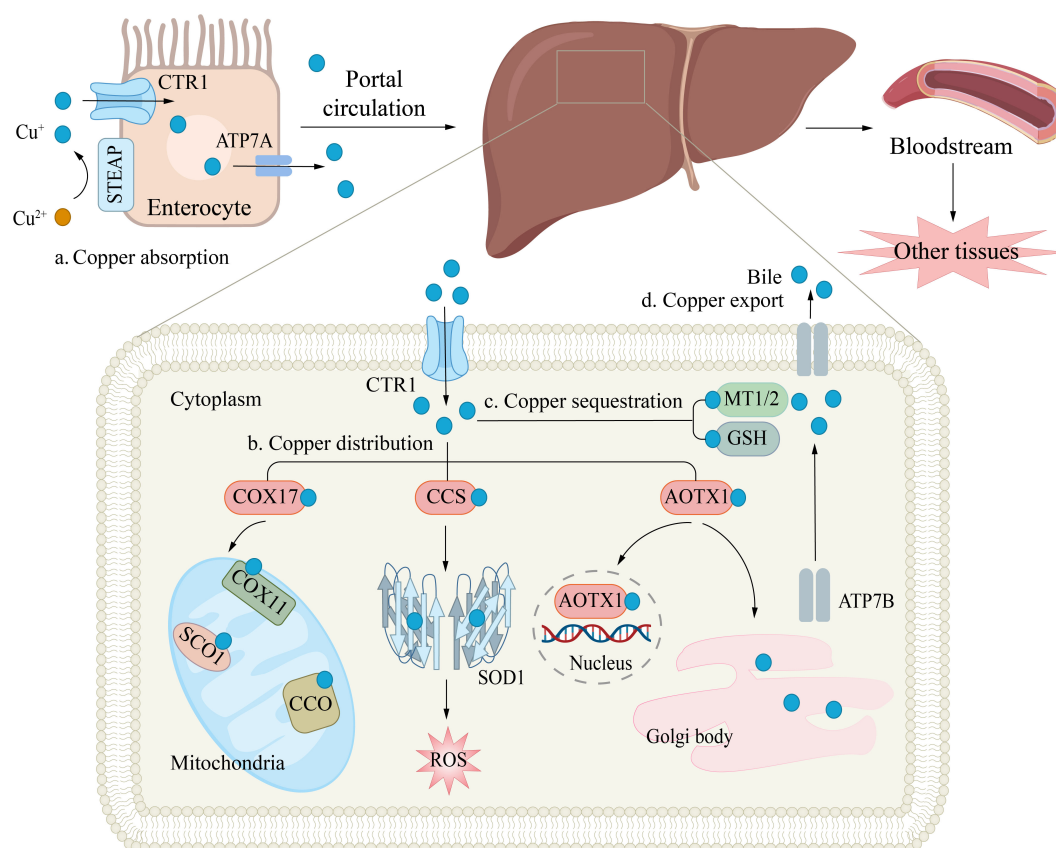


FIGURE 2

Copper Transport and Cellular Functions. (a) Copper absorption. Copper uptake in enterocytes is mediated by the CTR1 transporter, while ATPase copper transporter 7A (ATP7A) facilitates its efflux into the portal circulation. (b) Copper distribution. In hepatocytes, copper plays a critical role in antioxidant defense (e.g., by binding to superoxide dismutase, SOD) and supports mitochondrial energy production. The copper chaperones CCS and cytochrome c oxidase copper chaperone 17 (COX17) deliver Cu^+ to specific targets: CCS directs copper to cytosolic SOD1, enhancing free radical scavenging; COX17 transports copper to mitochondrial COX, aiding ATP synthesis. Intracellular copper shuttling is regulated by ATOX1, which distributes copper to: The nucleus; ATPB in the trans-Golgi network. (c) Copper sequestration. Excess copper binds to MT1/2 or GSH and is stored in the cytosol to prevent oxidative damage. (d) Copper export. Finally, copper enters the bloodstream and is delivered to other tissues and organs.

LIAS, acting as an electron donor to facilitate the synthesis of lipoic acid, rather than indirectly regulating it through modulation of Fe-S clusters (Figure 3) (56). The loss of FDX1 function, by affecting protein lipoylation, leads to the suppression of mitochondrial respiration, particularly under low-glucose conditions.

4 Abnormal copper metabolism and liver disease

The liver plays a central role in copper metabolism, including absorption, storage, transportation and excretion. Disruptions in these processes are linked to various liver diseases and can greatly affect immune responses and inflammation within the liver (57). Copper homeostasis finely regulates liver immunity. It is essential for immune cell function and host defense, but its imbalance can cause excessive immune activation and inflammation. Copper deficiency weakens the immune response to infections and damaged cell clearance, worsening liver injury (58–60). Conversely, excess copper can overactivate immune cells like Kupffer cells, T cells, and B cells, enhancing

inflammation (7, 61). Cuproptosis, as an immunogenic PCD, leads to the release of damage-associated molecular patterns (DAMPs), promotes inflammation and the infiltration of immune cells, and aggravates hepatocyte damage (12, 62, 63). In addition, immune system abnormalities can disrupt copper metabolism by altering copper transporter and binding protein expression and activity (64). The complex interplay between copper metabolism and the immune system highlights their importance in liver diseases. Overall, damage to one or more stages of copper metabolism in the liver can lead to copper metabolism disorders, which in turn cause abnormal liver immunity and aggravate hepatocyte damage. In the following sections, we will discuss the role of abnormal copper metabolism in WD, ALD, NAFLD, ALI and HCC.

4.1 Abnormal copper metabolism in Wilson disease

Menkes disease (MD) and WD are genetic disorders associated with copper metabolism, characterized by mutations in the *ATP7A*

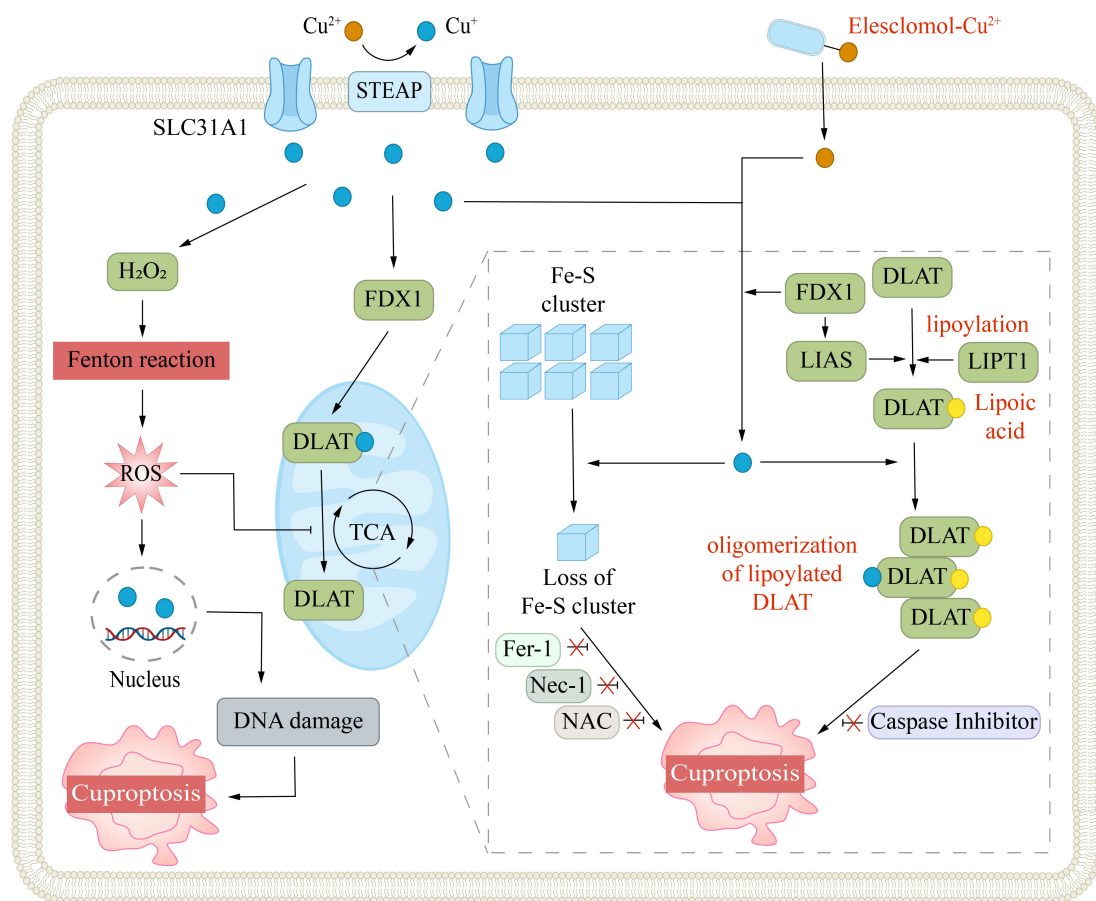


FIGURE 3

Mechanism of cuproptosis. Cuproptosis is triggered by excessive intracellular copper accumulation, which occurs either via SLC31A1-mediated uptake or through copper ionophores. Elevated copper levels promote ROS generation via the Fenton reaction, leading to DNA damage. Copper ionophores (e.g., elesclomol) facilitate copper transport into cells, where it binds to lipoylated enzymes in the mitochondrial TCA cycle, such as DLAT. This interaction causes protein aggregation and disrupts iron-sulfur cluster stability. The FDX1/LIAS pathway, which regulates protein lipoylation, further contributes to mitochondrial dysfunction. Collectively, these disruptions induce proteotoxic stress, culminating in cell death. Inhibitors targeting ferroptosis (Fer-1), necroptosis (Nec-1), or oxidative stress (NAC) do not prevent this form of cell death.

or *ATP7B* genes, respectively. MD arises from *ATP7A* gene mutations, which leads to a reduction in functional *ATP7A* in IECs and severe systemic copper deficiency (65). The main symptoms of MD include neurological deterioration and growth retardation, with relatively mild liver symptoms. Copper deficiency also leads to reduced synthesis of copper-dependent enzymes like CP. In contrast, WD is caused by *ATP7B* gene mutations. Since *ATP7B* is involved in CP synthesis and copper excretion, its missense mutations often result in copper accumulation within the liver, causing severe hepatotoxicity and systemic symptoms (66). In WD patients, the hepatic copper concentration can be more than 10 times the normal level (67). Meanwhile, the reduction of holo-CP in the circulation leads to a shortened half-life of CP, resulting in not only excessive copper but also excessive iron in the liver of WD patients, which in turn causes iron-induced Fenton reactions and iron-related lipid peroxidation (68). Compared with copper, the presence of a certain level of CP means that iron accumulation is not a primary feature of WD.

In WD patients, the absence of *ATP7B* expression in IECs leaves copper absorption unaffected. Additionally, the transfer of

copper from IECs to the liver is also not influenced by *ATP7B* mutations (69). This allows copper to easily accumulate in large amounts in the livers, subsequently triggering a series of pathological changes. Mitochondrial alterations often manifest in the early stages, such as the separation and expansion of the mitochondrial membrane, deformation, swelling, and the appearance of vacuoles in mitochondrial (70). Similar structural changes can also be observed in *ATP7B*^{-/-} rats (71, 72). As the disease advances, defects in the mtETC become increasingly pronounced, particularly in complex IV (73, 74). This leads to a diminished capacity for ATP production, thereby compromising cellular energy metabolism. Conversely, the Fenton reactions and ROS damage associated with copper and iron overload tend to occur at a later stage. The change in the glutathione (GSH)/glutathione disulfide (GSSG) ratio occurs at a later stage, reflecting a decline in antioxidant capacity (75).

Restricting copper intake in the diet can be somewhat helpful for patients with WD, but the current evidence is not sufficient to support a treatment plan based on dietary restrictions (76). At present, the treatment of WD mainly relies on copper chelators

(CCs) and zinc salts (77). CCs can specifically bind to copper ions to form stable complex, which promotes the excretion of copper (78). D-penicillamine and trientine are first-line drugs for WD. D-penicillamine is the earliest used CC. It is an amino acid containing a thiol group, which can remove copper bound to albumin in the circulation and excrete it through urine (78). The side effects of D-penicillamine mainly include nephrotoxicity and bone marrow suppression, etc (79). Trientine is an alternative for patients who cannot tolerate D-penicillamine (80, 81). Another CC, tetrathiomolybdate (TTM), has also demonstrated potential in treating WD. In a phase II clinical trial, bis-choline TTM was found to rapidly reduce the levels of non-CP-bound copper in patients, and improve neurological symptoms and liver function (82). Zinc salts are another first-line treatment option for WD. As mentioned, zinc can competitively inhibit the absorption of copper (19). Li et al. reported that ZnT1 is involved in transporting both zinc and copper and is essential for zinc's ability to inhibit copper absorption. ZnT1 has a unique inter-subunit disulfide bond that aids in the transport of Cu^{2+} , and Zn^{2+} and Cu^{2+} share a major binding site on ZnT1 (83). Therefore, ZnT1 may be a potential target for zinc-based therapeutic approaches in treating WD.

4.2 Abnormal copper metabolism in alcohol liver disease

The liver is the core organ for ethanol metabolism. As a result, long-term alcohol consumption can easily lead to liver damage, a prevalent form of hepatic injury. Copper is an important fungicide in organic viticulture and also an important catalyst in the wine-making process (84). Copper significantly contributes to the progression of ALD. Lin et al. reported that dietary copper can improve the intestinal barrier integrity and hepatic injury in ALD model mice (85). Dietary copper supplementation can increase the expression of hypoxia-inducible factor-1 α (HIF-1 α) in the small intestine, thereby enhancing intestinal barrier stability through the upregulation of P-glycoprotein and tight junction proteins (86). Additionally, copper supplementation can also increase the levels of GPX1 and occludin, ameliorate oxidative stress, and mitigate ethanol-induced damage to the small intestine (85). Conversely, some studies have reported that copper can increase the liver damage caused by alcohol (87, 88). Monooxygenase DBH-like 1 (MOXD1) is closely related to the transport of copper into cells (89). A bioinformatics analysis has revealed that MOXD1 is a key gene in ALD, and inhibiting MOXD1 can improve inflammation in ALD mice (90). Hou et al. reported that the livers of ALD model mice exhibited significant infiltration of M1 macrophages, a notable decline in FDX1 expression, and a pronounced upsurge in CTR1 expression. They also pinpointed five potential biomarkers associated with M1 macrophages, ferroptosis, and cuproptosis in patients with alcoholic hepatitis: LUM, ALDOA, THBS2, COL3A1, and TIMP1 (91). In another study, bioinformatics analysis revealed that three cuproptosis-related genes (CRGs)—*DLAT*, *GLS*, and *CDKN2A*—are closely associated with ALD (92). Their expression were markedly elevated in both ALD patients and ALD model mice.

GLS and *CDKN2A* exhibit a correlation with the p53 pathway, which can increase cellular sensitivity to cuproptosis through multiple pathways, such as inhibiting glycolysis, enhancing mitochondrial function and Fe-S cluster biogenesis, and inhibiting the SLC7A11-glutathione peroxidase 4 (GPX4)-GSH pathway to reduce GSH levels (93–95). In addition, the CRGs are associated with the hepatic infiltration of macrophages and CD8⁺ T cells, and may activate the complement pathway, thereby amplifying intrahepatic inflammation (92). Overall, copper significantly impacts ALD pathogenesis via multiple pathways.

4.3 Abnormal copper metabolism in non-alcoholic fatty liver disease

NAFLD is a highly prevalent liver disease. Its core pathological feature is the excessive lipid accumulation within hepatocytes, which primarily results from overconsumption of dietary fats, excessive fatty acid influx, and elevated *de novo* lipogenesis (96). The long-term lipid accumulation leads to mitochondrial oxidative stress. If left uncontrolled, this chronic damage can progressively develop into non-alcoholic steatohepatitis (NASH), and further induce fibrosis and HCC (97). NAFLD is closely associated with metabolic abnormalities. Patients typically have obesity, insulin resistance, or metabolic dysfunction (98). As the prevalence of these metabolic-related diseases increases, the incidence of NAFLD has also risen significantly, with approximately 38% of individuals affected by NAFLD (99). To emphasize the importance of metabolic dysfunction, NAFLD is also termed metabolic dysfunction-associated fatty liver disease (MAFLD) (100). Dysregulated copper metabolism is strongly associated with NAFLD and may intensify its pathological progression (101).

Abnormal copper homeostasis, including both elevated and deficient copper, can cause liver injury and exacerbate NAFLD progression (102). A study reported that serum copper levels correlate positively with NAFLD prevalence and the progression of fibrosis, with overweight women under the age of 60 having a higher susceptibility (103). In contrast, another study reported that elevated blood copper levels significantly protect male NAFLD patients, and this protective effect increases with the severity of NAFLD. In women, however, this protective effect is only observed in mild liver disease (104). A meta-analysis revealed that hepatic copper levels in NAFLD patients are significantly reduced. However, there is no significant correlation between serum copper levels, CP levels, and NAFLD (105). These contradictory results are closely tied to the complex pathogenesis of NAFLD and are also closely associated with the multifaceted physiological functions of copper. Copper can influence the progression of NAFLD through various pathways, such as regulating lipid metabolism, iron metabolism, mitochondrial function, oxidative stress, and cuproptosis. Jiang et al. reported that oral copper oxide nanoparticles cause copper accumulation in the liver, resulting in disordered hepatocyte arrangement, lipid vacuolation, and hepatic fibrosis (106). Mechanistically, CuO NPs increase bile acid (BA) reabsorption, disrupting BA homeostasis. This leads to BA

accumulation and induces NAFLD. The expression of the pregnane X receptor (PXR) in the liver was significantly upregulated, correlating with BA accumulation and promoting lipid synthesis (106, 107). Additionally, Liu et al. reported that copper can induce inflammatory responses in the mouse liver by activating the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF- κ B) pathways, leading to hepatic dysfunction (108). Copper deficiency can reduce the expression of ferroportin, thereby affecting hepatic iron metabolism, causing hepatic iron deposition and promoting liver fibrosis (109). Copper deficiency can also lead to increased ROS, thereby exacerbating the pathological progression of NAFLD (110). In addition, copper deficiency can affect the key enzyme in fructose metabolism, such as ketohexokinase, while high fructose intake can impair copper absorption, leading to copper deficiency (111). The copper-fructose interaction can exacerbate NAFLD through multiple pathways, including promoting hepatic iron overload, mitochondrial dysfunction, and abnormal gut function (112).

Copper also affects various metabolic disorders that contribute to the development of NAFLD/MAFLD. For example, copper and zinc compete for binding to ZnT1 and mucins, which means that elevated copper levels can suppress zinc absorption (19, 20). Zinc is an important cofactor for insulin synthesis and secretion, and zinc deficiency can exacerbate insulin resistance (113). In addition, high levels of copper can also promote oxidative stress through the Fenton reaction, damage pancreatic β cells, and thereby promote insulin resistance (114). Additionally, copper serves as a cofactor for enzymes involved in lipid metabolism such as semicarbazide-sensitive amine oxidase (SSAO) and amine oxidase copper-containing 3 (AOC3) (115, 116). Abnormal levels of copper can lead to dysregulation of lipid metabolism and increased fat accumulation, thereby heightening the risk of obesity (117).

At present, studies exploring cuproptosis in NAFLD remain relatively few, and its mechanisms remain to be elucidated. Xu et al. reported that overexpression of the *LIAS* gene in leptin receptor-deficient mice significantly enhances the mitochondrial antioxidant capacity in the liver, reduces the levels of inflammatory factors, and alleviates the progression of NAFLD/NASH (118). Zhao et al. identified that *FDX1* is closely associated with the progression from NASH to HCC. *FDX1* expression is significantly increased in areas of hepatocyte steatosis but is markedly decreased in HCC. Targeting *FDX1* may help prevent the malignant progression of NAFLD (119). However, another bioinformatics analysis did not identify *FDX1* as a CRG associated with NAFLD. In their study, *FDX1* showed no significant difference, whereas *NFE2L2*, *DLD*, and *POLD1* were identified as key CRGs and were closely related to the immune microenvironment (120). This further highlights the dynamic changes of *FDX1* in the NAFLD-NASH-HCC progression, but this still requires more research for validation. Another bioinformatics analysis showed that six CRGs changed significantly in NAFLD. *NFE2L2*, *LIAS*, and *ATP7B* were significantly downregulated, while *DLD*, *DLAT*, and *PDHB* were highly upregulated (121). In summary, copper ions regulate the progression of NAFLD through various pathways, and the

abnormal changes in their levels may exacerbate the pathological process of NAFLD.

4.4 Abnormal copper metabolism in acute liver injury

ALI is the extensive death of hepatocytes and inflammation that occur within a short period of time, leading to acute liver impairment. Common causes of ALI include hepatic ischemia-reperfusion (HIR), drug overdose, excessive alcohol consumption, heavy metal poisoning, autoimmune hepatitis, and viral hepatitis (122). Studies have reported that excessive copper intake or exposure can directly cause ALI (88, 123, 124). Other factors can also cause abnormal copper levels in the liver, affecting mitochondrial function within hepatocytes and pathways like oxidative stress and cuproptosis, thereby exacerbating ALI.

HIR is often accompanied by various PCDs, including cuproptosis (125). Inhibitors of cuproptosis have been shown to improve liver injury, whereas inducers can exacerbate it. Bioinformatics analysis has identified some characteristic CRGs that are highly expressed in HIRI (126). Acetaminophen (APAP) is frequently used as an antipyretic and anti-inflammatory drug. However, APAP exhibits a relatively limited therapeutic window, with overdose being a critical contributor to ALI. Guo et al. reported that after APAP treatment, the copper content in the liver is significantly increased (127). Bioinformatics analysis identified four CRGs that are closely associated with acetaminophen-induced liver injury (AILI): *PDHA1*, *SDHB*, *NDUFB2*, and *NDUFB6*. Their expression is markedly reduced in AILI and is correlated with the infiltration of M1 macrophages (127). Luo et al. reported that in concanavalin A-induced immune-mediated ALI, Merestinib can directly bind to Nrf2, thereby reducing oxidative stress. Additionally, it regulates copper homeostasis in hepatocytes, inhibits cuproptosis, and alleviates liver damage (128).

Viral hepatitis can also cause acute liver injury. However, studies on cuproptosis in viral hepatitis are still limited at present. Nevertheless, research has shown that in patients with chronic hepatitis B, serum copper levels are significantly reduced, antioxidant capacity is weakened, and ROS levels are significantly increased (129, 130). In chronic hepatitis C patients, hepatic copper levels correlate positively with the extent of hepatic fibrosis, yet serum copper levels show no significant difference (131). These findings suggest that copper metabolism disorders might contribute to the pathogenesis of viral hepatitis and are worthy of further detailed research.

4.5 Abnormal copper metabolism in hepatocellular carcinoma

HCC is the most common type of primary liver cancer (132). The pathogenesis of HCC is highly complex, encompassing genetic factors, metabolic disorders, viral infections, and environmental

exposures. These diverse risk factors contribute to liver cirrhosis development, fostering an environment conducive to the progression of HCC (133). Copper is vital for maintaining mitochondrial function and significantly impacts energy metabolism. Given that cancer cells proliferate rapidly, it is predictable that they require more copper than normal cells to satisfy their energy requirements. Moreover, since copper metabolism abnormalities play a vital role in various chronic liver diseases, the relevance of copper to HCC development is self-evident. Research has demonstrated that copper concentrations are markedly higher in various cancers (134–138). Li et al. reported that the expression levels of most copper metabolism-related pathways are decreased in HCC patients. The expression of MTs genes related to copper ion detoxification is significantly decreased in HCC (139).

In HCC, the abnormal elevation of copper ion levels can influence the biological behavior of tumors through various mechanisms (140). A bioinformatics analysis revealed that HCC patients presenting a high-copper phenotype typically exhibit higher pathological grades and poorer prognoses compared to those with a low-copper phenotype. Additionally, the high copper phenotype was characterized by higher expression of immune checkpoint genes, resulting in a poorer response to immunotherapy (141). Davis et al. reported that copper levels in HCC tumor tissues were significantly higher than those in adjacent liver tissues. The overexpression of CTR1 promoted the proliferative and migratory capacities of HCC cells. Conversely, silencing CTR1 or treatment with TTM significantly reduced glycolytic gene expression and downstream metabolite utilization in HCC cells, thus inhibiting cell survival in hypoxic conditions (142). Excess copper can promote the proliferation of HCC through the MYC-CTR1 axis. MYC is an important oncogene that can promote cell proliferation through the modulation of cell cycle-related gene expression (143). Dysregulation of MYC is crucial for the proliferation, invasion, and other processes of HCC (144). Porcu et al. reported that copper exposure upregulated MYC expression, and MYC could bind to the CTR1 promoter to promote its transcription. Silencing of CTR1 can offset the copper-induced cell proliferation (145). Excess copper within cells can also increase free radicals, exacerbate DNA damage, thereby promoting the proliferation of tumor cells (146). SOD1^{-/-} mice exhibit a higher incidence of HCC.

Angiogenesis is a vital pathway for the progression, invasion, and metastasis of HCC. Copper significantly influences angiogenesis and contributes to the malignant progression of various tumors (147, 148). Copper metabolizing MURR1 domain 3 (COMMD3) is a crucial regulator of copper metabolism, and its expression levels are closely correlated with intracellular copper ion concentrations (31). The high expression of COMMD3 is associated with adverse outcomes in a range of tumors and is related to the tumor's abilities of migration, invasion, and angiogenesis (149, 150). Zhu et al. reported that overexpression of COMMD3 significantly increased the expression of vascular endothelial growth factor (VEGF), p-VEGFR2/VEGFR2, HIF-1 α , and NF- κ B in HCC cells, thereby promoting tumor growth and angiogenesis

(151). Conversely, downregulation of COMMD3 effectively inhibited this tumor-promoting process. Studies have reported that copper chelation therapy can improve the progression and angiogenesis of HCC (152–154). Copper can also bind to CD147, promoting its self-aggregation and thereby facilitating the proliferation, invasion, and metastasis of HCC (155). CD147 is overexpressed in various malignant cancers and can activate matrix metalloproteinases (MMPs) -2, -3, and -9, thereby facilitating the migration of HCC cells. Additionally, CD147 can regulate the proliferation of HCC cells through the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) and p53 signaling pathway (155, 156).

Targeting copper homeostasis has become a potential therapeutic approach for treating HCC. By regulating the intracellular levels of copper ions or leveraging copper-induced PCD, the progression of HCC can be effectively inhibited. Numerous studies have elucidated diverse mechanisms to target copper ions for treating HCC. HCC cells need a higher level of copper ions to promote their proliferation, invasion, and metastatic ability. However, deviations from this optimal concentration—either a reduction or an increase—can effectively impede the progression of HCC.

CCs have been proven to significantly reduce the proliferation and invasive capacity of HCC cells by inhibiting the activity of copper ions (142, 152). Moreover, excess copper ions can inhibit the progression of HCC through various mechanisms. For example, an appropriate amount of copper can promote HCC through ROS-dependent mechanisms. However, an excess of copper can increase the intracellular ROS levels and induce apoptosis. Niu et al. reported that the copper (II) complex of salicylate phenanthroline [Cu(sal)(phen)] can significantly increase the ROS levels in HCC cells and promote apoptosis (157). The treatment with Cu(sal)(phen) significantly decreased Bcl-2 levels and triggered apoptosis in a dose-dependent manner. Similarly, Jiang et al. synthesized two Cu (II) 4-hydroxybenzoylhydrazone complexes, which can promote HCC apoptosis by increasing ROS generation and damaging mitochondrial DNA (158).

Cuproptosis is the primary pathway through which copper exerts its anticancer effects. Bioinformatics analyses have underscored the strong correlation of CRGs with the progression, prognosis, and tumor microenvironment (TME) of HCC (159–161). FDX1 can influence the prognosis of HCC by modulating cuproptosis and the TME (162). High expression of FDX1 promotes susceptibility to cuproptosis in HCC cells, enhances the infiltration of NK cells, Th1 cells, and macrophages, and increases sensitivity to oxaliplatin (163, 164). In contrast, low expression of FDX1 enhances tolerance to Cu²⁺ and correlates with a worse prognosis in HCC (162). In addition, Sun et al. reported that knockdown of *FDX1* promotes mitophagy, activates the PI3K/Akt pathway and facilitates HCC progression (165). DLAT also promotes the proliferation of HCC (166). Li et al. reported that maternal embryonic leucine zipper kinase (MELK) is highly expressed in HCC and promotes DLAT via the PI3K/Akt pathway, improving mitochondrial function (167). ES treatment inhibits MELK-induced

HCC progression by promoting DLAT oligomerization and inducing cuproptosis. In addition, LIPT1, LIAS, and GLS can also promote the malignant progression of HCC (168–170).

Moreover, cuproptosis and ferroptosis are synergistic in HCC (171). Ferroptosis is an iron-dependent PCD, characterized by the elevation of intracellular iron ion levels that generate massive ROS through the Fenton reaction, along with the depletion of the antioxidant GSH, which subsequently trigger lipid peroxidation. This damages the cell and mitochondrial membranes, and ultimately causing cell death (172). Ren et al. reported that DSF-Cu can promote the iron ion levels and lipid peroxidation in HCC cells, thereby facilitating ferroptosis. DSF-Cu reduced the GSH levels and FDX1 expression, while simultaneously promoting ferroptosis and cuproptosis (173, 174). Combined treatment with the ferroptosis inducer sorafenib enhanced the cytotoxicity against HCC cells. In addition, sorafenib can also promote copper death induced by ES-Cu. Treatment with sorafenib can enhance the stability of FDX1 and reduce the level of GSH, and the enhanced effect can be reversed by treatment with GSH or TTM (175). Combining ferroptosis inducers with CIs could offer a new and potentially more effective approach to treating HCC.

In addition to directly promoting PCDs, copper can also modulate the immune microenvironment of HCC. Copper-triggered Cuproptosis and ferroptosis release DAMPs, thereby enhancing antitumor immunity. Mao et al. developed a prognostic model for HCC containing 9 CRGs. The low-risk group exhibited high expression of GLS, LIPT1, ATP7A, and ATP7B, as well as increased immune infiltration and sensitivity to immune checkpoint inhibitors (176). However, copper can also promote immunosuppression in the HCC TME. A study reported that DSF-Cu demonstrates antitumor effects in immunodeficient mice, but it promotes the upregulation of programmed death ligand-1 (PD-L1) in immunocompetent mice, leading to a less favorable therapeutic outcome (177). PD-L1 binds to PD-1 on T cells, delivering inhibitory signals to T cells, thereby suppressing their proliferation, activation, and cytokine secretion (178). DSF-Cu achieves this by inhibiting Poly (ADP-ribose) polymerase 1 (PARP1) activity, increasing the phosphorylation of GSK3 β at the Ser9 site, thereby inhibiting GSK3 β activity and reducing the degradation of PD-L1. However, when DSF/Cu is combined with anti-PD-1 antibodies, the expression of PARP1 and PD-L1 is decreased, while the expression of CD8⁺ T cells and granzyme B is increased, significantly enhancing antitumor efficacy (177). This offers a novel combinatorial therapeutic strategy for treating HCC (Figure 4).

5 Conclusion

Copper participates in numerous biological processes, and its balance is crucial for normal cellular functions. Imbalances in copper homeostasis can trigger a wide range of diseases. Cuproptosis, a copper ion-dependent PCD, and has been implicated in various diseases, where it can either exacerbate or mitigate disease progression, depending on the context. The liver is

a key organ in copper metabolism, regulating its absorption, storage, transport, and excretion. In this manuscript, we focus on the mechanisms of copper metabolism and cuproptosis, and explore their significance in WD, ALD, NAFLD, ALI, and HCC.

Additionally, copper overload also activates cuproptosis, leading to mitochondrial dysfunction, activation of ferroptosis-related pathways, and the transmission of apoptotic signals, which further induce hepatocyte death. The extensive death of hepatocytes not only exacerbates liver damage but also triggers inflammatory responses, triggering the release of inflammatory mediators and the infiltration of immune cells. Chronic inflammatory stimulation, along with the repeated injury and regeneration of hepatocytes, leads to liver fibrosis, cirrhosis and drives the progression of HCC. Therefore, targeting the regulation of intracellular copper homeostasis is a key strategy for treating liver diseases.

Currently, the common copper-targeting drugs used in clinical practice mainly include CCs and CIs. CCs can bind to copper ions and facilitate their excretion. They are widely used to treat copper-related disorders like WD. CIs can transport copper ions across cell membranes, increase intracellular copper, and promote cuproptosis. This mechanism has potential applications in HCC treatment. However, there are still many gaps in the current research. CIs, such as DFS and ES, have demonstrated therapeutic potential in HCC, but most studies are still limited to animal or *in vitro* experiments, with a lack of relevant clinical research. Some copper-targeting drugs still encounter challenges in overcome resistance to immunotherapies, and do not achieve the expected therapeutic effects. Moreover, due to the complexity of copper's actions, further clinical studies are necessary to investigate how to precisely regulate copper levels in specific liver diseases. In addition, cuproptosis, along with ferroptosis, apoptosis, and autophagy, constitutes a network regulating cell fate. For instance, abnormal copper metabolism can cause redox imbalance, and such redox fluctuations are key factors in influencing other PCD pathways like ferroptosis and disulfidptosis (179–181). Further studies are required to investigate their interplay in liver diseases. Finally, copper is vital for normal cellular function. Finding methods to selectively target copper metabolism in liver diseases while minimizing harm to healthy cells and organs remains a significant challenge for future research.

Based on the current challenges, future research should prioritize several key aspects. Specifically, leveraging advanced imaging technologies alongside multi-omics sequencing of particular circulating biomarkers in the blood allows for the identification of biomarkers signaling copper metabolic disruption. These biomarkers can serve as early diagnostic indicators and facilitate the monitoring of disease progression and therapeutic outcomes. Similarly, identifying novel therapeutic drugs that specifically target copper metabolism is crucial. The primary objective is to develop drugs with heightened selectivity and efficacy while minimizing off-target toxicity to healthy cells. Researchers should meticulously assess the risk-benefit profile of these drugs to ensure they selectively modulate copper levels in diseased tissues

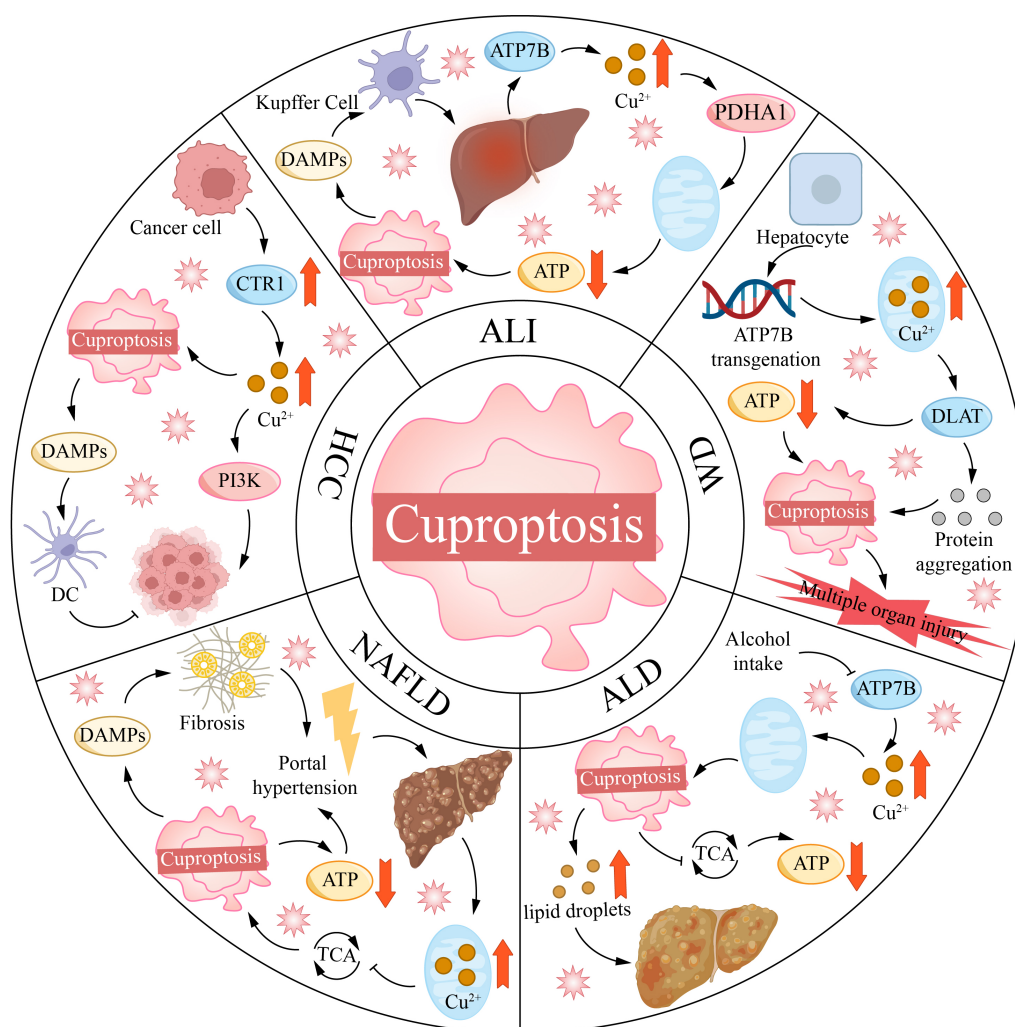


FIGURE 4

Copper mortality is associated with various liver diseases. ALI, acute liver injury; ALD, alcoholic liver disease; ATP7B, ATPase copper transporting 7B; CTR1, copper transporter 1; DAMPs, damage-associated molecular patterns; DC, dendritic cell; DLAT, dihydrolipoamide S-acetyltransferase; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; PDHA1, pyruvate dehydrogenase E1 alpha 1 subunit; PI3K, phosphoinositide-3-kinase; TCA, tricarboxylic acid cycle; WD, Wilson disease.

without compromising the normal physiological functions of copper in healthy cells. Moreover, investigating the synergistic effects of copper-targeting therapies with other therapeutic approaches represents a promising avenue. Combining copper-based strategies with immunotherapies or metabolic drugs could potentially enhance treatment efficacy and address the limitations of single-therapy resistance. Furthermore, personalized treatment plans should be developed based on the genetic makeup, disease subtype, and individual copper metabolism status. Patient-stratification approaches that account for these variables can help tailor therapies to improve treatment precision and efficacy. By integrating these research directions, the scientific community can make significant progress in understanding copper-related liver diseases and developing more effective therapies to combat them.

In summary, copper metabolism and cuproptosis play crucial roles in the pathogenesis and treatment of various liver diseases. Clarifying the mechanisms that disrupt copper homeostasis in liver diseases will help in the development of new therapeutic strategies.

Author contributions

HC: Writing – original draft. DL: Writing – original draft. HZ: Writing – original draft. MZ: Writing – original draft. YL: Writing – original draft. HH: Writing – original draft. AL: Writing – original draft. SS: Writing – original draft. YW: Writing – original draft. ZH: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AILI	acetaminophen-induced liver injury	HIR	hepatic ischemia-reperfusion
Akt	protein kinase B	IEC	intestinal epithelial cell
ALD	alcoholic liver disease	LIAS	lipoic acid synthase
ALI	acute liver injury	LIPT1/2	lipoyltransferase 1/2
APAP	acetaminophen	MAFLD	metabolic dysfunction-associated fatty liver disease
AOC3	amine oxidase copper-containing 3	MAPK	mitogen-activated protein kinase
ATOX1	antioxidant 1 copper chaperone	MD	Menkes disease
BA	bile acid	MELK	maternal embryonic leucine zipper kinase
CC	copper chelator	MMP	matrix metalloproteinase
CCO	cytochrome c oxidase	MOXD1	monooxygenase DBH-like 1
CCS	copper chaperone for superoxide dismutase	MT-1/2	metallothionein 1/2
CI	copper ionophore	mtETC	mitochondrial electron transfer chain
COMMD3	copper metabolizing MURR1 domain 3	NAFLD	non-alcoholic fatty liver disease
COX17	cytochrome c oxidase 17	NASH	non-alcoholic steatohepatitis
CP	ceruloplasmin	NF- κ B	nuclear factor-kappa B
CRG	cuproptosis-related gene	PARP1	Poly (ADP-ribose) polymerase 1
CTR1	copper transport protein 1	PCD	programmed cell death
DAMP	damage-associated molecular pattern	PDHX	pyruvate dehydrogenase complex component X
DCYTB	duodenal cytochrome b	PD-L1	programmed death ligand-1
DSF	disulfiram	PI3K	phosphoinositide-3-kinase
DLAT	dihydrolipoyl transacetylase	PXR	pregnane X receptor
DLST	dihydrolipoyllysine-residue succinyltransferase	ROS	reactive oxygen species
ES	elesclomol	SOD1	superoxide dismutase 1
FDX1	ferredoxin 1	SSAO	semicarbazide-sensitive amine oxidase
Fe-S	iron-sulfur	STEAP	six transmembrane epithelial antigen of the prostate
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	TCA	tricarboxylic acid
GCSH	glycine cleavage system protein H	TME	tumor microenvironment
GPX4	glutathione peroxidase 4	TTM	tetrathiomolybdate
GSH	glutathione	VEGF	vascular endothelial growth factor
GSSG	glutathione disulfide	WD	Wilson disease
HCC	hepatocellular carcinoma	ZnT1	zinc transporter 1
HIF-1 α	hypoxia-inducible factor-1 α		