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# Cell death mediated by nanotechnology via the cuproptosis pathway: a novel horizon for cancer therapy

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January 4, 2023

**Abstract**

Cuproptosis, the current form of regulated cell death characterized by copper overload, oligomerization of lipoacylated proteins, and loss of the Fe-S cluster proteins, has been proposed to function closely with human diseases including cancer. Since the first identification in 2022, a wide range of strategies have been developed to induce cuproptosis for cancer therapy, such as small-molecule drugs and nanomaterials. Although many reviews related to cuproptosis have been reported, they remain at a basic mechanism level and a summary covering recent progress in the field of nanotechnologies in cuproptosis-based cancer therapy has not yet been presented. Therefore, it is time to fill the gap and shed light on future directions for the application of this promising tool to fight against cancer. In this minireview, we first expounded the mechanism of action of cuproptosis and emphasized the feasibility of triggering cuproptosis for cancer therapy. The recent progress of cancer treatments based on nanoparticle-induced cuproptosis was then described. Finally, the challenges and future development directions of the emerging field of cuproptosis were also discussed.

## Cell death mediated by nanotechnology *via* the cuproptosis pathway: a novel horizon for cancer therapy

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**Abstract**

Cuproptosis, the current form of regulated cell death characterized by copper overload, oligomerization of lipoacylated proteins, and loss of the Fe-S cluster proteins, has been proposed to function closely with human diseases including cancer. Since the first identification in 2022, a wide range of strategies have been developed to induce cuproptosis for cancer therapy, such as small-molecule drugs and nanomaterials. Although many reviews related to cuproptosis have been reported, they remain at a basic mechanism level and a summary

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covering recent progress in the field of nanotechnologies in cuproptosis-based cancer therapy has not yet been presented. Therefore, it is time to fill the gap and shed light on future directions for the application of this promising tool to fight against cancer. In this minireview, we first expounded the mechanism of action of cuproptosis and emphasized the feasibility of triggering cuproptosis for cancer therapy. The recent progress of cancer treatments based on nanoparticle-induced cuproptosis was then described. Finally, the challenges and future development directions of the emerging field of cuproptosis were also discussed.

**KEYWORDS**

cuproptosis, nanomaterials, cancer therapy

## 1 INTRODUCTION

Cancer is one of the leading causes of human death worldwide, characterized by uncontrolled proliferation and locally invasive infiltration.[1-3] Because of the evading immune recognition through genetic mutations, the balance between cell death and proliferation is broken, leading to the unrestricted cell proliferation and ultimately cancer.[4,5] While advanced techniques have been applied to basic and clinical cancer research, most of them are arduous and unsatisfactory in performance, as existing approaches can barely kill cancer cells while sparing surrounding normal cells.[6,7] Selectively inducing programmed cell death (PCD) in cancer cells is a promising option for cancer therapy, including apoptosis, autophagy, necrosis. Among them, apoptosis is considered the preferred alternative, but the therapeutic effects are still far from satisfactory due to the intrinsic resistance induced by tumor heterogeneity.[8,9] Furthermore, acquired resistance results in high doses of medication, which brings severe side effects.[10,11] Thus, development of novel cell death mode with more efficiency and less side effect is an urgent concern in the field of cancer therapy. Fortunately, recent studies have proposed several unidentified cell death forms with unique regulatory pathways, including ferroptosis, pyroptosis and cuproptosis, which can circumvent the limitations of classical cell death methods and open up new opportunities for the cancer treatment.[12-15]

Among these non-apoptotic forms of PCDs, cuproptosis has received much attention as the most emerging regulatory pathways of cell death. Interestingly, the connection between copper homeostasis and physical health was explored long before the term cuproptosis was established. The disequilibrium of copper homeostasis was repeatedly found to be associated with development of various diseases, such as Menkes disease, Wilson's disease, neurodegenerative diseases, cardiovascular diseases, and cancer.[16-20] Despite the apparent importance of copper for physiology and pathology, the underlying cellular mechanisms are still largely unknown, which prompts extensive exploration of copper in the treatment of various diseases. For example, the same morphological and molecular changes were observed after treating cancer cells with disulfiram (copper ionophore), pyrazole-pyridine copper complexes and inorganic copper, indicating that copper overload was the cause of cell death.[21] Moreover, the killing effect of elesclomol (copper ionophore) was totally lost on coadministration of MDA-MB435 melanoma cells in the absence of serum (the source of copper), while it can be restored after adding copper instead of iron, manganese and zinc to the serum-free medium, suggesting a potential copper ion-regulated cell death mode.[22] Afterwards, the anti-cancer effect of elesclomol was further corroborated through inducing a variety of cells, including melanoma cells, lung cancer cells, glioblastoma stem cells (GSCs) and gynecological tumor cells, to produce reactive oxygen species (ROS).[23-26] However, the oxidative stress alone does not fully explain the mechanism of cell death, because the use of ROS scavenger N-acetylcysteine (NAC) can only partly reverse the elesclomol induced cancer cell death.[27,28] Therefore, apart from oxidative stress, elesclomol should have additional mechanisms to regulate cancer cell death.

Gratifyingly, the "cuproptosis" proposed by Tsvetkov *et al* . provides a definitive explanation for the anticancer mechanism of elesclomol (**Figure 1** ).[29] Firstly, different metal ions including copper were carried by elesclomol to verify that only copper ions can mediate cancer cell death, which could be reversed by the copper ion chelating agents glutathione (GSH) and tetrathiomolybdate (TTM) but not by known inhibitors of various cell death pathways (ferrostatin-1, necrostatin-1, NAC), confirming that cell death induced by copper ions, namely cuproptosis, may be a new type of cell death mode different from traditional cell death such

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as apoptosis, ferroptosis, necrosis and autophagy. Then, mitochondrial respiration-dependent cells showed higher sensitivity to copper ions compared with glycolysis-dependent cells, suggesting that cuproptosis was related to mitochondrial metabolism. Further investigation revealed that the respiratory reserve capacity was significantly reduced after copper ion treatment, while basic respiration or ATP-related respiration remained stable, indicating that copper acted on the components of the tricarboxylic acid (TCA) cycle rather than electron transport chain (ETC). After that, seven TCA cycle genes were identified as relevant for cuproptosis mechanism, including FDX1 (a reductase reducing $Cu^{2+}$ to $Cu^{+}$), LIPT1, LIAS, DLD (three key enzymes of the lipoic acid pathway), DLAT, PDHA1, and PDHB (three components of the pyruvate dehydrogenase complex). Moreover, FDX1 and LIAS knockdown alleviated copper ionophore-triggered cytotoxicity, emphasizing the inherent association between TCA cycle and cuproptosis. Furthermore, the copper ions reduced by FDX1 bound to the lipoacyl group of DLAT to promote its lipoacylation and aggregation, thereby exerting cytotoxicity. In addition, FDX1 also leaded to the instability of Fe–S cluster protein, which exacerbated cell death. Notably, *in vivo*experiments confirmed that cell death caused by copper homeostasis imbalance and cell death induced by copper ionophore belonged to the same cuproptosis mechanism. Altogether, cuproptosis is a copper-dependent form of novel cell death. The establishment of the concept not only illuminates the cytotoxic mechanism in copper ionophore, but also provides new insights for the treatment of various diseases including cancer.

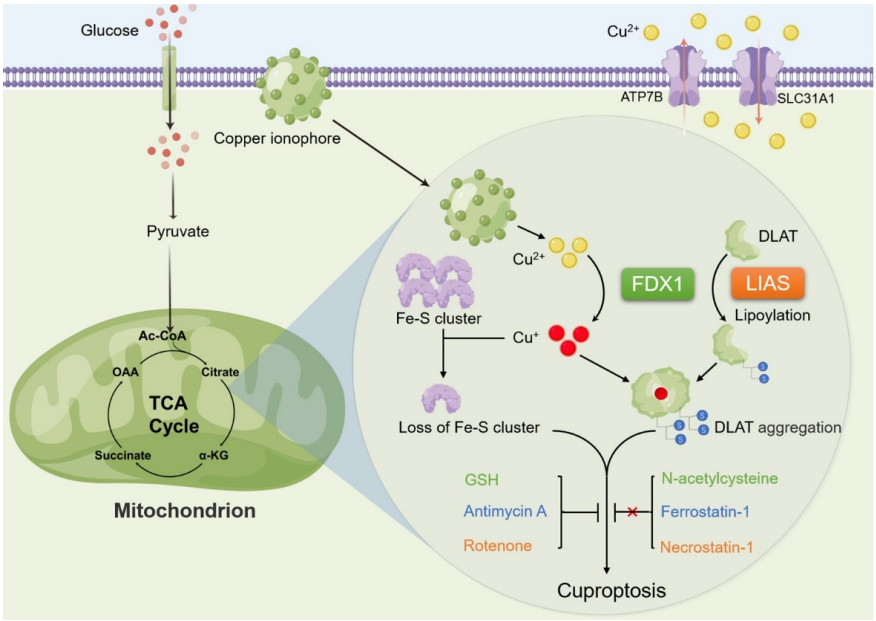


**FIGURE 1** Cuproptosis pathway. The copper ions released by the copper ionophore bind to DLAT, causing lipoacylated DLAT oligomerization and Fe-S cluster protein instability, which ultimately triggers cuproptosis.

However, cuproptosis still face several challenges before realizing effective cancer treatment, such as selectively increasing the concentration of copper ions in cancer cells, avoiding copper ion damage to normal cells, and prolonging the time of cuproptosis.[30-32] Nanotechnology may provide an alternative to deal with such a dilemma. The past few decades have witnessed the rapid development of nanotechnology, especially in nano-drug delivery, including improved drug solubility, prolonged circulation time, preferential accumulation of drug at lesion area and reduced systemic side effects.[33-35] Copper-based nanomaterials represent a novel class of cuproptosis inducers, which can achieve active targeting by surface modifications and passively accumulate to tumor site *via* enhanced permeability and retention (EPR) effect.[36,37] The excessive copper ion binding to DLAT in tumor cells causes aggregation of lipoacylated DLAT, and induces destabilization of Fe-S cluster proteins, which ultimately leads to cuproptosis of tumor cells, thus exert therapeutic effect. Although many

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reviews elaborate the close relationship between cuproptosis mechanism and cancer, the recent progress in the field of cuproptosis nanomedicine for cancer therapy has not yet been presented.

In this minireview, we first comprehensively elaborated the regulatory mechanism of cuproptosis in the introduction section, and then summarized the representative research on the use of different nanosystem to treat cancer based on the cuproptosis mechanism (**Figure 2** ). Finally, the challenges and future research directions were discussed.

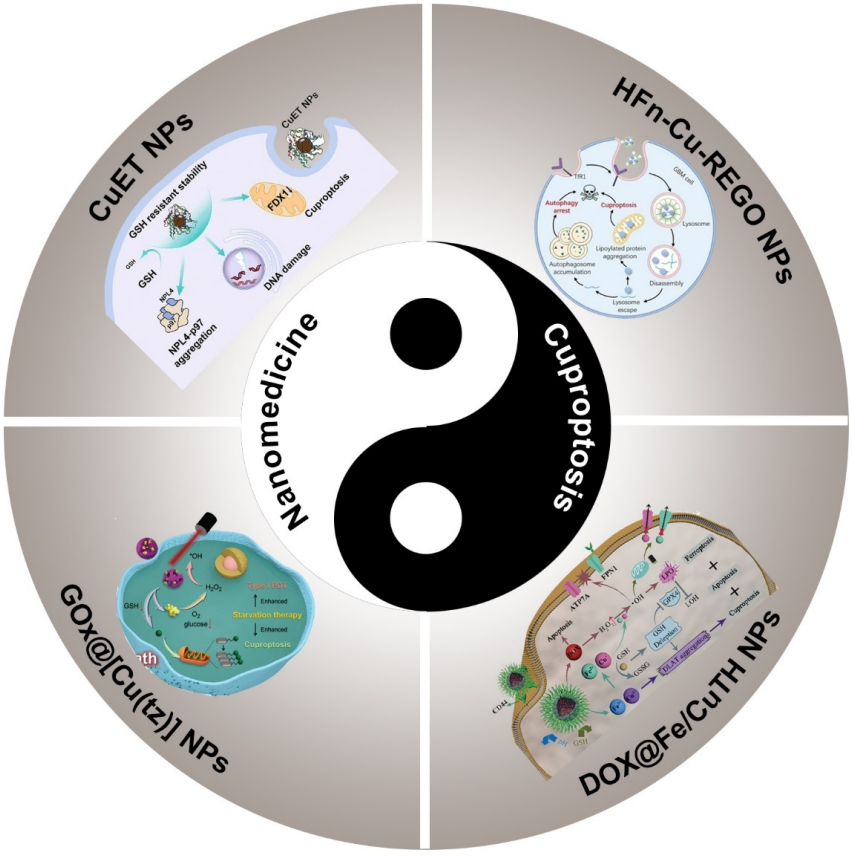


**FIGURE 2** Schematic illustration of the proposed nanomedicine-enabled anti-cancer *via* cuproptosis pathways.

## 2 NANOTHERANOSTICS FOR CUPROPTOSIS-BASED CANCER THERAPY

Since the concept was proposed, increasing evidence has demonstrated the anti-cancer promise of cuproptosis induction, and much effort has been devoted to the design and development of various cuproptosis-based nanomaterials for the eradication of malignancies. For example, He*et al* . reported a copper-based nanomedicine (CuET NP) including the copper (II) bis(diethyldithiocarbamate) (CuET) encapsulated by the bovine serum albumin (BSA) shell to replace drug-resistant cisplatin for the treatment of non-small-cell lung cancer.[38]Cisplatin resistance was attributed to the high concentration of GSH, and CuET could be candidate for alternative treatment because of its GSH-resistant performance endowed by the chelating geometry of CuET and the strong bonding of Cu–S. After intravenous injection, the CuET was found to accumulate obviously in tumor cells due to the EPR effect. CuET not only reduced the expression of FDX1 to induce cuproptosis, but also bound to the P97 segregase adaptor NPL4 and induced cytotoxicity, thus demonstrating excellent tumor inhibition ability (tumor inhibition rate: 56%). These results illustrated that

nanosystem induced cuproptosis of tumor cells may be a promising cancer treatment strategy.

Due to the heterogeneity of tumor cells, chemotherapy alone may be less efficient and less comfortable in the treatment of some cancers, so it is necessary to deliver combination therapies in a number of ways for improving the treatment effect.[39,40] For example, Pan*et al* . prepared a glucose oxidase (GOx)-engineered nonporous copper(I) 1,2,4-triazolate ([Cu(tz)]) coordination polymer (CP) nanocomposite (GOx@[Cu(tz)]) consisting of GSH-responsive nonporous [Cu(tz)] as a shell and GOx as a core for starvation-augmented cuproptosis and photodynamic synergistic cancer therapy (**Figure 3A** ).[41] After intravenous administration, GSH-responsive nonporous GOx@[Cu(tz)] not only achieved on-demand release of $Cu^{2+}$ and GOx at the GSH-enriched tumor site, but also consumed the content of GSH, which contributed to $Cu^{2+}$-induced cuproptosis. Moreover, the released GOx oxidized glucose to yield gluconic acid and $H_2O_2$, which cut off the energy supply of cancer cells, resulting in inhibition of glycolysis, thus exacerbating cuproptosis. After incubation with two cuproptosis inhibitors UK 5099 and Antimycin A, cancer cells treated with GOx@[Cu(tz)] showed higher cell viability than those treated with [Cu(tz)] and GOx, indicating that cuproptosis inhibitors effectively reversed GOx@[Cu(tz)]-induced cell death (**Figure 3B** ). Moreover, the treatment of copper chelating agent BCS restored 79.7% cell vitality of the GOx@[Cu(tz)]-treated cancer cells, showing that GOx@[Cu(tz)]-mediated cell death was related to cuproptosis (**Figure 3C** ). Furthermore, GOx@[Cu(tz)]-treated cells consistently exhibited lipoacylated DLAT oligomerization similar to that of elesclomol-treated cells, further confirming that GOx@[Cu(tz)] induced cell death through cuproptosis (**Figure 3D** ). In addition to cuproptosis, GOx@[Cu(tz)] can also be used as a photosensitizer for photodynamic therapy (PDT). Therefore, benefiting from the synergistic therapeutic effects of cuproptosis and PDT, after 21 days of GOx@[Cu(tz)] treatment of tumor-bearing mice, tumor growth in the GOx@[Cu(tz)]/laser group was suppressed by 92.4% compared to the PBS group, indicating the excellent anti-cancer effect of GOx@[Cu(tz)] (**Figure 3E** ). These results illustrated that the cuproptosis *via* consuming intracellular glucose and GSH concentrations is a promising cancer therapeutic strategy.

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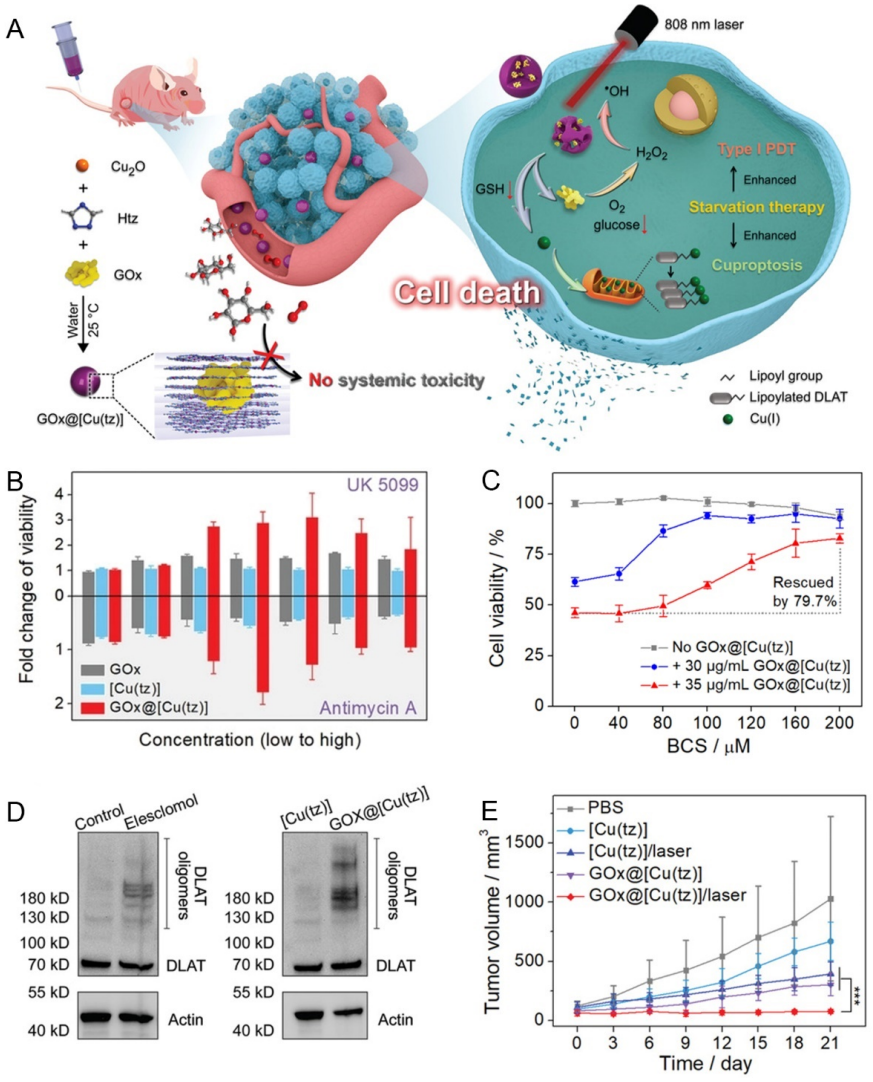


**FIGURE 3** (A) Schematic illustration of nonporous GOx@[Cu(tz)]. (B) Cell vitality after different treatments. (C) Cell viabilities treated with different concentrations of GOx@[Cu(tz)]. (D) Oligomerization analysis of DLAT after different treatments. (E) Tumor volume in mice after different treatments. (A-E) Reproduced with permission.[41] Copyright 2022, Wiley-VCH.

Recently, a variety of endogenous stimulus-responsive nanomaterials have been designed to respond to certain unique features in the tumor microenvironment, such as hypoxia, acidic pH, high ROS, overexpressed enzyme, and enriched GSH for improving the selectivity and specificity of cancer treatment.[42,43] For example, Zhang *et al* . developed a pH-responsive nano-delivery system (HFn-Cu-REGO NPs) consisting of human H-ferritin (HFn), chemotherapeutic agent regorafenib and $Cu^{2+}$ to induce autophagy and cuproptosis for glioblastoma treatment (**Figure 4A** ).[44]Benefiting from the modification of HFn, HFn-Cu-REGO NPs showed good blood-brain barrier (BBB) permeation, tumor-site accumulation, and pH-responsive disassembly capability. Upon treatment with HFn-Cu-REGO NPs, the pH-responsive nano-delivery system was responsive disassembled and released regorafenib and $Cu^{2+}$ in response to the acidic pH, causing concentrations of regorafenib and $Cu^{2+}$ was locally elevated in tumor region. On the one hand, excessive intracellular $Cu^{2+}$ activated the copper homeostasis system, leading to upregulation of copper efflux receptors and downregulation of copper uptake receptors (**Figure 4B** ); on the other hand, $Cu^{2+}$ bound to DLAT, causing the aggregation of

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lipoacylated DLAT (**Figure 4C** ) and triggering cuproptosis. In addition, the released regorafenib induced lethal autophagy arrest to exert the therapeutic effect through preventing autophagy lysosomal fusion. Based on the $Cu^{2+}$-induced cuproptosis and regorafenib-mediated lethal autophagy arrest, HFn-Cu-REGO NP-treated tumor-bearing mice showed delayed tumor growth and the lowest bioluminescence among all groups, indicating the optimal anti-cancer effect of HFn-Cu-REGO NP (**Figure 4D** ). This study provided new insights into the treatment of cancer *via* targeting the delivery of copper ions in response to endogenous stimulation to induce cuproptosis in cancer cells.

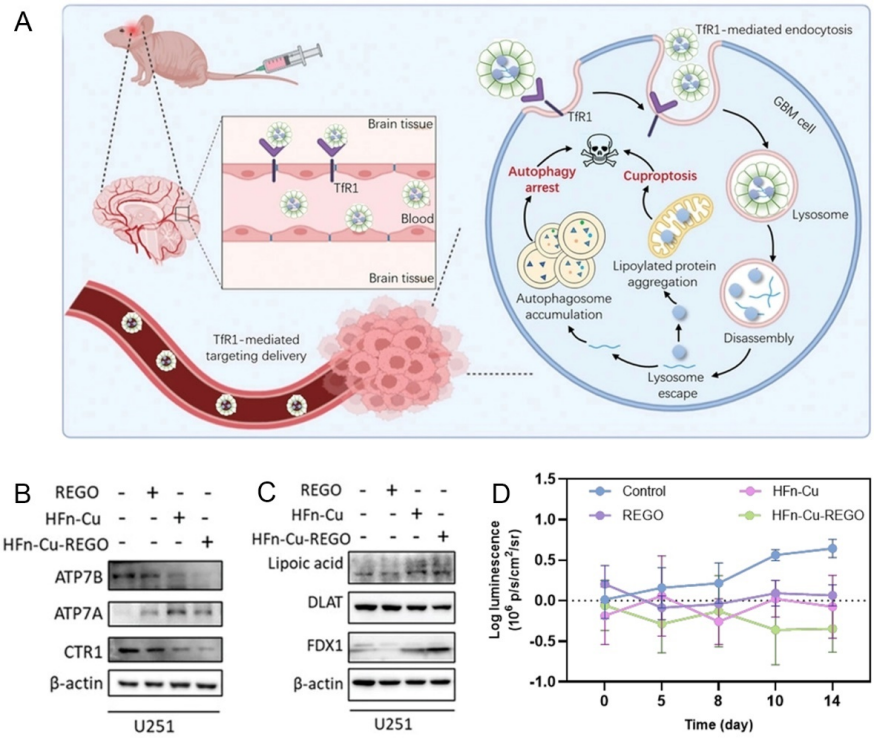


**FIGURE 4** (A) Schematic illustration of brain-targeted HFn-Cu-REGO. (B) Immunoblotting analysis of copper transporter in cells after different treatments. (C) Immunoblotting analysis of cuproptosis-related indicators in cells after different treatments. (D) The bioluminescence intensity of tumor-bearing mice after different treatments. (A-D) Reproduced with permission.[44]Copyright 2022, Wiley-VCH.

Because complicated pathophysiology involves multiple mechanisms, cancer exhibits similar acidic environments compared with other diseases such as inflammation, cardiovascular disease, leading to nonspecific accumulation of single-pH-responsive nanomaterials.[45,46] Multi-stimuli responsive nanomaterials have been explored to achieve responsiveness to multiple pathological environmental variations for improved specificity and targeting.[47,48] For example, Suo *et al* . designed a GSH/pH-responsive hollow amorphous metal organic framework (HaMOF) (DOX@Fe/CuTH) consisting of $Cu^{2+}$, disulfide bond (S-S)-bearing 3,3'-dithiobis(propionohydrazide) (TPH) and $Fe^{3+}$ encapsulated by hyaluronan shell with a good doxorubicin (DOX) loading ability for cuproptosis/ferroptosis/apoptosis synergistic cancer therapy (**Figure 5A** ).[49]Because of the high affinity between hyaluronan and CD44 receptor overexpressing on the surface of cancer cells, hyaluronan endowed the DOX@Fe/CuTH with cancer site-specific targeting capability, resulting in thus enhanced tumor-site accumulation and preferential internalization within cancer cells. After cell internalization, DOX@Fe/CuTH showed GSH/pH-responsive cargo ($Cu^{2+}$, $Fe^{3+}$and DOX) release due to the GSH-triggered fracture of disulfide bonds and acidic pH-triggered weakening of ion coordination. The $Cu^{2+}$ released from DOX@Fe/CuTH bound to DLAT, resulting in abnormal oligomerization of DLAT, with

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a more obvious DLAT foci than PBS-treated cells. In addition, the expression levels of FDX1 and LIAS in the DOX@Fe/CuTH-treated cells were 0.18-fold and 0.35-fold than those of PBS-treated cells, respectively, showing significant loss of FDX1 and LIAS (**Figure 5B** ). Meanwhile, the poor cell vitality after DOX@Fe/CuTH treatment was significantly restored by the copper chelating agent (**Figure 5C** ). These results collectively confirmed that $Cu^{2+}$ induced cancer cell death through the cuproptosis pathway. Apart from $Cu^{2+}$-mediated cuproptosis, $Fe^{3+}$-mediated ferroptosis and DOX-mediated apoptosis also exhibited synergistic therapeutic effects. Therefore, after intravenous injection, the tumor volume after nanodurg treatment was 0.7-fold that before treatment, remarkably smaller than those of control (4.1-fold), DOX (3.0-fold), CuTH (2.4-fold) and Fe/CuTH (1.4-fold) groups. The results demonstrated that DOX@Fe/CuTH had potent anti-cancer effect *via* cuproptosis/ferroptosis/apoptosis synergistic therapy (**Figure 5D** ).

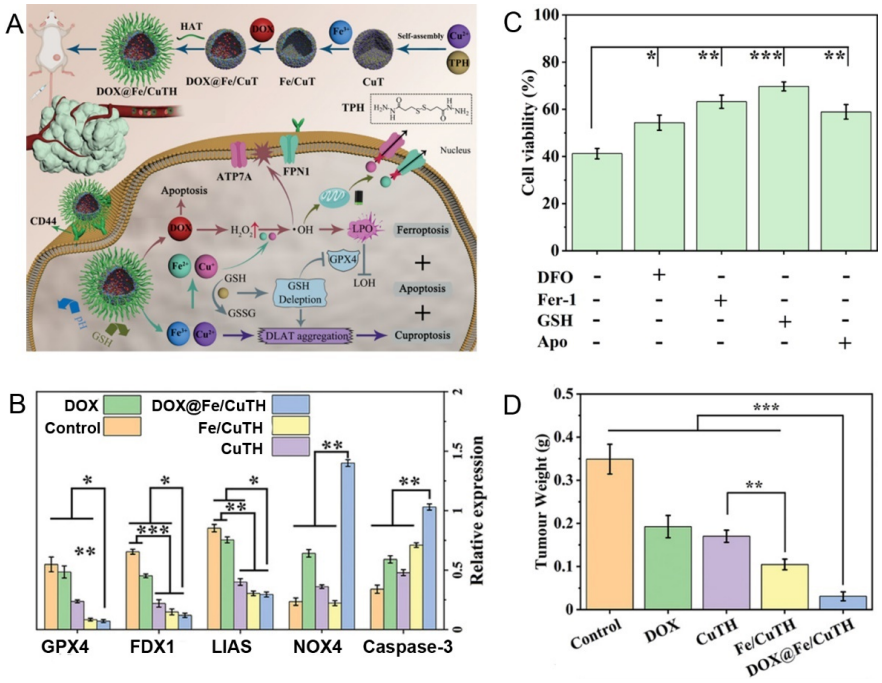


**FIGURE 5** (A) Schematic illustration of bimetallic hollow DOX@Fe/CuTH. (B) Western blot analysis of cell death indicators after different treatments. (C) Cell vitality after different treatments. (D) The weight of tumors in mice after different treatments. (A-D) Reproduced with permission.[49] Copyright 2022, Wiley-VCH.

## 3 CONCLUSION AND PERSPECTIVES

Cancer is already the second most lethal disease after cardiovascular disease, and this grave situation has led to the search for effective control and intervention techniques.[50-52] Cuproptosis is a new form of PCD proposed in 2022 in which copper ions play an important role.[29] Since then, the cellular regulatory mechanisms and signaling pathways involving cuproptosis have been investigated extensively, which propelled the movement toward cuproptosis inducers represented by copper-based nanomaterials for the eradication of malignant tumors. Copper-based nanomaterials can not only achieve targeted delivery of copper ions through surface modification, but also nicely circumvent the deficiencies of traditional cancer therapy, such as short blood circulation, poor solubility, low bioavailability, off-target effects, and nonspecific distribution.[53,54] In this minireview, we first comprehensively expounded the regulatory mechanism of cuproptosis in the introduction section, and then introduced the application of cuproptosis mechanism in the field of nanomedicine, which may provide new insights into designing copper-based nanomaterials for cancer therapy.

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Although the rapid development of studies on cuproptosis-based cancer therapy, challenges remain to be addressed, along with tremendous opportunities. Firstly, the understanding of the complicated molecular mechanism and associated regulatory pathways of cuproptosis are still in its infancy. Knowledge of the mechanism of cuproptosis may help in designing a more effective anti-cancer nanomaterial.[15,55] Secondly, cuproptosis is a process closely related to cellular copper metabolism, so it is very important to reasonably control intracellular copper ion concentration in both*in vitro* and *in vivo* studies. Regarding cancer, cuproptosis is a double-edged sword because it can not only kill cancer cells, but also induce copper toxicosis to destroy normal cells.[56,57] Therefore, particular attention should be paid to the parameters such as type, dosage, timing, to obtain an optimal relationship between efficacy and side effects in practical application.[58,59] Thirdly, copper-based nanomaterials might exert a cytotoxic effect *via* a cuproptosis-independent pathway. For example, copper ions may treat cancer through the Fenton reaction.[60] Thus, a clear understanding of the action mechanism could aid the rational design of highly selective and specific copper-based nanosystems. Meanwhile, this also suggests that combining crosstalk between different cell death phenotypes may be an effective therapeutic regimen and possess potential clinical application in cancer treatment.[61,62] Fourthly, the existing nanomaterials are weak in the responsive release of copper ions because of the small difference in enzyme activity or acidity between the tumor and normal tissue resulting from the diversity and heterogeneity of the tumor.[7] Hence, there is a pressing demand for designing ultra-sensitive nanomaterials which can be activated within a very narrow threshold.[63,64] Fifthly, during the circulation process, the dissolution of copper in copper-based nanomaterials seriously affects the therapeutic efficacy and cycle stability. Supramolecular nanomaterials exhibit strong stability due to their dynamic characteristics and high correlation constant between matching groups, and may be a promising cuproptosis inducer.[65,66] Lastly, it is highly anticipated that cuproptosis can be extended to the treatment of other diseases. In addition to chemotherapy, nanodrug-based cell cuproptosis therapies are also expected to be widely combined with other treatments, which can further improve the treatment efficiency of tumor therapies based on cell cuproptosis.

In conclusion, with the deepening of our understanding in cuproptosis and its relationship with nanomaterials, cancer therapeutic outcome would be continuously improved through the design and development of copper-based nanomaterials.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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