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REVIEW

Innovative cross-intervention: copper ions and metabolic pathways in cancer therapy

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ABSTRACT Copper ions are essential for cellular function but can induce cytotoxic effects when dysregulated. This review explores the multifaceted role of copper in cancer metabolism with a focus on the novel concept of cuproptosis, a regulated form of cell death triggered by copper accumulation. The mechanisms underlying copper homeostasis are detailed, including dietary absorption, systemic distribution, and intracellular utilization. Key transporters, such as copper transporter 1 (CTR1) and ATPase copper transporting alpha/b (ATP7A/B), are highlighted. Cancer cells often exhibit elevated copper levels, supporting proliferation and metastasis through pro-tumorigenic pathways. Recent studies have shown that disrupting copper homeostasis can induce cuproptosis, which is characterized by the aggregation of lipoylated mitochondrial proteins and disruption of iron-sulfur cluster biogenesis. Advances in copper-based nanotechnology have enabled targeted delivery of copper to tumors, enhancing therapeutic efficacy through synergistic effects with reactive oxygen species (ROS) generation and immunomodulation. However, the hypoxic tumor microenvironment poses significant challenges by upregulating copper-sequestering proteins and downregulating key cuproptosis mediators. Future directions include integrating multi-omics approaches to identify novel therapeutic targets and developing combination therapies to overcome hypoxia-induced resistance. This review provides a comprehensive overview of copper metabolism in cancer, emphasizing the potential of cuproptosis induction as a powerful strategy for oncologic intervention.

KEYWORDS Copper homeostasis; cuproptosis; tumor metabolism; nanotherapy; hypoxia resistance

Introduction

Copper is an essential redox-active micronutrient that serves as a critical cofactor for a vast array of enzymes governing fundamental biological processes, including mitochondrial respiration, antioxidant defense, and signaling cascades[1]. However, excessive intracellular copper can catalyze the generation of highly reactive hydroxyl radicals *via* the Fenton reaction, leading to severe oxidative damage to DNA, proteins, and lipids, and ultimately triggering cytotoxic effects[2]. To maintain this delicate balance, organisms have evolved a sophisticated regulatory network comprising copper chaperones, transporters (e.g., CTR1 and ATP7A/B), and storage proteins [e.g., metallothioneins (MTs)], which coordinate the absorption, distribution, utilization, and excretion of copper[3].

Cancer cells often exhibit elevated copper levels, which support proliferation, angiogenesis, and metastasis by activating pro-tumorigenic signaling pathways and enzymes[4,5]. This

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copper dependency, termed "cuproplasia," positions copper as an attractive target for anticancer therapy. Traditional strategies have focused on copper chelation [e.g., with tetrathiomolybdate (TTM)] to deplete bioavailable copper and suppress tumor growth[5]. In a fascinating paradox, forcing cancer cells to accumulate excess copper can also be lethal. Although copper-induced cell death was observed decades ago[6], the precise mechanism was elusive until the recent groundbreaking work by Tsvetkov et al.[1], who defined a novel, regulated form of cell death (cuproptosis).

Cuproptosis is mechanistically distinct from other programmed cell death pathways, such as apoptosis, ferroptosis, and necroptosis, because cuproptosis is not inhibited by corresponding specific inhibitors[1]. The translational potential of inducing cuproptosis in tumors is significant, primarily through copper ionophores, like elesclomol (ES)[1]. Furthermore, advances in nanotechnology have enabled the development of sophisticated copper-based nanoparticles that enhance tumor-selective copper delivery, synergizing cuproptosis with ROS generation and immunomodulation for improved antitumor efficacy[5]. However, a major therapeutic challenge arises from the hypoxic tumor microenvironment, which activates hypoxia inducible factor-1α (HIF-1α) and confers resistance to cuproptosis by upregulating copper-sequestering MTs (e.g., MT2A) and downregulating key mediators, like dihydrolipoylS-acetyltransferase (DLAT)[7]. Overcoming this resistance necessitates innovative combination strategies. As shown in **Figure 1**, this review comprehensively summarizes the fundamental principles of systemic and cellular copper homeostasis, elaborates on the unique molecular mechanisms of cuproptosis, and critically examines the latest advances in targeting copper metabolism for cancer therapy. The challenges posed by the tumor microenvironment are discussed and future directions are explored, including the integration of multi-omics approaches and combination therapies, to fully realize the potential of cuproptosis induction as a powerful weapon in the oncotherapeutic arsenal.

Copper homeostasis and metabolic regulation

Copper, an essential redox-active micronutrient, serves as a critical cofactor for enzymes governing fundamental biological

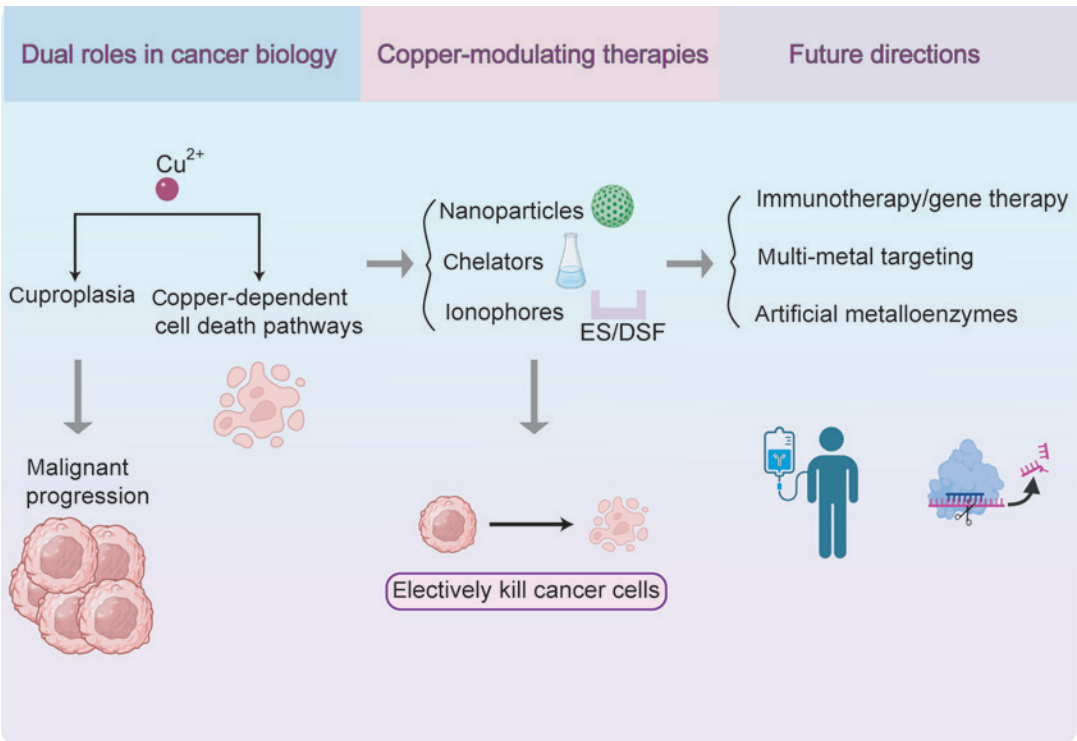


Figure 1 Schematic summary of the dual roles of copper in cancer biology and copper-modulating therapies. This figure illustrates the complex relationship between copper in cancer biology and potential copper-modulating therapies, showing how copper, through copper-dependent cell death pathways, contributes to malignant progression. Various therapies, such as nanoparticles, chelators, and ionophores, are shown as strategies to disrupt copper trafficking, selectively killing cancer cells. The figure also highlights future directions in therapy, including immunotherapy/gene therapy, multi-metal targeting, and artificial metalloenzymes to further enhance cancer treatment. DSF, disulfiram; ES, elesclomo.

processes, including mitochondrial respiration, antioxidant defense, and signaling cascades[1]. Although copper is an essential trace element for human body, excessive accumulation of copper can lead to the generation of hydroxyl radicals (·OH) *via* the Fenton reaction ($Cu^+ + H_2O_2 \rightarrow Cu^{2+} + \cdot OH + OH^-$). The hydroxyl radical is a highly reactive ROS capable of inducing oxidative damage to DNA, proteins, and lipids, thereby triggering cytotoxic effects[2]. To prevent such adverse outcomes, copper levels in the body are tightly regulated by a sophisticated network of copper-related proteins, including copper-dependent enzymes, copper chaperones, and membrane-bound transporters. These proteins collectively govern copper absorption, excretion, and intracellular utilization to maintain systemic copper homeostasis[3].

Dietary absorption and systemic distribution

The concentration of free copper ions is relatively low in the human body because most copper is either stored in a bound form or functions as a cofactor by associating with proteins or other biomolecules[8]. Dietary copper is primarily absorbed *via* the intestinal epithelium with the duodenum serving as the main site of absorption[9]. Dietary copper predominantly exists in the Cu^{2+} form but only the reduced Cu^+ form can be effectively absorbed and utilized by the body. As illustrated in **Figure 1**, ingested Cu^{2+} is initially reduced to Cu^+ by metal reductases, such as six-transmembrane epithelial antigen of the prostate (STEAP) or duodenal cytochrome b (Dcytb), after which Cu^{2+} enters intestinal epithelial cells *via* copper transporter 1 (CTR1)[10,11]. CTR1 is the principal mediator of intestinal copper absorption and intestinal-specific knockout of CTR1 has been shown to result in systemic copper deficiency[12]. The expression of CTR1 is modulated by the body copper status, it is downregulated under conditions of copper excess and upregulated in states of deficiency[13]. In addition to CTR1, other transporters, such as the low-affinity copper transporter 2 (CTR2)[14] and divalent metal transporter 1 (DMT1)[15], also contribute to copper uptake. Absorbed copper is transported into the bloodstream *via* ATP7A located on the basolateral membrane of intestinal epithelial cells[16]. Most copper in the blood binds to ceruloplasmin, although a minor fraction associates with albumin, transferrin, and free amino acids. This copper-bound ceruloplasmin is then transported to the liver *via* the portal venous system.

Hepatic storage, utilization, and excretion

Hepatocytes primarily take up copper through the CTR1 and the liver serves as the primary site for copper storage and excretion[17]. As illustrated in **Figure 1**, copper binds to glutathione (GSH) within the cytoplasm and is subsequently transferred to MT. Both GSH and MT contain abundant thiol groups, which confer a strong affinity for copper. MT1 and MT2 are the principal copper-binding proteins in the liver and serve as major copper storage sites[18]. MT3, which is predominantly expressed in the central nervous system, also has a role in maintaining copper homeostasis[19]. Copper is involved in the biosynthesis of ceruloplasmin within hepatocytes. Copper-bound ceruloplasmin is secreted into the bloodstream and delivered to specific tissues or organs, where copper-bound ceruloplasmin participates in various catalytic physiologic processes[8]. When systemic copper levels exceed physiologic requirements, hepatocytes transport excess copper into bile *via* ATP7B, where it is excreted into the intestine through the biliary tract and ultimately eliminated from the body *via* feces. Biliary excretion constitutes the primary route of copper elimination[20]. In summary, systemic copper metabolism is predominantly regulated by intestinal absorption and hepatic excretion. Under conditions of copper excess, absorption decreases and excretion increases, whereas the opposite pattern occurs during copper deficiency.

Intracellular copper trafficking and utilization

Copper primarily participates in physiologic cellular processes in the form of Cu^+. CTR1 serves as the primary pathway for cellular copper uptake[21]. As illustrated in **Figure 2**, copper can interact with various copper chaperones upon entering the cell, including cytochrome c oxidase copper chaperone 11/17 (COX11/17), copper chaperone for superoxide dismutase (CCS), and antioxidant protein 1 (ATOX1). These chaperones facilitate the delivery of copper to specific target proteins or subcellular compartments, where copper performs essential biological functions. The synthesis of cytochrome c oxidase (CCO) involves several key steps and molecular components. CCO consists of two core subunits in humans [cytochrome c oxidase subunits 1 (COX1) and 2 (COX2)], which bind copper ions at the CuB and CuA sites, respectively[22]. COX17 is responsible for transporting copper from the cytoplasm to the mitochondrial intermembrane space[23]. Copper ions are subsequently delivered to the COX2 subunit *via* cytochrome c oxidase synthesis proteins 1 and 2 (SCO1/2) or to the COX1 subunit through COX11[24,25]. These copper-binding events are essential for the proper functioning of the respiratory chain and oxidative phosphorylation. Mutations in COX17 or SCO1/2 have been shown to reduce CCO activity, thereby impairing cellular energy metabolism[26,27]. ATOX1 mediates the transfer of copper to ATP7A/B, which are the primary transporters responsible for copper efflux from cells. The localization and functional activities of ATP7A/B are dynamically regulated[28]. Under physiologic intracellular copper concentrations, these transporters reside in the trans-Golgi network (TGN), where they facilitate the transport of copper ions from the cytoplasm into the luminal compartment of the TGN. Upon elevation of intracellular copper levels, these proteins translocate from the TGN to the plasma membrane, enabling the excretion of

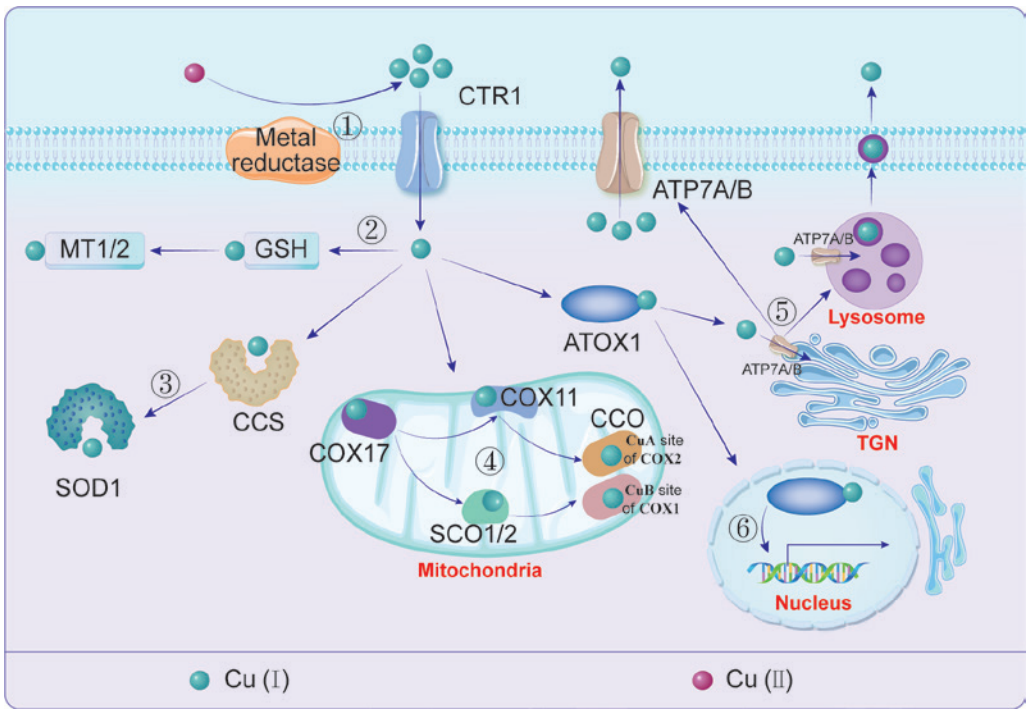


Figure 2 Schematic diagram of cellular copper metabolism. This figure illustrates the detailed process of copper metabolism within the cell. ① Extracellular copper exists primarily as Cu2+ in mammalian cells, which is reduced to Cu+ by membrane-associated metalloreductases prior to cellular uptake *via* the high-affinity copper transporter, CTR1. ② Copper is trafficked to specific intracellular compartments in the cytoplasm by dedicated chaperones and storage molecules. Copper can be buffered by binding to GSH and sequestered by MT1/2 to maintain homeostasis. ③ The chaperone, CCS, delivers Cu^+ to SOD1, promoting the formation of the CTR1–CCS–SOD1 complex and activating SOD1 to catalyze the dismutation of $O_2\cdot-$, thereby mitigating oxidative stress. ④ COX17 delivers copper to the intermembrane space for mitochondrial utilization, where SCO1/2 and COX11 facilitate copper incorporation into the CuA site of COX2 and the CuB site of COX1, respectively, which is essential for the assembly and function of CCO. ⑤ In addition, the chaperone ATOX1 transfers Cu^+ to ATP7A/B transporters in the TGN. Under normal conditions, these ATPases metallate cuproenzymes within the secretory pathway, when copper is overloaded, the ATPases relocalize to the plasma membrane or lysosomes to mediate efflux with ATP7A being widely expressed and ATP7B functioning primarily in hepatic and intestinal copper excretion into bile. ⑥ In addition, ATOX1 can deliver copper into the nucleus, where ATOX1 acts as a copper-dependent transcription factor to modulate gene expression. Collectively, these coordinated pathways ensure precise copper homeostasis, achieving a balance between its essential roles in cellular biochemistry and the prevention of cytotoxicity. ATP7A/B, ATPase copper transporting alpha/beta (also known as Menkes and Wilson disease protein, respectively); CCS, copper chaperone for SOD1; COX11, cytochrome c oxidase copper chaperone 11; COX17, cytochrome c oxidase assembly protein 17; CTR1, copper transporter 1; Cu, copper; Cu+, copper (I) ion (cuprous ion); Cu2+, copper (II) ion (cupric ion); CCO, cytochrome c oxidase; GSH, glutathione; MT1/2, metallothionein 1/2; $O_2\cdot-$, superoxide anion radical; SCO1/2, synthesis of cytochrome c oxidase 1/2; SOD1, superoxide dismutase 1; TGN, trans-Golgi network.

excess copper from the cell. ATP7A and ATP7B exhibit distinct expression patterns. ATP7A is broadly expressed across most tissues and organs, whereas ATP7B is predominantly expressed in the liver[29]. Notably, intestinal epithelial cells also express ATP7B, which primarily functions to sequester copper within intracellular vesicles, thereby maintaining copper homeostasis[30]. ATP7B can relocate from the TGN to lysosomes when hepatocyte copper levels are excessive, followed by copper excretion into bile *via* exocytosis. Alternatively, ATP7B can also translocate to the apical membrane to directly excrete copper into bile[31]. Consequently, mutations in ATP7A or ATP7B may lead to disturbances in copper metabolism, resulting in intracellular copper accumulation and the development of Menkes and Wilson's diseases, respectively[20,32]. ATOX1 binds to copper within the cell nucleus and functions as a transcription factor that promotes gene expression[29]. Superoxide dismutase 1 (SOD1), commonly referred to as copper-zinc superoxide dismutase, catalyzes the conversion of superoxide anions ($O_2\cdot^-$) into hydrogen peroxide ($2O_2\cdot^- + H^+ \rightarrow H_2O_2 + O_2$)[33]. $O_2\cdot^-$ has a key role in the production of ROS within the body. CCS interacts with CTR1 and SOD1 to form the CTR1-CCS-SOD1 complex, which facilitates the transfer of copper to SOD1, thereby activating SOD1 and modulating intracellular oxidative stress levels[34].

Copper ion homeostasis and tumor metabolism

The era of modern tumor metabolism research began with the discovery of a metabolic phenotype by Otto Warburg in 1924, which is now known as the Warburg effect[35]. The advent of high-throughput technologies and computational systems biology during the ensuing decades catalyzed a resurgence in cancer cell metabolism research. These innovative tools have enriched the understanding of the Warburg effect, enabling the identification of novel metabolic pathways and dependencies in cancer cells. Furthermore, the innovative tools have contributed to the development of potential therapeutic strategies aimed at targeting these metabolic alterations[36]. For example, the identification of metabolic reservoir cycles in cancer cells, including the storage and utilization of glycogen, triglycerides, and phosphocreatine, has yielded novel insights into the metabolic adaptability of cancer cells and potential therapeutic targets[37]. Numerous landmark discoveries have elucidated the role of copper in cancer metabolism. Xue et al. demonstrated that copper is intricately involved in cell death and autophagy induction in cancer cells[38].

Moreover, copper-based nanoparticles have been developed for cancer therapy that take advantage of elevated levels of copper in tumor tissues. These nanoparticles trigger oxidative stress and cuproptosis in cancer cells as single agent therapy or in combination with other treatment modalities[5] (**Table 1**). In addition to the therapeutic potential, copper ions (existing predominantly as Cu^+ in the reducing cytosolic environment) have fundamental roles in cancer mitochondrial metabolism. Cu^+-dependent enzymes (e.g., COX) sustain mitochondrial respiration, while Cu^+/Cu^{2+} redox cycling catalyzes Fenton-like ROS generation. Perturbation of mitochondrial copper homeostasis can result in mitochondrial dysfunction and subsequent cell death in cancer cells[39].

Recent advances in copper metabolism research have elucidated the pivotal role of copper transporters in cancer biology. The high-affinity copper transporter (CTR1), solute carrier family 31 member 1 (SLC31A1), not only maintains cellular copper homeostasis but also critically determines cisplatin sensitivity in cancer therapy[40]. Emerging studies revealed that additional metal transporters, including zinc transporter 1 (ZnT1/SLC30A1), participate in copper regulation and cuproptosis. Although primarily characterized as a zinc efflux transporter, ZnT1 has been confirmed to be involved in the modulation of Cu^+ entry into cells and is essential for Cu^{2+}-induced cell death[41]. Similarly, ATP7A/B are essential for maintaining cellular copper balance by transporting excess copper out of the cell. Recent studies have highlighted the significant roles of MT, particularly MT2A, MT1E, and MT1X isoforms, in copper metabolism[42]. Our research also indicated that HIF-1α induces the expression of MT2A and reduces mitochondrial copper accumulation by chelating cytoplasmic copper ions, thereby inhibiting cuproptosis[7]. Inhibition of these transporters disrupts cellular copper balance, which leads to elevated cellular copper levels and induces cell death[43]. Recent advances in the study of copper-dependent enzymes have highlighted the significance of copper-dependent enzymes as potential targets in cancer research. Enzymes, such as glutaminase C (GAC) and glutaminase 2 (GLS2), which facilitate the conversion of glutamine-to-glutamate, are pivotal in the glutamine dependency observed in cancer cells[44]. Elucidating the regulatory mechanisms and functions of these enzymes within the framework of copper metabolism may unveil novel therapeutic strategies. Furthermore, contemporary research has concentrated on the creation of artificial metalloenzymes and nanozymes for cancer treatment. By mimicking the catalytic activity of natural enzymes, these engineered enzymes exhibit tumor-selective targeting capabilities, demonstrating therapeutic potential against cancer cells. For example, single-atom catalysts have been investigated for application in nanocatalytic tumor therapy, leveraging distinct properties to induce oxidative stress and promote cell death in cancer cells. In addition, the exploration of copper-oxygen complexes within copper-containing enzymes as potential therapeutic targets remains a vibrant area of research[45]. Therefore, it is important to understand the functions and regulation of these transporters to develop strategies aimed at controlling cellular copper levels in cancer.

Cuproptosis

The earliest report of copper ion-induced cell death can be traced back to 1980[6]. However, a clear mechanistic explanation for this phenomenon was lacking, leading to prolonged debate regarding copper ion-induced cell death. It was not until 2022 that Tsvetkov et al. introduced the concept of "cuproptosis" and provided a detailed elucidation of the underlying mechanism of copper-induced cell death (**Figure 3**)[1]. Cuproptosis is a form of regulated cell death initiated by intracellular copper accumulation. Copper import occurs primarily *via* the transporter, SLC31A1, which mediates Cu^+ uptake, or through copper ionophores, such as ES and disulfiram (DSF), which facilitate Cu^{2+} entry. Copper binds to lipoylated components of the mitochondrial tricarboxylic acid cycle within the cell, particularly DLAT, prompting oligomerization and resulting in proteotoxic stress. The reductase, FDX1, has a dual role: reducing Cu^{2+} to Cu^+ and contributing to DLAT lipoylation. In addition, copper impedes the FDX1-dependent biosynthesis of iron–sulfur (Fe–S) clusters. The combined effects of DLAT aggregation and disruption of Fe–S cluster biogenesis ultimately induce cell death. This process can be suppressed by copper chelators, such as GSH and tetrathiomolybdate, which sequester copper ions and reduce intracellular copper bioavailability. It has been shown that cuproptosis is distinct from other known forms of programmed cell death. First, the copper ion-binding compound ES does not induce activation of caspase 3/7, key markers of apoptosis. Furthermore, the

Table 1 Main copper-related anti-cancer drugs

Type	Medicine	Mechanism	Cancer type	Reference
Copper chelators	DP	Anti-angiogenesis	Liver cancer	*Int J Cancer*. Dec 15 2001;94(6):768-73
	TTM	Anti-angiogenesis	Pancreatic cancer	*Proc Natl Acad Sci U S A*. Nov 26 2013;110(48):19507-12
		Inhibits the abnormal activation of the MAPK pathway	Melanoma, colorectal cancer	*Cancer Res*. Apr 1 2020;80(7):1387-1400; *Cancers (Basel). 2019;11(5):659*
		Chemotherapy sensitization	Lung cancer	*J Inorg Biochem*. Aug 2022;233:111865
		Mitochondrial toxicity	Triple-negative breast cancer	*Nat Commun*. Dec 15 2021;12(1):7311
Copper ionophores	TETD	Inhibits proteasome activity	Breast cancer, lung cancer	*Nature*. Dec 14 2017;552(7684):194-199; *Nat Commun*. Jan 5 2021;12(1):121
		Cell cycle arrest	Leukemia	*Biomed Pharmacother*. Mar 2018;99:561-569
		Ferroptosis	Nasopharyngeal carcinoma	*Cancers (Basel)*. 2020;12(1):138
		Cuproptosis	Ovarian cancer, pituitary neuroendocrine tumour, lung cancer, breast cancer	*Oncol Res*. 2023;31(3):333-343; *Int Immunopharmacol*. Jun 15 2024;134:112159; *Int J Mol Med*. 2024;53(2):19; *J Control Release*. Oct 2023;362:502-512
		Accumulation of ROS	Nasopharyngeal carcinoma, leukemia	*Cancers (Basel)*. 2020;12(1):138; *Cell Death Dis*. May 18 2017;8(5):e2797
	ES	Cell cycle arrest	Leukemia	*Biochem Pharmacol*. Feb 1 2015;93(3):266-76
		Ferroptosis	Colorectal cancer, liver cancer	*Nat Med*. May 2019;25(5):825-837; *J Exp Clin Cancer Res*. Jun 6 2023;42(1):142
		Cuproptosis	Stomach cancer, colorectal cancer, bladder cancer	*Nat Commun*. Oct 20 2023;14(1):6523; *Biomed Pharmacother*. Mar 2023;159:114301; *Adv Mater*. Jun 2023;35(22):e2212267
		Accumulation of ROS	Melanoma, glioblastoma	*Oncogene*. Jul 2022;41(27):3539-3553; *J Exp Clin Cancer Res*. 2021;40(1):228

DP, D-penicillamine; TTM, tetrasomolybdate; TETD, tetraethylthiuram disulfide; ES, elesclomol; MAPT, mitogen-activated protein kinase; ROS, reactive oxygen species.

cytotoxic effect of ES is unaffected when key apoptotic genes, BCL2 Associated X Protein *(BAX)* and BCL2-antagonist/killer 1*(BAK1)*, are genetically deleted or when apoptosis and pyroptosis are pharmacologically inhibited using Benzyloxycarbonyl-Val-Ala-Asp (OMe)-fluoromethylketone (Z-VAD-FMK) and Boc-Asp(OMe)-fluoromethylketone (Boc D-FMK), respectively. These findings suggest that cuproptosis is mechanistically distinct from apoptosis. Similarly, other established cell death inhibitors, such as ferrostatin-1 (Fer-1), which inhibits ferroptosis, necrostatin-1 (Nec-1), which blocks necrosis, and N-acetylcysteine, which mitigates oxidative stress, did not attenuate cuproptosis, further supporting the unique molecular basis. Only the copper ion chelator, tetrathiomolybdate (TTM), has the capability to inhibit cuproptosis and restore cellular activity, suggesting that this form of cell death is mediated through a unique mechanism that is distinct from the currently established cell death pathways.

Therapeutic targeting of cuproptosis in cancer

Copper-related anti-cancer drugs have become a significant focus in current cancer research. Therapeutic strategies targeting copper in cancer treatment include the use of copper ion chelators to reduce copper bioavailability or the application of copper ion carriers or copper-containing drugs based on the principle of "cuproptosis" to increase intracellular copper levels in cancer cells (**Figure 4**). Chelators (e.g., TTM) deplete bioavailable copper to suppress angiogenesis and metastasis, while

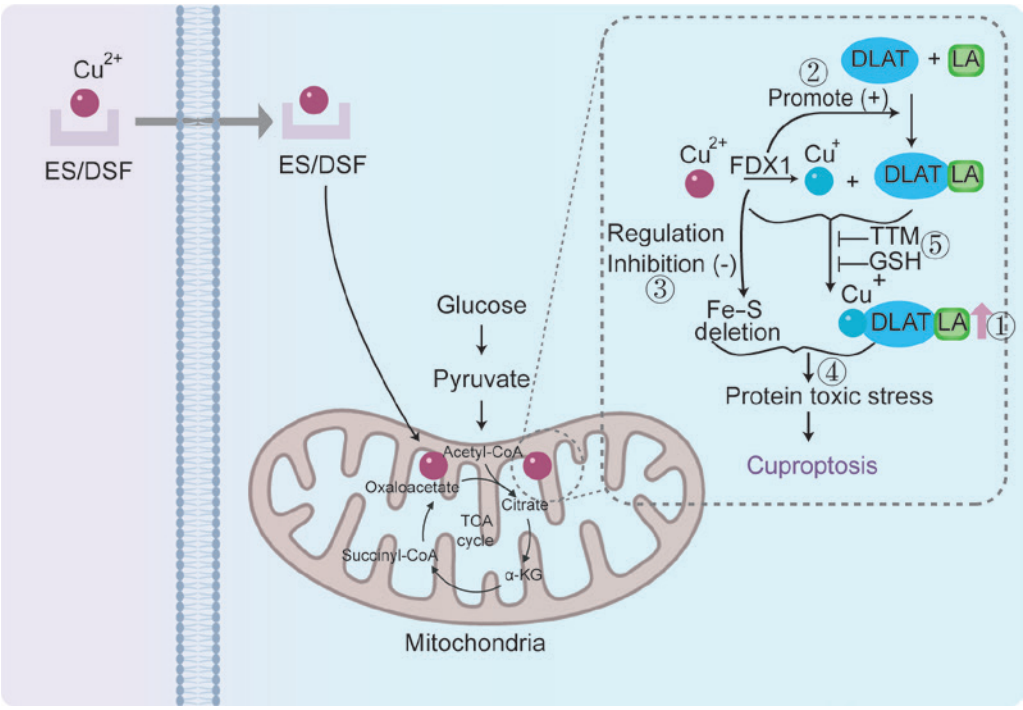


Figure 3 Schematic diagram of the mechanism underlying cuproptosis. This figure illustrates the molecular mechanism underlying cuproptosis, a copper-induced form of cell death. Copper ions (Cu2+) enter cells through copper ionophores, such as ES and DSF. ① Copper binds lipoylated DLAT (the substrate for lipoylation modification is LA) inside the mitochondria, leading to aggregation and subsequent proteotoxic stress. ② The copper also interacts with FDX1, reducing Cu2+ to Cu+ and promoting DLAT lipoylation. ③ However, copper inhibits the synthesis of Fe–S clusters by FDX1, disrupting cellular function. ④ This inhibition, in combination with DLAT aggregation, triggers a toxic response that culminates in cuprotosis. ⑤ The process of cuproptosis can be mitigated by the binding of copper ions to molecules, like GSH and TTM, which reduce the free copper ion concentration, thereby preventing DLAT aggregation and inhibiting cell death. DLAT, dihydrolipoamide S-acetyltransferase; DSF, disulfiram; ES, elesclomol; FDX1, ferredoxin 1; Fe-S, iron-sulfur cluster; GSH, glutathione; LA, lipoic acid; TTM, tetrathiomolybdate.

ionophores (e.g., ES) deliver copper into cells to induce cuproptosis or ferroptosis (**Table 1**). Nanotechnology platforms further enhance specificity. Copper-based nanoparticles exploit cancer-selective copper accumulation to synergize cuproptosis with ROS generation or immunomodulation (**Table 2**).

Future directions of copper ions in cancer metabolism research

Prospects of copper metabolism-targeted precision medicine in cancer therapy

Copper metabolism-targeted precision medicine is promising for anti-cancer treatment. Copper metabolism has emerged as a novel biomarker for molecular imaging and targeted therapy in hepatocellular carcinoma (HCC). The elevated accumulation of copper ions in HCC and other cancers indicates that copper modulation therapy, such as the application of copper chelators and short-interfering RNAs specific to CTR1, inhibit tumor growth by disrupting excessive copper uptake. Moreover, copper metabolism represents a promising target for radionuclide therapy utilizing therapeutic copper radionuclides, underscoring the dual potential as a theranostic biomarker for the imaging and treatment of HCC[46].

Advances in the fields of genomics, transcriptomics, and metabolomics have significantly enhanced our understanding of the complex metabolic alterations that occur in cancer cells, particularly the alterations related to copper metabolism. These omics technologies provide a comprehensive view of the molecular and cellular changes that underpin cancer development and progression. By integrating data from these diverse fields, researchers can identify specific metabolic pathways that are altered in cancer cells, offering potential targets for therapeutic intervention. Metabolomics has a crucial role in elucidating the metabolic reprogramming of cancer cells. This field focuses on the global analysis of small molecule metabolites, which can reveal critical information about the cancer state that might not be apparent through other methods. For example, metabolomics has been instrumental in identifying

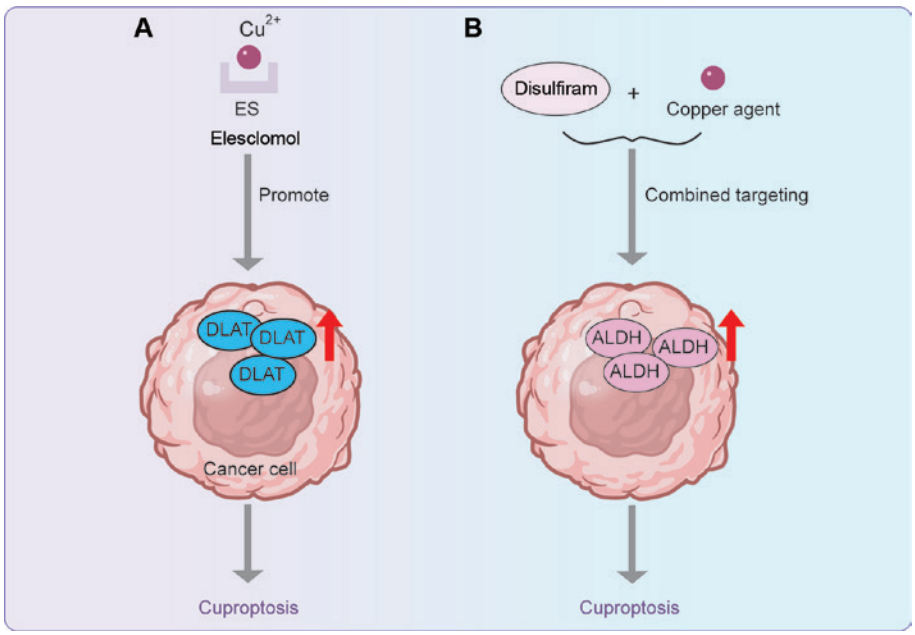


Figure 4 Cproptosis-targeted strategies for cancer therapy. This figure illustrates two targeted therapeutic strategies for inducing cuproptosis in cancer cells. (A) The copper ion carrier, ES, promotes cuproptosis in cancer cells by facilitating the accumulation of copper ions (Cu^{2+}), especially in cells with high expression of lipoylated mitochondrial enzymes, such as DLAT. The aggregation of DLAT due to copper binding induces proteotoxic stress, leading to cuproptosis. (B) The combination of DSF, a copper ionophore, with copper agents targets cancer cells that exhibit high levels of ALDH expression. This combination strategy enhances the targeting specificity and therapeutic efficacy by promoting cuproptosis in ALDH-positive cancer cells, resulting in a more precise and effective treatment. ALDH, aldehyde dehydrogenase; DLAT, dihydrolipoamide S-acetyltransferase; DSF, disulfiram; ES, elesclomol.

how cancer cells adapt metabolism to support rapid growth and survival, often under nutrient-poor conditions. This includes alterations in pathways, such as glycolysis, oxidative phosphorylation, and lipid metabolism, which are crucial for cancer cell proliferation and survival[47,48]. Furthermore, the integration of metabolomics with other omics technologies, such as genomics and transcriptomics, allows for a more detailed understanding of the molecular mechanisms driving cancer. This holistic approach can uncover novel metabolic vulnerabilities that could be exploited for cancer therapy. For example, the use of spatial metabolomics has provided insights into tumor-associated metabolic alterations, revealing potential metabolic vulnerabilities that might be targeted for therapeutic purposes[49,50]. In addition, application of metabolomics in cancer research has led to the discovery of specific metabolites and related enzymatic pathways directly associated with tumorigenesis. These findings underscore the importance of metabolites as building blocks of cellular structures and signaling molecules that can regulate cancer-related pathways[51,52]. In summary, the integration of genomics, transcriptomics, and metabolomics offers a powerful framework for understanding the metabolic alterations in cancer cells, including alterations related to copper metabolism. This integrated approach holds promise for identifying new therapeutic targets and developing more effective cancer treatments. Such information can be instrumental in developing personalized treatment plans that tailor the application of copper-based drugs, such as copper chelators [D-penicillamine (DP)] and TTM or copper ionophores (ES), to meet the specific needs of each patient (**Table 2**). Furthermore, precision medicine approaches may aid in minimizing the side effects of copper-based therapies by selectively targeting cancer cells with distinct copper-related vulnerabilities[53,54].

Therapeutic strategies against hypoxic tumor microenvironment

Therapeutic approaches addressing oxygen-deprived tumor environments focus on multiple intervention mechanisms. Current research emphasizes pharmacologic agents that disrupt hypoxia-mediated signaling pathways, particularly pharmacologic agents focusing on HIFs that regulate tumor adaptation to low-oxygen conditions. HIF-1α has a multifaceted role in cancer cells under hypoxia[7]. HIF-1α suppresses DLAT expression, an essential enzyme of the tricarboxylic acid cycle that interferes with mitochondrial metabolism to change the sensitivity of tumor cell to copper-induced cell death. Moreover, HIF-1α induces MT2A to sequester mitochondrial

Table 2 Representative review of the application of Cupr-based nanoparticles in cancer therapy

Material	Mechanism	Cancer type	Reference
A copper-based Prussian blue nanostructure loaded with a serine metabolic inhibitor (NCT-503@ Cu-HMPB)	Accumulation of ROS, disrupt serine metabolism	Breast cancer, colorectal cancer, liver cancer	*Small*. Feb 2025;21(5):e2406942
An intelligent cuproptosis-inducing nanosystem (ES@CuO) is constructed by encapsulating CuO nanoparticles with the copper ionophore, ES	Mitochondrial toxicity, blockade of immune evasion	Melanoma, triple-negative breast cancer, colorectal cancer	*Adv Sci (Weinh)*. May 2024;11(18):e2309984
A copper-based nanoinducer (CGBH NNs) loaded with GOx and BSO, and further coated with HA	Disulfide stress-driven cytoskeleton disintegration, pyroptosis, cuproptosis, blockade of immune evasion	Ovarian cancer, pancreatic cancer, lung cancer	*Adv Mater*. Jan 2025;37(1):e2410957
A multifunctional nanoplatfrom based on Cu_9S_8 (CAPSH); CAPSH is supported by hollow mesoporous Cu_9S_8 nanoparticles, loaded with AIPH, and coated with PAH to electrostatically adsorb siRNA (siATP7A)	Cuproptosis, gene therapy, thermodynamic therapy, blockade of immune evasion	Triple-negative breast cancer	*Nat Commun*. 2024;15(1):10060
Self-amplified cuproptosis nanoparticles (Cel-Cu NP) using Cel, a natural product isolated from a medical plant	Cuproptosis, blockade of immune evasion	Pancreatic cancer, melanoma, triple-negative breast cancer	*Adv Mater*. Aug 2024;36(35):e2404971

ROS, reactive oxygen species; CuO, copper oxide; ES, elesclomol; GOx, glucose oxidase; BSO, buthionine sulfoximine; HA, hyaluronic acid; AIPH, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride; PAH, polyacrylamide hydrochloride; Cel, celastrol.

Cu^+, reducing labile Cu^+ pools available for lipoyl-protein binding. This mechanism underlies the resistance of cancer cells to copper ion-based therapy under hypoxia. A comprehensive understanding of the interactions among HIF-1α, DLAT, and MT2A is essential for the development of more effective anti-cancer treatments in hypoxic tumor microenvironments. HIF-1α has a collaborative role in regulating mitochondrial metabolic reprogramming and metal homeostasis within tumor cells, leading to resistance against cuproptosis. HIF-1α upregulates genes associated with glycolysis under hypoxic conditions, while downregulating genes involved in mitochondrial oxidative phosphorylation, resulting in a metabolic shift within the cell. While copper chelation therapy has demonstrated clinical utility, the full therapeutic potential of copper modulation, particularly through cuproptosis induction, remains underexploited in oncology. In our preclinical study we confirmed that copper carriers, such as ES and $CuCl_2$ (Cu), synergistically inhibit tumor growth *in vivo*. Nevertheless, increasing the ES + Cu doses raises safety concerns. The addition of an HIF-1α inhibitor holds promise for further enhancing the effectiveness and safety of ES + Cu in tumor treatment. However, one of the major limitations of this study involved the specificity of the orally active HIF-1α inhibitor (PX-478) for HIF-1α inhibition. The findings suggest that developing highly specific and effective HIF-1α inhibitors could sensitize cancer cells to cuproptosis, thus enabling cuproptosis as a promising approach for cancer therapy[55].

Integration of metal homeostasis and tumor metabolism

Developing a therapeutic approach that integrates metal ion homeostasis with tumor metabolism is a promising future direction. Metal ions, like copper, iron, and zinc, have crucial roles in cellular functions, whose imbalance is linked to cancer[56]. By exploring the interactions between these ions and tumor metabolism, more comprehensive treatment strategies can be devised. For example, simultaneously targeting copper and iron metabolism may yield synergistic effects in cancer therapy. Because iron is vital for cancer cell growth, disrupting both iron and copper homeostasis could counteract the compensatory mechanisms used by cancer cells[5].

The combination of copper ion modulation with other emerging cancer treatment modalities, such as immunotherapy and gene therapy, may result in more effective treatment outcomes. For example, copper-induced cuproptosis could

potentially increase the immunogenicity of cancer cells, rendering cancer cells more vulnerable to immune-mediated destruction. In addition, gene therapy could be used to target genes involved in copper metabolism, thereby optimizing the effects of copper-based therapies. Ongoing research in this field is expected to reveal new and innovative approaches for incorporating copper ion modulation into cancer treatment.

Conclusions and future perspectives

The intricate relationship between copper homeostasis and tumor metabolism has emerged as a promising avenue for cancer therapy. This review has highlighted the dual role of copper ions in cancer biology: essential cofactors for cellular processes and inducers of cytotoxic effects through cuproptosis. The detailed elucidation of copper homeostasis mechanisms, including dietary absorption, systemic distribution, and intracellular utilization, underscores the importance of maintaining a delicate balance to prevent both copper deficiency and toxicity.

Recent advancements in copper-based nanotechnology and the identification of key transporters and enzymes involved in copper metabolism have opened new therapeutic avenues. Targeted delivery of copper to tumors, combined with the induction of cuproptosis, offers a novel approach to overcoming resistance mechanisms in cancer cells. However, the hypoxic tumor microenvironment remains a significant challenge because such an environment can upregulate copper-sequestering proteins and downregulate key mediators of cuproptosis.

Future directions in copper metabolism research should focus on integrating multi-omics approaches to identify novel therapeutic targets and elucidate the complex interactions between copper and other metabolic pathways. The development of combination therapies that target both copper homeostasis and hypoxia-induced resistance mechanisms holds promise for enhancing the efficacy of copper-based treatments. In addition, exploring the integration of copper ion modulation with emerging cancer treatment modalities, such as immunotherapy and gene therapy, may yield synergistic effects and improve patient outcomes.

In conclusion, the modulation of copper metabolism represents a powerful strategy for cancer therapy. By leveraging the unique mechanisms of cuproptosis and addressing the challenges posed by the tumor microenvironment, researchers can develop innovative approaches to target cancer cells more effectively. Further research in this area is essential to fully realize the potential of copper-targeted therapies in oncology.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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