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REVIEW ARTICLE

Role of cuproptosis in understanding diseases

Shihan Cao[1,2,3] · Qian Wang[1,2,3] · Zhenzhen Sun[1,2,3] · Yue Zhang[1,2,3] · Qianqi Liu[5,6] · Qun Huang[4] · Guixia Ding[1,2,3] · Zhanjun Jia[1,2,3]

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Abstract

Cell death is involved in a wide range of physiological and pathological processes. Recently, the term "cuproptosis" was coined to describe a novel type of cell death. This type of cell death, characterized by copper accumulation and proteotoxic stress, is a copper-dependent manner of death. Despite the progress achieved toward a better understanding of cuproptosis, mechanisms and related signaling pathways in physiology and pathology across various diseases remain to be proved. This mini review summarizes current research on cuproptosis and diseases, providing insights into prospective clinical therapies via targeting cuproptosis.

Keywords Cuproptosis · Cell death · Diseases · Cancer · Copper

Introduction

The life span of cells ranges from a few days to years depending on the type. Numerous physiological activities can be carried out in response to cell death. Cells have the capacity to control their own demise and produce immunological responses under specific circumstances, enabling the body to adjust to environmental changes [1]. Regulated cell death (RCD), also known as programmed cell death (PCD), is characterized by distinct biochemical, morphological, and immunological characteristics. The most studied forms of RCD include apoptosis, necroptosis, pyroptosis, and ferroptosis [2].

The fundamental feature of apoptosis is the formation of apoptosome when cytochrome c released from mitochondria binds to a pro-apoptotic factor apoptotic protease activating factor-1 (APAF1). Subsequently, a series of caspase cascade responses are elicited. The inner nuclear membrane of cells is damaged, membrane bubbling occurs, and DNA is disassembled into the DNA ladder [3]. Necrosis and necroptosis share morphological and mechanistic similarities. Receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain-like pseudokinase (MLKL) are all involved in necroptosis. RIPK3-mediated phosphorylation causes MLKL activation. Activated MLKL forms oligomers. This alteration causes MLKL translocation to plasma membrane, changes in membrane permeability, and ultimately cell death [4]. Ferroptosis is a type of cell death characterized by intracellular iron accumulation and lipid peroxidation [5]. Different forms of RCD have been identified to be involved in various pathological and physiological processes, such as cell homeostasis and the occurrence and development of neoplasms. Understanding the exact signaling pathways associated with the pathogenesis is significantly essential to define therapeutic targets [6].

✉ Qun Huang
huangqun333@126.com

✉ Guixia Ding
bhgyuan@163.com

✉ Zhanjun Jia
jiazj72@hotmail.com

1 Department of Nephrology, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing 210008, China

2 Nanjing Key Laboratory of Pediatrics, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing 210008, China

3 Jiangsu Key Laboratory of Pediatrics, Nanjing Medical University, Nanjing 210029, China

4 Department of Otorhinolaryngology, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing 210008, China

5 Department of Child Health Care, Children's Hospital of Nanjing Medical University, Nanjing, China

6 Department of Endocrinology, Children's Hospital of Nanjing Medical University, Nanjing, China

Cuproptosis, a new distinct type of RCD caused by copper ionophores or chelators, was identified by Tsvetkov et al. in 2022 [7]. This surprising discovery will help researchers to gain a better grasp of the pathogenesis and shed light on possible clinical medicines that target cuproptosis.

Copper and cuproptosis

Copper is a trace element that is crucial for mammals and is normally maintained at a low level [8]. Copper, an intracellular catalytic cofactor for key enzymes, regulates energy conversion, peptide amination, and intracellular oxidative metabolism [9]. Copper can also promote angiogenesis, which is necessary for tumor development and metastasis. Accumulating evidence shows that copper can activate many angiogenic factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor 1 (FGF1). Furthermore, copper can balance nuclear hypoxia-inducible factor 1 (HIF-1) and boost the expression of pro-angiogenic factors [10, 11]. Changes of intracellular environment and metabolic demands can have an impact on copper levels. Improper amounts of copper will cause enormous damage to physiology [12]. Binding of copper to nonspecific sites has long been regarded as a potential mechanism of copper toxicity and is often cited as a critique of metal isomerism [13]. To facilitate regulation of lipolysis and proliferation, copper allosteric is utilized as certain signaling molecular except for catalytic protein sites over the last decade [14]. Copper chelators, such as tetrathiomolybdate (TTM), have shown great efficacy in the early stage of clinical trials as treatments for a variety of tumors [15].

Cuproptosis, caused by the combination of copper and lipoylated protein, is an example of specific binding to a previously unidentified site [13]. Physiologically, copper imported by a copper chaperone is stored in the mitochondrial matrix, which is utilized for the composition of cytochrome C oxidase in the electron transport chain [16]. Copper can be exchanged with proteins or combined with specific targets. Ionophore-induced copper accumulation can cause severe damage, resulting in the disruption of homeostasis [17, 18]. The effects of copper may be exerted by a transient allosteric regulator which changes protein activity. However, this regulation can be impaired by excess copper induced by protein carriers or ion transporters [19] (Fig. 1). Ferredoxin 1 (FDX1) can rescue cells from death induced by elesclomol through CRISPR–Cas9 screening, and FDX1 particularly facilitates copper-dependent cell death [20]. FDX1 encodes a small iron–sulfur protein that transfers electrons from NADPH to mitochondrial cytochrome P450 via ferredoxin reductase. FDX1 is therefore the upstream regulator of lipoylation and is indispensable for cuproptosis [21] (Fig. 1). Lipoylation, a type of post-translational modification that occurs only in the four multimer-metabolizing enzymes in mitochondria, is unique to tricarboxylic acid cycle (TCA) cycle enzymes. In summary, the key step of cuproptosis occurs when copper is exposed to contact with lipoylated proteins, leading the proteins to be oligomerized abnormally. Finally, proteotoxic stress initiates and results in cell death [22] (Fig. 1).

Copper ionophores are vital for the transportation of intracellular copper. Therefore, copper ionophores are robust tools for inducing copper toxicity [23]. Elesclomol, a copper carrier and oxidative stress inducer, is a very lipophilic copper ion-binding molecule which can cause cuproptosis [24, 25]. Copper importer (SLC31A1) and copper exporters (ATP7A and ATP7B) are important factors in maintaining copper levels. Copper transporter 1 (CTR1), encoded by SCL31A1, plays a significant role in high-affinity copper absorption [26]. SLC31A1, a member of copper transporter

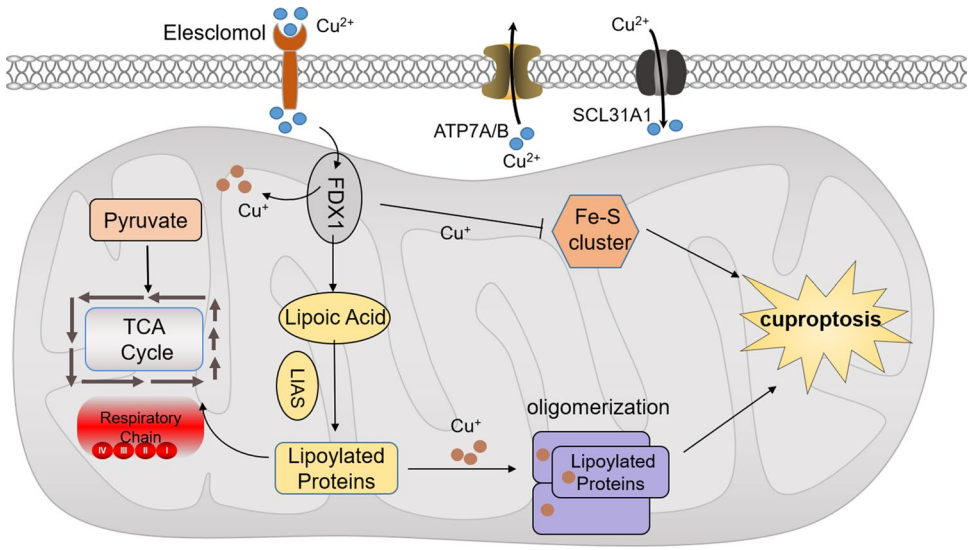

Fig. 1 Mechanism of cuproptosis. Extracellular copper is transported to the inner cell via a copper ionophore (elesclomol, disulfiram, etc.) or transporter (ATP7A/B). A proportion of copper is carried by a chaperone to mitochondrial matrix. On one hand, FDX1 reduces more Cu^{2+} to toxic Cu^{+} in mitochondria. The Fe–S cluster is suppressed. This is one reason for the formation of cuproptosis. On the other hand, Cu^{+} binds to lipoylated TCA cycle proteins. This combination leads to the oligomerization of lipoylated proteins. These variations induce proteotoxic stress and ultimately cuproptosis occurs

family, has a crucial role in preserving copper homeostasis and modulating the absorption of chemotherapeutic medicines [27]. Barresi et al. reported upregulation of the mRNA level of SLC31A1 in colorectal cancer (CRC), accompanied by upregulation of a series of cuproptosis-related genes (CRGs) (SCO1, and COX11) [27]. SLC31A1 can interfere with the increase in reactive oxygen species (ROS) and reduction in adenosine-triphosphate (ATP) level caused by copper absorption [28]. ATP7A is mainly expressed in tissues other than liver, whereas ATP7B is mostly expressed in liver and brain [29]. ATP7B (or ATP7A) can balance copper level by transfer from cytosol to Golgi apparatus, whereas excess copper will alter the localization of ATP7B/ATP7A to lysosome, leading to the release of copper via vesicles [21]. As a result, overexpression of SCL31A1 or deficiency of ATP7A/B sensitizes cells to cuproptosis. The main copper transporter of the mitochondrial carrier family (MCF) described in yeast is Pic2, which imports metal ions into the matrix. Pic2 ortholog SLC25A3, one of 53 mammalian MCFs, acts as both copper and phosphate transporter. Exhausted SLC25A3 can lead to reduced copper in the matrix, deficiency in cytochrome c oxidase, and disordered regulation of superoxide dismutase (SOD) abundance in the cytoplasm [30]. Glutathione, an endogenous copper chelator, also participates in TCA. Depletion of glutathione will change copper levels and trigger cuproptosis [31]. Although copper ionophores and copper chelators have been demonstrated to be anticancer agents, the lack of alternatives is still a major challenge. In the future, more attention should be focused on identifying specific targets for medical treatment.

Cuproptosis in cancers

Given that copper and energy metabolism are essential in cancers, cuproptosis may play an important role in cancer pathology [32]. FDX1, the upstream regulator of lipoylated proteins in cuproptosis, is involved in the development and metastasis of many types of cancers, including hepatocellular carcinoma (HCC), kidney renal clear cell carcinoma (KIRC) and so on [33]. Copper(II) bis(diethyldithiocarbamate) (CuET) is a copper organic complex that functions as a potent anticancer agent and a bioactive metabolite of disulfiram [34, 35]. CuET decreases FDX1 level and triggers cuproptosis in lung cancer cells (LC) [36]. Therefore, targeted therapies could be developed via associated pathways. Clear cell renal cell carcinoma (ccRCC) is the most common type of renal cell carcinoma (RCC) [37]. FDX1 expression is decreased in ccRCC [38]. Low FDX1 expression indicates poor prognosis and high risk [38]. Pan-cancer analyses have shown that FDX1 is downregulated in the majority of cancers. Different cancers present different FDX1 expressions and prognosis value, including breast cancer (BC), adrenocortical carcinoma (ACC), head and neck squamous cell carcinoma (HNSC), thyroid carcinoma (THCA), brain lower grade glioma (LGG) and colon adenocarcinoma (COAD) [39–41] (Table 1). As a result, FDX1 is a significantly vital gene in the mechanistic study of cuproptosis, and detailed research should be undertaken to clarify its importance.

Disequilibrium in copper homeostasis caused by genetic mutations is a threat to life in diseases including esophageal carcinoma (ESCA), pancreatic adenocarcinoma (PAAD), and BC [12, 28, 42]. Copper transporters can affect carcinomas via changes of copper levels. Higher expression of SLC31A1 in BC patients is associated with poorer prognosis and potentially affects immune and chemotherapeutic responses [43]. The probable SLC31A1-associated pathway could be exploited and studied in the development of treatment options. Another basic research showed the same expression trend of SLC31A1 in PAAD [28]. The level of SLC31A1 affects copper absorption, changes ROS and ATP levels, and finally contributes to cell death of pancreatic cancer [28]. In colorectal cancer (CRC), SLC31A1, SCO1, and COX11 have been verified to be elevated in a coordinated manner, leading to disruption of copper homeostasis [27]. Further experiments should be conducted to explore the related pathways for use in the development of CRC therapies. Copper exporter ATP7A was found to be a biomarker for the prognosis and survival of ESCA patients [42]. Nucleophosmin 1 (NPM1) is a protein transported between nucleus and cytoplasm and is the most studied protein in blood system diseases [44]. NPM1 expression is higher in ESCA patients than in healthy people, and higher expression is associated with poorer outcomes [45] (Table 1). NPM1 is thought to affect the progression of cuproptosis by changing copper concentration. Therefore, the specific pathway affecting copper expression could be explored to gain a deeper understanding for the pathogenesis of cancers.

Lipoic acid synthetase (LIAS) and pyruvate dehydrogenase E1 component subunit alpha (PDHA1) are cuproptosis-related genes (CRGs) that have been found to be linked to the synthesis of mitochondria-related metabolic enzymes [46, 47]. They all display different expression levels in different cancers, such as KIRC, BC, and lung adenocarcinoma (LUAD) [48, 49]. Through a series of analyses, LIAS and PDHA1 have been identified as potential biomarkers for the prediction of prognosis and immune response in pan-cancers [48, 49]. Lipoyltransferase 1 (LIPT1), which is involved in the metabolism of lipoic acid, is upregulated and associated with prognosis and immune response in skin cutaneous melanoma (SKCM) patients [50]. Further mechanisms need to be discovered for the treatment of melanoma. Cyclin-dependent kinase inhibitor 2A (CDKN2A), a cuproptosis-related gene, has been reported to predict overall survival (OS)

Table 1 Potential cuproptosis-related biomarkers for cancers

Target	Cancer type	Potential biomarker	References
FDX1	HCC, KIRC, BC, COAD, etc	FDX1	[36, 38–41]
Copper	BC	SLC31A1	[43]
	PAAD	SLC31A1	[28]
	CRC	SLC31A1, SCO1, COX11	[27]
	ESCA	ATP7A, NPM1	[42] [45]
Mitochondrial metabolism	KIRC	LIAS, PDHA1	[48, 49]
	BC	LIAS, PDHA1	[48, 49]
	LUAD	LIAS, PDHA1	[48, 49]
	SKCM	LIPT1	[50]
	TNBC	CDKN2A	[51]
	WHO2/3 glioma	CDKN2A	[52]
	UCEC	CDKN2A, GLS, LIPT1	[53]
	AFOC	LIAS, PDHB, GLS, CDKN2A	[56]
	ESCA	SLC25A5, SLC23A2, PDHX, COX7B	[42]
	HNSC	MRPS7	[59]
LncRNA	UCEC	XIST	[53]
	LUAD	AC008764.2, AL022323.1, ELN-AS1, LINC00578, AL031667.3, AL606489.1, MIR31HG	[66, 67]
	OS	AL645608.6, AL591767.1, UNC5B-AS1, CARD8-AS1, AC098487.1, AC005041.3	[62]
	STSs	ADAMTS9-AS1, CASC2, LINC00680, SNHG1, TRG-AS1	[8]

HCC hepatocellular carcinoma, *KIRC* kidney renal clear cell carcinoma; *BC* breast cancer, *COAD* colon adenocarcinoma, *PAAD* pancreatic adenocarcinoma, *CRC* colorectal cancer, *ESCA* esophageal carcinoma, *LUAD* lung adenocarcinoma, *SKCM* skin cutaneous melanoma, *TNBC* triple-negative breast cancer, *UCEC* uterine corpus endometrial carcinoma, *AFOC* arecoline-associated fibrosis-related OSCC (oral squamous cell carcinoma), *HNSC* head and neck squamous cell carcinoma, *OS* osteosarcoma, *STSs* soft tissue sarcomas

and is used to make a prognostic model for triple-negative breast cancer (TNBC) and WHO 2/3 glioma [51, 52]. CDKN2A could provide new insight into therapeutic targets for TNBC and WHO 2/3 glioma patients. A study of uterine corpus endometrial carcinoma (UCEC) identified CDKN2A, glutaminase (GLS), and LIPT1 as potential prognostic biomarkers [53]. Oral squamous cell carcinoma (OSCC) is among the oral malignancies with the highest morbidity [54]. Areca, whose active ingredient is arecoline, can contribute to the pathogenesis of OSCC [55]. Based on protein–protein interaction (PPI) networks and Spearman's correlation analysis, arecoline-associated fibrosis-related OSCC differentially expressed genes (AFOC-DEGs), LIAS, PDHB, GLS, and CDKN2A, were found to be closely related to cuproptosis [56]. Thus, the specific upstream mechanism of AFOC could be determined. CRGs including SLC25A5, SLC23A2, PDHX, and COX7B, all of which can impede mitochondrial energy metabolism, have been reported to be correlated with prognosis of ESCA patients [42, 57]. MRPS7, a ribosomal protein, is involved in protein synthesis in mitochondria [58]. MRPS7 expression is higher in HNSC patients [59] (Table 1). As a result, we could further explore signaling pathways on the information of MRPS7 as well as related upstream factors.

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that have specific cellular functions in tumors and many other diseases [60, 61]. An increasing number of bioinformatic analyses have shown a close relationship between prognosis and cuproptosis-related lncRNAs in many cancers, including SKCM, osteosarcoma (OS), and COAD [50, 62, 63]. X inactivate-specific transcript (XIST), a newly validated lncRNA, has a vital role in various kinds of cancers [64, 65]. Based on database analyses, the lncRNA XIST/miR-125a-5p/CDKN2A axis has been potentially implicated in the progression of UCEC [53]. Further research should be done to confirm this finding. Mo et al. also constructed a risk prognostic model of the immune microenvironment for LUAD via seven screened lncRNAs. AC008764.2, AL022323.1, ELN-AS1, and LINC00578 were found to be protective lncRNAs, whereas AL031667.3, AL606489.1, and MIR31HG are risk-related lncRNAs. They also verified that cuproptosis-related RNA TNFRSF21 was upregulated in LUAD patients and the progression could be

affected via the MIR31HG/miR-193a-3/TNFRSF21 pathway [66, 67]. A risk grade model and immune microenvironment for OS were constructed based on six lncRNAs (AL645608.6, AL591767.1, UNC5B-AS1, CARD8-AS1, AC098487.1, and AC005041.3) [62]. Soft tissue sarcomas (STSs) is a malignancy originating from mesenchymal tissue [68]. Patients with STSs have unsatisfactory prognosis even when comprehensive treatments including surgery, radiation, chemotherapy, and immunotherapy are all adopted [68]. Five cuproptosis-associated lncRNAs (ADAMTS9-AS1, CASC2, LINC00680, SNHG1, and TRG-AS1) have been found to be related to prognosis of STSs [8] (Table 1). Cuproptosis-related lncRNAs are upstream factors of signaling pathways which are valuable in clinical research and applications.

Potential role of cuproptosis in non-cancer diseases

There is also increasing evidence showing the potential of cuproptosis in non-cancer diseases. A plethora of studies reveal that copper is critical in neurodegenerative diseases including Alzheimer's disease (AD), Wilson's disease (WD), Menkes disease (MD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [69]. The concentration of copper may promote or hinder the occurrence and development of certain neurodegenerative diseases. AD is one of the most common diseases in aging people. In AD patients, copper is elevated in brain and serum [69]. Then copper could combine with Aβ peptides to induce plaque formation and reduce Cu^{2+} to Cu^{+}, which subsequently results in neurotoxicity [70, 71]. Another bioinformatic analysis showed that five CRGs (MYT1L, PDE4D, SNAP91, NPTN, and KCNC2) were proved to be diagnostic indicators of AD [72]; however, whether these CRGs function on AD via cuproptosis is still unclear. It is recognized that WD is an autosomal recessively inherited disease associated with the variation of ATP7B [73]. The mutation of this copper exporter could result in copper accumulation in brain, liver and other organs, which induces pathological changes on tissues [73]. Probably, ATP7B-induced cuproptosis is involved in the progression of WD. As another neurodegenerative disease, MD is a fatal genetic disease caused by the mutation of ATP7A. The defection of ATP7A leads to the retention of copper in intestines, which results in decreased copper in blood and brain [74]. The reduction of copper in brain will inactivate copper-dependent enzymes including dopamine-β-hydroxylase (DβH), which is required for neurotransmitter formation [75]. So, copper salts are used for the treatment of MD in clinic. HD is also one of the common neurodegenerative diseases, chiefly characterized by motor, cognitive and mental symptoms [76]. Copper accumulates in the striatum of HD patients and interacts with mutant Huntingtin proteins. Subsequently, the proteins will aggregate abnormally and promote the emergence of HD [77]. As a result, copper metabolism is significantly vital in the progression of HD. ALS is a progressive degeneration of motor neurons [78]. It has been proven that copper is overloaded in the spinal cord tissue of ALS patients, and copper chelator can improve motor dysfunction and delay disease progression [79] (Fig. 2). Given the role of copper metabolism in neurodegenerative diseases, cuproptosis may participate in the

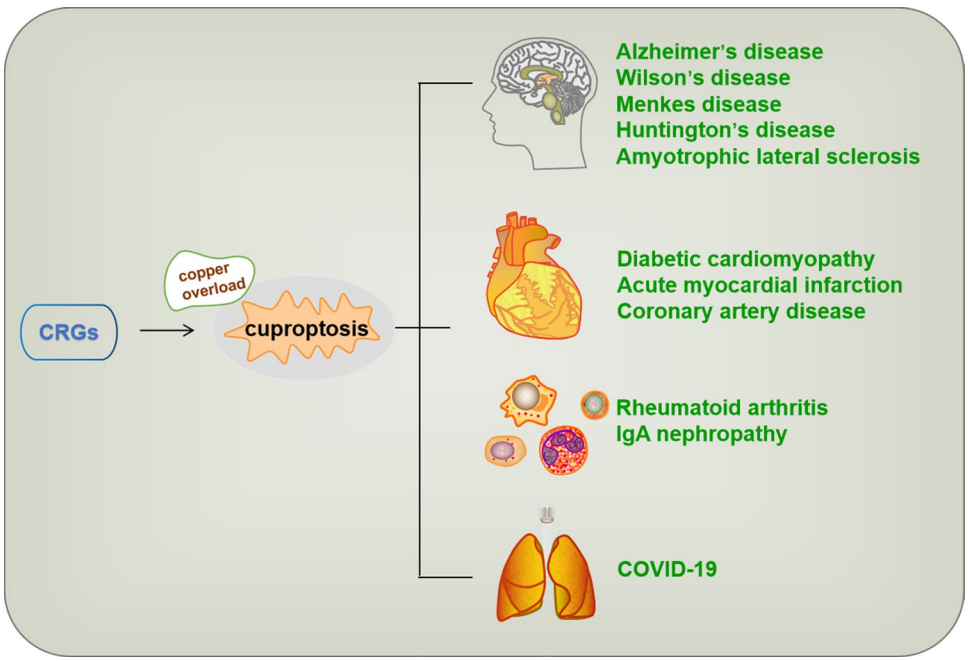

Fig. 2 Cuproptosis-related genes (CRGs) are assumed to contribute to Cu overload and subsequently trigger cuproptosis in tissues. Till now, we summarize that cuproptosis may participate in these diseases, including cardiovascular disease, neurodegenerative disease, COVID-19 and immune disease. But whether it can promote or hamper the disease remains to be proved

pathogenesis of these diseases. However, more evidence is still required.

Rheumatoid arthritis (RA), characterized by chronic persistent synovitis, is a kind of immune disease [80]. Through theoretical analysis on the metabolic cross-link between CRGs and RA, Zhao et al. found that CRGs (PDHA1, PDHB, GLS1, LIPT1, DLAT, FDX1, MTF1, LIAS, and CDKN2A) may influence the metabolic pathway of RA via cuproptosis [81]. Another immune disease, IgA nephropathy (IgAN), was found to be connected with LIPT1. LIPT1 has been observed to promote the onset of IgAN via NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) signaling [82, 83]. Based on database analysis, this CRG can predict the risk of IgAN [84]. Probably, it can also initiate IgA by this new pathway (Fig. 2).

Till now, cardiovascular disease (CVD) remains to be the first killer of human health. It has been reported that cuproptosis can affect the progression of CVD. Zhang's team found five CRGs (F5, MT4, RNF7, S100A12, and SORD) to be the potential diagnostic biomarkers for coronary artery disease (CAD) [85]. Huo et al. discovered that advanced glycosylation end products (AGEs) can promote cuproptosis via ATF3/SPI1/SLC31A1 pathway and thus worsen diabetic myocardial function [86]. Acute myocardial infarction (AMI) is another type of CVD. A bioinformatic analysis showed that GLS was lower in AMI and was negatively correlated with cuproptosis in AMI patients. This means that GLS may play a protective role via anti-cuproptosis in AMI patients [87] (Fig. 2). Since we have known that cuproptosis probably participates in and promotes the pathogenesis of CVD, in-depth experiments could be conducted for detailed mechanisms in the future.

As is well known, coronavirus disease 2019 (COVID-19) is a prevalent acute infectious disease. Intriguingly, Julian et al. found elevated copper level in surviving patients than non-surviving patients [88]. Furthermore, copper and copper-based alloy surfaces are reported to have stronger anti-coronavirus ability than other materials [89] (Fig. 2). Given the evidence, we suppose that copper may play a protective role in anti-coronavirus through cuproptosis.

Conclusions and perspectives

In summary, cuproptosis has opened up a new horizon in the study of cell death. We now summarized its potential as biomarkers for diseases. In-depth work should be done to identify the importance and unique of cuproptosis as the biomarkers. Research on the detailed signaling pathway of cuproptosis will be helpful for better understanding cuproptosis. Since cuproptosis involves many diseases, such as neurodegenerative diseases, cancers and so on, potential therapeutic strategy targeting cuproptosis could be developed via future studies. Given the finding that mitochondrion can affect cuproptosis and copper can change the stability of iron, cross talk may exist between ferroptosis and cuproptosis. How cuproptosis interact with other cell death and how these cell death pathways participate in the cell events remain to be proved. Overall, the study of cuproptosis is still at its beginning. A reference of effective prognostic and diagnostic biomarkers would be valuable. We believe that comprehensive exploration related to cuproptosis will be of great importance for physiology and pathology and targeting cuproptosis will be novel and promising in the clinical management of diseases.

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Data availability All data that support the findings of this study are included within the article.

Declarations

Conflict of interest The authors declared no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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