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REVIEW

Song et al: Tumor glucose metabolism and cuproptosis

Tumor glucose reprogramming suppresses cuproptosis: A review

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ABSTRACT

Cuproptosis is a copper-dependent form of regulated cell death that begins when ferredoxin 1 (FDX1) reduces Cu^{2+} to Cu^{1+}, allowing the ion to bind lipoylated enzymes of the tricarboxylic-acid (TCA) cycle, drive protein aggregation, dismantle iron–sulphur clusters and trigger fatal proteotoxic stress. Most tumours, despite accumulating copper, evade this fate through glucose-metabolic rewiring. First, oncogenic stabilisation of hypoxia-inducible factor-1 alpha (HIF-1α) and MYC increases pyruvate dehydrogenase kinase (PDK) activity, which phosphorylates and inactivates the pyruvate dehydrogenase complex (PDC), shrinking the lipoylated target pool in mitochondria and cutting the feed into the TCA cycle. Second, glycolytic signalling suppresses cuproptosis-promoting genes such as FDX1 and dihydrolipoamide S-acetyltransferase while inducing the negative regulator glutaminase (GLS), further lowering copper sensitivity. Third, diversion of glycolytic intermediates into the pentose-phosphate pathway (PPP) supplies abundant nicotinamide adenine dinucleotide phosphate (NADPH), whereas enhanced glutamine catabolism furnishes glutamate; together these fuels expand reduced glutathione (GSH) and metallothionein (MT) pools that chelate Cu^{1+} and quench reactive oxygen species exactly where cuproptosis is executed. Consequently, glycolysis-dependent cancer cells are far less sensitive to copper-ionophore drugs such as elesclomol or disulfiram than respiration-dependent counterparts, and clinical datasets consistently link high PDK and low PDC-subunit expression with poor prognosis. These insights highlight rational combination strategies: re-activating the TCA cycle with PDK inhibitors, draining PPP- or GLS-driven NADPH/GSH supply, and concurrently delivering copper ionophores could reopen the cuproptotic trap in tumours. Validating such approaches in vivo, charting upstream regulators of FDX1 and mapping crosstalk between cuproptosis and other lethal programmes remain key steps toward exploiting this copper-centred vulnerability in cancer therapy.

Keywords: Cuproptosis, cell death, glucose metabolic reprogramming, tumor.

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INTRODUCTION

Copper is a trace element involved in the cofactors of many enzymes [1,2]. Excess copper can lead to cell death. The specific mechanism by which copper induces cell death was recently revealed. Cuproptosis is a novel form of cell death that distinguished itself from previously known forms of cell death. Cuproptosis is highly associated with mitochondrial respiration and lipoylated proteins of the mitochondrial tricarboxylic acid cycle (TCA cycle) [3].

Tumor glucose metabolic reprogramming is an important hallmark of tumors, including aerobic glycolysis and the highly active PPP pathway. Aerobic glycolysis rapidly supplies tumors with ATP, while its metabolically generated lactic acid creates an acidic tumor microenvironment that promotes tumor migration [4-7]. The PPP pathway has been demonstrated to provide raw material for tumor proliferation and to generate nicotinamide adenine dinucleotide phosphate (NADPH), which plays an important role in cellular proliferation [8]. Cuproptosis is closely related to tumor glucose metabolic reprogramming. Cuproptosis-related genes are associated with aerobic oxidation of glucose, and these genes are often repressed in tumor glucose metabolic reprogramming. Meanwhile, glycolysis-dependent cells were insensitive to cuproptosis compared to mitochondrial respiration-dependent cells. Ultimately, the highly active PPP pathway generates NADPH, which facilitates the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH), thereby expanding cellular GSH pools—a critical mechanism for inhibiting cuproptosis via copper chelation[3,8]. Thus, glucose metabolic reprogramming may be an efficient strategy for tumor to suppress cuproptosis. This review focuses on the mechanisms of cuproptosis and the important link between cuproptosis and tumor glucose metabolic reprogramming. We aim to provide possible directions for research on cuproptosis and tumors.

Literature search and selection

A comprehensive literature search was conducted to identify relevant studies

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published up to June 2025. Databases including PubMed, Web of Science, Scopus, and Google Scholar were systematically queried using the following core keywords and their combinations:cuproptosis, copper metabolism, glucose metabolic reprogramming, Warburg effect, pentose phosphate pathway, glycolysis, tumor metabolism, PDH complex, FDX1, DLAT, glutathione, GSH, PDK, PKM2, LDHA, HK2, GLUT.

Inclusion criteria encompassed: 1. Original research articles and reviews focusing on molecular mechanisms of cuproptosis and glucose metabolism in tumors. 2.Studies elucidating crosstalk between copper-induced cell death and metabolic pathways. 3.Publications in English with full-text availability.

Exclusion criteria were:1. Articles unrelated to tumor metabolism or copper biology. 2.Studies based solely on non-mammalian models or non-cancerous contexts. 3.Abstracts, conference proceedings, or non-peer-reviewed works.

Initial screening of titles/abstracts was followed by full-text review of eligible articles. Key references were further expanded via citation tracking. Emphasis was placed on high-impact studies published within the past 5 years, supplemented by seminal historical papers.

Copper homeostasis

Copper (Cu) is a vital element in the human body, with an average content of approximately 110 mg [9]. The human body is able to obtain copper ions from a variety of dietary sources on a daily basis. These include meats, grains, water sources, and vegetables. Animal offal and nuts are also important sources of copper [9]. Copper is a widely distributed metal in the human body, with an estimated concentration of approximately 110 mg of copper ions, 10 mg in the liver, 1 μg/ml in plasma, and 28 mg in muscle tissue, with a maximum concentration of approximately 46 mg in bone [9-11].

In general, dietary copper exists as Cu (II), while biological systems require Cu(I) [11]. The process of copper absorption is a complex physiological phenomenon.

Copper absorption is a complex physiological process occurring primarily in small intestinal epithelial cells. Initial reduction of Cu (II) to Cu (I) is facilitated by six-transmembrane epithelial antigens of the prostate 2–4 (STEAP2–4) [12,13].

Copper binds to copper chaperone proteins in the cytoplasm to fulfill its physiological functions. Antioxidant 1 copper chaperone (ATOX1) plays an important role in the Cu-trafficking pathway. ATOX1 is capable of accepting Cu (I) from SLC31A1, thioltransferase-1 (GRX1) and GSH-binding Cu [17]. Subsequently, ATOX1-bound copper can shuttle to ATPase copper transporting Alpha (ATP7A) on the basolateral membrane, where it is pumped into the plasma or transported to the nucleus [10,18,19]. In plasma, copper exists in a variety of protein-bound forms, the most common of which is ceruloplasmin (CP), in addition to alpha-2-macroglobulin (A2M) and superoxide dismutase 3 (SOD3) [20]. Transhepatic is the main metabolic pathway for copper, and in the hepatic metabolism copper is stored after binding to metallothionein-1/2A (MT1/2) [21,22]. ATPase copper transporting Beta (ATP7B) is specifically highly expressed in the liver and its expression is located on the Golgi apparatus, which is essential for copper metabolism. In the event of elevated intracellular copper levels, ATP7B is transported to the surface of intrahepatic bile ducts, where it facilitates copper excretion into the bile ducts [21,23].

Copper chaperone for superoxide dismutase (CCS) is another copper chaperone protein present in the cytoplasm. In vitro, CCS can interact with ATOX1 and deliver Cu [19]. Intracellular CCS delivers Cu to superoxide dismutase 1 (SOD1) and inserts disulfide to activate SOD1[20]. The activated SOD1 scavenges reactive oxygen species (ROS) in vivo via Cu(I) reduction [24].

Cytochrome C Oxidase Copper Chaperone COX17(COX17) was identified in mitochondria, where it functions as a cofactor in the anti-oxidative stress action of SOD1 in mitochondria and assists in the entry of copper into the oxidative respiratory chain. Solute carrier family 25 member 3 (SLC25A3) and COX17 facilitate the translocation of copper to the mitochondria. [2,25]. The binding of copper to COX17 is essential for the maintenance of the integrity of the mitochondrial electron transfer chain. COX17 transports copper to Cytochrome C Oxidase Copper Chaperone

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COX11(COX11), and copper in COX11 under the reduction of Cytochrome C Oxidase Copper Chaperone COX19(COX19) maintains Cu(I) and promotes copper binding to the Cu(B) site of Cytochrome C Oxidase Copper Chaperone COX1(COX1) [25,17]. Conversely, COX17 acts as a copper donor for SCO1/2 and is translocated to the Cu(A) binding site of COX2 with the assistance of COA6 [17]. Ultimately, COX1 and COX2 are integral to the synthesis of cytochrome c oxidase (CcO) [26,27] (Fig.1).

The mechanism of cuproptosis

Proper regulation of copper homeostasis is essential for biological growth, development and normal physiological function. Deficiency of intracellular copper can result in severe developmental delays and morphological abnormalities [27,28]. Copper overload has been observed to result in cell death, as evidenced by the production of copper and other elemental residues in the nuclei of hepatocytes in male rats following a high copper diet (1500 ppm). These residues have been suggested to be strongly associated with subsequent hepatocyte death [29]. Furthermore, Keswani et al. demonstrated that excess copper induces cell cycle arrest and apoptosis in spleen and thymus cells, suggesting that copper-induced cell death may be a common phenomenon in a wide range of cell types [3]. Nevertheless, the precise mechanism by which copper induces cell death remains elusive.

In 2022, a study by Tsvetkov et al. identified the mechanism of copper-induced cell death and named as cuproptosis. Cell death occurred only with copper-bound ionophores (e.g., elesclomol/disulfiram), confirming cuproptosis is specifically triggered by intracellular copper overload mediated through these carriers—not by ionophores alone or extracellular copper. This distinguishes it from other cell death forms [3].

Mechanistically, cuproptosis is characterized by three defining features: (1) strict copper dependence, (2) functional mitochondrial respiration requirement, and (3) multilayer regulatability. A specific mechanism of cuproptosis has been identified,

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which involves the overloading of copper, which promotes the aggregation and the loss of function of lipoylation proteins by binding to lipoylation proteins in the TCA cycle. This ultimately leads to the loss of Fe-S cluster proteins, proteotoxic stress and cell death. A total of 10 cuproptosis-associated genes were identified, comprising 7 cuproptosis-positive and 3 cuproptosis-negative genes. The cuproptosis-positive genes include ferredoxin1(FDX1), the components of lipoic acid pathway [lipolytransferase 1 (LIPT1), lipoic acid synthetase (LIAS), and dihydrolipoamide dehydrogenase (DLD)] and the pyruvate dehydrogenase (PDH) complex [dihydrolipoamide S-acetyltransferase (DLAT), pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1) and pyruvate dehydrogenase E1 subunit beta (PDHB)] [3]. The cuproptosis-negative genes include metal regulatory transcription factor 1 (MTF1), glutaminase (GLS) and cyclin dependent kinase inhibitor 2A(CDKN2A) [3].

FDX1 is the upstream regulator of cuproptosis, which promotes the lipoylation of DLAT through direct binding to LIAS. In addition, FDX1 facilitates the reduction of Cu (II) to the more cytotoxic Cu(I) [3,30]. Knockout of FDX1 blocks protein lipoylation and rescues cuproptosis [3]. Lipoic acid-dependent protein lipoylation is a highly conserved lysine post-translational modification that occurs on four enzymes. These enzymes include DLAT, dihydrolipoamide S-succinyltransferase (DLST), glycine cleavage system protein H (GCSH) and dihydrolipoamide branched chain transacylase E2 (DBT), all of which are associated with metabolic complexes that regulate the entry of carbon into the TCA cycle [3]. The lipoylation of DLAT is a prerequisite for its binding to copper. Copper binds directly to lipoylated DLAT, inducing the aggregation of DLAT. This results in proteotoxic stress and the loss of Fe-S cluster proteins [3]. Furthermore, abnormalities in SLC31A1, ATP7A and ATP7B have been associated with dysregulation of copper homeostasis. This dysregulation of copper homeostasis ultimately results in cell death through a mechanism similar to cuproptosis [3]. Additionally, numerous factors were identified that were negatively associated with cuproptosis, including a low-oxygen environment, glycolysis-dependent and GSH-rich cells [3].

Tsvetkov et al. established cuproptosis as a distinct form of cell death mediated

through copper targeting of lipoylated TCA cycle proteins [3] (Fig.2). This discovery has profound implications for understanding copper homeostasis disorders (e.g., Wilson's and Menke's diseases) [31,32] and has opened new therapeutic avenues for cancer and metabolic diseases [33,34]. Importantly, recent translational studies have validated these mechanistic insights, demonstrating that LIPT1—a core component of the lipoylation pathway—serves as both a prognostic biomarker and therapeutic target in NSCLC. Tumor-specific LIPT1 downregulation not only impairs protein lipoylation but also coordinately suppresses ATOX1 expression, thereby establishing a dual resistance mechanism against cuproptosis[35].

However, several critical aspects of cuproptosis remain to be elucidated: (1) the causal relationship between Fe-S cluster protein loss and cuproptosis execution, (2) upstream regulators governing FDX1 expression and activity, and (3) the context-dependent functions of other cuproptosis-related genes.

Prospective on mechanisms underlying the regulation of cuproptosis by tumor glucose metabolic reprogramming

In the 1920s, Otto Warburg observed that tumors exhibited a preference for glycolysis as a means of supplying energy, rather than oxidative phosphorylation, even in an aerobic environment. This phenomenon was subsequently named the Warburg effect, also known as aerobic glycolysis. Although the generation of ATP is less efficient relative to oxidative phosphorylation, aerobic glycolysis is capable of rapidly generating ATP to meet the energy demands of tumor metabolism [4]. The production of lactic acid by aerobic glycolysis results in the formation of an acidic tumor microenvironment. The acidic environment has been demonstrated to promote tumor proliferation, invasion and migration [5-7]. Furthermore, the activity of the pentose phosphate pathway (PPP pathway) is elevated in tumors. [8,36]. The elevated activity of the PPP pathway provides a sufficient supply of substrates for tumor proliferation, while its high production of NADPH acts as a reductant to reduce oxidative stress in tumors. Finally, the reduction of glucose entry into the TCA cycle in tumor glucose

metabolic reprogramming is accompanied by an increase in glutamine utilization [37]. Copper is a cofactor for several enzymes and plays an important role in tumor development. Elevated serum copper concentrations have been observed in patients with a range of malignant tumors, including breast, lung, liver and colorectal cancers [38-43]. Copper is involved in the activation of multiple tumor-related signaling pathways. In hepatocellular carcinoma, copper accumulation activates hypoxia inducible factor 1 subunit alpha (HIF-1α) [44], and HIF-1α activation is strongly associated with hepatocellular carcinoma growth, angiogenesis, metastasis, and drug resistance [45-47]. Copper has been demonstrated to mediate tumor immune escape through the promotion of programmed cell death 1 ligand 1 (PD-L1) expression in neuroblastoma, in conjunction with interferon gamma (IFNγ) [48]. Copper activates ligand-independent activation of RTK and downstream PI3K phosphorylation and activates AKT to promote tumor cell growth and migration in lung, prostate and breast cancer cell lines [49,50]. The dependence of tumors on copper creates an environment conducive to the onset of cuproptosis. However, the avoidance of cuproptosis by tumors may be closely associated with tumor glucose metabolic reprogramming. The investigation of the relationship between cuproptosis and tumor glucose metabolic reprogramming is important for future research and the potential application of cuproptosis in tumor therapy.

Tumor glucose metabolic reprogramming inhibits cuproptosis by increasing dependence on aerobic glycolysis

Cells with different glucose metabolism-dependent modalities have different sensitivities to cuproptosis. Tsvetkov et al. demonstrated that cells dependent on mitochondrial respiration exhibited markedly greater sensitivity to copper ionophore-induced cuproptosis than glycolytic cells, as quantified by dose-response assays [3]. The reliance on aerobic glycolysis, a common metabolic modality in tumours, may confer a selective advantage on tumours in avoiding the occurrence of cuproptosis [51,52]. The expression of numerous genes involved in glucose

metabolism is altered in tumors. This alteration of gene expression is associated with the promotion of aerobic glycolysis in tumors. To promote glucose uptake, tumors upregulate the expression of multiple solute carrier family 2 members (GLUTs). In pancreatic cancer, forkhead box D1 (FOXD1) promotes GLUT1 expression by facilitating its transcription and inhibiting GLUT1 degradation. The overexpression of GLUT1 has been demonstrated to facilitate the aerobic glycolysis, proliferation, invasion and metastasis of pancreatic cancer [53]. In pancreatic cancer, the mutations in K-Ras upregulate GLUT2 expression and promote aerobic glycolysis [54]. A previous study demonstrated that the inhibition of aerobic glycolysis in tumors can be achieved through the use of glycolysis inhibitors. Conversely, the expression of GLUT1/3 in a tumor glucose-deficient environment is sufficient to maintain tumor aerobic glycolysis [55]. In tumor glucose metabolic reprogramming, the expression and activity of multiple proteins in the glycolytic pathway are altered. Hexokinases (HKs) are the first key enzymes in the glycolytic, responsible for the production of glucose-6-phosphate. Hexokinases (HKs) include five distinct phenotypes, HK1-4 and hexokinase domain-containing protein-1 (HKDC1). In a variety of physiological conditions, HK1 is relatively conserved in a number of different tissues. In contrast, HK2 and HKDC1 are overexpressed in a number of different tumors, and are associated with a poor prognosis [56]. Multiple tumor-related pathways are activated to promote the expression of HK2. In Hepatitis B (HBV)-associated hepatocellular carcinoma, activation of the nuclear factor kappa-B (NF-κB) /p65/hexokinase 2 (HK2) signaling pathway leads to the induction of aerobic glycolysis in tumors and promotes the development of hepatocellular carcinoma [57]. SNHG26 interacts with nucleolin (NCL) to increase Myc proto-oncogene protein (c-MYC) expression, which subsequently promotes aerobic glycolysis and facilitates tumor progression by promoting HK2 expression. [58]. Furthermore, the expression of the HK2 gene was found to be strongly correlated with aerobic glycolysis and to play a role in the progression of breast and lung cancers [59,60]. Phosphofructokinases (PFKs) is the second key enzyme in the glycolytic pathway, with the capacity to catalyze fructose 6-phosphate(F-6-P) to fructose 1,6-bisphosphate (F-1,6-BP) [61]. Multiple studies

have shown that PFK is involved in the regulation of aerobic glycolysis. In colorectal cancer, the activation of mutant tumor protein 53 (p53) inhibits the progression of breast cancer by inhibiting PFK, which reduces tumor proliferation, migration and extracellular lactate levels.[62]. In head and neck squamous cell carcinoma, the inhibition of PFKFB3 also resulted in a significant inhibition of glucose uptake, lactate production and ATP production [63]. Pyruvate kinase (PK) is the last key enzyme in the glycolytic pathway that produces pyruvate [64]. The PK is comprised of four isoforms (1, PKM2, PKR, PKL), with PKM2 being the most widely expressed in tissues and being closely related to aerobic glycolysis and tumor development [64]. In breast cancer, the methylation of coactivator-associated arginine methyltransferase 1 (CARM1) modifies PKM2, resulting in the conversion of PKM2 from a dimer to a tetramer. This process increases PKM2 activity. The highly active form of PKM2 significantly promotes aerobic glycolysis in breast cancer [65]. In hepatocellular carcinoma, the activation of the HIF-1α/Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ)/PKM2 axis results in the upregulation of PKM2 expression, which in turn leads to the aerobic glycolysis of tumors. This process contributes to the development of drug resistance in hepatocellular carcinoma [66]. The generation of lactic acid from pyruvate catalyzed by lactate dehydrogenase (LDHA) is the final step in aerobic glycolysis. LDH is comprised of six distinct types, with LDH1-5 representing a combination of LDHA and LDHB, and LDH6 being LDHC [67]. Among the six types of LDH, LDHA demonstrated a higher affinity for pyruvate and facilitated the conversion of pyruvate to lactate [67]. The LDHA appears to be highly expressed in a variety of tumors and is strongly associated with tumor aerobic glycolysis. In colorectal cancer (CRC), methyltransferase 3, N6-Adenosine-Methyltransferase complex catalytic subunit (METTL3) promotes aerobic glycolysis in CRC by triggering the translation of LDHA mRNA via HIF-1α mRNA, as well as methylating the coding sequence region of LDHA and recruiting YTH N6-Methyladenosine RNA binding protein F1 (YTHDF1) [68]. The high expression of LDHA in pancreatic cancer is also closely associated with high levels of aerobic glycolysis.Nucleolar and spindle associated protein 1 (NUSAP1) has been

demonstrated to promote the expression of LDHA and aerobic glycolysis in pancreatic cancer by directly binding to the c-Myc and HIF-1α. [69]. Furthermore, Aurora-A has been demonstrated to promote glycolysis by phosphorylating LDHB, suggesting that tumor cells may alter their metabolic state by regulating the balance between LDHA and LDHB [70]. Taken together, tumor glucose metabolic reprogramming altered the expression and activity of multiple enzymes involved in the glycolytic pathway, including GLUTs, HKs, PFKs, PKMs and LDHs (Fig.3A). The aerobic glycolysis is a necessary alteration for tumors to adapt to metabolic demands and the surrounding growth environment. This altered metabolic state also reduces the flux of pyruvate into the TCA cycle thereby decreasing the tumor's dependence on oxidative phosphorylation and increasing its dependence on glycolysis. Tumor's over-reliance on aerobic glycolysis also subtly avoids cuproptosis.

Tumor glucose metabolic reprogramming and cuproptosis-related genes

Multiple cuproptosis-related genes are closely associated with tumor glucose metabolic reprogramming. Consequently, alterations in tumor glucose metabolic status may directly influence the expression profile of cuproptosis-related genes, thereby inhibiting the occurrence of cuproptosis.

The pyruvate dehydrogenase complex (PDC) is a key enzyme that converts pyruvate to acetyl-CoA, linking TCA cycle. The PDC consists of three components, pyruvate dehydrogenase (E1), DLAT and dihydrolipoamide dehydrogenase (E3), of which DLAT, PDHA1 of the E1 subunit and PDHB of the E1 subunit are the key genes for cuproptosis [3,71,72]. During the aerobic oxidation of glucose, pyruvate binds to the E1 subunit in the presence of thiamine pyrophosphate (TPP) and decarboxylates, followed by lipoylation of DLAT coupling the E1 and E3 subunits leading to the synthesis of CoA into Acetyl-CoA [73]. The activation of the PDC is both essential for the aerobic metabolism of glucose and a requirement for the occurrence of cuproptosis [3].

The activity of PDC in tumor glucose metabolic reprogramming is significantly

diminished. PDHA1 is a subunit of E1, and the inhibition of PDHA1 in tumor glucose metabolic reprogramming represents a pivotal step in the inhibition of PDC. Pyruvate dehydrogenase kinases (PDKs) include PDK1-4 types, and PDKs are responsible for the inactivation of PDC by phosphorylating serine residues of PDHA1. In colorectal cancer, the non-SMC condensin II complex subunit D3 (NCAPD3) inhibits PDC and TCA cycle by increasing the level of E2F1 and interacting with E2F1, which is recruited to the promoter region of the PDK1 and PDK3 genes [74]. Furthermore, the up-regulation of HIF-1α has been demonstrated to be strongly associated with glucose metabolic reprogramming, driven by HIF-1α stabilization-induced upregulation of PDK and LDHA[75,76]. In colorectal and cervical cancers, the up-regulation of HIF-1α has been shown to promote the expression of PDK3. Highly expressed PDK3 significantly inhibited PDC activity, thereby promoting aerobic glycolysis [77,78]. PDK2 also plays an essential role in tumor glucose metabolic reprogramming. c-Myc, an important oncogene, is also associated with glucose metabolic reprogramming. A study has shown that the c-Myc gene promotes the expression of PDK2, which in turn promotes tumor glucose metabolic reprogramming and inhibits the TCA cycle in colorectal cancer [79]. p53 plays a pivotal role in suppressing the growth of tumors. It inhibits the metabolic reprogramming of glucose and the proliferation of cells by downregulating the expression of PDK2 [80]. Abnormally elevated PDK4 in high-grade bladder cancer is strongly associated with poor tumor prognosis, with studies suggesting that activation of the HIF-1α pathway inhibits PDC activation by promoting pdk4 expression in bladder cancer ultimately leading to tumor aerobic glycolysis [81-83].

PDHB is an important subunit of E1, and high expression of PDHB promotes cuproptosis. In tumors, high PDHB expression of PDHB also predicts a good prognosis [84-86]. Research has shown that in colorectal cancer, miR-146b-5p can promote aerobic glycolysis, growth, invasion, and metastasis of tumors by inhibiting the expression of PDHB [87]. In ovarian cancer, miR-203 was also found to promote aerobic glycolysis with tumor growth and migration by inhibiting the expression of PDHB [88].

Glutaminase (GLS) is a negative cuproptosis-related gene that converts glutamine (Gln) to glutamate (Glu) [3]. In tumor glucose metabolic reprogramming, the use of glucose by the TCA cycle is reduced, however to accommodate tumor metabolism and synthesis, Gln is involved in the tumor TCA cycle as an important carbon source. To accommodate the tumor demand for Gln, GLS expression was significantly upregulated and strongly correlated with poor tumor prognosis [89]. In hepatocellular carcinoma, aberrant activation of thehepatocyte growth factor- hepatocyte growth factor receptor pathway (HGF-MET) is closely associated with growth, invasion and tumor glucose metabolic reprogramming. It has been shown that activation of this pathway promotes GLS activity and inhibits PDC activity thus promoting aerobic glycolysis and inhibiting cuproptosis in tumors [90]. In leukaemia, GLS was also found to promote glutamine utilization by the TCA cycle as an alternative carbon source following reprogramming of tumor glucose metabolism. The use of Gln is achieved by NF-κB, which promotes GLS expression [91]. In colorectal cancer, increased expression of aerobic glycolysis-related genes, including GLUT1, HK2 and PKM2, is associated with increased GLS [92].

A variety of cuproptosis-related genes are altered in tumor glucose metabolic reprogramming, which on the one hand promotes the onset of tumor glucose metabolic reprogramming and on the other hand inhibits the occurrence of cuproptosis (Fig.3B). Exploring the relationship between cuproptosis-related genes and tumor glucose metabolic reprogramming could both alter the metabolic state of tumors and promote the onset of cuproptosis, thereby inhibiting tumor progression. However, there are still several cuproptosis-related genes whose association with tumor glucose metabolic reprogramming remains to be explored. Refining the mechanism of cuproptosis and exploring the association of cuproptosis-related genes with tumor glucose metabolic reprogramming are of great significance for the application of cuproptosis in tumors.

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Tumor glucose metabolic reprogramming inhibits cuproptosis by regulating mitochondrial labile copper pool

The PPP is a key pathway upregulated in tumor glucose metabolic reprogramming. The PPP generates pentose phosphates as essential substrates for DNA and RNA synthesis and NADPH, a dedicated electron donor for biosynthetic reactions and redox maintenance [3]. GSH plays critical roles in anti-ROS defense and detoxification. In cells, GSH exists in both thiol-reduced (GSH) and disulfide-oxidized (GSSG) states. GSH synthesis occurs via two primary routes: 1) De novo synthesis where cysteine (Cys) and glutamate (Glu) form γ-glutamylcysteine (γ-Glu-Cys) catalyzed by glutamate-cysteine ligase (GCL), followed by the addition of glycine (Gly) catalyzed by glutathione synthetase (GSS); and 2) Reduction of GSSG back to GSH, which is directly dependent on NADPH [93]. Crucially, the PPP is the primary cellular source of NADPH. Within the PPP, the oxidative branch (initiated by glucose-6-phosphate dehydrogenase, G6PD) is the direct generator of NADPH. The non-oxidative branch (involving transketolase, TKT, and transaldolase) primarily functions to interconvert sugar phosphates, replenishing glycolytic intermediates (like fructose-6-phosphate and glyceraldehyde-3-phosphate) to sustain flux through the NADPH-producing oxidative branch [93, 99]. GSH levels are elevated in many tumors and are closely associated with proliferation, metastasis, and chemoresistance. Importantly, GSH serves as a major intracellular copper chelator, directly inhibiting cuproptosis [3, 93]. However, the subcellular compartmentalization of GSH is paramount for its function in copper detoxification. While the cytosol contains the majority of cellular GSH, the mitochondrial pool (mGSH), imported via specific carriers like SLC25A11 (the 2-oxoglutarate carrier), is critical for neutralizing copper ions at the execution site of cuproptosis within the mitochondrial matrix [99, 100]. Limitations in SLC25A11-mediated transport capacity can restrict mGSH availability, potentially limiting copper chelation efficiency in mitochondria despite high cytosolic GSH levels [99, 100].

Gln is an important substrate providing Glu for the de novo synthesis of GSH. Tumors

exhibit increased Gln utilization. Blocking Gln metabolism inhibits tumor aerobic glycolysis, disrupts the TME, and suppresses tumor growth [94]. The oncogene c-Myc, involved in promoting aerobic glycolysis, also enhances Gln uptake. Highly expressed c-Myc promotes Gln entry into the TCA cycle and facilitates GSH synthesis by providing Glu [95]. Furthermore, Gln metabolites can contribute to NADPH production via mechanisms like malic enzyme, providing the essential coenzyme for reducing GSSG back to GSH [93, 96]. As noted, the PPP pathway remains the predominant source of cellular NADPH. Key pathways in aerobic glycolysis are interconnected with PPP regulation. For instance, oncogenic k-Ras in pancreatic ductal adenocarcinoma stimulates glycolysis and diverts glycolytic intermediates into the PPP pathway [97]. In colorectal cancer, aberrant activation of both aerobic glycolysis and the PPP promotes tumor progression and reduces oxidative stress and apoptosis, likely mediated by increased NADPH and consequently GSH levels [98].

In conclusion, reprogramming of tumor glucose metabolism enhances flux through the PPP, particularly its oxidative branch, to generate abundant NADPH, which is essential for maintaining GSH in its reduced, active form (by reducing GSSG). Simultaneously, this reprogramming increases tumor uptake of Gln, providing the substrate Glu (and indirectly Cys via the transsulfuration pathway) for de novo GSH synthesis. The resulting high levels of GSH in tumors scavenge ROS and, critically, act as a copper chelator to inhibit cuproptosis. However, the efficiency of this protection at the mitochondrial execution site depends critically on the availability of mGSH, which can be constrained by transport limitations [99, 100]. (Fig. 3C). Beyond GSH, metallothioneins (MTs) synergistically contribute to copper detoxification. Tumor glycolysis-derived NADPH maintains MTs in a reduced state, enhancing their copper-binding capacity [101]. Notably, HIF-1α–mediated suppression of MTs in hypoxic tumor niches may render cells transiently vulnerable to copper overload, but this is counterbalanced by GSH upregulation and glycolytic flux redirection. This dual system (MTs/GSH) exemplifies metabolic plasticity in evading copper toxicity.

Limitations and future directions

While this review discusses how glucose metabolic reprogramming may suppress cuproptosis in tumors, key limitations exist. First, most evidence comes from in vitro studies, requiring validation in animal models and clinical samples [3,52]. Second, copper's role in cancer is complex - while generally tumor-promoting, it can also suppress tumors in certain contexts [28,48]. Future work should clarify these opposing effects. Additionally, how cuproptosis interacts with other cell death pathways like ferroptosis needs exploration [33,93]. Finally, tumor metabolic flexibility may limit copper-targeting therapies [55,97].

CONCLUSION

As an essential trace element, excess copper can lead to cellular death as well. Tsvetkov et al.'s study revealed the specific mechanism by which copper causes cell death. Cuproptosis represents a novel form of cell death, and cuproptosis-related genes are strongly associated with glucose metabolism. Glycolysis-dependent cells demonstrate resistance to cuproptosis. Cuproptosis may be an effective strategy to anti-tumor.

Tumors are a serious threat to human health, the existing medical treatments for tumors are very limited. Tumorigenesis is influenced by a multitude of factors, with tumor glucose metabolic reprogramming representing one of the hallmarks of tumors. Tumor glucose metabolic reprogramming promotes aerobic glycolysis to accelerate energy supply and alter the tumor microenvironment. The highly active PPP pathway provides sufficient ribose and NADPH to the tumor.

The glucose metabolic reprogramming results in tumor dependence on glycolysis and alters the activity of several cuproptosis-related genes. Tumor glucose metabolic reprogramming also stimulates the activity of the PPP pathway, the product of which, NADPH, is an essential factor in the reduction of GSSH to GSH. Finally, the dependence of tumors on Gln resulting from tumor glucose metabolic reprogramming is also a substrate for GSH synthesis. In conclusion, tumor glucose metabolic

reprogramming collectively inhibits cuproptosis by promoting aerobic glycolysis, increasing GSH synthesis, and altering the activity of cuproptosis-related genes. Therefore, inhibition of tumor glucose metabolic reprogramming may be an effective strategy to promote the onset of tumor cuproptosis.

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TABLES AND FIGURES WITH LEGENDS

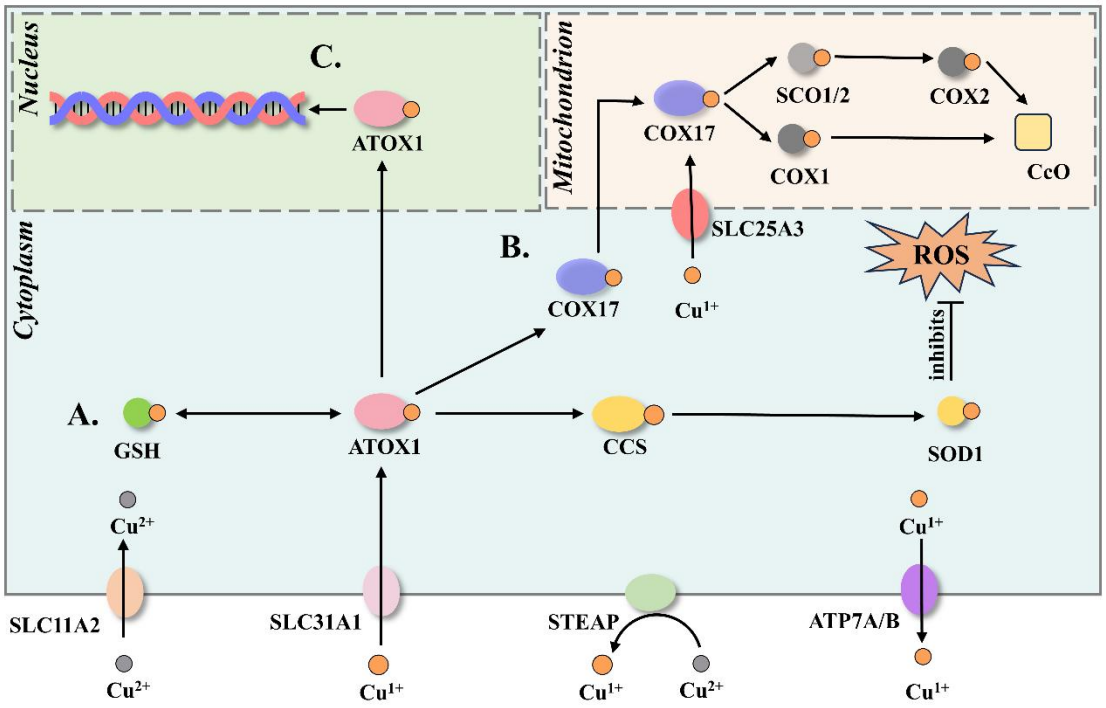

Figure 1. Summary of copper metabolism. (A) Extracellular Cu^{2+} is first reduced to $Cu1^{+}$ by STEAP reductases, followed by primary uptake via the SLC31A1 transporter. Concurrently, SLC11A2 mediates auxiliary Cu^{2+} transport. Within the cytosol, Cu^{1+} binds either to ATOX1—which delivers copper to CCS for loading onto SOD1 to enable ROS scavenging—or to glutathione (GSH) forming complexes. Cellular copper efflux is ultimately mediated by ATP7A/B transporters. (B) $Cu1^{+}$ enters mitochondria via COX17/SLC25A3. COX17 delivers copper to SCO1/SCO2 for Cu incorporation into CcO's COX1 subunit, enabling CcO assembly and ETC function. (C) ATOX1 transports $Cu1^{+}$ into the nucleus to regulate gene expression.

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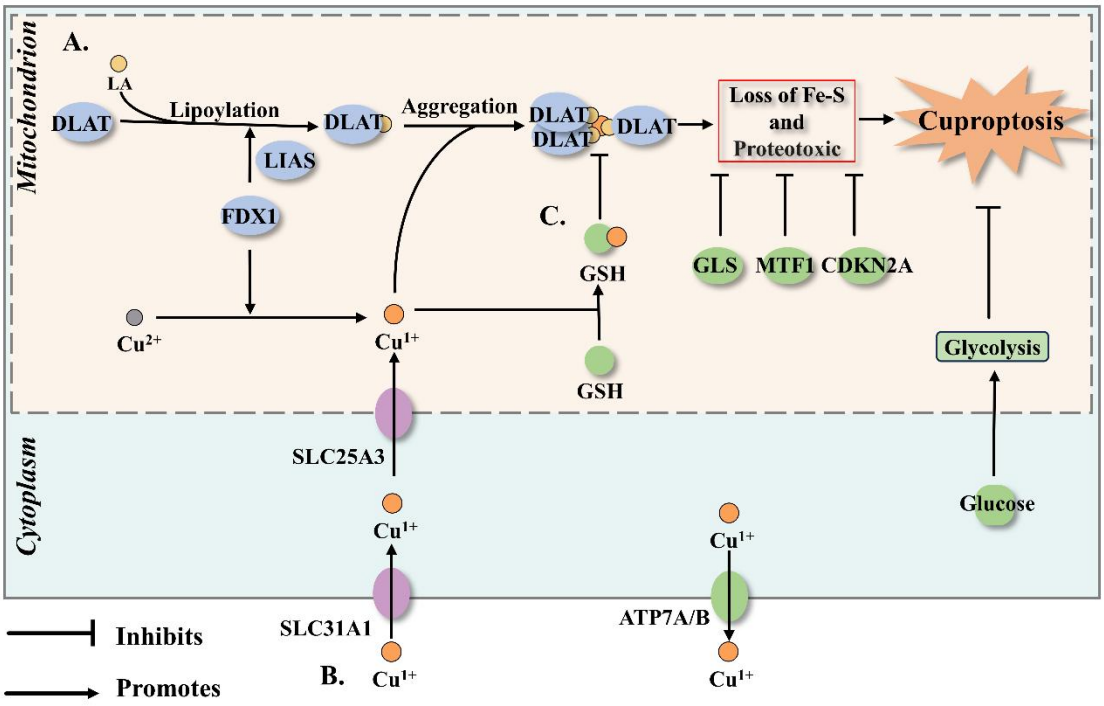

Figure 2. Mechanism and regulation of cuproptosis. (A) The major pathway of cuproptosis. FDX1 is the upstream regulator of cuproptosis and promotes DLAT lipoylation through direct binding to LIAS. The lipoylation of DLAT binds to Cu^{1+}, resulting in aggregation. This process leads to proteotoxic stress, loss of Fe-S and cell death. (B) Copper in the pathway of cuproptosis. Cu^{1+} is transported into the cytoplasm via SLC31A1 and into the mitochondria via SLC25A3. In mitochondria, Cu^{2+} can be reduced to Cu^{1+} by FDX1. Cu^{1+} binds to the lipoylation of DLAT to facilitate the process of cuproptosis and can also be bound by GSH. (C) Factors negatively associated with cuproptosis. The green labels represent factors that are negatively associated with cuproptosis. These include genes that are negatively associated with cuproptosis (GLS, CDKN2A and MTF1), glycolysis, GSH and ATP7A/B.

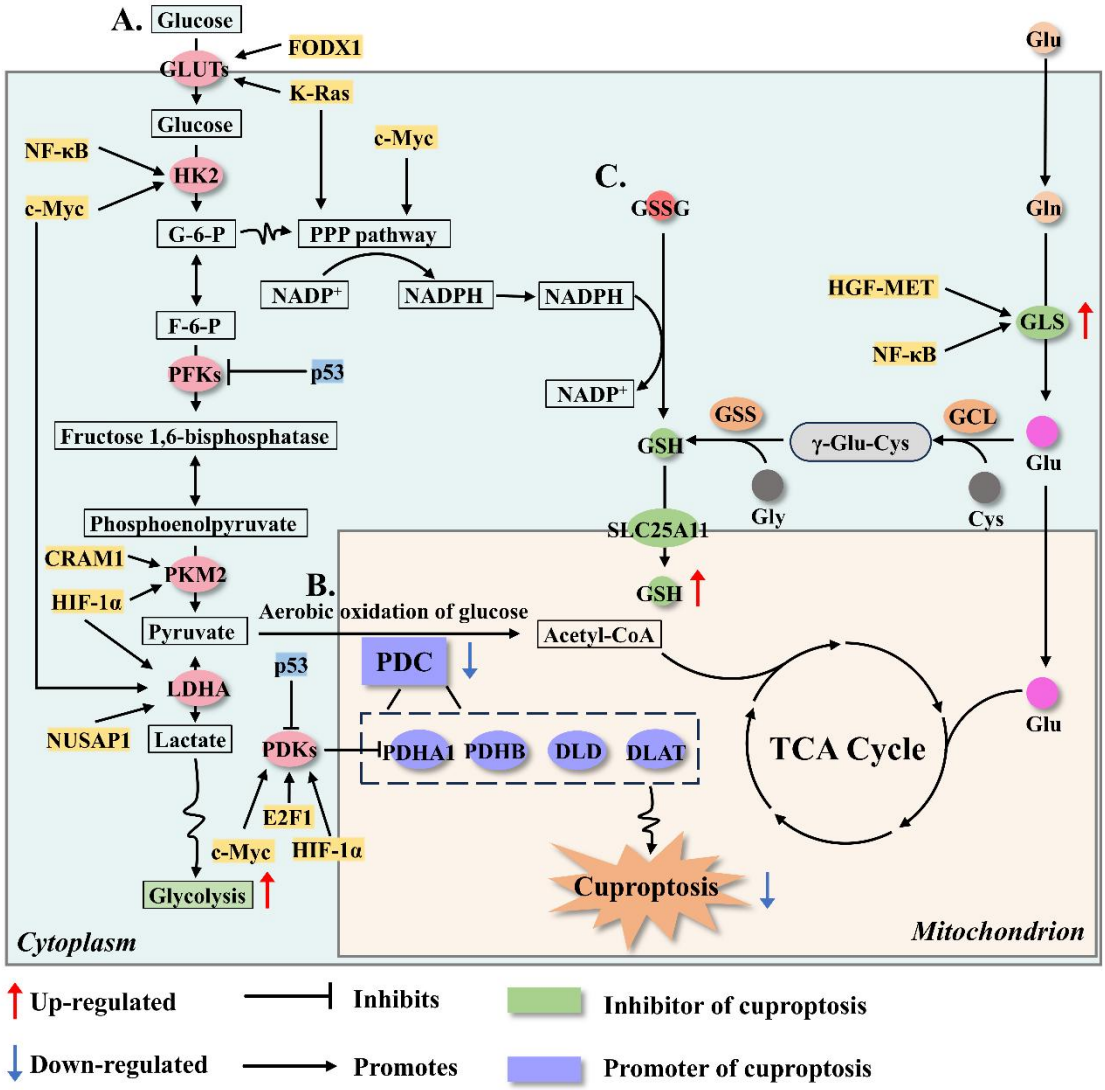

Figure 3. Comprehensive overview of the potential mechanisms through which tumor glucose metabolic reprogramming regulates cuproptosis.

(A) Tumors promote aerobic glycolysis by regulating glycolysis-related genes, which subsequently inhibits cuproptosis. (B) Tumor glucose metabolic reprogramming inhibits cuproptosis-related genes via PDKs, subsequently suppressing cuproptosis. (C) Fig. 3C. PPP sustains reduced GSH via NADPH for Cu^{+}-chelation, depleting mitochondrial labile copper to block cuproptosis.