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Metal ion-induced programmed cell death: implications for cancer progression and treatment

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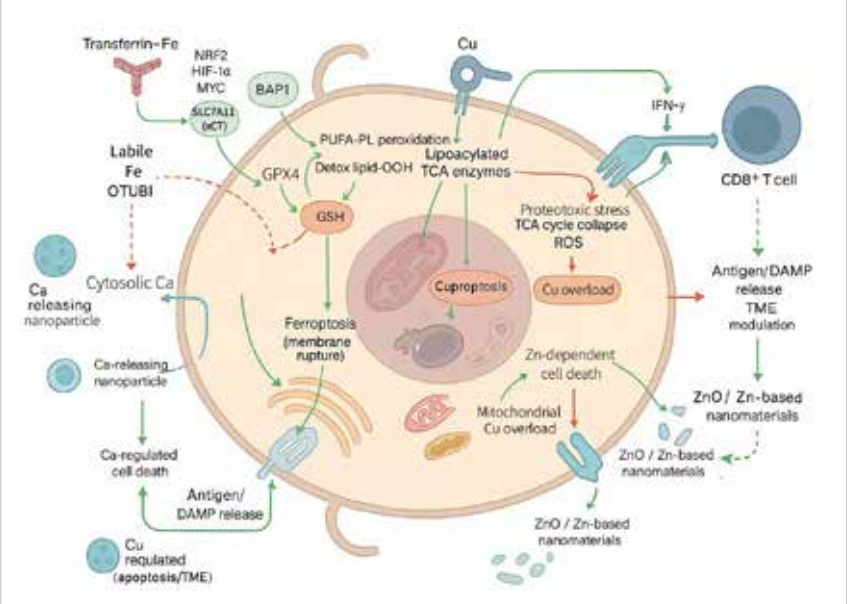

Metal ion-induced programmed cell death in cancer and therapeutic exploitation.

Iron-dependent ferroptosis is driven by expansion of the labile Fe pool and PUFA-phospholipid peroxidation, which is counteracted by the SLC7A11-GSH-GPX4 antioxidant axis (representatively regulated by BAP1 and stress-response programs such as NRF2/HIF-1α/MYC). Copper accumulation, particularly in mitochondria, induces cuproptosis by binding lipoacylated TCA-cycle enzymes, leading to protein

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aggregation, proteotoxic stress, TCA cycle collapse, and ROS. Ca^{2+} overload (e.g. Ca-releasing nanoparticles) and Zn^{2+} overload (e.g. ZnO/Zn-based nanomaterials) trigger Ca-regulated and Zn-dependent cell death pathways, respectively. These metal ion-induced deaths can promote antigen/DAMP release and reshape the TME, while immune effectors such as $CD8^+$ T cell-derived IFN-γ may further sensitize tumors, supporting metal-based and combination therapeutic strategies.

Abstract

Metal ions such as iron, copper, calcium and zinc are indispensable for cellular metabolism, yet their local overload or mislocalization can trigger distinct forms of programmed cell death (PCD). Over the past decade, ferroptosis and cuproptosis have emerged as prototypical "metal ion-induced deaths", while Ca^{2+}- and Zn^{2+}-associated death programs and multi-metal "metal overload" are beginning to be appreciated. This review summarizes the mechanisms and translational studies of metal ion-regulated cancer cell death, illustrating how these pathways are linked to tumor cell metabolism, plasticity, and the tumor microenvironment (TME). The dual nature of metal ion-induced deaths in cancer is explored here. As a tumor-suppressive mechanism engaged by tumor suppressors, immune effector cells and cytotoxic therapies, but also as a driver of chronic inflammation, clonal selection and therapy resistance when incompletely executed. Next, small molecules, metal-based nanomedicines and combination strategies that exploit ferroptosis, cuproptosis, Ca^{2+} overload or Zn-dependent death to overcome resistance and reshape the TME are evaluated in detail. Together, the evidence argues that "metal ion-induced deaths" constitutes a central node linking metabolism, stress signaling and immunity.

KEYWORDS

Metal ion-induced cell death, Cancer progression, Tumor microenvironment, Cancer therapy

Introduction

Programmed cell death (PCD) represents a fundamental process in maintaining tissue homeostasis, with its dysregulation being a hallmark of cancer(1). In physiological settings this machinery eliminates superfluous or damaged cells, prevents propagation of oncogenic mutations, and constrains chronic inflammation(2, 3). Once transformed, however, tumor cells frequently rewire PCD circuits, dampening death signals or diverting them into non-lethal outcomes. The balance between survival pathways and death programs therefore emerges as a central determinant of cancer initiation, progression, metastatic spread, as well as response to therapy. For decades, research has primarily focused on a few classic PCD patterns; however, many tumors exhibit strong resistance to these patterns, and drug-mediated modulation of classic PCD can lead to excessive inflammation, tissue damage, or treatment-induced immune paralysis(4, 5). These limitations have intensified the search for alternative death programs that might be more selectively vulnerable in malignant cells. The execution of these forms is highly dependent on metal ion homeostasis, including iron-driven ferroptosis, cuproptosis, and other emerging concepts of "metal ion-induced deaths." Together, these modalities redefine how fluctuations in intracellular metal pools, redox balance, and metabolic wiring can be exploited to kill cancer cells, offering a fresh conceptual framework for understanding tumor biology and designing next-generation therapies.

Metal-ion-driven PCD can directly couple lethal signaling directly to metabolic and redox circuits that are frequently distorted in tumors. Excess transition metals serve as catalysts for oxidative reactions, disturb protein folding, disrupt organellar function, and eventually tip stressed cancer cells over a fatal threshold(6, 7). Ferroptosis represents the best-characterized example. Ferroptosis is characterized by unique morphological changes such as shrunken mitochondria with condensed membranes, alongside the biochemical hallmarks of glutathione depletion and inactivation of glutathione peroxidase 4 (GPX4)(8). The discovery of

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ferroptosis fundamentally established the paradigm that specific metal ions can act as central executors of programmed cell death. Subsequently, this paradigm has broadened into the more comprehensive concept of "metal ion–driven programmed cell death," a class of pathways whose initiation and execution are intrinsically dependent on the aberrant accumulation or dyshomeostasis of redox-active metal ions, notably iron and copper, and potentially zinc(9). The core hallmark unifying these pathways is the metal-ion-dependent, non-enzymatic catalysis of radical reactions, primarily leading to the uncontrolled peroxidation of polyunsaturated fatty acids (PUFAs) within cellular membranes (10). This results in catastrophic membrane damage, a mechanism fundamentally divergent from the proteolytic cascades of apoptosis or the lysosomal degradation in autophagy. While sharing this foundational principle of oxidative membrane rupture, distinct metal ion–driven pathways exhibit specific dependencies: ferroptosis on iron, the newly described cuproptosis on mitochondrial copper, with each involving distinct metabolic targets and signature biomarkers(11). The elucidation of these pathways underscores a critical vulnerability in cancer cells, which often exhibit altered metal metabolism to support rapid proliferation, thereby rendering them potentially susceptible to metal ion–mediated cytotoxicity.

The elucidation of these distinct metal-dependent pathways necessitates a synthesized and critical analysis to fully comprehend their impact on oncology. This review aims to provide a comprehensive exploration of the specific molecular mechanisms underlying major forms of metal ion–driven programmed cell death, with a focus on ferroptosis and cuproptosis. We will systematically dissect the intricate, context-dependent roles these pathways play across various cancer types, highlighting their capacity to function as both tumor-suppressive mechanisms and drivers of tumor progression and therapeutic resistance. Furthermore, the article will critically evaluate the latest translational advances, focusing on emerging strategies that target these pathways for cancer therapy. By integrating mechanistic insight with translational perspective, this review seeks to clarify the therapeutic potential of manipulating metal ion–mediated cell death, outlining a roadmap for future research and drug development in this rapidly evolving field.
glutathione synthesis(8). Lipid metabolism is likewise profoundly remodeled in tumors, encompassing enhanced de novo fatty acid synthesis, accelerated β-oxidation, and dynamic phospholipid turnover. These alterations not only provide structural components essential for rapid cell division but also modulate signaling cascades and membrane properties that collectively promote proliferation and survival (9). In addition, nucleotide biosynthesis is frequently upregulated to sustain the high demand for DNA and RNA replication, while amino acid metabolism undergoes extensive rewiring to support protein synthesis, epigenetic modification, and immune escape(10, 11). Such multifaceted metabolic remodeling exemplifies the exceptional adaptability of tumor cells to intrinsic biosynthetic needs as well as extrinsic pressures from the surrounding microenvironment. Through the coordinated operation of these interconnected pathways, cancer cells construct a tightly regulated metabolic network integrating energy production, macromolecule biosynthesis, and signaling control (Figure 1). Recognition of this metabolic plasticity has fundamentally transformed our understanding of tumor pathogenesis, underscoring that cancer represents not merely a genetic disease but a metabolically distinct state endowed with specific vulnerabilities.

Core mechanisms of metal ion-dependent cell death

Ferroptosis

Iron handling and the labile iron pool

Ferroptosis is defined as an iron-dependent PCD driven by unchecked phospholipid peroxidation and catastrophic membrane damage. Mechanistically, ferroptosis hinges on the size and redox state of the labile iron pool. Transferrin-bound Fe^{3+} is internalized via transferrin receptor 1, reduced to Fe^{2+} in the endosome, and either stored in ferritin or released into the cytosol(12, 13). Existing studies have highlighted that ferritin autophagy (selective autophagy that degrades ferritin) and iron-sulfur cluster biosynthesis are key upstream regulators of ferroptosis sensitivity. Zhou and colleagues systematically discuss how chemotherapeutics such as doxorubicin disrupt

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endogenous metal ion homeostasis—including iron and copper—to provoke cardiotoxicity through ferroptotic mechanisms, underscoring the importance of tightly controlling iron-dependent ROS not only in tumors but also in normal tissues(14). In colorectal cancer (CRC), ferroptosis-focused work shows that tumor cells often exhibit elevated expression of transferrin receptor and altered ferritin levels(15), suggesting a state of "iron addiction" that may create a therapeutic window.

Polyunsaturated phospholipids and lipid peroxidation

Ferroptosis is distinguished from other forms of PCD by its requirement for PUFA-containing phospholipids within cellular membranes(16). Acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) play roles in the esterification of arachidonic acid and adrenaline to phosphatidylethanolamine, thereby providing substrates for the peroxidation reaction(17). Lipoxygenases (LOXs) and non-enzymatic Fenton chemistry then oxidize these PUFAs, generating lipid hydroperoxides and reactive aldehydes such as 4-hydroxynonenal (4-HNE), which accumulate in ferroptotic cells(18). The composition of the lipidome is a major determinant of ferroptosis susceptibility. Tumors with high ACSL4 expression and PUFA enrichment—such as subsets of CRC and hepatocellular carcinoma (HCC)—appear particularly sensitive to ferroptosis induction, whereas tumors that channel fatty acids into monounsaturated species via SCD1 or increase lipid droplets are relatively resistant(19).

Antioxidant defense

The best-characterized cell-intrinsic brake on ferroptosis is the GPX4-glutathione (GSH) axis. A series of mechanistic reviews and drug-focused articles catalog how GPX4, fueled by GSH derived from cystine imported via the cystine/glutamate antiporter System Xc⊠ (SLC7A11/SLC3A2), reduces phospholipid hydroperoxides to non-toxic alcohols, thereby preventing the execution of ferroptosis(20–22). Classical ferroptosis inducers such as erastin disrupt System Xc⊠, whereas RSL3 and newer GPX4 inhibitors directly inactivate GPX4(23). Beyond GPX4, other parallel antioxidant systems exist, including ferroptosis suppressor protein 1 (FSP1)-CoQ_{10}, the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin axis and dihydroorotate dehydrogenase (DHODH) in mitochondria(24). These systems safeguard distinct lipid compartments and subcellular membranes, implying that tumor cells can develop ferroptosis resistance by "layering" antioxidant modules. Importantly, several cancer-focused studies note that oncogenic pathways (e.g. NRF2, HIF-1α, MYC) upregulate these defense systems, thereby decoupling iron overload from lethal peroxidation(19, 25).

Crosstalk with calcium, metabolism and immune signaling

Furthermore, study has explicitly linked Ca^{2}+ signaling to ferroptosis. For example, Yan HX and colleagues review how Ca^{2+} influx and ER-mitochondria Ca^{2+} transfer modulate ROS production, GSH levels and mitochondrial metabolism, thereby tuning ferroptosis sensitivity in cancer cells(26). Ca^{2+}-sensitive phospholipases and mitochondrial permeability transition further integrate metal ion fluxes with lipid peroxidation and bioenergetic collapse(27, 28). Finally, several ferroptosis-immunology-oriented studies highlight macrophage-tumor interactions. Yang Y. and colleagues show that macrophage iron handling, lipid metabolism and amino acid pathways shape not only their own ferroptosis susceptibility but also the availability of iron and cytokines that bias tumor cell ferroptosis in the TME(29). Others on HCC and other tumor types similarly underscore ferroptosis as a node where tumor metabolism intersects with inflammation and antitumor immunity(19).

Cuproptosis

Copper homeostasis and cuproptosis

Copper is a redox-active cofactor for numerous enzymes in oxidative phosphorylation, antioxidant defense and matrix remodeling. Disruption of copper homeostasis has long been implicated in cancer, but only recently has cuproptosis been defined as a distinct copper-dependent PCD modality. Recent studies have explored the full picture of copper metabolism, including high-affinity transporters, molecular chaperones (ATOX1, CCS, COX17), storage proteins and efflux pumps (such as ATP7A/B), and their roles in tumor biology(30–32). Importantly, multiple articles specifically focused on cuproptosis converge on a core mechanistic model: excess copper accumulates in mitochondria, where it binds to lipoacylated TCA enzymes (e.g. DLAT, DLST), triggering their aggregation and loss of function, accompanied by Fe-S cluster protein destabilization and proteotoxic stress(33, 34). This model has been continuously integrated into multiple

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cancer-centric studies, linking the sensitivity of cells to copper-induced apoptosis with the expression of lipoic acid pathway components (FDX1, LIAS, LIPT1) and metabolic connectivity in tumor cells(35, 36).

Cuproplasia in copper metabolism

In addition, recent research on copper metabolism has demonstrated a key conceptual advance, namely the distinction between cuproplasia (copper-driven proliferation) and cuproptosis(37). Cancer cells often exhibit elevated copper uptake and dependency, using copper-containing enzymes to sustain mitochondrial respiration, angiogenesis and matrix remodeling. When copper levels are modestly elevated, this “addiction” manifests as cuproplasia; when copper exceeds a threshold, especially in cells reliant on mitochondrial respiration and rich in lipoacylated enzymes, cuproptosis is triggered. Zhang S. and colleagues emphasize this duality in their review of copper homeostasis and copper-induced cell death in cancer and immunology(38). Gao et al. further argue that cancer cells’ higher copper dependency relative to normal tissues may be exploited by cuproptosis-inducing agents, provided that copper delivery and buffering can be spatially controlled(39). These concepts provide a mechanistic rationale for therapies that either deprive tumors of copper (to disable cuproplasia) or overload copper locally (to trigger cuproptosis).

Cuproptosis in immune regulation and TME remodeling

Multiple studies and pan-cancer analyses examine cuproptosis-related gene signatures in relation to immune infiltration and prognosis across tumor types(40, 41). High expression of cuproptosis-related genes often associates with more inflamed TMEs, increased $CD8^+$ T cell infiltration and upregulation of immune checkpoints, although the direction and magnitude of these associations vary by cancer type. Suwara et al. propose a model in which copper chelators and copper ionophores can reprogram the immune landscape: chelators may attenuate cuproplasia and angiogenesis, whereas localized copper overload via nanomaterials or small molecules can drive cuproptosis in tumor cells and potentially enhance antigen release and danger-associated molecular patterns (DAMPs)(37). These hypotheses are supported by preclinical data using copper-based nanomaterials in syngeneic tumor models, in which cuproptosis induction correlates with improved immune infiltration and checkpoint inhibitor response.

Calcium, zinc and other metal ion-associated death programs

endoplasmic reticulum (ER)-mitochondria signaling and Ca^{2+} overload

Ca^{2+} function as ubiquitous intracellular secondary messengers, critically governing diverse cellular processes including proliferation, metabolism, and apoptosis(42). A key nexus in this dysregulation is the communication between the ER and mitochondria. At membrane contact sites, the ER, as a major Ca^{2+} reservoir, releases Ca^{2+} into the cytoplasm via channels such as inositol 1,4,5-trisphosphate receptors (IP3Rs)(43). This Ca^{2+} is subsequently taken up by mitochondria through the voltage-dependent anion channel (VDAC) and the mitochondrial calcium uniporter (MCU). In malignant cells, this ER-mitochondria signaling axis is often altered to favor survival; however, excessive or sustained Ca^{2+} transfer can trigger mitochondrial Ca^{2+} overload(44). This overload precipitates a lethal cascade characterized by mitochondrial permeability transition pore (mPTP) opening, membrane potential collapse, excessive ROS production, and the release of pro-apoptotic factors(45). Multiple articles argue that acute or spatially confined Ca^{2+} overload can trigger various forms of cell death, including apoptosis, necrosis and possibly ferroptosis-sensitized states(26-28). Zhai K. and colleagues highlight TRPV1-mediated Ca^{2+} entry as a potential anti-cancer target, where pharmacological modulation can tip the balance from pro-survival signaling to Ca^{2+}-regulated cell death in specific tumor contexts(46). Several nanomedicine-oriented reviews propose Ca^{2+} overload as a deliberate therapeutic strategy. Wang C. et al. and Gu et al. summarize Ca^{2+}-releasing nanoparticles and Ca-containing biomaterials that accumulate in tumors, release Ca^{2+} in response to acidic or enzymatic cues, and induce mitochondrial dysfunction and cell death(47, 48).

Zn homeostasis and Zn-dependent cell death

Zinc is redox-inert but plays structural and catalytic roles in a vast array of proteins, including transcription factors and DNA repair enzymes(49). Loss of Zn^{2+} can impair genomic stability, whereas Zn^{2+} overload can perturb mitochondrial function and induce oxidative stress. In cancer, this meticulous homeostasis

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is frequently disrupted, contributing to tumor progression. While certain tumors exhibit zinc depletion, which may support proliferation, emerging evidence highlights that inducing intracellular zinc overload represents a potent cytotoxic strategy, triggering a distinct form of metal-dependent PCD. From a therapeutic perspective, multiple articles analyze Zn-based nanomaterials as anti-tumor agents. Mu et al. review Zn-based nanomaterials in cancer therapy, emphasizing ZnO nanoparticles that release Zn^{2+} in acidic TMEs, disrupt mitochondrial membrane potential and generate ROS(50). Tseriotis et al. discuss ZnO-based nanoparticles for targeted cancer chemotherapy and photodynamic therapy, highlighting their ability to act as both drug carriers and nanozymes that catalyze ROS production(51). Xi ZY et al. present a “nanocatalytic system” that releases overloaded Zn^{2+} specifically in tumor cells, where Zn^{2+} participates in Fenton-like reactions and mitochondrial damage, thereby inducing a Zn-dependent death phenotype(52). Together, these studies support the emerging notion of a Zn-dependent cell death program that is mechanistically distinct from ferroptosis and cuproptosis yet converges on oxidative stress and organelle dysfunction.

Other metal-induced cell death

Beyond Fe, Cu, Ca and Zn, environmental metals such as cadmium and arsenic promote breast and prostate cancer progression by modulating BCL-2, caspase-3 and other apoptotic components, linking chronic low-level metal exposure to malignant transformation(53). Nagakannan et al. discuss oxidative lysosomal damage in regulated cell death, providing a broader perspective on metal-rich organelles and their rupture as cell death triggers(54). You et al. and Wang J. independently propose integrative frameworks — “intracellular metal ion–based chemistry for programmed cell death” and “metal overload”—to unify diverse metal ion–dependent deaths. They emphasize that Fe, Cu, Zn and Ca can each engage distinct chemistries (Fenton reactions, coordination with lipoacylated proteins, disruption of protein–nucleic acid complexes) yet converge on common endpoints such as catastrophic ROS production, protein aggregation, membrane damage and organelle failure(55, 56). These studies are increasingly meaningful in viewing "metal ion-induced deaths" as a series of interconnected, environment-dependent PCD patterns, rather than isolated pathways. These patterns share common upstream triggers and downstream consequences in tumors.

Metal ion-induced deaths in cancer

Tumor-suppressive functions

Engagement by tumor suppressor pathways

Some articles focusing on ferroptosis have summarized how classic tumor suppressor factors work together to kill metal ions, and discussed how p53 inhibits the transcription of SLC7A11, thereby reducing cystine uptake, weakening GSH synthesis, and making tumor cells more sensitive to ferroptosis(15, 25). Zimta et al. show that p53 also integrates metal exposure signals—such as cadmium and arsenic—to modulate BCL-2 and caspase-3, which may intersect with ferroptosis and apoptotic pathways in hormone-dependent tumors(53). Existing studies have provided direct in vivo evidence that ferroptosis is a bona fide tumor-suppressive activity of p53 and BAP1. Zhang et al. demonstrated that BAP1 represses SLC7A11, thereby lowering GSH and promoting ferroptosis; BAP1 loss leads to ferroptosis resistance and enhanced tumorigenesis(57). Subsequent studies have generalized this concept, highlighting that multiple tumor suppressors—including p53, BAP1 and OTUB1—modulate ferroptosis through antioxidant and lipid metabolism pathways. These external studies are consistent with the p53/ferroptosis axis discussed in our core set, strengthening the view that metal ion-induced deaths are embedded within canonical tumor suppressor networks. Cuproptosis-related reviews similarly link tumor suppressor pathways to copper metabolism. Gao et al. and others note that tumor suppressor loss can deregulate copper transporters and lipoic acid metabolism, shifting the balance from controlled copper utilization to either cuproplasia or cuproptosis(39). Together, these data justify treating metal

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ion-induced deaths as an integral component of tumor-suppressive signaling rather than as mere drug-induced curiosities.

Effector mechanisms of immune surveillance

Metal ion-induced deaths functions as an effector arm of adaptive and innate immunity. Yang Y. et al. dissect how macrophage iron, lipid and amino acid metabolism regulate ferroptosis in both macrophages and neighboring tumor cells, influencing cancer progression(29). Tu S. et al. and others, focusing on HCC, emphasize that ferroptosis intersects with inflammatory signaling and may contribute to the anti-tumor effects of interferons and cytokines(19). Wang et al. showed that immunotherapy-activated $CD8^+$ T cells promote tumor ferroptosis by releasing IFN-γ, which downregulates SLC7A11/SLC3A2 and enhances lipid peroxidation(58). Follow-up work revealed that $CD8^+$ T cells can also promote ferroptosis by modulating fatty acid metabolism in tumors and by downregulating GPX4 in tumor cells(59). Cuproptosis may play a similar role. Cuproptosis-related gene signatures correlate with inflamed TMEs, and that copper ionophores can enhance antigen release and potentially immunogenic cell death in preclinical models(60, 61). Although direct evidence that immune cells actively trigger cuproptosis in tumors is still nascent, the conceptual framework parallels that of ferroptosis.

Tumor-promoting roles and adaptive resistance

Chronic metal ion dysregulation and clonal selection

The same chemical reactivity that enables metal ion-induced deaths can also promote oncogenesis when sub-lethal. Zimta et al. show that chronic cadmium and arsenic exposure fosters breast and prostate cancer by inducing DNA damage and modulating apoptosis, potentially selecting for clones with heightened stress tolerance and altered metal handling(53). Zhou N. et al. underscore that doxorubicin-induced cardiotoxicity arises from metal-mediated oxidative damage, illustrating that ferroptosis-like processes can be deleterious in normal tissues(14). Some studies repeatedly emphasize that tumors evolve sophisticated mechanisms to survive in metal-rich, oxidative environments. Upregulation of ferritin, metallothioneins, metal transporters and antioxidant pathways enables cancer cells to accumulate iron and copper without succumbing to ferroptosis or cuproptosis(22, 32). This "preconditioning" may actually enhance malignant potential, as metal-dependent enzymes in mitochondrial respiration, angiogenesis and matrix remodeling become overactive.

Epithelial-mesenchymal transition (EMT), plasticity and metastasis

Ferroptosis-related studies have linked ferroptosis resistance to EMT, stemness, and metastasis. Wang D. et al. describe how ferroptosis-related long non-coding RNAs and signaling pathways shape EMT programs, with ferroptosis-resistant cells often exhibiting mesenchymal traits and heightened motility(25). Tu S. et al. and others note that in HCC and other solid tumors, sub-lethal lipid peroxidation can activate NF-κB and TGF-β signaling, thereby promoting fibrotic and pro-metastatic microenvironments(19). Calcium signaling reviews add another dimension: Ca^{2+}-dependent kinases and transcription factors enhance migration and invasion, and chronic Ca^{2+} signaling rewiring in cancer cells may allow them to tolerate episodic oxidative and metabolic stress that would otherwise trigger death(62, 63). Thus, persistent exposure to metal-induced stress may foster highly plastic, invasive clones.

Immunosuppressive microenvironments and immune cell ferroptosis

Metal ion-induced deaths can also undermine antitumor immunity when they occur in immune cells or stromal components. Ferroptosis has been shown to impair dendritic cell-mediated antitumor immunity in various in vivo prophylactic and therapeutic vaccination programs. While most studies have predominantly focused on ferroptosis as a tumor cell death pathway that promotes immunogenicity, several studies note that ferroptosis in T cells, dendritic cells or neutrophils can be detrimental, impairing immune surveillance(48, 64). The study by Ma et al. strongly supports this view, finding that CD36-mediated ferroptosis in intratumoral $CD8^+$ T cells attenuate their effector function and compromises antitumor immunity(65). In addition, ferroptosis of tumor-associated neutrophils generates immunosuppressive signals that favor tumor growth(66). In summary, indiscriminate induction of ferroptosis or cuproptosis in the TME may kill not only tumor cells but also key immune effectors, resulting in net immunosuppression.

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Therapeutic strategies targeting metal ion-dependent cell death

Direct pharmacologic induction of ferroptosis or cuproptosis

Classical ferroptosis inducers and novel small molecules

Existing research has explored the pharmacological properties of ferroptosis inducers in a thorough and multifaceted manner. Erastin and its analogues inhibit System Xc⊠, RSL3 and related compounds inhibit GPX4, and sorafenib and sulfasalazine possess context-dependent ferroptosis-inducing activity(20, 67). Xiang S. et al. summarize newer agents that target iron metabolism, lipid metabolism or emerging regulators (FSP1 and GCH1), such as cyclophosphamide, tamoxifen, paclitaxel, and anthracyclines, may induce excessive ROS production and promote ferroptosis in breast cancer cells(21). Several papers connect these inducers to specific cancer types. Yan H. et al. propose ferroptosis-based strategies for CRC, noting that erastin, RSL3 and experimental GPX4 inhibitors synergize with 5-FU or oxaliplatin in preclinical models(15). Tu S. et al. discuss sorafenib-induced ferroptosis in HCC and the potential to enhance its efficacy by co-targeting antioxidant defenses(19). These works emphasize that ferroptosis inducers rarely function as monotherapies; instead, they are most effective in combination with standard treatments or in genetically defined subgroups with high ferroptosis vulnerability.

Cuproptosis inducers and copper-modulating agents

Several classic copper-modifying drugs have been identified in studies related to cuproptosis. Disulfiram and elesclomol act as copper ionophores, forming complexes with copper that preferentially accumulate in tumor cells, whereas tetrathiomolybdate (TTM) and other chelators sequester copper to inhibit cuproplasia and angiogenesis(37, 68). Wu T. et al. explored in depth the mechanisms by which these drugs reverse drug resistance by remodeling mitochondrial metabolism and inducing cuproptosis in drug-resistant clones(60). Pan-cancer analyses suggest that tumors with high expression of lipoic acid pathway genes and mitochondrial respiratory dependency may be particularly sensitive to cuproptosis inducers(69). However, most evidence remains preclinical, and clinical trials specifically designed to exploit cuproptosis mechanisms are still lacking.

Nano-enabled ferroptosis, cuproptosis and other

Iron-based nanomaterials and ferroptosis

Currently, there are many studies on nano-oncology that utilize metal ions to induce PCD. Polyoxometalate (POM)-based nanoplatforms have been discovered that can catalyze ROS production and induce ferroptosis, often in combination with photothermal or photodynamic modalities(70). Wang Y. et al. and others describe Fe-based nanomaterials, including Fe_3O_4 nanoparticles and Fe-doped metal–organic frameworks (MOFs), that deliver iron to tumors, amplify Fenton reactions and trigger ferroptosis(71). Iron oxide nanoparticles are also used as therapeutic tools, enhancing radiotherapy-induced lipid peroxidation, delaying tumor growth, and sometimes synergizing with immunotherapy(72). However, several articles caution that iron-based nanomedicines can also exacerbate off-target toxicity and may induce ferroptosis in non-malignant cells if not rigorously targeted.

Cuproptosis-oriented nanomaterials

Cuproptosis is also being harnessed via nanotechnology. Sahoo et al. and Masuri et al. describe copper (II)-based complexes and nanostructures that deliver copper selectively to tumor cells, where it accumulates in mitochondria and triggers cuproptosis and other copper-dependent PCD pathways(73, 74). In addition, a multi-metal nanoplatform that can deliver iron and copper simultaneously can activate iron death and cuproptosis, and may overcome the heterogeneity of metal death susceptibility(56). These nano-enabled strategies often incorporate tumor-targeting ligands, pH-sensitive coatings or stimuli-responsive release systems to confine metal-induced cell death to tumors. Preclinical studies in murine models demonstrate robust tumor regression and enhanced immunogenicity, but the long-term fate of metal nanoparticles and their accumulation in organs such as liver and spleen remain major translational barriers(75).

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Ca^{2+} and Zn^{2+} nanotherapeutics

Ca^{2+}-releasing nanoplatforms have been shown to induce intratumoral Ca^{2+} overload and are often used in combination with photothermal therapy or chemotherapy(48). These constructs exploit acidic pH or enzymatic triggers to release Ca^{2+} intracellularly, causing mitochondrial swelling, cytochrome c release and multi-modal cell death. For Zn, ZnO-based nanoparticles and Zn-containing frameworks can deliver chemotherapeutic agents and release Zn^{2+} simultaneously, thereby inducing ROS and mitochondrial dysfunction(50, 51). Xi ZY et al. describe a "nanocatalytic" system that accumulates Zn^{2+} to levels that provoke a distinct Zn-dependent death phenotype(52). Collectively, these works position Ca^{2+} and Zn^{2+} as promising but less mature axes of metal-induced cell death therapy.

Combination strategies with radiotherapy, targeted therapy and immunotherapy

Radiotherapy and metal ion-induced deaths

Previous studies have identified an interaction between radiotherapy and ferroptosis(72). Radiotherapy generates ROS and lipid peroxidation, providing a natural context for ferroptosis. Iron-based nanoparticles and POM platforms enhance these effects by supplying additional redox-active metal ions. Preclinical evidence suggests that combining ionizing radiation with ferroptosis inducers (e.g. GPX4 inhibitors) yields supra-additive tumor control, though normal tissue toxicity is a concern(76). Furthermore, radiation-induced lipid peroxidation synergizes with ferroptosis inducers, and that ferroptosis contributes to the tumor-suppressive effects of radiotherapy.

Targeted therapy combinations

The integration of metal ion-modulating agents with established anticancer therapies presents a promising strategy for enhancing therapeutic efficacy and overcoming resistance. Combining these agents with conventional chemotherapy or radiotherapy often yields synergistic effects. For instance, zinc ionophores can sensitize tumor cells to DNA-damaging chemotherapeutics by exacerbating mitochondrial dysfunction and proteotoxic stress(77). Similarly, leveraging calcium channel modulators alongside radiotherapy can amplify radiation-induced cell death through enhanced mitochondrial calcium overload and subsequent apoptosis(78). These combinations exploit the ability of metal ions to lower the apoptotic threshold, rendering resistant cells vulnerable to traditional cytotoxic insults. Building upon this rationale, more precise combinations with molecularly targeted agents have shown significant potential. Research demonstrates that KRAS-mutant cancers, reliant on altered iron metabolism, exhibit heightened sensitivity to ferroptosis inducers(79, 80). Combining these inducers with MEK inhibitors creates a synergistic lethal effect, effectively bypassing adaptive resistance pathways(81). Likewise, TP53-deficient tumors, which often exhibit impaired antioxidant defenses, become exquisitely susceptible to pro-oxidant copper chelators or zinc ionophores, offering a targeted strategy based on genetic context(82).

Furthermore, combining metal ion therapy with immune checkpoint inhibitors (ICIs) is an innovative strategy for cancer treatment. Ferroptosis induction can enhance tumor antigen release, DAMP exposure and dendritic cell activation, thereby augmenting checkpoint blockade(83). In lung cancer adenocarcinoma models, the combination of metal ion therapy and ICIs significantly enhances anti-tumor efficacy(84). For example, the combination of carbon ion radiotherapy (CIRT) and ICIs can produce a synergistic tumor-killing effect through ferroptosis, increasing interferon-β (IFN-β) expression and $CD8^+$ T cell infiltration, superior to monotherapy(85). This multi-pathway activation strategy overcomes the limitations of single-drug therapy and provides a new therapeutic direction for drug-resistant tumors. $CD8^+$ T cell–derived IFN-γ downregulates SLC7A11 and promotes ferroptosis, and that T cell–driven ferroptosis contributes to the efficacy of PD-1/PD-L1 blockade(86). Cuproptosis-focused studies likewise propose combinations with immunotherapy, particularly in tumors with high copper dependency and immunologically "cold" TMEs(87). Localized copper overload may increase immunogenic cell death while disrupting cuproplasia-dependent immune evasion, but robust in vivo evidence remains preliminary.

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Conclusion

Metal ion–driven programmed cell death has emerged as a unifying framework that links metal homeostasis, redox biology, and oncogenic signaling. Ferroptosis, cuproptosis, as well as Ca^{2+}- and Zn^{2+}-dependent death programs expose a metabolic Achilles' heel of cancer cells that rely on dysregulated metal handling to sustain proliferation. Yet the same chemistry that enables selective tumor killing can promote clonal evolution, EMT, metastasis, or immunosuppression when activation is chronic or spatially uncontrolled. Translational efforts now exploit metal ion-induced deaths through small molecules, copper/iron modulators, or nano-enabled platforms, often in combination with radiotherapy, targeted agents or immune checkpoint blockade. Moving forward, the field must deliver robust biomarkers of "metal addiction", clarify context-specific effects within the TME, and design strategies that spare antitumor immune cells. A deeper integration of systems-level metalomics, single-cell profiling, and early-phase clinical trials will be essential to convert metal-induced cell death from an attractive concept into durable patient benefit.

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