Copper and Cancer

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7760327/

The Multifaceted Roles of Copper in Cancer: A Trace Metal Element with Dysregulated Metabolism, but Also a Target or a Bullet for Therapy. 2020

Copper is an essential element for human life. However, its redox activity can be detrimental for the cell that developed highly coordinated pathways to chelate and traffic copper through the cell or the organism. Owing to its important role in functions essential for cell growth and metabolism, copper concentrations are frequently dysregulated in tumors. In this review, we describe normal and cancer-altered copper homeostasis mechanisms. Moreover, on the basis of this knowledge, we expose not only copper-related diagnostic and prognostic markers for oncology but also therapeutic strategies to act on copper homeostasis to fight against cancer.

It has been clearly demonstrated that copper homeostasis is deregulated in many cancers.

Cu is an essential trace element with a short half-life of about a month. The required daily intake of Cu is 0.8 mg [1]. Cu concentrations fluctuate from 1 to 10 mg/g of tissues, and the Cu concentration in blood plasma is approximately 1000 ng/mL. However, Cu concentration may vary depending on various factors [2].

To conclude, copper (Cu) is able to bind to various cytosolic proteins such as growth factors, cell signaling proteins, or structural proteins [23]. Within the cell, Cu can directly regulate the activity of these protein partners such as kinases. Therefore, many signaling pathways are copper dependent.

When compared with nonpathological conditions, variations in Cu concentrations or in the Cu/Zn ratios were associated with many cancers. The Cu/Zn ratio is of clinical importance because of its relationship with aging, nutritional status, oxidative stress, inflammation, and immune abnormalities [38,39]. Increased Cu levels were associated with decreased Zn levels in a meta-analysis in bladder cancer [40] and in breast cancer, colorectal cancer (CRC), and prostate cancers [41,42,43,44,45,46,47]. Importantly, some discrepant studies reported decreases in Cu levels in CRC and breast cancers [48,49].

It appears that copper also influences the spread and formation of secondary tumors via the activation of enzymes responsible for cell proliferation. It is therefore not surprising that Cu concentration is increased in tumor areas [50,51,52]. More recently, it was shown that specific Cu accumulation can be observed in cancer cells themselves [51,53]. It is worth noting that the accumulation of Cu in the nuclear region has been found in breast cancer cells [54].

Moreover, early reports described the increases of serum Cu in cancer patients, sometimes even correlated with the grade of the cancer [55]. High serum Cu levels were also found in cancer patients resistant to chemotherapy compared to patients responding to treatment [55]. However, this remains unexplained up to now, and several data on different types of cancer where published, sometimes being contradictory.

Altogether, it is clear that Cu is central for cancer development at each step from tumorigenesis to metastasis. Cancer cell metabolism is also affecting Cu metabolism. Therefore, it is expected that prognostic and diagnostic markers for cancer can be identified in relation with Cu.

Some chelators such as curcumin or D-penicillamine penetrate cancer cells with difficulty because of their physicochemical properties. The development of innovative delivery systems for Cu-chelating agents should overcome these limitations and increase their efficacy and limit potential side effects [197,198,199].

https://www.nature.com/articles/s41568-021-00417-2

Connecting copper and cancer: from transition metal signalling to metalloplasia. 2021

Copper is an essential nutrient whose redox properties make it both beneficial and toxic to the cell. Recent progress in studying transition metal signalling has forged new links between researchers of different disciplines that can help translate basic research in the chemistry and biology of copper into clinical therapies and diagnostics to exploit copper-dependent disease vulnerabilities. This concept is particularly relevant in cancer, as tumour growth and metastasis have a heightened requirement for this metal nutrient.

https://pubmed.ncbi.nlm.nih.gov/37105071/

Copper in cancer: From pathogenesis to therapy. 2023

Interestingly, a growing body of research reports that diverse cancers have raised serum and tumor copper levels. Tumor cells depend on more copper for their metabolism than normal cells, and a decrease in copper or copper overload can have a detrimental effect on tumor cells.

https://pubmed.ncbi.nlm.nih.gov/39068453/

Cuproptosis, the novel type of oxidation-induced cell death in thoracic cancers: can it enhance the success of immunotherapy? 2024

Notably, copper-induced cell death was defined as cuproptosis which was also observed in malignant cells, representing an attractive anti-cancer instrument. Excess of intracellular copper leads to the aggregation of lipoylation proteins and toxic stress, ultimately resulting in the activation of cell death. Accordingly, copper-activated network was suggested as an attractive target in cancer therapy. Mechanisms of cuproptosis and regulation of cuproptosis-related genes in different cancers and tumor microenvironment are discussed in this study. The analysis of current findings indicates that therapeutic regulation of copper signaling, and activation of cuproptosis-related targets may provide an effective tool for the improvement of immunotherapy regimens.

https://pubmed.ncbi.nlm.nih.gov/39152464/

Targeting cuproptosis for cancer therapy: mechanistic insights and clinical perspectives. 2024

Cuproptosis is a newly identified form of cell death induced by excessive copper (Cu) accumulation within cells. Mechanistically, cuproptosis results from Cu-induced aggregation of dihydrolipoamide S-acetyltransferase, correlated with the mitochondrial tricarboxylic acid cycle and the loss of iron-sulfur cluster proteins, ultimately resulting in proteotoxic stress and triggering cell death. Recently, cuproptosis has garnered significant interest in tumor research due to its potential as a crucial therapeutic strategy against cancer. In this review, we summarized the cellular and molecular mechanisms of cuproptosis and its relationship with other types of cell death

https://pubmed.ncbi.nlm.nih.gov/37979442/

Cuproptosis: A novel therapeutic target for overcoming cancer drug resistance. 2024

Cuproptosis has garnered enormous interest in cancer research communities because of its great potential for cancer therapy. Copper-based treatment exerts an inhibiting role in tumor growth and may open the door for the treatment of chemotherapy-insensitive tumors. In this review, we provide a critical analysis on copper homeostasis and the role of copper dysregulation in the development and progression of cancers. Then the core molecular mechanisms of cuproptosis and its role in cancer is discussed, followed by summarizing the current understanding of copper-based agents (copper chelators, copper ionophores, and copper complexes-based dynamic therapy) for cancer treatment. Additionally, we summarize the emerging data on copper complexes-based agents and copper ionophores to subdue tumor chemotherapy resistance in different types of cancers. We also review the small-molecule compounds and nanoparticles (NPs) that may kill cancer cells by inducing cuproptosis, which will shed new light on the development of anticancer drugs through inducing cuproptosis in the future. Finally, the important concepts and pressing questions of cuproptosis in future research that should be focused on were discussed. This review article suggests that targeting cuproptosis could be a novel antitumor therapy and treatment strategy to overcome cancer drug resistance.

https://pubmed.ncbi.nlm.nih.gov/38850661/

Cuproptosis in cancers: Function and implications from bench to bedside 2024

Copper, an indispensable micronutrient, is implicated in numerous vital biological processes and is essential for all physiological activities. Recently, the discovery of a novel type of copper-dependent cell death, known as cuproptosis, has shed light on its role in cancer development. Extensive research is currently underway to unravel the mechanisms underlying cuproptosis and its correlation with various cancer types. In this review, we summarize the findings regarding the roles and mechanisms of cuproptosis in various cancer types, including colorectal cancer, lung cancer, gastric cancer, breast cancer, liver cancer and cutaneous melanoma. Furthermore, the effects of copper-related agents such as copper chelators and copper ionophores on cell proliferation, apoptosis, angiogenesis, tumor immunity, and chemotherapy resistance have been explored in cancer preclinical and clinical trials. These insights provide promising avenues for the development of prospective anticancer drugs aimed at inducing cuproptosis.

https://pubmed.ncbi.nlm.nih.gov/38662225/
Unveiling the promising anticancer effect of copper-based compounds: a comprehensive review. 2024
Copper and its compounds are capable of inducing tumor cell death through various mechanisms of action, including activation of apoptosis signaling pathways by reactive oxygen species (ROS), inhibition of angiogenesis, induction of cuproptosis, and paraptosis.
Despite the promising anticancer activity of copper-based compounds, their use in clinical trials is subject to certain limitations. Elevated copper concentrations may promote tumor growth, angiogenesis, and metastasis by affecting cellular processes.

https://pubmed.ncbi.nlm.nih.gov/32673842/
Anticancer potency of copper(II) complexes of thiosemicarbazones. 2020
Being a structural and catalytic cofactor in a number of biological pathways, copper accumulates in tumors owing to selective permeability of the cancer cell membranes. Copper(II) ion forms the active centers in a large number of metalloproteins. The coordination of Schiff's base ligands to the metal ion results in the high extent of increase in anticancer activity. The copper(II) complexes can cleave DNA through oxidative and hydrolytic pathways, cell apoptosis via intrinsic reactive oxygen species (ROS) mediated mitochondrial pathway due to excessive production of ROS and hence, are found more active than Ni and Pt complexes. Flexible Cu(I/II) redox behavior helps the copper complexes to form more potent, clinically effective and less toxic copper based antiproliferative drugs of lower IC50 value and higher growth inhibitory activity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9309082/
Copper in the tumor microenvironment and tumor metastasis. 2022
Significant Cu accumulation is observed in several tumor tissues.
Accordingly, restricted Cu regulation may be a novel strategy for the inhibition of tumor metastasis. However, it is unclear how these Cu disturbances occur in tumor tissues and the exact molecular mechanisms underlying Cu secretory enzymes. In this review article, I discuss the role of Cu transporters, Cu chaperones, and Cu-containing secretory enzymes in tumor progression to better understand the role of Cu homeostasis in tumor tissues.
On the other hand, excess Cu accumulation in the tissues facilitates reactive oxygen species (ROS) generation, and is closely associated with Wilson's disease and neurodegeneration.(4,5) Recent studies suggested that Cu levels increase in several tumor tissues and angiogenic lesions, and promote neovascularization.(6) Accordingly, Cu chelators, such as bathocuproinedisulfonic acid, tetrathiomolybdate, and penicillamine, may function as anti-tumor agents to prevent Cu-related tumorigenesis.(7)

https://pubmed.ncbi.nlm.nih.gov/34740035/
Copper in tumors and the use of copper-based compounds in cancer treatment. 2022
However, being endogenous and displaying a tremendous potential to generate free radicals, copper is a perfect candidate, once opportunely complexed, to be used as a drug in cancer therapy with low adverse effects.

https://pubmed.ncbi.nlm.nih.gov/26313539/
Targeting copper in cancer therapy: 'Copper That Cancer'. 2015
Copper is an essential micronutrient involved in fundamental life processes that are conserved throughout all forms of life. The ability of copper to catalyze oxidation-reduction (redox) reactions, which can inadvertently lead to the production of reactive oxygen species (ROS), necessitates the tight homeostatic regulation of copper within the body. Many cancer types exhibit increased intratumoral copper and/or altered systemic copper distribution.

https://link.springer.com/article/10.1007/s12094-023-03107-7
The huge potential of targeting copper status in the treatment of colorectal cancer. 2023
Copper is a mineral nutrient whose intrinsic properties have a two-way effect on the production and treatment of cancer. Copper's redox properties allow it to be used in developing anti-cancer drugs, while its potential toxicity leads to oxidative stress and even cancer. Copper status is closely related to colorectal tumors' proliferation and metastasis.

https://www.sciencedirect.com/science/article/abs/pii/S0162013421002816
Copper in tumors and the use of copper-based compounds in cancer treatment. 2022
Copper homeostasis is strictly regulated by protein transporters and chaperones, to allow its correct distribution and avoid uncontrolled redox reactions. Several studies address copper as involved in cancer development and spreading (epithelial to mesenchymal transition, angiogenesis). However, being endogenous and displaying a tremendous potential to generate free radicals, copper is a perfect candidate, once opportunely complexed, to be used as a drug in cancer therapy with low adverse effects.

https://news.weill.cornell.edu/news/2021/12/reducing-copper-in-the-body-alters-cancer-metabolism-to-reduce-risk-of-aggressive
Reducing Copper in the Body Alters Cancer Metabolism to Reduce Risk of Aggressive Breast Cancer 2021
Depleting copper levels may reduce the production of energy that cancer cells need to travel and establish themselves in other parts of the body by a process referred to as metastasis, according to a new study by investigators from Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center (MSK). The discovery of the underlying mechanisms of how copper depletion may help reduce metastasis in breast cancer will help inform the design of future clinical trials.
In a series of research papers from 2013 to 2021, Weill Cornell Medicine researchers showed that in a phase II clinical trial when patients who had high-risk triple-negative breast cancer (TNBC) were treated with a drug that lowers the levels of copper in their bodies, it prolonged the period of time before their cancer recurred and spread or metastasized.
Many of the biological processes that take place inside cells require metal atoms. Although iron is perhaps more well-known, copper has begun to emerge to be an important player. Copper is required for a process called oxidative phosphorylation (OXPHOS), which cells use to generate energy in organelles called mitochondria. Dr. Mittal showed that metastatic cancer cells in TNBC had high levels of intracellular copper and elevated levels of OXPHOS compared to non-metastatic cells.

https://pubmed.ncbi.nlm.nih.gov/33091507/

Copper metabolism as a unique vulnerability in cancer 2021

Although dietary copper is required in trace amounts, sufficient quantities of this metal are needed to sustain growth and development in humans and other mammals. However, copper is also a rate-limiting nutrient for the growth and proliferation of cancer cells.

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2023.1209156/full

Copper in cancer: from limiting nutrient to therapeutic target. 2023

As an essential nutrient, copper's redox properties are both beneficial and toxic to cells. Therefore, leveraging the characteristics of copper-dependent diseases or using copper toxicity to treat copper-sensitive diseases may offer new strategies for specific disease treatments. In particular, copper concentration is typically higher in cancer cells, making copper a critical limiting nutrient for cancer cell growth and proliferation. Hence, intervening in copper metabolism specific to cancer cells may become a potential tumor treatment strategy, directly impacting tumor growth and metastasis.

Copper levels are higher in many tumor tissues than in normal tissues, and serum copper concentrations are also higher in many tumor patients than in normal individuals. Treatment with oral copper chelators has been shown to inhibit tumor growth and metastasis in animal cancer models and human patients (8).

Copper is the third most abundant essential trace element in the human body, following zinc and iron. The average copper content in an adult human body is about 80mg, with the highest concentrations found in tissues such as the eyes, heart, liver, and brain (41). Typically, the serum copper concentration in healthy adults ranges from 70-110 μg/dL (42). About 5% of the total copper content in the body is found in the serum, with approximately 95% bound to ceruloplasmin (CP). Copper is mainly absorbed into the body through the small intestine (43). According to recommendations, adults should ingest 0.9mg of copper daily. The average diet of most individuals can meet or exceed this requirement (44).

The above studies suggest that elevated copper concentrations can promote tumor growth by enhancing mitochondrial energy metabolism, causing misfolding of tumor-associated proteins, inducing upregulation of tumor-associated pathway signaling and affecting autophagy kinase activity.

Application of elesclomol to colon cancer cells significantly increased the level of Cu2+ in mitochondria, increased oxidative stress pressure within cells, and caused ferroptosis (154).

https://pubmed.ncbi.nlm.nih.gov/36089608/

Elesclomol: a copper ionophore targeting mitochondrial metabolism for cancer therapy 2022

Elesclomol is an anticancer drug that targets mitochondrial metabolism. In the past, elesclomol was recognized as an inducer of oxidative stress, but now it has also been found to suppress cancer by inducing cuproptosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10589935/

Elesclomol, a copper-transporting therapeutic agent targeting mitochondria: from discovery to its novel applications 2023

Elesclomol (ELC) is a mitochondrion-targeting copper ionophore developed as a chemotherapeutic agent. This bis(thiohydrazide) amide binds to copper(II) in a 1:1 ratio [12] in the extracellular environment, generating a membrane-permeable complex that can enter and transport copper to mitochondria. After the reduction of copper(II), copper(I) is released in mitochondria [13].

https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-024-02696-x

Rationally designed catalytic nanoplatform for enhanced chemoimmunotherapy via deploying endogenous plus exogenous copper and remodeling tumor microenvironment. 2024

Tumor chemodynamic therapy (CDT) make use of Fenton or Fenton-like reactions to produce a large number of hydroxyl radicals (·OH), thereby killing tumor cells [17]. Metal ions with Fenton effect can promote hydrogen peroxide (H_2O_2) to catalyze the formation of hydroxyl radical (·OH), and induce tumor cell apoptosis and necrosis. Among these, iron-based nanomaterials have been widely reported to be used for chemical dynamic treatment of tumors. Iron based nanomaterials mainly utilize the Fenton reaction mediated by excessive ferrous ions to yield highly toxic ·OH from H_2O_2. Magnetic iron oxide nanoparticles have gained widespread attention because of their biological safety and excellent magnetic resonance imaging performance [18]. Later research found that the Fenton reaction catalyzed by magnetic iron oxide only occurs under high acidic conditions (pH 2 ~ 4), and ferrous ions are easily oxidized in the air or biological system, especially in the blood system, resulting in the loss of Fenton catalytic performance. Inspiringly, cuprous ion (Cu^{1+}) demonstrates a high catalytic activity in mild acid or even neutral environment, and thus copper-based Fenton catalyst holds a great promise in developing novel tumor treatment reagents [19].

Despite abnormally high expression of hydrogen peroxide in the tumor microenvironment [20], however, an increasing number of reports have indicated that endogenous H_2O_2 still cannot meet the requirement of chemical kinetic reactions to produce sufficient ·OH for high efficient CDT [21, 22]. Therefore, Given CDT efficiency is highly dependent on the concentration of H_2O_2, several literature have put forward Fenton-type metal peroxide nanoagents for more active CDT via self-supplied H_2O_2 in tumor acidic microenvironment [23]. Among these, copper peroxide (CP) nanoparticles, reportedly, the first proposed Fenton-type metal peroxide nanomaterial, exhibit a high efficient CDT by virtue of high efficient Fenton catalytic reaction rate of cuprous ions and self-supporting H_2O_2 in tumor acidic microenvironment [23].

Inefficient intracellular H_2O_2 content is one of the major barriers to achieve satisfactory chemodynamic therapy (CDT) efficacy. To surmount these obstacles, researchers have come up with various optimized CDT agents.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10076572/

Regulatory roles of copper metabolism and cuproptosis in human cancers. 2023

Copper is thought to have a great connection with cancer, such as elevated levels in cancer tissue and serum. Copper also affects tumor progression by affecting angiogenesis, metastasis and other processes. Notably, cuproptosis is a novel form of cell death that may provide novel targeting strategies for developing cancer therapy. Copper chelators and copper ionophores are two copper coordinating compounds for the treatment of cancer.

In recent years, a novel form of cell death induced by intracellular copper, discovered by Tsvetkov and co-workers (15), which is distinct from oxidative stress-related cell death, is a type of copper-dependent cell death, termed cuproptosis.

In fact, copper in the human body has a great association with cancer, and there are a large number of medical studies showing that the serum copper levels in cancer patients, as well as in tumor tissues, can be higher or lower (mostly high) compared with normal individuals (Tables 1, 2). When tumor is removed, serum copper return to comparable levels with healthy individuals (13). In several serum medical detections of breast cancer patients, it was found that copper levels were significantly elevated in the serum of breast cancer patients compared with the healthy population (51). Similarly, elevated levels of copper have been reported in the serum of patients with oral cancer (47), gallbladder cancer (46), liver cancer (49), pancreatic cancer (57), and prostate cancer (61). Serum copper levels were found to be decreased in the serum of patients with certain cancers, such as colorectal cancer (56) and endometrial cancer (68).

Copper is redox active and easily interconverts between Cu^{+} and Cu^{2+}. Many important enzymes utilize this property of copper to exert their functions in redox reactions in living organisms (69). Because copper is capable of generating excess ROS, copper transporters and chaperones have evolved to regulate copper uptake, efflux, and distribution within cells (33). Dysregulation of copper metabolism may lead to oxidative stress, such as decreased SOD1 activity and increased

superoxide anion in different animal models (90, 91). Copper deficiency may also increase oxidative stress in mitochondria by inhibiting cytochrome c oxidase activity (92)
Ceruloplasmin is involved in copper metabolism, which is the main carrier of copper in the human body, and about 90% of copper in plasma is found in ceruloplasmin. In addition, ceruloplasmin is a multi-copper oxidase that plays an important role in iron homeostasis (101). When Fe2+ exported from ferroportin, the sole iron exporter, ceruloplasmin promotes cellular iron export by oxidizing iron ion from Fe2+ to Fe3+ (102). Although ceruloplasmin synthesis and secretion are not affected by copper levels, copper deficiency may result in decreased ceruloplasmin stability and activity (103). Ceruloplasmin is also closely linked to cancer, and studies have indicated that significant ceruloplasmin gene expression occurs in many tumors and that the overall incidence of cancer is positively correlated with serum ceruloplasmin levels and may be able to serve as a prognostic marker in some cancers (104–107).
Recently, a novel mode of cell death was discovered by Tsvetkov et al. (15). It is a copper-dependent, regulated, distinct from other known cell death regulatory mechanisms, and this copper-dependent manner of death has been termed “cuproptosis”. Heavy metal overload such as iron will cause deleterious effect on cells. An example is ferroptosis, an iron-dependent form of cell death caused by unrestricted lipid peroxidation (124). Cuproptosis results from mitochondrial stress. Copper can directly bind to ester acylated components of the tricarboxylic acid cycle, with subsequent aggregation of copper bound lipidated mitochondrial enzymes and loss of iron sulfur protein clusters, finally leading to the occurrence of cuproptosis (15).

https://www.ncbi.nlm.nih.gov/books/NBK557456/
Copper Toxicity. 2023
Copper is a trace element (minerals required in amounts 1 to 100 mg/day by adults) found in high concentrations in the brain, liver, and kidney. However, because of their size, bone and muscle contain more than half of the copper in the body.[1] Copper is bound to ceruloplasmin in the liver, which transports the copper from the liver to the peripheral tissues.

https://pubmed.ncbi.nlm.nih.gov/25194954/
The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease. 2014
Tetrathiomolybdate (TM) is a unique anticopper drug developed for the treatment of the neurologic presentation of Wilson's disease, for which it is excellent. Since it was known copper was required for angiogenesis, TM was tested on mouse cancer models to see if it would inhibit tumor growth based on an antiangiogenic effect. TM was extremely effective in these models, but all the tumors in the models started small in size - micrometastatic in size. Later, TM was tested in numerous human cancer trials, where it showed only modest effects. However, the mouse lesson of efficacy against micro disease was forgotten - all the trials were against bulky, advanced cancer. Now, the mouse evidence is coming back to life. Three groups are curing, or having major efficacy of TM, against advanced human cancers, heretofore virtually incurable, particularly if the cancer has been reduced to no evidence of disease (NED) status by conventional therapy. In that situation, where the remaining disease is micrometastatic, TM therapy appears to be curative. We have designed and initiated a study of TM in canine osteosarcoma at the micrometastatic phase to help put these findings on a firm scientific basis. TM also has major anti-inflammatory properties by inhibiting copper dependent cytokines involved in inflammation. This anti-inflammatory effect may be involved in TM's anticancer effect because cancers, as they advance, attract inflammatory cells that provide a plethora of additional proangiogenic agents.

https://pubmed.ncbi.nlm.nih.gov/32600223/
Cancer Pro-oxidant Therapy Through Copper Redox Cycling: Repurposing Disulfiram and Tetrathiomolybdate. 2020
Background: Copper (Cu) is a transition metal active in Fenton redox cycling from reduced Cu+ and H2O2, to oxidized Cu2+ and the hydroxyl radical (·OH) highly reactive oxygen species (ROS). At homeostatic Cu levels, ROS promote cell proliferation, migration, angiogenesis, and wound repair.
Because Cu helps drive tumor cell proliferation by promoting growth factor-independent receptor tyrosine kinase signaling, and Cu-dependent MEK1 involved in oncogenic BRAF-V600E signaling, further augmenting bioavailable Cu may promote ROS overproduction, cancer progression and eventually tumor cell death.
For these reasons, the following clinically approved copper chelators are being repurposed as anti-cancer agents: a) ammonium tetrathiomolybdate (TTM) used to treat Wilson's disease (copper overload) and Menkes disease (copper deficiency); b) Disulfiram (DSF), used against alcoholism, since it inhibits Aldehyde Dehydrogenase (ALDH1) enzyme, important in ethanol detoxification, and a key target against cancer stem cells.

https://pubmed.ncbi.nlm.nih.gov/39194715/
Is Copper Still Safe for Us? What Do We Know and What Are the Latest Literature Statements? 2024
Copper (Cu) is a precious metal and one of the three most abundant trace elements in the body (50-120 mg). It is involved in a large number of cellular mechanisms and pathways and is an essential cofactor in the function of cellular enzymes. Both its excess and deficiency may be harmful for many diseases. Even small changes in Cu concentration may be associated with significant toxicity.
The main purpose of this article is to review the literature with regard to both the healthiness and toxicity of copper to the human body. A secondary objective is to show its widespread use and sources, including in food and common materials in contact with humans. Its biological half-life from diet is estimated to range from 13 to 33 days. The retention or bioavailability of copper from the diet is influenced by several factors, such as age, amount and form of copper in the diet, lifestyle, and genetic background. The upper limit of normal in serum in healthy adults is approximately 1.5 mg Cu/L, while the safe upper limit of average intake is set at 10-12 mg/day, the reference limit at 0.9 mg/day, and the minimum limit at 0.6-0.7 mg/day. Cu is essential, and in the optimal dose, it provides antioxidant defense, while its deficiency reduces the body's ability to cope with oxidative stress.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113679/
Copper levels in plasma and free serum copper levels are known to elevate with aging and to be elevated in AD brains (Noda et al. 2013; Eskici and Axelsen 2012).
Some authors demonstrated that free copper (also known as NCBC or non-ceruloplasmin-bound Cu) is elevated in the blood of AD patients, negatively correlates with cognition, and predicts the rate of loss of cognition (Arnal et al. 2013). Other studies suggest that copper can promote amyloid β aggregation. In addition, unusually high concentration of copper (400 μM) has been observed in Alzheimer’s senile plaques.

https://pubmed.ncbi.nlm.nih.gov/38833473/
Cu(II) complex that synergistically potentiates cytotoxicity and an antitumor immune response by targeting cellular redox homeostasis 2024
Upon entering tumor cells, this Cu(II) complex enhances the production of intracellular radical oxidative species while concurrently depleting glutathione (GSH). As the result of heightening cellular oxidative stress, **Cu-1** gives rise to a relatively high cytotoxicity to cancer cells, whereas normal cells with low levels of GSH are relatively unaffected.

https://pubmed.ncbi.nlm.nih.gov/38555819/
The copper (II) complex of salicylate phenanthroline induces immunogenic cell death of colorectal cancer cells through inducing endoplasmic reticulum stress 2024

In our previous study, Cu(sal)phen was found to have anti-tumor effects, yet its precise mechanism remains unknown.
Results: Cu(sal)phen induced the release of calreticulin (CRT), adenosine triphosphate (ATP) and high mobility group box 1 (HMGB1), the main molecular markers of ICD, by promoting the accumulation of ROS and inducing ERS. Furthermore, Cu(sal)phen promoted the maturation of dendritic cells (DCs) and activation of $CD8^+$T cells, as well as the secretion of interleukin-12 (IL-12) and interferon-γ (IFN-γ), while downregulating transforming growth factor-β (TGF-β) levels, thereby activating the anti-tumor immune response.

https://pubs.rsc.org/en/content/articlelanding/2020/dt/d0dt01742f
A simultaneously GSH-depleted bimetallic Cu(ii) complex for enhanced chemodynamic cancer therapy 2020
A bimetallic Cu(II) complex as a novel antitumor chemodynamic therapy agent with glutathione (GSH) depletion properties is successfully synthesized and well characterized. In tumor cells, the Cu2+ ions of the complex are reduced to Cu+ ions by GSH and then catalyzed by the overexpressed H2O2 to generate highly cytotoxic hydroxyl radicals (˙OH) that kill cancer cells. The complex is quickly taken up by cancer cells and distributed in multiple organelles including mitochondria and the nucleus. The complex demonstrates good cytotoxicity toward various cancer cell lines. However, its toxicity toward normal cells is significantly lower than that toward cancer cells due to the limited expression of H2O2. In addition, the complex could arrest the cell cycle of the G0/G1 phase, thereby inducing apoptosis rather than necrosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10926878/
Glutathione Depletion-Induced ROS/NO Generation for Cascade Breast Cancer Therapy and Enhanced Anti-Tumor Immune Response 2024
Cu_2O was incorporated into BP to exhaust the overexpressed intracellular GSH in cancer cells via the Fenton reaction, thereby decreasing ROS consumption. Apart from being used as biocompatible carriers, BP nanoparticles served as sonosensitizers to produce excessive ROS under ultrasound irradiation.

https://pubmed.ncbi.nlm.nih.gov/35929814/
Copper-Catalyzed Glutathione Oxidation is Accelerated by the Anticancer Thiosemicarbazone Dp44mT and Further Boosted at Lower pH 2022
Glutathione (GSH) is the most abundant thiol in mammalian cells and plays a crucial role in maintaining redox cellular homeostasis. The thiols of two GSH molecules can be oxidized to the disulfide GSSG. The cytosolic GSH/GSSG ratio is very high (>100), and its reduction can lead to apoptosis or necrosis, which are of interest in cancer research. Cu^{II} ions are very efficient oxidants of thiols, but with an excess of GSH, $Cu^{I}_{n}(GS)_{m}$ clusters are formed, in which Cu^{I} is very slowly reoxidized by O_2 at pH 7.4 and even more slowly at lower pH.

https://www.nature.com/articles/s41571-024-00876-0
Targeting cuproplasia and cuproptosis in cancer 2024
Copper, an essential trace element that exists in oxidized and reduced forms, has pivotal roles in a variety of biological processes, including redox chemistry, enzymatic reactions, mitochondrial respiration, iron metabolism, autophagy and immune modulation; maintaining copper homeostasis is crucial as both its deficiency and its excess are deleterious. Dysregulated copper metabolism has a dual role in tumorigenesis and cancer therapy. Specifically, cuproplasia describes copper-dependent cell growth and proliferation, including hyperplasia, metaplasia and neoplasia, whereas cuproptosis refers to a mitochondrial pathway of cell death triggered by excessive copper exposure and subsequent proteotoxic stress (although complex interactions between cuproptosis and other cell death mechanisms, such as ferroptosis, are likely and remain enigmatic). In this Review, we summarize advances in our understanding of copper metabolism, the molecular machineries underlying cuproplasia and cuproptosis, and their potential targeting for cancer therapy.
Ferredoxin 1 has a key role in cuproptosis by reducing Cu(II) to Cu(I) in mitochondria, facilitating excessive protein lipoylation and subsequent aggregation related to mitochondrial respiration.
Both copper chelators and copper ionophores can suppress tumour growth and enhance chemotherapy, immunotherapy or radiation therapy by suppressing cuproplasia and inducing cuproptosis, respectively.

https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2023.1203447/full
Targeting copper metabolism: a promising strategy for cancer treatment 2023
This review article explores the potential of targeting copper metabolism as a promising strategy for cancer treatment. Excessive copper accumulation in cancer cells has been associated with tumor growth and metastasis. By disrupting copper homeostasis in cancer cells and inducing cell death through copper-dependent mechanisms (cuproplasia and cuprotosis, respectively), therapies can be developed with improved efficacy and reduced side effects. The article discusses the role of copper in biological processes, such as angiogenesis, immune response, and redox homeostasis. Various approaches for targeting copper metabolism in cancer treatment are examined, including the use of copper-dependent enzymes, copper-based compounds, and cuprotosis-related genes or proteins. The review also explores strategies like copper chelation therapy and nanotechnology for targeted delivery of copper-targeting agents.
Numerous studies showed that accumulation of copper ions can cause cytotoxicity, increasing the intracellular copper concentration can induce specific killing effect (Kahlson and Dixon, 2022).
Copper in the diet is mainly stored in the muscular and bone tissues, with 20% stored in the liver and 10% in the blood (Miranda et al., 2010). Copper is absorbed in the form of Cu2+ and then reduced to Cu + by reductases on the surface of epithelial cells in the digestive tract .
Cancer cells have been shown to have higher copper levels compared to normal cells. Thus, by reducing the amount of copper available to cancer cells, it is possible to sensitize them to chemotherapy and radiotherapy.
Copper compounds have been studied for their potential use in cancer treatment, as cancer cells are known to have a higher copper uptake and retention compared to normal cells. The idea behind using copper compounds in cancer treatment is to selectively target cancer cells by inducing excessive copper accumulation in them, leading to cuprotosis. Several copper compounds have been studied for their ability to induce cell death in cancer cells.
Copper oxide nanoparticles
CuO NPs are nanoparticles composed of copper and oxygen atoms (Singh et al., 2016). They have a high surface area-to-volume ratio, which allows them to interact more efficiently with cells and tissues.
Copper-bis(thiosemicarbazone) complexes
These complexes consist of a copper ion coordinated with two thiosemicarbazone ligands, which can bind to intracellular copper and induce oxidative stress and disruption of copper homeostasis, ultimately leading to cancer cell death.
Copper (II) complexes of curcumin
They are copper-containing compounds that consist of a copper ion coordinated with curcumin ligands. Copper (II) complexes of curcumin have been shown to have enhanced anti-cancer activity compared to curcumin alone due to their ability to induce cancer cell death via multiple mechanisms, including the generation of reactive oxygen species, inhibition of cell proliferation, and induction of apoptosis. Studies have shown that copper (II) complexes of curcumin can selectively target cancer cells while sparing normal cells, indicating their potential as cancer therapeutics with reduced toxicity.
Copper-doxorubicin conjugates
The goal of these conjugates is to improve the efficacy and reduce the toxicity of doxorubicin by enhancing its selectivity and delivery to cancer cells via multiple

mechanisms, including DNA damage, inhibition of topoisomerase II, and generation of reactive oxygen species. Study showed that the hybrid nanoparticles had increased cytotoxicity against liver cancer cells compared to doxorubicin alone, the hybrid nanoparticles were found to selectively accumulate in cancer cells due to the targeting effect of folic acid while sparing normal cells (Xu et al., 2020).

Targeting copper-dependent enzymes

Lysyl oxidase (LOX)

It is a Copper-dependent enzyme that is involved in the cross-linking of collagen and elastin fibers in the extracellular matrix, which is important for the formation and stabilization of blood vessels. LOX has been shown to promote tumor growth and metastasis by promoting angiogenesis and enhancing the invasiveness of cancer cells.

Superoxide dismutase (SOD)

It is a copper-dependent enzyme that plays an important role in protecting cells from oxidative stress (Bresciani et al., 2015). In cancer treatment, one strategy for targeting SOD in cancer treatment involves the use of SOD inhibitors, which can increase the levels of reactive oxygen species (ROS) in cancer cells and induce cell death.

Copper's proteasome-inhibitory anticancer strategy

It refers to the use of copper-chelating agents such as clioquinol and tetrathiomolybdate to disrupt the function of proteasomes in cancer cells (Zhang et al., 2017). Proteasomes are large protein complexes that play a critical role in the degradation and recycling of intracellular proteins, including those involved in cell cycle regulation, DNA repair, and apoptosis. Cancer cells are known to have high levels of proteasome activity, which helps them to survive and proliferate. By chelating copper ions, clioquinol and tetrathiomolybdate can inhibit proteasome activity in cancer cells, leading to the accumulation of toxic protein aggregates and ultimately causing cell death (Wehbe et al., 2017).