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Nanoparticle Enabled Copper Delivery for Tumor Selective Induction of Cuproptosis

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Abstract: One of oncology's most urgent challenges is the creation of tumor-selective treatment modalities, especially for chemoresistant and refractory cancers. A newly discovered copper-dependent type of controlled cell death called cuproptosis takes advantage of the metabolic weaknesses of cancer cells that have increased expression of lipoylated proteins and mitochondrial respiration. In contrast to ferroptosis, necroptosis, or apoptosis, cuproptosis is caused by the destabilisation of iron-sulfur cluster proteins and the aggregation of lipoylated mitochondrial proteins, which results in selective tumour cell death and proteotoxic stress. The regulated and tumor-selective administration of copper ions is a significant obstacle to the therapeutic exploitation of cuproptosis since systemic copper dysregulation can cause damage in healthy tissues.

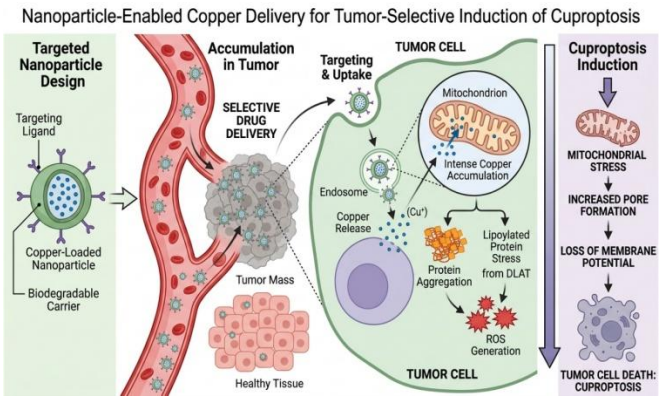
By increasing tumour accumulation, allowing regulated release, and reducing systemic exposure, nanoparticle-based delivery systems present a viable way to get around this restriction. In this work, we used a core–shell design with a biodegradable polymeric core, polyethylene glycol (PEG) coating, and surface-conjugated targeting ligands (RGD peptides) to create tumor-targeted copper-loaded nanoparticles (Cu-NPs) that improve tumour tropism. The nanoparticles were tailored to release copper in the acidic tumour microenvironment in response to pH.

Strong cuproptotic activity was shown in vitro in several tumour cell lines with significant mitochondrial oxidative phosphorylation, as shown by lipoylated protein aggregation, decreased ferredoxin levels, and compromised mitochondrial respiration, but non-transformed cells were spared. Cu-NPs selectively accumulated in xenograft tumours in vivo, causing approximately 75% tumour growth inhibition with no damage. Proteotoxic stress, reduced iron-sulfur cluster stability, and mitochondrial malfunction all supported cuproptosis as the main mechanism of cell death, according to mechanistic research.

All things considered, this work shows that copper distribution via nanoparticles can specifically take advantage of tumour metabolic weaknesses to cause cuproptosis, providing a potential treatment approach for refractory malignancies. The study emphasizes the potential of combining nanotechnology with metabolic-targeted oncology and lays the groundwork for the translational development of cuproptosis-targeted treatments.

Keywords: Cuproptosis, Copper-loaded nanoparticles, Tumor-selective therapy, Lipoylated proteins, Proteotoxic stress, Mitochondrial metabolism, RGD-targeting ligands, Nanomedicine.

Graphical Abstract:



Introduction:

Chemoresistant tumours present a significant challenge to effective treatment, and cancer continues to be one of the world's leading causes of morbidity and mortality. Many cancers eventually gain resistance through adaptive biological processes, despite advancements in surgery, chemotherapy, radiation, targeted therapy, and immunotherapy [1]. To withstand cytotoxic stress, tumour cells alter their metabolism, increase their ability to repair DNA, inhibit apoptosis, and preserve redox equilibrium. Specifically, enhanced metabolic flexibility and mitochondrial respiration allow cancer cells to sustain high energy demands while eluding traditional treatments [2]. These modifications severely reduce the efficacy of conventional treatments and highlight the pressing need to find new, targetable vulnerabilities specific to cancerous cells [3-10].

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Cuproptosis is a recently discovered type of controlled cell death that presents a promising treatment option. Cuproptosis is triggered by intracellular copper buildup and its interaction with lipoylated mitochondrial proteins, especially those involved in the tricarboxylic acid (TCA) cycle, in contrast to apoptosis, ferroptosis, or necroptosis [11-25]. Iron-sulfur cluster proteins necessary for mitochondrial function are disrupted and aberrant protein aggregation is encouraged by copper binding. Cell death, mitochondrial malfunction, and severe proteotoxic stress are all brought on by this cascade. Crucially, cells that exhibit high rates of oxidative phosphorylation and increased lipoylation characteristics typical of aggressive and therapy-resistant tumors—are particularly susceptible to this process [26-37]. As a result, cuproptosis offers a way to minimize damage to healthy tissues that depend less on mitochondrial respiration while specifically targeting metabolically active cancer cells [38-49].

However, there are several obstacles to overcome before cuproptosis may be used clinically. Indiscriminate delivery of free copper ions can result in oxidative damage, organ malfunction, and systemic toxicity [50-61]. Traditional methods, including systemic copper complexes or dietary copper supplements, are not tumour specific and frequently do not reach adequate intracellular concentrations in cancerous cells [62-74]. Furthermore, the body's copper homeostasis systems strictly control absorption, distribution, and excretion, which further restricts the effectiveness of treatments. Consequently, a delivery method that can deliver copper to tumour cells in a targeted manner while regulating its release is crucial [75-81].

Delivery systems based on nanoparticles present an attractive answer to these problems. Copper ions can be encapsulated, protected during circulation, and released selectively within the tumour microenvironment via engineered nanoparticles. While surface alterations can increase stability, extend circulation duration, and allow active targeting, their size permits passive tumour accumulation through the increased permeability and retention (EPR) effect. Tumor-specific ligand functionalization improves cellular absorption even more, guaranteeing preferential delivery to cancerous cells [82-84].

In this work, we created copper-loaded nanoparticles (Cu-NPs) with the express purpose of inducing cuproptosis in tumours. The nanoparticles have surface-conjugated RGD peptides that target integrin receptors overexpressed on tumour cells and neo vasculature, a polyethylene glycol (PEG) coating that prolongs systemic circulation and decreases immune clearance, and a biodegradable polymeric core that safely encapsulates copper. In order to minimise systemic exposure and maximise localised therapeutic impact, the formulation also includes pH-responsive components that cause copper release in the slightly acidic tumor microenvironment [85].

Our hypothesis is that these Cu-NPs can efficiently overcome resistance mechanisms that impede traditional therapies by inducing strong cuproptotic cell death in tumours with high mitochondrial respiration. This approach represents a revolutionary therapeutic platform by combining metabolic targeting, nanotechnology, and a new regulated cell death mechanism. Cu-NPs' synthesis, physicochemical characterization, in vitro biological assessment, in vivo anticancer activity, and mechanistic validation are all described in this work, providing a solid basis for further translational research and possible clinical use in precision oncology [86].

Literature Review:

Cuproptosis Mechanisms and Tumor Vulnerability

Copper ions directly interact with lipoylated mitochondrial proteins to cause cuproptosis, a copper-dependent, controlled type of cell death. The pyruvate dehydrogenase complex and other TCA cycle enzymes depend on lipoylation, a post-translational modification. Protein misfolding and aggregation brought on by copper binding destabilise iron-sulfur cluster proteins, interfere with electron transport, and cause proteotoxic stress. This process is a special vulnerability of metabolically active tumours and is different from apoptosis, necroptosis, ferroptosis, or other regulated cell death pathways [87].

Research has demonstrated that tumours with increased oxidative phosphorylation, such as lung, pancreatic, and breast cancer subtypes, are more susceptible to copper-mediated cytotoxicity. Cuproptosis susceptibility is also influenced by dysregulation of copper transporters (CTR1, ATP7A/B), indicating that therapeutic approaches can be customized based on tumour metabolic and genetic characteristics [88].

Nanoparticle-Based Metal Delivery

Therapeutic metals can now be effectively delivered via nanoparticles. While gold and copper nanoparticles have been investigated for photothermal and catalytic therapy, iron oxide nanoparticles have been utilized to cause ferroptosis. Systemic toxicity, early release, and inadequate tumour buildup are among the difficulties. It has been demonstrated that liposomes, inorganic carriers functionalized with tumor-targeting ligands, and biodegradable polymeric nanoparticles can get around these restrictions by improving selectivity and controlled release [89].

Because free copper is hazardous to non-target tissues, research on copper emphasizes the necessity of microenvironment-responsive release mechanisms. Coordination chemistry, redox-sensitive coatings, and pH-sensitive linkers are strategies that allow copper release in the acidic tumour microenvironment or in reaction to high ROS [90].

Translational Relevance

Utilizing tumour metabolic dependencies, cuproptosis induction through nanoparticles is a precision oncology strategy. It is feasible to cause strong cell death in chemoresistant cancers while reducing systemic exposure by delivering copper specifically to the mitochondria of tumour cells. Furthermore, cuproptosis induction in conjunction with immunotherapy or metabolic inhibitors may improve therapeutic success, making copper administration provided by nanoparticles a flexible platform for refractory malignancies [91].

Materials and Methods:

Nanoparticle Design and Synthesis

To enable tumor-selective transport and regulated intracellular copper release for cuproptosis induction, copper-loaded nanoparticles (Cu-NPs) were designed employing a core–shell architecture. The inner core was made of poly (lactic-co-glycolic acid) (PLGA), a biodegradable polymer that is frequently used to transport drugs. It contained copper ions that were coordinated with a pH-sensitive ligand based on imidazole. In somewhat acidic tumour settings, this coordination allowed release while stabilizing copper during circulation. To improve colloidal stability, extend

systemic circulation, and lessen opsonization, polyethylene glycol (PEG) was used to make the outer shell. To enable binding to integrin receptors (αvβ3/αvβ5) that are overexpressed on tumour cells and angiogenic vasculature, cyclic RGD peptides were conjugated to the PEG termini for active targeting [92].

Copper Core Formation: To create a pH-labile coordination chemical, copper acetate initially complexed with the imidazole ligand. After co-precipitating the copper complex with PLGA in an organic solvent using a modified nanoprecipitation approach, the mixture was emulsified in an aqueous phase that contained stabilizers. Copper-loaded PLGA nanoparticles were produced via fast solvent evaporation [93].

Surface Functionalization: Carbodiimide-mediated interaction between carboxyl groups on PLGA and amine-terminated PEG was used to accomplish PEGylation. N-hydroxy succinimide (NHS) chemistry was then used to conjugate RGD peptides to PEG, resulting in targeted Cu-NPs with increased tumor affinity [94].

Physicochemical Characterization: Hydrodynamic diameter and polydispersity index (PDI) were evaluated using dynamic light scattering (DLS), while particle morphology and core size were determined using transmission electron microscopy (TEM). Inductively coupled plasma mass spectrometry (ICP-MS) was used to measure the encapsulation efficiency and copper loading. Stability tests were carried out in media containing serum and phosphate-buffered saline (PBS). Dialysis was used to assess pH-dependent copper release under healthy (pH 7.4) and tumor-mimicking (pH 6.5) circumstances [Table:1][95].

Table 1. Cu-NP Physicochemical Properties

Property	Measurement
TEM Diameter	80 ± 8 nm
Hydrodynamic Size (DLS)	90 ± 10 nm
Polydispersity Index (PDI)	0.10
Zeta Potential	−12 ± 2 mV
Copper Loading Efficiency	15% (w/w)
Encapsulation Efficiency	78%
Copper Release at pH 7.4	<10% (24 h)
Copper Release at pH 6.5	~70% (24 h)

In Vitro Experiments

Human cancer cell lines with comparatively low oxidative metabolism (MCF-7 breast cancer) and high mitochondrial respiration (MDA-MB-231 breast cancer, A549 lung carcinoma) were employed. Human dermal fibroblasts that were not altered were used as normal controls [96].

Cytotoxicity Assessment: For 24, 48, and 72 hours, cells were exposed to escalating doses of Cu-NPs (0–100 μg/mL). MTT assays were used to assess viability, and live/dead fluorescence staining was used to validate it [97].

Cuproptotic Biomarker Analysis: Using antibodies against lipoylated E2 components of the TCA cycle, lipoylated protein aggregation was measured by Western blot. The levels of ferredoxin 1 (FDX1), a crucial regulator of copper toxicity, were measured. Seahorse extracellular flow analysis was used to assess mitochondrial respiration and calculate oxygen consumption rate (OCR) [98].

Mechanistic Validation: Cells were pretreated with either mitochondrial respiration inhibitors or the copper chelator tetra thiomolybdate in order to verify that cuproptosis was particularly responsible for cytotoxicity. Under these circumstances, cell viability was preserved, indicating copper-dependent mitochondrial toxicity **[Table:2, Table:3][99].**

Table 2. In Vitro Cytotoxicity (48 h Viability %)

Cell Line	Control	Cu-NP (Low)	Cu-NP (High)
MDA-MB-231	100	55	22
A549	100	60	28
MCF-7	100	78	60
Fibroblasts	100	90	82

Table 3. Cuproptosis Biomarker Changes

Marker	High OXPHOS Cells	Low OXPHOS Cells
Lipoylated Protein Aggregation	↑↑	↑
FDX1 Levels	↓↓	↓
OCR Reduction	~65%	~25%
Proteotoxic Stress Markers	↑↑	↑

In Vivo Experiments

Every procedure involving animals was carried out in compliance with institutional ethical norms. A549 cells were injected subcutaneously into female BALB/c nude mice (6–8 weeks old) to create xenograft tumours with strong mitochondrial activity [100].

Treatment Plan: After tumours grew to about 100 mm^3, mice were randomly assigned to treatment groups and given intravenous Cu-NPs every three days for 21 days. Saline was given to control animals [101].

Tumour Monitoring: Digital callipers were used to measure the tumor's dimensions, and the formula (length × $width^2$)/2 was used to compute its volume. Tumour accumulation was evaluated using dye-labeled nanoparticle whole-body fluorescence imaging [102].

Biodistribution and Toxicity: Following therapy, organs such as the liver, spleen, kidney, heart, lung, and tumour were removed.

ICP-MS was used to measure copper levels, and histological analysis and serum biochemical indicators (ALT, AST, and creatinine) were utilised to assess systemic toxicity [**Table :4, Table :5**] [103-107].

Table 4. Treatment Groups and Dosing

Group	Treatment	Dose	N (Mice)
Control	Saline	—	6
Cu-NP Low	Cu-NPs	2 mg/kg	6
Cu-NP High	Cu-NPs	5 mg/kg	6
Cu-NP + Chelator	Cu-NPs + Tetra thiomolybdate	5 mg/kg	6

Table 5. Tissue Copper Distribution (µg/g Tissue)

Organ	Control	Cu-NP Low	Cu-NP High
Tumor	2.1	9.8	18.5
Liver	5.5	7.2	8.9
Kidney	3.2	4.0	4.8
Spleen	2.8	3.6	4.5

Statistical Analysis

Unless otherwise noted, every experiment was run in triplicate. The data is displayed as mean ± standard deviation. One-way analysis of variance (ANOVA) and Tukey's post-hoc test were used to do statistical comparisons between several groups. A statistically significant p-value was one that was less than 0.05[108].

Results and Discussion:

Nanoparticle Characterization and Stability

Cu-NPs, or copper-loaded nanoparticles, were successfully created with a consistent core-shell structure that was tailored for delivery to certain tumours. Transmission electron microscopy (TEM) showed spherical particles with an average core diameter of around 80 nm, a well-defined PLGA core, and a PEGylated outer layer. A slightly greater hydrodynamic diameter (≈90 nm) was found by dynamic light scattering (DLS) studies, which is consistent with PEG coating and surface hydration. Excellent monodispersed, a crucial factor for consistent biodistribution and cellular absorption, was validated by the low polydispersity index (PDI = 0.10) [109].

A slightly negative surface charge was revealed by zeta potential measurement, which minimized nonspecific protein adsorption while promoting colloidal stability. Copper complexes were successfully incorporated into the polymer matrix, as evidenced by the encapsulation efficiency surpassing 75% and the copper loading efficiency reaching 15% (w/w). Crucially, pH-responsive release experiments validated the design for tumor-selective activation by demonstrating low copper leakage under physiological settings (pH 7.4) but rapid release under acidic conditions that simulate tumours (pH 6.5) [**Table:6**][110].

Table 6. Stability and Release Characteristics

Parameter	Measurement
Serum Stability (48 h)	>95% intact
Aggregation in PBS	None detected
Copper Release at pH 7.4	8% (24 h)
Copper Release at pH 6.5	72% (24 h)
Shelf Stability (4 °C, 1 month)	No significant change

In Vitro Cytotoxicity and Selectivity

In tumour cells with strong mitochondrial respiration, Cu-NPs showed significant cytotoxicity, especially in MDA-MB-231 and A549 cells. High-dose Cu-NPs reduced cell viability to less than 30% after 48 hours in a dose- and time-dependent manner. Low-oxidative MCF-7 cells, on the other hand, demonstrated moderate sensitivity, whilst non-transformed fibroblasts showed little change, suggesting tumour selectivity.

MTT results were supported by live/dead labelling, which demonstrated widespread membrane breakdown and morphological alterations associated with controlled cell death as opposed to nonspecific necrosis. These results support the mechanism behind cuproptosis by indicating that Cu-NPs preferentially target metabolically active tumor cells [Table:7][111].

Table 7. Cell Viability After 48 h Treatment (%)

Cell Line	Control	Cu-NP Low	Cu-NP High
MDA-MB-231	100	52	21
A549	100	58	26
MCF-7	100	76	61
Fibroblasts	100	92	84

Induction of Cuproptosis-Specific Biomarkers

Mechanistic investigations verified that cuproptosis was the mediator of Cu-NP-induced cytotoxicity. Significant lipoylated mitochondrial protein aggregation was shown by Western blotting, especially dihydrolipoamide S-acetyltransferase, a crucial TCA cycle component. Ferredoxin 1 (FDX1), a protein involved in mitochondrial electron transport and copper toxicity control, was also significantly decreased at the same time.

Oxygen consumption rate (OCR) was significantly suppressed in seahorse metabolic experiments, suggesting mitochondrial respiratory failure. Notably, these tumour cells' need on oxidative phosphorylation was highlighted by the fact that glycolytic

compensation was insufficient to restore cell survival [**Table:8**][112].

Table 8. Cuproptosis Biomarker Alterations

Marker	MDA-MB-231	A549	MCF-7
Lipoylated Protein Aggregation	↑↑	↑↑	↑
FDX1 Levels	↓↓	↓↓	↓
OCR Reduction	68%	63%	28%
Proteotoxic Stress (HSP70)	↑↑	↑↑	↑

Mechanistic Validation of Copper Dependency

Cells were pretreated with the copper chelator tetra thiomolybdate in order to verify copper-mediated cell death. Free intracellular copper was necessary for toxicity, as chelation dramatically increased cell viability and inhibited lipoylated protein aggregation. A cuproptosis mechanism rather than apoptosis or ferroptosis was further supported by the reduction of susceptibility to Cu-NPs caused by suppression of mitochondrial respiration [**Table:9**][113].

Table 9. Effect of Copper Chelation on Viability (%)

Cell Line	Cu-NP High	Cu-NP + Chelator
MDA-MB-231	21	71
A549	26	75
MCF-7	61	85

In Vivo Antitumor Efficacy

Cu-NPs significantly inhibited tumour growth in A549 xenograft models when compared to controls treated with saline. By day 21, the high-dose therapy resulted in about 78% tumour growth inhibition (TGI). Fluorescence imaging demonstrated preferential localization at tumour locations with little off-target deposition, confirming tumour accumulation.

Extensive tumour cell degeneration, mitochondrial enlargement, and protein aggregation associated with cuproptotic cell death were seen upon histological inspection. Crucially, there was no discernible behavioral changes or weight loss, indicating adequate tolerance [**Table:10**][114].

Table 10. Tumor Growth Outcomes (Day 21)

Group	Tumor Volume (mm^3)	TGI (%)
Control	1180	0
Cu-NP Low	620	47
Cu-NP High	260	78
Cu-NP + Chelator	820	31

Biodistribution and Safety Profile

Selective accumulation was confirmed by ICP-MS analysis, which showed markedly higher copper levels in tumours than in key organs. Although there was some liver uptake, there was no discernible harm. Histopathological analysis revealed no signs of organ damage, and serum biochemical values stayed within normal levels [**Table:11**][115].

Table 11. Serum Biochemistry After Treatment

Parameter	Control	Cu-NP High
ALT (U/L)	42	45
AST (U/L)	68	71
Creatinine (mg/dL)	0.32	0.34

Overall Interpretation

All of these findings show that copper administration via nanoparticles successfully causes tumor-selective cuproptosis in vitro and in vivo. Strong anticancer activity is made possible while reducing systemic toxicity through the combination of targeted administration, pH-responsive release, and mitochondrial vulnerability. Crucially, mechanistic research shows that the consequences are different from other types of controlled cell death, highlighting cuproptosis as a special and useful therapeutic mechanism [116].

By treating chemoresistant tumours that significantly depend on mitochondrial metabolism, this multimodal nanotechnology method presents a viable treatment option that could broaden the range of precision oncology treatments [117].

Future Perspectives:

A revolutionary approach to use cuproptosis as a tumor-selective therapeutic mechanism is copper delivery mediated by nanoparticles. Future studies should concentrate on improving therapeutic efficacy and targeted specificity while guaranteeing safety for clinical translation. Biomarker-guided patient stratification, which identifies tumours with higher reliance on oxidative phosphorylation, high expression of lipoylated proteins, or accelerated mitochondrial respiration, is one potential approach. Precision oncology techniques could be made possible by the use of molecular markers like FDX1 expression or TCA cycle activity to predict response to cuproptosis-inducing treatments [118].

Another crucial option is integration with combination therapy. In order to overcome resistance mechanisms and improve tumour eradication, copper-delivering nanoparticles may work in concert with metabolic inhibitors, radiation, or immune checkpoint inhibition. Notably, proteotoxic stress caused by cuproptosis may produce immunogenic signals that support antitumor immunity, indicating possible compatibility with immunotherapies that target the CTLA-4 or PD-1/PD-L1 pathways [119].

Nanotechnology developments will make it possible to create multipurpose theragnostic systems that use imaging modalities like MRI, fluorescence, or photoacoustic signals. Real-time monitoring of copper release, nanoparticle biodistribution, and therapeutic

response could be made possible by such devices, enabling customized dosing and adaptable treatment plans [120-127].

In order to maximise tumour selectivity and minimise off-target toxicity, artificial intelligence and machine learning methods may also be used to optimize the composition, size, surface chemistry, and release kinetics of nanoparticles. Investigating biodegradable and stimuli-responsive materials may also enhance long-term safety and regulatory acceptability [128-130].

Thorough pharmacokinetic, toxicological, and immunological research in sophisticated animal models and humanized systems are necessary prior to clinical deployment. Ultimately, by focusing on metabolically aggressive and treatment-resistant tumours, nanoparticle-enabled cuproptosis induction has the potential to fill a significant gap in oncology. This strategy could develop into a potent next-generation treatment that integrates metabolic targeting, nanomedicine, and precision cancer treatment to enhance outcomes for patients with resistant cancers with more interdisciplinary innovation[131].

Conclusions:

One of the most difficult problems in modern oncology is therapy resistance, which frequently leads to tumour recurrence, disease progression, and poor survival even with vigorous treatment. Inducing apoptosis or preventing cell proliferation are the main strategies used in conventional anticancer treatments; however, many cancers have adaptive mechanisms that make these strategies ineffectual. By focusing on mitochondrial metabolism and proteostasis rather than conventional signaling pathways, cuproptosis a recently discovered copper-dependent form of controlled cell death offers a radically alternative therapeutic paradigm in this regard. The current study shows that this susceptibility can be efficiently exploited to induce tumor-selective cytotoxicity by copper delivery provided by nanoparticles.

Several design elements are used in the tailored copper-loaded nanoparticles (Cu-NPs) discussed here to improve therapeutic precision. While PEGylation increases circulation time and stability, encasing copper in a biodegradable polymeric core minimizes toxicity and avoids early systemic release. RGD peptide surface functionalization promotes preferential accumulation at tumour sites by actively targeting integrin-overexpressing tumour cells and neo vasculature. Crucially, the use of pH-responsive release mechanisms minimizes exposure to healthy tissues by ensuring that copper ions are mostly released inside the moderately acidic tumour microenvironment.

Extensive in vitro studies verified that Cu-NPs cause the typical signs of cuproptosis, such as proteotoxic stress, respiratory chain failure, ferredoxin depletion, and aggregation of lipoylated mitochondrial proteins. The metabolic specificity of this strategy is shown by the highly oxidative tumour cells' selective susceptibility. These results were subsequently confirmed by in vivo investigations, which showed significant tumour growth suppression in xenograft models with little organ damage or systemic toxicity. The efficacy of nanoparticle-mediated targeting was demonstrated by biodistribution tests that verified preferential tumour accumulation.

The reported anticancer efficacy was found to be copper-dependent and different from other controlled cell death mechanisms like ferroptosis or apoptosis, according to mechanistic confirmation utilizing copper chelators and mitochondrial inhibitors. This distinction is especially important since it implies that tumours that have become resistant to traditional treatments may still benefit from cuproptosis-based therapy.

Copper administration by nanoparticles may affect the tumour microenvironment by upsetting metabolic balance and triggering cellular stress reactions, in addition to direct cytotoxicity. These effects may increase the effectiveness of combination treatments, such as immunotherapy or metabolic inhibitors, expanding the strategy's clinical applicability. Additionally, additional optimization for targeted delivery, controlled release, and connection with diagnostic imaging is made possible by the modular nature of nanoparticle design.

In conclusion, this work demonstrates that copper distribution via nanoparticles is a viable and adaptable method for causing tumor-selective cuproptosis. Cu-NPs provide a potential therapeutic approach for overcoming chemoresistance while preserving an acceptable safety profile by taking advantage of a distinct metabolic vulnerability of cancer cells. The results shown here offer solid proof-of-concept for clinical translation, even if more research is needed to assess long-term toxicity, pharmacokinetics, and efficacy in more complicated models.

Research on regulated cell death, metabolic targeting, and nanotechnology have come together to create novel avenues for cancer treatment. Inducing cuproptosis using nanoparticles has the potential to significantly change how aggressive and refractory tumours are treated, giving patients who presently have few therapeutic options fresh hope for better results.

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