Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 30s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Targeting Copper Dysregulation In Cancer: Molecular Insights Into Cuproptosis and The Promise of Copper-Based Nanomedicine

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Cite this paper as: Aditi Srivastava, Abu Shahma, Jyoti Nanda Sharma, (2025) Targeting Copper Dysregulation In Cancer: Molecular Insights Into Cuproptosis and The Promise of Copper-Based Nanomedicine *Journal of Neonatal Surgery*, 14 (30s), 134-151

ABSTRACT
Copper is an essential transition metal that plays a vital role in cellular metabolism as a cofactor for key enzymes. While necessary for biological processes such as mitochondrial respiration, antioxidant defense, and gene expression, copper must be tightly regulated to prevent cytotoxicity. This review investigates copper homeostasis at both cellular and systemic levels, highlighting the significance of dietary intake, absorption, transport, and excretion. Dysregulation of copper can lead to cell death, especially in cancer cells, through mechanisms such as cuproptosis, a newly recognized form of copper-induced cell death. Cuproptosis involves mitochondrial copper accumulation, disrupting protein function, and triggering cell death. The study explores how copper imbalance contributes to cancer progression, metastasis, drug resistance, and immune evasion. Therapeutic approaches targeting copper metabolism are discussed, including the use of copper chelators and copper-based nanomaterials to improve cancer treatment. Although cuproptosis has sometimes been misinterpreted as the result of ionophore-induced nanoparticle formation, it stems from mitochondrial copper toxicity. The review further evaluates the emerging role of copper nanotechnology in sensitizing tumors to chemotherapy, offering a promising strategy to overcome drug resistance. Overall, the findings underscore copper's dual role in health and disease and its potential as a therapeutic target in oncology.

Keywords: *Copper, Cuproptosis, Cancer therapy, Drug resistance, Apoptosis*

1. INTRODUCTION

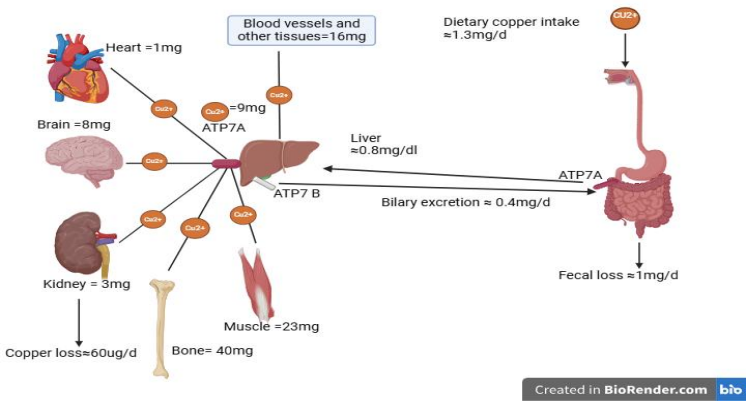
Tumor incidence has recently risen, presenting Substantial hazards to Well-being [1]. Cancer is distinguished by its capacity to withstand Apoptosis, allowing Neoplastic tissue to replicate indefinitely and achieve immortality. This presents an enormous task in Oncology treatment [2]. According to biochemistry, function, and morphology, the Cell Death Committee's Nomenclature developed criteria to classify apoptosis into Uncontrolled and Programmed cell death [3]. Accidental Cell Death is characterized as an uncontrollable process of apoptosis brought on by damage to the human body. At the same time, RCD mentions a regulated and organized Apoptosis coordinated by genetic processes to maintain internal homeostasis [4]. Apoptosis, ferroptosis, necroptosis, pyroptosis, and cuproptosis are the most common forms of RCD currently occurring in cancer. One type of RCD (regulated cell death) triggered by an

increased Cu2+ level is cuproptosis. Numerous biological functions, especially iron absorption, detoxification, antioxidant mechanisms, and mitochondrial respiration, depend on copper [5]. The accumulation of ROS (reactive oxygen species) and cell death caused by copper, which involves mitochondrial energy metabolism, are hallmarks of cuproptosis [6]. There has been increasing evidence that cuproptosis is linked to the progression and occurrence of a range of illnesses, including neurodegenerative diseases, Wilson's disease, and Menkes disease [7]. In addition, many cancer patients have been found to have changes in copper amount in their tumor tissue and serum [8]. Recent research has revealed that cuproptosis affects tumor cell proliferation, angiogenesis, metabolism, tumorigenesis, and migration by directly or indirectly linking to several signaling pathways in tumor cells [9]. In our review, we present a summary of research findings about cuproptosis's implications and mechanisms in diverse types of cancer. We also examine the impact of copper-based compounds like Cu ionophores and Cu chelators to clarify their impacts on oncogenic attributes like apoptosis, cytokinesis, and vasculogenesis. Additionally, we examine the potential of copper-based compounds to overcome tumor chemotherapy resistance and their role in immunotherapy. These amazing discoveries set a tone for future developments in developing anticancer medications created to trigger cuproptosis. Tsvetkov and colleagues first proposed the notion of a unique type of controlled, copper (Cu)-induced cell death in 2022, and they also coined the term cuproptosis. Lipoylated dihydrolipoamide S-acetyltransferase aggregates as a result of a buildup of copper in the mitochondria, causing cuproptosis, a form of cell death. This process is attached to the mitochondrial tricarboxylic acid cycle (TCA cycle) and results in protein strain, which ultimately leads to cell death.

Copper is an Essential trace nutrient in well-being that has been connected to numerous tumor-related biological behaviors and signaling pathways. For many physiological functions in the body, such as mitochondrial respiration, energy conversion, and other metabolic processes linked to daily activities, it serves as a structural cofactor and catalytic component. Additionally, excessive consumption of copper may be evident in Autolysis, Nevertheless, it has long been unclear what the precise processes and forms of copper-induced cytotoxicity Cuproptosis is a type of cytotoxicity that is not influenced by the lipoic acid (LA) pathway or mitochondrial respiration [10].

CELLULAR AND SYSTEMIC HOMEOSTASIS OF COPPER

One type of vital transition metal, which has two sides for the cells, is copper. Copper is a cofactor for several enzymes by offering or receiving electrons [11], but it can also accumulate to trigger numerous kinds of metabolic dysfunctions in cells, and this can ultimately lead to cell death. Copper is mainly obtained for human consumption through diet, with seafood and organ meats being the most nutrient-dense foods. Currently, humans should consume 0.8–2.4 mg of copper daily to preserve the homeostasis of copper throughout the body. Plenty of foods contain copper, which is mostly taken in the small intestine, with a little taking a position in the gut [12]. Nutritional copper enters the body through the hepatic portal blood, travels to the Glandular organ, is made into ceruloplasmin, and then travels through the circulation to all of the body's tissues. Bile is the key process by which copper is eliminated from the body. It subsequently passes through the gastrointestinal tract as well as is finally eradicated as waste products. Copper that goes into the gastrointestinal tract, and some of it is produced by intestinal bacteria in the small intestine, is involved in this process [13] (Fig. 1A). Copper can be used in at least five different ways in the cell. (1) Glutathione, which is a bearer for transporting Cu to metallothionein (MT), can bind to copper [14]. (2) To scavenge free radicals, copper utilizes its copper chaperone for SOD1 (CCS) to target inside the cell copper/zinc-superoxide dismutase (SOD1) [15]. (3) Cu into the mitochondrial intermembrane gap within the cell by the cytochrome c oxidase assembly protein (COX17), which attaches to complex IV. It participates in the redox pathway and the mitochondrial respiratory chain. The copper needed to produce cytochrome c oxidase 11 (COX11) in the mitochondria's intermembrane space is supplied by COX17. These proteins then move copper to the cytochrome oxidase subunits, which help to produce ATP [16]. Copper is transported by Cu-transporting ATPase B (ATP7 B) and copper-transporting ATPase A (ATP7A) via the secretory pathway in the trans-Golgi network (TGN) via copper partner antioxidant 1 (ATOX1). (5) Sp1's zinc finger domain functions as a Cu detector, modulating Copper transporter1 expression in reciprocate to variations in cu levels.



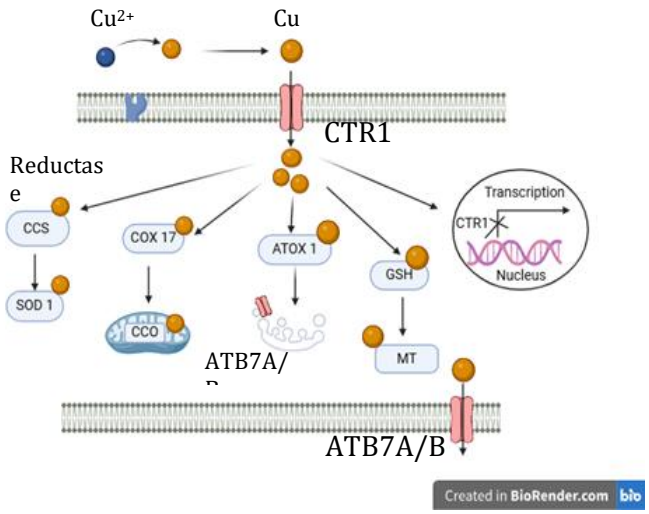


Figure 1. Copper's source and absorption. A: The body's copper distribution. Copper is transported to the liver via the portal blood after being absorbed through food and integrated there. After that, it is released into the circulation to be dispersed throughout the various bodily tissues. B: Cellular absorption of copper. Cu+ is imported into cells with the help of CTR1. After this uptake, copper is passed to its partners CCS, COX17, and ATOX1, who subsequently pass it on to ATP7A/B, mitochondrial CCO, and cytoplasmic SOD1 in the TGN, respectively. Furthermore, when copper in cells binds with GSH, it can be transferred to MT more readily. Variations in copper concentration can alter gene expression and regulate CTR1 expression by interacting with transcription factors in the nucleus.

Essential Discoveries in Cuproptosis Research

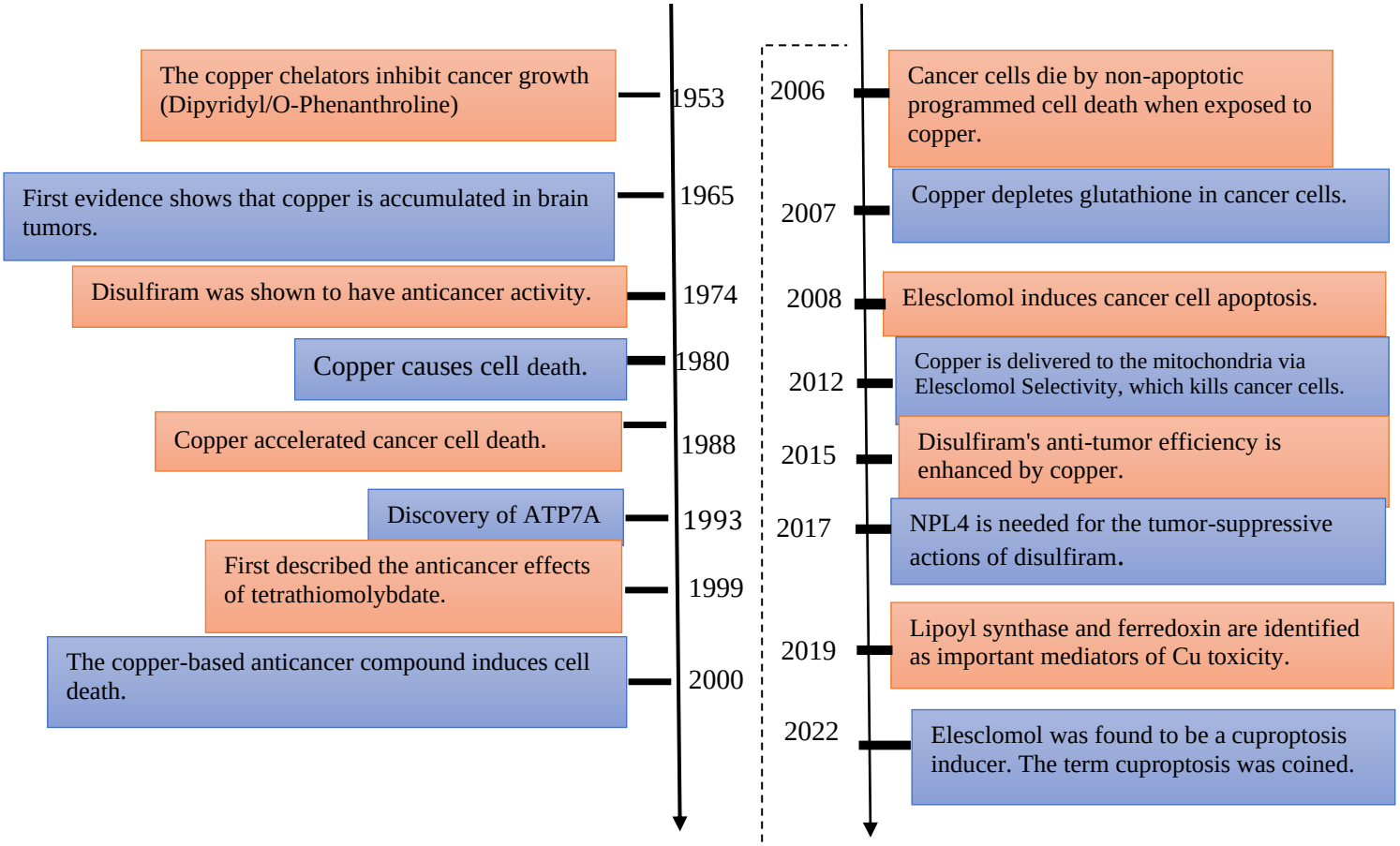


Figure 2. A timeline graphic showing significant findings in the study of Cuproptosis.

DYSREGULATION AND COPPER HOMEOSTASIS IN CANCER CELLS

One of the vital micronutrients needed for several body functions is copper ions [17]. Cu+(The cuprous ion's reduced form) and Cu2+ (electron-deficient form) are two of its different ionic forms, which are actively entangled in the enzymatic control and a wide range of physiological methods within cells, such as biological metabolic processes, gene expression, antioxidation, and mitochondrial respiration [18]. Copper ions have unique redox properties due to their conversion into Cu+ to Cu2+, which makes them a potent source of reactive oxygen species (ROS) as well as essential for ROS scavenging [19]. Because of a variety of variables, including elevated metabolic activity, gene changes, and relative hypoxia, cancer cells frequently contain a greater quantity of ROS than normal cells [20]. Tumorigenesis and the advancement of cancer may be aided by this imbalance between oxidants and antioxidants [21]. Additionally, because copper ions serve as a vital component for many biological functions that encourage tumor development and progression, cancer cells frequently demonstrate an increased reliance on them. With high cuprous ion concentrations in cancer cells, resistance to cell death can be coordinated with metastasis and angiogenesis [22]. A vital component for maintaining the malignant characteristics of cancer cells, copper ions stimulate signaling pathways and enzymes that promote these activities. The metabolism and homeostasis of copper are introduced in this section, along with the role that copper dysregulation plays in cancer cell development.

3.1. Dysregulation of Copper ions in Cancer

Cu^{2+} and cancerous growth have been linked for many years; studies have repeatedly shown that tumors or the serum of cancer patients and test models had greater levels of cuprous ion and ceruloplasmin [23]. Enzymes involved in vital physiological functions such as hormone synthesis, neurotransmitter production, antioxidant defense, mitochondrial respiration, and pigmentation require ions of copper as a cofactor. Nevertheless, oxidative stress and cytotoxicity may result from disruptions in copper ion homeostasis [24]. Increased concentrations of copper ions have been found in the serum or tissues of individuals with a variety of cancers, including thyroid, gallbladder, and colorectal tumors, based on recent research. Additionally, to sustain angiogenesis, development, resistance to cell death, and metastasis, malignancies frequently need higher concentrations of cuprous ions than the Encompassing Thriving tissues [25].

3.2. Angiogenesis

Various physiological functions are dependent upon vasculogenesis, the process by which novel vascular networks, especially capillaries, originate from preexisting vascular systems [26]. In healthy physiology, angiogenesis makes sure that tissues and organs receive sufficient oxygen and nutrients to support their development, repair, and metabolic requirements. However, several forms of cancer, including gliomas, large intestine, melanoma, and breast malignancies, have been linked to intussusceptive angiogenesis [27]. Cancers have the potential to develop and expand by promoting the expansion of neovascularization, which ensures a constant distribution of nutrients and oxygen [28].

Promoting angiogenesis is completely associated with copper ions. In Cell culture and live models, copper ions have been shown to promote vasculogenesis and endothelial cell proliferation (Gerard et al.,29). In particular, copper ions stimulated the establishment of a cross-linked hyaluronic acid (HA) encased in a vascularised capsule-composed hydrogel and minimized the possibility of Flap necrosis risk. By promoting the synthesis of numerous proangiogenic factors, such as vascular endothelial growth factor (VEGF) [30], angiogenin, and Tumor Necrosis Factor, Pro-inflammatory cytokine IL-1, Interleukin-6, Interleukin-8, [31], fibronectin [32] and the Oxygen-regulated subunit of HIF-1[33], it has been proven that copper ions play vital functions in angiogenesis and metastasis. Serum ceruloplasmin levels in rabbits throughout the growth of tumors and remission were documented in additional cases by Ungar-Waron et al.[34]. Ceruloplasmin, a key copper ion binder in blood, elevated significantly as the tumor expanded and then reduced during regression, although it stayed high throughout metastasis. Furthermore, the spread and progression of tumors involve cancer angiogenesis, and copper ions play a role in tumor neovascularization via their direct interactions with angiogenic factors (fibroblast growth factor and VEGF) [35]. Cys189 at its cytoplasmic C-terminal, CTR1, is quickly sulfonated in response to VEGF stimulation. By establishing a disulfide linkage between VEGFR2 and CTR1, this process causes them to internalize with early endosomes, maintaining VEGFR2 signaling. In vivo, mice showing mutations or abnormalities in CTR1 related to endothelial cells showed inadequate reparative and developmental angiogenesis [36]. Put another way, the fact that copper ions bind to angiogenin indicates that angiogenin that has been activated by copper ions may interact with endothelial cells more effectively, which might improve its ability to boost the Structure of Neovascularization. In addition, as multifunctional regulators of multiple proangiogenic pathways, vascular copper ion transport systems have significant effects on the initiation and progression of angiogenesis. The role of copper ions may be a crucial factor in controlling the development of novel vascular conduit routes, offering important information for creating cutting-edge cancer therapy treatments.

3.3. Drug Resistance

One of the biggest challenges in the treatment of cancer is drug resistance, which impacts many subjects with Cancer metastasis. It can take numerous forms, such as restricting medication absorption, changing drug targets, deactivating pharmaceuticals, and actively releasing medicines [37]. These and other processes counteract cytotoxicity therapy and may result in therapeutic failure and amplification of the illness [38]. There is increasing evidence that resistance to medicines may be linked to copper ions being transported through pathways. As a way to identify patients who were not responding to treatment, Majumder et al. [39] probed the connection between drug resistance and cuprous ion levels to create better treatment plans. They discovered that, in comparison to healthy normal mice, the blood serum of those with tumor-bearing animals had elevated copper ion levels. Additionally, the copper level in serum is substantially greater in mice as well as Doxorubicin-resistant relative to animals, Ehrlich tumor cell-derived ascites, or Cyclophosphamide-insensitive Lewis lung carcinoma with drug-sensitive tumors. A connection between cu ions, tumor progression, and medication obstruction was also found by comparing the amounts of copper ions in cancer patients with healthy volunteers. Additionally, Jin et al. [40] explored how heightened Cu^{2+} concentration helped cancer cells repair damaged DNA and become resistant to drugs. DNA Damage Checkpoint 1 Mediator (MDC1), a polypeptide that is essential for the repair of double-strand DNA damage, exhibits activity in response to ATOX1.

Particularly, upon exposure to various genotoxic chemicals, ATOX1, functioning as a copper-binding protein, translocates to the nucleus to focus the Mediator of DNA Damage Checkpoint 1 promoter, therefore increasing MDC1 transcription in a copper ion-dependent way. Therefore, in transplanted cancer mouse models, ATOX1 elimination or blockage made tumors responsive to gemcitabine. These results imply that in individuals who are resistant to drugs, adjusting copper ion levels could boost the potency of cytotoxic therapy for cancer. It could be possible to enhance outcomes from therapy by improving the receptivity of cancer cells to oncolytic therapy by focusing on the higher Cu^{2+} concentration linked to chemoresistance. This approach is probably to outcome of the improvement of fresh approaches to therapy meant to assist cancer patients in overcoming their medication resistance.

3.4. Immune Evasion

Tumor-infiltrating lymphocytes are believed to be suppressed by programmed death-ligand-1 (PD-L1), which is activated in carcinoma, enhancing adaptive immunological resistance [41]. Curiously, these immune system reactions are affected by copper ions. PD-L1 expression in cancer cells was shown to be associated with intra-tumorous copper ion levels by Voli et al.[42]. Supplementing with copper ions elevated PD-L1 expression in cancer cells at the mRNA and protein levels. Additionally, copper ion regulates crucial signaling pathways that are in charge of PD-L-mediated cancer immune evasion, according to RNA sequencing. A comprehensive investigation of tissue microarrays and, according to the Cancer Genome Atlas database, a strong link between PD-L1 expression and CTR1 in a variety of malignancies, yet not in comparable normal tissues. Furthermore, Zhou et al.[43] found that DSF-Cu2 suppresses poly (ADP-ribose) polymerase 1 activity and induces glycogen synthase kinase-3β inactivation via phosphorylation at the Ser9 site, inhibiting CD8+ T cell infiltration and activity and upregulating PD-L1 expression. In addition, the use of copper chelators enhanced the ubiquitin-mediated degradation of PD-L1 and inhibited the phosphorylation of the signal transducer and activator of transcription 3 and epidermal growth factor receptor [44]. Copper binding agent tetraethylenepentamine additionally elevated rodents' longevity by reducing expression of PD-L1 in pediatric neural crest tumor xenografts, which in turn improves tumor-infiltrating T-cell infiltration. Copper ions might regulate Programmed Death Ligand 1 activity and influence Tumor immune resistance, based on these findings. Therefore, there may be a chance that multiple strategies that diminish intra-tumor Cu^{+} concentrations may increase cancer immunotherapy's efficacy.

3.5. Cancer Metastasis

One crucial stage in the development of cancer is metastasis, which also significantly increases the death rate from the disease. It includes the progression of cancer cells from the main lesion to other locations, where they develop Metastatic lesions, making therapy harder and diminishing overall Viability chances [45]. The epithelial-mesenchymal transition, a biological process required for embryogenesis and tissue repair, is a prime example of how cancer cells frequently take on properties similar to stem cells and invasiveness to facilitate metastasis [46]. By triggering metabolic enzymes and proliferation, among other mechanisms, copper ions facilitate the spread of cancer via the advancement of angiogenesis, epithelial–mesenchymal transition, and cancer cell invasion, the malfunction of copper-containing secretory enzymes, such as lysyl oxidase (LOX) and superoxide dismutase 3 (SOD3), is a major effect on cancer metastasis [47]. Oxidative stress, which is connected to several elements of cancer progression, becomes stronger when SOD3 is lost in tumor tissues. On the contrary, Laukkanen [48] has shown that cancer cell metastasis can be prevented by boosting SOD3 activity or expression through endogenous administration of recombinant SOD3 or induction of SOD3 expression. Another example is the enhancement of cancer cell invasion and migration via the copper-dependent amine oxidase LOX. Members of the LOX family of extracellular copper-dependent enzymes have been linked to the development of a favorable extracellular matrix environment that encourages the invasion and metastasis of cancer cells. The extracellular matrix may become more rigid

due to elevated collagen fiber cross-linking, which could give cancer cells the physical support they need to spread throughout tissues [49]. Numerous cancer forms, including breast cancer [50], head and neck squamous cell carcinoma (HNSCC), prostate cancer, and colorectal cancer [51], have been shown to exhibit up-regulation of protein expression and LOX mRNA. Furthermore, through encouraging cell migration and invasion, copper-dependent redox enzymes, like the ErbB2-driven cell motility (MEMO1) mediator, play a vital role in mammary cancer. By altering cytoskeletal dynamics and encouraging the development of adhesion sites, MEMO1 has been shown to enhance cell migration [52]. Therefore, copper ions have a key role in angiogenesis, metastasis, cancer invasion, differentiation, and cellular proliferation [53].

2. MECHANISM OF CUPROPTOSIS

Cuproptosis, a phenomenon connected to modifications in mitochondrial enzymes, is brought on by the body's high copper ion levels, resulting in cell death [54]. Catalysts participating in the Krebs cycle, frequently referred to as the citric acid cycle or TCA cycle, can be disrupted by elevated Cu2+ levels, which can also oxidatively damage mitochondrial membranes. Extra Cu2+ enters the cell and goes to the mitochondria, where it is changed into Cu+. The oligomerization of lipoylated proteins and the reduction of Fe-S cluster proteins caused by these excessive Cu+ levels promote cell death by interfering with the TCA cycle and the ETC. Cu ion-induced cell death was much decreased by blocking ETC complexes I and II, and research showed that cells exposed to copper ionophores showed a time-variant dysfunction of numerous Krebs cycle-related adducts [55]. Researchers use genome-wide CRISPR-Cas9 screening to examine the mechanism of cuproptosis. Seven genes - lipoic acid synthetase (LIAS), ferredoxin-1 (FDX1 lipoyl transferase 1, DLAT, pyruvate dehydrogenase E1 subunit alpha 1, dihydrolipoamide dehydrogenase, and pyruvate dehydrogenase E1 subunit beta—have been identified as cuproptosis regulators [56]. Glycine cleavage system protein H, dihydrolipoamide succinyl transferase, dihydrolipoamide branched chain transacylase E2 (DBT), and DLAT are the four specific enzymes that are lipoylated within the mitochondria by FDX1, a vital enzyme with potent reducing capabilities. This indicates that lipoylation is crucial for maintaining cellular metabolic processes and guaranteeing healthy mitochondrial activity [57]. Interestingly, the disulfide link on the terminal cysteine residue of lipoylated TCA cycle proteins is where Cu+ may attach directly. Fe-S cluster proteins can break down as a result of this interaction, causing these proteins to aggregate and disulfide independently and perhaps interfere with the TCA cycle. Additionally, copper ions may interfere with the ubiquitinated protein degradation function of valosin-containing protein (p97) by interacting with nuclear protein localization protein 4 (Npl4). This interaction could lead the protein to form an aggregate or directly bind to Npl4 and inhibit its conformational transition, leading to proteotoxic stress and ultimately cell death [58]. In a similar manner, FDX1 and LIAS act as upstream regulators of protein lipoylation. When dysregulated, they enhance the reduction of Fe-S clusters. Conversely, the deletion of FDX1 or LIAS results in the accumulation of α-ketoglutarate and pyruvate, which subsequently leads to decreased lipoylation and cell death [59]. Furthermore, altered the genes associated with copper ion transport in both in vitro and in vivo to investigate the impacts of intracellular copper ion levels on cuproptosis. Cell susceptibility to copper ion-induced protein aggregation and Fe-S cluster protein degradation has been improved by overexpression of the copper ion importer SLC31A1. The depletion of crucial cuproptosis regulators, such as FDX1 or LIAS, and copper chelators partially reversed this impact. A mouse model of Wilson's disease with Atp7b elimination (Atp7b−/−) consistently validated these results. Compared to Atp7b+/ and wild-type mice, the livers of Atp7b−/− mice showed a significant decrease in lipoylated and Fe-S clustered polypeptides. Cuproptosis in vivo is linked to intracellular copper ion buildup, as this discovery demonstrates. The primary mechanisms and modulators of cuproptosis are shown in Figure 3.

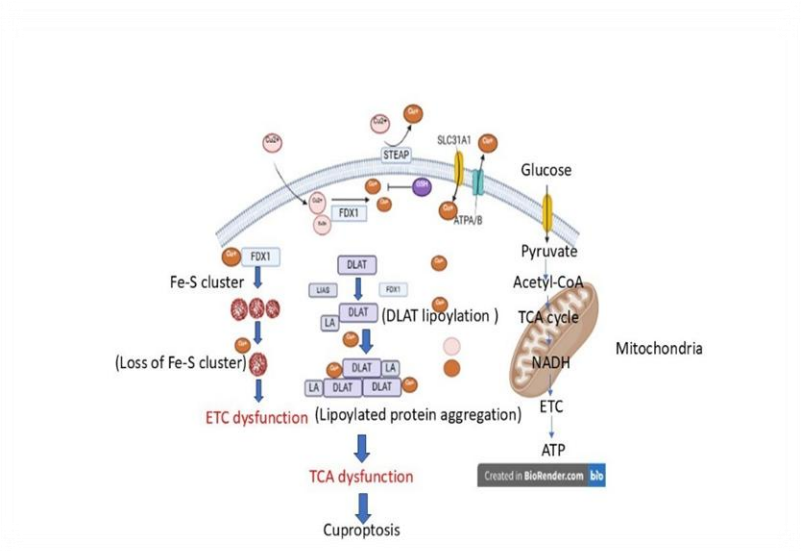


Figure 3. The cuproptosis mechanism's schematic. Cu ionophores such as ES and DSF help extracellular copper ions internalize into intracellular spaces by first binding to them. Once inside, the copper ion interacts with DLAT and other lipoylated mitochondrial enzymes involved in the TCA cycle. These proteins aggregate as a result of this interaction. As an upstream regulator of protein lipoylation, FDX1/LIAS encourages mitochondrial protein aggregation. As a result of this process, Npl4-p97 becomes inactive, and Fe-S clusters are lost. These abnormal occurrences lead to proteotoxic stress, which in turn causes cell death. Prostate 6-transmembrane epithelial antigen, or STEAP.

CUPROPTOSIS'S ROLES IN CANCER

Several studies reveal that malignancies have greater quantities of copper in comparison to unaffected tissues. This growing need for copper is owing to its function as an auxiliary factor for mitochondrial CCO, which is necessary for meeting the energy demands of cells that divide rapidly [60]. So, cancer cells have a greater copper requirement in comparison to non-dividing cells [61]. By promoting migration, angiogenesis, and cell proliferation within numerous kinds of malignancies, copper-induced RCD, or cuproptosis, may be vital in expanding the growth and progression of cancer.

Cuproptosis in Colorectal Cancer

The third most widespread cause of mortality, cancer, is colorectal cancer (CRC)[62]. Overgrown intestinal epithelial cells may result in a beginning tumor, which in the end compromises the stability of the mucosa as well as leads to colorectal cancer [63].

Table 1. Cuproptosis in Colorectral Cancer

Connected pathways and proteins	Uses	Role in cupro ptosis	Clinical significance	Ref.
ATOX1	Inhibits the release of ROS and promotes the development of cells with CRC by binding with Cu to control cyclin D1 and decrease the level of expression of p47 phox.	Cu Hauling	NA	[64]
ATP7A	Cu ion pump driven by ATP	Cu Hauling	NA	[65]

Cuproptosis in Gastric Carcinoma

Among the most prevalent cancers in the world is gastric cancer [66]. Patients usually have a poor prognosis because it is typically detected at a late stage. For patients for whom surgery is not an option, multidisciplinary approaches like systematic anti-cancer therapy and biological therapy are currently their first choice. On the other hand, adverse consequences and treatment failures are frequently revealed. Thus, the study of innovative therapies for gastric carcinoma becomes important. Cuproptosis is a promising treatment option for gastric cancer because it has a strong connection to the progression, spread, and metastases of gastric cancer cells.

Table 2. Cuproptosis in Gastric Cancer

Connected proteins and pathways	Functions	Role in cuproptosis	Clinical significance	Ref.

DSF	By inhibiting glycolytic-related molecules, c-Myc, S6K1, and DSF/Cu avoid the growth of gastric carcinoma in vivo and increase the impact of DSF on the formation of gastric carcinoma cell colonies and ROS-persuade apoptosis.	Transports copper straight up into cells by functioning as a copper ionophore.	NA	[67]
Cu/Zn-SOD	Supports disproportionate superoxide radicals into oxygen and hydrogen peroxide.	NA	The frequency of immune reactivity is closely related to the histological type of cancer of the stomach and proportional to the risk of gastric carcinoma.	[68]

Cuproptosis in Hepatic Cancer

The fourth most common cause of cancer-related mortality is hepatic cancer [69]. HCC is the most common of the three morbid forms of hepatic cancer: cholangiocellular cancer, mixed types, and hepatocellular carcinoma (HCC). HCC may also develop as a result of cirrhosis, fatty liver disease that is not alcoholic, hepatolenticular degeneration, and hepatitis B virus infection [70]. Thus, the growth of molecular medicine research associated with Hepatocellular carcinoma gene mutations is imperative.

Table 3. Cuproptosis in Hepatic Cancer

Connected proteins and pathways	Functions	Role in cuproptosis	Clinical significance	Ref.
CTR1	suppresses HCC cell growth and activity.	Copper accumulates in cells as an indication of overactivation.	NA	[71]
LIPT1	In enzymes that rely on lipoates, the lysine residue within the lipoyl domain receives the transport of lipoyl-AMP.	Contributes to DLAT lipoylation.	A better prognosis is connected with increased concentrations of LIPT1 expression.	[72]

Cuproptosis in Lung Cancer

Approximately 1.44 million new cases (14.3%) are reported annually. Lung cancer ranks among the most frequent cancers in males worldwide and has one of the highest fatality rates of any type of cancer [73]. Cu-related genes (CRGs) significantly influence the prognosis of lung cancer, as recent research shows that mice with BRAFV600E-driven lung cancer exhibit increased lung tumor growth after receiving high amounts of copper [74]. Consequently, cuproptosis and its associated genes present a promising path for innovative treatment methods for lung cancer.

Table 4. Cuproptosis in Lung Cancer

Connected proteins and pathways	Functions	Contribution to cuproptosis	Clinical significance	Reference
ULK1/2	To increase autophagy and enhance the activity of the autophagy process kinases ULK1 and ULK2 copper tie to them.	NA	NA	[75]
LIAS	uses octanoylated domains to produce lipoylated derivatives.	FDX1 is regulated and participates in lipoylation.	A final stage of bronchogenic carcinoma, poorer OS and FP are linked to high LIAS expression.	[76]

Cuproptosis in Breast Cancer

The unchecked proliferation of breast epithelial cells is known as breast cancer, brought on by a variety of factors. While distant metastases progress, they can lead to multiorgan diseases, which can be potentially fatal [77]. The majority of cancers in people to be diagnosed is now breast cancer, far exceeding lung cancer [78]. Nevertheless, dropping the mortality rate and the total amount of new cases of breast cancer remains very challenging.

Table 5. Cuproptosis in Breast Cancer

Connected proteins and pathways	Functions	Contribution to cuproptosis	Clinical significance	Ref.
ATOX1	Helps the migration of mammary cancer cells	encourages the migration of mammary carcinoma cells	NA	[79]
CDKN2A	blocks the G1 and G2 phases of the cell cycle by progressing.	manages the sensitivity of cuproptosis	In breast cancer, CDKN2A has a protective role.	[80]

Cuproptosis in Malignant Skin Neoplasm

The most fatal and hostile form of skin cancer, known as skin cutaneous melanoma (SKCM), is brought by a malignant transformation of the melanocytes [81]. Although SKCM makes up 1% of all cases of skin cancer, it is responsible for 80% of associated mortality. To make matters worse, its annual incidence rate has gradually been increasing over the past dozen years. Roughly 40–50% of melanoma individuals had BRAF mutations that are linked to tumors, ensuring SKCM is the solid tumor with the greatest responsibility for genetic variations among all types of solid tumors.

Table 6. Cuproptosis in Malignant Skin Neoplasm

Connected proteins and pathways	Functions	Contribution to cuproptosis	Clinical significance	Ref.
MEK1	To promote the growth of cancer, copper and MEK1 combine to form Cu MEK1, which boosts ERK1/2 phosphorylation and initiates MARK.	NA	NA	[82]

Cuproptosis in Additional Malignancies

Numerous investigations have demonstrated that CRGs can be used as markers to assess survival in different cancer types. The fourth greatest cause of mortality for women is cervical cancer, which is mostly caused by the human papillomavirus [83]. Higher risk scores, variable OS, and more advanced clinical stages are all linked to ATP7A and DLAT in cervical cancer [84]. One cancer with a high incidence rate is head and neck squamous cell cancer (HNSCC), which develops from the mouth cavity's epithelial cells, throat, and voice box [85]. With a greater risk score associated with worse OS and clinical pathological features, COX11 has been recognized as a precursor for HNSCC [86]. Pancreatic cancer, one of the most severe types of digestive system cancer, progresses rapidly and has an elevated mortality rate.

Table 7. Cuproptosis in Additional Malignancies

Connected proteins and pathways	Functions	Contribution to cuproptosis	Clinical significance	Reference
COX11	Provides copper to the cytochrome oxidase component so that ATP may be produced.	NA	A greater risk level is linked to worse clinicopathological outcomes and a worse overall survival rate.	[87]
DLAT	turns pyruvate into acetyl-CoA by interacting with the pyruvate dehydrogenase complex.	Copper causes cell death by the oligomerization of lipoylated DLAT.	An elevated risk of DLAT is associated with a worse overall survival rate (OS).	[88]

CUPROPTOSIS: A RISING FOCUS IN COPPER NANOMATERIAL-MEDIATED ANTI-CANCER STRATEGIES

With its redox activity and ability to bind proteins, copper is one of the most prevalent and vital trace metals in the human body [89]. In addition, it participates in energy conversion, mitochondrial respiration, and other metabolic processes of life activities and works as the structural cofactor and catalytic component needed for a variety of physiological processes in the body [90]. Since high copper buildup (copper glut) may result in cellular abnormalities and even cell death, there is often stringent control over the absorption, distribution, and metabolism of copper in the cells to keep its concentration at a relatively low level. There is frequently strict regulation of the absorption, distribution, and metabolism of copper in the cells to maintain the amount present at a relatively low level, since excessive copper buildup (copper overload) can lead to cellular abnormalities and even cell death [91]. This paper initially provides an overview and classification of the produced copper-based nanomaterials that have been shown to trigger cuproptosis. Three possible cuproptosis sensitization methods using copper-based nanomaterials are then shown to boost cuproptosis's efficacy. Afterwards, several kinds of combination treatments that utilize cuproptosis from copper-based nanoparticles are discussed to optimize therapeutic outcomes. Lastly, issues and prospects for Nanomaterials based on copper for cancer caused by cuproptosis treatment are examined. With the

help of nanomaterials, this study offers recommendations for future studies on cuproptosis-based cancer treatment.

TARGETS FOR CUPROPTOSIS AND COPPER METABOLISM

Copper Metabolism: An extensive variety of foods, including seafood, cereal grains, fruits, vegetables, and animal offal, are rich in copper. The body acquires an important quantity of copper via drinking water. Adults must currently consume 2–3 milligrams of copper per day [92]. The duodenum is the primary site of absorption for copper, which is mostly absorbed by the intestinal epithelium after ingestion [168]. Divalent copper ions are frequently found in food, but the body can only retain and use monovalent copper ions. Divalent copper ions are initially converted to monovalent copper ions by metallo reductases, such as the six-transmembrane epithelial antigen of the prostate (STEAP), which is found on the intestinal epithelial cell membrane. Then, the copper transporter 1 (CTR1) or solute carrier family 31 member 1 (SLC31A1) permits the copper ions to enter the intestinal epithelial cells. The copper transporter antioxidant 1 (ATOX1) carries copper from the intestinal epithelial cells to the other side of the cells, where it is released into the circulatory system by the ATPase copper transporter alpha (ATP7A) [93]. The majority of the copper ions in the blood are attached to ceruloplasmin, while the rest are attached to amino acids and human serum albumin [94]. The portal vein system transports the blood's copper ions to the liver. The primary organ for storing copper is the liver. The metallothionein 1/2 (MT1/2) binds to the copper ions, which are transported to hepatocytes via CRT1. MT1 and MT2 have a strong affinity for copper ions because they are plentiful in sulfhydryl groups. Hepatocytes store copper primarily in MT1 and MT2. The liver cells release excess copper into the bile and evacuate it from the body through the activity of ATPase copper transporter beta (ATP7B) when the body's copper concentration is beyond the usual threshold.

Cuproptosis Targets

Prior research has demonstrated that copper can kill cells by causing oxidative damage to the mitochondria or by harming tricarboxylic acid cycle-related enzymes [95]. Utilizing genome-wide CRISPR-Cas9 screening, Tsvetkov et al. [96] discovered important targets that foster cuproptosis, including lipoic acid synthase (LIAS), ferredoxin 1 (FDX1), dihydrolipoamide dehydrogenase (DLD), and DLAT. These aims have been identified, which improves our knowledge of the molecular process behind cuproptosis and offers possible avenues for upcoming medication development.

Copper-based Nanomaterial Construction Alternatives

The ability to cause copper accumulation in tumor cells is crucial for initiating copper-induced cell death, or cuproptosis. Choosing the right copper-based nanomaterials is critical for achieving this since they act as a "Reservoir for copper ions." These nanomaterials must be able to transport and release copper ions into the tumor efficiently.

Nanomaterials Integrated with Copper Ionophores

Small molecules called ionophores can attach to copper ions and carry them through membranes into cells [97]. Thus, a top prevalent Current strategy in the field of nanomedicine is the administration of copper ions using such unique molecules. Additionally, it has been shown that several ionophores, such as elesclomol (ES), diethyldithiocarbamate (DTC), and disulfiram (DSF), elevate intracellular copper levels sufficient to trigger cuproptosis [98]. These ionophores' short blood circulation time, easy metabolism, and inadequate tumor targeting have ultimately resulted in their low clinical success.

Metal-Organic frameworks Nanomaterials

With their organic ligands that strongly coordinate, transition metal ions self-assemble to create metal-organic frameworks (MOFs), which are periodic network-shaped nanoparticles. However, these MOF structures have a lot of coordination interactions among organic groups and metal ions. These interactions are weak in the particular microenvironment of carcinomas, leading the metal-organic framework to dissociate and making it possible to use them for the specific distribution of metal ions [99]. To activate cuproptosis-mediated tumor treatment, a lot of work has gone into creating different copper-based MOF nanomaterials.

Other Copper-coordinated Nano assembly

By adjusting the organic molecule species, cooperation between organic molecules and metal ions can create versatile Nano assemblies that vary from MOF structures. Hollow mesoporous core-shell nanoparticles can be created by combining metal sulfides or oxides. By loading hydrophobic organic compounds through its apertures, Mesoporous spheres with hollow cores may be employed as a dais to enable the controlled release of organic medications via the porous architecture.

Inorganic Nanomaterials

Assessed to polymer or nanoparticles, inorganic nanoparticles exhibit distinct Chemophysical characteristics, greater mechanical stability while retaining a certain level of biological function, and ease of compounding with a range of carriers [100]. The most prevalent type of inorganic nanomaterials is metal oxides. It has been demonstrated that copper oxide and

cuprous oxide, the two primary forms of copper-based metal oxides, serve as copper sources to initiate cuproptosis.

CUPROPTOSIS AND THE SIGNALLING PATHWAYS OF CANCER

Copper is believed to have a direct connection to several signaling pathways in tumor cells because it binds to and activates important components in these pathways. The ability of Cu to attach to and activate receptor tyrosine kinase (RTK) without ligand interaction was thought to be vital to RTK-related signaling pathways, which in turn can activate RTK. Following activation of RTK, agammaglobulinemia tyrosine kinase (ATK) and downstream extracellular regulated protein kinase (ERK) become phosphorylated, which in turn causes cell migration and proliferation. Through their impact on various parts of the AKT-phosphoinositide-3-kinase (PI3K) signaling pathway, Cu ions are also believed to induce subsequent activation. On the other hand, Copper can directly activate PI3K, which in turn triggers downstream AKT activation [101]. Copper, on the other hand, binds to pyruvate dehydrogenase kinase 1's (PDK1) histidine117 and histidine203 sites, activating AKT. Copper-induced AKT activation can also speed up the subcellular relocation and phosphorylation of forkhead box O4 (FoxO4) and O1a (FoxO1a), which enhances tumor growth and cancer cell proliferation. Copper ions are also required for the activation of the mitogen-activated protein kinase (MAPK) signaling pathway. Direct copper binding to mitogen-activated protein kinase 1 (MEK1) can activate the downstream c-Jun N-terminal kinase (JNK) to regulate tumor growth by phosphorylating ERK1/2 [102]. Tumor cell growth can result from the autophagy pathway's ability to recycle metabolic waste from tumor cells to fulfill their energy demands or prevent them from dying. Copper attaches itself to Unc-51-like autophagy activating kinase (ULK) and acts as its regulator to promote phosphorylation and activation of autophagy-related 13 (ATG13), which in turn promotes the formation of the autophagic complex and ultimately tumor growth [103]. According to the MAPK signaling pathway, the autophagic pathway, which is directly affected by copper ions, may additionally boost the survival of cancer cells. The absence of CTR1 causes a drop in copper ion concentration in B-Raf protooncogene (BRAF)-driven cells of lung adenocarcinoma, which is directly linked to a reduced activity of Mitogen-activated protein kinase kinase 1/2, and Unc-51-like autophagy activating kinase 1/2, essential kinases in both signaling pathways. To control the biological activity of malignancies, copper ions can influence key proteins in the route both directly and indirectly. The Notch pathway, which is highly implicated in the genesis of malignant tumors, is frequently thought of as a tumor suppressor. The migration of tumor cells is facilitated by copper ions, which additionally cause the notch ligand Jagged1 to be shed on the cell membrane. Several studies have shown that copper ions are closely linked to lesion angiogenesis [104], which depends on the interaction of copper with signaling pathways connected to Oxygen-regulated transcription factor.

In a CCS-dependent way, Copper increases HIF-1α's ability to bind to important motifs in mutated gene enhancers, which causes genes like hypoxia-inducible factor 1 (HIF1) to be upregulated [105]. Copper can directly raise HIF-1α stability even in normoxic conditions. This, in turn, may enhance the production of modulated genes like (VEGF) vascular endothelial growth factor, which in turn can lead to tumor angiogenesis. In addition, prior studies have shown the vital role of copper in inducing inflammation through its interaction with NFκB pathways. The actuate of X-linked inhibitor of apoptosis (XIAP) and heightened intracellular copper concentration are triggered by inflammatory cytokines, which in turn promote NFκB activation and carcinogenesis. Previous Investigations have shown a substantial correlation between copper and lipolysis pathways. The Wnt communication system maintains human cells in a state of renewal equilibrium, and tumor cells are caused to proliferate when their genes become active [106]. Whether copper raised or dropped the total amount of C-myc is a hotly contested topic. According to recent research, disulfiram (DSF) enhances intracellular copper ion concentration, which inhibits tumor development by reducing the expression of two essential Wnt pathway components, β-catenin and c-Myc. Recent studies, however, suggest that copper improves C-myc stability through enhancing phosphorylation at its serine 62 and threonine 58 sites [107]. Copper ions can control cancerous cell metabolism by interacting with associated compounds in the lipid or sugar Enzymatic pathways. The biological activity of tumors is also influenced by the amount of tumor cell metabolism. Cu has been revealed to influence fat breakdown by dealing with the cysteine metabolites of the 3B phosphodiesterase (PDE3 B), the PDE enzymes that break down Cyclic AMP. Furthermore, Copper has been shown to decrease tumor development by inhibiting the expression of S6K1 and its glycolytic-related molecules, such as PKM2, LDHA, and GLUT1 [108]. Copper's significance in tumors is further highlighted by the fact that it functions in both direct and indirect ways in oncogenic signaling pathways and cancer characteristics.

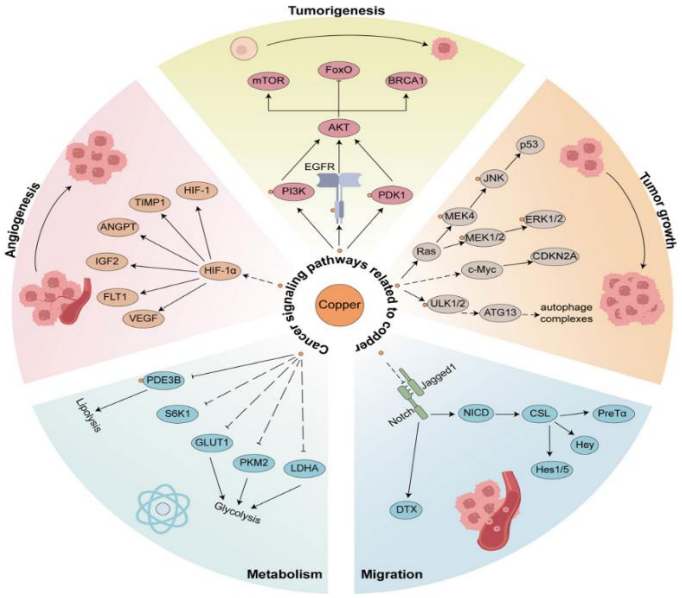


Figure 4. Signaling pathways between copper and cancer. Copper has a direct or indirect impact on cancer and is closely linked to the disease process. To stimulate carcinogenesis, copper directly binds to or activates EGFR, PDK1, or PI3K. Additionally, copper affects autophagic and MAPK pathways or indirectly modifies c-Myc stability to affect tumor growth. Through indirect inhibition of the Notch pathway ligand Jagged1 or promotion of HIFα, copper ions facilitate the migration of vascular neoplasms. Copper can also control S6K1 or PDE3B, which alters tumor metabolism.

A NEW THERAPEUTIC AIM FOR COPPER-BASED CANCER TREATMENT IS CUPROPTOSIS

A noteworthy development in cancer therapy is the discovery of cuproptosis. Although elesclomol (ES) has been shown to cause Programmed cell death, its Capacity to cause cellular death, more especially, via loading of copper ions, represents a unique mechanism distinct from more conventional forms of cellular death, including necroptosis, apoptosis, or ferroptosis [109]. Meanwhile, at this stage, caspase-3 in the caspase cascade is activated, but ES causes excess copper ions to build up and bind to cancer cells' dihydrolipoamide S-acetyltransferase (DLAT). This outcome results in aberrant thioctylated protein aggregation in the Krebs cycle and suppression of a cluster of Fe-S proteins, which eventually leads to cancer cells to cuproptosis [110]. This series of actions offers important new information on the cytotoxic mechanism of copper ionophores and creates novel therapies for cancer and other illnesses. New therapeutic approaches can be created to take advantage of this process for more accurate and effective treatment of cancer by emphasizing the unique weaknesses of copper metabolism in cancer cells. Excess cell-bound copper compounds or copper ions may produce OH radicals and enhance intracellular ROS levels, which may lead to ferroptosis and severe oxidative damage-based apoptosis. Additionally, copper (II) ions and copper-induced ROS can damage the heredity of neoplastic cells, which leads to necroptosis. Copper can raise levels of programmed cell death-related aggregated forming protein, cleaved caspase-1, Interleukin-1 beta protein, and the Nucleotide-binding oligomerization domain-like receptor family pyrin area holding protein 3, which can cause inflammatory responses and cellular pyroptosis [111]. All of this, Cu-mediated regulated cell death (RCD) may not be a stand-alone procedure of RCD and may be intimately linked to other cell death pathways. This suggests that numerous therapies may be created by uniting various RCDs. Using information from the interaction's gene signaling channels amid Cu^{2+} and biological parts, this section mainly explains the regulation route of cuproptosis. First, to especially lead to cuproptosis, researchers are exploring methods to alter the metabolism of copper in cancer cells. This includes creating biomaterials, including copper ionophores that promote the buildup of copper ions within Malignant cells.

Secondly, cuproptosis-targeting medicines might boost the effectiveness of therapy when combined with additional cancer treatments like chemotherapy or targeted therapies. These combination applications have the potential to overcome cancer cells' resistance mechanisms and provide synergistic effects. Finally, developing individualized treatment plans may be made possible by comprehending the molecular pathways driving cuproptosis in certain cancer types. Targeting the different vulnerabilities of various malignancies linked to copper ion metabolism will result in the development of more efficient and customized treatments.

3. CONCLUSION

The discovery of cuproptosis as a unique form of regulated cell death induced by copper ions presents a promising avenue

for cancer therapy. This mechanism diverges from traditional apoptosis and offers new insights into how copper metabolism can be exploited to target cancer cells effectively. While copper is essential for various physiological functions, its dysregulation in cancer cells leads to increased reliance on copper for tumor growth, angiogenesis, and metastasis. Understanding the balance of copper homeostasis is crucial for developing effective therapeutic strategies. The potential of copper-based compounds, including ionophores and chelators, to induce cuproptosis highlights their role in overcoming chemotherapy resistance and enhancing the efficacy of existing cancer treatments. This opens up possibilities for combination therapies that leverage cuproptosis alongside traditional modalities. Continued research into the molecular pathways governing cuproptosis and its interaction with other forms of cell death will be essential. Developing targeted therapies that manipulate copper levels in cancer cells could lead to more personalized and effective treatment options. The integration of copper-based nanomaterials in cancer therapy represents a cutting-edge approach to enhance the delivery and efficacy of copper in inducing cuproptosis, paving the way for innovative cancer treatment strategies.

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