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Review

Research progress on cuproptosis and copper related anti-tumor therapy

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Abstract
Copper is a trace element which is essential for biological organisms, and its homeostatic balance is important for living organisms to maintain the normal function. When the copper homeostasis is disordered, the cellular function and structure will be disrupted. Excess copper cause oxidative stress and DNA damage in cells, thereby inducing regulated cell death such as apoptosis and necroptosis. Excess copper in mitochondria can bind to lipoylated proteins in the tricarboxylic acid (TCA) cycle and cause them to aggregate, resulting in proteotoxic stress and eliciting a novel cell death modality: cuproptosis. Cancer cells have a greater demand for copper compared to normal tissue, and high levels of copper ions are closely associated with tumour proliferation and metastasis. The anti-tumor mechanisms of copper include the production of oxidative stress, inhibition of the ubiquitin–proteasome system, suppression of angiogenesis, and induction of copper-dependent cell death. Targeting copper is one of the current directions in oncology research, including the use of copper ion carriers to increase intracellular copper levels to induce oxidative stress and cuproptosis, as well as the use of copper ion chelators to reduce copper bioavailability. However, copper complexes have certain toxicity, so their biosafety needs to be improved. Emerging nanotechnology is expected to solve this problem by utilizing copper-based nanomaterials (Cu-based NMs) to deliver copper ions and a variety of drugs with different functions, thereby improving the anti-tumor efficacy and reducing the side effects. Therefore, a thorough understanding of copper metabolic processes and the mechanism of cuproptosis will greatly benefit anti-tumor therapy. This review summarizes the processes of copper metabolism and the mechanism of cuproptosis. In addition, we discuss the current anti-tumor paradigms related to copper, we also discuss current nanotherapeutic approaches to copper mortality and provide prospective insights into the future copper-mediated cancer therapy.

Keywords Copper · Copper metabolism · Tricarboxylic acid cycle · Cuproptosis · Antitumor therapy

1 Introduction

Cell death is a normal biological phenomenon that plays a key regulatory role in the development and homeostatic maintenance of organisms [1]. There are various forms of cell death, which can be categorized into accidental cell death (ACD) and regulated cell death (RCD) based on the different mechanisms of occurrence. ACD includes necrosis, a form of cell death that is triggered by an unexpected injurious stimulus and cannot be regulated. It is characterized by cellular swelling, biofilm rupture, spillage of cellular contents, and dissipation of ionic gradients, which triggers an inflammatory

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response [2]. RCD is a modifiable form of cell death that involves signaling cascades with unique biochemical features, morphological characteristics, and immunological consequences [3]. The currently known modalities of RCD include Apoptosis, Autophagy, Necroptosis, Pyroptosis, Ferroptosis, cuproptosis, programmed cell death (PCD), lysosomal cell death (LCD), Oxeiptosis, PANoptosis and so on [4–8], and each pathway is characterized by corresponding morphological changes in the cells (Fig. 1). Apoptosis is a highly regulated form of cell death which can be achieved by the extrinsic pathway and the intrinsic pathway, and its morphological manifestations are cell membrane blistering, cell shrinkage, and the formation of apoptotic body [9]. Autophagy is an intracellular catabolic pathway that degrades and recycles cellular contents within the lysosome, providing the cell with material for repair, survival, and growth [10]. The mechanism of cellular pyroptosis is divided into classical and non-classical pathways. In the classical pathway, inflammasome activate and shear into Caspase-1, which in turn shears gasdermin D (GSDMD), leading to cell membrane perforation and cell death [11]. In the nonclassical pathway, Caspase-4, 5, and 11 activation shears GSDMD, leading to perforation of the cell membrane, cell rupture, and triggering an inflammatory response [11]. Ferroptosis is driven by iron accumulation and lipid peroxidation. It is characterized by smaller mitochondria, reduced mitochondrial cristae, increased mitochondrial membrane density and increased mitochondrial membrane rupture [12].

Copper is a biologically essential trace element with redox properties, it serves as a cofactor for many enzymes and plays a vital role in mitochondrial respiration, antioxidant defense, and hormone biosynthesis [13]. A growing number of studies have confirmed its involvement in cell proliferation and death pathways [14]. Cells maintain the copper concentration at a relatively low range through active homeostasis mechanisms, so as to prevent excessive accumulation of copper ions [15]. However, abnormal copper metabolism leads to cell death and organismal damaging effects [15, 16]. In the case of copper overload, excess copper binds to proteins and lipids within the cell, leading to the destruction of cell structure and function [17]. Copper ions also react with reactive oxygen species (ROS) to generate more ROS, further exacerbating cellular damage. This cellular damage may trigger regulatory cell death pathways such as apoptosis and auto, leading to cell death [18, 19]. Copper is a cofactor for a number of enzymes, so the deficiency of Copper affects the physiological function and

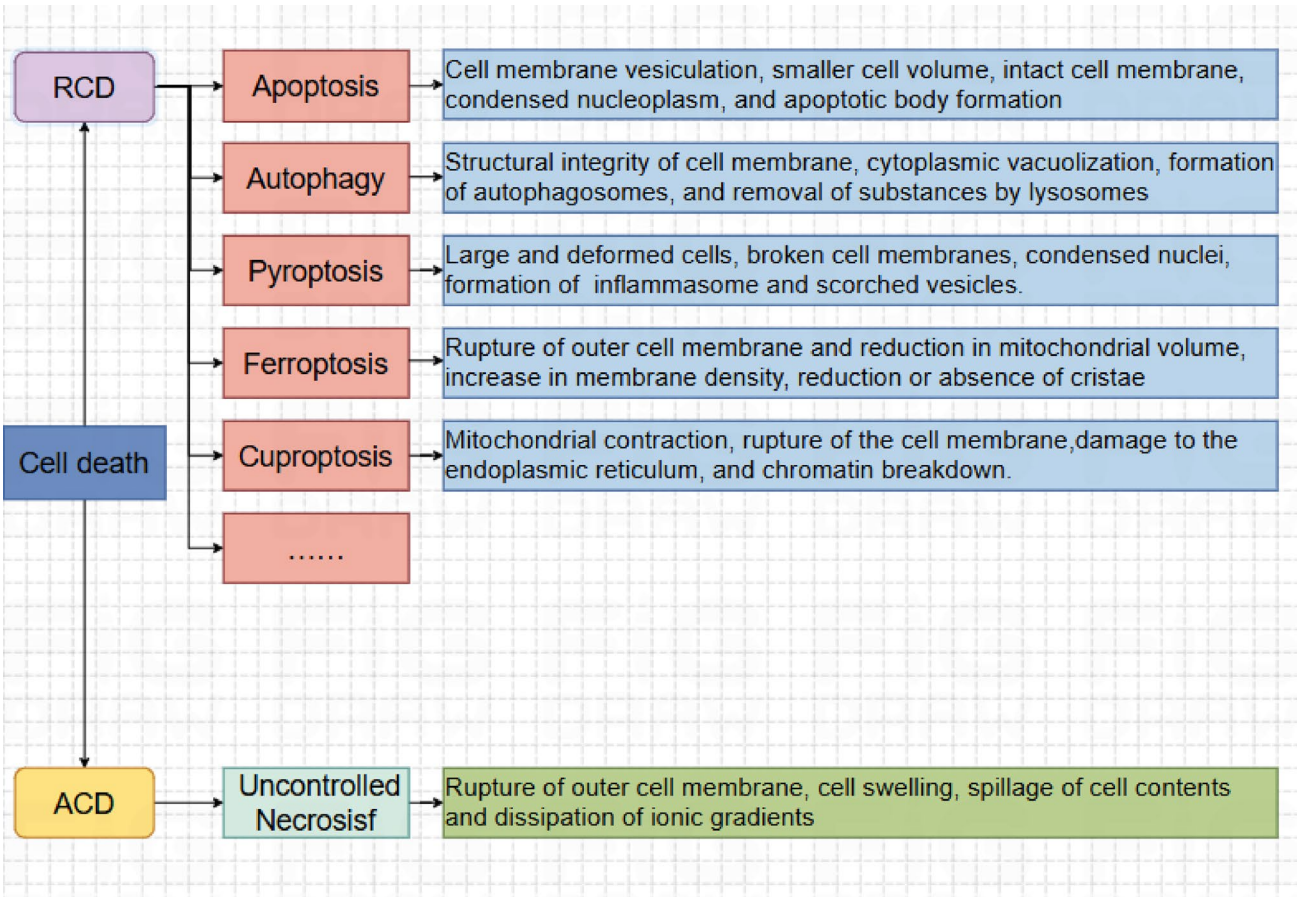

Fig. 1 Different forms of cell death and corresponding morphological characteristics of the PCD pathways

metabolism of Cu-dependent enzymes such as dopamine-β-hydroxylase (DβH) [20]. Prolonged copper deficiency may lead to cellular energy depletion and impaired protein synthesis, leading to regulated cell death. In a paper published in March 2022, Tsvetkov proposed a new mode of cell death and named it "cuproptosis" [21]. Its mechanism relies on mitochondrial respiration but is clearly distinct from other mechanisms of RCD. There are similarities between cuproptosis and ferroptosis. Excessive copper ions promote cell death by binding to lipoylated proteins, inducing the aggregation of lipoylated proteins, and inhibiting mitochondrial metabolic functions [21]. In addition, copper ions reduce the levels of Fe-S cluster proteins, triggering a proteotoxic stress response. This study explains the pathology associated with hereditary copper overload disorders and proposes new methods for treating cancer: increasing the concentration of copper in cells can be used to selectively kill cancer cells [21]. The current anti-tumor mechanisms of copper include the production of oxidative stress, inhibition of the ubiquitin–proteasome system, suppression of angiogenesis, and induction of copper-dependent cell death. Targeting copper is one of the current directions in oncology research, including the use of copper ion carriers to increase intracellular copper levels to induce oxidative stress and cuproptosis, as well as the use of copper ion chelators to reduce copper bioavailability. In this review, we comprehensively outline the connections between copper metabolism, the mechanism of copper death, and the mechanism of cuproptosis. We clarify the mechanism of cuproptosis and its impact on the pathogenesis of cancer. Furthermore, we emphasize current nanotherapeutic approaches to copper mortality and provide prospective insights into the future copper-mediated cancer therapy.

2 Overview of copper metabolism

An adult harbors approximately 100–200 mg of copper within their body [15]. Based on the data provided by the United States Food and Nutrition Commission, it has been established that a daily copper intake of approximately 0.8 mg is sufficient to preserve the copper levels. There are two principal forms of copper, Cu II and Cu I, which are integral to a variety of physiological functions. Copper is derived from the daily diet and it is absorbed in the duodenum and small intestine [22]. Small intestinal epithelial cells absorb copper ions through the high-affinity copper transporter CTR1 [23], and then transport them to the intestinal lateral membranes through the antioxidant 1 copper chaperone (ATOX1) [24]. The absorbed copper ions are bound to ceruloplasmin (CP) in the liver and then it will be transported throughout the body via the bloodstream [25]. When there is an excess of copper stored in the hepatocytes, the excess copper will be excreted into the bile and eliminated from the body under the regulation of ATP7B [26, 27]. When the peripheral copper concentration decreases, ATP7A pumps copper ions from liver into the bloodstream [28]. This mechanism facilitates the dissemination of copper ions across the organism, ensuring a consistent copper ion concentration within the peripheral bloodstream [26, 27]. It is evident that the metabolic pathway of copper encompasses a series of regulated stages, including absorption, transportation, storage, and elimination. These stages are instrumental in preserving the equilibrium of copper ions within the body (Fig. 2). Once the concentration of copper surpasses the level necessary to preserve cellular equilibrium, it triggers a cascade of metabolic disruptions within the cell [29]. Copper plays a crucial role in the formation of numerous enzymes, and its insufficiency can disrupt the collagen cross-linking within connective tissues, leading to conditions such as anemia, leukopenia, diminished arterial wall elasticity, and neurological manifestations [30, 31]. The most prevalent genetic disorders affecting copper metabolism are Wilson disease (WD) and Menkes disease (MD), both of which are characterized by defective copper absorption, resulting in reduced copper concentrations in the liver and brain [32]. Consequently, this leads to diminished activity of copper-dependent enzymes within the tissues. These conditions manifest as growth delays, hyperpigmentation, and defects in connective tissue [33]. Furthermore, the metabolism of copper is intimately associated with the development of tumors [34]. It has been frequently observed that tumors demand elevated copper concentrations, surpassing those found in normal tissue [35]. Certain metallic drugs, such as cisplatin, exploit the copper transporter protein Ctr1 to gain cellular entry, ultimately contributing to the induction of apoptosis in tumor cells [36].

3 The mechanism of cuproptosis

Cuproptosis exhibits a series of main morphological features, such as mitochondrial shrinkage, compromise of the cell membrane integrity, disruption of the endoplasmic reticulum, and fragmentation of chromatin [37–39]. These attributes resemble the apoptotic process, yet the underlying mechanisms diverge from those of other regulated cell death modalities.

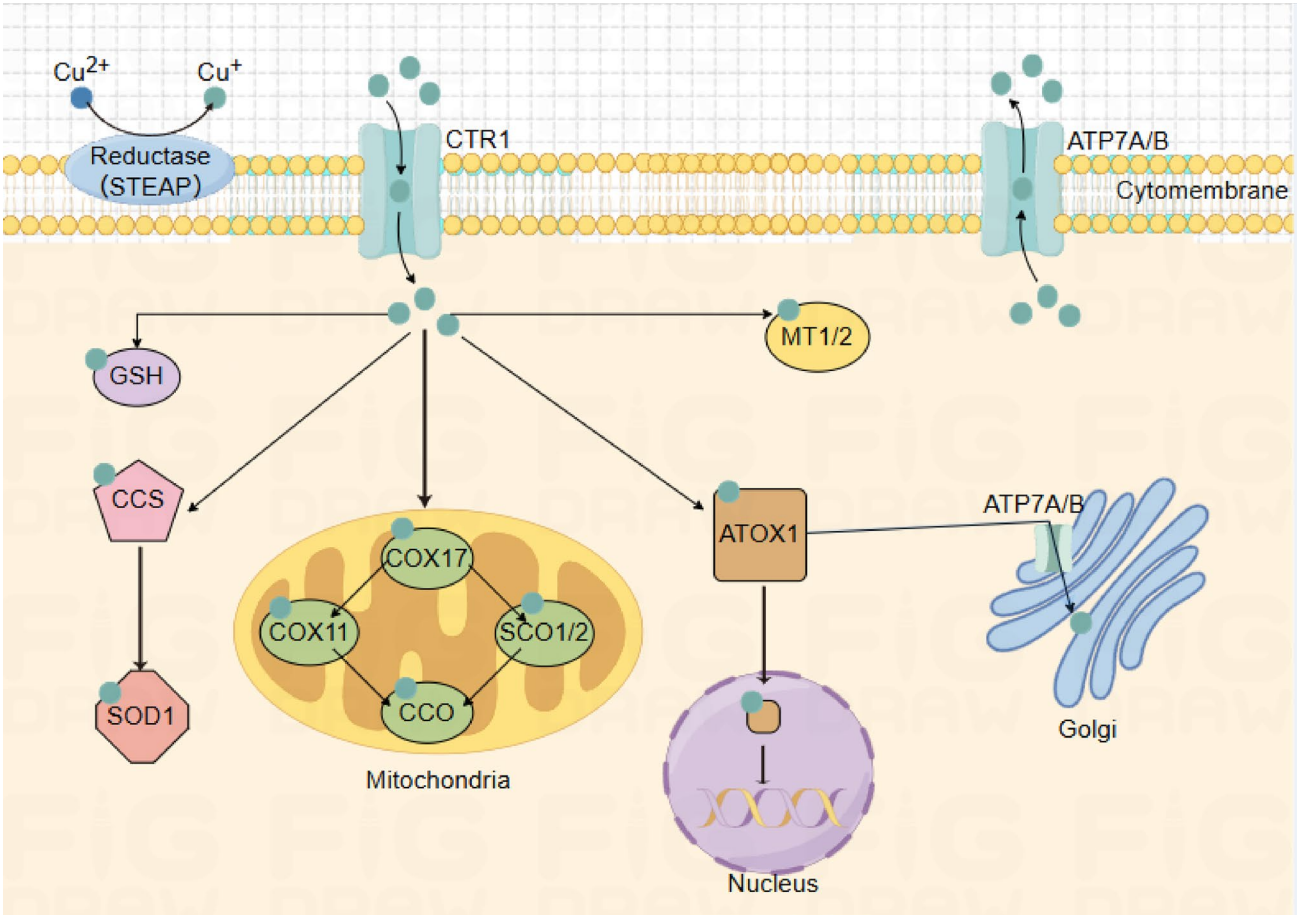

Fig. 2 The maintenance of cellular copper equilibrium engages a complex network of interactions. At the cell surface, Cu II is catalytically reduced to Cu I by STEAP proteins and then translocated into the cell via CTR1. Once inside, these ions can enter the mitochondrial matrix via COX17 to produce ATP or be transported by Atox1 to the nucleus and the Golgi network. Within the cytoplasm, copper ions bind to the copper chelators GSH and MT to neutralize the cytotoxicity of copper, or are carried by the copper chaperone CCS to SOD1 to regulate intracellular reactive oxygen species homeostasis. Excess copper ions in cells can be efficiently eliminated by Cu-ATPases such as ATP7A and ATP7B

3.1 Activation of oxidative stress

Under the normal physiological conditions, cells preserve a delicate equilibrium between oxidation and antioxidant defense mechanisms. When this equilibrium is disturbed, oxidative stress ensues, characterized by an elevation in the steady-state concentration of reactive oxygen species (ROS). The Fenton reaction, a prevalent metal-catalyzed process, is responsible for the generation of substantial quantities of ROS. In the Fenton reaction, copper ions oscillate between their oxidized and reduced states, thereby catalyzing the production of substantial quantities of reactive oxygen species (ROS) from H2O2 [40]. This process inflicts a multitude of cellular damages, encompassing DNA damage, mitochondrial dysfunction, and the disruption of cell membrane integrity [41]. Numerous studies have indicated that copper ions can trigger the death of cancer cells by elevating the production of ROS and activating signaling pathways associated with oxidative stress. For example, the copper ion carrier NSC319726 stimulates Cu II and facilitates the production of ROS, resulting in the depletion of deoxynucleotides and inhibition of DNA synthesis. This causes cells to remain in G1 phase and induces cell death [42]. Furthermore, disulfiram (DSF) also triggers the demise of cancer cells. It complexes with Cu II, which in turn enhances the production of ROS, activates the P38 signaling pathway, and suppresses the NF-kB signaling pathway [43].

3.2 Inhibition of the ubiquitin–proteasome system

The ubiquitin–proteasome system (UPS) serves as a pathway for protein degradation and it is accountable for approximately 80% cellular protein degradation [44]. Protein degradation involves two different pathways, ubiquitination and degradation. Ubiquitination refers to the process by which target proteins are tagged with ubiquitin, allowing the proteasome complex to selectively recognize and subsequently degrade these proteins [45]. UPS modulates the expression levels and activities of a diverse array of proteins, and it also plays a role in the regulation of cellular processes, including the cell cycle, proliferation, and apoptosis [46]. Currently, protease inhibitors such as bortezomib have been widely used in the treatment of multiple myeloma and other diseases, showing strong anti-tumor activity [47]. Research has shown that copper ions can interfere with the normal function of the UPS through different mechanisms. For example, the disulfiram-copper complexes disrupt cancer cells by inhibiting proteasome activity and increasing ubiquitin-protein interactions [48]. It also impedes the degradation of ubiquitin proteins by obstructing signal transduction upstream of the proteasome and suppressing ubiquitination-dependent ATP synthase activity [49].

3.3 Copper induces cell death by targeting acylated TCA circulating protein

In the TCA cycle of the mitochondrial respiratory chain, excess copper binds with a suite of mitochondrial proteins, including pyruvate, α-ketoglutarate, branched-chain cuprate dehydrogenase, and the glycine cleavage systems, leading to their aberrant aggregation and subsequent dysfunction [21]. This process triggers the instability of iron-sulfur cluster proteins, thereby inhibiting mitochondrial metabolic functions, leading to proteotoxic stress and ultimately resulting in cell death (Fig. 3) [50]. Ferredoxin 1 (FDX1) serves as a crucial regulator of cuproptosis and acts as a principal upstream modulator of protein lipid acylation. The protein product of FDX1 can be directly targeted by the copper ion carrier elesclomol, which converts Cu II to Cu I [51]. Knockdown of FDX1 or attenuation of enzymes associated with lipid acylation prevented the onset of cuproptosis. In contrast, treating cells with inhibitors of known cell death patterns (such as apoptosis, autophagy, ferroptosis, etc.) does not rescue cuproptosis [52]. The abundance of FDX1 and lipoylated proteins is highly correlated with various human tumors. Studies have shown that cell lines with high levels of lipoylated proteins are more sensitive to cuproptosis [53]. This finding suggests that copper ion carriers could be a potential therapeutic approach for cancer cells with such metabolic profiles.

4 Copper related tumor treatment

In contrast to typical tissue types, cancer cells exhibit an augmented requirement for copper, with elevated levels of copper ions being intricately linked to the proliferation and metastasis of tumors. Enhanced copper concentrations have been observed within tumor tissues and the sera of patients afflicted with diverse forms of cancer, including breast cancer, lung cancer, gastrointestinal cancer, and gallbladder cancer [54–57]. The pivotal role of copper ions in relation to cancer is underscored by their involvement in regulating the cell cycle, fostering angiogenesis, and influencing cell signaling pathways [58]. For instance, the presence of copper ions has been shown to exacerbate tumor cell metastasis and infiltration by stimulating the secretion of matrix metalloproteinases (MMPs) from cancerous cells [59]. Copper ions have the capacity to directly activate and interact with EGFR, PDK1, and PI3K, thereby fostering tumorigenic processes [60]. Furthermore, copper ions impact the MAPK pathway and modulate the stability of c-Myc, which in turn affects tumor progression [61]. Copper ions can promote vascular tumor migration by indirectly promoting HIF-α or indirectly inhibiting the the Jagged1 ligand of the Notch signaling pathway [62]. Moreover, they can regulate tumor metabolism by controlling the activity of PDE3B or S6K1 [18]. Various copper-binding compounds, such as copper chelators and copper ion carriers, hold significant promise for the therapeutic management of cancer. Two main strategies have been proposed: 1. Using copper ion carriers to transport copper ions into cells to increase intracellular copper content, thereby inducing cell death by excessive copper ions. 2. Using copper chelators to deplete copper ions, thereby inhibiting copper proliferation and reducing the concentration of copper within the cells. However, it is noteworthy that long-term use of copper-binding compounds can disrupt the

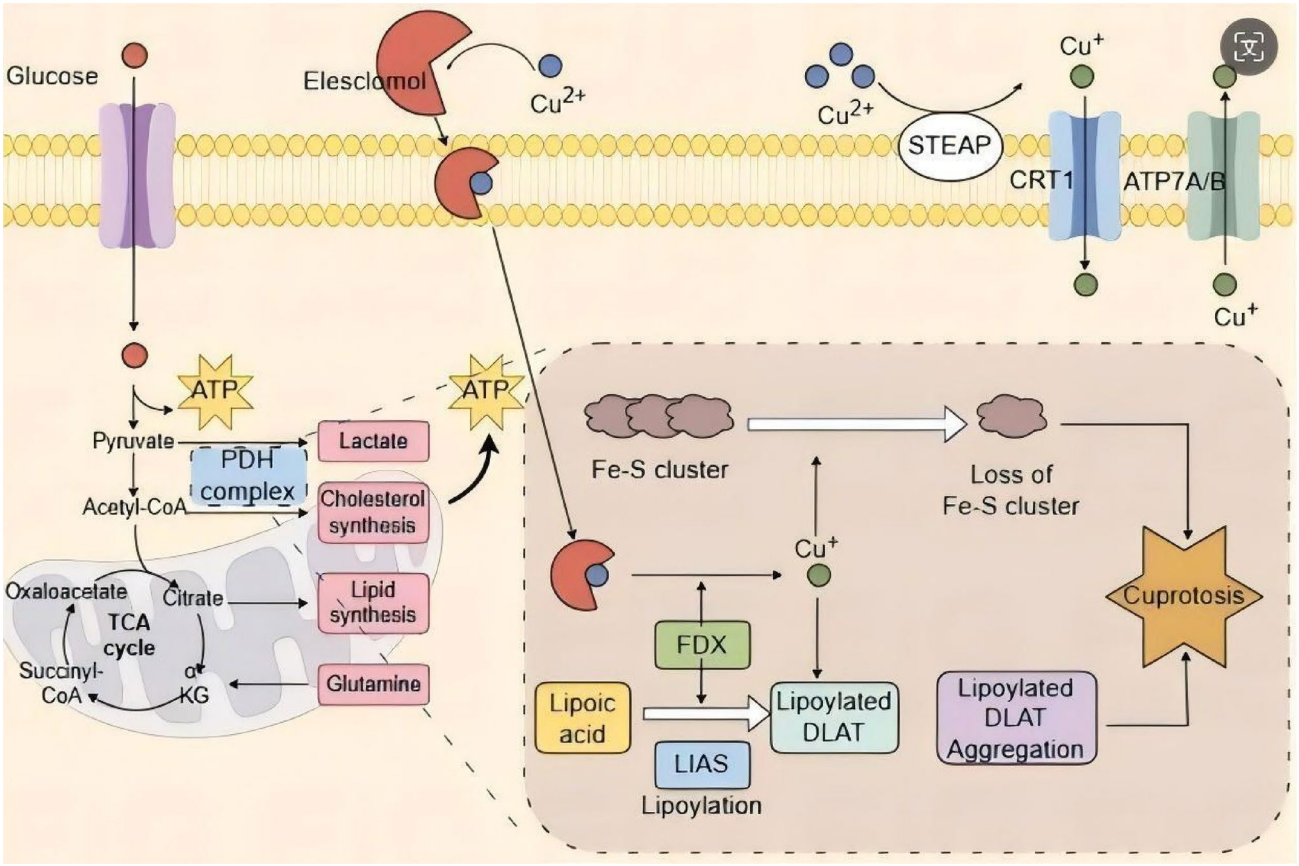

Fig. 3 Schematic representation of copper death. Elesclomol, a copper ion carrier, sequesters extracellular Cu II and facilitates its intracellular transport. Subsequently, copper ions interact with thiooctyl-modified mitochondrial enzymes such as DLAT, which are integral to the TCA cycle. FDX1/LIAS is an upstream regulator of protein thiooctylation that promotes mitochondrial protein aggregation and loss of Fe-S clusters. These processes trigger proteotoxic stress, culminating in cellular demise

balance of base metals and cause severe side effects in patients undergoing treatment [63]. With the widespread discovery of nanomaterials, copper-based materials have become a therapeutic option for tumors treatment. Currently, researchers are working to improve the selectivity of copper ion carriers, such as nanodrug delivery systems, with the aim of enhancing the precision targeting capabilities for the upcoming generation of copper ion carriers.

4.1 Copper supplementation

Enhancing copper concentration through copper supplementation to induce tumor cell death is a mainstream research strategy in copper-related cancer therapy. Currently, common copper ion carriers include eletrochloromal, NSC319726 and disulfides, which can suppress natural antioxidant systems such as mitochondria, leading to oxidative stress [34]. Copper ion carriers exhibit antitumor activity through various mechanisms, including DNA binding, anti-angiogenesis, proteasome inhibition, and the induction of apoptosis [64–66]. Elesclomol (ES) selectively transports Cu II from the extracellular environment into the mitochondria, where it reduces the copper to Cu I, thus inducing the generation of ROS [67]. Elesclomol has been shown to enhance the therapeutic efficacy of paclitaxel in patients with refractory solid tumors and in patients with stage IV metastatic melanoma [68]. Moreover, during a phase III clinical trial involving patients with advanced melanoma (NCT00522834), Elesclomol exhibited enhanced anti-tumor effects in those with elevated mitochondrial metabolic activity [69]. Disulfiram (DSF) serves as a precise inhibitor of acetaldehyde dehydrogenase type 1 (ALDH1), selectively eliminating ALDH + cancer stem cells and thus diminishing the likelihood of tumor relapse [70]. DSF exhibits robust suppression of GSDMD pore formation, inflammasome-mediated apoptosis, and secretion of IL-1β in liposomes derived from both human and murine cells [71, 72]. Numerous investigations have demonstrated that DSF in conjunction with cupric ion Cu II can elevates intracellular reactive oxygen species (ROS) levels and elicits copper-dependent cell death [73]. DSF is capable of crossing the blood–brain barrier, through the induction of ROS and inhibition

of both ALDH and the NFkB pathway, it augments the anti-cancer efficacy against glioblastoma multiforme (GBM) [74]. Furthermore, the continuous build-up of copper ions has the potential to elevate the expression of PD-L1 on the surface of cancer cells, thereby amplifying the anticancer efficacy of immune checkpoint blockers αPD-L1 [75]. Guo B et al. have developed a nanomedicine called NP@ESCu, which was able to be triggered by excess reactive oxygen species in cancer cells and release ES and copper after entering cancer cells [76]. This drug utilizes the characteristic of high levels of reactive oxygen species within cancer cells and achieves specific killing of cancer cells through nanotechnology [76]. The dual action of ES and copper collaboratively orchestrates the demise of cancer cells and transforms the immunosuppressive tumor microenvironment. The conjunction of NP@ESCu with αPD-L1 not only boosts the therapeutic impact against cancer but also markedly curbs tumor progression [76].

4.2 Copper depletion

Tumor cells have a higher demand for copper ions, using copper-depleting agents to effectively deplete copper ions can reduce intracellular copper concentration, thereby inhibiting the activity of copper-based enzymes and suppressing the growth of tumor cells [77]. Various established copper chelating agents decelerate the progression of cancer metastasis by diminishing copper levels and mitigating factors associated with vascular proliferation. The reduction of copper can deactivate the angiogenic trigger, thereby inhibiting endothelial cell multiplication and halting cellular progression at the G0 phase [78]. Apart from directly sequestering intracellular copper ions, another strategy for achieving copper depletion involves inhibiting the function of copper transporters and chaperones such as ATOX1 and CTR1 [79]. Tetrathiomolybdate (TM) is one of the most common copper chelators. It has antiangiogenic effects and can delays disease progression in patients with stage I or II malignant mesothelioma [80]. In addition, TM has the capability to selectively reduce copper ions within primary tumors, effectively halting copper-mediated metastasis while preserving the integrity of adjacent healthy tissues [81]. Lysyloxidase (LOX), a copper-dependent monoamine oxidase, serves as a crucial enzyme that orchestrates the cross-linking of collagen fibers [82]. Activated LOX reduces cell adhesion molecules by activating the FAK/Src signaling pathway, thereby promoting cancer cell metastasis and spread. Some studies have found that the upregulation of LOXL2 is associated with the progression of breast cancer, and copper depletion related to TM leads to a decrease in LOXL2 levels, thereby promoting immune activation and preventing breast cancer metastasis [83]. TM can also regulate the copper homeostatic process by reducing the expression of ATP7B. This results in a reduction of the efflux of platinum-based drugs, thereby enhancing the accumulation and apoptotic effects of cisplatin within tumor cells and preventing the development of drug resistance [84]. In addition, copper chelators can also be used in combination therapy to enhance the efficacy of kinase inhibitor drugs on cancer-causing signaling pathways. Employing copper chelators to reduce copper levels affects the activity of MEK1/2 kinases and the BRAF-driven MAPK signaling pathway, subsequently diminishing the proliferation of xenografted BRAFV600E tumors [85]. Copper also plays an important role in regulating tumor immunity [86]. Copper supplementation can induce PD-L1 gene transcription and protein stabilization, while copper depletion can reverse the inhibition of PD-L1 transcription and promote the degradation of PD-L35, thereby enhancing the immune response [87]. This indicates that copper-depleting drugs can be used as immune checkpoint inhibitors for tumor immunotherapy.

4.3 Application of copper-based nanomaterials

Traditional cancer treatments, including surgery, radiotherapy, and chemotherapy, are often accompanied by numerous adverse effects that can significantly impede the therapeutic efficacy [88, 89]. In recent years, a significant number of copper-based nanomaterials (Cu-based NMs) have been investigated as potential experimental anticancer agents in vitro, owing to their favorable biocompatibility [90, 91]. Combining nanomedicine carriers with chemotherapy, phototherapy, and photothermal therapy enables the selective targeting of malignant tissues, modulation of the tumor microenvironment, and enhancement of cancer treatment efficacy [92]. Photothermal therapy (PTT) and photodynamic therapy (PDT) are effective anti-tumour therapeutic strategies that are widely used currently [93] and their main components are photothermal agents (PAs) and photosensitisers (PSs), which can absorb light energy and convert it into localized heat, thereby increasing the ambient temperature, killing tumor cells and inducing anti-tumor immunity [94]. Due to their excellent near-infrared absorption and outstanding photothermal properties, copper-based nanomedicines (NMs) are often used as photosensitizers (PS), generating a large amount of ROS through the Fenton reaction, inducing cellular oxidative stress and damage [95]. The catalytic activity of the copper-based NMs is many times higher than that of traditional reagents [96]. The photothermal reactivity of copper-based NMs significantly curtails the leakage of non-specific

drugs from the bloodstream, thereby diminishing toxicity to healthy tissues [97]. Moreover, Copper-based NMs have a relatively large surface area, which can be loaded with different chemotherapeutic drugs for tumor chemotherapy. The synergistic effect of Chemodynamic Therapy (CDT) and PTT can precisely release chemotherapy drugs, effectively inhibiting tumor growth and recurrence [98, 99].

5 Conclusion and future prospects

Copper is an essential trace element and its uptake and efflux processes are tightly regulated. Copper homeostasis is crucial for maintaining cell proliferation and metabolism, its dysregulation can lead to cell death through various mechanisms. The specific pathways through which copper ions mediate cell death encompass: 1. Inducing DNA damage and lipid peroxidation via the Fenton reaction; 2. Impairing the mitochondrial pathway, resulting in an imbalance of redox reactions; 3. Interfering with protein conformation and function, inhibiting the synthesis of iron-sulfur cluster proteins; 4. Disrupting copper homeostasis, impeding the expression of copper transport proteins. Cuproptosis is a newly identified mode of cell death, in which FDX1 is a key factor in the process. Excess copper induces cell death by promoting aberrant oligomerization of lipoylated proteins in the tricarboxylic acid cycle and decreasing Fe-S cluster protein levels. Cuproptosis is associated with the occurrence and progression of various diseases, including breast cancer, lung cancer, neurodegenerative diseases, Wilson's disease, obesity, etc. Recent studies indicate that copper death is related to the occurrence and progression of various cardiovascular diseases. Although the basic mechanism of cuproptosis has been preliminarily elucidated, the complex relationship between it and oxidative stress, as well as various forms of cell death, has not yet been fully described. Therefore, the role of copper levels and copper metabolism in the pathophysiology of diseases needs to be further clarified.

There are currently two main strategies for tumor treatment, which involve causing copper overload or copper depletion through copper complexes, thereby disrupting copper homeostasis. However, the application of copper complexes is limited by their high systemic toxicity and low bioavailability, so there is a need to improve their biosafety [100].

In the development of emerging tumor therapeutic strategies, copper-based NMs can be harnessed to deliver copper alongside a range of drugs that serve various functions. This approach can lead to enhanced antitumor efficacy and a reduction in side effects. Additionally, copper-based NMs can be employed for PTT, CDT, and therapies related to ROS due to their distinctive physicochemical properties. Nevertheless, the biocompatibility and biosafety of these copper-based NMs remain challenges that require resolution. It is anticipated that further research will be conducted to explore these aspects in depth, ultimately paving the way for copper-related tumor therapies to genuinely benefit patients.

Author contributions Yichen Li (First Author): conceptualization, methodology, software, data curation, writing original draft and visualization. Lifei Han: resources, supervision, review and editing. Haolin Hu (Corresponding Author): conceptualization, funding acquisition, resources, supervision, review and editinng. All authors reviewed the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Approval of the research protocol by an Institutional Reviewer Board: N/A. Informed consent: N/A. Registry and the Registration No. of the study/trial: N/A. Animal Studies: N/A.

Competing interests The authors declare no competing interests.

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