Role of cuproptosis in digestive system tumors (Review)

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Abstract. In cells, copper levels are tightly regulated because copper deficiency leads to Menkes disease, anemia and neurodegeneration, whereas copper overload is associated with Wilson disease, liver injury, neurodegeneration and several cancers. Cuproptosis, a form of regulated cell death, depends on the intracellular accumulation of excessive copper. This process induces mitochondrial dysfunction and cell death by disrupting the stability of mitochondrial lipoylated proteins and iron-sulfur cluster proteins. The present review aimed to summarize the mechanisms underlying cuproptosis in gastrointestinal cancer, with a focus on the relationship between copper metabolism imbalance and tumor initiation and progression, as well as the potential therapeutic applications of cuproptosis-associated agents in oncology. The application prospects of cuproptosis in gastrointestinal tumor therapy are broad, offering novel therapeutic options that may improve prognosis in patients and survival outcomes.

Contents

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1. Introduction

Copper is an essential trace mineral required for numerous physiological processes, including aerobic respiration, oxidative stress regulation and biosynthesis (1-4). Despite its key role in biological activities, intracellular copper levels are tightly regulated because both copper deficiency, such as in Menkes disease, anemia, and neurodegeneration, and copper excess, as seen in Wilson disease, liver injury, neurodegenerative disorder and several types of cancer, can lead to severe pathological conditions (5-9). When intracellular copper accumulates excessively, the organism initiates specific regulatory programs to decrease the copper content (10,11). Programmed cell death (PCD) refers to an orderly, gene-regulated process that maintains cell and systemic homeostasis and is key for both physiological and pathological cell turnover (12). The classical forms of PCD include apoptosis, necroptosis, pyroptosis, ferroptosis and autophagy (13). Apoptosis is characterized primarily by caspase activation and the release of cytochrome C from mitochondria under genetic control (14). Necroptosis involves both necrosis and apoptosis and is typically triggered by the binding of death receptors (such as tumor necrosis factor receptor 1 and the Fas receptor) to their respective ligands (15). Pyroptosis is mediated by pore-forming gasdermin proteins, which are activated by caspase-1 and the inflammasome complex, leading to cell membrane rupture (16). Ferroptosis is an iron-dependent process driven by lipid peroxidation of unsaturated fatty acids under the action of ferrous ions or lipoxygenase (17). Autophagy promotes the degradation and recycling of intracellular components under stress conditions to maintain cell homeostasis (18). In recent years, as the mechanisms of cell death have been elucidated, cuproptosis has emerged as a newly discovered form of PCD (19). Unlike traditional pathways such as apoptosis, necroptosis, autophagy or ferroptosis, cuproptosis depends on the intracellular accumulation of copper, which directly binds lipoylated proteins in the tricarboxylic acid (TCA) cycle, causing protein aggregation and iron-sulfur cluster degradation. This results in proteotoxic stress, mitochondrial dysfunction and cell death (19). In addition to direct copper accumulation, copper also induces other forms of cell death. For example, copper-induced apoptosis occurs via the catalytic generation of reactive oxygen species (ROS), leading to oxidative stress, DNA damage and the activation of apoptotic pathways (20). Copper can also directly or indirectly modulate apoptosis-associated proteins, such as by activating

p53 and enhancing its pro-death function (21). Copper-induced ferroptosis may occur via promotion of iron absorption and utilization, increasing intracellular iron levels and exacerbating lipid peroxidation, thereby increasing ferroptotic death (22). Copper also produces hydroxyl radicals through Fenton-like reactions, triggering lipid peroxidation and ferroptosis (23). In addition, copper may induce the autophagic degradation of GPX4, facilitating ferroptosis (24). Copper-induced autophagy is triggered by the activation of AMPK, inhibition of mTOR or direct interaction with UNC-51-like kinase ½ (25). This process also occurs via upregulation of autophagy-related genes and activation of the transcription factor (TF)EB, promoting autophagosome and autolysosome formation, which may lead to autophagy-dependent cell death (26). Moreover, copper-induced ROS generation and endoplasmic reticulum stress promote NLRP3 inflammasome assembly and gasdermin D activation, thus triggering pyroptosis (6). Recent research has revealed an association between copper metabolism dysregulation and tumor initiation and progression (6). Copper serves a dual role in cancer: Imbalanced copper metabolism promotes tumor cell proliferation and survival by activating the receptor tyrosine kinase, PI3K/Akt/mTOR, and MAPK/ERK signaling pathways (6,27) and modulating the tumor microenvironment (TME) through angiogenesis and immune evasion (28), while cuproptosis suppresses tumor growth by inducing cell death and activating immune responses (6). Copper stimulates apoptosis, necrosis, autophagy, ferroptosis and cuproptosis and enhances antitumor immunity by activating immune cells (11). As copper dysregulation is common in cancer cells, targeting copper levels or metabolic pathways can trigger cuproptosis, thereby inhibiting tumor growth and progression. Cuproptosis may thus represent a promising anticancer strategy. Furthermore, the potential effects of cuproptosis and other forms of cell death, such as ferroptosis and apoptosis, provide a theoretical basis for combination therapy (22). In recent years, therapeutic strategies for gastrointestinal cancer have shifted from local surgical resection to systemic, multimodal therapy (29). Although progress has been made in terms of conventional chemotherapy and targeted therapies in certain patients, drug resistance and relapse remain challenges. With the advent of precision medicine and immunotherapy, gastrointestinal cancer management has evolved from single-modality chemotherapy to integrated metabolic regulation, immune remodeling, and microenvironmental intervention. Immune checkpoint inhibitors (PD-1/PD-L1 and CTLA-4 antibodies) and antiangiogenic agents have demonstrated promising efficacy and potential for application in patients with gastrointestinal and hepatocellular tumors (30,31). Concurrently, metabolism-immune integrated therapy has been proposed to enhance immune responses by modulating tumor energy metabolism and redox balance (32). The regulation of metal ion homeostasis has been recognized as a key component of systemic therapy, with copper serving a pivotal role in the regulation of mitochondrial respiration and oxidative stress (19). As a copper-dependent PCD pathway, cuproptosis may serve as a link between metabolism and immunity. Studies (30,31,33) have highlighted the interplay between ion metabolism, oxidative stress and immune signaling as a central axis in systemic therapy for gastrointestinal tumors, thereby providing a theoretical foundation for incorporating cuproptosis into therapeutic frameworks. Accordingly, the present review systematically summarizes the mechanisms of copper metabolism and cuproptosis to understand metabolic and immune microenvironmental remodeling in gastrointestinal cancer, offering conceptual and theoretical support for metabolic targeting and systemic treatment strategies.

2. Copper metabolism, transport, regulation and function

Copper metabolism. Copper, a widely distributed metallic element in nature, is an essential trace element for the human body. Most dietary copper exists in the form of Cu^{2+} and is absorbed primarily in the duodenum and small intestine (34). After absorption through the gastrointestinal tract into the bloodstream, ~90% of copper binds to ceruloplasmin in the plasma, while the remaining portion is associated with albumin, transcuprein and histidine. These copper complexes are transported via the portal vein to the liver and other organs where copper exerts physiological effects (35). The liver serves as the primary storage organ for copper (5). Mitochondria are the notable sites of copper utilization due to the presence of copper-dependent enzymes such as cytochrome c oxidase, which is involved in oxidative phosphorylation, and 1-5% of total cellular superoxide dismutase 1 (SOD1), which serves a critical role in mitigating oxidative stress within the mitochondrial matrix. These enzymes highlight the essential role of copper in maintaining mitochondrial function and cellular health (36). Excess copper is secreted into the bile and blood, excreted via the intestine or delivered to peripheral tissues to catalyze physiological reactions (37). A small portion is excreted in urine, sweat and menstrual fluid (37). Extracellular copper exists predominantly in the divalent Cu^{2+} state and cannot be directly used by cells (38,39). At the cellular level, Cu^{2+} enters through divalent metal transporter 1 or is reduced to Cu^{+} by six-transmembrane epithelial antigens such as Six-Transmembrane Epithelial Antigen of the Prostate 1 (STEAP1) or duodenal cytochrome b, after which Cu^{+} is imported into the cytoplasm via the high-affinity copper transporter 1 (CTR1) (40,41). Once inside the cytosol, excess copper is sequestered by metallothioneins (34) or delivered to specific organelles by copper chaperone proteins. For example, the copper chaperone for SOD (CCS) transfers copper to SOD1, enabling copper insertion, disulfide bond formation and the localization of SOD1 to the cytosol or mitochondria (42). Cytochrome c oxidase 17 (COX17) transfers copper to the mitochondrial inner membrane subunits COX1 and COX2 (38), which participate in the assembly of the respiratory chain. In addition, copper is transported through the secretory pathway via antioxidant-1 copper chaperone (ATOX1), which delivers copper to the trans-Golgi network (TGN) and copper-transporting ATPases (ATP7A and ATP7B) located in the Golgi or plasma membrane, maintaining cell copper homeostasis (26). The overall process of copper metabolism is illustrated in Fig. 1.

Copper import proteins. In addition to the aforementioned transporters, CTR1 is the primary plasma membrane protein responsible for cellular copper uptake. CTR1, which has the highest copper-binding affinity among known transporters, specifically binds extracellular Cu^{2+} and transports it into the cytoplasm, where it serves as a major copper chaperone for

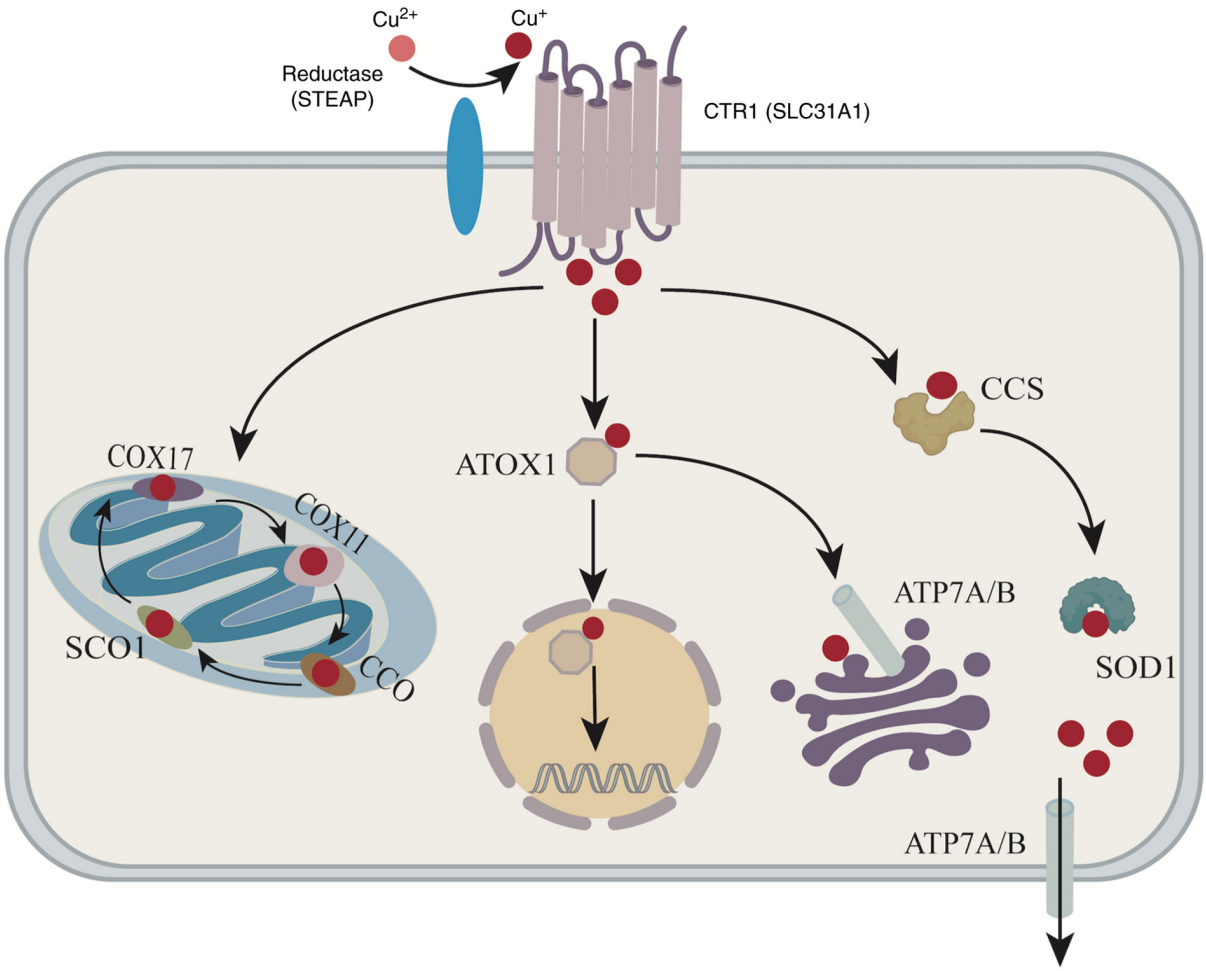

Figure 1. Copper metabolism. Extracellular Cu^{2+} is reduced to Cu^{+} by the reductase STEAP. Some Cu^{+} is transported to the cell through the transporter CTR1 to bind to CCS and SOD1, and the remaining portion is transported to the mitochondria, TGN and nucleus. In mitochondria, Cu^{+} participates in the respiratory chain and redox pathway by binding CCO. In the mitochondrial intermembrane space, COX17 binds and transfers Cu^{+} to SCO1 or COX11, which transfers Cu^{+} to the cytochrome oxidase subunit. In the nucleus, Cu^{+} binds to transcription factors and drives gene expression. In the TGN, the Cu^{+}-ATPase transporters ATP7A and ATP7B transfer Cu^{+} from the cytoplasm to the lumen of the TGN, where Cu^{+} activates Cu-dependent enzymes in the secretory pathway. When the intracellular Cu^{+} concentration is high, ATP7A and ATP7B withdraw from the TGN and promote Cu^{+} output. ATOX1, antioxidant 1 copper chaperone; ATP7A, ATPase copper-transporting α; CCO, cytochrome c oxidase; CCS, copper chaperone superoxide dismutase; COX17, cytochrome c oxidase copper chaperone protein 17; SCO1, synthetic cytochrome c oxidase 1; SOD1, superoxide dismutase 1; STEAP, prostate six-transmembrane epithelial antigen; SLC31A1, solute carrier family 31 member 1; TGN, trans-Golgi network.

enzymes such as SOD (5,43) (Table I). Following exposure to extracellular copper, CTR1 recognizes and binds copper, undergoes conformational changes and transports copper into cells to sustain normal physiological function (44). Once internalized, copper binds to chaperones such as ATOX1 and COX17, which deliver copper to target enzymes, mitochondria or metalloproteins in the endoplasmic reticulum, ensuring proper copper distribution (45). The upregulation of CTR1 leads to cellular copper overload (46). Additionally, solute carrier family 25 member 3 (SLC25A3), a mitochondrial phosphate carrier, is capable of copper transport, and its upregulation results in mitochondrial matrix copper overload (47).

Copper export proteins. ATPase copper-transporting α (ATP7A) and β (ATP7B) are P-type copper-transporting ATPases that regulate copper efflux and intracellular distribution (48). They use the energy derived from ATP hydrolysis to actively transport copper across membranes against their concentration gradients, thereby maintaining copper homeostasis (48,49). ATP7A is expressed ubiquitously, whereas ATP7B is expressed primarily in the liver (50). In hepatocytes, ATP7B mediates the excretion of excess copper into bile, while unabsorbed copper is eliminated through feces (51). Copper efflux is essential for preventing copper-induced cytotoxicity. When the intracellular Cu^{+} concentration increases above a threshold, ATOX1 mediates Cu^{+} transfer to ATP7A/B in the TGN, after which these proteins relocate to the plasma membrane to export Cu^{+} (26). ATP7A and ATP7B thus serve central roles in maintaining systemic copper balance. Dysfunction of these ATPases leads to severe multisystem disorders such as Menkes (52) and Wilson's disease (53). Copper imbalance contributes to cardiovascular disease (54), retinal disorders (55) and tumorigenesis (43) and also perturbs mitochondrial respiration, glycolysis, insulin resistance and lipid metabolism (56-58).

Copper function. As a heavy metal element, copper is typically associated with toxicity, however, copper also has essential physiological functions as a cofactor for numerous proteins

Table I. Functions of copper death-associated genes and their roles in cuproptosis.

Gene	Subcellular location	Function	Role in cuproptosis	(Refs.)
CTR1	Cell membrane	Transports extracellular copper intracellularly; copper chaperones of enzymes such as superoxide dismutase	Its increase leads to intracellular copper accumulation	(5,43,46)
FDX1	Mitochondrial matrix	Upstream regulator of lipid acylation of mitochondrial proteins; Fe-S cluster biosynthesis; reduces Cu^{2+} to Cu^{+}; synthesizes steroid hormones and electron transport intermediates for mitochondrial cytochrome P450	Cu^{2+} to Cu^{+}	(78-83)
LIAS	Mitochondria	Converts octanoylated domains into lipoylated derivatives	Involved in the lipoylation pathway	(84,85)
DLAT	Mitochondrial matrix	Mediates the conversion of pyruvate to acetyl-CoA	Lipoylated DLAT oligomerization leads to cell death	(86,87)
GLS	Mitochondria, cytoplasm and cytosol	Catalyzes the catabolism of glutamine	Its decrease leads to sensitivity to cuproptosis	(88)
CDKN2A	Nucleus, cytosol	Induces cell cycle arrest in G1 and G2 phase	Its decrease leads to sensitivity to cuproptosis	(89-91)
ATP7A	Cell membrane, trans-Golgi network membrane, plasma membrane	Regulates the excretion or distribution of copper in the intracellular space	Its decrease leads to intracellular copper accumulation	(92,93)
ATP7B	Cell membrane, trans-Golgi network and membrane	Regulates the excretion or distribution of copper in the intracellular space	Its decrease leads to intracellular copper accumulation	(94,95)

FDX1, ferredoxin 1; LIAS, Lipoic Acid Synthetase; DLAT, Dihydrolipoamide S-Acyltransferase; GLS, Glutaminase; CDKN2A, Cyclin-Dependent Kinase Inhibitor 2A; ATP7A, ATPase, Cu^{2+} Transporting, Alpha Polypeptide; CTR, Copper Transporter.

and enzymes (5). For example, cytochrome c oxidase is a copper-dependent enzyme that is key for the final step in the electron transport chain, where it facilitates the transfer of electrons to oxygen during oxidative phosphorylation (59). SOD1), another copper-containing enzyme, protects cells from oxidative damage by converting superoxide radicals to hydrogen peroxide and oxygen (60). Its versatile redox activity, which involves cycling between Cu^{+} and Cu^{2+}, enables copper to serve as a crucial catalytic cofactor in biochemical reactions (61), including oxidative stress regulation (1,2), cellular respiration (56), neurotransmitter synthesis and metabolism (62) and epigenetic modification (63). In addition to redox functions, copper contributes to hematopoiesis, immune regulation, melanin and connective tissue formation and central nervous system protection (8,64,65). Copper has also been implicated in cancer diagnosis and therapy. Advances in metal-based medicine have focused on achieving targeted toxicity through chemical coordination and controlled drug delivery (19,66). Conversely, copper-depleting therapy [tetrathiomolybdate (TTM)] exerts antitumor effects by chelating copper in the serum, decreasing vascular endothelial growth factor expression and modulating the immunosuppressive TME. These mechanisms demonstrate antimetastatic and antiangiogenic effects in models of breast, colorectal and hepatocellular carcinoma (HCC) (67-69). Although other metals, such as platinum and technetium, have been applied in chemotherapy, imaging and radiotherapy (70,71), the dual nature of copper, in which it is both physiologically essential and potentially toxic, links it with energy metabolism and immune regulation. Consequently, copper homeostasis has emerged as a frontier topic in the study of metal-based anticancer therapeutics (72,73).

3. Mechanisms of cuproptosis

Mitochondrial damage and lipoylated protein aggregation. Copper can trigger multiple forms of cell death, including apoptosis, oxidative stress-induced necrosis, autophagy and ferroptosis (74). Recent study have revealed that under the action of copper ionophores such as elesclomol (ES), copper induces cuproptosis, a distinct form of PCD, through unique mechanisms involving the disruption of iron-sulfur (Fe-S) cluster proteins and the induction of lipid peroxidation (19). The key hallmark of cuproptosis is the abnormal aggregation of lipoylated proteins and depletion of Fe-S cluster proteins, leading to mitochondrial contraction, chromatin fragmentation

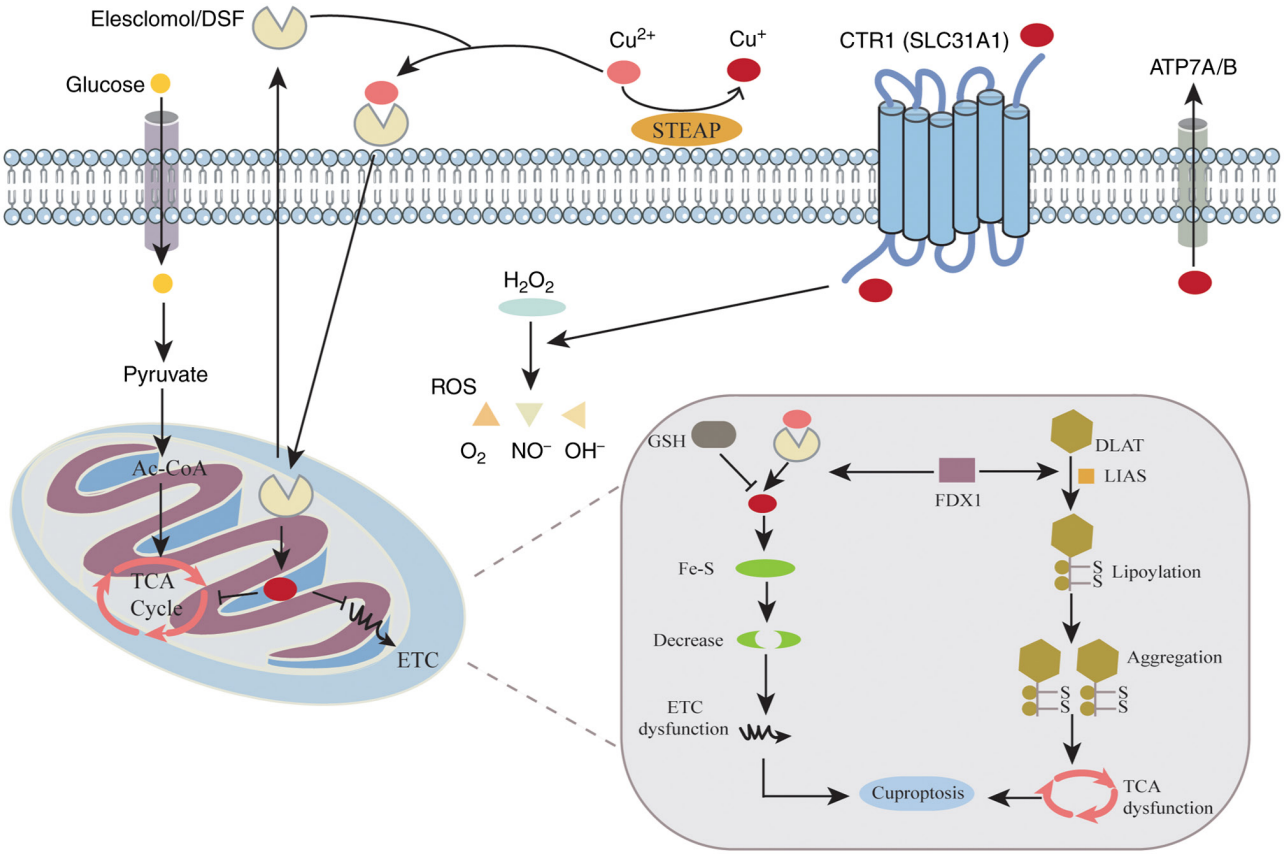

Figure 2. Molecular mechanism of cuproptosis. Excess Cu^{2+} is imported into cells via CTR/SLC31A1 and as well as copper ionophores elesclomol and DSF. Cu^{2+} is reduced to Cu^{+} mainly through FDX1 and STEAP, increasing the bioactive Cu^{+} pool. Mitochondrial Cu^{+} directly binds lipoylated TCA-cycle enzymes, particularly the pyruvate dehydrogenase complex, inducing aberrant aggregation of DLAT and other lipoylated proteins. This aggregation disrupts lipoylation-dependent TCA activity and Ac-CoA production, and is accompanied by loss of Fe-S clusters, thereby impairing Fe-S-dependent enzymes and the ETC. These events drive excessive ROS generation, oxidative stress, mitochondrial dysfunction and ultimately cuproptosis-related cell death. Copper homeostasis is counterbalanced by ATP7A/B-mediated copper efflux/redistribution, while GSH buffering mitigates copper-associated oxidative stress. FDX1, ferredoxin 1; TCA, tricarboxylic acid cycle; DLAT, Dihydrolipoamide S-Acyltransferase; ROS, Reactive Oxygen Species; DSF, Disulfiram; STEAP, Six-Transmembrane epithelial Antigen of the Prostate; CTR, Copper Transporter; SLC31A1, Solute Carrier Family 31 Member 1; ATP7A/B, ATPase, Cu^{2+} Transporting, α/β polypeptide; Ac-CoA, Acetyl-Coenzyme A; ETC, Electron Transport Chain; GSH, Glutathione; LIAS, Lipoic Acid Synthase.

and cell membrane rupture (75). Mechanistically, ES transports Cu^{2+} into the cytoplasm, where it is reduced to Cu^{+} by ferredoxin 1 (FDX1). The reduced Cu^{+} enters mitochondria and binds directly to key lipoylated enzymes in the TCA cycle, such as dihydrolipoamide S-acetyltransferase (DLAT) and dihydrolipoamide S-succinyltransferase (DLST). This interaction induces protein aggregation and the loss of Fe-S clusters (19). Fe-S clusters are key cofactors for numerous mitochondrial enzymes and respiratory chain complexes, such as succinate dehydrogenase subunit A and NADH:ubiquinone oxidoreductase subunit S1. Their disruption impairs the electron transport chain and decreases ATP synthesis and mitochondrial membrane potential (76). Consequently, mitochondrial energy production decreases, accompanied by increased inner membrane permeability, elevated Ca^{2+} concentration and the accumulation of ROS (77). The aggregation of lipoylated proteins further induces proteotoxic stress, disrupting proteostasis and exacerbating mitochondrial injury. Together, these molecular events define the mitochondrial mechanism of cuproptosis (Fig. 2).

Oxidative stress. Cu^{2+} catalyzes the Fenton-like reaction, generating hydroxyl radicals that initiate oxidative stress, leading to extensive cell damage and death (96). Hydroxyl radicals are highly reactive and attack DNA molecules to cause strand breaks, base modification and cross-linking, thereby interfering with DNA replication and transcription (97,98). These radicals also induce lipid peroxidation, compromising the integrity and fluidity of cell membranes and increasing membrane permeability (99). Additionally, oxidative modification alters protein structure and function, thereby disrupting intracellular protein homeostasis (100). Mitochondria are notable targets of copper-induced oxidative stress. Excess ROS decrease the mitochondrial membrane potential and ATP synthesis and promote cytochrome c release, ultimately activating caspase cascades and triggering apoptosis (101). Oxidative stress also activates TFs such asp53 and Nrf2, which regulate antioxidant responses and cell death pathways (102). Although Nrf2 activation enhances the antioxidant capacity by promoting the expression of antioxidant genes, when oxidative stress becomes excessive, these defense mechanisms are overwhelmed, leading to the accumulation of reactive oxygen species (ROS) and disruption of redox balance, ultimately resulting in cell death. Collectively, these molecular events constitute the oxidative stress-mediated mechanism of cuproptosis.

4. Cuproptosis in digestive system tumors

Increasing evidence has demonstrated that the dysregulation of copper metabolism is associated with the onset and progression of various diseases, particularly malignancy (6,7,103). As a key signaling metal, copper participates in cancer development by promoting cell proliferation, angiogenesis and metastasis (104). Copper serves dual roles in cancer biology; it is indispensable for cellular metabolism, but its dysregulation is associated with oncogenesis. Elevated copper levels have been detected in tumor tissue or serum in patients with multiple types of cancer, including breast (105-109), lung (110-112) and gastrointestinal cancer (113-116), oral (117), thyroid (118) and gallbladder carcinoma (119) and gynecological (115,116) and prostate cancer (120). These findings indicate that copper is not only a key factor in tumor growth and metastasis but also a necessary micronutrient for tumor cells (73,121). Mechanistically, copper promotes tumor progression through multiple pathways. First, copper stimulates angiogenesis by activating angiogenic factors and enhancing the proliferation and migration of vascular endothelial cells (122), thereby supporting tumor initiation, growth and metastasis (73,74,123,124). Newly formed vasculature provides key nutrients and serves as a conduit for tumor cell dissemination. Second, copper serves as a cofactor for several metalloenzymes, including MMP-9, SOD1, vascular adhesion protein-1 and lysyl oxidase (LOX), all of which are key for cancer invasion and metastasis (125-128). The ATOX1-ATP7A-LOX axis promotes metastatic dissemination by facilitating the copper-dependent activation of LOX and LOX-like enzymes, which remodel the extracellular matrix and increase tumor invasiveness (73,129). Third, copper activates the MAPK/ERK signaling pathway, thereby promoting tumor cell proliferation (130). In addition to these direct mechanisms, copper also modulates the TME to promote cancer progression. Copper influences tumor metabolic reprogramming, enhancing cell survival under hypoxic conditions (6). Moreover, copper contributes to immune evasion by regulating immune cell activity or promoting the expansion of immunosuppressive cell populations, allowing tumor cells to escape host immune surveillance (131). For example, copper alters macrophage polarization, shifting tumor-associated macrophages toward the M2 phenotype, which enhances immune suppression and facilitates tumor invasion and metastasis (11,132). Collectively, these findings suggest that copper serves multiple roles in tumorigenesis and disease progression, including roles in cell proliferation, angiogenesis, metastasis, metabolic reprogramming and immune escape, positioning copper as both a potential biomarker and therapeutic target in cancer biology.

Esophageal cancer (ESCA). The global incidence of ESCA in 2020 was ~604,000 new cases, and about 544,000 people died from ESCA; ESCA ranks 11th in terms of global cancer incidence and 7th in terms of cancer-associated mortality (133). Despite notable advances in diagnosis and therapy, the 5-year survival rate of patients with esophageal squamous cell carcinoma remains 20% owing to its late detection and rapid progression (134). Therefore, identifying novel diagnostic biomarkers and therapeutic strategies is key for improving prognosis and survival outcomes. Methyltransferase-like 3 (METTL3) expression is markedly elevated in ESCA tissue compared with that in normal esophageal epithelium, particularly in highly malignant tumors, and is associated with disease progression (135). Liu *et al* (136) investigated the role of METTL3 in ESCA and revealed its association with glycolysis, cuproptosis and the competing endogenous (ce) RNA regulatory network. These findings demonstrated that METTL3 serves as a critical mediator of ESCA progression by modulating glycolysis-associated gene expression. Upregulation of METTL3 in esophageal carcinoma enhances glycolytic flux, increases glucose uptake and lactate production and promotes tumor growth (128). Moreover, METTL3 expression is associated with the expression of genes associated with cuproptosis. Mechanistically, METTL3 serves dual regulatory roles in glycolysis and cuproptosis via N6-methyladenosine (m6A) RNA modification. Specifically, METTL3 alters and stabilizes glycolysis-associated mRNAs, thereby altering tumor cell energy metabolism and proliferation. Concurrently, METTL3 may regulate genes associated with copper homeostasis, affecting intracellular copper levels and inducing cell death. Additionally, METTL3 is involved in the ceRNA network, in which long non-coding (lnc) and circular RNAs compete for shared microRNAs (miRNAs or miRs), influencing posttranscriptional regulation. By modulating the stability or function of ceRNA components, METTL3 indirectly affects gene expression and tumor progression. These findings indicate that targeting METTL3 and its associated pathways may represent a promising therapeutic strategy for ESCA, especially in highly glycolytic and copper-enriched subtypes. The aforementioned study provides valuable insights into the epigenetic and metabolic regulation of ESCA, underscoring the potential of METTL3 as a therapeutic target that links epigenetic modification, metabolic reprogramming and copper-induced cell death. Further study have identified the cuproptosis-associated genes Centromere Protein E and SHC SH2 Domain-Binding Protein 1 as key biomarkers of Barrett's esophagus (BE) progression to esophageal adenocarcinoma (EAC) (137). These genes may influence the immune microenvironment and promote the transformation from BE to EAC, offering molecular targets for early diagnosis and treatment. Metabolic abnormalities (lactate accumulation and mitochondrial dysfunction) within tumor cells and the surrounding microenvironment impair immune responses and promote immune evasion (33). Moreover, disruption of metal ion homeostasis, particularly copper imbalance, alters oxidative stress and mitochondrial metabolism, further influencing tumor survival and therapeutic resistance (32,138). Therefore, integrating cuproptosis pathways into chemoradiotherapy or immunotherapy regimens may enhance radiosensitivity and remodel the tumor immune microenvironment, offering a rational framework for combination treatment strategies in ESCA.

Gastric cancer (GC). GC is an epithelial malignancy originating in the stomach. In 2022, there were ~968,000 new cases of GC worldwide, accounting for 4.9% of all new cancer cases, making it the fifth most common cancer by incidence globally (139). At the same time, gastric cancer accounted for approximately 6.8% of cancer-related deaths globally, with around 660,000 deaths, ranking fifth among the leading causes

of cancer death worldwide (139). Disruptions in PCD serve a crucial role in GC pathogenesis (140,141). Copper levels are notably elevated in gastric tumor tissue compared with normal gastric mucosa, particularly in high-grade malignancy. Moreover, the copper content is positively associated with the TNM stage of GC (142). In a recent study, Sun *et al* (79) investigated the mechanism of cuproptosis in GC, identifying its association with METTL16, an atypical m6A RNA METTL involved in m6A modification. METTL16 serves as a key mediator of cuproptosis by regulating FDX1 mRNA through m6A modification (79). Elevated copper levels in GC tissue promote the lactylation of METTL16 at lysine residue K229, which enhances its enzymatic activity and upregulates FDX1 expression, inducing cell death. Mechanistically, SIRT2 serves as a critical delactylase, removing lactyl groups from METTL16-K229 and inhibiting METTL16 activity. Treatment with (Z)-2-cyano-3-[5-(2,5-dichlorophenyl) furan-2-yl]-N-quinolin-5-ylprop-2-enamide, a selective SIRT2 inhibitor, increases METTL16 lactylation and FDX1 expression, thereby promoting cuproptosis. These findings suggest that the combined use of copper ionophores (such as ES) and SIRT2 inhibitors may represent a promising therapeutic strategy for GC, particularly in aggressive, high-copper and high-lactate subtypes such as mucinous adenocarcinoma. Sun *et al* provided valuable mechanistic insight into the role of METTL16-mediated RNA modification and lactylation in copper-induced cell death, highlighting the therapeutic potential of targeting the METTL16-SIRT2-FDX1 axis in GC treatment. Polypyrimidine tract-binding protein 3 (PTBP3) is markedly upregulated in peritoneal metastases of GC and is associated with poor prognosis (143). Single-cell RNA sequencing and transcriptome analysis reveal that PTBP3 regulates its downstream target COX11, impairing its function and decreasing the mitochondrial copper content, which enables tumor cells to evade cuproptosis. Researchers have developed an antisense oligonucleotide (ASO) targeting the short isoform of COX11 pre-mRNA exon 4 (136), effectively degrading COX11 mRNA and disrupting copper homeostasis. In a patient-derived organoid xenograft model combination therapy using exogenous copper ionophores and ASO drugs leads to excessive mitochondrial copper accumulation, proteotoxic stress and the induction of cuproptosis, thereby suppressing peritoneal metastasis (143). This provides a new therapeutic strategy targeting PTBP3-mediated COX11 splicing to restore copper-dependent cell death in metastatic GC. In stomach adenocarcinoma (STAD), FDX1, lipoic Acid Synthase (LIAS), Metal Regulatory Transcription Factor 1 (MTF1) and Pyruvate Dehydrogenase E1 Subunit Alpha 1 have been identified as key genes associated with cuproptosis (144). FDX1 is highly expressed in STAD tumor tissues, associated with poor prognosis and increased chemosensitivity to cisplatin and 5-fluorouracil, making FDX1 a potential predictive biomarker for chemotherapy response (145). LIAS and MTF1 exhibit notable prognostic value, where higher expression levels are associated with improved survival. Collectively, these molecular markers not only contribute to prognostic evaluation but also provide a foundation for the development of copper-targeted anticancer drugs. Aberrant copper homeostasis in GC is associated with mitochondrial dysfunction and ROS accumulation, whereas cuproptosis promotes energy metabolism collapse and cell death (146,147). Future studies should explore the potential synergy between copper-modulating drugs (such as ES) and immunotherapy or antiangiogenic therapy with the aim of achieving a coordinated antitumor effect through the simultaneous regulation of metabolic, immune and redox networks.

HCC. Based on GLOBOCAN 2020, HCC ranks sixth in incidence and third in cancer-associated mortality worldwide (148). Although notable therapeutic progress has been made over the past decade, the prognosis of HCC remains poor, largely because most patients are diagnosed at advanced stages, precluding surgical or localized treatment (149,150). Hence, identifying effective molecular targets and therapeutic strategies for HCC is key. Clinical studies have reported significantly elevated serum copper levels (151,152), increased copper-protein complexes and enhanced expression of copper-binding proteins in patients with HCC (153,154), as well as the downregulation of copper transporters such as ATP7A/B and SLC31A1/2 (155). Copper concentrations in HCC tissue are markedly higher than those in normal liver tissue and elevated serum copper levels are associated with tumor progression (156). In a recent study, Li *et al* (157) investigated the mechanism of cuproptosis in HCC, focusing on DLAT, a key gene associated with copper-induced cell death. The aforementioned study reported that maternal embryonic leucine zipper kinase (MELK) serves as a key mediator of cuproptosis by activating the PI3K/mTOR signaling pathway. Elevated copper levels in HCC promote MELK expression and activity, which upregulate DLAT expression and support mitochondrial function, thus facilitating HCC progression. Mechanistically, treatment with the copper ionophore ES decreases the expression of translocase of outer mitochondrial membrane 20 and enhances DLAT oligomerization, thereby suppressing MELK activity and triggering cuproptosis. These findings indicate that the combination of copper ionophores and PI3K/mTOR pathway inhibitors may represent a promising therapeutic approach for treating HCC. Li *et al* (157) provided key mechanistic insight into the MELK-DLAT regulatory axis, highlighting its potential as a therapeutic target in liver cancer. Exposure of Hep3B hepatoma cells to Cu^{2+} suppresses histone acetyltransferase activity, leading to hypoacetylation of histones H3 and H4, which promotes cell proliferation (19). Copper also binds pyruvate dehydrogenase kinase 1 (PDK1), enhancing its interaction with AKT, thereby activating the PDK1-AKT oncogenic signaling cascade and promoting HCC progression (158). Conversely, copper chelators or CTR1 inhibitors downregulate the CTR1-AKT axis, thus inhibiting tumor growth (158). CTR1 is aberrantly upregulated in breast cancer and is negatively regulated by NEDD4-like E3 ubiquitin ligase (NEDD4l), which promotes CTR1 ubiquitination and degradation. NEDD4l exerts tumor-suppressive effects by inhibiting CTR1-mediated AKT signaling. These findings reveal an association between the CTR1/Cu pathway and PDK1-AKT oncogenic signaling, underscoring the therapeutic potential of targeting the CTR1-Cu axis in cancers driven by AKT hyperactivation. By contrast with copper accumulation, FDX1 expression is notably lower in HCC tissues than in normal liver tissue, and its expression is positively associated with patient

survival, with higher FDX1 expression predicting longer overall survival. Moreover, FDX1 levels are positively associated with oxaliplatin sensitivity. In a recent study, Quan *et al* (159) elucidated the molecular mechanism of cuproptosis in HCC, focusing on the FDX1-associated lncRNA/miRNA regulatory axis. Through bioinformatic analyses, the aforementioned study identified LINC02362 as a ceRNA that modulates miR-18a-5p, which directly targets FDX1. Upregulation of the LINC02362/miR-18a-5p/FDX1 pathway signaling suppresses HCC cell proliferation. Conversely, LINC02362 knockdown decreases intracellular copper concentrations and induces resistance to ES-Cu-mediated cell death. Additionally, upregulation of this axis enhances the sensitivity of HCC to oxaliplatin by promoting cuproptosis. These findings suggest that LINC02362/miR-18a-5p/FDX1 is a novel regulatory pathway capable of overcoming oxaliplatin resistance in HCC through cuproptotic mechanisms. Recent preclinical studies have shown that copper chelators, including triethylenetetramine and D-penicillamine, significantly decrease copper levels and inhibit tumor growth in HCC (160). By restoring copper homeostasis, these agents may also overcome resistance to conventional therapy, supporting their potential clinical use in HCC treatment. Emerging research indicates that metabolic reprogramming and copper imbalance are common features of HCC (161). Excess copper disrupts mitochondrial oxidative phosphorylation and lipoyl enzyme complex activity, leading to lipid metabolic disorder and energy collapse (19). Moreover, the expression of genes associated with cuproptosis, such as FDX1, LIAS and DLAT, is downregulated in HCC tissue and the expression of these genes is significantly associated with immune phenotypes and overall survival (162). In conclusion, copper serves as both a metabolic cofactor and a potential therapeutic target in HCC. Regulation of copper levels or exploitation of its bioactive properties offers a promising avenue for novel anticancer strategies. Future studies should elucidate the mechanisms of copper-targeted therapy, optimize therapeutic regimens and conduct rigorous clinical trials to validate their safety and efficacy.

Pancreatic cancer. According to GLOBOCAN 2020, pancreatic cancer is a highly aggressive malignancy, ranking twelfth in incidence but sixth in overall cancer-associated mortality worldwide (163). Despite advances in treatment, the 5-year overall survival rate remains ~ 10% (164). Pancreatic cancer remains among the most common types of treatment-refractory malignancy. Elevated serum copper levels may contribute to pancreatic cancer development (165). Novel nanomaterial-based strategies to exploit cuproptosis for therapeutic benefit (166). For example, tussah silk fibroin (TSF)-based nanoparticles (NPs) use TME-responsive release mechanisms to deliver copper and the cuproptosis-inducing drug ES directly to pancreatic cancer cells. Upon targeted delivery, TSF@ ES-Cu NPs induce cuproptosis, releasing damage-associated molecular patterns that activate antitumor immunity (166). This promotes dendritic cell maturation and macrophage M1 polarization, thereby reshaping the TME and enhancing immune responses. Collectively, these findings demonstrate that TSF@ ES-Cu NPs suppress pancreatic cancer growth through a dual mechanism of cuproptosis induction and immune microenvironment remodeling, offering a promising avenue for clinical translation. In addition, other research have explored the prognostic and therapeutic roles of cuproptosis-associated lncRNAs in pancreatic ductal adenocarcinoma (PAAD) (167). Researchers have developed a cuproptosis-immune-related (CIR) score to characterize the interaction between cuproptosis and the tumor immune microenvironment (168). By integrating single-cell sequencing and transcriptomic data, researchers have identified immune- and cuproptosis-related genes associated with PAAD and constructed a CIR score model (168). This score not only predicts prognosis in patients and the immune landscape but also reflects the tumor mutational burden (TMB), immune checkpoint sensitivity, and drug responsiveness. Patients in the high CIR score group exhibit higher TMB and poorer survival, whereas those in the low CIR score group exhibit stronger immune activation and greater potential responsiveness to immunotherapy. Mouse model experiments have validated the predictive power of the CIR score in guiding combination therapy involving immunotherapy, targeted therapy and chemotherapy (168). Such combined regimens significantly inhibit PAAD progression, highlighting the translational potential of cuproptosis-based prognostic markers in personalized immunotherapy. Mechanistically, these findings indicate that the cuproptosis-metabolic reprogramming-immune activation axis represents a novel paradigm for the systemic treatment of pancreatic cancer. The integration of copper homeostasis regulation into individualized therapeutic frameworks provides both theoretical and practical foundations for precision medicine in PAAD.

Colorectal cancer (CRC). CRC, one of the most common malignant tumors of the digestive system, is the third most commonly diagnosed cancer worldwide, with approximately 1.9 million new cases annually (169). Cuproptosis-related genes, such as FDX1, SDHB, DLAT and DLST, are expressed at higher levels in normal compared with tumor tissues (170). Moreover, higher expression of these genes in tumor tissue is associated with better prognosis (170). When ES, a copper carrier, combines with copper, the proliferation of CRC cells is significantly inhibited and apoptosis is promoted. This effect is markedly suppressed by the copper chelator TTM, further confirming the mechanism of copper-induced cell death. Furthermore, 2-deoxy-D-glucose, a glycolysis inhibitor, can significantly enhance cuproptosis (170). In addition, galactose promotes oxidative phosphorylation by inhibiting the glycolytic pathway in tumor cells, thereby enhancing copper-induced cell death (170). These results indicate that the inhibition of glycolysis can increase the sensitivity of tumor cells to cuproptosis. Studies have also shown that 4-octyl itaconate (4-OI), a cell-permeable derivative of itaconic acid, inhibits glycolysis by targeting the key glycolytic enzyme GAPDH, thereby enhancing cuproptosis. 4-OI suppresses GAPDH activity, decreases lactate production and subsequently promotes copper-induced cell death. Furthermore, *in vivo* experiments demonstrated that 4-OI has significant antitumor effects and that its combination with ES markedly decreases tumor volume. Yang *et al* (170) provided new insights into the role of cuproptosis in CRC and revealed that 4-OI enhances copper-induced cell death by inhibiting glycolysis. These findings not only provide a novel therapeutic strategy for CRC but

also establish theoretical support for cuproptosis as a potential anticancer approach. Cuproptosis-associated genes demonstrate important prognostic value in colon adenocarcinoma because their expression levels are associated with patient survival, TME characteristics and drug sensitivity (171). To the best of our knowledge, the aforementioned study was the first to systematically analyze the roles of genes associated with cuproptosis in colon adenocarcinoma and to elucidate their potential mechanisms in tumor progression and immune microenvironment regulation. Similarly, genes associated with cuproptosis serve a significant role in the prognosis and treatment of rectal adenocarcinoma (172). Copper chelators or carriers may synergize with chemotherapy or immunotherapy, thereby improving the prognosis of liver-metastatic CRC (173).

Status and prospects for the clinical application of cuproptosis-associated drugs. Cuproptosis-associated drugs have demonstrated antitumor potential in clinical trials for gastrointestinal cancer (174,175). For example, the disulfiram/copper complex inhibits the proliferation of GC cells by inducing oxidative stress and DNA damage while increasing the sensitivity of tumor cells to chemotherapeutic agents (174). In addition, TTM, a copper chelator, exerts antiangiogenic and chemosensitizing effects in metastatic CRC (175). The potential clinical applications of these drugs include combining them with chemotherapy to enhance therapeutic efficacy, targeting copper metabolism-associated proteins to improve treatment precision and using biomarkers such as serum copper levels to guide medication strategies. Nevertheless, further research is needed to optimize the design of cuproptosis-associated drugs to improve their efficacy and decrease side effects. However, future in-depth studies on the molecular mechanisms of these drugs and additional clinical trials to verify their safety and effectiveness are needed.

5. Conclusion

As a newly identified form of regulated cell death, cuproptosis has become a prominent focus in tumor biology, particularly in gastrointestinal cancer. The present review summarizes the mechanistic pathways and therapeutic potential of cuproptosis, emphasizing key molecular events such as mitochondrial damage, oxidative stress and protein lipoylation, as well as copper imbalance and its association with tumor initiation and development. Current evidence indicates that disruption of copper metabolism is associated with tumor growth and progression. By modulating intracellular copper levels, cuproptosis inhibits tumor cell proliferation through various mechanisms, including the induction of PCD and the enhancement of antitumor immune responses. Moreover, cuproptosis-associated drugs, such as disulfiram/copper complexes and TTM, have demonstrated promising anticancer potential in preclinical and clinical studies because they induce oxidative stress, increase chemosensitivity and inhibit angiogenesis. However, the clinical application of these drugs faces several challenges, including limited efficacy, toxicity management and a lack of large-scale validation. Future studies should further clarify the molecular mechanisms of cuproptosis, develop novel copper-dependent therapeutic agents with improved selectivity and safety and conduct clinical trials to assess their translational value. In conclusion, cuproptosis offers a novel conceptual and therapeutic direction for gastrointestinal oncology, holding promise for treatment options that could improve prognosis and survival outcomes.

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Authors' contributions

LZ and YC conceived the study. LT, JZ and BT edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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