**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 85445

**Manuscript Type:** MINIREVIEWS

**Progress in the research of cuproptosis and possible targets for cancer therapy**

Wang J *et al*. Cuproptosis and possible target for cancer therapy

Jiang Wang, Lan-Zhu Luo, Dao-Miao Liang, Chao Guo, Zhi-Hong Huang, Guo-Ying Sun, Jie Wen

**Jiang Wang, Lan-Zhu Luo, Zhi-Hong Huang,** Children Medical Center, Hunan Provincial People’s Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

**Dao-Miao Liang, Chao Guo,** Department of Hepatobiliary Surgery, Hunan Provincial People’s Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

**Guo-Ying Sun,** Department of Histology and Embryology, Hunan Normal University School of Medicine, Changsha 410013, Hunan Province, China

**Jie Wen,** Department of Pediatric Orthopedics, Hunan Provincial People’s Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

**Author contributions:** Wang J and Luo LZ contributed equally to this study, and share joint first authorship; Wang J wrote the paper; Luo LZ and Liang DM did the literature review; Guo C and Huang ZH did the data analysis; Luo LZ conceived and coordinated the study; Sun GY and Wen J contributed equally to this study, and are joint corresponding authors; All authors reviewed the results and approved the final version of the manuscript.

**Supported by** Scientific Research Project of Hunan Education Department, No. 21A0054.

**Corresponding author: Jie Wen, PhD, Associate Professor,** Department of Pediatric Orthopedics, Hunan Provincial People’s Hospital, the First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Rd, Changsha 410013, Hunan Province, China. cashwj@qq.com

**Received:** April 28, 2023

**Revised:** August 5, 2023

**Accepted:** September 4, 2023

**Published online:**

**Abstract**

Developing novel cancer therapies that exploit programmed cell death pathways holds promise for advancing cancer treatment. According to a recently published study in Science, copper death (cuproptosis) occurs when intracellular copper is overloaded, triggering aggregation of lipidated mitochondrial proteins and Fe–S cluster proteins. This intriguing phenomenon is triggered by the instability of copper ions. Understanding the molecular mechanisms behind cuproptosis and its associated genes, as identified by Tsvetkov, including ferredoxin 1, lipoic acid synthase, lipoyltransferase 1, dihydrolipid amide dehydrogenase, dihydrolipoamide transacetylase, pyruvate dehydrogenase α1, pyruvate dehydrogenase β, metallothionein, glutaminase, and cyclin-dependent kinase inhibitor 2A, may open new avenues for cancer therapy. Here, we provide a new understanding of the role of copper death and related genes in cancer.

**Key Words:** Cuproptosis; Cuproptosis-related genes; Cancer; Targeted therapy

Wang J, Luo LZ, Liang DM, Guo C, Huang ZH, Sun GY, Wen J. Progress in the research of cuproptosis and possible targets for cancer therapy. *World J Clin Oncol* 2023; In press

**Core Tip:** Developing novel cancer therapies that exploit programmed cell death pathways holds promise for advancing cancer treatment. Cuproptosis-related genes were identified by Tsvetkov, including ferredoxin 1, lipoic acid synthase, lipoyltransferase 1, dihydrolipid amide dehydrogenase, dihydrolipoamide transacetylase, pyruvate dehydrogenase α1, pyruvate dehydrogenase β, metallothionein, glutaminase, and cyclin-dependent kinase inhibitor 2A. Here, we provide a new understanding of the role of copper death and related genes in cancer.

**INTRODUCTION**

Tsvetkov *et al*[1] have proposed an intriguing new form of programmed cell death related to the mitochondrial tricarboxylic acid (TCA) cycle, resulting in proteotoxic stress and copper-induced death, referred to as cuproptosis. These forms of oxidative-stress-induced cell death are characterized by mitochondrial stress, including the accumulation of fatty acylated mitochondrial enzymes and the loss of Fe–S cluster proteins[1]. The dysregulation of copper homeostasis promotes cancer growth and causes irreversible cellular damage. A variety of mechanisms have been suggested for the ability of copper to induce cell death, such as oxidative stress, proteasome inhibition, and antiangiogenesis[2].

The exact molecular mechanism underlying cuproptosis remains unclear, but recent studies have shed light on potential contributors. For instance, knockout of the ferredoxin (FDX) 1 gene attenuates copper ionophore-induced cell death. Additionally, genes associated with the loss of lipidated mitochondrial enzymes and Fe-S cluster proteins loss, such as lipoic acid synthase (LIAS), lipoyltransferase (LIPT) 1, and dihydrolipoamide transacetylase (DLAT), may contribute to cuproptosis[1,3].

Although the precise correlation between cuproptosis and cancer is yet to be fully understood, imbalances in copper homeostasis have been implicated in cancer growth and cause irreversible cellular damage. Copper metabolism *in vivo* and cancer therapy has been extensively studied[4,5]. Certain genes involved in the cuproptosis pathway, such as FDX1, may also play a role in cancer development, serving as a key regulator of proptosis and associated with poor prognoses in specific cancer types[6]. Here, we review the progress of copper ions in cancer therapy, the function of cuproptosis-related genes in cancer, and the possible target in cuproptosis.

**Copper ions and cancer therapy**

Recent studies have revealed three distinct mechanisms through which copper ions may induce cancer cell death. (1) Oxidative stress induction: Anticancer drug elesclomol has been found to exert its therapeutic effects through the transfer of copper ions to mitochondria, leading to oxidative stress[7]. Liu *et al*[8] demonstrated that flavonoids can induce mitochondrial apoptosis through modification of the redox cycle of copper ions; (2) inhibition of proteasomes: Chen *et al*[9] synthesized copper diethyldithiocarbamate [Cu(DDC)(2)] nanoparticles (NPs) that improved the resistance of prostate cancer to treatment. Copper-ion-mediated endoplasmic reticulum (ER) stress is induced by proteasome inhibition and accumulation of ubiquitinated proteins. Proteasome inhibitors like bortezomib and carfilzomib have been explored for their potential as cancer treatment options in the form of various complexes, such as clioquinol and dithiocarbamates[10]; and (3) reduce angiogenesis: Copper ions play a significant role in endothelial cell migration, proliferation, and fibronectin synthesis, crucial steps in angiogenesis[11,12]. However, copper depletion can act as an antiangiogenic switch, blocking the growth of endothelial cells and preventing their proliferation. By inhibiting copper transporters or chaperones like human antioxidant protein 1 and consolidation tumor ratio-1, in addition to direct capture of intracellular copper, copper imbalance can be induced, leading to antiangiogenic effects[13,14]. Combining this approach with vascular targeting techniques, such as immunotherapy, can enhance the cancer-killing effects[15]. The tumor microenvironment (TME) is a complex ecosystem where various immune cells interact and influence tumor growth and progression[16,17]. In the early stage of tumor growth, neutrophils promote inflammation and tumor cell apoptosis by releasing cytokines. However, in the middle and late stages of tumor formation, neutrophils contribute to angiogenesis, accelerating tumor progression and local infiltration. Different T cell populations are involved in TME, among which CD8+ T cells can target and destroy tumor cells, secrete interferon, and inhibit angiogenesis. CD4+ T cells coordinate immune responses, with Th1 cells promoting cancer and T regulatory cells promoting tumor formation and survival, by secreting auxin and cytokines, which then interacts with fibroblasts and epithelial cells. Although less prevalent than T cells, tumor-infiltrating B cells have antitumor effects, including antigen presentation to T cells, production of antitumor antibodies, and secretion of cytokines that promote cytotoxic immune responses. Regulatory B cells, in contrast, promote tumors by producing cytokines that promote the immunosuppressive phenotype in macrophages, neutrophils, and cytotoxic T cells. Tumor-associated macrophages (TAMs) are the predominant immune cells in the TME. They are involved in coordinating cancer-related inflammation and can release macrophage colony-stimulating factor to recruit TAMs, which have been implicated in cancer development. Moreover, TAMs can release epidermal growth factor, modify cancer cells, and accelerate cell migration and metastasis. Medullary suppressive cells promote tumor invasion by weakening innate and adaptive antitumor responses.

In light of the mechanisms described above for copper ions in cancer treatment, copper complexes have been extensively studied for their potential in anticancer therapy (Figure 1). For instance, copper-amino acid sulfhydryl NPs can reduce Cu2+ to Cu+ when reacting with localized glutathione. The generated Cu+ then reacts with hydrogen peroxide, resulting in an increase in reactive oxygen species (ROS) levels. Excessive ROS can induce apoptosis of cancer cells[18]. A copper-containing complex known as Cu-tuberous sclerosis complex (TSC) is another widely used complex to enhance cytotoxicity of TSC and ROS production[19]. Chronic inflammation in the body can induce carcinogenesis and facilitate cancer spread. Copper complexes containing nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammation and prevent cancer development (Table 1). In breast cancer stem-cell-like cells, Boodram *et al*[20] demonstrated that Cu-NSAID complexes could induce ROS accumulation, DNA damage, and cyclooxygenase-2 inhibition. Copper complexes with subcellular targeting properties can deliver more precise attacks on cancer cells. Kaur *et al*[21] reported that copper complexes containing polypyridine ligands could enter the ER in situ, leading to increased ROS levels and ER-stress-induced immunogenic cell death in cancer cells[22]. Although copper-complex-related therapies hold promise as a new anticancer strategy, their biocompatibility and application safety are critical challenges. Researchers have shown that copper complexes are cancer-killing, but long-term stability and biosafety tests remain to be conducted before these therapies can be translated into clinical applications.

**The role of cuproptosis-related genes in cancer**

Cuproptosis remains an area of active exploration in its relationship with cancer. However, significant research has been conducted to understand the mechanisms through which cuproptosis-related gene molecules contribute to cancer development (Table 2). Figure 2 illustrates how these genes induce cuproptosis.

**FDX1**

FDX1 is a FDX protein primarily found in mitochondria, with diverse physiological functions, including the conversion of cytochromes during steroid hormone synthesis and vitamin D metabolism[23]. Shi *et al*[24] demonstrated that FDX1 is critical for Fe–S cluster biogenesis. Recent research has identified FDX1 as a key gene in the regulation of cuproptosis[25]. Zhang *et al*[26] study found that FDX1 expression did not significantly differ across clinical stages in most cancers. Although the reduction in FDX1 expression may not directly impact the growth, apoptosis, or cell cycle distribution of LUAD cells, it could affect their metabolism, as FDX1 knockout has been shown to promote glycolysis and fatty acid oxidation. Further investigations into the mechanisms of FDX1 in cancer pathogenesis revealed significant positive correlations between FDX1 expression and immune cells in most cancers. FDX1 has been associated with major histocompatibility complex, immune activation, immune suppression, chemokines, and chemotaxis[27]. Additionally, the products of factor receptors were positively coexpressed with FDX1, except for 1-aminocyclopropane-1-carboxylic acid and tetrahydrocannabinolic acid. This indicates that FDX1 expression is closely related to the immune response of cancer cells, which has implications for prognosis and represents a potential target for immunosuppressants[28,29]. Given the crucial role of copper ions in cuproptosis, the significance of FDX1 as a key gene in this process makes it an intriguing target for cancer therapy. Studies exploring its role may offer valuable insights as it directly influences the protein fatty acylation cycle, leading to the aggregation of these proteins and interference with respiratory chain iron-sulfur cluster proteins.

**LIAS**

LIAS encodes a protein belonging to the biotin and LIAS families. Located in the mitochondria, this Fe–S enzyme contributes to lipoic acid biosynthesis, serving as the final step in the process. Diseases like diabetes, atherosclerosis, and neonatal epilepsy are associated with a lack of LIAS expression. Current studies on the association between the LIAS gene and cancer have predominantly focused on lung cancer[29].

Using in situ hybridization and real-time quantitative PCR, Mabeta *et al*[30]investigated the differential expression of the LIAS gene in normal lung tissue and lung cancer samples. Their findings suggest that alteration in LIAS expression levels can promote lung cancer development, making LIAS an attractive target for novel therapies[29]. However further studies are warranted to confirm its therapeutic effectiveness.

**LIPT1**

As a member of the fatty acyltransferase family, LIPT1 encodes an enzyme that catalyzes the transfer of fatty acyl groups from fatty acyl-AMPs to specific lysine residues in fatty-acid-dependent enzymes. LIPT1-related disorders include fatty acyltransferase 1 deficiency and leukodystrophy[31]. While there have been relatively few studies on LIPT1 in cancer, Chen *et al*[32] conducted a systematic investigation of genes related to prognosis in bladder cancer using the pathological atlas of the Cancer Genome Atlas. Their findings revealed a correlation between LIPT1 expression and bladder cancer prognosis[32]. However, further research is needed to elucidate the role of LIPT1 in other cancer types.

**dihydrolipoamide dehydrogenase (DLD)**

DLD, encoded by the DLD gene, is an essential enzyme that significantly impacts cell metabolism, particularly pyruvate metabolism and the TCA cycle[33]. There is evidence that DLD could be used as a cancer-targeted therapy. In head and neck squamous cell carcinoma, DLD has been shown to be closely related to cystine deprivation and glutaminolysis. The biological function of DLD enhances mitochondrial KDH, MMP, and glutaminase activity. Increasing mitochondrial iron levels can facilitate mitochondrial lipid peroxidation, or silencing DLD, which effectively reduces the proportion of cells undergoing death from cystine deprivation and reduces ROS levels in cystine-deprived cells. These processes have been closely related to cancer-programmed death[34]. Patients with endometrial cancer have exhibited abnormal levels of IgA and non-DLD IgG autoantibodies in their sera, indicating a correlation with mitochondrial DLD protein[35]. Comparing DLD protein expression levels between breast cancer and normal tissues revealed significant differences, highlighting the potential of DLD as a diagnostic and therapeutic target in breast cancer[36]. Using DLDH-based exogenous ROS to target skin cancer cells, Avraham *et al*[37] developed a method for targeting cancer cells, which could be a potential approach for melanoma treatment in the future.

**DLAT**

DLAT is an essential component of the pyruvate dehydrogenase complex, along with DLD and pyruvate dehydrogenase. This enzyme complex plays a crucial role in the synthesis of pyruvate acetyl-CoA. As the sole enzyme capable of converting citric acid into acetyl-CoA, DLAT can control the citric acid cycle–oxidative phosphorylation pathway, thus affecting the energy supply of cancer cells[38]. In gastric cancer cells, DLAT expression was significantly upregulated[39], making it a potential therapeutic target. DLAT promotes the growth of cancer cells by activating the pentose phosphate pathway[40]. Alternol, a compound that binds to multiple Krebs cycle enzymes, inhibits mitochondrial respiration and ATP production. This discovery offers a novel therapeutic strategy for treating prostate cancer[41].

**pyruvate dehydrogenase α1 (PDHA1) and pyruvate dehydrogenase β (PDHB)**

PDHA1 and PDHB encode subunits of the pyruvate dehydrogenase complex, an essential enzyme complex within the mitochondria responsible for catalyzing pyruvate oxidation to acetyl-CoA, connecting glycolysis and the TCA cycle.

PDHA1 inhibition can increase proliferation, glycolysis, and Warburg effect in certain cancer cells. Gastric cancer has been shown to downregulate PDHA1, and elevated expression of PDHA1 correlates with poor prognosis[42]. Downregulation of PDHA1 promotes the growth of gastric cancer. Exosomal miR-21-5p suppresses PDHA1 expression, thereby promoting glycolysis and cell proliferation in gastric cancer cells. PDHA1 expression in gastric cancer samples is negatively correlated with miR-21-5p levels[42]. Additionally, miR-21-5p/PDHA may influence ovarian cancer drug resistance through exosomal miR-21-5p-mediated regulation of PDHA1 expression[43]. The knockout strains had increased glycolysis, glucose intake, and glutamine consumption, while oxidative phosphorylation was inhibited, indicating enhanced Warburg effect and PDHA1. The proliferative capacity, angiogenic capacity, and drug resistance of the knockout esophageal cancer cells were significantly improved[44]. PDHA1 is closely associated with prostate cancer growth, where it is involved in mitochondrial lipid synthesis. Therefore, PDHA1 may be useful as a therapeutic target for prostate cancer[45].

PDHB also acts as a cancer suppressor gene. PDHB overexpression inhibits colon cancer cell proliferation, invasiveness, and glycolysis as it targets miR-146b-5p at the 3'-UTR end of the gene, promoting cancer cell growth[46]. Gastric cancer cells overexpressing PDHB exhibit reduced proliferation and migration[47]. PDHB inhibitors have also been shown to suppress cancer growth in various studies. For instance, reduced PDHB expression in non-small cell lung cancer indicates poor prognosis for patients[48], while PDHB may serve as a biomarker for breast cancer[49]. Thus, the progress made in the research on PDHA1 and PDHB in cancer highlights the broad potential applications of therapeutic drugs targeting these molecular targets.

**Metallothionein (MTF1)**

MTF1 plays a crucial role in the treatment resistance of malignant cancers[50]. Cells stimulated with heavy metals, such as copper, trigger the production of products encoded by MTF1, leading to the induction of metal sulfur production. During tumor biogenesis and progression, coexpression of proteins and other genes involved in metal homeostasis is implicated. Notably, MTF1 is highly expressed in ovarian cancer tissues, and its high expression is associated with poor patient survival and disease recurrence[51]. MTF1 knockout can inhibit the epithelial–mesenchymal transition process of ovarian cancer cells, thereby suppressing their proliferation, migration, and invasion, indicating that MTF1 may serve as a novel biomarker and therapeutic target for ovarian cancer[50]. Given the multiple aspects of MTF-1 activities, monitoring changes in its expression and activity during cellular stress and cancer may prove valuable for cancer screening and prognosis studies.

**Glutaminase (GLS)**

GLS encodes mitochondrial glutaminase K, which is dysregulated in many cancers. GLS can modulate promoter methylation modification and influence the clinical prognosis. In both in vitro and in vivostudies, GLS-targeted therapy has demonstrated its potential to inhibit cancer growth[52,53]. Similarly, GLS has been detected in clinical samples from breast cancer, esophageal cancer, head and neck cancer, and leukemia. The expression of GLS is associated with poor prognosis in statistical analysis. Therefore, GLS can be considered a prognostic biomarker for certain types of cancer[54]. However, its use as a prognostic biomarker remains controversial and further research is necessary to clarify its role and potential clinical applications[55].

**cyclin-dependent kinase inhibitor 2A (CDKN2A)**

During cancer development, aberrant gene silencing is highly associated with cell cycle regulation. Dysregulation of CDKN2A, which encodes the p16INK4a protein, has been causally linked to the pathogenesis of various cancer types, contributing to cancer recurrence, poor prognosis, cancer genesis, and metastasis[56]. CDKN2A mutations are responsible for 20%-40% of familial cancers and 2%-3% of sporadic melanomas[57]. Nonsynonymous mutations of CDKN2A were found in approximately 16% (9/56) of cutaneous melanoma metastases[58]. Activation of CDKN2A has been reported in 95% of pancreatic adenocarcinoma cases due to promoter hypermethylation[59]. In lung cancer, CDKN2A inactivation has been observed in 75% of cases (30/40), including 16 homozygous deletions, 10 methylations, and four mutations[60]. CDKN2A gene mutations and abnormal methylation have also been reported in ovarian, gastric, and colorectal cancers, among others[56]. Reactivating CDKN2A genetically and epigenetically could offer promising approaches for cancer prevention and treatment.

**Discussion**

Copper ion concentration in the human body is tightly regulated by a homeostatic mechanism to maintain trace levels, as excess copper becomes toxic and leads to cell death. However, the mechanism underlying copper-induced cytotoxicity is still unclear [61,62]. Recently, a novel form of cell death, cuproptosis, was discovered, which operates independently of known cell death mechanisms[1]. Cuproptosis-related genes were identified using CRISPR-Cas9 loss-of-function screens, which revealed seven positively regulated and three negatively regulated genes.

So far, the identified copper-ionophore-induced death genes include DLD, fatty acylated protein targets PDH complex including DLAT, PDHA, and PDHB. While studies on these genes in cancer have been more extensive[3], other components of the lipoic acid pathway, such as fatty acyl synthase LIAS and FDX1, remain relatively understudied in cancer, and further experiments are needed to verify their roles in different cancer types[1,3]. High cuproptosis activity status has been found to be a good prognostic indicator.

While some progress has been made in utilizing other types of programmed cell death for cancer treatment, there are still limitations in their application. Cuproptosis, being a novel form of programmed cell death, offers new perspectives on the correlation between its related genes and cancer prognosis. The combination of cuproptosis-targeted molecular drugs with existing therapies might open up new avenues for cancer treatment.

Currently, cuproptosis research is still in its infancy, and the existence of other signaling pathways for cell cuproptosis is not yet clear. Additionally, existing copper agents have poor targeting specificity and can cause serious side effects in patients undergoing treatment. These limitations and deficiencies impede the development and clinical implementation of cancer treatment strategies based on cuproptosis mechanisms.

In the future, researchers should focus on improving our understanding of the mechanism of cuproptosis in cancer cells and conducting thorough investigations into relevant mechanisms. Additionally, efforts should be directed towards developing copper-related formulations with high targeting and specificity (such as targeted nano-drug delivery systems) to maximize the targeting of cancer treatment while reducing toxic side effects. Lastly, it is necessary to develop and improve copper treatment plans in clinical practice in order to conduct relevant clinical trials and treatments for patients with cancer.

**CONCLUSION**

Cuproptosis is triggered by the direct interaction of copper ions with the fatty acylated components in the citric acid cycle of mitochondrial respiration. This interaction results in the aggregation of fatty acylated proteins and subsequent down regulation of Fe–S cluster proteins, leading to protein toxic stress and, ultimately leading to cell death (Figure 3). The elucidation of this mechanism provides a clear understanding of how previous copper ion drugs exert their antitumor effects. This provides potential possibilities for the clinical application of these drugs in antitumor therapy and also broadens the path for the development of new drugs targeting copper in the future.

**REFERENCES**

1 **Tsvetkov P**, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, Eaton JK, Frenkel E, Kocak M, Corsello SM, Lutsenko S, Kanarek N, Santagata S, Golub TR. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 2022; **375**: 1254-1261 [PMID: 35298263 DOI: 10.1126/science.abf0529]

2 **Oliveri V**. Selective Targeting of Cancer Cells by Copper Ionophores: An Overview. *Front Mol Biosci* 2022; **9**: 841814 [PMID: 35309510 DOI: 10.3389/fmolb.2022.841814]

3 **Tang D**, Chen X, Kroemer G. Cuproptosis: a copper-triggered modality of mitochondrial cell death. *Cell Res* 2022; **32**: 417-418 [PMID: 35354936 DOI: 10.1038/s41422-022-00653-7]

4 **Allensworth JL**, Evans MK, Bertucci F, Aldrich AJ, Festa RA, Finetti P, Ueno NT, Safi R, McDonnell DP, Thiele DJ, Van Laere S, Devi GR. Disulfiram (DSF) acts as a copper ionophore to induce copper-dependent oxidative stress and mediate anti-tumor efficacy in inflammatory breast cancer. *Mol Oncol* 2015; **9**: 1155-1168 [PMID: 25769405 DOI: 10.1016/j.molonc.2015.02.007]

5 **Babak MV**, Ahn D. Modulation of Intracellular Copper Levels as the Mechanism of Action of Anticancer Copper Complexes: Clinical Relevance. *Biomedicines* 2021; **9** [PMID: 34440056 DOI: 10.3390/biomedicines9080852]

6 **Zhang C**, Zeng Y, Guo X, Shen H, Zhang J, Wang K, Ji M, Huang S. Pan-cancer analyses confirmed the cuproptosis-related gene FDX1 as an immunotherapy predictor and prognostic biomarker. *Front Genet* 2022; **13**: 923737 [PMID: 35991547 DOI: 10.3389/fgene.2022.923737]

7 **Nagai M**, Vo NH, Shin Ogawa L, Chimmanamada D, Inoue T, Chu J, Beaudette-Zlatanova BC, Lu R, Blackman RK, Barsoum J, Koya K, Wada Y. The oncology drug elesclomol selectively transports copper to the mitochondria to induce oxidative stress in cancer cells. *Free Radic Biol Med* 2012; **52**: 2142-2150 [PMID: 22542443 DOI: 10.1016/j.freeradbiomed.2012.03.017]

8 **Liu ZH**, Yang CX, Zhang L, Yang CY, Xu XQ. Baicalein, as a Prooxidant, Triggers Mitochondrial Apoptosis in MCF-7 Human Breast Cancer Cells Through Mobilization of Intracellular Copper and Reactive Oxygen Species Generation. *Onco Targets Ther* 2019; **12**: 10749-10761 [PMID: 31849483 DOI: 10.2147/OTT.S222819]

9 **Chen W**, Yang W, Chen P, Huang Y, Li F. Disulfiram Copper Nanoparticles Prepared with a Stabilized Metal Ion Ligand Complex Method for Treating Drug-Resistant Prostate Cancers. *ACS Appl Mater Interfaces* 2018; **10**: 41118-41128 [PMID: 30444340 DOI: 10.1021/acsami.8b14940]

10 **Zhang Z**, Wang H, Yan M, Wang H, Zhang C. Novel copper complexes as potential proteasome inhibitors for cancer treatment (Review). *Mol Med Rep* 2017; **15**: 3-11 [PMID: 27959411 DOI: 10.3892/mmr.2016.6022]

11 **Park KC**, Fouani L, Jansson PJ, Wooi D, Sahni S, Lane DJ, Palanimuthu D, Lok HC, Kovačević Z, Huang ML, Kalinowski DS, Richardson DR. Copper and conquer: copper complexes of di-2-pyridylketone thiosemicarbazones as novel anti-cancer therapeutics. *Metallomics* 2016; **8**: 874-886 [PMID: 27334916 DOI: 10.1039/c6mt00105j]

12 **Baldari S**, Di Rocco G, Toietta G. Current Biomedical Use of Copper Chelation Therapy. *Int J Mol Sci* 2020; **21** [PMID: 32041110 DOI: 10.3390/ijms21031069]

13 **Yee EMH**, Brandl MB, Pasquier E, Cirillo G, Kimpton K, Kavallaris M, Kumar N, Vittorio O. Dextran-Catechin inhibits angiogenesis by disrupting copper homeostasis in endothelial cells. *Sci Rep* 2017; **7**: 7638 [PMID: 28794411 DOI: 10.1038/s41598-017-07452-w]

14 **Karginova O**, Weekley CM, Raoul A, Alsayed A, Wu T, Lee SS, He C, Olopade OI. Inhibition of Copper Transport Induces Apoptosis in Triple-Negative Breast Cancer Cells and Suppresses Tumor Angiogenesis. *Mol Cancer Ther* 2019; **18**: 873-885 [PMID: 30824611 DOI: 10.1158/1535-7163.MCT-18-0667]

15 **Zhou P**, Qin J, Zhou C, Wan G, Liu Y, Zhang M, Yang X, Zhang N, Wang Y. Multifunctional nanoparticles based on a polymeric copper chelator for combination treatment of metastatic breast cancer. *Biomaterials* 2019; **195**: 86-99 [PMID: 30623789 DOI: 10.1016/j.biomaterials.2019.01.007]

16 **El-Arabey AA**, Abdalla M, Abd-Allah AR. SnapShot: TP53 status and macrophages infiltration in TCGA-analyzed tumors. *Int Immunopharmacol* 2020; **86**: 106758 [PMID: 32663767 DOI: 10.1016/j.intimp.2020.106758]

17 **Labani-Motlagh A**, Ashja-Mahdavi M, Loskog A. The Tumor Microenvironment: A Milieu Hindering and Obstructing Antitumor Immune Responses. *Front Immunol* 2020; **11**: 940 [PMID: 32499786 DOI: 10.3389/fimmu.2020.00940]

18 **Ma B**, Wang S, Liu F, Zhang S, Duan J, Li Z, Kong Y, Sang Y, Liu H, Bu W, Li L. Self-Assembled Copper-Amino Acid Nanoparticles for in Situ Glutathione "AND" H(2)O(2) Sequentially Triggered Chemodynamic Therapy. *J Am Chem Soc* 2019; **141**: 849-857 [PMID: 30541274 DOI: 10.1021/jacs.8b08714]

19 **Sîrbu A**, Palamarciuc O, Babak MV, Lim JM, Ohui K, Enyedy EA, Shova S, Darvasiová D, Rapta P, Ang WH, Arion VB. Copper(ii) thiosemicarbazone complexes induce marked ROS accumulation and promote nrf2-mediated antioxidant response in highly resistant breast cancer cells. *Dalton Trans* 2017; **46**: 3833-3847 [PMID: 28271099 DOI: 10.1039/c7dt00283a]

20 **Boodram JN**, Mcgregor IJ, Bruno PM, Cressey PB, Hemann MT, Suntharalingam K. Breast Cancer Stem Cell Potent Copper(II)-Non-Steroidal Anti-Inflammatory Drug Complexes. *Angew Chem Int Ed Engl* 2016; **55**: 2845-2850 [PMID: 26806362 DOI: 10.1002/anie.201510443]

21 **Kaur P**, Johnson A, Northcote-Smith J, Lu C, Suntharalingam K. Immunogenic Cell Death of Breast Cancer Stem Cells Induced by an Endoplasmic Reticulum-Targeting Copper(II) Complex. *Chembiochem* 2020; **21**: 3618-3624 [PMID: 32776422 DOI: 10.1002/cbic.202000553]

22 **Zhang L**, Wan SS, Li CX, Xu L, Cheng H, Zhang XZ. An Adenosine Triphosphate-Responsive Autocatalytic Fenton Nanoparticle for Tumor Ablation with Self-Supplied H(2)O(2) and Acceleration of Fe(III)/Fe(II) Conversion. *Nano Lett* 2018; **18**: 7609-7618 [PMID: 30383966 DOI: 10.1021/acs.nanolett.8b03178]

23 **Ewen KM**, Ringle M, Bernhardt R. Adrenodoxin--a versatile ferredoxin. *IUBMB Life* 2012; **64**: 506-512 [PMID: 22556163 DOI: 10.1002/iub.1029]

24 **Shi Y**, Ghosh M, Kovtunovych G, Crooks DR, Rouault TA. Both human ferredoxins 1 and 2 and ferredoxin reductase are important for iron-sulfur cluster biogenesis. *Biochim Biophys Acta* 2012; **1823**: 484-492 [PMID: 22101253 DOI: 10.1016/j.bbamcr.2011.11.002]

25 **Kahlson MA**, Dixon SJ. Copper-induced cell death. *Science* 2022; **375**: 1231-1232 [PMID: 35298241 DOI: 10.1126/science.abo3959]

26 **Zhang Z**, Ma Y, Guo X, Du Y, Zhu Q, Wang X, Duan C. FDX1 can Impact the Prognosis and Mediate the Metabolism of Lung Adenocarcinoma. *Front Pharmacol* 2021; **12**: 749134 [PMID: 34690780 DOI: 10.3389/fphar.2021.749134]

27 **Bian Z**, Fan R, Xie L. A Novel Cuproptosis-Related Prognostic Gene Signature and Validation of Differential Expression in Clear Cell Renal Cell Carcinoma. *Genes (Basel)* 2022; **13** [PMID: 35627236 DOI: 10.3390/genes13050851]

28 **Ohtani H**. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human colorectal cancer. *Cancer Immun* 2007; **7**: 4 [PMID: 17311363]

29 **Burr SP**, Costa AS, Grice GL, Timms RT, Lobb IT, Freisinger P, Dodd RB, Dougan G, Lehner PJ, Frezza C, Nathan JA. Mitochondrial Protein Lipoylation and the 2-Oxoglutarate Dehydrogenase Complex Controls HIF1α Stability in Aerobic Conditions. *Cell Metab* 2016; **24**: 740-752 [PMID: 27923773 DOI: 10.1016/j.cmet.2016.09.015]

30 **Mabeta P**, Hull R, Dlamini Z. LncRNAs and the Angiogenic Switch in Cancer: Clinical Significance and Therapeutic Opportunities. *Genes (Basel)* 2022; **13** [PMID: 35052495 DOI: 10.3390/genes13010152]

31 **Solmonson A**, Faubert B, Gu W, Rao A, Cowdin MA, Menendez-Montes I, Kelekar S, Rogers TJ, Pan C, Guevara G, Tarangelo A, Zacharias LG, Martin-Sandoval MS, Do D, Pachnis P, Dumesnil D, Mathews TP, Tasdogan A, Pham A, Cai L, Zhao Z, Ni M, Cleaver O, Sadek HA, Morrison SJ, DeBerardinis RJ. Compartmentalized metabolism supports midgestation mammalian development. *Nature* 2022; **604**: 349-353 [PMID: 35388219 DOI: 10.1038/s41586-022-04557-9]

32 **Chen Y**, Xu T, Xie F, Wang L, Liang Z, Li D, Liang Y, Zhao K, Qi X, Yang X, Jiao W. Evaluating the biological functions of the prognostic genes identified by the Pathology Atlas in bladder cancer. *Oncol Rep* 2021; **45**: 191-201 [PMID: 33200223 DOI: 10.3892/or.2020.7853]

33 **Wang Y**, Guo YR, Liu K, Yin Z, Liu R, Xia Y, Tan L, Yang P, Lee JH, Li XJ, Hawke D, Zheng Y, Qian X, Lyu J, He J, Xing D, Tao YJ, Lu Z. KAT2A coupled with the α-KGDH complex acts as a histone H3 succinyltransferase. *Nature* 2017; **552**: 273-277 [PMID: 29211711 DOI: 10.1038/nature25003]

34 **Shin D**, Lee J, You JH, Kim D, Roh JL. Dihydrolipoamide dehydrogenase regulates cystine deprivation-induced ferroptosis in head and neck cancer. *Redox Biol* 2020; **30**: 101418 [PMID: 31931284 DOI: 10.1016/j.redox.2019.101418]

35 **Yoneyama K**, Shibata R, Igarashi A, Kojima S, Kodani Y, Nagata K, Kurose K, Kawase R, Takeshita T, Hattori S. Proteomic identification of dihydrolipoamide dehydrogenase as a target of autoantibodies in patients with endometrial cancer. *Anticancer Res* 2014; **34**: 5021-5027 [PMID: 25202086 DOI: 10.1158/0008-5472.can-05-3365]

36 **Abdullah Al-Dhabi N**, Srigopalram S, Ilavenil S, Kim YO, Agastian P, Baaru R, Balamurugan K, Choi KC, Valan Arasu M. Proteomic Analysis of Stage-II Breast Cancer from Formalin-Fixed Paraffin-Embedded Tissues. *Biomed Res Int* 2016; **2016**: 3071013 [PMID: 27110560 DOI: 10.1155/2016/3071013]

37 **Avraham H**, Avraham S, Taniguchi Y. Receptor protein tyrosine phosphatases in hematopoietic cells. *J Hematother Stem Cell Res* 2000; **9**: 425-432 [PMID: 10982240 DOI: 10.1089/152581600419080]

38 **Patel MS**, Nemeria NS, Furey W, Jordan F. The pyruvate dehydrogenase complexes: structure-based function and regulation. *J Biol Chem* 2014; **289**: 16615-16623 [PMID: 24798336 DOI: 10.1074/jbc.R114.563148]

39 **Goh WQ**, Ow GS, Kuznetsov VA, Chong S, Lim YP. DLAT subunit of the pyruvate dehydrogenase complex is upregulated in gastric cancer-implications in cancer therapy. *Am J Transl Res* 2015; **7**: 1140-1151 [PMID: 26279757 DOI: 10.5772/48582]

40 **Shan C**, Elf S, Ji Q, Kang HB, Zhou L, Hitosugi T, Jin L, Lin R, Zhang L, Seo JH, Xie J, Tucker M, Gu TL, Sudderth J, Jiang L, DeBerardinis RJ, Wu S, Li Y, Mao H, Chen PR, Wang D, Chen GZ, Lonial S, Arellano ML, Khoury HJ, Khuri FR, Lee BH, Brat DJ, Ye K, Boggon TJ, He C, Kang S, Fan J, Chen J. Lysine acetylation activates 6-phosphogluconate dehydrogenase to promote tumor growth. *Mol Cell* 2014; **55**: 552-565 [PMID: 25042803 DOI: 10.1016/j.molcel.2014.06.020]

41 **Li C**, He C, Xu Y, Xu H, Tang Y, Chavan H, Duan S, Artigues A, Forrest ML, Krishnamurthy P, Han S, Holzbeierlein JM, Li B. Alternol eliminates excessive ATP production by disturbing Krebs cycle in prostate cancer. *Prostate* 2019; **79**: 628-639 [PMID: 30663084 DOI: 10.1002/pros.23767]

42 **Liu Z**, Yu M, Fei B, Fang X, Ma T, Wang D. miR‑21‑5p targets PDHA1 to regulate glycolysis and cancer progression in gastric cancer. *Oncol Rep* 2018; **40**: 2955-2963 [PMID: 30226598 DOI: 10.3892/or.2018.6695]

43 **Zhuang L**, Zhang B, Liu X, Lin L, Wang L, Hong Z, Chen J. Exosomal miR-21-5p derived from cisplatin-resistant SKOV3 ovarian cancer cells promotes glycolysis and inhibits chemosensitivity of its progenitor SKOV3 cells by targeting PDHA1. *Cell Biol Int* 2021; **45**: 2140-2149 [PMID: 34288231 DOI: 10.1002/cbin.11671]

44 **Liu L**, Cao J, Zhao J, Li X, Suo Z, Li H. PDHA1 Gene Knockout In Human Esophageal Squamous Cancer Cells Resulted In Greater Warburg Effect And Aggressive Features In Vitro And In Vivo. *Onco Targets Ther* 2019; **12**: 9899-9913 [PMID: 31819487 DOI: 10.2147/OTT.S226851]

45 **Chen J**, Guccini I, Di Mitri D, Brina D, Revandkar A, Sarti M, Pasquini E, Alajati A, Pinton S, Losa M, Civenni G, Catapano CV, Sgrignani J, Cavalli A, D'Antuono R, Asara JM, Morandi A, Chiarugi P, Crotti S, Agostini M, Montopoli M, Masgras I, Rasola A, Garcia-Escudero R, Delaleu N, Rinaldi A, Bertoni F, Bono J, Carracedo A, Alimonti A. Compartmentalized activities of the pyruvate dehydrogenase complex sustain lipogenesis in prostate cancer. *Nat Genet* 2018; **50**: 219-228 [PMID: 29335542 DOI: 10.1038/s41588-017-0026-3]

46 **Zhu Y**, Wu G, Yan W, Zhan H, Sun P. miR-146b-5p regulates cell growth, invasion, and metabolism by targeting PDHB in colorectal cancer. *Am J Cancer Res* 2017; **7**: 1136-1150 [PMID: 28560062 DOI: 10.11569/wcjd.v31.i10.397]

47 **Cai Z**, Zhao JS, Li JJ, Peng DN, Wang XY, Chen TL, Qiu YP, Chen PP, Li WJ, Xu LY, Li EM, Tam JP, Qi RZ, Jia W, Xie D. A combined proteomics and metabolomics profiling of gastric cardia cancer reveals characteristic dysregulations in glucose metabolism. *Mol Cell Proteomics* 2010; **9**: 2617-2628 [PMID: 20699381 DOI: 10.1074/mcp.M110.000661]

48 **Giannos P**, Kechagias KS, Gal A. Identification of Prognostic Gene Biomarkers in Non-Small Cell Lung Cancer Progression by Integrated Bioinformatics Analysis. *Biology (Basel)* 2021; **10** [PMID: 34827193 DOI: 10.3390/biology10111200]

49 **Carlini MJ**, Recouvreux MS, Simian M, Nagai MA. Gene expression profile and cancer-associated pathways linked to progesterone receptor isoform a (PRA) predominance in transgenic mouse mammary glands. *BMC Cancer* 2018; **18**: 682 [PMID: 29940887 DOI: 10.1186/s12885-018-4550-z]

50 **Ji L**, Zhao G, Zhang P, Huo W, Dong P, Watari H, Jia L, Pfeffer LM, Yue J, Zheng J. Knockout of MTF1 Inhibits the Epithelial to Mesenchymal Transition in Ovarian Cancer Cells. *J Cancer* 2018; **9**: 4578-4585 [PMID: 30588241 DOI: 10.7150/jca.28040]

51 **Günther V**, Lindert U, Schaffner W. The taste of heavy metals: gene regulation by MTF-1. *Biochim Biophys Acta* 2012; **1823**: 1416-1425 [PMID: 22289350 DOI: 10.1016/j.bbamcr.2012.01.005]

52 **Choi YK**, Park KG. Targeting Glutamine Metabolism for Cancer Treatment. *Biomol Ther (Seoul)* 2018; **26**: 19-28 [PMID: 29212303 DOI: 10.4062/biomolther.2017.178]

53 **Momcilovic M**, Bailey ST, Lee JT, Fishbein MC, Magyar C, Braas D, Graeber T, Jackson NJ, Czernin J, Emberley E, Gross M, Janes J, Mackinnon A, Pan A, Rodriguez M, Works M, Zhang W, Parlati F, Demo S, Garon E, Krysan K, Walser TC, Dubinett SM, Sadeghi S, Christofk HR, Shackelford DB. Targeted Inhibition of EGFR and Glutaminase Induces Metabolic Crisis in EGFR Mutant Lung Cancer. *Cell Rep* 2017; **18**: 601-610 [PMID: 28099841 DOI: 10.1016/j.celrep.2016.12.061]

54 **Sheikh TN**, Patwardhan PP, Cremers S, Schwartz GK. Targeted inhibition of glutaminase as a potential new approach for the treatment of NF1 associated soft tissue malignancies. *Oncotarget* 2017; **8**: 94054-94068 [PMID: 29212209 DOI: 10.18632/oncotarget.21573]

55 **Saha SK**, Islam SMR, Abdullah-Al-Wadud M, Islam S, Ali F, Park KS. Multiomics Analysis Reveals that GLS and GLS2 Differentially Modulate the Clinical Outcomes of Cancer. *J Clin Med* 2019; **8** [PMID: 30871151 DOI: 10.3390/jcm8030355]

56 **Zhao R**, Choi BY, Lee MH, Bode AM, Dong Z. Implications of Genetic and Epigenetic Alterations of CDKN2A (p16(INK4a)) in Cancer. *EBioMedicine* 2016; **8**: 30-39 [PMID: 27428416 DOI: 10.1016/j.ebiom.2016.04.017]

57 **Kostaki M**, Manona AD, Stavraka I, Korkolopoulou P, Levidou G, Trigka EA, Christofidou E, Champsas G, Stratigos AJ, Katsambas A, Papadopoulos O, Piperi C, Papavassiliou AG. High-frequency p16(INK) (4A) promoter methylation is associated with histone methyltransferase SETDB1 expression in sporadic cutaneous melanoma. *Exp Dermatol* 2014; **23**: 332-338 [PMID: 24673285 DOI: 10.1111/exd.12398]

58 **Jonsson A**, Tuominen R, Grafström E, Hansson J, Egyhazi S. High frequency of p16(INK4A) promoter methylation in NRAS-mutated cutaneous melanoma. *J Invest Dermatol* 2010; **130**: 2809-2817 [PMID: 20703244 DOI: 10.1038/jid.2010.216]

59 **Jiao L**, Zhu J, Hassan MM, Evans DB, Abbruzzese JL, Li D. K-ras mutation and p16 and preproenkephalin promoter hypermethylation in plasma DNA of pancreatic cancer patients: in relation to cigarette smoking. *Pancreas* 2007; **34**: 55-62 [PMID: 17198183 DOI: 10.1097/01.mpa.0000246665.68869.d4]

60 **Tam KW**, Zhang W, Soh J, Stastny V, Chen M, Sun H, Thu K, Rios JJ, Yang C, Marconett CN, Selamat SA, Laird-Offringa IA, Taguchi A, Hanash S, Shames D, Ma X, Zhang MQ, Lam WL, Gazdar A. CDKN2A/p16 inactivation mechanisms and their relationship to smoke exposure and molecular features in non-small-cell lung cancer. *J Thorac Oncol* 2013; **8**: 1378-1388 [PMID: 24077454 DOI: 10.1097/JTO.0b013e3182a46c0c]

61 **Tan MS**, Tan L, Jiang T, Zhu XC, Wang HF, Jia CD, Yu JT. Amyloid-β induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease. *Cell Death Dis* 2014; **5**: e1382 [PMID: 25144717 DOI: 10.1038/cddis.2014.348]

62 **Ghobrial IM**, Witzig TE, Adjei AA. Targeting apoptosis pathways in cancer therapy. *CA Cancer J Clin* 2005; **55**: 178-194 [PMID: 15890640 DOI: 10.3322/canjclin.55.3.178]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** April 28, 2023

**First decision:** July 28, 2023

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): E

**P-Reviewer:** Amin A, United Arab Emirates; El-Arabey AA, Egypt; Suvvari TK, India **S-Editor:** Qu XL **L-Editor:** Kerr C **P-Editor:**

**Figure Legends**



**Figure 1 Effects of excess copper and copper deficiency in cancer.** Four copper-related pathways with cancer inhibition effects are described. Elesclomol mediates the entry of Cu2+ into the mitochondria and causes reactive oxygen species accumulation. Flavonoids interfere with copper ion oxidation and reduction, inducing mitochondrial apoptosis pathway activation. Copper diethyldithiocarbamate can inhibit proteasome and result in endoplasmic reticulum stress. Copper deficiency can suppress the proliferation and migration of endothelial cells and the formation of connexin, bridling tumor angiogenesis. TCA: Tricarboxylic acid; ROS: Reactive oxygen species; FDX1: Ferredoxin 1; MTF1: Metallothionein; CTR1: Consolidation tumor ratio-1.



**Figure 2 General molecular biological process of cuproptosis.** Copper can be transported into cells through the action of consolidation tumor ratio-1 and elesclomol encapsulation. When Cu2+ encapsulated by elesclomol enter the mitochondria, it gains an electron from ferrodoxin 1 (FDX1) (FDX1 expression can be promoted by metallothionein) and converts into Cu+. Concurrently, proteins responsible for dehydrogenation and acyl transfer (dihydrolipoamide transacetylase, dihydrolipoamide S-succinyltransferase, dihydrolipoamide dehydrogenase, pyruvate dehydrogenase α1, and pyruvate dehydrogenase β) undergo electron loss and are liporated by lipoic acid synthase. Subsequently, Cu+ promotes the oligomerization of liporated proteins. This cascade of events leads to a series of phenomena, including reactive oxygen species accumulation, mitochondrial dysfunction, and tricarboxylic acid inhibition, ultimately culminating in cuproptosis. CTR1: Consolidation tumor ratio-1; (Cu (DDC)2): Copper diethyldithiocarbamate; FDX1: Ferrodoxin 1.



**Figure 3 The mechanisms underlying cuproptosis in cancer cells.** GSH: Glutathione**.**

**Table 1 Copper-related compounds and their antitumor mechanism**

|  |  |  |
| --- | --- | --- |
| Compounds | Mechanism | Ref. |
| Elesclomol | Transferring copper ions to mitochondria and increasing ROS level | Nagai *et al*[7] |
| Flavonoid drugs | Interfering with copper ion redox and inducing mitochondrial apoptosis | Liu *et al*[8] |
| (Cu(DDC)2) | Inhibiting proteasome and leading to ER stress activation | Chen *et al*[9] |
| Copper ion chelating agent | Inhibiting endothelial cell proliferation and angiogenesis | Zhou *et al*[15] |
| Copper ion transporter inhibitor | Inhibit endothelial cell proliferation and angiogenesis | Yee *et al*[13], Karginova *et al*[14] |
| NPs(Cu-CysNPs) | Reacting with glutathione to increase ROS level | Ma *et al*[18] |
| Cu-TSC | Inducing ROS accumulation | Sîrbu *et al*[19] |
| Cu-NSAID compound | Inducing ROS accumulation, DNA damage and COX-2 activity inhibition | Boodram *et al*[20] |
| Copper complexes containing polypyridine ligands | Increasing ROS level and inducing ER stress | Kaur *et al*[21] |

ROS: Reactive oxygen species; TSC: Tuberous sclerosis complex; COX-2: Cyclooxygenase-2; NSAID: Non-steroidal anti-inflammatory drugs; (Cu(DDC)2): Copper diethyldithiocarbamate; ER: Endoplasmic reticulum.

**Table 2 Functions of cuproptosis-related genes in cancer**

|  |  |  |
| --- | --- | --- |
| **Genes** | **Mechanism** | **Ref.** |
| FDX1 | FDX1 knockout promotes glycolysis and fatty acid oxidation and alters amino acid metabolism | Zhang *et al*[26] |
| LIAS | Involved in lipoic acid biosynthesis. Abnormally elevated transcript levels of LIAS contribute to the development of lung cancer | Burr *et al*[29] |
| LIPT1 | Participating in the tricarboxylic acid cycle and is related to the prognosis of bladder cancer | Solmonson *et al*[31], Chen *et al*[32] |
| DLD | Affecting pyruvate metabolism and tricarboxylic acid cycle.Leading to mitochondrial lipid peroxidation and is a potential targeted therapeutic molecule | Wang *et al*[33] |
| DLAT | Converting pyruvate to acetyl-COA Promoting cancer cell growth by activating pentose phosphate pathway | Shan *et al*[40] |
| PDHA1 | Inhibition of PDHA1 expression promotes glycolysis and cell proliferation | Zhuang *et al*[43] |
| PDHA1 promotes mitochondrial lipid synthesis | Chen *et al*[45] |
| PDHB | Overexpression of PDHB inhibits the proliferation and invasiveness | Zhu *et al*[46] |
| MTF1 | Induced co-expression of metallothionein with other genes involved in metal homeostasis contributes to tumor biogenesis and development | Günther *et al*[51] |
| GLS | Encoding K-type mitochondrial glutaminase and is dysregulated in many tumors | Choi and Park[52], Momcilovic *et al*[53] |
| CDKN2A | A cyclin with mutations and aberrant methylation in a variety of tumors | Zhao *et al*[56], Tam *et al*[60] |

FDX1: Ferredoxin 1; LIAS: Lipoic acid synthase; LIPT1: Lipoyltransferase 1; DLD: Dihydrolipoamide dehydrogenase; DLAT: Dihydrolipoamide transacetylase; PDHA1: Pyruvate dehydrogenase alpha 1; PDHB: Pyruvate dehydrogenase beta; MTF1: Metallothionein; GLS: Glutaminase; CDKN2A: Cyclin dependent kinase inhibitor 2A.