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Review article

Copper metabolism and cuproptosis in human malignancies: Unraveling the complex interplay for therapeutic insights

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ABSTRACT

Copper, a vital trace element, orchestrates diverse cellular processes ranging from energy production to antioxidant defense and angiogenesis. Copper metabolism and cuproptosis are closely linked in the context of human diseases, with a particular focus on cancer. Cuproptosis refers to a specific type of copper-mediated cell death or copper toxicity triggered by disruptions in copper metabolism within the cells. This phenomenon encompasses a spectrum of mechanisms, such as oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and perturbations in metal ion equilibrium. Mechanistically, cuproptosis is driven by copper binding to the lipoylated enzymes within the tricarboxylic acid (TCA) cycle. This interaction participates in protein aggregation and proteotoxic stress, ultimately culminating in cell death. Targeting copper metabolism and its associated pathways in cancer cells hold therapeutic potential by selectively targeting and eliminating cancerous cells. Strategies to modulate copper levels, enhance copper excretion, or interfere with cuproptotic pathways are being explored to identify novel therapeutic targets for cancer therapy and improve patient outcomes. Understanding the relationship between cuproptosis and copper metabolism in human malignancies remains an active area of research. This review provides a comprehensive overview of the association among copper metabolism, copper homeostasis, and carcinogenesis, explicitly emphasizing the cuproptosis mechanism and its implications for cancer pathogenesis. Additionally, we emphasize the therapeutic aspects of targeting copper and cuproptosis for cancer treatment.

1. Introduction

Copper, an indispensable trace metal, requires meticulous homeostatic regulations. These regulations encompass various biological

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processes, including the uptake of copper in the gastrointestinal system, targeted delivery to copper enzymes within cells, elimination of excess copper through the biliary tract, and transportation of copper to the brain during growth and developmental processes [1]. The primary execution of these functions is attributed to two copper-transporting ATPases, ATP7A and ATP7B. Copper's intrinsic oxidation–reduction (redox) characteristic renders it advantageous and potentially hazardous to the cell. The two physiologically significant oxidation states of copper are Cu (II) and Cu (I), where Cu (I) prevails as the dominant form within the cell cytoplasm's reducing environment [2]. During the transition of copper ions between different valence states, electron transfer will occur, which results in oxidative stress due to the production of reactive oxygen species (ROS). These species inhibit the synthesis of iron-sulfur clusters and can damage important biomolecules like DNA, lipids, and proteins. Also, the effectiveness of Cu (II) is amplified when exposed to oxidants like superoxide radicals, hydroxyl radicals, and singlet oxygen, resulting in irreversible alterations in the structure of DNA and proteins [3,4].

The human body tightly regulates copper levels to maintain homeostasis via a sophisticated network of transporters, chaperones, and regulatory proteins. This ensures that copper is distributed appropriately and used correctly within the cells. Therefore, maintaining copper homeostasis is crucial for organisms to prevent disorders related to copper metabolism and to support optimal physiological functioning.

Copper's role in cancer has been the subject of extensive research, unveiling a connection between abnormal copper levels and certain cancer types. Significantly higher copper echelon has been observed in the blood or tissues of individuals with colorectal, gallbladder, and thyroid cancer, in contrast to healthy counterparts [5–7]. These escalated copper levels may facilitate cancer cell proliferation, angiogenesis, and metastasis [8]. Moreover, the latest study elucidated an idiosyncratic type of cell destruction triggered by intracellular copper called cuproptosis [9]. Unlike cell death driven by oxidative stress, which is linked to diverse cell demise mechanisms, cuproptosis underscores the intricate interplay between copper and cellular processes, particularly cell survival and death, in cancer pathobiology. However, it is noteworthy that the exact mechanisms by which copper influences cancer development and progression are still being investigated. The reciprocation of copper homeostasis and cancer is complex and multifaceted, involving various molecular pathways and bodily interactions.

Here, our review aims to provide a rationalize updated comprehension of Cu uptake, metabolism, and the intricate cellular mechanisms underpinning the impact of copper on various facets of cancer initiation and progression, angiogenesis, and metastasis. Furthermore, we also focus on potential therapeutic avenues targeting copper metabolism in cancer treatment based on current

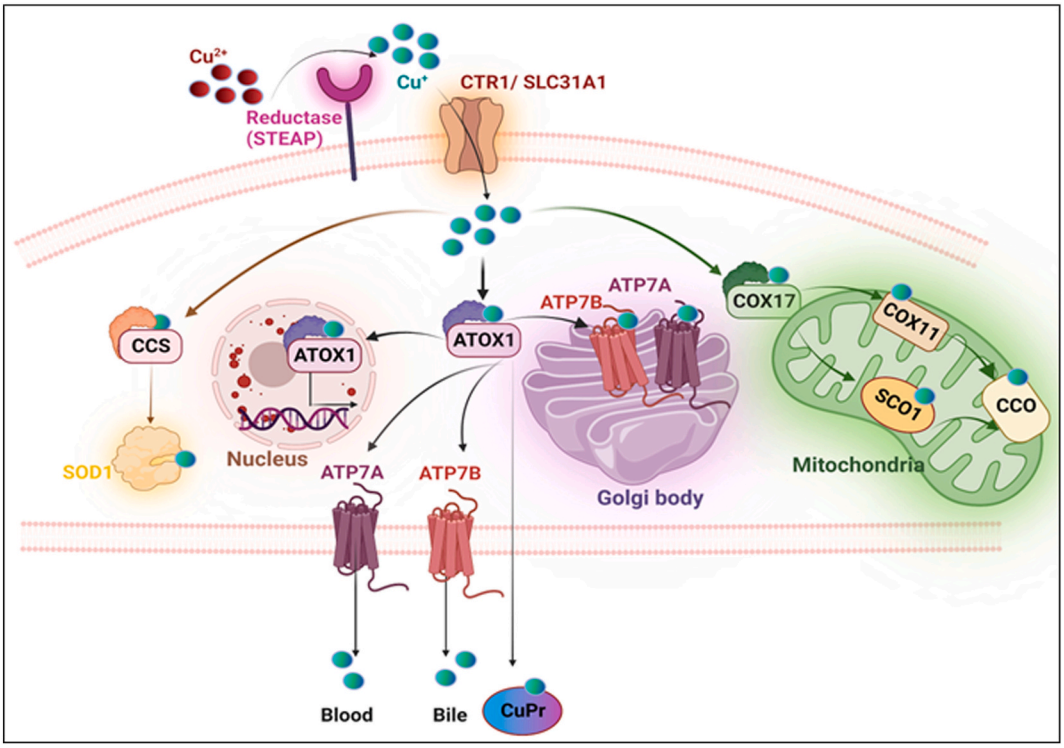

Fig. 1. Intracellular trafficking and metabolism of copper: In extracellular conditions, copper is predominantly present as Cu^{2+} ions. The Steap protein, which belongs to the family of cellular reductases, reduces Cu^{2+} to Cu^{+}, and then SLC31A1 imports Cu^{+} into the cell. The copper chaperone CCS and COX17 target Cu^{+} to cytosolic SOD1 to scavenge free radicals and carry some copper to the mitochondrial Cox to produce ATP. For the transport of copper ions within the cell, Atox1 acts as a carrier. It conveys copper to ATP7A/B located in the *trans*-Golgi network. Here, ATP7A/B orchestrates the assembly and secretion of cuproproteins (CuPrs). ATP7A serves a different function: it pumps Cu^{+} ions into the circulation via enterocyte plasma membranes, whereas ATP7B drives Cu^{+} into hepatocyte bile.

research findings. Through an in-depth examination of the recent scientific literature, this comprehensive review will enhance our knowledge of the intricate relationship between copper metabolism and cancer biology, paving the way for future research and therapeutic breakthroughs.

2. Copper uptake and metabolism

Copper is present in various plant and animal foods, and a balanced human diet provides essentially 1.4 mg/day and 1.1 mg/day for men and women, respectively, which is absorbed predominantly in the upper small intestine [10,11]. Around 0.8 mg/day of copper is sufficient to sustain copper levels in the body; thus, the level of copper in cells is tightly monitored [10]. Approximately two-thirds of the body's copper is present in bones and muscles. Although the percentage of copper absorption increases in states of insufficiency, the relative amount of copper in the diet seems to be the main predictor of intestinal absorption [12]. It has been reported that dietary factors like iron, zinc, and ascorbic acid, hinder the bioavailability of copper. The liver is regarded as the primary organ of copper metabolism because it has a prominent role in eliminating excess copper and the distribution of copper to multiple destinations following intestinal absorption. Copper in ingested food is absorbed by enterocytes in the mammalian digestive tract. The transporter that mediates copper absorption is copper transporter receptor 1 (Ctr1) (regarded as SCL1A1) in a high-affinity manner [13]. Ctr1 is ubiquitously expressed in all tissues [14]; it is generally acknowledged that Ctr1-dependent copper uptake is the predominant approach of cupric ion absorption in peripheral tissues.

Recent structural evidence revealed that Ctr1 creates a pore for the motion of Cu (I) across the lipid membrane, as shown in Fig. 1 [15]. In the extracellular milieu, copper ions are primarily present as Cu (II), they can be integrated instantly by DMT1 (divalent metal transporter 1). Following incorporation, some of the Cu^{+2} will be directed toward several cuproproteins (CuPrs) via the mitochondrial, cytosolic, and Golgi pathways with the help of various enzymes, including copper-transporting ATPase 1 & 2 also known as ATP7A & B respectively (Fig. 1). Copper chaperones, including superoxide dismutase (CCS), cytochrome *c* oxidase copper chaperone 17 (Cox17), and antioxidant protein 1 (Atox1), help in the intracellular transport of copper to various organelles and to those enzymes which require copper for their activity [13,16]. These chaperones facilitate copper in reaching important endpoints without causing harm or getting stuck with unwanted binding sites [17]. The primary responsibility of CCS is the intracellular loading of Cu^{+} and activation of superoxide dismutase [17,18]. Atox1 binds Cu (I) and transports it to P1B-type ATPases, including ATP7A & B [19]. Since free copper ions have the potential to induce ROS generation in cells and can leads to toxicity, hence extra intracellular Cu (I) needs to be tucked away by molecules like metallothioneins (MTs) and glutathione (GSH) and is stored as copper reservoirs [12,20]. Thus, an optimal intracellular concentration of Cu ions is maintained by MT or GSH by binding to the free Cu^{+} [21]. In vertebrates, the export of copper ions relies on large multi-transmembrane proteins, with ATP7A facilitating this process from intestinal epithelial cells into the bloodstream, while ATP7B pumps copper from hepatocytes into the bile [22] (Fig. 1). Remarkably, an autosomal recessive illness caused by defects in copper metabolism is Wilson disease (WD), where faulty copper export causes copper overload in the liver [23]. Patients suffering from WD harbor excessive copper overloads in their circulation, leading to a detrimental impact on various organs, with the brain being particularly vulnerable [24]. Menkes disease is another condition associated with defects in copper metabolism, distinguished by a condition called infantile-onset cerebral and cerebellar neurodegeneration, which is further characterized by failure to flourish, boorish hair, and peculiarities in connective tissue [25]. The main characteristic of this disease is an enhanced proportion of dopamine (DA) to norepinephrine (NE) due to lower Dopamine-β-hydroxylase (DBH) activity, which serves as an expeditious diagnostic tool for this disease [26]. This disorder results from mutations in the ATP7A gene present on the X-chromosomes, which causes severe copper deficiency. DBH requires a bound Cu cofactor to catalyze the conversion of DA to NE [27,28]. Furthermore, occipital horn syndrome and isolated distal motor neuropathy are two other conditions associated with mutations in the ATP7A. The CNS remains unharmed in occipital horn syndrome because the leaky splice junctions or the hypomorphic missense mutations in the ATP7A gene mediates copper trafficking. Although copper transport is mediated here, the deficiencies in cuproenzyme may cause dysautonomia and other complications [25]. On the contrary, isolated distal motor neuropathy is a consequence of missense mutations that leads to mis trafficking of the ATP7A gene and copper indeed [29]. Eventually, maintaining copper-homeostasis is of utmost importance because copper ions when present in excess or deficient, may pose a possible threat to human health at some point.

3. Copper homeostasis in cancer

Cancer, a pathophysiological disorder, has appeared as a significant disease that has led to many deaths worldwide [30]. Among various sort of malignancies, like lung, and breast cancer, has been recently reported to be associated with higher mortality rates worldwide. The third-highest cancer with high incidence stated lately is colon cancer, followed by prostate, liver, and pancreatic cancer [31]. The role of copper metabolism is well-defined and researched in the progression and proliferation of these cancers [32]. In fact, associations of copper homeostasis and cancer have been documented for over a century. Many data indicate that tumors need elevated concentrations of copper for uncontrolled copper-mediated cell amplification, leading to the condition called 'Cuproplasia' compared to unaffected tissue. Cuproplasia is another form of metal-dependent cell proliferation which regulates and garrisoned copper at cellular and subcellular levels which in turn modulates the proteins involved in cellular transformation and proliferation [33]. The ratio of Cu/Zn is considered clinically important due to its involvement in oxidative stress, nutritional status, aging, inflammation, and abnormalities at the immune level. Elevated copper levels are often related to decreased zinc levels in various cancers which includes prostate, breast, renal cell carcinoma, and lung cancer [34–37]. Indeed, the level of copper and its role in the formation of tumors and metastasis has been proved by various medical research, as discussed in Table 1.

Tumors initially develop in normal tissues, leading to the formation of a tumor microenvironment (TME). In the meantime, these

tumor cells can proliferate, migrate, and metastasize to distant sites and form pre-metastatic niches. However, in this process, copper can activate extracellular or intracellular pathways in the parenchymal or stromal cells in the tumor microenvironment, leading to metastasis [38]. It is noteworthy that prolonged use of elevated concentrations of copper in potable water may significant stimulate the cancer cells growth and the development of pancreatic tumors in mice [39]. For instance, accumulation of Cu^{+1} can result in the production of extremely reactive free species like hydroxyl radicals by inhibiting the function of enzymes through addition of oxygen in the cysteine residues of iron-sulfur cluster proteins [40]. Hydroxyl radicals act as strong DNA oxidants, causing mutagenesis and lethality [41]. Moreover, extracellular matrix (ECM) remodeling is necessary for permitting the transformed cancer cells to migrate. In this context, copper-containing enzymes such as lysyl oxidase (LOX) mediate an important part in catalyzing the oxidation process of lysine residues present on elastin and collagen, favoring the crosslink formation among proteins and thus causing tumorigenesis, metastasis, and invasion of different cancer [42]. Furthermore, it is the transcriptional regulator Snail, which controls the expression of critical epithelial genes such as E-calmodulin, that affects the epithelial-mesenchymal transition (EMT) process in its final step [43]. Portillo et al. conducted a study which demonstrated that Cu-centered lysyl-oxidase-like 2 and 3 (LOXL2 and LOXL3) promote EMT by inhibiting the epithelial proteins expression such as E-cadherin via interaction with lysine residues located at positions 98 and 137 in the snail [44]. The metastasis of breast cancer to the lung is dependent on the LOX activity by obtaining copper via ATPase7A; therefore, the knockout of ATPase7A by CRISPR/Cas9 method in the 4T1 cell line decreased the growth of tumor and metastasis of breast cancer cells to the lung in mice [45]. In 2021, Li et al. and coworkers demonstrated that hypoxia-inducible factor RNF144A-AS1 accelerated the proliferation, angiogenesis, and tumor metastasis by upregulation of LOX expression in gastric cancer [46]. In a recent bioinformatic study, the upregulation of LOX gene expression was seen in the tumor progression and infiltration of various breast cancer patients. Thus suggesting the possible role of LOX as a therapeutic target [47]. Additionally, copper is crucial in promoting blood vessel formation by triggering the activation of various angiogenic components like tumor necrosis factor (TNF), angiogenin, vascular endothelial growth factor (VEGF), ceruloplasmin, fibroblast growth factor 2 (FGF2), and interleukin-1 (IL-1) [38,48,49]. Nevertheless, angiogenin is overexpressed in multiple malignancies. It has a significant impact on ribonucleolytic activity translocating into the nucleus and binding to actin, thus leading to the proliferation and metastasis of transformed tumor cells. It has also been exhibited that copper ion binds to angiogenin, initiating migration and proliferation [48,50,51].

Furthermore, it was shown that stimulating copper transporter CTR1 with VEGF promoted angiogenesis, and CTR1 knockout mice showed impaired angiogenesis [52]. Treatment with copper chelator trientine alone and with carboplatin showed angiogenic activity in mice and humans, thus inhibiting hepatic and ovarian cancers [53,54]. Hence, these findings suggest that either the excess of copper or a decrease in copper levels can be used to determine the composition of TME and the stages of cancer. The use of chemotherapy or radiation therapy in cancer may result in the induction of DNA damage and cellular apoptosis. However, this can lead to the activation of metalloenzymes and increased copper levels. Also, enhanced copper levels were seen in patients who underwent chemotherapy and radiotherapy [55,56].

Indeed, it is known that changes in pumps and chaperones implicated in the distribution and uptake of copper get disrupted in cancer, which can induce cell proliferation and spreading. For example, in breast cancer cell lines, silencing of copper chaperone ATOX1 decreased the cell proliferation and migration, which implies that expression of ATOX1 is associated with poor survival of patients suffering from malignancies of breast [57]. Furthermore, the involvement of Cu and Cu-binding proteins in the signaling pathway, mainly the kinase cascade, can also induce the multiplication of cancerous cells. Recently, Grasso et al. showed that the

Table 1
Copper levels and associated mechanism(s) in various cancer types.

Cancer type	Level of copper	Mechanism	References
Breast cancer	Elevated	Upregulation of copper-dependent genes along with higher serum copper levels in breast cancer patients as compared to healthy control; copper-dependent LOX gene led to breast cancer bone metastasis.	[62]
Oral cancer	Elevated	Upregulation of 14 genes associated with the metabolism of copper in the immune microenvironment. Increased serum copper levels associated with oral cancer risk.	[149]
Liver cancer	Elevated	Upregulation of copper transporter genes was associated with an increased level of copper in liver cancer tissues which led to elevated migration, invasion, and cell growth of liver cancer cells by the MYC/CTR1 axis.	[150,151]
Pancreatic cancer	Elevated	Increased copper-related genes such as EPS8, TATDN1, CASC8, NT5E, and LDHA; high infiltrating M2 macrophages resulting in poor survival in pancreatic cancer patients. Increased level of SLC31A1 copper-dependent gene associated with malignancy in pancreatic cancer.	[152,153]
Lung cancer	Elevated	Elevation of circular RNA copper chaperone (circ-CCS) in lung cancer that led to increased cell growth, invasion, and migration by the miR-383/E2F7 axis. Increased levels of copper metabolism domain protein (COMMD4) in non-small cell lung cancer showed poor prognosis in adenocarcinoma.	[154,155]
Colon cancer	Elevated	Inflammatory cytokine IL-17 causes the STEAP4-dependent cellular uptake of copper thus promoting colon tumor formation by the IL-17-STEAP4-XIAP axis.	[156]
Cervical cancer	Elevated	Elevated serum levels of copper in 747 cervical patients were associated with heterogeneity as compared to control patients, thus indicating copper is a risk factor for cervical cancer.	[157]
Prostate cancer	Elevated	Elevated level of copper among prostate cancer patients as compared to control patients thus suggesting the role of copper in the initiation of prostate cancer.	[34]
Ovarian cancer	Elevated	Increased copper levels elevated the VEGF and angiogenesis expression in ovarian cancer cell lines.	[158]
Esophageal cancer	Elevated	Increased level of copper and its association with risk of esophageal cancer by regulating angiogenesis factors as compared to healthy control and non-cancerous tissues.	[159]

stimulation of MAPK (mitogen-activated protein kinase signaling) by the interaction of copper with MEK1/2 kinases [58]. Moreover, a study showed the regulation of AKT kinase by copper transporter CTR1 through the copper-PDK1 signaling pathway [59]. Similar to the MAPK, a study showed the role of autophagic kinases such as ULK1/2 activating the signaling cascade upon binding to copper at the intracellular levels. However, mutating the copper-binding motif of ULK1 impaired the copper transporter and inhibited ULK-dependent signaling, thus inhibiting lung adenocarcinoma [60]. So, targeting copper-dependent signaling pathways is essential for inhibiting proliferation and metastatic tumor formation at distant sites. In addition, the metabolism of copper is also known to affect the metabolism of cancer cells, as discussed above, thus enhancing its tumorigenic and metastatic potential. Altogether, more diagnostic and prognostic markers need to be identified in cancer in relation to copper to inhibit tumor proliferation, spreading, and metastasis.

4. Modulation of intracellular copper levels and cancer therapy

Significant progress has been made in the last few decades in developing innovative therapies that target cancers with specific molecular alterations responsible for tumor progression and growth. These novel therapy choices, known as targeted treatments, have altered the treatment paradigm for certain malignancies [61]. Copper is a critical component for mitochondrial metabolism, which is required to supply the energy needs of rapidly proliferating cells; hence, malignant cells have a greater demand for copper than non-dividing cells [62]. Compounds that bind to copper, such as ionophores and copper chelators, have considerable potential in targeted cancer therapeutics, and almost a century of research studies have illustrated the importance of copper in the progression of cancer cells [63].

Copper chelators reduce angiogenesis, metastasis, and tumor growth by binding to copper and decreasing its bioavailability [64]. The atoms' structure in the chelator helps in their binding property and forms stable ring-like structures [65]. D-penicillamine, also known as D-pen, was discovered in the 1950s and is regarded as a potent metal chelator, as it was observed that in in-vivo experiments, it helps remove Cu. Several studies have shown that when D-pen and Cu are combined, they may generate ROS and inhibit ICAM and LOX. Furthermore, the combination was seen to inhibit tumor vascularization and inhibited the growth of the tumor, which ultimately resulted in the death of endothelial lymphocytes [66,67]. Tetrathiomolybdate (TM), another Cu chelator that has been intensively researched for anticancer action since 1990, has been shown to decrease angiogenesis by targeting numerous pathways, such as the

Table 2
Status of copper-based drugs in various cancer type(s).

Interventions	Phase	Status	Outcomes	Condition(s)	References
Disulfiram-copper	II	Recruiting		Metastatic breast cancer	[160] NCT03323346
Disulfiam/copper-gluconate	II	Active, not recruiting		Glioblastoma multiforme	NCT02715609
Elesclomol-paclitaxel	I	Completed	The combination was well tolerated with a toxicity profile similar to single-agent paclitaxel.	Refractory solid tumors/neoplasms	[161]
Copper-64 labeled SAR-bombesin	II	Recruiting		Prostate cancer	NCT05613842
Copper-64 labeled granzyme B (64 Cu GRIPB)	I	New	Recruiting	Prostate cancer, renal cancer, urethral cancer	NCT05888532
Chlorophyllin, Sodium copper complex	II	New	Recruiting	Rectal neoplasms	NCT05856305
Temozolomide, copper and disulfiram	II	Completed	The addition of DSF/Cu to TMZ for TMZ-resistant Isocitrate Dehydrogenase-wild type glioblastoma appears well tolerated in the patients under study trial but has limited activity for unselected populations.	Recurrent glioblastoma	[162]
Copper-64 DOTA trastuzumab	II	Active	The study represents for the first time that combining multiple modalities of ^{64}Cu-DOTA-trastuzumab PET-CT and MRI imaging data in a mathematical model will be helpful in the prediction of individualized therapy response.	HER2 Positive Breast Carcinoma	[163] NCT02827877
Elesclomol-paclitaxel compared to paclitaxel alone	II	Completed	Encouraging efficacy and anti-tumour activity of the combination along with tolerable toxicity profile of elesclomol when coadministered with paclitaxel.	Metastatic melanoma	[164]
64Cu-DOTATATE	III	Completed	64Cu-DOTATATE is a highly safe and accurate technique for imaging somatostatin receptor (SSTR) expressing tumors. Additionally, diagnostic potential is reproducible and accurate.	Neuroendocrine tumors	[165]
67-Cu SARTATE	I	Recruiting		Neuroblastoma	NCT04023331
ATN-224 (tetrathiomolybdate analogue)	II	Active		Prostate cancer	NCT00405574
D-penicillamine	I	Completed	Penicillamine is well tolerated and copper levels in serum was reduced significantly but this does not improve overall survival in the patients of glioblastoma multiforme.	Brain and CNS tumors	[166]

reduction in the activities of LOX, NF-κB, HIF-1, and SOD1. Furthermore, TM may increase the cytotoxic potential of sorafenib, an inhibitor of BRAF kinase [68,69]. It is noteworthy that although copper chelators have anticancer potential, they alone are insufficient to destroy cancer cells. Therefore, pairing them with other medications is paramount for designing and obtaining an effective cancer therapeutic strategy [70].

While researchers are more focused on Cu chelators, another class of copper-binding molecules called ionophores that induce cuproptosis are also widely explored for their anticancer properties. Cu-ionophores are known for increasing the intracellular bioavailability of copper [71]. These copper-binding molecules exert their effects through numerous modes like DNA interaction, proteasome inhibition, and ROS generation [72]. Cu ionophores include chloroquinol, disulfiram (DSF), docosahexaenoic acid, and thiosemicarbazone [55,73]. Chloroquinol and DSF decrease proteasomal activity in cancer cells via intracellular production of ROS, which ultimately triggers apoptosis [74]. The use of DSF and chloroquinol in breast cancer has been shown to reduce tumor growth, which also holds positive for prostate cancer models [75–77]. Analogues of choloroquinol are continuously being studied in preclinical trials with various ways of administration to improve their anticancer potential [78]. Although clinical studies have been completed and can provide some strategies for treating cancer, as discussed in Table 2, additional research is required to address the limitations of copper metal-binding compounds for cancer treatment, which are still in the initial phases of development. A major challenge in this area is the difficulty in selective targeting of cancer cells.

Copper transporters are other candidates that may act as guidelines for cancer therapeutics. In this direction, we have gone through the Gene Expression Profiling Interactive Analysis database [79] (Fig. 2) and analyzed the overall survival rate of cancer patients related to the expression profile of copper importers. We infer that there is a correlation between patients' survival and the expression profile of SLC31A1. In Bladder urothelial carcinoma (BLCA), Thyroid carcinoma (THCA), and Uveal melanoma (UVM), the analysis of survival plots between SLC31A1 expression patterns and the survival rate of patients suffering from cancer revealed that individuals having lower expression pattern of SLC31A1 shows better overall survival as compared to persons having higher SLC31A1 expression profile. According to the pan-cancer analysis by Ma et al. to establish the correlation between SLC31A1 expression and tumor progression, atrocious overall survival was found in skin cutaneous melanoma, testicular germ cell tumors, adrenocortical carcinoma and tymoma with higher expression of SLC31A1 [80]. The negative correlation between the expression pattern of SLC31A1 and survival of patients indicates that enhanced copper intake is strongly linked to the development and spread of cancers, influencing the patient's expected lifespan. Therefore, it may be possible to develop novel cancer therapies by suppressing the expression of SLC31A1 or eliminating considerable quantities of copper ions from tumor tissues.

5. Cuproptosis: a copper-mediated programmed cell death

According to a recently conducted study, it was observed that cuproptosis is a unique kind of copper-mediated cell death [9]. This type of cellular demise is distinctly regulated compared to other forms of cell regulatory mechanisms already known. It has been well-established that the accumulation of heavy metals like iron causes toxicity in cells that affect well-being and health [81]. A classic example of metal-associated programmed cell demise is ferroptosis, which is identified and named initially through experiments on cancer cells involving ras mutations [82]. It results from the dysregulation of cellular iron homeostasis, which distinguishes itself from other types of cellular demise like autophagy, apoptosis, since it depends on iron and is activated by elastin and RAS selective lethal 3 by stimulating ras-ref-mek-erk signaling [82,83]. Strikingly, cancer cells with ras mutations are selectively vulnerable to erastin than wild-type cells [82] Moreover, cancer cells that have undergone genetic alterations become very susceptible and vulnerable to iron-dependent cell death [84]; therefore, cancer cells having genetic mutations can be leveraged to trigger ferroptosis in order to eradicate them [85,86]. Additionally, Ferroptosis may also be governed by the tumor suppressor genes and oncogenes; for instance, upregulation of the former and downregulation of the latter leads to either inhibition or promotion of iron-dependent cell death via particular signaling. These factors present potential therapeutic targets for different cancer types [87]. Interestingly, the iron levels in

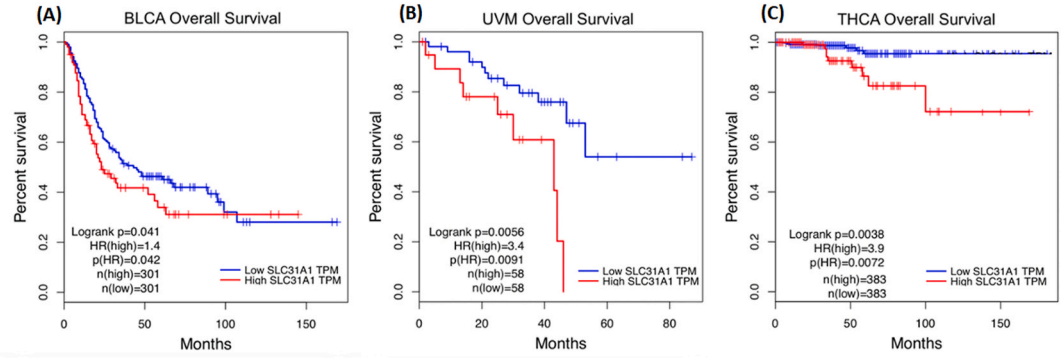

Fig. 2. Survival plots for high versus low expression of SLC31A1: (A) Bladder urothelial carcinoma (BLCA); (B) Uveal melanoma (UVM); and (C) Thyroid carcinoma (THCA). The overall survival rate was higher in the patients having a low expression of SLC31A1 than that with an increased expression of SLC31A1. The plots were generated using the GEPIA tool. Samples were split into high and low using the Custom option for the Group Cutoff (Cutoff-High = 25% and Cutoff-Low = 75%).

cancer cells are notably high due to their elevated metabolic state, eventually leading to an overabundance of ROS production compared to normal cells [88]. Therefore, ample research evidence has shown that modulation of iron homeostasis can cause toxicity induced by ferroptosis in cancer cells, especially in the case of lung, liver, and ovarian cancer [89–91]. One important features of cancer cells are EMT transformation, which is mainly responsible for drug resistance, notably cancer cells showing EMT have substantial sensitivity for ferroptosis [92,93]. On that account, directing cancer therapeutics towards ferroptosis as a key target to skirmish therapy-resistant cancer cells having EMT characteristics will provide novel opportunities in the area. Furthermore, several established chemotherapeutic agents and radiations achieve their antineoplastic effects by the induction of iron-dependent cell death [94–96]. In conclusion, the utilization of ferroptosis in the context of cancer therapy and progression is arbitrary and exceedingly persuasive.

Numerous mechanisms have been hypothesized, which include apoptosis induction, ubiquitin-proteasome system inhibition, and ROS production but the precise regulatory pathway which carried out copper-mediated cell death remains unknown. One of the possible mechanisms is due to the accumulation of copper during mitochondrial stress and the instability of the Fe-S cluster proteins, leading to cuproptosis (Fig. 3).

Elesclomol (ES), copper ionophores, facilitate the delivery of copper to cells [97]. This copper ionophore has recently been used to investigate the mechanism of cuproptosis [9]. The authors explored the possibility that the already-known or well-established cell death pathways mediate copper-induced cell death. According to a previously conducted study, Cu^{+2}-ES was carried to the mitochondria, where it was reduced to Cu^{+1} and subsequently resulted in ROS-mediated programmed cell death [98]. Nevertheless, the researchers discovered that copper-induced cell death deviates from recognized patterns of cell death because copper treatment did not stimulate caspase-3 activation, a typical marker of apoptosis. Additionally, the use of inhibitors to block apoptotic pathways or other known programmed cell death pathways did not prevent copper-induced cell death [99].

Tsvetkov et al. discovered that cells depending on glycolysis were around thousand times less susceptible to copper ionophores than cells dependent on oxidative metabolic cycles. Moreover, the electron transport chain inhibitors decreased cell death in the meantime. The FDX1 gene encodes the reductase ferredoxin 1, which transforms Cu^{2+} to Cu^{+} and is a crucial cuproptosis regulator and an upstream regulator of protein lipoylation [9]. According to genome-wide CRISPR/Cas9 malfunction screening, seven gene knockouts,

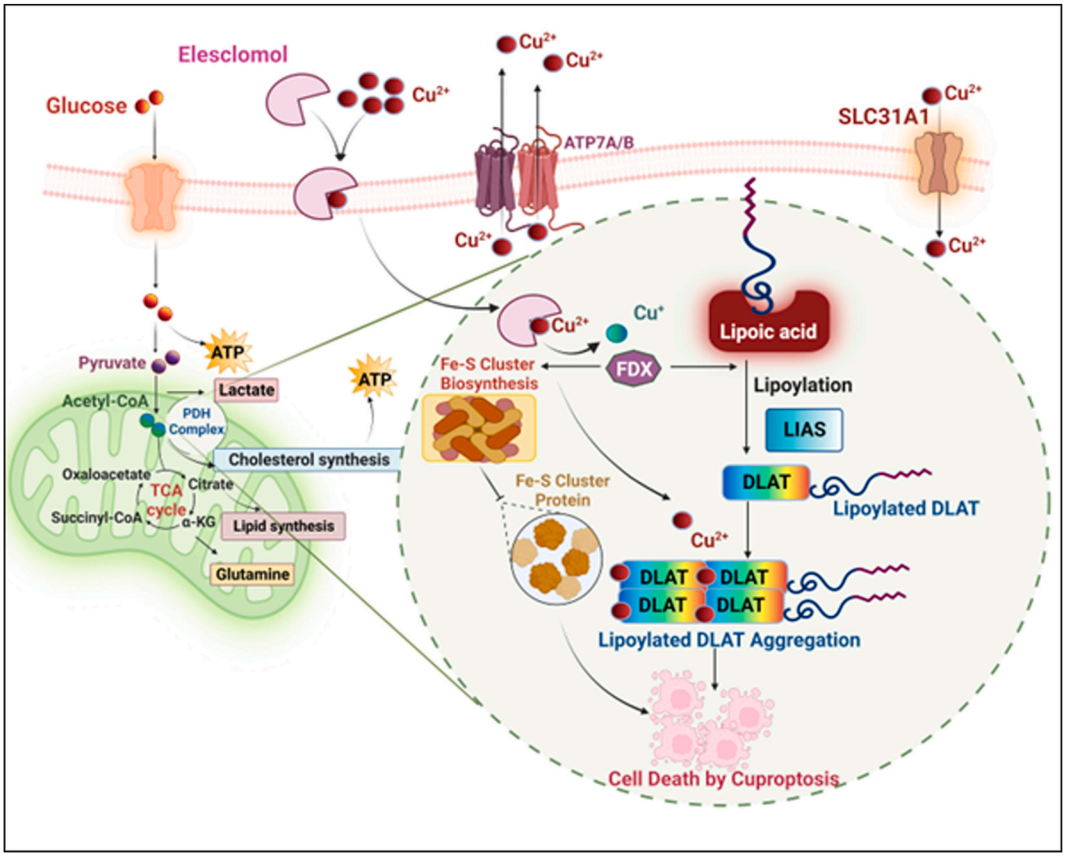

Fig. 3. Schematic representation of cuproptosis-mediated cell death: In cellular contexts reliant on oxidative metabolism, the undue intracellular mobility of copper ions facilitated by ionophores results in their binding to lipoylated DLAT. This interaction triggers abnormal oligomerization of DLAT. The elevated aggregation of lipoylated DLAT gives rise to cellular proteotoxic stress, ultimately culminating in cuproptosis. Ferrodoxin is a pivotal regulator of lipoylation processes. Additionally, FDX1 plays a role in reducing Cu (II) to Cu (I). This reduction step inhibits Fe-S cluster synthesis, further influencing downstream cellular processes.

which include FDX1 and six other genes that encode the fundamental elements of lipoic acid pathways which include enzymes of lipoic acid synthesis like lipoic acid synthetase-LIAS, lipoyltransferase-LIPT1, and dihydrolipoamide dehydrogenase-DLD or proteins which are decorated by the process of lipoylation like DLAT, pyruvate dehydrogenase E1 subunit alpha 1-PDHA1, and pyruvate dehydrogenase E1 subunit beta 1-PDHB, can rescue cuproptosis [9,100]. After FDX1 and LIAS were deleted, cuproptosis resistance was developed in the cancer cells, showing how closely FDX1, protein lipoylation, and cuproptosis are related. In addition, FDX1 serves as a target for ES, and its encoded reductase converts Cu^{2+} to the more lethal Cu^{+} [99]. Protein lipoylation is an exceptionally conserved post-translational modification of lysine. Four known enzymes control the influx of carbon skeleton into the tricarboxylic acid cycle with the help of metabolic complexes, namely-DLAT, DBT, GCSH, and DLST [100,101]. Furthermore, it was also found that DLAT and DLST halted copper binding when FDX1 was depleted; this indicated that the lipoyl component is essential for binding to copper. Copper interacts with lipoylated protein to produce functional toxicity and lipoyl DLAT oligomerization. The hazardous gain of function of lipoylated proteins exposed to ionophores of copper is partially due to the anomalous oligomerization of DLAT [102]. Additionally, these results demonstrate that protein lipoylation and FDX1 are the prime mediators of cuproptosis.

Furthermore, the mass spectrometry analysis revealed an overload of copper-depleted Fe-S cluster proteins. These proteins are components of numerous metabolic enzymes that rely on FDX1 [103]. Previous studies indicated that reducing the Fe-S cluster formation markedly abrogated mitochondrial lipoylation [104], implying a potential connection between Fe-S protein and lipoylation; however, further research is needed to establish this association [105]. The findings of this study act as the backbone for the notion that mitochondria are a crucial regulator of cell death in various ways [106], which includes copper-induced cell death [107]. Also, the widely accepted belief that metal-induced cytotoxicity is a consequence of oxidative stress is contradicted here [108]. A part of the cuproptosis mechanism has been validated in yeast and bacteria [109]. Cuproptosis can, therefore, shed light on numerous biological processes, such as the antibacterial characteristics of microbes that create copper ionophores [110]. Interestingly, using Zinc pyrithione, 4-Br-A23187, and Dimethyldithiocarbamate can impede the growth of yeast and bacteria, respectively, by increasing intracellular copper levels and thus play an antibacterial role [111,112]. In addition, cuproptosis may provide a groundwork for the expansion and growth of viable alternative therapeutics, such as treating malignancies resistant to conventional cell death mechanisms and may affect the future therapy of diseases [113].

A major challenge cancer therapies face is cancer cells' ability to escape the programmed cell death pathway. The discovery of copper-induced cell death may serve as a new therapeutic approach to conquer the ability of cancer cells to escape the cell death pathways. The study conducted by Tsetkov et al. demonstrated that ES, which serves as a Cu^{2+}ionophore, potentially targets drug-resistant cancer cells [99]. Cuproptosis-related genes (CRGs) may greatly assist the diagnosis and prognosis of several malignancies, as indicated by the extensive use of web databases by researchers in the numerous genes that link to cuproptosis and cancer. In a recent study conducted on triple-negative breast cancer, Sha et al. discovered a strong link between cuproptosis-related genes and infiltration of the immune cells. They observed that the signatures provided by the CRG could be utilized to evaluate the infiltration of the tumor immune cells, assess their clinical features, and be helpful in their prognosis [114]. CRGs serve specific functions in numerous forms of cancer. More importantly, Dihydrolipoamide dehydrogenase (DLD) possesses the characteristics of a risk factor for uveal melanoma (UVM), glioma, and LUAD [115–118]. Interestingly, LIAS, another gene related to cuproptosis, was a protective factor in UVM, pancreatic ductal adenocarcinoma (PDAC) glioma, and [116,119–122]. Studies on PDAC have reported DLAT as a risk factor [122], while the same gene has shown a protective relationship with glioma [119,123]. Indeed, different research groups have investigated the same tumor and they described FDX1 and PDHAI as a risk or protective factor, respectively [115,124]. FDX1-expression levels were noticeably lower in clear cell renal carcinoma (ccRCC) samples compared to normal tissues in the study by Wang et al. These low FDX1 levels correlated with higher score of malignancies along with more advanced metastatic profile and reduced overall survival [125]. Lv et al. conducted comprehensive research on cuproptosis-related gene patterns on skin cutaneous melanoma (SKCM) and discovered that eleven out of twelve genes were exclusively expressed in melanoma. Also, three of these (PDH1, LIPT1, and SLC31A1) had prognostic significance in the prognosis of melanoma. Further investigation revealed that the expression profile of LIPT1 was high in melanoma samples and may serve as an independent predictive factor for patient diagnoses [126]. Another study of cuproptosis-related molecular patterns based on 16 key regulators of copper-dependent cell death in 1274 samples of colorectal cancer (CRC) revealed a significant and novel link between TME phenotypes and cuproptosis pattern [127]. A separate study that links TME phenotypes and the effects of immunotherapy with 46 cuproptosis-related genes was carried out in patients of bladder cancer (BLCA). Individual patients were assigned a cuproptosis risk score (CRS) for prognosis and immunotherapy efficacy prediction, as well as a cuproptosis signature for particular TME characteristics. Furthermore, it was discovered that the CRS and cuproptosis pattern might play an important role in determining the prognosis and success of immunotherapy in patients with bladder cancer [128]. Additionally, researchers are formulating a predictive model for liver cancer that is grounded on the lncRNA and mRNAs related to cuproptosis. This model will be helpful in accurately predicting the potential survival rate and, secondly, in the analysis of the infiltration of immune cells in patients with hepatic malignancy. Moreover, this model will also aid in the assessment of tumor mutation burden as well as medication sensitivity [129]. An investigation of several cancer types revealed that the FDX1 expression at RNA and protein level was considerably lower in most cases. The infiltrating immune cells, immunological checkpoint genes, and immune regulatory genes were also significantly associated with FDX1 expression. As a result of its importance in carcinogenesis, and immune profile of tumor, it can potentially be a target for therapeutical approach along with the well-defined prognostic marker in a range of malignant tumors [130,131]. In general, the identification of cuproptosis could provide an innovative approach to the development of cancer diagnostic and therapeutic techniques.

The climactic point is that cuproptosis and ferroptosis have a key role in the progression and advancement of cancer. Still, the question remains whether there is any correlation between them. Emerging evidence have provided a robust connection between iron- and copper-dependent cell death across many cancers. For instance, in hepatocellular carcinoma and lung adenocarcinoma, the

reciprocity between regulators of ferroptosis and cuproptosis elucidates the tumor microenvironment, which ultimately governs prognosis and sensitivity for chemotherapeutics [132,133]. Apart from the association of cuproptosis and ferroptosis with cancer, further studies have significantly uncovered their interplay. Interestingly, a study conducted by Huang et al. in 2021 revealed that excessive accumulation of copper mediated by ES, a known copper ionophore, impedes the growth and proliferation of CRC through ferroptosis. ES intensifies the reactive oxygen species production, which leads to the enhancement in oxidative stress in CRC cells and further reduction in the expression of copper transporter ATP7A and induction of ferroptosis and SLC7A11 degradation [134]. Thus, ES, a known inducer of cuproptosis has a key role in ferroptosis and can be illustrated as a co-regulator of both the form of cell death. Furthermore, another copper ionophore and FDA-approved drug for alcohol abuse, disulfiram (DSF), has promising antineoplastic potential with copper [135]. DSF induces ferroptosis by increasing free iron through mitochondrial disruption and hampering the proliferation and migration of liver and nasopharyngeal cancer [135,136]. More importantly, a study conducted in mouse models of pancreatic cancer, overburden of copper through ionophore, enhanced the ferroptosis mechanism exhibited by tumor cells [137,138]. Prior to the recognition of cuproptosis, it was broadly accepted that an excess of intracellular copper would produce ROS via the Fenton reaction or mitochondrial damage which ultimately results in the oxidation of lipids present in the cell membrane and leading to iron dependent programmed cell death [139]. Therefore, any dysregulation in the copper metabolism and homeostasis affects not only cuproptosis but ferroptosis also [134]; despite these postulations, which further require experimental conformation, a recent study conducted by Feng et al. on liver cancer, mechanistically explained the interplay between copper and iron centered cell death. This study disclosed that sorafenib and erastin a, known inducers of iron-dependent cell death, potentially inhibit the degradation of FDX1 protein, which reduces intracellular GSH synthesis and ultimately leads to cuproptosis by enhancing the oligomerization of lipoylated proteins [140]. Inevitably, an extensive study of the correlation between cuproptosis and ferroptosis may pave a novel substructure for designing and developing new drugs in cancer therapeutics.

6. Conclusive remarks and future perspectives

Copper's pivotal role within the cellular microenvironment is indispensable for various cellular processes, but surpassing a critical threshold leads to cell demise [14]. Copper-binding molecules have been the subject of many studies, identifying a hitherto unknown mechanism of cell death dependent on copper. However, a rigorous literature review in this area is still required.

The discovery that copper ionophores have anticancer properties leads to the observation that these molecules exert their functions by importing copper inside the cell [98]. Despite extensive studies on copper-dependent cell death and how it occurs [134,135], the exact mechanism of this planned cell death was previously debated until the well-explained and specific pathway of cuproptosis was investigated last year [9]. Cuproptosis was investigated and shown to have a close association with mitochondrial metabolism. However, additional investigation into the mechanism of cuproptosis is required. On the one hand, the action paths of essential regulators such as FDX1 remain unknown. On the contrary, the suppression of cuproptosis in normal cells is poorly understood. Ultimately, morphological and molecular alterations indicative of cells experiencing cuproptosis have not been characterized.

With the emergence of the concept of cuproptosis, the scientific community is focused on exploring its association with the development of malignancies. Numerous studies have assessed the connection between CRGs and various characteristics of the most prevalent cancer types. However, the literature supporting the relationship between carcinogenesis and cuproptosis is still insufficient due to a lack of scientific evidence and experimental tests. Various researchers have discovered numerous genes in these investigations to create signatures that could potentially play a more significant role in the connection between cuproptosis and malignancies. Further research must investigate this association to better understand the relationship between these frequently highlighted CRGs and cuproptosis.

Copper research in past years has also provided a solid foundation for future studies to demonstrate a link between the mechanism of cuproptosis and certain cancers. Recent advancements have identified copper chelators, copper ionophores, and diverse copper ion complexes exhibiting copper-binding properties. These compounds can increase or decrease the intracellular copper ion concentration and promote or suppress cuproptosis. Researchers have always been interested in using the copper modulator in clinical trials of anticancer medications [141]. It has been hypothesized that the number of patients who benefit from cancer therapies targeting cuproptosis will increase dramatically in the near future as tumors with higher oxidative respiration [142] and stem cell-like properties are still unclear [143]. The platinum-centered drugs like carboplatin, oxaloplatin, and cisplatin have been widely used as primary options for chemotherapy. However, the challenge of drug resistance and the antitumor efficacy of these drugs is still in question, especially in patients having metastasized tumors [144–146]. Contemporary approaches to prevail over the challenge of drug resistance in cancer patients include using copper-based drugs in the form of ionophores and chelators, which have demonstrated promising results [147,148]. The finding of cuproptosis propels current research on copper-based therapeutics to new heights, and there is now a solid foundation for future mechanistic studies on copper-dependent cell death pathways.

Furthermore, a substantial body of literature indicates an indirect link between cancer and cuproptosis, which may be helpful in future studies to establish direct links between the two. The available information thus far supports the notion that cuproptosis is an original and separate process of cell death. However, the intricate mechanisms governing cuproptosis and its potential interplay with cancer require further investigation.

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CRediT authorship contribution statement

K.M. Abdullah: Writing – original draft, Conceptualization. **Jyoti B. Kaushal:** Writing – original draft. **Simran Takkar:** Writing – original draft. **Gunjan Sharma:** Writing – original draft. **Zahraa W. Alsafwani:** Formal analysis. **Ramesh Pothuraju:** Writing – original draft. **Surinder Kumar Batra:** Writing – review & editing. **Jawed Akhtar Siddiqui:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

SKB is co-founder of Sanguine Diagnostics and Therapeutics, Inc. Other authors declare no competing interest.

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