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Cuproptosis: emerging biomarkers and potential therapeutics in cancers

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The sustenance of human life activities depends on copper, which also serves as a crucial factor for vital enzymes. Under typical circumstances, active homeostatic mechanisms keep the intracellular copper ion concentration low. Excess copper ions cause excessive cellular respiration, which causes cytotoxicity and cell death as levels steadily rise above a threshold. It is a novel cell death that depends on mitochondrial respiration, copper ions, and regulation. Cuproptosis is now understood to play a role in several pathogenic processes, including inflammation, oxidative stress, and apoptosis. Copper death is a type of regulatory cell death(RCD).Numerous diseases are correlated with the development of copper homeostasis imbalances. One of the most popular areas of study in the field of cancer is cuproptosis. It has been discovered that cancer angiogenesis, proliferation, growth, and metastasis are all correlated with accumulation of copper ions. Copper ion concentrations can serve as a crucial marker for cancer development. In order to serve as a reference for clinical research on the product, diagnosis, and treatment of cancer, this paper covers the function of copper ion homeostasis imbalance in malignant cancers and related molecular pathways.

KEYWORDS

copper, cuproptosis, cell death, cancer, metabolism, immunotherapy, molecular targeted therapy

1 Introduction

Cell death plays an important role in maintaining normal body homeostasis by inhibiting the uncontrolled proliferation of tumor cells and other biological processes. Cell death includes RCD and non-RCD (1). RCD is a genetically determined cell-active programmed death, including apoptosis, iron death, pyroptosis, necroptosis, etc., which can be induced by inducing the generation of Reactive Oxygen Species (ROS), regulating protein ubiquitylation, acetylation, and other functionally regulating cell death (2) (Table 1). Tsvetkov et al. reported a new mechanism of cell death different from the known ones and named it cuproptosis. Cuproptosis is closely related to cellular

mitochondrial respiration: excess intracellular copper can be transported to the mitochondria via ion carriers and bind directly to the lipoylation component of the mitochondrial respiratory tricarboxylic acid cycle (TCA). Copper ions can interfere with iron-sulfur clusters, which in turn causes lipoylation protein aggregation and iron-sulfur cluster protein loss, inducing proteotoxic stress and ultimately cell death (3, 4). Previous findings have shown that, compared with normal human serum and tissues, copper ions are found at higher levels in the serum and tumor tissues of patients with a variety of human malignant tumors (5). Cuproptosis further reinforces the importance of cell death in tumorigenesis and progression and reveals the mechanisms of malignant tumorigenesis and progression, which provides a more theoretical basis for the search for new therapeutic strategies (6) (Figure 1).

2 Copper

One of the most essential heavy metals in the human body is copper (7). Copper is also a significant cofactor in biological redox reactions and is involved in various biosynthetic processes in the body (8). Food is the primary source of copper intake, and both Cu+ and Cu2+ forms of copper can be found in the human body. In the human body, the copper ion is present as Cu2+, which is then converted to Cu+ by reductase after binding to the divalent metal transporter 1 (DMT1), which then enters the cell after binding to the transmembrane copper transporter 1 (CTR1) (9, 10). The Cu+ bound copper proteins enter the bloodstream through particular organelles and are then transported to the tissues and organs where they are required (11). A sufficient amount of copper in cells is essential for life activities as a catalytic cofactor for enzymes involved in energy conversion, iron collection, oxygen transport, and intracellular oxidative metabolism (12). Copper levels in the human body are in dynamic balance under physiological settings. If copper homeostasis is disturbed in an organism, some issues are brought about, including the induction of cell death and the suppression of angiogenesis (13, 14). Iron intake, antioxidant activity, and mitochondrial respiration are all highly dependent on copper (15). Copper plays a crucial role in cell signaling, a biological process that regulates the environment inside the body's cells (16).

TABLE 1 Cell death pathways and their characteristics.

Cell death pathway	Morphological changes	Biochemical characteristic
Cuproptosis	Cell membrane rupture, fatty acylated protein aggregation, Fe-S reduction.	Binding of copper ions to lipoylated modified proteins.
Ferroptosis	Rupture of the outer mitochondrial membrane, reduction of mitochondrial ridges, and mitochondrial membrane density increased, normal nucleus.	Iron ion and ROS accumulation, system Xc - activation, GSH consumption, lipids Peroxide.
Autophagy	Formation of double membrane autolysosomes, including large autophagy, microautophagy and partner-mediated autophagy.	LC3 -Ito LC3 -II conversion and substrate degradation.
Pyroptosis	Organelle loss, cell membrane rupture, DNA condensation rupture, release Radioactive pro-inflammatory cytokines.	Activation of caspase and gastrin, the release of neutrophil elastase and myeloperoxidase by a large number of proinflammatory factors, and activation of PAD4.
Necrosis	Plasma membrane rupture, cytoplasmic organelle swelling, chromatin concentration.	ATP depletion, protein hydrolysis and DAMP release involving calpain and cathepsin.
Apoptosis	Agglutination of chromatin, formation of apoptotic bodies, disintegration of the cytoskeleton, reduction of cell and nuclear volume.	Caspase activation, PS exposure, mitochondrial membrane potential.

ROS, reactive oxygen species; GSH, Glutathione; LC3,Microtubule-associated protein light chain3; DNA, deoxyribonucleic acid; PAD4,Peptidylarginine deiminase 4; ATP, Adenosine Triphosphate; DAMP, Damage-associated molecular patterns; PS, Phosphatidyl serine.

3 Homeostatic regulation of copper

The concentration of copper in normal cells is very low. It mainly prevents the accumulation of harmful intracellular free copper through the Dynamic equilibrium mechanism across concentration gradients, thus maintaining the homeostasis of copper in cells (17). In eukaryotic cells, mitochondria are important organelles for copper storage and mobilization; Cytochrome C oxidase copper chaperone protein 17 located in the gap between the cytoplasm and mitochondrial membrane can bind Cu+, carry Cu+ from the cytoplasm to the mitochondrial gap, and transmit it to cytochrome oxidase deficient homolog 1, transfer to the cytochrome C oxidase II and I subunits to activate enzyme activity in the respiratory chain. Regulating the expression of copper Ion channel proteins can affect the transport and metabolism of copper ions (18). Copper signals can be inhibited by copper-selective chelating agents, activated by metal ion carriers to increase copper levels, or redistributed spatially and temporally to cells and subcells (19). Ceruloplasmin (CP) is the main protein carrier for exchangeable copper in mammalian plasma, with the functions of copper translocation and metal chaperone, jointly maintaining appropriate intracellular copper bioavailability and ensuring the metallization of copper-dependent enzymes (20, 21). CP is a multicopper oxidase that initially binds to most of the copper output from liver cells to the systemic circulation, and enters the secretion pathway through copper transport driven by ATP7B. Due to the rapid degradation of ceruloplasmin when not bound to metals, the concentration of ceruloplasmin in plasma can serve as a biomarker for copper deficiency in the body. Considered the primary transporter of copper ions entering cells, solute carrier family 31 member 1 (SLC31A1) is a member of the CTR family with an extracellular copper binding domain. It is a high-affinity transporter protein for reduced Cu+ and has high expression

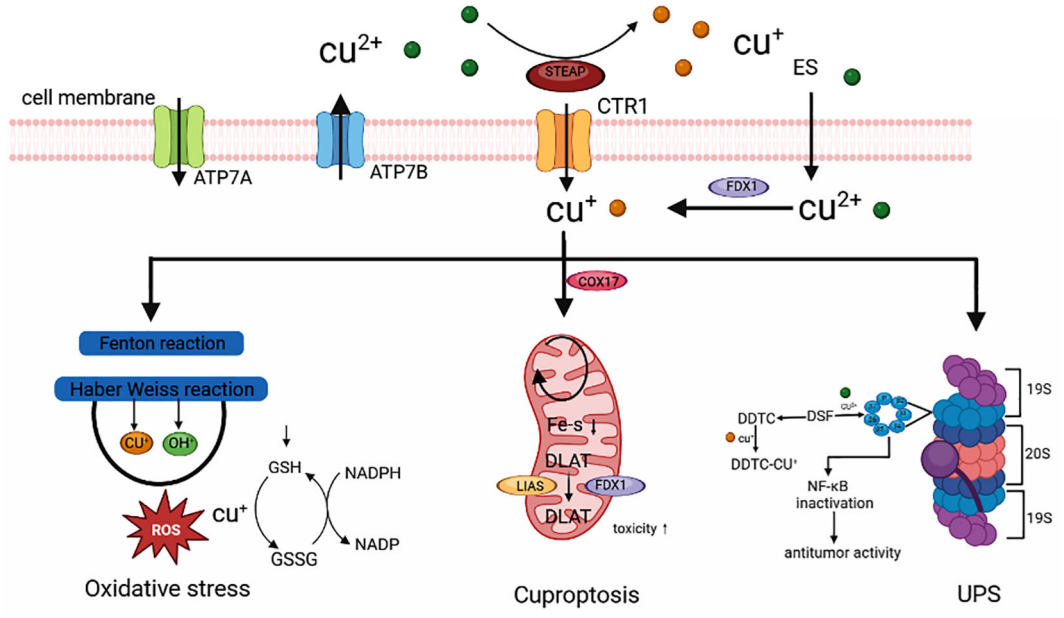

FIGURE 1
Cuproptosis is involved in the occurrence and development of cancer (3).

levels in human cancer tissues (22). However, copper's natural redox properties make it advantageous and potentially harmful to cells (23). Low copper ion concentrations have been linked to albinism, osteoporosis, and other illnesses (24). Because copper is also found in the brain's copper protein in the central nervous system, a copper deficiency can impact brain development, demonstrating copper's vital role in the body (25, 26).

4 Cancer prevention and control

Cancer is a major global public health problem, which seriously threatens human health, and incidence rate and mortality are rising. The International Agency for Research on Cancer (IARC) has released a 2020 global cancer statistics report, with approximately 19.3 million new cancer cases worldwide and nearly 10 million deaths from cancer. Female breast cancer has surpassed lung cancer to become the cancer with the highest incidence rate, accounting for 11.7% of all new cancer cases, followed by lung cancer (11.4%), rectal cancer (10.0%), prostate cancer (7.3%) and gastric cancer (5.6%). Lung cancer is the leading cause of death among all cancers, accounting for 18% of all cancer deaths. The second were rectal cancer (9.4%), liver cancer (8.3%), gastric cancer (7.7%) and female breast cancer (6.9%). Compared to 2018, there has been an increase in data, resulting in huge population losses and a heavy economic and medical burden. As the population ages, this trend will become more apparent. It is expected that there will be 28.4 million new cases of cancer in 2040, an increase of 47% compared to 2020. This result suggests that promoting cancer prevention and control measures and conducting early diagnosis and treatment of cancer are crucial for global cancer prevention and control.

5 Correlation between copper and cancers

Direct copper binding to the TCA's lipoylation component causes proteotoxic stress, which ultimately results in cell death (27). Abnormal accumulation of copper ions can facilitate malignant cell transformation (28). The serum or cancer tissue of patients with various malignancies has been found to contain high copper contents (29). An imbalance in copper alters lipid metabolism, glycolysis, and insulin resistance while affecting mitochondrial respiration. Unbalanced levels of copper activate vascular endothelial growth factor (VEGF), fibroblast Growth Factor2 (FGF2), tumor necrosis factor (TNF), and interleukin (IL) -1, which start ULK1 and ULK2, which regulate autophagy. This promotes angiogenesis, enabling cancer cell proliferation and spread (30). Human angiogenesis is the result of the combined action of multiple small molecules such as VEGF, FGF2, IL-1, IL-6, and IL-8. Research has shown that copper can stimulate angiogenesis by directly binding to angiopoietin or by binding to HIF-1 to activate these small molecules. Abnormally elevated copper within cells can activate autophagy related ULK1 and ULK1 dependent signaling pathways to induce autophagy, thereby inhibiting copper induced cell apoptosis. Both copper ion carriers and copper chelators are regarded as therapeutically beneficial treatment agents for conditions linked to copper homeostasis and are often used. Using biological markers in copper ion carrier clinical trials will be crucial for creating copper-targeted treatment approaches. The Ubiquitin Proteasome System (UPS), copper deficiency-induced angiogenesis inhibition in cancer cells, and cuproptosis, as identified by recent studies, are the

primary mechanisms by which copper has been shown to cause cancer cell death (31).

5.1 Catalyzing oxidative stress

The death of normal or cancer cells results from oxidative stress caused by altered oxidative-antioxidant equilibrium *in vivo* and is primarily characterized by high ROS concentrations (32, 33). The Cu+ in the body maintains the overall copper homeostasis through the absorption and excretion of copper. Excessive copper drives the Fenton reaction, producing a large amount of ROS, causing protein oxidation, DNA damage, nuclear damage, and dysfunction of mitochondria and various enzymes. Oxidative stress caused by copper primarily manifests itself in two ways. ROS can directly oxidize and cleave some copper complexes through the Fenton reaction, leading to necrotic apoptosis and toxic damage to cancer cells (34). Copper also mediates the synthesis of the most active -OH, which causes elevated ROS concentrations in cancer cells and kills cancer cells. Copper can deplete the antioxidant glutathione (GSH) by oxidizing reduced GSH to oxidized glutathione disulfide (GSSG), which disrupts the GSH-related antioxidant defence system and reduces the system's ability to scavenge highly reactive -OH, which causes cancer cells to die (35). Copper complexes can induce apoptosis and autophagy through mitochondrial malfunction caused by oxidative stress because copper-induced high quantities of ROS are likewise fatal to mitochondria (36, 37). According to studies, the copper chelator elesclomol (ES), a highly lipophilic copper-binding molecule that chelates extracellular Cu2+, forms an ES-Cu2+ complex that transports copper to mitochondria for redox reactions and causes oxidative stress, which causes cancer cells to undergo apoptosis (38).

5.2 UPS

One of the mechanisms for the breakdown of many proteins in the human body is the UPS (39). UPS is essential in cancer cell growth, apoptosis, angiogenesis, and metastasis. Cu2+ can inhibit the proteasome through direct binding, according to studies (40). Disulfiram (DSF) (41) and other copper complexes have been employed as proteasome inhibitors in cancer treatment. A promising anticancer drug, DSF is an acetaldehyde dehydrogenase inhibitor that binds to Cu2+ to kill cancer cells (42). Diethyldithiocarbomate (DDTC) is similarly quickly formed *in vivo* from DSF (43, 44). It has been discovered that DDTC can form a dinuclear complex with Cu+, or DDTC-Cu+ and that this copper complex causes an accumulation of ubiquitinated proteins, an increase in p27, and inhibition of nuclear factor-kappa B (NF-κB) expression, which inhibits the growth of cancer cells and the activity of the proteasome both *in vivo* and *in vitro*. As a crucial transcription factor, NF-κB is vital for cell growth, invasion, metastasis, and angiogenesis (45). Cu2+ dramatically lowers the cancer cells' bortezomib resistance, making its anticancer activities appear more promising. A new approach to conventional ubiquitin-proteasome inhibitor anticancer treatment is provided by copper complex-targeted UPS (46).

5.3 Inhibiting angiogenesis

Malignant angiogenesis encourages cancer cell growth, invasion, and metastasis since neoangiogenesis is the first stage of cancer proliferation and metastasis (47). The main component in stimulating angiogenesis is copper, which can directly promote endothelial cell migration, expansion, and the production of fibronectin (48). Hypoxia-inducible factor (HIF-1) can bind to copper and activate essential elements that control angiogenesis (49, 50). Angiogenin is a molecule that copper attaches to, stimulating endothelial cells to initiate angiogenesis (51). Copper deficiency will shut off the angiogenic switch, stop endothelial cells from proliferating, and stop the cell cycle. A novel therapeutic approach used in the treatment of cancers is copper depletion to prevent cancer angiogenesis (52). Tetrathiomolybdate (TTM), which inhibits cancer angiogenesis by reacting with copper ions to generate insoluble copper-molybdenum-sulfur clusters, is receiving much attention in cancer therapy (53, 54). TTM has shown good promise when combined with anti-cancer medications as an adjuvant. Since copper-mediated anti-angiogenic effects can block blood vessels required for cancer growth and metastasis and reshape the cancer immune microenvironment, immune checkpoint inhibitors (ICI) can promote vascular normalization, making the combination of immunotherapy with copper complexes a new target for anticancer therapy (55), which is vital in reducing cancer cell proliferation and inducing cell death (56, 57).

6 Cuproptosis

6.1 Definition of cuproptosis

Apoptosis, scorch death, autophagy, necroptosis, and metal-induced iron death are the principal types of cell death that are now understood (58, 59). Although the human body needs heavy metal ions, too little or too much can cause cell death (60). Cuproptosis, a recently identified unique form of cell death, is copper-dependent, changeable, and intricately linked to mitochondrial respiration (61). Tsvetkov et al. put out this idea. The researchers first tested 489 distinct cell types utilizing carriers for copper ions and showed that too many accumulated copper ions could result in cell death. The researchers discovered a failure to inhibit ES-induced death of non-small cell lung cancer A549 cells and NCIH2030 cells using all known inhibitors of cell death modalities after targeted knockdown of the BCL2-Associated X (BAX) and Recombinant Bcl2 Antagonist/Killer 1 (BAK1) genes. This suggests that ES-induced cancer cell death differs from known cell death mechanisms. They therefore proposed the name "cuproptosis" for this novel cell death process. Cuproptosis is a unique RCD route with a different lethal tool from oxidative stress-related cell death (62). Research shows that cuproptosis plays an important role in the occurrence and progress of many diseases, including cancer, atherosclerosis,

rheumatoid arthritis, acute liver injury, novel coronavirus pneumonia, Wilson disease, Alzheimer's disease, Parkinson's disease etc.

6.2 Mechanism of cuproptosis

Tsvetkov et al. discovered that ES-induced cell death might be connected to mitochondrial respiration. Cells relying on glycolysis are around 1000 times more sensitive to copper ion inducers than cells depending on mitochondrial respiration. Conversely, ferredoxin 1 (FDX1) lowers CU2+ to CU+, encouraging lipoylation and aggregation of enzymes responsible for controlling the mitochondrial TCA cycle (63). On the other hand, FDX1 results in the instability of iron-sulfur proteins (Fe-S), which sets off a stress response in the mitochondria and produces cuproptosis (64). In addition to copper ion carriers, copper importers and the ATP-dependent copper transporter 7A (ATP7A) (65) control the intracellular concentration of copper ions to hold the degree of cuproptosis sensitivity (66). The copper chelator GSH, which contains thiols, protects against cuproptosis. The electron transfer chain (ETC) complex inhibitor and the mitochondrial pyruvate carrier (MPC) inhibitor UK5099 prevent ES-induced cuproptosis. cuproptosis brought on by ES (Figure 2).

6.3 Copper death-related genes

Tsvetkov et al. identified ten copper death-related genes (CRGs) associated explicitly with the cuproptosis metabolic pathway (67), including seven positively regulated genes: FDX1, lipoic acid synthase (LIAS), lipoyl transferase-1 (LIPT1), dihydrolipoamide dehydrogenase (DLD), dihydrolipoamideS-acetyltransferase (DLAT), recombinant Pyruvate dehydrogenase alpha 1 (PDHA1), and pyruvate dehydrogenase (PDHB) (68–70). Metal transcription factor 1 (MTF), glutaminase (GLS), and cyclin-dependent kinase inhibitor 2A (CDKN2A) are three genes that are negatively regulated (71–73). A future study will focus on the precise function of these genes in cuproptosis and the potency of copper toxicity in cancer management (74).

As an ETC carrier, FDX, a member of the small molecular family Fe-S, is frequently utilized in various metabolic activities in

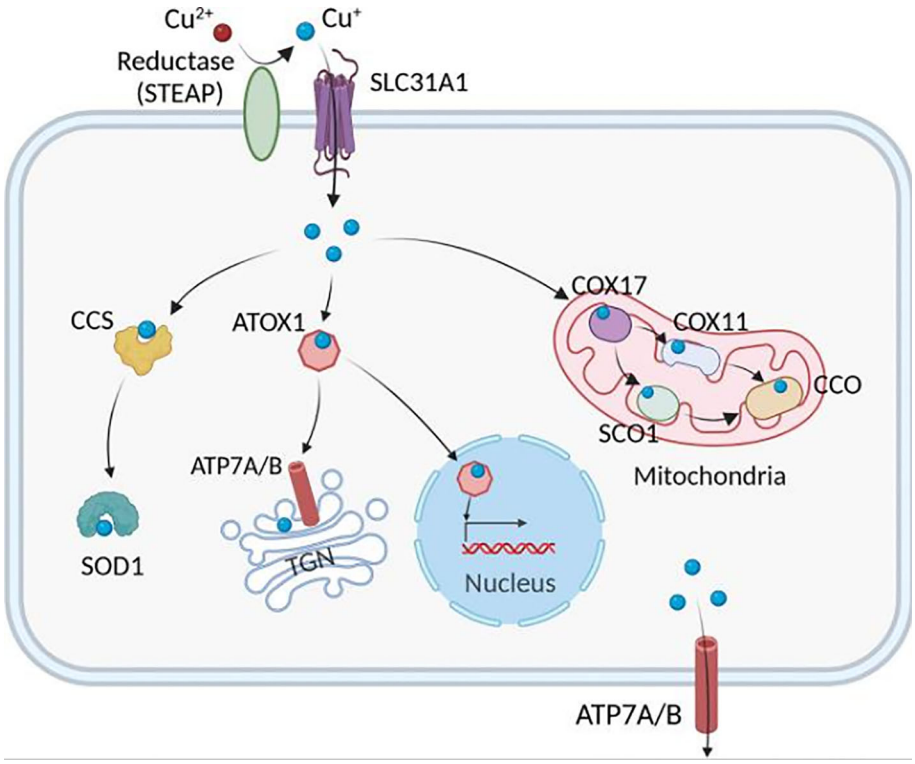

FIGURE 2
The pathways that mediate cellular Cu metabolism. Extracellular Cu2+ is reduced by the reductase STEAP to Cu+, which is transported into the cell by the Cu transporter CTR1, where it is delivered to cytosolic Cu chaperones such as CCS and SOD1 and then delivered to specific subcellular compartments such as the mitochondria, TGN, and nucleus. In the mitochondria, Cu is involved in the respiratory chain and redox pathways via binding to CCO. In the mitochondrial intermembrane space, COX17 binds to and delivers Cu to either SCO1 or COX11, which transfers Cu to the cytochrome oxidase subunit. In the nucleus, Cu can bind to transcription factors and drive gene expression. Finally, in the TGN, the Cu+-ATPase transporters ATP7A and ATP7B transfer Cu from the cytosol to the TGN lumen, where it activates Cu-dependent enzymes in the secretory pathway. ATOX1, antioxidant 1 copper chaperone; ATP7A and ATP7B, ATPase copper transporter 7A and 7B, respectively; CCO, cytochrome c oxidase; CCS, copper chaperone for superoxide dismutase; COX17, cytochrome c oxidase copper chaperone 17, COX11, cytochrome c oxidase copper chaperone 11, SCO1, synthesis of cytochrome c oxidase 1, SOD1, superoxide dismutase 1, STEAP, the six-transmembrane epithelial antigen of the prostate, SLC31A1, solute carrier family 31 members 1, TGN, trans-Golgi network (17).

living things (75). The decrease of mitochondrial cytochrome and the manufacture of different steroid hormones are both processes that FDX1, an isoform of the FDX family, aids. Cuproptosis, which converts Cu2+ to the more toxic Cu+, causes cytotoxic stress and, as a result, causes cellular cuproptosis, and FDX1 is a co-regulator of this process (76). protein Lysine can be modified post-translationally by a process known as lipoylation, and FDX1 and protein lipoylation share a family relationship (77). A considerable reduction in cellular respiration is caused by the total loss of lipoylation of the DLAT and DLST proteins when FDX1 is knocked down. These findings imply that FDX1, an essential gene in ES-induced copper-dependent cell death and an upstream regulator of protein lipoylation (78), is involved in ES-induced copper-dependent cell death. The lipoylation of mitochondrial proteins was enhanced by copper (79). The degradation of Fe-S cluster proteins by FDX1 may promote copper toxicity. Unrelated to the cuproptosis protein in cancer, FDX1 may act as an oncogene (80). Copper overload causes the aggregation of DLAT, a decrease in Fe-S cluster protein levels, an increase in the number of heat shock protein 70, and protein toxicity stress, leading to the occurrence of cuproptosis.

Three significant genes that code for the mitochondrial lipoic acid pathway are LIAS, LIPT1, and DLD (81). LIAS and LIPT1 are intricately connected to mitochondrial fatty acid production. An essential gene for mitochondrial protein lipoylation is DLAT. By acetylating 6-glucose-phosphate dehydrogenase (6PGD), DLAT increases enzyme activity, boosting nucleic acid synthesis and encouraging the growth of cancer cell lines (82). The oxidative decarboxylation of pyruvate to acetyl-CoA is made possible by the catalytic action of the pyruvate dehydrogenase complex (PDHC), which connects glycolysis, TCA, and oxidative phosphorylation. PDHA1, the PDHC's active regulatory site The cuproptosis-related gene PDHA1 is crucial for the metabolic transformation of cancer as it regulates the cuproptosis process (83). The level of PDHA1 expression is significantly higher in cervical squamous cell carcinoma tissues than in paraneoplastic squamous epithelial tissues. It is correlated with patient age, the depth of cancer infiltration, pelvic lymph node metastasis, and International Federation of Gynecology and Obstetrics (FIGO) staging (84, 85). In hepatocellular cancer cell lines, overexpression of PDHA1 controls the activity of the TCA enzyme, prevents aerobic glycolysis, and intensifies mitochondrial-regulated apoptotic signaling pathways (86). According to specific research, CDKN2A changes in melanoma patients with CDKN2A loss may serve as a possible signal for anticipating the effectiveness of melanoma immunotherapy (87).

6.3.1 CRGs regulate metabolism in cancer cells

Pathway Enrichment Analysis revealed that glutamate metabolism, TCA, and p53 signaling pathways were primarily enriched in CRGs (88). The amino acids alanine, glutamate, and aspartate all have metabolic signaling pathways connected to glucose metabolism. Metabolic reprogramming involves the p53 signaling pathway (89). TCA, glycolysis, and other processes are part of the central carbon metabolism in cancer (90). Cellular metabolism is closely tied to each of the signaling pathways mentioned above. The sensitivity of cancer cells to therapeutic drugs can be impacted by cellular metabolism, which is essential for cancer development and metastasis. Through control of cancer cell metabolism, CRGs and their related genes may influence the onset and progression of the disease (91).

6.3.2 CRGs and immune cell infiltration

Analysis of immune cell infiltration revealed a strong correlation between the expression of CRGs and the quantity of various immune cells present (92). The presentation of CRGs was negatively connected with plasma cell-like follicular dendritic cells, while the expression of CRGs was favorably correlated with T helper cells. Major mitochondrial autoantigens known as DLAT-associated complexes increase CD4+ T cell and CD8+ T cell reactivity. The cancer CDKN2A was discovered. CRGs may influence cell metabolism in tumor microenvironment (TMT) by controlling several pathways, including cancer cell growth and apoptosis and the proportion of immune cells and other non-cancer cells. As a part of the TMT, immune cell infiltration may also control the growth and remission of cancers (93).

6.4 Cuproptosis affects mitochondrial function

Mitochondrial respiration and cuproptosis are related (94, 95). Since copper ions are primarily stored in mitochondria, an imbalance in intracellular copper metabolism can have cytotoxic effects and lead to disease onset (96). Cuproptosis may be related to altered mitochondrial activity, as evidenced by a considerable reduction in sensitivity to copper degradation when cells are placed in a hypoxic environment and forced to conduct anaerobic glycolysis (97). Both apoptosis and iron death are caused by mitochondrial stress, which can result in a severe decrease in mitochondrial membrane potential. Inhibiting glucose metabolism reduces the malignant potential of cancer cells and makes them more sensitive to copper ion carrier therapy for the treatment of cancers (98). This is because glycolysis is crucial for the proliferation of cancer cells. According to recent research, antioxidants for the mitochondria can considerably lower cuproptosis levels (99). Cuproptosis, therefore, has a high potential for use in anti-cancer therapy due to its superior anti-cancer mechanism (100).

6.5 Cuproptosis regulates the mechanism of cancer damage

The inflammatory response to cellular damage is impacted by cuproptosis (101). By lowering CD45 levels following cerebral ischemia injury, increasing Iba1 immunoreactivity, and changing the shape of Iba1-positive cells to modify the inflammatory response, cuproptosis can be cerebro protective. Cellular carcinogenesis depends on apoptosis (102). Burgering

(103) et al. discovered that Cu, Superoxide Dismutase (SOD1) may be impacted by cuproptosis since protein kinase B (Akt) is important in regulating cell survival and death. In the bad signaling pathway, SOD1 might be necessary (104, 105). Protein lipoylation was found to be closely linked with FDX1 abundance in many cancers, and cell lines with high levels of protein lipoylation were highly susceptible to cuproptosis, indicating that copper ion carrier therapy should focus on malignancies with this metabolic profile.

7 Opportunities for cuproptosis cancer treatment

One of the most promising therapeutic modalities is cancer immunotherapy (106), and research on ICI, in particular, has advanced quickly (107). Current therapeutic approaches aim to selectively promote cancer cell death and prevent harming normal cells because cancer is characterized by dysregulated cell death and altered inflammatory responses (108). The need for copper is greater in cancer cells compared to normal cells. Numerous lipoylated mitochondrial proteins are expressed in high concentrations in some cancers with active respiration (109). Cu2 + in humans through bidirectional regulation has become a new target for cancer therapy since elevated copper ion levels stimulate cancer cell proliferation, metastasis, and angiogenesis (110). The fundamental component of current techniques to combat copper-induced apoptosis is using copper ion chelators and copper ion carriers to control the level of copper *in vivo* to induce apoptosis in cancer cells and produce anti-cancer effects (111). By chelating copper ions, copper ion carriers DSF and ES influence the breakdown of proteins in cancer cells, leading to copper-dependent cancer cell death (112). As a cofactor of cytochrome c oxidase, ES can control intra-mitochondrial copper ion levels, regulating cytochrome c oxidase activity and treating diseases brought on by abnormalities in human copper metabolism (113). Cytochrome C oxidase is a crucial enzyme in the mitochondrial respiratory chain.

In tumor cells, copper deficiency results in inhibition of angiogenesis, elevated ROS levels, proteasome inhibition, and mitochondrial dysfunction (114). The relationship between cuproptosis and cancer can provide new ideas for tumor salvage, and the effect of cuproptosis on cancer cells can be studied in order to reduce the copper content of cancer cells in order to mitigate the damage. When TTM is used as an antitumor drug with platinum-based chemotherapeutic drugs, the chemotherapeutic drugs become more effective and have positive synergistic effects (115). Some researchers have also discovered that Cu2+ regulates the expression of the immune checkpoint protein PD-L1 and promotes tumor immune evasion, demonstrating the potential of copper chelators as anti-tumor immune enhancers. In some cases, it is necessary to artificially increase the cellular copper content in order to alleviate inflammatory damage, and this balance must be continuously investigated in both fundamental and clinical research (116). In light of the fact that the mechanisms by which copper induces tumor cell demise vary between cancer types, their targeting and specificity must be considered in future research.

8 Conclusion

Copper induces tumor cell death in a variety of ways, and "cuproptosis" is a novel RCD mechanism distinct from apoptosis, iron death, autophagy, and programmed necrosis (117, 118). After a series of safety and efficacy tests, it can help translate basic chemical and biological studies of copper into potential clinical therapies and drug candidates, and it has promising applications in the field of tumor therapy. The exact mechanisms by which cuproptosis works in cancer are currently unknown, and a large number of high-quality basic studies are needed to demonstrate a causal relationship between cuproptosis and tumors. The molecular mechanisms of copper toxicity in tumors and the specific modes of evolution of cuproptosis into definitive cell death need to be further elucidated. As research continues, it is believed that more new and relevant targets and drugs will emerge to establish rational and personalized therapeutic strategies and bring new hope for the treatment of cancer patients.

Author contributions

MW: Conceptualization, Data curation, Resources, Software, Writing – original draft, Writing – review & editing. LZ: Investigation, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. SM: Conceptualization, Formal Analysis, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. RL: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. JL: Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. SY: Formal Analysis, Funding acquisition, Supervision, Validation, Visualization, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Glossary

RCD	Regulatory cell death
ROS	Reactive oxygen species
GSH	Glutathione
LC3	Microtubule-associated protein light chain3
DNA	deoxyribonucleic acid
PAD4	Peptidylarginine deiminase 4
ATP	Adenosine Triphosphate
DAMP	Damage-associated molecular patterns
PS	Phosphatidyl serine
TCA	tricarboxylic acid cycle
DMT1	divalent metal transporter 1
CTR1	copper transporter 1
SLC31A1	solute carrier family 31 member 1
VEGF	vascular endothelial growth factor
FGF2	fibroblast growth factor2
TNF	tumor necrosis factor
IL	interleukin
UPS	Ubiquitin proteasome system
GSSG	oxidized glutathione disulphide
ES	elesclomol
DSF	Disulfiram
DDTC	Diethyldithiocarbomate
NF-κB	nuclear factor-kappa B
HIF-1	Hypoxia-inducible factor
TTM	Tetrathiomolybdate
ICI	immune checkpoint inhibitors
BAX	BCL2-Associated X
BAK1	Recombinant Bcl2 Antagonist/Killer 1
FDX1	ferredoxin 1
Fe-S	iron-sulfur proteins
ATP7A	ATP-dependent copper transporter 7A
ETC	electron transfer chain
MPC	mitochondrial pyruvate carrier
ATOX1	antioxidant 1 copper chaperone
ATP7B	ATP-dependent copper transporter 7B
CCO	cytochrome c oxidase
CCS	copper chaperone for superoxide dismutase
COX17	cytochrome c oxidase copper chaperone 17
COX11	cytochrome c oxidase copper chaperone 11
SCO1	synthesis of cytochrome c oxidase 1
SOD1	superoxide dismutase 1
STEAP	the six-transmembrane epithelial antigen of the prostate
TGN	trans-Golgi network
CRGs	copper death-related genes
LIAS	lipoic acid synthase
LIPT1	lipoyl transferase-1
DLD	dihydrolipoamide dehydrogenase
DLAT	dihydrolipoamideS-acetyltransferase
PDHA1	ecombinant Pyruvate dehydrogenase alpha 1
PDHB	pyruvate dehydrogenase
MTF	Metal transcription factor 1
GLS	glutaminase
CDKN2A	cyclin-dependent kinase inhibitor 2A
6PGD	6-glucose-phosphate dehydrogenase
PDHC	pyruvate dehydrogenase complex
FIGO	International Federation of Gynecology and Obstetrics
TMT	tumor microenvironment
Akt	protein kinase B.

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