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Review Article

Cuproptosis: A Copper-Triggered Unique Cell Death Targeting Cancer

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Abstract

A recently discovered type of copper-driven cell death is regarded as Cuproptosis. The significance of copper and copper-triggered cell death in the development of malignancies has garnered attention recently. Cuproptosis has shown remarkable promise for cancer therapy, which has sparked a great deal of interest in the cancer research community. Treatments based on copper have the potential to treat malignancies that are resistant to chemotherapy by impeding the growth of the tumor. We offer a critical examination of copper homeostasis and the part copper dysregulation plays in the onset and spread of cancer in this review. After outlining the fundamental molecular underpinnings of Cuproptosis and its connection to cancer, the present state of knowledge regarding copper-based cancer treatment agents - copper chelators, copper ionophores, and copper complexes-based dynamic therapy is summarized. We also provide an overview of the latest research on the use of copper ionophores and complexes-based medicines to reduce tumor treatment resistance in various cancer types. We also go over the small-molecule substances and nanoparticles (NPs) that have the potential to induce Cuproptosis in cancer cells, which will provide fresh insight into the future development of Cuproptosis-inducing anticancer medications. Ultimately, the key ideas and urgent issues surrounding Cuproptosis that need to be addressed in further research were covered. Targeting Cuproptosis may be a potential anticancer therapy and treatment approach to overcome drug resistance in cancer, according to this review article.

Keywords: Cuproptosis, cancer, chemo-resistance, malignancies, Cu homeostasis, Cu chelators

Introduction

Tsvetkov and associates coined the word Cuproptosis in 2022 to describe a particular type of controlled, copper (Cu)-induced cell death.[1] Cuproptosis is a type of cell death brought on by an accumulation of Cu in the mitochondria. This causes lipoylated dihydrolipoamide S-acetyltransferase (DLAT) to aggregate and is linked to the TCA cycle in the mitochondria. This results in proteotoxic stress and, eventually, cell death.[2] Cuproptosis generally arises in energy-producing cells that largely use OXPHOS, or oxidative phosphorylation, as their primary metabolic pathway. Iron-sulphur cluster (Fe-S) protein depletion and the aggregation of lipoylated mitochondrial enzymes DLAT are indicators of cuproptosis.[3] Cells are poisonous to copper in excess or insufficient amounts.[4] Research is beginning to indicate that cancer patients have far greater levels of Cu in their serum and tumor tissues than do healthy individuals.[5] A number of tumours have high Cu levels, which are linked to the genesis, severity, and advancement of cancers. A growing body of research has demonstrated that copper promotes tumours primarily through the induction of drug resistance, stimulation of angiogenesis, enhancement of cell proliferation (cuproplasia), and metastasis, among other mechanisms.[6] Since the term Cuproptosis was coined, scientists have investigated the part that copper and copper-triggered cell death play in the pathophysiology of malignancies, bringing copper back into the forefront of the field. Cuproptosis has attracted a lot of attention in the field of cancer research lately, in part because of its immense therapeutic potential. Treatments based on copper are essential in preventing the formation of malignancies and have opened up new avenues for the treatment of tumours that are resistant to chemotherapy. Growing data indicates that copper-based therapy inhibits the growth of cancers, offering fresh hope for the treatment of chemotherapy-resistant malignancies. After discussing the fundamental molecular underpinnings of Cuproptosis and its function in cancer, the current understanding of employing copper-based medicines (copper chelators, copper ionophores, and copper complexes-based dynamic therapy) to target Cuproptosis for cancer treatment is summarized. Additionally, we provide an overview of the latest research on the use of small molecules, nanoparticles (NPs), and nanomaterials in dynamic therapy to induce cuproptosis in various cancer types in order to suppress tumor chemotherapy resistance.[7] Lastly, we address key ideas and urgent Cuproptosis-related issues that need to be the focus of further study. According to this review paper, Cuproptosis targeting may be a potential anticancer therapy and therapeutic approach for overcoming drug resistance.

Molecular mechanism of Cuproptosis

Tsvetkov and associates presented the idea of Cuproptosis in 2022. Disulfiram (DSF) has been demonstrated to exhibit anti-cancer activity; cell death is induced by a copper-based anti-cancer compound;[8] copper induces non-apoptotic programmed cancer cell death;[8] elesclomol induces apoptosis in cancer cells,[8] ferredoxin (FDX1) and lipoyl synthase (LIAS) were found to be important regulators of Cu toxicity.[9] copper preferentially delivers copper to the mitochondria to kill cancer cells.[10] copper enhances the anti-tumor action of disulfiram.[8] based on significant discoveries on copper-induced apoptosis, which offer the fundamental knowledge of Cuproptosis. As seen in Figure 1, Cuproptosis is distinct from necroptosis, apoptosis, pyroptosis, and ferroptosis.[11] Copper is a trace metal that is necessary for life as an essential micronutrient. Redox active Cu serves as a crucial structural or catalytic cofactor for enzymes and is necessary for a variety of biological processes in practically all organisms, such as signal transmission, bio compound synthesis, OXPHOS, connective tissue cross-linking, ROS detoxification, and bio compound synthesis.[12] Cu is sometimes cytotoxicity. Iron-sulphur cofactors are disrupted and harmful ROS production is induced by Cu overload through Cu-mediated Fenton reactions. Chronic or extended exposure to copper causes toxicity, and elevated intracellular copper is linked to a number of illnesses, including but not limited to malignancies. Cu is essential for the growth and spread of tumors.[13] The chemical pathways behind copper-induced toxicity and copper-induced cell death, however, are still poorly understood. Furthermore, the way that cells respond to Cu toxicity is not entirely described by the recognized cellular machinery and enzyme targets for Cu. Tsvetkov made the discovery of Cuproptosis in an effort to comprehend how copper build-up results in cellular damage. Tsvetkov reported on Cu-dependent death while delving into the mechanism underlying elesclomol's (Cu ionophores anticancer action. They discovered that in a mouse model of multiple myeloma, ES lessens the cancer cells' resistance to the damage caused by proteasome inhibitors. The process by which ES-bound Cu2+ interacts with the mitochondrial enzyme ferredoxin 1 (FDX1) and is reduced to Cu+ raises ROS levels. Lipid peroxidation was once thought to be the cause of ES's lethality.[14] Cuproptosis, a distinct kind of Cu-dependent cell death characterized by the aggregation of lipoylated mitochondrial enzymes and a loss of Fe-S proteins, was termed after this discovery in 2022.[1] Tsvetkov et al.'s study made significant progress in defining how copper excess impairs mitochondrial function by discovering that copper-induced toxicity entails the disruption of particular mitochondrial metabolic enzymes.[1] Ionophores have the ability to carry extracellular Cu2+ to the mitochondria. Cu2+ is reduced to Cu+ by the FDX1. Cu+ concentration increases cause lipoylated DLAT to directly attach to it. This causes the lipoylated proteins to aggregate and destabilize Fe-S cluster proteins, which causes proteotoxic stress and ultimately cuproptosis.[1] Interestingly, in some cancer cell lines, pharmacological or genetic inhibition of ferroptosis, necroptosis, and apoptosis was unable to prevent ES-Cu complex-induced cell death. N-acetylcysteine, α-tocopherol, ebselene, and JP4-039 are among the other antioxidants that were unable to reverse the growth inhibition mediated by ES-Cu, indicating that ROS, especially mitochondrial ROS, are not necessary for Cuproptosis. Interestingly, by chelating intracellular Cu, the hydrophilic antioxidant glutathione (GSH) prevents ES-Cu-induced damage. These findings imply that Cuproptosis is distinct from other cell death pathways that have been previously discovered.[1] According to Tsvetkov et al., there is a direct correlation between copper poisoning activity and mitochondria. They discovered that compared to cells that rely on glucose-induced glycolysis, lung cancer cells that depend on galactose-mediated mitochondrial respiration were almost 1000 times more sensitive to ES-Cu-induced growth suppression. Therefore, Cuproptosis is stopped by rotenone, antimycin A (which inhibits respiratory chain complexes I and III), UK5099 (which inhibits mitochondrial pyruvate uptake), or genetic inhibiting complex I. The sensitivity of cancer cells to Cuproptosis is decreased by hypoxia (1% O2), which forces cells to rely on glycolysis rather than OXPHOS. However, ES-Cu has no effect on basal or adenosine 5′-triphosphate-linked respiration in cells. This distinguishes ferroptosis, which necessitates pyruvate oxidation and glucose absorption, from Cuproptosis. Therefore, there are specific changes in energy metabolism and mitochondrial function associated with Cuproptosis and ferroptosis. When combined, Cuproptosis represents a novel type of mitochondrial-induced, oxidative stress-independent, and Cu-dependent cell death.

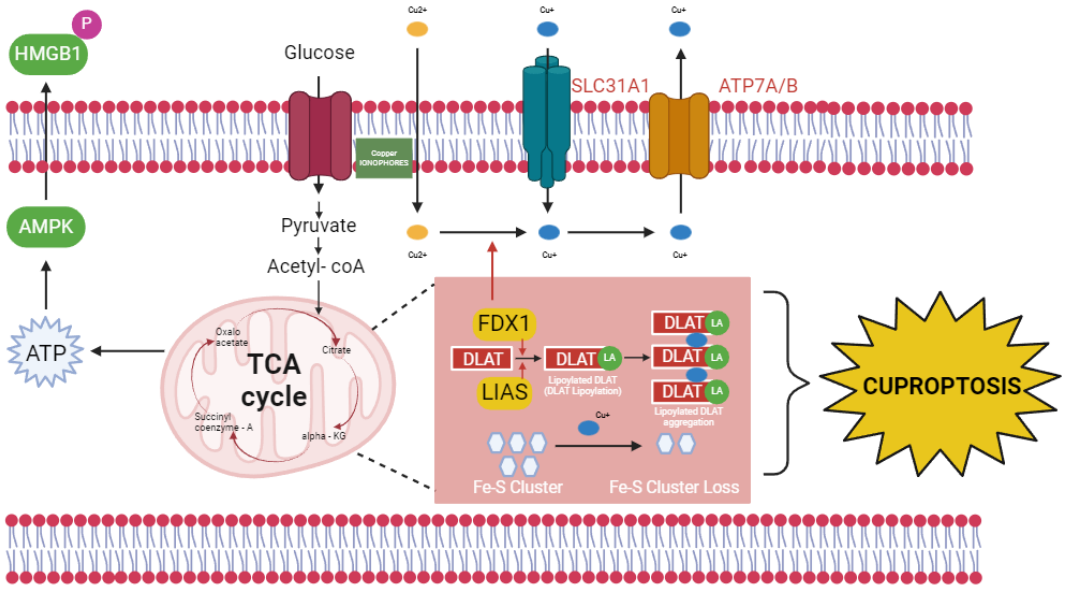

Figure 1: molecular mechanism of Cuproptosis

Application of copper-based agents to treat cancer by inducing Cuproptosis

Copper chelators

Two major strategies to address Cu homeostasis are Cu chelators that bind to Cu and decrease Cu bioavailability. According to Gupte and Mumper (2009), Cu plays a crucial part in the metastatic cascade that occurs inside tumor cells and the surrounding environment. This suggests that depleting Cu may be a desirable therapeutic approach for the treatment of cancer.[15] Cu chelators are an appealing target for anti-cancer treatments since they decrease tumor growth in cultured cell models and animal tumor models,[16] suppress angiogenesis, and hinder cancer growth and spread.[17]Baldari et al. identified D-penicillamine (D-Pen), ammonium tetrathiomolybdate (TTM), and trientinetriethylenetetraminee dihydrochloride as representative examples of Cu chelators with anti-cancer activity, along with their chemical structures and clinical trials.[18] According to Brewer et al. (1991), TTM, a copper chelating agent, dramatically reduces copper absorption. In 1999, Brewer and Merajver published the first report on TTM's anticancer properties. TTM has anti-tumor actions by reducing NF-kB activity, down regulating HIF-1α, and lowering SOD1 activity, which all work together to prevent angiogenesis. Moreover, TTM inhibits ATOX1 copper chaperone action by binding the cytoplasmic copper transport protein ATOX1, forming a stable TTM-ATOX1 complex that transfers Cu to LOX.[19]Recent researchhas demonstrated that TTM inhibits MEK1/2 kinase activity by lowering Cu levels, consequently suppressing papillary thyroid and colon cancer as well as BRAFV600E-driven carcinogenesis in melanoma.[20] TTM specifically increases the antitumor activity of BRAFV600E and MEK1/2 inhibitors, including vemurafenib and sorafenib.[20] It has been demonstrated that trientine, a copper chelating agent first created in 1969, reduces Cu-chelating ability in comparison to D-Pen.[5] When high-grade epithelial cells in ovarian cancer patients have platinum resistance, trentin suppresses this resistance.[21]Cu-lowering drugs have the ability to overcome cDDP resistance by up-regulating Sp1 in cultured cells, which enhances human CTR1 expression. This provides a molecular basis for Cu chelators to overcome cDDP resistance in ovarian cancer. Cu chelators have been shown to exhibit antitumor activities against a variety of tumor types, such as head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), breast cancer (BC), hepatocellular carcinoma (HCC), cervical cancer (CC), malignant melanoma (MM), non-small-cell lung cancer (NSCLC), and pancreatic ductal adenocarcinoma (PDAC) (Table 1).

Copper ionophores

Compounds or substances that can increase intracellular copper levels are known as copper ionophores.[5] Using distinct processes, copper ionophores cause cancer cells to die instead of dying from oxidative stress, necrosis, or apoptosis. Cuproptosis can be induced by copper ionophores. The extra intracellular Cu2+ is transported by elsclomol into the mitochondria, where it is reduced to Cu+ by ferredoxin 1 (FDX1). Cu+ concentration increases cause lipoylated DLAT to directly attach to it. This causes lipoylated proteins to aggregate and destabilize Fe-S cluster proteins, which causes proteotoxic stress and cuproptosis.[1] The copper ionophores that have the ability to eradicate cancer are elsclomol (ES), Disulfiram (DSF), and NSC319726.Copper is essential to elesclomol's anticancer actions. It is well known that elesclomol has an anticancer effect by inducing mitochondrial oxidative stress and consequent death via the Cu II-I redox cycling pathway.[22]There is growing evidence that intracellular copper build-up may also facilitate ferroptosis.[23] Cu2+ is maintained inside cells due to the rise in mitochondrial Cu2+ concentration and down regulation of ATP7A expression caused by ES.[13] This accumulation of ROS ultimately results in the destruction of SLC7A11 and ferroptosis in CRC cells. Fe2+ might be directly bonded by ES.[24] By turning on the copper-dependent iron import machinery; ES raised the amount of copper in cells and indirectly raised the quantities of iron in mitochondria. Dysregulation of iron homeostasis results from the use of ES-Cu2+ derived-Cu2+ that pumps into the Golgi lumen to metalate the iron transport multicopper oxidase Fet3, which oxidizes Fe2+ to Fe3+ and permits mitochondrial iron enrichment via the iron importer transferrin receptor 1 (TfR1). Anti-proliferation, reversal of drug resistance, and immunomodulatory action are the anti-cancer mechanisms of DSF for cancer treatment.[25] DSF can cause ferroptosis by down regulating GPX4, which in turn can cause apoptosis.[26]Cuproptosis can also be induced by DSF.[1]The possibility that these copper ionophores may target drug-resistant cancer cells as well as cancer stem cells provides a significant motivation for their development.

Copper complexes-based dynamic therapy

Solid tumours can be effectively treated with a unique dynamic therapy mediated by Nanosensitizers. Nanosensitizers with special physicochemical properties that react to highly penetrating excitations have been developed in recent years to kill a variety of deep-seated malignant tumours. These techniques include photo thermal therapy (PTT), X-ray-induced photodynamic therapy (PDT), [27] chemo dynamic therapy (CDT), [28] and others. Many studies have reported on the use of copper in the treatment of cancer, including CDT, [29] PDT,[30]PTT,[31] chemotherapy[32] or a mix of these treatments.[33]

Small compounds inducing Cuproptosis in cancer

Cuproptosis is a unique cell death mechanism that has generated a lot of interest in the field of cancer research because, like ferroptosis, it may be able to reverse cancer drug resistance and provide novel therapeutic regimens by inhibiting tumor cell proliferation.[34] It's interesting to note that in preclinical settings, newly developed drugs have been shown to encourage Cuproptosis. In colorectal cancer primary tumor tissues, the genes FDX1, DLAT, SDHB, and DLST were down-regulated.[35]A better prognosis is shown in patients whose tumor tissues express more of these genes, indicating a potential role for Cuproptosis in the advancement of colorectal cancer.[36] In CRC cells, ES-Cu treatment dramatically reduces cell viability. TTM significantly inhibits Cuproptosis as copper chelators, suggesting that TTM has a Cuproptosis-inhibiting role. 2-Deoxy-D-glucose, an inhibitor of glucose metabolism, makes cancer cells more susceptible to cuproptosis.[35] Galactose further encourages Cuproptosis. Cuproptosis is markedly aided by octyl itaconate (4-OI). 4-OI inhibits GAPDH-mediated aerobic glycolysis, making cancer cells more susceptible to Cuproptosis. In the meantime, FDX1 silencing inhibited 4-OI's capacity to induce Cuproptosis. 4-In vivo studies, 4-OI increases elesclomol-Cu's anti-tumor activities.[35]Significantly, 4-OI promotes Cuproptosis by inhibiting aerobic glycolysis by targeting GAPDH.[35]Anisomycin (p38MAPK signalling pathway agonist) significantly inhibits the proliferation of ovarian cancer stem cells (OCSCs) in vitro, in a manner similar to that of elesclomol and buthionine sulfoximine (BSO). This suggests that anisomycin may encourage the Cuproptosis of OCSCs.[37] The transcriptional levels of the FeS cluster proteins, PDH complex, lipoid acid pathway, and metallothionein are all markedly decreased by isomycin.[37] Curcumin has a cell-specific effect on ferroptosis and Cuproptosis in several HCC cells. Curcumin may be a Cuproptosis inducer, according to single-cell transcriptome data analysis.[38]The Cuproptosis-related gene CDKN2A has been linked to HNSCC's malignant tendencies. Strong binding between CDKN2A and plicamycin is revealed by molecular docking investigations and molecular dynamics

simulations. Plicamycin suppresses the progression of HNSCC, indicating that it may be an inducer of Cuproptosis. Sorafenib is the first multi-tyrosine kinase inhibitor approved for treating patients with unrespectable HCC and other cancers.[39] It induces ferroptosis by blocking the activity of the cystine-glutamate transport receptor (system Xc−), which results in GSH depletion. By suppressing the action of the system Xc−, erythrin acts as a ferroptosis inducer, causing GSH to be depleted. According to the most recent research, sorafenib and erastin can increase the amount of copper ionophores ES and ES-Cu-induced Cuproptosis in HCC cells by suppressing the FDX1 protein degradation mediated by mitochondrial matrix-related proteases, which promotes copper dependent lipoylated protein aggregation, and by inhibiting cystine importing, which reduces intracellular GSH synthesis.[40] This significant study indicates that ferroptosis and Cuproptosis interact, and that co-targeting ferroptosis and Cuproptosis with a combination of copper ionophores and inducers of ferroptosis could be a potential therapeutic approach for HCC. These results offer compelling evidence for the dual role of ferroptosis inducers and Cuproptosis inducers. The idea that Cuproptosis inducers or inhibitors, respectively, may function as ferroptosis inducers or inhibitors is alluring.

Nanoparticles (NPs) inducing Cuproptosis in cancer

It is challenging to maintain a high amount of copper in the cytoplasmic fluid to induce Cuproptosis because ATP7A keeps intracellular copper at abnormally low levels.[13] The aforementioned challenges can be solved by nanodrug delivery devices.[41]By causing Cuproptosis, some nanoparticles (NPs) have been investigated as potential anticancer medicines (Fig.2).CuMoO4 nanodots have the potential to cause Cuproptosis in tumor cells, offering a viable nanoplatform for combination cancer therapy.[25]In local cancer therapy, HD/BER/GOx/Cu hydrogel can reduce dose frequency and prevent invasiveness-related problems. In clinical applications, the HD/BER/GOx/Cu hydrogel system can be used to limit tumor growth and shrink breast cancer before surgery. Disulfiram (DSF) that had been released chelated with Cu2+ in situ to produce extremely cytotoxic bis (Diethyldithiocarbamate) copper (CuET), which led to cell death. The Cu+ species that were generated also caused Cuproptosis. DLAT, LIAS, and NPL4 are reduced by Au@MSN-Cu/PEG/DSF. When combined with PTT, Au@MSN-Cu /PEG/DSF efficiently kills tumor cells and stops them from growing. By simultaneously generating Cuproptosis and immunological responses, the intracellular ROS-mediated release of ES and Cu from NP@ESCu kills cancer cells. In vitro Cuproptosis is induced by NP@ESCu transporting Cu. In a mouse model of subcutaneous bladder cancer, NP@ESCu induces Cuproptosis and increases αPD-L1's antitumor activity. In SCLC brain metastatic tumor-bearing mice, TP-M-Cu-MOF/siATP7a inhibits copper trafficking, enhances copper intake, and causes Cuproptosis to improve treatment efficacy.[25]GSH and glucose deficiency makes cancer cells more susceptible to Cuproptosis, which is mediated by GOx@[Cu(tz)]. Increased intracellular H2O2 levels brought on by glucose oxidation stimulates GOx@'s type I PDT effectiveness [Cu (tz)]. In athymic mice with 5637 bladder tumours, GOx@[Cu(tz)] suppresses tumor growth with low systemic damage. A2780 cells were able to undergo Cuproptosis when exposed to Complexes 4 and 6. Cuprous oxide nanoparticle (Cu2O)/TBP-2 Cuproptosis sensitization system (PTC) coated platelet vesicles (PV) can sustain long-term blood circulation and tumor-inhibiting capacity. PTC breaks down quickly in acidic environments, releasing hydrogen peroxides and copper ions in tumor cells.[42]Subsequently, during light irradiation, TBP-2 swiftly penetrates the cell membrane and generates hydroxyl radicals to reduce GSH and prevent copper outflow. PTC raises the quantity of central memory T cells in peripheral blood, inhibits tumor rechallenge, and dramatically reduces lung metastasis by causing Cuproptosis in tumor cells both in vitro and in vivo.[38]Cuproptosis, which is induced in NSCLC by CuET with a reduced reduction potential and reaction inertness with GSH, reverses cisplatin resistance. The anticancer impact of CuET to overcome drug resistance in A549/DDP cells is influenced by intracellular GSH levels. In A549/DDP cells, CuET NPs cause Cuproptosis, as opposed to cisplatin-induced apoptosis. In a tumor model resistant to cisplatin, CuET NPs exhibit strong anticancer efficacy and improved biosafety.[43]

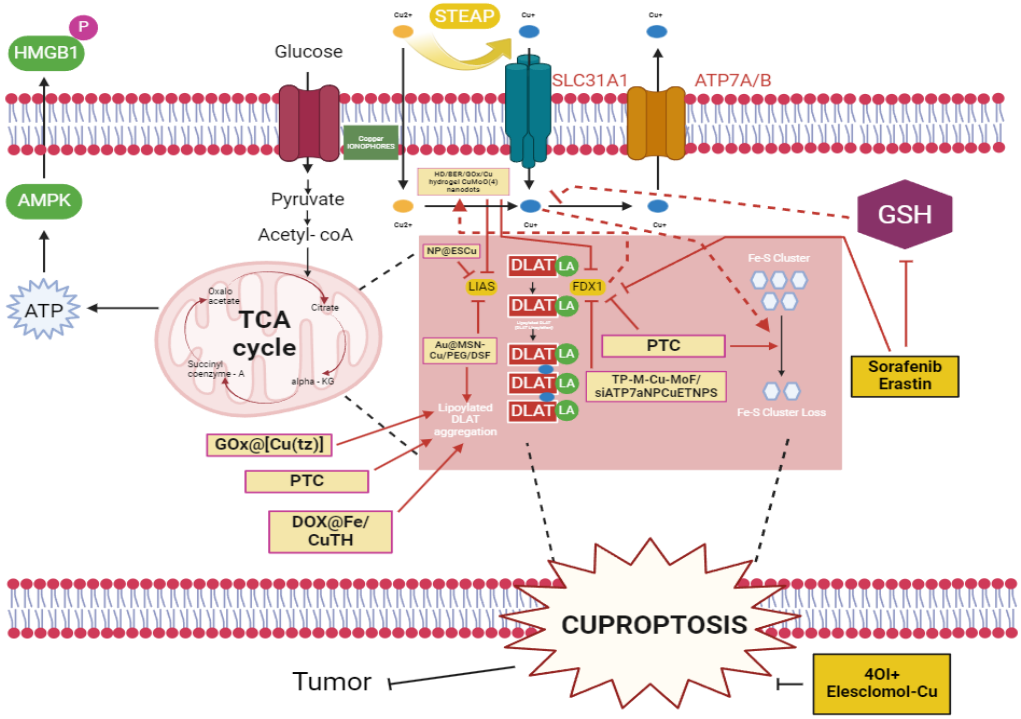

Figure 2: Cuproptosis induction by nano-particles and small compounds to kill cancerous cells

Copper-based agents for chemo-resistance

Overcoming cancer drug resistance via copper-based agents

Chemotherapy, which uses platinum-based antitumor drugs such as carboplatin, oxaliplatin, and cisplatin as the primary agents, is still the mainstay of cancer treatment, despite the development of several innovative strategies in recent years.[44] But the biggest problem with chemotherapy is drug resistance, which also compromises its effectiveness and is still a major cause of anticancer therapy failure, particularly when tumor cells have spread.[45-47]The use of ionophores and transition metal chelators to specifically alter the concentrations of copper, iron, and zinc in cancer cells is one of the new tactics being used to combat chemotherapy drug resistance.[48] A growing variety of medicines based on copper complexes have demonstrated cytotoxicity by specifically targeting cancer cells that are resistant to drugs. Over the past few decades, numerous complexes based on other metals, like copper, have gone through clinical trials in addition to a dozen more platinum compounds.

Overcoming of cancer drug resistance via copper ionophores

According to earlier research, endogenous copper plays a crucial role in dictating the effectiveness and result of chemotherapy drugs. Recent research indicates that drug resistance may be overcome by combining chemotherapeutic drugs with copper ionophores. The potential effects of copper ionophores on chemotherapy drugs include chemosentisizing effects, increased anti-tumor activity, and the ability to overcome chemo resistance in a variety of cancer models, such as acute myeloid leukemia (AML), GBM,[49] bladder cancer,[50] CRC/BC, CC, and non-small cell lung cancer.[51] By causing apoptosis in HCC, DSF increases the antineoplastic activity of 5-fluorouracil (5-FU). This suggests that adjusting the Cu-level can significantly increase the antineoplastic activity of 5-FU.[52]In colorectal carcinoma (CRC) 3D models, the combination of Disulfiram/copper and 5-FU effectively killed cancer cells by down regulating the expression of thymidylate synthase and CD133/CD44, the markers linked to 5-FU resistance. In mouse Pancreas tumours, DSF/Cu increases the anticancer efficacy of radiation with 5-FU or IR plus FOLFRINOX therapy.[53] DSF up regulated actin filament associated protein 1 like 2 (AFAP1L2), which in turn elevated the phosphorylation of proto-oncogene tyrosine-protein kinase SRC. By preventing the phosphorylation of activator of transcription 3 (STAT3) in PDAC cells, DSF causes apoptosis. By reversing DSF-induced enhanced SRC phosphorylation, small molecule inhibitors (PP2, dasatinib) potentiated the anticancer effect of DSF and produced apoptosis. The DS/Cu combination greatly increased the cytotoxicity of gemcitabine and totally reversed the resistance to the drug in the recalcitrant cell lines of breast cancer (BC) and colorectal cancer (CRC). Disulfiram combined with copper (DSF/Cu) particularly reduced the population of ALDH+tumor initiating cells (TIC), while the pan-PI3K inhibitor BKM120 considerably reduced the population of CD44 + /CD24-TIC, possibly by causing apoptosis in triple negative breast cancer (TNBC) cells.DSF/BKM120 enhanced the anticancer activity of Taxol and postponed tumor recurrence in vivo. Tumor model, DSF increases the anticancer activity of radiation and carboplatin.[51]By preventing cancer stemness and causing cervical cancer cells to enter an S-phase, the DSF/Cu combination increases the anticancer efficacy of cisplatin. DSF/Cu selectively causes H292 NSCLC cells to become toxic by increasing the intercellular concentration of Cu. DSF also reduces radiation and chemotherapy resistance in hypoxia and specifically increases the death of non-small cell lung cancer (NSCLC) caused by these treatments. In a xenograft tumor model, DSF increases the anticancer activity of radiation and carboplatin.[51]By inhibiting the expression of aldehyde dehydrogenase 2 (ALDH2), DSF/Cu overcomes microtubule inhibitor resistance, and Cu increases DSF's action in non-small cell lung cancer (NSCLC). In brain TICs resistant to temozolomide and the highly infiltrative quiescent stem-like population, DSF/Cu suppressed tumor at low nanomolar efficacy. In vitro temozolomide activity is enhanced by DSF/Cu, and in patient-derived BTIC models, in vivo survival is prolonged. DSF/Cu functions as a strong proteasome inhibitor in this state, which enhances the effects of radiation and DNA alkylating chemicals by disrupting DNA repair pathways.[49] In vitro temozolomide activity is enhanced by DSF/Cu, and in patient-derived BTIC models, in vivo survival is prolonged. DSF/Cu functions as a strong proteasome inhibitor in this state, which enhances the effects of radiation and DNA alkylating chemicals by disrupting DNA repair pathways.[49] GBM cell lines are killed by DSF in a Cu-dependent manner, and in the presence of Cu, DSF enhanced gemcitabine's antitumor efficacy. In GBM cell lines, DSF/Cu increases reactive oxygen species (ROS), triggers the JNK and p38 pathways, and reduces nuclear factor-kappa B activity. By altering the Bcl2 family, DSF/Cu may start an intrinsic apoptotic pathway. By altering the Bcl2 family, DSF/Cu may start an intrinsic apoptotic pathway. In GBM cell lines, DSF/Cu eliminates the stem-like cell population. These findings suggested that DS/Cu increases ROS generation and inhibits the NF-kB and ALDH pathways, hence promoting the anticancer activity of gemcitabine in GBM stem-like cells. DSF and cisplatin have synergistic effects in bladder cancer because they change the cisplatin efflux transporter ATP7A's cellular location, increase DNA-platinum adducts, and encourage apoptosis. In patient-derived and cell-based xenograft models, micellar DSF-NP (DSF nanoparticles) enhances the anticancer efficacy of cisplatin.[50]By causing apoptosis in cell lines from AML patients with Down syndrome; DSF/Cu overcomes resistance to cytarabine (Ara-C) and bortezomib (BTZ).

Conclusion

This article concludes by reviewing the most recent findings about Cuproptosis involvement in the etiology of malignancies. Cuproptosis has garnered significant attention in cancer research over the last two years because of its anticancer activity, which has the potential to increase the effectiveness of chemotherapy. We talk about using natural substances and nanoparticles to induce Cuproptosis, which kills cancer cells. According to this review paper, Cuproptosis targeting may be a novel anticancer therapy and a way to treat patients who are resistant to medications. One novel kind of RCD that has been shown to be capable of killing cancer cells is Cuproptosis. Consequently, Cuproptosis induction has enormous potential for treating cancer, particularly when combined with traditional chemotherapy. Cuproptosis induction may be a viable treatment plan to eradicate cancer cells and get around drug resistance in the disease.

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Authors Contribution:

- Dr. Trilochan Satapathy and Mohammad Altaf Khan - Preparation of manuscript
- Kalpana Sen and Shailesh Sahu- Diagrammatic representation
- Bharti Pradhan, Abinash Satapathy, and Ayushi Gupta - Review of manuscript
- Ashu Vishwakarma - Grammar correction

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