Vol. 4 No. 4 (2025)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Noorulain et al., - 2025

Targeting Copper Metabolism in Cancer: Mechanisms and Therapeutic Strategies

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Keywords:

Copper; Copper Metabolism; Copper Homeostasis; Cancer; Copper-Binding Proteins; Copper-Targeted Therapy

Received on 18 Nov, 2025

Accepted on 07 Dec, 2025

Published on 10 Dec, 2025

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Abstract

Copper is an essential trace element that plays a critical role in numerous cellular processes including enzymatic reactions, signaling pathways, and redox homeostasis. Dysregulation of copper levels, whether through excess accumulation or abnormal intracellular distribution, can lead to cellular toxicity and has been implicated in the development and progression of various cancers. Elevated copper levels in tumor cells contribute to cancer hallmarks

such as enhanced cell proliferation, angiogenesis, and metastasis. Therapeutic strategies targeting copper homeostasis including copper chelators and copper ion carriers have shown promise in modulating copper levels and inhibiting tumor growth. This review summarizes current knowledge on copper regulation within cells, the role of copper and copper binding proteins in cancer pathophysiology, and recent advances in the development of copper based anticancer therapies.

Introduction

Copper, as a catalytic cofactor, participates in many biological reactions and plays a vital role in organisms. Copper ions can be converted between Cu^{+}/Cu^{2+}, and some key proteins or enzymes also use the high redox activity of copper to complete their respective physiological functions, such as superoxide dismutase, cytochrome C oxidase COX and lysyl oxidase. Free copper is toxic and can damage cell membranes, proteins, and nucleic acids. Therefore, a delicate network of copper transporters in cells is essential to regulate its homeostasis by transporting copper to target copper-dependent proteins to avoid unnecessary reactions. Studies have found that copper levels in the serum and tumors of cancer patients are significantly higher than those of healthy subjects. Copper is essential for cancer proliferation, angiogenesis, and metastasis, and copper transporters also play a key role in cancer. Copper-binding compounds have great potential in the treatment of cancer, including copper-specific chelators to reduce copper utilization, and specific ionophores that deliver copper to cells to increase intracellular copper levels. This study reviews the regulation of copper in cells and how copper and copper-binding proteins play a role in the occurrence and development of cancer, and then clarifies the therapeutic effect of copper derivatives as anticancer agents.

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Copper Metabolism In Cells

Copper is an essential trace nutrient required for normal organ function and metabolism in animals and humans. The human body mainly obtains sufficient copper from food. After food is digested in the stomach and duodenum, copper is absorbed by the intestinal epithelial cells and transported to the liver thru the portal vein. In the liver, copper is released into the blood to meet the needs of the surrounding organs or discharged into the bile. Thru genetic mutations or changes in environmental conditions, imbalances in the utilization of copper in the human body will lead to its deficiency or toxicity, resulting in pathological results. Imbalance not only affects mitochondrial respiration, but also affects glycolysis, insulin resistance and lipid metabolism. Therefore, cells must tightly regulate copper homeostasis thru a complex network of copper transporters and chaperones. **Figure 1.** Schematic representation of copper metabolism in normal cells, copper dysregulation in cancer, and therapeutic interventions. In normal cells, copper uptake through CTR1 transporter and delivery via copper chaperones (ATOX1, COX17, CCS) ensures balanced redox activity and normal cellular functions. In cancer cells, elevated copper levels promote cell proliferation, angiogenesis, and metastasis through copper-binding proteins such as ATOX1, SOD1, LOX, and MEMO1. Therapeutic strategies include copper chelators to deplete excess copper, copper ionophores to induce cytotoxicity, and targeted inhibition of copper-binding proteins to reduce tumor progression.

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Print ISSN 3007-2379

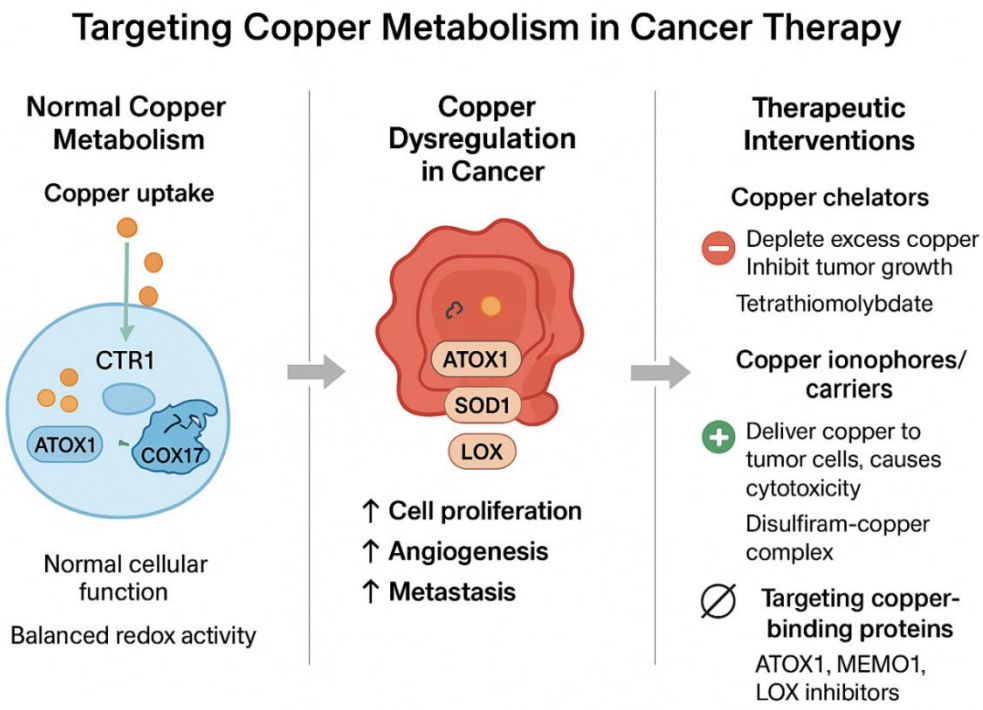

Figure 1. Schematic representation of copper metabolism in normal cells, copper dysregulation in cancer, and therapeutic interventions. Elevated copper, often mediated by proteins like ATOX1 and LOX, drives cancer hallmarks (proliferation, metastasis), which can be targeted by copper chelators (to deplete) or copper ionophores (to induce cytotoxicity).

Copper Entry into Cells

Dietary copper is taken up into intestinal cells via a high-affinity membrane transporter, copper transporter 1 (CTR1). CTR1 is located on the plasma membrane and in most tissues, and is structurally related to channel proteins. Studies have shown that copper promotes tumorigenesis/development by activating the 3-phosphoinositide-dependent protein kinase 1 protein kinase B (PDK1/AKT) pathway in a CTR1-dependent manner, and that depletion of CTR1 or blocking the CTR1-copper axis with copper chelators lacks

AKT signaling and reduces tumorigenesis. In addition, CTR1 is also involved in the uptake of platinum, and the deletion of CTR1 gene in yeast and mammalian cells leads to reduced tissue uptake and increased resistance to metal drugs. Experiments have shown that in vitro copper in non-small cell lung cancer tumor cells inhibits the activation of protein kinase (AMPK) signaling pathway of glucose metabolism reactive oxygen species (ROS) and increases CTR1 expression. The increased levels of AMPK and CTR1 expression indicate a worse prognosis for lung cancer.

Intracellular Copper Transport and Oxidoreductase Synthesis

After being reduced to Cu^{+} by the reductase of the STEAK family, Cu^{+} is reduced to Cu^{+} by the reductase of the CTR1family. Once copper enters the cell, copper chaperones distribute copper to specific copper-dependent superoxide dismutase copper chaperone protein (CCS) and superoxide dismutase 1 (SOD1) in the cytosol. With similar copper-binding sites, CCS transfers copper to SOD1 by forming a highly specific protein-protein complex. SOD1 is a key enzyme for maintaining ROS homeostasis in different cellular compartments, and the only known copper chaperone protein that directly interacts with and activates human SOD1 is CCS. CCS is highly specific for SOD1 and plays a role in each stage of SOD1 maturation. As the main intracellular free radical scavenger, SOD1 mutation can lead to amino acid, lipid and nucleic acid damage. In addition, oxidative stress caused by SOD1 lacking metallization or existing in variant forms is associated with a variety of diseases, including Parkinson's disease, cancer and amyotrophic lateral sclerosis. Knocking out SOD1 may be a promising new therapeutic target. Table 1 gives the overview of Key Copper Transporters and Chaperones in Cellular Copper Homeostasis

Table 1: *Key Copper Transporters and Chaperones in Cellular Copper Homeostasis*

Protein	Function	Role in Cancer	Reference
CTR1	Copper uptake transporter	Overexpressed in some cancers, enhances copper influx	[7,11,16]
ATOX1	Copper chaperone to Golgi, transcription factor	Promotes proliferation and angiogenesis	[27,31]
CCS	Delivers copper to SOD1	Enhances ROS detoxification	[9,10]
COX17	Mitochondrial copper delivery	Supports energy metabolism	[13,14]
Metallothioneins	Copper binding and storage	Regulate copper toxicity	[11]

Copper Secretion Pathway

Most eukaryotes store copper in vesicles and secrete it thru the lipid membrane. Therefore, copper transport must insert copper into the secretory pathway. An important function of copper-transporting ATPases A (ATP7A) and B (ATP7B) is to regulate copper transport between the trans-Golgi network (TGN) and the cell periphery. Copper is delivered to the copper-transporting ATPases in the TGN by the chaperone protein antioxidant 1-copper chaperone (ATOX1), and copper is loaded into newly synthesized cuproenzymes via the secretory pathway. Once the intracellular copper concentration increases and becomes excessive, the two ATP7A/B proteins migrate to the cell membrane to discharge copper out of the cell. Table 2 gives the details of Copper Dysregulation Mechanisms in Cancer

Table 2: *Copper Dysregulation Mechanisms in Cancer*

Mechanism	Effect on Cancer Cells	Key Proteins Involved	Reference
Increased copper uptake	Promotes proliferation	CTR1, ATOX1	[7,16,21]
Enhanced ROS generation	Promotes cell survival signaling	SOD1, MEMO1	[24,36]
Activation of angiogenesis	Supports tumor vascularization	ATOX1, LOX, CTR1	[26,30]
Promotion of metastasis	Enhances migration and invasion	MEMO1, LOX	[30,36]

Mitochondrial Pathway

Mitochondria are an important site for copper utilization, and subunit 2 of COX in the inner mitochondrial membrane is one of the major copper enzymes in mitochondria. COX is the main component of the respiratory chain, which is used for oxidative phosphorylation and to complete the function of the particles. Therefore, cell survival must be achieved by transporting copper to the mitochondria. COX has two core binding specialized genes, COX1 and COX2. Copper metallation during mitochondrial COX assembly. The translation and insertion of COX1 into the inner membrane is mediated by a set of structural post-translational activators and chaperones, and COX1 promotes the formation of the CuB. COX2 binds the binuclear CuA site, the formation of which requires the transfer of Cu from COX1 to SCO1. It is then catalytically inserted into COX2. CuA can affect the binding of c-receptor electrons required by the COX2 chain,

which are transferred to the chain of COX1, first to heme a, and then to the heme a3-CuB site, where oxygen is bound.

Copper Importance in Cancer

The serum copper level in cancer patients is higher than that in healthy people, and the elevated serum copper is related to the disease stage and treatment effect. Copper is involved in three basic processes of cancer progression: cell proliferation, angiogenesis and metastasis. Analysis of breast cancer in the Cancer Genome Atlas database showed that copper metabolism-related proteins, including CTR1, ATOX1, ATP7B, and COX1, were increased.

Copper role in Angiogenesis

Angiogenesis is the process of new capillaries growing from the original blood vessels, involving the migration, proliferation and differentiation of endothelial cells. Angiogenesis is essential for the proliferation of cancer cells and the metastasis of tumors. Copper ions promote tumor cell proliferation and migration by inducing or BRAF signaling. BRAF-driven lung cancer requires copper to maintain cell proliferation signals were sufficient to allow Braf signaling to be studied as a means of purifying BRAF-driven oncogenic properties. It has been shown that copper activates the MAPK pathway thru CTR1-mediated copper uptake. CCS protein levels are elevated in breast cancer patients, and the ability of CCS to promote diffusion may involve serine-activated protein kinase/extracellular signal-regulated kinase (MAPK)/serine-threonine protein kinase and cell proliferation, and copper directly binds to serine/threonine kinase UNC51-like kinase 1 and 2 (ULK1, ULK2) to regulate the activity of ULK1/2. In addition, in terms of angiogenesis, vascular endothelial growth factor receptor 2 (VEGFR2) signaling in endothelial cells is copper-deficient. CTR1 does not present sustained VEGFR2

signaling to promote angiogenesis under the stimulation of vascular endothelial growth factor VEGF, while streptomycin sulfate can block VEGF-induced endothelial migration and angiogenesis without affecting endothelial proliferation. ATOX1 binds to the transcription factor YAP, which is associated with cancer cell growth, and increases the expression of cyclin D1. ATOX1 is also involved in the growth factor-induced dependent cell migration of mouse vertebral bodies, and promotes inflammatory generation and angiogenesis, which may regulate malignant tumor occurrence and angiogenesis.

Role of Copper in Tumor Metastasis

Copper transport from primary to secondary lesions is the main cause of cancer death. Cell-extracellular matrix interactions or stable calcium-dependent cell adhesion are key processes in cell migration, and lysyl oxidase (LOX) plays a key role in this process. The LOX family, consisting of LOX and four homologues LOX-like C, are copper-dependent amine oxidases that cross-link collagen and elastin in the extracellular matrix to stabilize it. Studies have found that LOX is highly expressed in metastatic breast cancer, and inhibition of LOX can alter collagen and fibrin cross-linking and inhibit focal adhesion kinase/tyrosine kinase SRC (FAK/SRC) signaling. In addition, LOX can also promote the metastasis and invasion of tumor cells by promoting the epithelial-mesenchymal transition (EMT). The LOX family is abnormally expressed in a variety of cancers, including colon cancer, gastric cancer, and hepatocellular carcinoma, and is associated with disease progression. The LOX family also alters the prognosis of cancer patients. In addition, the copper chaperone protein ATOX1 requires ATP7A. ATOX1 reduces ATOX1-mediated breast cancer cell migration thru ATP7A, and perhaps copper transport is a potential strategy for inhibiting tumor migration. In addition, LOX can also activate cysteine-rich acidic secretory protein (SPARC) and ERRB2-driven cell motility protein

mediator 1 (MEM1) to promote cancer cell metastasis. migration. Inhibiting the expression of E-cadherin, enhancing migration and invasion, and increasing the expression of EMT transcription factor HGF-induced B-LUX binding regulatory source 1. MEM1 promotes EMT by activating the phosphatidylinositol-3 kinase/protein kinase B (PI3K/AKT) signaling pathway thru interaction with adenovirus receptor body 1, and can produce ROS to control the redox state of cells. Recent studies have suggested that there is no evidence of MEM1 and Cu^{2+} coordination, and MEM1 may guide Cu^{2+} to ATOX1, clear Cu^{+} into the secretory pathway, and reduce the formation of ROS. The interaction of MEM1 with ATOX1 can protect copper-mediated redox activity. One report found that MEM1 was one of two new interacting factors for human papillomavirus (HPV) cancers, and that AKT activation in HPV-positive cell lines was lowest in MEM1. This is in stark contrast to previous results in breast and colon cancer where MEM1 promoted cancer cell proliferation, and may be a specific result of HPV-positive cell lines in cervical cancer.

Copper Derivatives in Anticancer Therapy

Since the discovery of the antitumor activity of platinum derivatives in the 1960s, the role of metal derivatives in cancer treatment has attracted much attention, mainly because the redox activity of metals, the adjustable coordination mode and the reactivity to organic substrates enable these metal compounds to selectively bind to biomolecular targets, thereby changing the cell proliferation mechanism and achieving antitumor effects. In recent years, more and more metal derivatives have been synthesized and tested on tumor cells, such as copper, gold and nickel compounds, but only a few drugs have entered clinical trials. Platinum compounds, as the most classic metal derivative anticancer drugs, have a significant anticancer effect, but often cause

severe nausea, vomiting, and blood toxicity, which seriously affect the quality of life of patients. In this regard, copper, as a metal required in the body, may be a chemotherapeutic drug with great potential.

Copper Chelators

Copper is responsible for the abnormal elevation in many types of tumors, and copper is associated with tumor burden and recurrence. Serum copper levels return to normal after successful tumor surgery and resection or remission, and depleting copper to affect tumor growth is an effective treatment. Copper chelators can significantly reduce copper concentrations by promoting the excretion of chelated copper. The first copper chelator to be tested in clinical trials was D-penicillamine. D-penicillamine binds to copper, resulting in increased steady-state levels of hydrogen peroxide in cells, which is selectively more toxic to tumor cells than normal epithelial cells, and is more lethal to cancer cells when used in combination with ionizing radiation or carboplatin. In recent years, in vitro studies have shown that D-penicillamine significantly reduces the primary. Another copper chelator that has been tried is tetrathiomolybdate TM. TM has been studied for the treatment of copper overload-related diseases such as Wilson's disease. In the blood, TM easily binds to serum proteins or plasma copper-binding proteins to form a trithiomolybdate (TM) copper complex, which prevents copper from being absorbed by cells. TM can inhibit copper-dependent enzymes required by tumor cells, such as SOD1, and can also enhance the activity of chemotherapeutic drugs such as doxorubicin, apatinib, and cisplatin by inhibiting cell proliferation by inducing apoptosis. A phase I-II study of patients with stage II-IV breast cancer showed that patients with TM-treated patients were more likely to be affected by TM treatment than patients with other breast cancer subtypes. In summary, various clinical trials have shown that copper

chelator therapy is relatively well tolerated, but its efficacy as a single-agent therapy may be limited, especially for large or metastatic tumors, and its combination with conventional chemotherapy regimens or other anti-angiogenic drugs may achieve better efficacy. There have been many reports of co-loading copper ions and Cu^+ probe X into liposome carriers constructed by multi-arm systems, and the compounds and agents are simultaneously delivered to tumor cells. In addition, copper ion carriers have been used to target tumor neovascularization. In addition, there are not many clinical trials on copper chelators for cancer treatment, and more and larger studies are needed to explore their role in cancer treatment.

Copper ionophore

Elesclomol, a copper ionophore, is an injectable small molecule compound that can be used alone or in combination with other anti-tumor drugs. Elesclomol binds to active copper-transporting compounds, effectively absorbing these compounds, and once inside the cell, the copper in the complex undergoes a redox reaction, reducing Cu^{+} to $Cu^{2+,}$ producing ROS and oxidative stress in the cell. The anticancer activity of Elesclomol is due to its ability to directly increase this level of oxidative stress. Studies have shown that the mechanism of Elesclomol killing tumor cells is resolved in specific tumor types. In colorectal cancer, Elesclomol promotes the degradation of ATP7A, resulting in copper retention in tumor cells, and induces ROS accumulation and mitochondrial disorders, showing anti-tumor activity. The copper-binding agent elesclomol has higher activity against cancer stem cells (such as tumor-initiating cells in ovarian cancer and pancreatic cancer tumor stem cells) and tumor-initiating cells (such as ovarian melanoma and tumor cells) outside the mitochondria. In a phase II clinical study, Elesclomol was combined with paclitaxel for women with refractory ovarian cancer, and the results

showed that the combination was well tolerated. This suggests that Elesclomol has good development prospects as a sensitizer for conventional chemotherapy in cancer treatment. In recent years, although copper derivatives have made great progress in tumor therapy, it is worth noting that the use of copper-binding compounds, including copper ion carriers, will disrupt the homeostasis of basic metals in the human body, which may cause serious side effects to patients receiving treatment. In future studies, the use of copper ion carriers should be more inclined to improve the selectivity of copper ion carriers (such as nano-drug delivery systems) to make the next step of copper ion carriers obtain more lean targeting effects.

Conclusion and Outlook

Copper is an indispensable trace element for maintaining the operation of human life. Understanding the metabolism surrounding copper helps to provide direction for the clinical treatment of cancer. The redox properties of copper determine that tumor cells need more copper. At present, the importance of copper in cell proliferation, angiogenesis and tumor spread has been explored, and copper is becoming a new target for anti-cancer therapy. In recent years, the study of copper metabolism and its regulatory mechanism is of great significance, revealing that copper is directly involved in cancer progression and copper can be indirectly involved by regulating the expression of copper-binding proteins. The potential of copper-binding proteins in anticancer research has not yet begun to show. Given that the transport of copper in cells is inseparable from copper-binding proteins, determining the specific role of these copper-binding proteins and their relationship with the occurrence and development of cancer is also a new field, and a large number of studies are needed to develop accurate biomarkers from copper-binding proteins. In recent years, the research and

development of copper derivatives has made great progress in tumor treatment, but its clinical efficacy is not fully clear, and there is a lack of a large amount of data to prove the complications caused by these drugs. Clinical trials should be increased to better apply to clinical practice.

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