Review

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Copper and Gastric Cancer: Looking Back from the Perspective of Cuproptosis

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Copper (Cu), an essential trace element, plays a crucial role in various physiological processes within the human body. Recently, cuproptosis, a novel form of cell death induced by copper overload, has been identified. Despite numerous studies investigating the association between copper and gastric cancer (GC), a comprehensive review of the existing literature on this topic is notably lacking. This review provides a retrospective analysis of the correlation between copper and gastric cancer, outlines the aberrant copper metabolism in gastric cancer and its potential mechanisms, and synthesizes current bioinformatics research on cuproptosis in gastric cancer. Furthermore, the review delves into copper-related synthetic materials and drugs that have been pivotal in the diagnosis and treatment of gastric cancer. We have emphasized that the association between copper and gastric cancer has not been fully investigated, indicating the possibility of discovering copper-related synthetic materials, chelating agents, and complexing agents as potential therapeutic approaches for gastric cancer.

Keywords: gastric cancer (GC); cuproptosis; copper (Cu); chemotherapy

Introduction

Gastric cancer (GC) is the fifth most prevalent malignancy worldwide, with over one million new cases occurring annually [1]. Despite a decrease in mortality rates over recent decades, gastric cancer remains the third leading cause of cancer-associated deaths [2]. Consequently, there is an urgent need to enhance early detection methods and improve the efficacy of treatments for stomach cancer.

Copper (Cu) is a metallic trace element that plays a vital role in the biological processes of all organisms, such as mitochondrial respiration, antioxidant defense, and compound synthesis. Maintaining a low intracellular Cu concentration is essential, as a moderate increase can lead to cytotoxicity and potentially result in cell death. Consequently, the absorption, distribution, and elimination of Cu are subject to stringent regulatory mechanisms.

Cuproptosis represents a novel form of programmed cell death. Cu specifically interacts with and binds to fatty acylated constituents of the tricarboxylic acid (TCA) cycle within cells. This interaction results in the aggregation of these fatty acylated mitochondrial proteins that copper binds to, subsequently leading to the formation of protein-S aggregates in iron-sulfur (Fe-S) clusters. The accumulation of these aggregates induces cellular stress, ultimately culminating in cell death [3]. An increasing number of researchers have employed bioinformatics to elucidate the correlation between Cu-induced cell death and gastric cancer, focusing on cuproptosis-related genes (CRGs) and cuproptosis-related long non-coding RNAs (CRLs). It is worth noting that the association between gastric cancer and Cu has been investigated as far back as 1956 [4]. However, the significance of copper in gastric cancer has not been fully elucidated in the literature. To provide contemporary scholars with a comprehensive overview of research advancements, this review offers an in-depth analysis of the interaction between Cu and gastric cancer, highlighting potential avenues for future research on cuproptosis and cancer.

Cuproptosis: Basic Concept and Mechanisms, Correlation with Diseases

Tsvetkov *et al.* [3] first identified that the copper ionophore elesclomol induces cytotoxic effects on cells, leading to cell death primarily due to copper accumulation. Conventional inhibitors targeting established cell death pathways are ineffective against elesclomol-induced cell death, indicating a unique form of cell death. Cells reliant on mitochondrial respiration exhibit heightened sensitivity to copper ionophores. Interestingly, the impact of ATP ase inhibitors, FCCP uncoupling agents, and electron transport chain inhibitors on cuproptosis is negligible, suggesting that cuproptosis primarily occurs within the tricarboxylic acid cycle. The electron transport chain complex and ATP production component were not found to be associated with cuproptosis. Extensive whole-genome knockout screening, metabolic profiling, and targeted gene

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knockout studies revealed that the absence of ferrodoxin 1 (*FDX1*), lipoic acid synthetase (*LIAS*), lipoyltransferase 1 (*LIPT1*), dihydrolipoamide S-acetyltransferase (*DLAT*), dihydrolipoamide dehydrogenase (*DLD*), pyruvate dehydrogenase E1 subunit alpha 1 (*PDHA1*), and pyruvate dehydrogenase E1 subunit beta (*PDHB*) resulted in the elimination of cuproptosis. These findings highlight the critical role of these seven genes in copper-induced mortality. *FDX1* and proteolipid acylation are crucial in modulating cuproptosis. The interaction between copper ions and the fatty acylation constituents of the tricarboxylic acid cycle results in the accumulation of fatty acylated proteins and the reduction of iron-sulfur cluster proteins. This process ultimately triggers proteotoxic stress, culminating in cell death.

Tsvetkov's research [3] revealed that cuproptosis, a form of cell death, is regulated by the genes solute carrier family 31 member 1 (*SLC31A1*), ATP ase copper transporting alpha (*ATP7A*), and ATP ase copper transporting beta (*ATP7B*) involved in copper homeostasis. An imbalance in copper levels can result in various diseases such as Menkes disease [5], Wilson's disease [6], and neurodegenerative disorders [7]. Moreover, disruptions in copper homeostasis have been observed in various cancers such as breast [8], lung [9], prostate [10], and pancreatic cancer [11].

Cuproptosis and Gastric Cancer

The introduction of the cuproptosis concept has prompted numerous scholars to investigate the association between gastric cancer and CRGs and CRLs using online databases, resulting in the identification of several relevant genes. Table 1 (Ref. [12–23]) represents a detailed list of CRGs and CRLs found in the literature.

Cuproptosis Key Genes in Gastric Cancer: A Research Gap

The genes associated with cuproptosis play a crucial role in copper-induced cell death. However, due to the intricate nature of their interactions and variations in research methodologies, several studies have omitted these key genes in subsequent investigations, resulting in insufficient evidence. Elevated levels of ferrodoxin 1 (*FDX1*), lipoic acid synthetase (*LIAS*), pyruvate dehydrogenase E1 subunit alpha 1 (*PDHA1*), lipoyltransferase 1 (*LIPT1*), and dihydrolipoamide S-acetyltransferase (*DLAT*), along with reduced expression of dihydrolipoamide dehydrogenase (*DLD*), have been associated with a more favorable prognosis [12,17]. In a recent study, a significant correlation was observed between *LIPT1* and *FDX1* with ferroptosis. Additionally, solute carrier family 31 member 1 (*SLC31A1*), *DLAT*, *PDHA1*, *FDX1*, *LIPT1*, and ATP ase copper transporting beta (*ATP7B*) were significantly correlated with gene methylation [13]. These findings suggest a potential link between cuproptosis, methylation pathways, and ferroptosis.

A recent study has demonstrated that METTL16 mediates the regulation of *FDX1* in gastric cancer through the methylation of *FDX1* mRNA [24]. Moreover, high copper levels have been found to induce lactoacylation of METTL16 at residue K229, resulting in cuproptosis [24].

DLAT has been previously observed to be upregulated in gastric cancer cell lines, indicating its potential involvement in cell proliferation and carbohydrate metabolism [25]. The alteration of carbohydrate metabolism is a hallmark of cancer, positioning DLAT as a promising drug target within the mitochondria. Recent research interest in cuproptosis has led to the discovery of mRNA expression of *DLAT* in gastric cancer [26]. Additionally, an analysis of immunohistochemical data from an online database demonstrates a significantly higher expression of DLAT in gastric cancer tissues compared to normal tissues.

ITGB1 has been identified as one of the genes associated with cuproptosis, showing a negative correlation with *FDX1*, *DLAT*, and *DLST*, while the cyclic expression of tricarboxylic acid is upregulated [27]. This suggests that *ITGB1* potentially serves as a crucial regulatory gene in gastric cancer and cuproptosis. The current understanding of key genes like *ITGB1* in gastric cancer remains an area for further investigation due to their potential impact on disease progression and patient outcomes.

Cuproptosis-Related Genes in Gastric Cancer

Currently, relevant research employs online databases to analyze associated genes, and then uses these data to forecast the clinical features and prognosis for individuals with gastric cancer.

The correlation between cancer and genetic mutations is crucial, particularly in the context of gastric cancer where CRGs exhibit a high susceptibility to mutations. The tumor mutation burden of CRGs in gastric cancer can reach levels as high as 49.83% [12]. This mutation burden has been linked to the efficacy of immune checkpoint inhibitors in therapeutic interventions [28]. A high tumor mutation burden in gastric cancer is linked to a more favorable prognosis. He *et al*. [18] found that elevated tumor mutation burden in *LIPT1* and ATP ase copper transporting alpha (*ATP7A*) correlated with improved immunotherapy outcomes, although the precise underlying mechanism remains unclear. Currently, there is limited research on biomarkers for tumor mutation burden in gastric cancer.

Furthermore, it has been observed that CRGs are intricately linked to the prognosis, level of tumor immune infiltration, and drug sensitivity in patients with gastric cancer. Cuproptosis has emerged as a novel therapeutic approach for cancer treatment, with higher levels of CRGs indicating a greater likelihood of cuproptosis induction. Consequently, elevated expression of CRGs is correlated with a favorable prognosis, reduced immune infiltration, and heightened drug sensitivity in gastric cancer patients [12]. Moreover, the levels of neuropilin 1 (*NRP1*), C-X-

Table 1. Cuproptosis-related genes and long non-coding RNAs in gastric cancer.

Ref	CRGs and CRLs in gastric cancer (GC)	Correlation with GC
Chen *et al.* [12]	*AASDHPPT, CYCS, DHX15, EARS2, FDX1, HCCS, IDH3A, LIAS, LIPT1, MRPS14, MRRF, NDUFA8, NDUFA9, PRKDC, RPAIN, TARS2*	16 CRGs were related to diagnosis, prognosis, immune infiltration, and drug susceptibility
Hu *et al.* [13]	*ACLY, FGD6, SERPINE1, SPATA13, RANGAP1, ADGRE5*	6 CRGs correlated with prognosis
Jiang *et al.* [14]	*ENTPD3, PDZD4, CNN1, GTPBP4, FPGS, UTP25, CENPW, FAM111A*	8 CRGs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility
Li *et al.* [15]	*ANOS1, CTLA4, ITGAV, CXCR4, NRP1, FABP3, LGR6*	7 CRGs correlated with prognosis, immune infiltration, drug susceptibility; CTLA4, ITGAV, CXCR4, and NRP1 correlated with progression of GC
Nie *et al.* [16]	*PDHA1, FDX1, SLC31A1, ATP7B, ATP7A, DBT, LIPT1, DLD, PDHB, DLAT, GCSH, LIAS*	12 CRGs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility
Wang J *et al.* [17]	*SLC27A2, NAT2, TAGLN, SFRP2, KRT17*	5 CRGs correlated with prognosis, immune infiltration, MSI, CSC, TMB, and somatic mutations
He *et al.* [18]	AL512506.1, AC016737.1, AC090204.1, AP001363.2, TYMSOS, AL353804.2	6 CRLs were related to diagnosis, prognosis, immune infiltration, drug susceptibility and expression of ferroptosis, methylation, and immunity related genes
Wang Y *et al.* [19]	AC016737.1, AL121748.1, LINC01980, TYMSOS, AL355574.1, AL391152.1, AL353804.2, AL353796.1, AL512506.1, AC104809.2	10 CRLs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility and TMB; AL121748.1 correlated with poor prognosis and GC cell lines cell proliferation and migration
Feng *et al.* [20]	LINC01150, LINC00571, SNAP25-AS, HAGLR	4 CRLs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility; LINC01150 expression correlated with CD209 and HAVCR2 expression
Tu *et al.* [21]	LINC01094, AC147067, HAGLR, AL590705, AC023511.1, AC016394.2	5 CRLs correlated with diagnosis, prognosis, drug susceptibility
Wang L *et al.* [22]	AC129926.1, AP002954.1, AC023511.1, LINC01537, TMEM75	5 CRLs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility; overexpressed AC129926.1 in GC cell lines and the serum of GC patients and correlated with GC cell proliferation and migration
Yin *et al.* [23]	CDKN2B-AS1, VCAN-AS1, AL359704.2, HAGLR	4 CRLs correlated with diagnosis, prognosis, immune infiltration, drug susceptibility

CRGs, cuproptosis-related genes; CRLs, cuproptosis-related long non-coding RNAs; *FDX1,* ferrodoxin 1; *LIAS*, lipoic acid synthetase; *LIPT1,* lipoyltransferase 1; *DLAT*, dihydrolipoamide S-acetyltransferase; *DLD*, dihydrolipoamide dehydrogenase; *PDHA1,* pyruvate dehydrogenase E1 subunit alpha 1; *PDHB*, pyruvate dehydrogenase E1 subunit beta; *SLC31A1,* solute carrier family 31 member 1; *ATP7A*, ATP ase copper transporting alpha; *ATP7B*, ATP ase copper transporting beta; *NRP1*, neuropilin 1; *CXCR4*, C-X-C motif chemokine receptor 4; *LGR6*, leucine rich repeat containing G protein-coupled receptor 6; *CTLA4*, cytotoxic T-lymphocyte associated protein 4.

C motif chemokine receptor 4 (*CXCR4*), leucine rich repeat containing G protein-coupled receptor 6 (*LGR6*), cytotoxic T-lymphocyte associated protein 4 (*CTLA4*) were elevated in gastric cancer tissues and exhibited a positive association with *FDX1* expression [15]. Enrichment analysis has revealed that the biological functions of cuproptosis-related genes primarily target the extracellular matrix [13]. Additionally, single-cell analysis indicated that a majority of CRGs were upregulated in endothelial cells, suggesting their potential involvement in angiogenesis [18]. In Nie *et al.*'s study [16], analysis of immunotherapy response confirmed that the high-CpS group could derive greater benefits from immunotherapy and exhibit improved susceptibility to chemotherapy drugs. Individuals with a higher CpS level might potentially experience enhanced therapeutic outcomes from immunotherapy and demonstrate increased sensitivity to chemotherapy agents. This finding suggests that CRGs possess predictive potential in the context of immunotherapy. Prognostic risk models derived from online databases undeniably demonstrate the potential of CRGs in the diagnosis and treatment of gastric cancer, an area currently lacking sufficient empirical investigations. Furthermore, a study suggests that dasatinib may induce cuproptosis through molecular docking experiments. However, empirical evidence supporting this claim is currently insufficient [14].

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Cuproptosis-Related Long Non-Coding RNAs in Gastric Cancer

The importance of long non-coding RNAs in gastric cancer has garnered considerable attention, prompting scholarly interest in the involvement of CRLs in gastric cancer. The research methods and outcomes employed in these investigations closely resemble those used for previously discussed CRGs, leading to promising outcomes.

According to the risk score model established by CRLs, the high-risk group usually has a lower tumor mutation burden, a poor response to immunotherapy, and a poor prognosis [19,22,23]. Interestingly, one study showed that the high tumor mutation burden group had a worse prognosis compared to the low tumor mutation burden group [21].

There is *in vitro* and *in vivo* evidence for their involvement in gastric cancer. Specifically, the regulatory impact of LINC01150 on immune checkpoint genes *CD209* and *HAVCR2* was demonstrated *in vitro* [20]. Subsequently, these findings were corroborated through *in vitro* experiments, suggesting that AL121748.1 may be significantly involved in the progression of gastric cancer [19]. Previous research has reported notable variations in several serum lncRNAs, including AC129926.1, AP002954.1, AC023511.1, LINC01537, and TMEM75, between healthy individuals and patients with gastric cancer [22]. Further *in vitro* experiments have indicated higher levels of AC129926.1 in gastric cancer cells compared to normal gastric cells, emphasizing its involvement in promoting tumor cell growth. These findings provide a promising avenue for future research into the role of lncRNAs in gastric cancer.

Copper and Copper Metabolism in Gastric Cancer

Serum Copper: A Potential Diagnosis and Treatment Biomarkers

Several researchers have examined the association between serum copper levels and gastric cancer. Individuals with higher serum copper levels are more likely to develop stomach cancer, and there is a link between ceruloplasmin levels and disease advancement in patients diagnosed with stomach cancer. In the studies, the risk of gastric cancer was found to be higher in a group with elevated serum copper levels, and a dose-response relationship was observed between serum copper levels and both cardiac and non-cardiac cancers [29,30]. Conversely, another group of researchers did not observe any significant difference in serum Cu levels among patients with GC [31]. Another previous study found no significant difference in serum copper levels between gastric cancer patients with and without *Helicobacter pylori* infection [32]. Therefore, the association between serum copper ion levels and gastric cancer remains unclear. Further investigation is needed to explore the potential utility of Cu ions as diagnostic and prognostic indicators in patients with gastric cancer, highlighting the importance of prioritizing research on cuproptosis.

Tissue and Cellular Copper

Several studies have explored alterations in Cu-ion levels and proteins related to Cu-ion metabolism in gastric cancer tissues and cell lines. Specifically, some researchers have observed a substantial increase in copper concentration in gastric cancer tissues compared to non-cancerous tissues [33,34], while others have reported lower copper levels in gastric cancer tissues than in normal gastric mucosa [35,36].

One study confirmed a disparity in the expression of ATP7B, a protein associated with Cu metabolism in human gastric cancer. These findings indicate that the expression levels in gastric cancer tissues surpass those observed in normal mucosal tissues. Additionally, the diagnostic positivity rate of immunohistochemical staining is higher in poorly differentiated adenocarcinoma [37]. Furthermore, ATP7B protein was found to be overexpressed in gastric cardia cancer and exhibited a correlation with the degree of differentiation in cardia cancer, consistent with previous research. ATP7B expression in cardiac carcinoma was significantly elevated compared to that in distal gastric carcinoma [38]. The role of ATP7A, a homolog of ATP7B, in the development of chemotherapeutic resistance in gastric cancer has been comprehensively established. Resistance to oxaliplatin and cisplatin is primarily attributed to the simultaneous increase in DNA repair mechanisms and ATP7A expression [39]. Conversely, the downregulation of thymidylate synthetase in S3 cells made them more susceptible to the cytotoxic effects of 5-fluorouracil.

Immunohistochemical analysis of gastric cancer tissue samples revealed the absence of copper transporter protein SLC31A1 (commonly referred to as hCTR1), except for significantly high expression in gastric G cells [40]. This observation contrasts with recent bioinformatics studies, most of which reported elevated expression of *SLC31A1* mRNA levels in gastric cancer compared to normal tissues. Furthermore, a human proteomics investigation revealed a significant upregulation of SLC31A1 protein in gastric cancer tissues compared to their healthy counterparts. However, immunohistochemical analyses from online databases indicated minimal expression of the SLC31A1 protein in gastric cancer [41]. Despite this, a prognostic risk model incorporating this gene remains applicable. Nevertheless, the mechanisms underlying this discrepancy remain unclear.

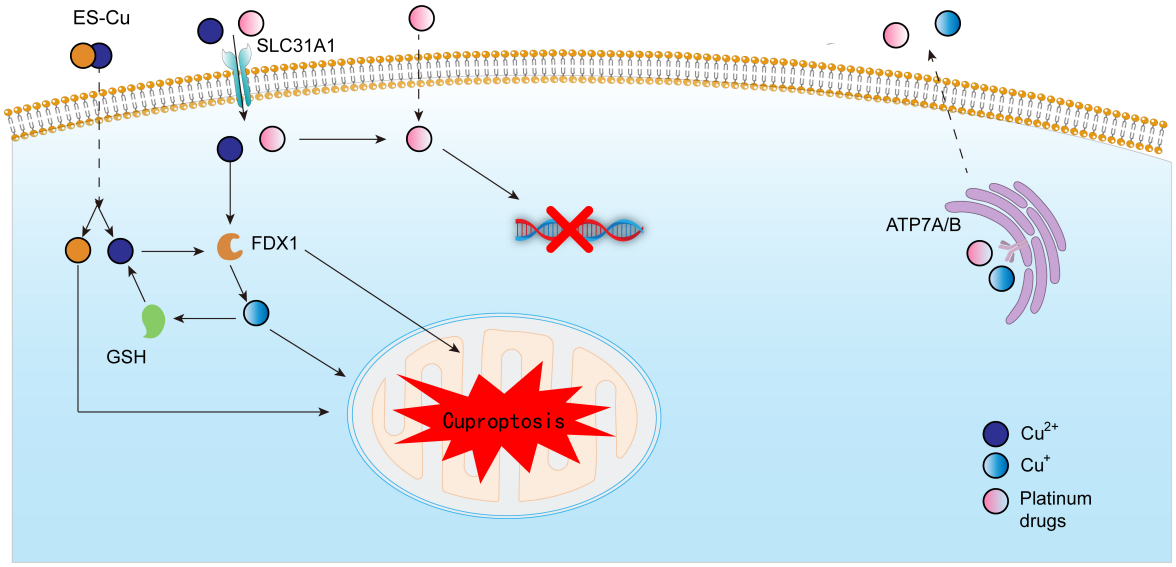

Fig. 1. Mechanisms of cuproptosis and Copper (Cu) metabolism in gastric cancer. The SLC31A1 receptor has been identified as a potential entry pathway for platinum drugs, whereas ATP7A and ATP7B have been found to facilitate the efflux of platinum drugs from cells. The primary impact of platinum drugs on cancer cells is the impairment of DNA synthesis, mismatch repair, and DNA repair processes. GSH, glutathione; *FDX1*, ferredoxin 1; ES-Cu, elesclomol-copper (created with Adobe Illustrator 2022, 26.3.1.1103, Adobe, Adobe Systems Incorporated, San Jose, CA, USA).

Insufficient research has been conducted on copper ion metabolism and its associated proteins in the context of gastric cancer. Copper ions are crucial factors in cuproptosis and hold significant potential. The correlation between cuproptosis and Cu metabolism is shown in Fig. 1.

Copper-Related Diagnosis and Treatment Methods in Gastric Cancer

Copper-Related Synthetic Materials Improve the Therapeutic Effect and Diagnosis of Gastric Cancer

Currently, copper is primarily utilized in the form of isotopes within synthetic materials employed for the diagnosis and treatment of gastric cancer. For instance, the clinical application of ^{64}Cu-NOTA-trastuzumab has proven its effectiveness as a pioneering tracer with enhanced tumor uptake, aiding in the detection of HER2-positive mice [42]. Similarly, the ^{64}Cu-DOTA-F56 probe shows promise in localizing tumors through microPET imaging, and its PET imaging features correspond to VEGFR1 staining, thereby enabling its non-invasive imaging functionality [43]. Fujiwara *et al.* [44] successfully developed a ^{64}Cu-labeled minibody D2101 probe, based on previous research that exhibited enhanced diagnostic efficacy in mice xenolabelled with AGS cells expressing CDH17. A magnetic nanoassembly containing copper demonstrated the ability to activate T1-weighted MR signals during T1 tests in magnetic resonance, thereby serving a diagnostic function [45]. Furthermore, magnetic semiconductor Gd-doped CuS nanoparticles created by Shi *et al.* [46] enhanced the precise localization of tumors through photothermal therapy. These CuS nanoparticles also showed promise for tumor identification and the diagnosis of sentinel lymphatic metastasis [47]. The use of biodegradable hollow mesoporous organosilica nanotheranostics augments the efficacy of magnetic resonance T1 in the context of gastric cancer [48].

Copper has made significant contributions to the field of photothermal therapy. The mechanism of action of photothermal therapy in gastric cancer has only been partially elucidated. The nanomaterial CuS-NiS_2 has been successfully applied in magnetic resonance imaging (MRI)-guided photothermal and photodynamic therapies, inducing apoptosis through mitochondria-mediated mechanisms and necrosis via mixed lineage kinase domain-like protein/macrophage-capping protein (MLKL/CAPG)-mediated pathways [49]. The promotion of apoptosis is a significant outcome of the photothermal therapy-induced production of biodegradable hollow mesoporous organosilica nanotheranostic reactive oxygen species (ROS). Additionally, this material induces mitochondrial damage, thereby initiating the Caspase-9/Caspase-3-dependent apoptosis pathway [48]. During *in vitro* experimental photothermal therapy, SiO_2@Cu_2-xSe nanospheres inhibit cell progression in the S phase [50]. Cu-encapsulating magnetic nanoassemblies can catalyze the production of harmful substances by demonstrating peroxidase-like activity through the formation of Cu^+ [45]. Ultimately, the application of laser irradiation can effectively impede tumor growth and extend the lifespan of mice with MGC-803 tumors. The CuS nanoparticles mentioned above were employed in a

Table 2. Copper-related synthetic materials correlated with the diagnosis and treatment of gastric cancer.

Ref	Materials	Object of study	Diagnosis/Therapeutic effect	Mechanism of action
X. Guo *et al*. [42]	^{64}Cu-NOTA-Trastuzumab	HER2-positive and HER2-negative gastric cancer patient-derived xenografts mice models and patients	Good lesion detection ability compared with ^{18}F-FDG PET/CT imaging	Not mentioned
Zhu *et al*. [43]	^{64}Cu-DOTA-F56	VEGFR1 positive BCG823 cells, VEGFR1 positive BCG823 tumor-bearing mice	Clearer tumor images compared with ^{18}F-FDG	Not mentioned
Fujiwara *et al*. [44]	^{64}Cu-labeled minibody D2101	The CDH17-positive AGS cells and the CDH17-negative MKN74 cells, CDH17-positive AGS and CDH17-negative MKN74 xenograft mice	Rapid and highly accurate diagnosis of CDH17-positive tumors	Not mentioned
Li *et al*. [45]	GSH-/H_2O_2-responsive copper-encapsulating magnetic nanoassemblies	MGC-803 cells, MGC-803 xenograft mice	"Turning on" the T1-weighted MR signal; efficient tumor inhibition	High intratumoral reactive oxygen species (ROS) generation
Shi *et al*. [46]	A tumor-targeted and matrix metalloprotease-2 activatable nanoprobe	MKN45 and GES-1 cells, MKN45 and GES-1 xenograft mice	High-spatial-resolution magnetic resonance imaging (MRI) and low-background fluorescence imaging of gastric tumors as well as LNM; high tumor clearance efficiency	Activated by $\alpha v\beta 3$-bound MMP-2 and MMP-2 overexpressed in the extracellular matrix
Shi *et al*. [47]	Fluorescent copper sulfide nanoparticle RGD-CuS-Cy5.5	MKN45 cells, MKN45 lymph node metastasis tumor model	Enabling both non-invasive multimodality imaging; targeting photothermal therapy of metastatic gastric cancer cells in lymph nodes	Overexpressed integrin $\alpha v\beta 3$ trigger efficient cell uptake via receptor-mediated endocytosis and subsequently accumulate in the lymph node
W. Guo *et al*. [48]	Gd doped hollow mesoporous organosilica nanoparticles decorated by CuS nanocrystals	HGC-27 cells, HGC-27 tumor-bearing mice	Good fluorescence imaging, enhanced T1 imaging under MRI and infrared thermal imaging capacities; efficient tumor inhibition	Mitochondria damage induce by high intratumoral ROS generation; apoptosis related protein expression
Chen *et al*. [49]	CuS–NiS_2 nanomaterials	AGS and MKN45 cells, AGS and MKN45 xenograft mice	Excellent contrast enhancement according to MRI; efficient tumor inhibition	Mitochondria-mediated apoptosis induced by ROS generation; MLKL/CAPG-mediated necroptosis
Zhang *et al*. [50]	Cu_2-xSe@mSiO_2 core–shell nanospheres	MGC-803 cells, human gastric cancer cells xenograft mice	High tumor clearance efficiency	Apoptosis induced by S phase

MLKL/CAPG, mixed lineage kinase domain-like protein/macrophage-capping protein.

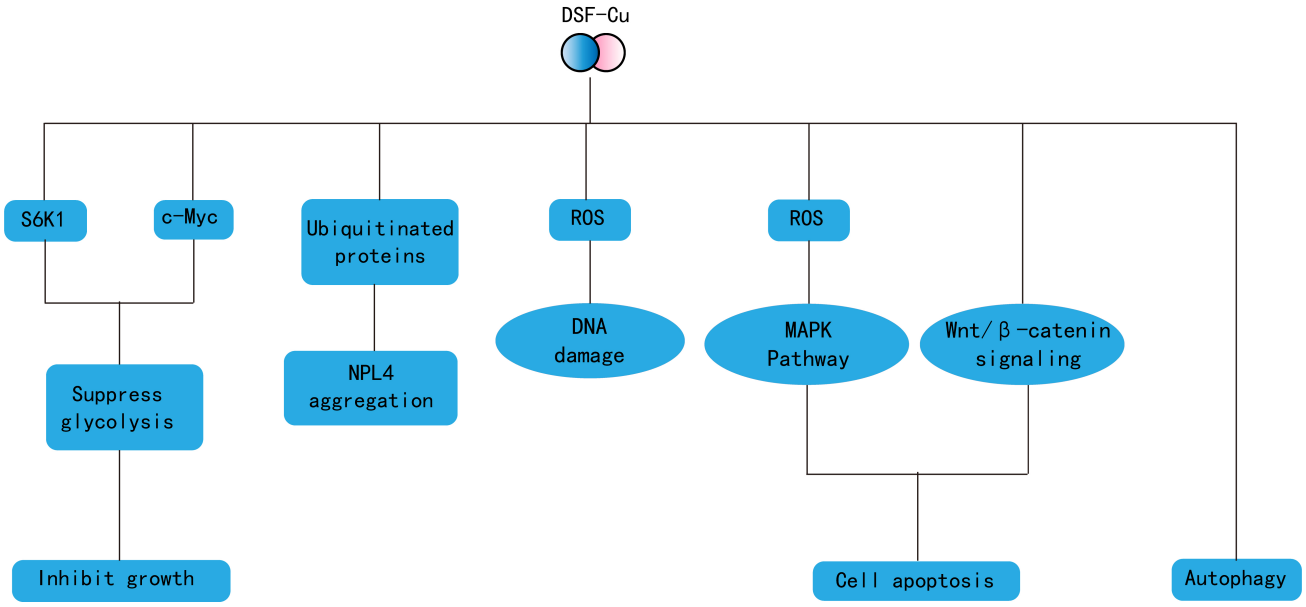

Fig. 2. Mechanism of action of Disulfiram (DSF)-Cu in gastric cancer. The impact of the DSF-Cu compound on gastric cancer cells is evident in its regulation of glycolysis by inhibiting S6K1 and c-Myc, along with the ROS/mitogen-activated protein kinases (MAPK) pathway and Wnt/β-catenin signaling pathway, ultimately promoting apoptosis. Additionally, the drug directly induced autophagy within cells (created with Adobe Illustrator 2022, 26.3.1.1103, Adobe, Adobe Systems Incorporated, San Jose, CA, USA).

mouse model for conducting photothermal therapy, resulting in the complete eradication of metastatic tumor cells from sentinel lymph nodes, while exhibiting no signs of toxicity [47].

The crucial role of Cu-containing synthetic materials in the diagnosis and treatment of gastric cancer has not been fully recognized. Although the studies mentioned above did not reveal any evidence of cuproptosis, which may be attributed to limited understanding at the time. With the emergence of novel concepts, it is essential to reassess how these materials contribute to the diagnosis and treatment of gastric cancer. All synthetic materials are summarized in Table 2 (Ref. [42–50]).

Copper Chelators and Complexing Agents: Chemotherapeutic Solution in Gastric Cancer

Some researchers have elucidated the cytotoxic effects of Cu-based complexes on gastric cancer cells [51,52]. The efficacy of these complexes in gastric cancer cell lines has only been validated through *in vitro* experiments, whereas *in vivo* investigations and the associated mechanisms remain unexplored. This highlights the need to explore the origin of toxicity in Cu-related complexes, specifically discerning whether it arises from the Cu element or the complex structure itself. Certain complexes containing copper have been demonstrated to exhibit toxicity when interacting with DNAs [52–54]. Bo *et al.* [55,56] conducted an experiment in which Cu^{2+} ions were combined with the hydrolyzed products of bovine lactoferrin. The results revealed that the presence of Cu^{2+} ions effectively hindered cell cycle stagnation in the G0/G1 phase, leading to detrimental effects on the mitochondrial membrane and ultimately inducing cell apoptosis. Additionally, the activation of apoptosis-related proteins by Cu^{2+} ions further enhances the anticancer activity in gastric cancer cell lines.

Limited studies have been conducted on the mechanism of action of Cu-based complexes based on Schiff bases in inhibiting gastric cancer cells [57,58]. These complexes have demonstrated an inhibitory effect on the proliferation of gastric cancer cells by inducing apoptosis and arresting the cell cycle at the G1 phase, while also inhibiting the NF-K-β pathway [59]. Additionally, some of the observed cytotoxicity was attributed to ROS-dependent DNA cleavage.

Disulfiram, used in the treatment of alcohol abuse, forms a complex with copper known as Disulfiram (DSF)/Cu. Understanding the mechanism through which this chelate functions in gastric cancer is progressively advancing. The chelated compound has exhibited inhibitory effects on the proliferation and migration of gastric cancer cells. A study revealed that the Disulfiram/Cu compound effectively suppressed the growth and metastasis of gastric cancer cells through the regulation of stress response and the Wnt/β-catenin signaling pathway [60]. DSF/Cu induced autophagy-mediated cell death. Furthermore, inhibiting S6K1, c-Myc, and their downstream effectors GLUT1, PKM2, and LDHA impedes glycolysis and hinders tumor progression in gastric cancer cells [61]. Additionally, this drug can trigger apoptosis in gastric cancer cells by generating ROS in a ROS-dependent manner [62]. This effect may be associated with the primary inhibi-

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tion of GC induced by DSF/Cu through the ROS/mitogen-activated protein kinases (MAPK) pathway. Additionally, the disrupted transportation of ubiquitinated proteins may contribute to this process. The detailed mechanism is illustrated in Fig. 2.

Conclusions and Future Directions

The discovery of cuproptosis as a novel mode of cell death represents a significant milestone in the field. Numerous studies have extensively investigated the association between cuproptosis and gastric cancer. However, the absence of adequate biological evidence and experimental validation has resulted in the establishment of an indirect correlation between cuproptosis and gastric cancer. The exact role of these genes in the direct interplay between cuproptosis and tumor development remains unclear, as it is uncertain whether they are directly implicated or indirectly influenced by both factors. In the afore-mentioned studies, various researchers successfully identified multiple genes that contribute to the development of traits that potentially exert a significant influence on the correlation between cuproptosis and gastric cancer. However, additional studies are required to comprehensively investigate the association between these commonly referenced CRGs and cuproptosis.

Furthermore, an increasing number of studies have demonstrated that cuproptosis has potential as a viable therapeutic approach for cancer. Certain researchers have sought to improve the effectiveness of immunotherapy by increasing the levels of copper ions within cancer cells or inducing mitochondrial damage, thereby triggering cuproptosis [63–65]. Additionally, certain drugs have been identified as inducers of cuproptosis [66,67]. Taken together, these findings demonstrate the therapeutic potential of cuproptosis in the context of cancer treatment.

The exploration of cuproptosis as a prospective therapeutic strategy for gastric cancer remains insufficiently examined, requiring further investigation of its interaction with other types of cell death. Moreover, the relationship between copper and gastric cancer is still unclear, underscoring the need for further research to determine the viability of using copper as a diagnostic tool and treatment option for gastric cancer.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, XD and SZ; methodology, XD and JP; software, SZ and LG; investigation, SZ; data curation, SZ and LG; writing—original draft preparation, SZ and JP; writing—review and editing, XD; supervision, XD. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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