ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Targeting pyroptosis, ferroptosis, and cuproptosis: An updated view of regulated cell death pathways for cancer therapy

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Abstract

Introduction: Cancer treatment has long relied on inducing apoptosis; however, tumors frequently develop resistance through apoptosis-evasion mechanisms, leading to recurrence and metastasis. In recent years, three emerging forms of programmed cell death—pyroptosis, ferroptosis, and cuproptosis—have attracted intense interest. Thanks to their distinct molecular pathways and strong immunogenic properties, they offer promising ways to overcome the limitations of traditional therapies. These mechanisms, driven by inflammatory signaling or dysregulation of metal ions (iron or copper), trigger mitochondrial dysfunction, lipid peroxidation, or membrane pore formation. Beyond directly killing tumor cells, they release damage-associated molecular patterns that activate immunogenic cell death. This process reshapes the tumor microenvironment and significantly enhances the efficacy of immune checkpoint inhibitors.

Objective: This review systematically summarizes the molecular regulation, network interactions, and therapeutic advances of these three novel cell death pathways, providing new theoretical foundations and potential translational strategies for treating refractory cancers.

Conclusion: Pyroptosis, ferroptosis, and cuproptosis represent interconnected, non-apoptotic cell death pathways with substantial potential to overcome therapeutic resistance, remodel the immunosuppressive tumor microenvironment, and enhance responses to immune checkpoint blockade. Further mechanistic validation, biomarker development, improved tumor-specific delivery, and well-designed clinical trials are required to translate these strategies into safe, precise, and effective cancer therapies.

Keywords: Cell death; Cancer therapy; Pyroptosis; Ferroptosis; Cuproptosis

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Citation: Zhao J, Du X, Fang W, *et al*. Targeting pyroptosis, ferroptosis, and cuproptosis: An updated view of regulated cell death pathways for cancer therapy. *Eurasian J Med Oncol.*
doi: 10.36922/EJMO026260298

Received: June 22, 2026

Revised: July 24, 2026

Accepted: July 30, 2026

Published online: August 6, 2026

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1. Introduction

Cancer remains one of the leading global public health challenges, and a cornerstone of cancer treatment has long been the induction of programmed cell death (PCD) in tumor cells to eliminate malignant clones.[1,2] However, tumor cells frequently develop resistance

to apoptosis by upregulating anti-apoptotic proteins (such as B-cell lymphoma 2 [BCL-2] family members), acquiring p53 mutations, activating pro-survival pathways, such as phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin, and undergoing metabolic reprogramming. These adaptations have become major drivers of drug resistance, metastasis, and disease recurrence.[3-7] Conventional chemotherapy, radiotherapy, and targeted therapies primarily depend on the classical apoptotic pathway. As a result, their effectiveness is often severely limited, and many patients eventually experience treatment failure due to acquired resistance.[3,8-10] In parallel with these molecular challenges, modern medicine is rapidly advancing through novel diagnostic and pre-processing technologies. For example, artificial intelligence in radiation oncology via magnetic resonance imaging, thermal imaging, near-infrared optical imaging of the breast, and Monte Carlo simulations for light propagation in biological tissues are significantly improving cancer detection.[11] These engineering breakthroughs reflect a broader technological convergence in healthcare. Alongside these macroscopic diagnostic advances, at the microscopic level, deeper insights into PCD have shifted attention toward non-apoptotic mechanisms. Exploring these novel pathways to bypass apoptosis resistance and trigger immunogenic cell death (ICD) has emerged as a promising breakthrough in oncology. These alternative forms of cell death not only directly kill tumor cells but also release damage-associated molecular patterns (DAMPs) that remodel the tumor microenvironment (TME), offering new strategies to overcome the shortcomings of traditional treatments.[12-14]

Apoptosis is a highly ordered, non-inflammatory, caspase-dependent form of PCD. It is characterized by cell shrinkage, chromatin condensation, DNA fragmentation, and the formation of apoptotic bodies.[15-17] Because it does not trigger a strong immune response, it has long been considered the classic target in cancer therapy.[18,19] In contrast, the newly identified forms of PCD exhibit distinct biochemical features, often involving metal ion dependence or inflammatory properties, and largely operate independently of the classical apoptotic pathway.[20] The term pyroptosis was first coined in 2001, and then in 2015, gasdermin D (GSDMD) was identified as its key executioner protein. It is an inflammatory, GSDM family-mediated form of cell death that involves pore formation in the cell membrane. This leads to cell swelling and rupture, along with the release of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18.[21,22] Ferroptosis is an iron-dependent, non-apoptotic PCD driven primarily by lipid peroxidation (LPO), first reported in 2012 by Dixon *et al.*[23] Its morphological, biochemical, and genetic characteristics clearly distinguish it from apoptosis, necrosis, and autophagy.[23-25] Cuproptosis, on the other hand, is a copper-dependent form of PCD discovered in 2022 by Tsvetkov and colleagues.[26] It occurs when excess copper ions in mitochondria promote lipoylation and oligomerization of tricarboxylic acid (TCA) cycle proteins, thereby disrupting iron–sulfur clusters. This results in protein toxicity, stress, and mitochondrial dysfunction, and, importantly, operates completely independently of apoptosis, ferroptosis, and other known pathways.[26] Although all three belong to the broader category of PCD, they differ significantly from apoptosis in morphology, regulatory molecules, and immunogenicity. These differences open up entirely new therapeutic opportunities for cancer treatment.

During cancer progression, tumor cells can evade these novel forms of PCD by downregulating key regulators—such as GSDMD/E in pyroptosis, glutathione peroxidase 4 (GPX4)/solute carrier family 7 member 11 (SLC7A11) in ferroptosis, or ferredoxin 1 (FDX1)/dihydrolipoamide S-acetyltransferase (DLAT) in cuproptosis—thereby gaining a survival advantage and driving tumor advancement.[27] At the same time, these mechanisms play a dual role in reshaping the TME. On the one hand, moderate induction of these cell death pathways triggers the release of DAMPs (such as mitochondrial DNA and high mobility group box 1) and activates the cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) pathway. This promotes dendritic cell maturation, enhances $CD8^+$ T cell and natural killer (NK) cell infiltration, and elicits robust antitumor immune responses, ultimately suppressing tumorigenesis. On the other hand, chronic or non-specific activation may foster a sustained pro-inflammatory microenvironment that paradoxically supports tumor progression.[28] From a therapeutic perspective, these three novel PCD pathways offer powerful strategies to bypass apoptosis resistance. They have shown considerable promise in difficult-to-treat cancers such as hepatocellular carcinoma (HCC), breast cancer, and lung cancer. When combined with chemotherapy, radiotherapy, immune checkpoint inhibitors (ICIs), or nano-delivery systems and natural products, they can achieve synergistic tumor cell killing and immune sensitization.[29,30] While other clinically relevant regulated cell death (RCD) mechanisms—such as necroptosis, PANoptosis, parthanatos, alkaliptosis, and oxeiptosis—represent vital alternative pathways in oncology, this review focuses exclusively on the triad of pyroptosis, ferroptosis, and cuproptosis. This selection is rationalized by their unique positioning at the precise intersection of metabolic reprogramming, severe metal–ion dependency (iron and copper), and highly distinct immunogenic profiles. Unlike highly descriptive compilations that superficially cover all known RCDs,

examining this specific triad allows for a more granular synthesis of how intracellular metal homeostasis and lipid/protein toxicity cross-regulate the TME. This review aims to provide a systematic overview of the molecular regulation, network interactions, and therapeutic advances of pyroptosis, ferroptosis, and cuproptosis.

2. Pyroptosis: Immune regulation and therapeutic applications in cancer

Pyroptosis is a highly inflammatory form of PCD mediated by GSDM family proteins. Its hallmark features include the formation of membrane pores, cell swelling and rupture, and the massive release of pro-inflammatory cytokines such as IL-1β and IL-18.[31-33] Members of the GSDM family share a similar structural architecture: an N-terminal pore-forming domain with intrinsic cytotoxicity and a C-terminal autoinhibitory domain, connected by a flexible linker region. In addition to the best-studied GSDMD, other members—including GSDMA, GSDMB, GSDMC, GSDMD, and GSDME—can also induce pyroptosis in a tissue-specific manner.[34] Pyroptosis strongly amplifies immune responses through the activation of inflammasomes or non-canonical pathways, and it is closely linked to tumorigenesis, TME remodeling, and treatment outcomes.[35] In cancer, moderate pyroptotic induction can effectively kill tumor cells while releasing DAMPs that boost antitumor immunity. However, excessive or nonspecific activation may exacerbate tumor-associated inflammation and cause organ damage.[36,37] This section explores pyroptosis from three perspectives: its molecular mechanisms, its complex relationship with cancer, and current antitumor strategies that harness pyroptosis induction. Together, these highlight the "double-edged sword" potential of pyroptosis in cancer immune regulation and clinical translation.

2.1. Molecular mechanisms of pyroptosis

Pyroptosis is mainly divided into two major pathways: the classical (caspase-1-dependent) pathway and the non-classical (caspase-4/5/11-dependent) pathway.[38,39] In the classical pathway, inflammasomes such as NOD-like receptor protein 3 (NLRP3) sense DAMPs and recruit the adaptor protein apoptosis-associated speck-like protein containing a caspase activation and recruitment domain along with pro-caspase-1, leading to caspase-1 activation. Activated caspase-1 then cleaves GSDMD to generate its N-terminal fragment (GSDMD-N), which oligomerizes to form membrane pores.[40] At the same time, it processes pro-IL-1β and pro-IL-18 into their mature forms. This results in cell swelling, rupture, leakage of cytoplasmic contents, and amplified inflammation.[41-44] The thioredoxin-interacting protein (TXNIP)/NLRP3/GSDMD axis is a key pathway linking oxidative stress to pyroptosis. TXNIP can directly activate the NLRP3 inflammasome, thereby intensifying pyroptotic signaling.[45]

The non-classical pathway does not rely on caspase-1. Instead, it is triggered when bacterial lipopolysaccharide (LPS) directly activates caspase-4/5 in humans or caspase-11 in mice, leading to GSDMD cleavage and membrane pore formation.[46,47] In addition, apoptosis-related caspases and granzyme-mediated pathways contribute to the regulation of pyroptosis. For example, although caspase-3 and caspase-8 have traditionally been viewed as key executors of apoptosis, recent studies have shown that in GSDME-expressing cancer or normal cells, tumor necrosis factor or chemotherapeutic agents can activate caspase-3, which cleaves GSDME and switches the mode of cell death to pyroptosis.[48-50] Specifically, activated caspase-3 cleaves GSDME at the 267DMPD270 site in the linker region between its domains in both human and mouse proteins. This releases the N-terminal fragment (GSDME-N), which possesses intrinsic pore-forming activity and ultimately causes cell lysis.[51] Certain chemotherapeutic drugs can also induce pyroptosis in cancer cells through the caspase-8/GSDMC pathway.[52] Granzymes are a family of homologous serine proteases primarily expressed in cytotoxic T lymphocytes (CTLs) and NK cells. They induce PCD by cleaving specific substrates in target cells.[53,54] For a long time, granzyme-mediated cell death was considered to occur mainly through apoptosis.

However, in 2020, Zhao *et al.*[55] first reported that cytotoxic lymphocytes can kill GSDMB-expressing target cells by inducing pyroptosis. Mechanistically, lymphocyte-derived granzyme A (GZMA) cleaves GSDMB at Lys244 in the linker region between its domains, releasing an N-terminal fragment with pore-forming activity that triggers pyroptosis.[55] In addition, interferon secreted by activated cytotoxic lymphocytes significantly upregulates GSDMB transcription, further enhancing the GZMA/GSDMB-mediated pyroptotic effect. In the same year, Zhang *et al.*[50] reported that GZMB secreted by cytotoxic lymphocytes can directly cleave GSDME after the D270 site, inducing caspase-independent pyroptosis in GSDME-positive cells. These two landmark studies challenged the traditional view and demonstrated that, in GSDMB- or GSDME-positive cells, granzymes can not only induce pyroptosis but also trigger caspase-independent pyroptosis. In summary, the classical and non-classical pathways, together with supplementary routes mediated by apoptosis-related caspases and granzymes, form a sophisticated regulatory network for pyroptosis. Under different stimuli, this network ultimately leads to pore formation by GSDMD or GSDME, resulting in cell lysis

and amplified inflammation (Figure 1).

2.2. The relationship between pyroptosis and cancer

Unlike classical apoptosis, pyroptosis is highly immunogenic. It can effectively suppress tumor cell proliferation and migration by activating antitumor immune responses. At the same time, because prolonged exposure to inflammatory environments significantly increases the risk of tumorigenesis, pyroptosis can also promote tumor progression under certain conditions, through chronic inflammation or immune suppression. This gives it a complex, context-dependent dual role in

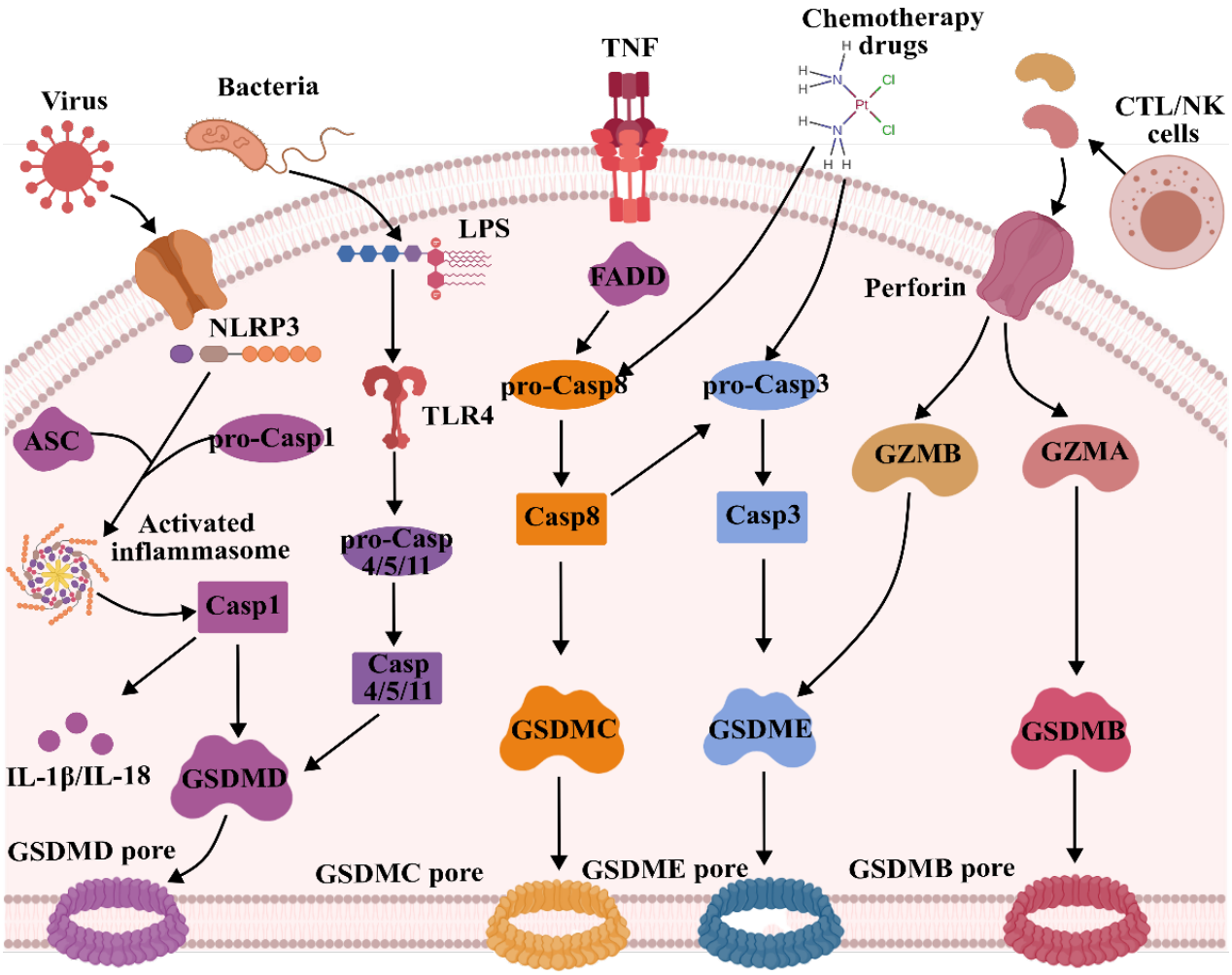


Figure 1. Schematic overview of gasdermin-mediated membrane pore formation in pyroptosis. Pathogen-associated molecular patterns such as viral components and LPS trigger canonical and non-canonical inflammasome pathways. In the canonical pathway, NLRP3 recruits ASC and pro-caspase-1 to form the activated inflammasome, leading to caspase-1 maturation. Active caspase-1 cleaves GSDMD, generating N-terminal pores in the plasma membrane and promoting the maturation and release of the pro-inflammatory cytokines IL-1β and IL-18. In the non-canonical pathway, LPS activates caspase-4/5/11, which in turn cleaves GSDMD, forming membrane pores. TNF signaling through FADD activates caspase-8, which can cleave GSDMC. Chemotherapy drugs and other intrinsic apoptotic stimuli activate caspase-3, which processes GSDME into pore-forming fragments. CTL and NK cells release perforin together with GZMA and GZMB, which activate GSDMB and GSDME, respectively, thereby inducing gasdermin pore formation and lytic cell death. The diagram illustrates the convergence of multiple upstream signals on gasdermin family members (GSDMD, GSDMC, GSDME, and GSDMB), resulting in the formation of characteristic transmembrane pores that drive inflammatory or ICD. Orange, blue, purple, and pink color-coding denote distinct caspase–gasdermin axes. The diagram was generated using MedPeer (www.medpeer.cn).

Abbreviations: ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain; CTL: Cytotoxic T lymphocyte; FADD: Fas-associated death domain protein; GSDMB: Gasdermin B; GSDMC: Gasdermin C; GSDMD: Gasdermin D; GSDME: Gasdermin E; GZMA: Granzyme A; GZMB: Granzyme B; ICD: Immunogenic cell death; IL: Interleukin; LPS: Lipopolysaccharide; NK: Natural killer; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; PAMP: Pathogen-associated molecular pattern; TNF: Tumor necrosis factor.

cancer development.[56,57]

2.2.1. Activation pathways of pyroptosis in tumors

The core executors of pyroptosis are GSDM family proteins, including GSDMD, GSDME, and GSDMC. Once their N-terminal domains are cleaved by specific proteases, they oligomerize and form 10–20 nm pores in the plasma membrane, ultimately causing cell lysis.[21,58] In the classical pathway, inflammasome activation leads to caspase-1-mediated cleavage of GSDMD. In tumor cells, however, the apoptotic executioner caspase-3 can cleave GSDME, effectively switching apoptosis to pyroptosis.[59,60] Additionally, the immune checkpoint molecule programmed death-ligand 1 (PD-L1) can specifically upregulate GSDMC expression, converting tumor necrosis factor alpha-induced apoptosis into pyroptosis.[52] Recent studies have also shown that caspase-6 can mediate GSDMC cleavage, while organelle stress (such as mitochondrial or lysosomal stress) further modulates pyroptosis induction.[61,62] These mechanisms position pyroptosis as a major form of ICD within the TME. It exhibits clear molecular differences from classical apoptosis, particularly in the crosstalk between cancer cells and immune cells.[60]

2.2.2. Antitumor effects of pyroptosis

Mounting evidence shows that pyroptosis can effectively inhibit tumor initiation and progression, primarily by triggering ICD and remodeling the TME. For instance, PD-L1-mediated upregulation of GSDMC can switch tumor cell apoptosis to pyroptosis, resulting in tumor necrosis and massive release of DAMPs that strongly activate antitumor immunity. This mechanism has been validated in both breast cancer and lung cancer.[52] The caspase-3/GSDME pathway acts as a molecular "switch" between apoptosis and pyroptosis. It enhances inflammatory cell death in tumor cells and promotes immune cell recruitment, offering a new target for sensitizing tumors to chemotherapy.[60] In addition, blocking endosomal sorting complex required for transport (ESCRT)-dependent plasma membrane repair significantly amplifies GSDM-mediated pyroptosis in tumors, further boosting antitumor immune responses.[63] In breast cancer, caspase-3/GSDME-dependent pyroptosis directly drives antitumor immunity.[64] Interestingly, in colorectal cancer (CRC), nuclear localization of GSDMD (rather than cytoplasmic) is associated with favorable clinical outcomes. Under hypoxic or chemotherapeutic conditions, GSDMD translocates to the nucleus, where it interacts with PARP-1 to inhibit DNA damage repair. This promotes apoptosis rather than pyroptosis, revealing a previously unrecognized, pyroptosis-independent function of GSDMD.[65] Furthermore, pyroptosis induced by natural compounds or chemotherapeutic agents has demonstrated clear potential to suppress tumor cell proliferation and migration.[58,66] Collectively, these findings suggest that carefully controlled induction of pyroptosis could serve as a powerful strategy to enhance the efficacy of existing cancer therapies.

2.2.3. Pro-tumor effects of pyroptosis

Although pyroptosis often exerts antitumor effects, it can also promote tumor progression in certain cancer types or microenvironments, highlighting its clear context-dependent and dual nature. The molecular bifurcation determining whether pyroptosis acts as a tumor suppressor or a promoter depends heavily on the baseline immune status of the TME and treatment timing. Acute, high-dose activation of gasdermins triggers a robust release of immunogenic DAMPs that effectively recruit and prime cytotoxic T cells. Conversely, chronic, low-grade pyroptosis in established, immunologically "cold" tumors fosters a persistent inflammatory milieu that paradoxically recruits myeloid-derived suppressor cells via a C-X-C motif chemokine ligand 2-dependent manner, thereby driving tumor progression and immune evasion. For example, while GSDME generally mediates antitumor pyroptosis across many cancer types, chemotherapy-induced GSDME-dependent pyroptosis may paradoxically accelerate tumor progression and chemoresistance in pancreatic cancer.[67] Similarly, GSDME displays specific pro-tumor activity in HCC.[68] In CRC, caspase-6/GSDMC-mediated pyroptosis in tumor cells recruits myeloid-derived suppressor cells via a C-X-C motif chemokine ligand 2-dependent mechanism, thereby driving tumor advancement.[61] These findings indicate that the biological outcomes of pyroptosis are highly dependent on tumor type, microenvironmental conditions, and the expression levels of specific GSDM proteins. Chronic or dysregulated pyroptosis may foster a pro-TME through persistent inflammation and immunosuppression.[69,70] Therefore, in clinical translation, it is essential to carefully evaluate the dual role of pyroptosis to avoid potential adverse effects.[67,71]

2.3. Antitumor strategies based on pyroptosis induction

In recent years, accumulating evidence has shown that precisely triggering pyroptosis in tumor cells can produce multiple anti-cancer effects, including direct tumor necrosis, enhanced chemosensitivity, and robust immune activation. This approach has become an important

emerging strategy in cancer immunotherapy.

2.3.1. Targeting the gasdermin family for pyroptosis induction in cancer

The GSDM family proteins are the central targets for inducing pyroptosis. For instance, GSDME-mediated pyroptosis plays multiple roles in antitumor immunity. Strategies aimed at restoring GSDME expression or promoting its cleavage are promising, though they must overcome the common epigenetic silencing of GSDME observed in many cancer cells.[72] GSDMD regulation in tumors is particularly complex. Depending on the context, it can either facilitate immune evasion or promote tumor cell death. Moreover, GSDMD contributes to chemosensitization through both nuclear translocation and membrane pore formation. It therefore represents an attractive therapeutic target that small molecules or genetic approaches can modulate.[21,65] GSDMC, specifically induced downstream of PD-L1, has opened new therapeutic possibilities in breast cancer and lung cancer.[52,61] Other family members, such as GSDMB, also modulate inflammation and antitumor immunity through distinct mechanisms.[60] Taken together, the GSDM family serves as a key nexus connecting pyroptosis, inflammation, and the TME. It regulates not only the fate of tumor cells but also the function of immune cells. Developing highly specific agonists or inhibitors targeting these proteins is likely to become a major focus in future research.[70,73,74]

2.3.2. Drug- and natural product-induced pyroptosis via gasdermin proteins

The dual regulatory characteristics of endogenous and exogenous pyroptosis provide strong support for the development of personalized antitumor strategies targeting the GSDM protein.[75] Traditional chemotherapeutic agents have long been among the most direct inducers of pyroptosis. Various chemotherapeutic agents can trigger pyroptosis via the caspase-3/GSDME or GSDMD pathways, thereby inhibiting tumor cell proliferation and migration while releasing pro-inflammatory factors that recruit immune cells.[58,66] In renal cell carcinoma, the SHP2 allosteric inhibitor SHP099 synergizes with interferon alpha to markedly enhance antitumor immunity. SHP099 upregulates pro-caspase-1 expression, activates the NLRP3 inflammasome, and induces caspase-1-dependent pyroptosis. At the same time, it promotes T cell proliferation and infiltration, leading to effective tumor clearance and the establishment of systemic immune memory. Notably, this effect is superior to that of conventional enzymatic inhibitors.[76] Natural compounds also show considerable promise. Small-molecule agents can specifically activate GSDMD or GSDME, inducing pyroptosis and exerting antitumor effects.[58] Interestingly, many natural products exhibit bidirectional regulation of pyroptosis in the context of cancer-related inflammation. For instance, astragaloside IV exerts context-dependent effects through the nuclear factor erythroid 2-related factor 2 (NRF2)/heme oxygenase-1 pathway or the reactive oxygen species (ROS)–NLRP3 axis: it protects normal tissues by inhibiting chronic inflammation-associated pyroptosis, while simultaneously inducing tumor cell pyroptosis via the caspase-1/GSDMD pathway in cancers such as gastric cancer (GC).[77] Curcumin stabilizes the NLRP3 inflammasome by inhibiting Smurf2-mediated ubiquitination, promoting pyroptosis in the TME, while suppressing the NLRP3/ROS pathway during chronic inflammation. This dual regulatory capacity offers a solid rationale for combining natural products with anti-cancer therapies.[78] Yuan *et al.*[79] demonstrated that cucurbitacin B induces GSDMD-dependent pyroptosis in non-small cell lung cancer by activating the NLRP3 inflammasome, promoting mitochondrial ROS production, Tom20 accumulation, and Ca^{2+} influx following direct binding to Toll-like receptor 4. Additionally, cucurbitacin B can trigger GSDME-mediated cell death in oral squamous cell carcinoma and inhibit tumor growth.[80,81] In breast cancer, GSDME-mediated pyroptosis directly enhances antitumor immune responses.[64] However, tissue specificity must be carefully considered. For instance, chemotherapy-induced GSDME pyroptosis may actually promote tumor progression and chemoresistance in pancreatic cancer, underscoring the need for tumor type-specific evaluation in clinical applications.[67] Overall, these drug-induced strategies are relatively straightforward to implement and have demonstrated synergistic antitumor effects across multiple tumor models.[66,75]

2.3.3. Nanotechnology-enhanced pyroptosis and combination therapy

Nanomaterial-assisted combination therapy has emerged as another promising frontier. It enables precise delivery and controlled release of GSDM for activation, while also helping manage the double-edged effects of pyroptosis—essentially allowing researchers to fine-tune the process with "brakes or acceleration" as needed. Nano-delivery systems can trigger tumor-specific pyroptosis by precisely modulating the intracellular environment. For example, Shi *et al.*[82] developed a photo-chemodynamic nanoplatform ($Na_2S_2O_8$-IR780 nanoparticle) that reshapes osmotic pressure and redox homeostasis in CRC cells. This led to a ROS burst, NLRP3 inflammasome activation, and GSDMD cleavage, effectively reversing chemoresistance and driving tumor regression. By regulating osmotic and redox balance, this platform offers a novel therapeutic

paradigm for CRC and shows strong potential for clinical translation.[82] However, simply inducing pyroptosis can sometimes be limited by rapid plasma membrane repair. Therefore, blocking ESCRT-dependent membrane repair has become an important enhancement strategy in recent years. Studies show that inhibiting ESCRT significantly prolongs the lifetime of GSDM-induced membrane pores, thereby amplifying tumor pyroptosis and strengthening antitumor immune responses.[63] In addition, stress regulation of organelles such as mitochondria and lysosomes provides a fresh perspective for pyroptosis induction. Targeting these organelles can further enhance ICD and robustly activate antitumor immunity.[62] When combined with traditional chemotherapy or ICIs, these innovative strategies are expected to significantly improve therapeutic efficacy.

Despite its substantial therapeutic promise, pyroptosis induction still faces several notable challenges: low GSDME expression in many cancer cells, the risk of pro-tumor effects following induction (such as immunosuppression in specific tumor types), and significant tissue-specific differences. A pressing issue that needs to be addressed is how to trigger pyroptosis while avoiding unwanted chronic inflammatory side effects effectively.[71,83] Looking forward, advances in single-cell sequencing and clustered regularly interspaced short palindromic repeats screening technologies are expected to enable the development of GSDM expression-based biomarkers to guide precision therapy. Moreover, the combination of smart nano-delivery systems and ESCRT inhibitors holds great potential for safer, more efficient induction of pyroptosis. Ultimately, pyroptosis-targeted strategies are poised to form synergistic networks with existing immunotherapies and chemotherapies, offering new hope for patients with refractory cancers.

3. Ferroptosis: Its role in cancer therapy and regulatory strategies

Ferroptosis is an iron-dependent, non-apoptotic form of PCD driven by lethal LPO. Morphologically, it is characterized by mitochondrial shrinkage, reduced or absent cristae, and increased membrane density. Biochemically, it features intracellular accumulation of free ferrous iron (Fe^{2+}), fatal accumulation of peroxides of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), and inactivation of cellular antioxidant defense systems. This process differs markedly from apoptosis, autophagy, and necroptosis. It has emerged as a critical regulatory mechanism of cell death in various pathological conditions, including cancer, cardiovascular diseases, and neurodegenerative disorders.[84-86] In recent years, the discovery of key regulators such as GPX4 and ferroptosis suppressor protein 1 (FSP1) has helped clarify the molecular framework of ferroptosis, which is now understood as a "drive–defense" dual-system balance. This conceptual advance has laid a solid theoretical foundation for precise therapeutic intervention.[87] This section reviews ferroptosis from three perspectives: its molecular mechanisms, its relationship with cancer, and current antitumor strategies that induce ferroptosis. It also explores the dual regulatory potential of ferroptosis in precision cancer therapy and its prospects for clinical translation.

3.1. Molecular mechanisms of ferroptosis

The occurrence of ferroptosis depends on the synergistic interplay among three key processes: LPO, dysregulated iron metabolism, and excessive ROS generation. LPO is the hallmark of ferroptosis. PUFAs serve as the primary substrates for LPO during ferroptosis, but they are not the direct drivers of LPO. They must first be esterified into PLs before undergoing peroxidation. Acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the esterification of PUFAs to form PUFA-CoA, which is then incorporated into membrane PLs by the lysophosphatidylcholine acyltransferase 3 (LPCAT3). This generates PUFA-PLs that are highly susceptible to oxidation into PL hydroperoxides (PL–OOH).[88] Enzymatic LPO of PUFA-PLs primarily involves lipoxygenases (ALOX) and cytochrome P450 oxidoreductase (POR).[89,90] Several ALOX inhibitors have been shown to possess antioxidant properties and effectively protect cells from LPO. In contrast, POR directly supplies electrons to P450 enzymes, which catalyze PUFA-PL peroxidation in an ALOX-independent manner.[84,91] In summary, the accumulation of PL-OOH compromises membrane integrity, ultimately resulting in cell death.

Dysregulation of iron metabolism is a central driver of ferroptosis. Circulating iron primarily exists as ferric iron (Fe^{3+}), which binds to transferrin (TF) and enters cells via TF receptor 1 (TFR1)-mediated endocytosis. Inside the endosome, six transmembrane epithelial antigen of the prostate 3 (STEAP3) reduces Fe^{3+} to Fe^{2+}, which is then released into the cytoplasm through SLC11A2 (DMT1), forming the labile iron pool (LIP). Fe^{2+} in the LIP catalyzes the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$), generating highly reactive hydroxyl radicals that drive non-enzymatic LPO of PUFA-PLs, ultimately triggering ferroptosis.[85,92,93] Excess intracellular iron is mainly stored in ferritin, composed of FTH1 and FTL subunits, and can be released through NCOA4-mediated ferritinophagy. Excess Fe^{2+} is exported from the cell via SLC40A1. Consequently, loss of TF, TFR1, DMT1, or

NCOA4, or overexpression of FTH1/FTL and SLC40A1, reduces LIP levels and suppresses ferroptosis. Conversely, increased iron uptake, decreased storage, or blocked export markedly sensitizes cells to ferroptosis. In particular, TFR1 upregulation, combined with FTH1/FTL downregulation, further increases LIP levels and accelerates the Fenton reaction.

Amino acid metabolism also plays a critical role. The cystine/glutamate antiporter System Xc⁻ (composed of SLC7A11 and SLC3A2) mediates cystine uptake, which is essential for glutathione (GSH) synthesis. GSH serves as a crucial cofactor for GPX4, whose primary function is to reduce PL-OOH, thereby preventing ferroptosis. When System Xc− is inhibited or GPX4 activity is reduced, PL-OOH cannot be effectively cleared, leading to excessive ROS accumulation and ferroptosis.[94,95] In summary, both exogenous triggers (such as reduced cystine uptake or increased iron import) and endogenous pathways (such as direct GPX4 inhibition) can induce ferroptosis through ROS accumulation and lipid peroxide overload (Figure 2).

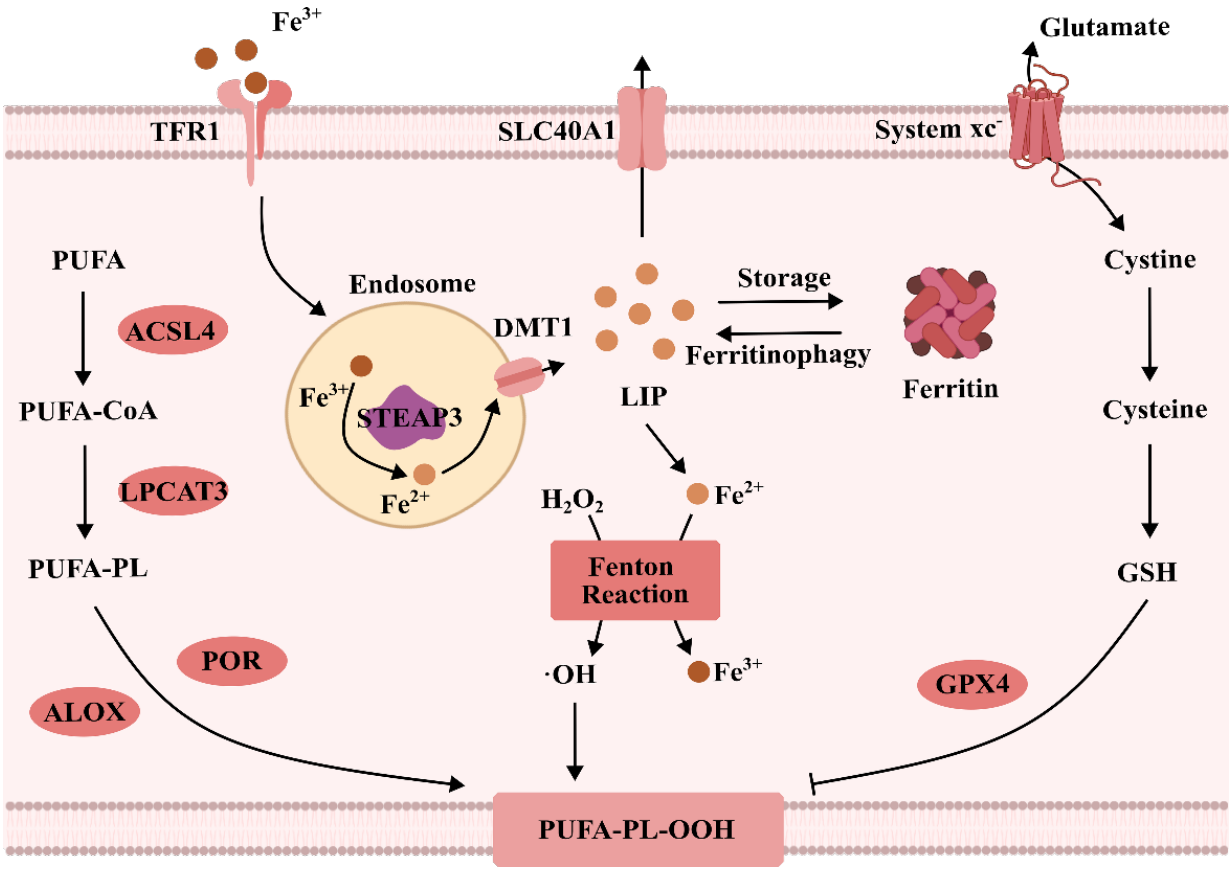


Figure 2. Schematic overview of the ferroptosis regulatory pathways. The diagram illustrates the key molecular mechanisms underlying ferroptosis, an iron-dependent form of regulated cell death characterized by lethal lipid peroxidation. Iron (Fe^{3+}) is imported via TFR1 and reduced to Fe^{2+} by STEAP3 within the endosome, followed by transport into the cytosol via DMT1. Cytosolic LIP Fe^{2+} can participate in the Fenton reaction with hydrogen peroxide (H_2O_2) to generate highly reactive hydroxyl radicals (•OH), which initiate lipid peroxidation. PUFAs are activated by ACSL4 to PUFA-CoA and incorporated into phospholipids by LPCAT3 to form PUFA-PL. These membrane phospholipids are then oxidized to PUFA-PL-OOH through the actions of POR and ALOX. GPX4 counteracts ferroptosis by reducing PUFA-PL-OOH to non-toxic alcohols using GSH as a cofactor. GSH is synthesized from cysteine, which is imported via the System xc⁻ antiporter (SLC7A11) in exchange for glutamate. Excess iron is stored in ferritin, and its autophagic degradation (ferritinophagy) can increase the LIP. SLC40A1-mediated iron export. Disruption of antioxidant defenses or excessive iron and lipid peroxidation drives ferroptotic execution. The diagram was generated using MedPeer (www.medpeer.cn).

Abbreviations: ACSL4: Acyl-CoA synthetase long-chain family member 4; ALOX: Arachidonate lipoxygenase; DMT1: Divalent metal transporter 1; Fe: Iron; GPX4: Glutathione peroxidase 4; GSH: Glutathione; H_2O_2: Hydrogen peroxide; LIP: Labile iron pool; LPCAT3: Lysophosphatidylcholine acyltransferase 3; •OH: Hydroxyl radical; POR: Cytochrome P450 oxidoreductase; PUFA: Polyunsaturated fatty acid; PUFA-CoA: Polyunsaturated fatty acyl-coenzyme A; PUFA-PL: Polyunsaturated fatty acid-containing phospholipid; PUFA-PL-OOH: Phospholipid hydroperoxide; SLC7A11: Solute carrier family 7 member 11; SLC40A1: Solute carrier family 40 member 1; STEAP3: Six-transmembrane epithelial antigen of prostate 3; System xc⁻: Cystine/glutamate antiporter; TFR1: Transferrin receptor 1.

3.2. The relationship between ferroptosis and cancer

Ferroptosis is characterized by the accumulation of free ferrous iron (Fe^{2+}), fatal buildup of PUFA-PLs, and inactivation of cellular antioxidant defense systems. This process is closely intertwined with cancer initiation, progression, and treatment response. On one hand, ferroptosis can act as a natural tumor-suppressive mechanism, effectively restraining cancer development. On the other hand, under certain conditions, it may paradoxically promote tumor progression. This context-dependent dual role makes its relationship with cancer particularly complex.

3.2.1. Activation pathways of ferroptosis in tumor cells

Ferroptosis in tumor cells is primarily triggered by disrupting the delicate balance between the "drive" and "defense" systems. The drive system comprises dysregulated iron metabolism, LPO, and excessive ROS production. Upregulation of TFR1 increases Fe^{2+} uptake, while downregulation of ferritin enlarges the LIP. This leads to the generation of hydroxyl radicals via the Fenton reaction. Meanwhile, ACSL4 and LPCAT3 promote the esterification of PUFAs into oxidizable PUFA-PLs, further amplifying LPO.[87] The defense system is centered on the System Xc^-/GSH/GPX4 axis. Reduced cystine uptake mediated by SLC7A11/SLC3A2 causes GSH depletion, which in turn inactivates GPX4 and prevents the clearance of PL-OOH. In addition, emerging bypass defense pathways such as FSP1-CoQ10, DHODH-CoQ10, and GCH1-BH4 also play important regulatory roles within the TME.[87,96] Ferroptosis can be activated through two main routes: exogenous pathways (e.g., inhibition of transporters like System Xc^- leading to reduced cystine import) and endogenous pathways (e.g., direct suppression of enzyme activity, such as GPX4 inhibition). Metabolic reprogramming in tumor cells (e.g., aberrant NRF2 or p53 signaling) can further amplify these pathways, making ferroptosis more readily triggered in certain cancers such as pancreatic cancer and G.[97-100] Notably, in cisplatin-resistant intrahepatic cholangiocarcinoma (ICC) cells, METTL3 overexpression stabilizes NRF2 mRNA through m6A modification, leading to elevated NRF2 protein levels. This suppresses ferroptosis and promotes chemoresistance. The METTL3/NRF2 axis thus represents a key regulatory mechanism in ICC cisplatin resistance and a potential therapeutic target for reversing drug resistance.[101] These molecular mechanisms lay the foundation for both the antitumor and pro-tumor effects of ferroptosis observed in different contexts.

3.2.2. Tumor-suppressive role of ferroptosis

Ferroptosis generally exerts a strong tumor-suppressive effect and acts as a natural defense mechanism against cancer, particularly in mesenchymal-like or dedifferentiated cancer cells that are resistant to apoptosis.[102,103] By triggering LPO and membrane damage, ferroptosis can directly kill tumor cells, inhibit proliferation, invasion, and metastasis, and has shown clear antitumor effects in various solid tumors, including lung, gastric, and pancreatic cancers.[97,104,105] Its anti-cancer effect also involves immune activation and remodeling of the TME.[106] Ferroptotic cells release DAMPs that promote dendritic cell maturation, enhance $CD8^+$ T cell infiltration, and stimulate antitumor immune responses, thereby improving the effectiveness of immunotherapy.[107,108] Within the TME, ferroptosis can act synergistically with radiotherapy, chemotherapy, and ICIs, producing a cascading amplification effect that helps overcome multidrug resistance (MDR) and improve treatment outcomes.[109,110] Multiple studies have shown that targeting ferroptosis pathways is an important strategy to overcome the limitations of conventional therapies and holds great promise for clinical application.[102,111]

3.2.3. Pro-tumor effects of ferroptosis

Similarly, the dual nature of ferroptosis is rigorously shaped by the tissue-specific metabolic context and disease stage. While ferroptotic lipid peroxidation directly restrains malignancy in early-stage, dedifferentiated tumors, sustained ferroptotic cell death in advanced, inflammation-associated solid cancers can release chronic inflammatory mediators such as arachidonic acid metabolites. These products impair local dendritic cell maturation and facilitate tumor angiogenesis, transforming a potentially antitumor event into a pro-tumor supportive mechanism.[108] In particular, in TME or inflammatory settings, ferroptosis-derived DAMPs and LPO products may trigger chronic inflammation, promote the recruitment of immunosuppressive cells, or support tumor cell survival through metabolic reprogramming, ultimately facilitating tumor growth.[96,107,112] For instance, in gastric and pancreatic cancers, aberrant activation of ferroptosis-related pathways may interact with the local inflammatory milieu, indirectly enhancing angiogenesis and metastasis.[105] This pro-tumor effect is strongly tissue-dependent. Variations in the expression of ferroptosis defense pathways, such as GPX4 and SLC7A11, lead to differences in ferroptosis sensitivity across cancer types. In inflammation-associated tumors, ferroptosis may further aggravate tissue damage and contribute to the formation of a tumor-promoting microenvironment.[108] These findings suggest that careful evaluation of tumor type, microenvironmental context, and patient-specific factors is necessary when considering ferroptosis-targeted therapies to minimize potential adverse effects. In summary, the

relationship between ferroptosis and cancer is inherently dualistic. While its activation provides a molecular basis for tumor suppression, it may also, in certain tissues and microenvironments, drive tumor progression. A deeper understanding of this complexity could open new avenues for more precise and individualized cancer treatment strategies.

3.3. Antitumor strategies based on ferroptosis

The therapeutic value of ferroptosis stems primarily from its ability to induce the accumulation of PL-OOH in tumor cells, thereby circumventing conventional apoptosis resistance and effectively eliminating malignant cells. Notably, this approach appears particularly effective in tumor subtypes with mesenchymal features, poor differentiation, or resistance to chemotherapy. In recent years, efforts to harness ferroptosis have expanded from targeting specific molecular pathways to incorporating nanocarrier-based delivery systems and combination treatment strategies. Together, these developments are shaping a more integrated therapeutic framework and offer new possibilities for overcoming drug resistance in clinical settings.[110,111,113]

3.3.1. Molecular targets and pharmacological strategies

At the molecular level, one of the best-characterized targets is the system Xc^-/GSH/GPX4 axis. Blocking SLC7A11 disrupts cystine uptake, thereby depleting GSH and inactivating GPX4,[114] ultimately leading to the accumulation of compounds such as RSL3 or ML162, which prevent the detoxification of phospholipid peroxides and drive ferroptotic cell death.[87,115,116] Beyond this classical pathway, several parallel defense systems have also been identified, including FSP1-CoQ10, DHODH-CoQ10, and GCH1-BH4. Targeting these pathways can further increase cellular susceptibility to ferroptosis.

Drug repurposing has emerged as a practical approach in this context. For example, tyrosine kinase inhibitors such as sorafenib can indirectly inhibit system Xc^-. At the same time, approved drugs like fenbendazole have been reported to induce ferroptosis by modulating iron metabolism or promoting LPO.[110,111] In HCC, sorafenib-induced ferroptosis is accompanied by a dose- and time-dependent reduction in DDX39B expression. Mechanistically, DDX39B enhances GPX4 expression by facilitating the splicing and cytoplasmic export of GPX4 pre-mRNA, thereby reducing lipid ROS accumulation and suppressing ferroptosis. This effect contributes to sorafenib resistance in HCC cells.

In contrast, inhibiting DDX39B markedly increases ferroptosis and improves the response to sorafenib, suggesting that DDX39B is a potential therapeutic target to enhance drug sensitivity.[117] In pancreatic cancer cells, the ferroptosis inducer erastin promotes ROS accumulation and cell death while simultaneously upregulating clusterin. Overexpression of clusterin, however, counteracts this effect by maintaining GPX4 enzymatic activity—without altering GSH levels—thereby reducing ROS production and limiting ferroptosis.[118] Another example comes from a linoleic acid–glucosamine conjugate (LA-GlcN) developed by Chen *et al.*[119] This compound leverages GLUT1 overexpression in tumor cells to enhance uptake via its glucosamine moiety. At the same time, the linoleic acid component drives iron-dependent LPO in the high-iron environment of high-grade serous ovarian cancer, ultimately triggering ferroptosis and achieving selective cytotoxicity.[119] In difficult-to-treat cancers such as gastric and pancreatic tumors, these ferroptosis-based strategies have been shown to suppress tumor growth and metastasis effectively.[97,104,105] More broadly, by precisely targeting iron metabolism—such as upregulating *TFR1* and downregulating *FTH1*—and reshaping lipid pathways through activation of ACSL4 and LPCAT3, ferroptosis inducers can selectively eliminate apoptosis-resistant cancer cells, providing a molecular basis for more personalized anti-cancer therapies.[104]

3.3.2. Natural products inducing ferroptosis in cancer

Bioactive compounds can also suppress tumor growth and metastasis by triggering ferroptosis.[120] Among natural products, alkannin has been shown to markedly inhibit the proliferation, migration, and invasion of GC cells, while simultaneously inducing apoptosis and ferroptosis. Mechanistically, it downregulates c-Fos expression, thereby blocking c-Fos–mediated transcriptional activation of the SREBF1 promoter. This leads to reduced lipid biosynthesis, disruption of lipid homeostasis and redox balance, and ultimately exerts antitumor effects, highlighting its potential as a therapeutic candidate for GC.[121] Resveratrol, a natural polyphenol, has also been reported to induce ferroptosis in tumor settings. It appears to act by influencing LPO, iron accumulation, and signaling pathways such as Sirt1/Nrf2, contributing to its anti-cancer activity.[122] Gambogenic acid, a derivative of gambogic acid, shows broad antitumor activity across multiple cancer types, including lung, liver, colorectal, and breast cancers. As a novel enhancer of zeste homolog 2 inhibitor, it suppresses tumor growth and metastasis through multiple mechanisms, including induction of apoptosis, ferroptosis, necroptosis, autophagy, and cell-cycle arrest. In addition, it enhances sensitivity to chemotherapy and helps overcome MDR.[123] The natural PLA2 inhibitor manoalide induces ferroptosis through

several interconnected mechanisms, including promoting mitochondrial ROS generation and LPO, inhibiting fatty acid oxidation, and activating endoplasmic reticulum stress. At the same time, it suppresses the Kirsten rat sarcoma viral oncogene homolog–extracellular signal-regulated kinase pathway and the NRF2–SLC7A11/FTH1 axis. These effects significantly increase the sensitivity of *KRAS*-mutant and osimertinib-resistant lung cancer cells and organoids to osimertinib, suggesting a potential role in enhancing epidermal growth factor receptor–tyrosine kinase inhibitor efficacy.[124] Another compound, tanshinol A, induces cell death in lung cancer cells through a ROS-dependent mechanism that activates mixed lineage kinase domain-like pseudokinase phosphorylation and membrane translocation. This process represents a noncanonical form of programmed necrosis that is independent of RIP1/RIP3 signaling and is characterized by cell swelling, membrane rupture, and adenosine triphosphate (ATP) depletion, indicating its potential therapeutic relevance in lung cancer.[125] Despite the extensive preclinical promise of these plant-derived natural products, their clinical translation is strictly bottlenecked by formidable pharmacological limitations. Most bioactive compounds suffer from poor oral bioavailability, low aqueous solubility, and rapid systemic clearance, requiring high doses that elevate the risk of off-target toxicities. Furthermore, the lack of strict target specificity, variable batch-to-batch quality control of herbal extracts, and a scarcity of large-scale, well-validated clinical trials mean that current evidence remains largely preliminary and far from therapeutic readiness.

3.3.3. Combination strategies and nano-delivery systems for ferroptosis therapy

The combination of ferroptosis induction with chemotherapy, radiotherapy, immunotherapy, and photodynamic therapy (PDT) has become a key direction in current anti-cancer strategies.[14,126] Ferroptosis is also closely linked to reversing MDR. In many chemotherapy-resistant tumors, GPX4 and SLC7A11 are often upregulated; introducing ferroptosis inducers in this context can markedly improve chemosensitivity.[102,111] Radiotherapy generates ROS, which can directly enhance LPO. When combined with ferroptosis-inducing agents, this effect is further amplified, helping to overcome radioresistance and resulting in a stronger cytotoxic response.[104] In the context of immunotherapy, ferroptotic cells release DAMPs that promote dendritic cell maturation and facilitate $CD8^+$ T cell infiltration. These changes reshape the TME and can improve the efficacy of PD-1/PD-L1 blockade.[107,108] Ferroptosis can also be integrated with PDT. PDT-generated singlet oxygen boosts the ROS–LPO axis, creating a "photo-chemical" cascade that further amplifies tumor cell damage.[127] Taken together, these combination approaches have demonstrated strong antitumor activity in solid tumors such as lung and CRCs, offering a more integrated framework for systemic cancer treatment.[109,110,127,128]

To overcome the instability and off-target toxicity of ferroptosis inducers *in vivo*, nano-delivery systems have become a key platform for anti-cancer therapy. Liposomes, polymeric nanoparticles, and graphene oxide can efficiently deliver GPX4 inhibitors, Fe^{2+} donors, or system Xc^- inhibitors, enabling tumor-specific release and improving therapeutic precision.[102,111,129] These systems also enable co-delivery with chemotherapeutic agents, thereby enhancing efficacy while reducing systemic toxicity.[104] Several nanoplatforms have demonstrated promising synergistic effects. Matrix metalloproteinase-2-responsive PTX@CPG enhances ROS generation and induces ferroptosis in combination with PDT, overcoming chemoresistance in triple-negative breast cancer.[130] Kanglaite combined with iron promotes ferroptosis via PI3K/AKT inhibition and mitochondrial dysfunction, and its nanoformulation (DMSN/Fe_3O_4–Kanglaite) shows strong *in vivo* antitumor activity.[131] Multifunctional nano-reactors further integrate ferroptosis with other therapeutic modalities. For instance, IR780/Ce@EGCG nanoplatforms induce ROS generation, mitochondrial damage, and ferroptosis while enhancing antitumor immunity.[132] GSH-responsive CPT-IR820 systems deplete GSH, inactivate GPX4, and amplify LPO via photothermal effects, thereby effectively suppressing CRC growth.[133] Similarly, Fe–HCOF–PEG2000 combines photodynamic effects with ferroptosis induction, achieving enhanced tumor killing under both normoxic and hypoxic conditions.[134] Other designs further highlight combinational potential. FSR–Fin56 integrates photothermal and chemodynamic therapy to induce ferroptosis in osteosarcoma,[135] while DOC@TA–Fe^{3+} simultaneously triggers ferroptosis and apoptosis for synergistic antitumor effects.[136] Biomimetic AE@RBC/Fe nanoparticles improve oxygen delivery for PDT and induce ferroptosis, thereby enhancing tumor targeting and therapeutic efficacy.[137] In addition, HL/MOS@M780&LOD nanoparticles combine metabolic starvation, PDT, and ferroptosis induction to suppress tumor metastasis.[138] Overall, nanotechnology-based ferroptosis strategies provide a versatile platform for combination therapy, offering improved targeting, enhanced efficacy, and potential for clinical translation.

Although ferroptosis-based therapies show considerable promise in cancer treatment, several challenges remain. Issues such as the lack of standardized biomarkers, tumor heterogeneity, and the potential risk of tumor-promoting

effects still need to be addressed. Sensitivity to ferroptosis varies widely across cancer types, necessitating more precise patient stratification, for example, by integrating single-cell sequencing with metabolomic profiling.[108] In addition, the systemic toxicity and long-term safety of ferroptosis inducers require further evaluation.

4. Molecular mechanisms and therapeutic potential of cuproptosis in cancer

Cuproptosis is characterized by copper-induced mitochondrial protein toxicity and largely depends on the disruption of intracellular copper homeostasis, particularly the abnormal accumulation of copper within the mitochondrial matrix, which ultimately impairs mitochondrial respiration and leads to cell death.[139] In this section, we focus on three aspects: the molecular mechanisms underlying cuproptosis, its relationship to cancer, and emerging therapeutic strategies to induce cuproptosis. Together, these perspectives highlight its potential role in understanding cancer biology and its possible applications in clinical settings.

4.1. Molecular mechanisms of cuproptosis

Intracellular copper homeostasis is tightly regulated by a series of transporters, including copper transporter 1 and ATP7A/B. Under physiological conditions, copper mainly exists as Cu^{2+} in the cytosol. After entering mitochondria, it must be reduced to Cu^{+} by specific reductases to become biologically active.[139] When copper overload occurs, or its transport is disrupted, excess Cu^{2+} accumulates in the mitochondrial matrix, thereby initiating cuproptosis.[140] Studies have shown that mitochondrial copper overload is essential for this process, whereas increased cytosolic copper or lysosomal copper accumulation alone is insufficient to trigger it.[141,142] In addition, depletion of copper-buffering molecules such as metallothioneins and GSH, or dysregulation of the iron–sulfur cluster reductase FDX1, can further exacerbate mitochondrial copper toxicity.[143]

At the upstream level, FDX1 plays a central role. It catalyzes the reduction of Cu^{2+} to Cu^{+} within mitochondria, a step required for copper to exert its toxic effects.[26,141] Loss of FDX1 effectively blocks copper-induced cell death, whereas its overexpression increases cellular sensitivity to copper.[142] Beyond this, FDX1 is also involved in the biogenesis of iron–sulfur cluster proteins. Impaired FDX1 activity can destabilize downstream iron–sulfur proteins, such as lipoic acid synthetase and NADH: ubiquinone oxidoreductase iron–sulfur proteins, thereby further compromising mitochondrial function.[144,145] For this reason, FDX1 is often considered a key regulatory switch in the cuproptosis pathway. Once generated, Cu^{+} directly binds with high affinity to lipoylated proteins in the TCA cycle. Major targets include dihydrolipoamide S-acetyltransferase (DLAT; the E2 subunit of the PDH complex) and other lipoylated enzymes such as dihydrolipoamide S-succinyltransferase and oxoglutarate dehydrogenase.[26,146] This interaction drives abnormal oligomerization of these proteins, leading to the formation of high-molecular-weight aggregates and triggering severe proteotoxic stress and activation of the mitochondrial unfolded protein response.[140,147] The accumulation of protein aggregates disrupts TCA cycle enzyme complexes and impairs electron transport in the mitochondrial respiratory chain, ultimately resulting in ATP depletion and cell death.[148,149] Multi-omics analyses further indicate that lipoylation provides the structural basis for Cu^{+} recognition, as non-lipoylated TCA proteins remain largely unaffected, highlighting the specificity of cuproptosis.[150]

Another key event in cuproptosis involves the loss of iron–sulfur cluster proteins. Proteotoxic stress induced by Cu^{+} can disrupt iron–sulfur cluster assembly, leading to the inactivation of essential components of the respiratory chain and the TCA cycle, including NADH: ubiquinone oxidoreductase core subunit S1, succinate dehydrogenase complex iron sulfur subunit B, and lipoic acid synthetase.[26,151] This process shows some overlap with ferroptosis, as both involve mitochondrial metal ion toxicity. However, their underlying mechanisms differ: cuproptosis is primarily driven by protein aggregation, whereas ferroptosis is centered on LPO.[151] In later stages, cuproptosis is typically accompanied by mitochondrial membrane depolarization, a burst of ROS, and mitochondrial structural fragmentation.[140,152] Experimental evidence indicates that cuproptosis proceeds independently of canonical apoptosis (caspase-dependent), necroptosis (receptor-interacting protein kinase/mixed lineage kinase domain-like protein), and ferroptosis (GPX4/LPO) pathways.[26,153] Inhibiting BCL-2 family proteins, caspases, or GPX4 does not prevent copper-induced cell death. In contrast, supplementing with lipoylation precursors, such as lipoic acid, or reducing DLAT expression can markedly attenuate this process.[141,154] This independence highlights cuproptosis as a distinct form of cell death and provides a rationale for developing selective copper ionophores.

In brief, cuproptosis follows a cascade: mitochondrial copper overload to FDX1-driven Cu^{2+} reduction to Cu^{+}, followed by binding to lipoylated TCA proteins (e.g., DLAT), protein aggregation and proteotoxic stress, iron–sulfur cluster disruption, and mitochondrial failure and cell death. This mechanism has been confirmed across multiple cellular models[155-157] (Figure 3). With the development of

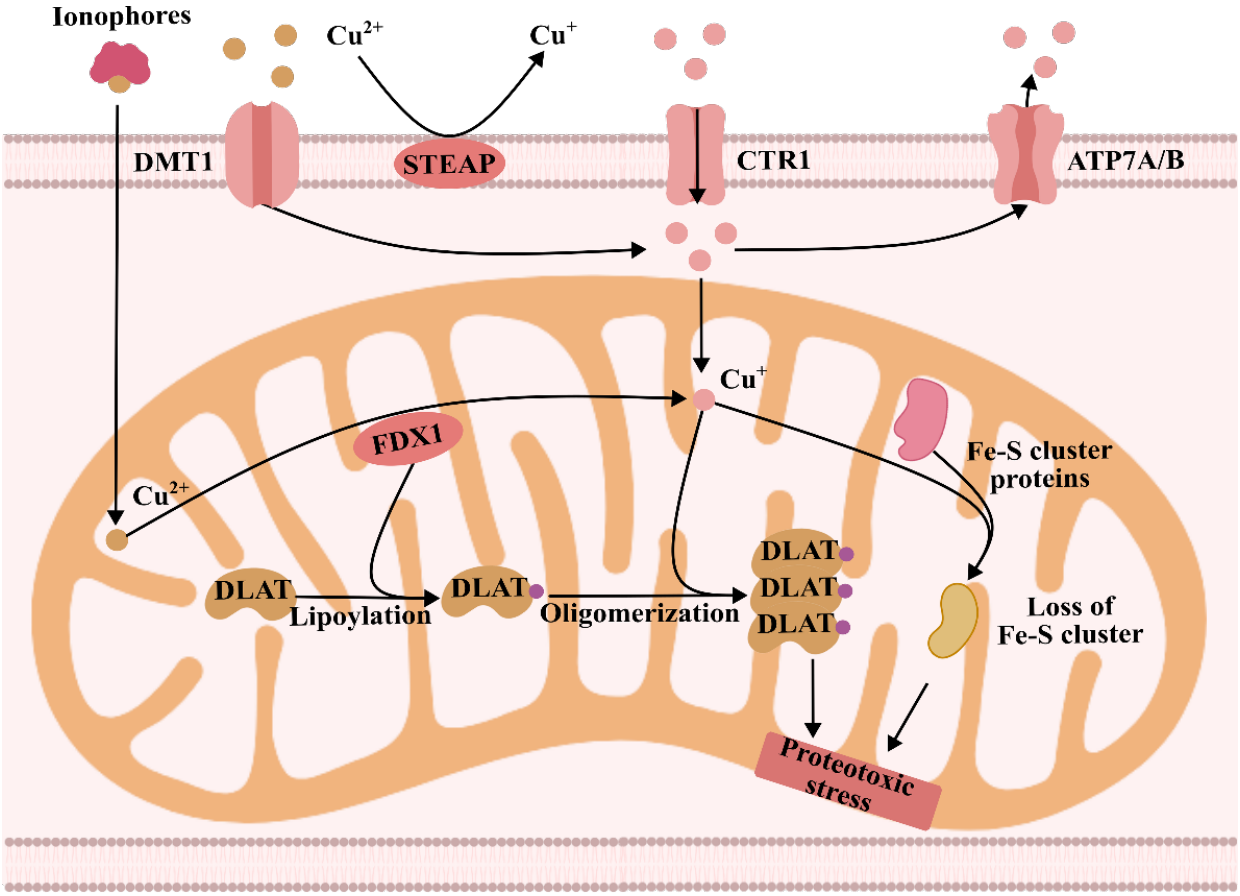


Figure 3. Schematic illustration of copper uptake, intracellular trafficking, and copper-induced proteotoxic stress via DLAT oligomerization in mitochondria. Copper ions (Cu^{2+}/Cu^{+}) enter cells through multiple routes, including DMT1 (ionophore-facilitated), the metalloreductase STEAP, and the high-affinity copper transporter CTR1. ATP7A/B exports excess cytosolic Cu to maintain copper homeostasis. Within mitochondria, FDX1 plays a central role by catalyzing the reduction of Cu^{2+} to Cu^{+}, a critical step in copper toxicity. The resulting Cu^{+} binds to the lipoylated lysine residues of the E2 subunit of the pyruvate dehydrogenase complex (DLAT) and other lipoylated TCA cycle proteins. This binding induces DLAT oligomerization, triggering profound proteotoxic stress. In parallel, copper disrupts iron–sulfur cluster proteins, further contributing to mitochondrial dysfunction. The pathway culminates in mitochondrial respiratory failure and cell death. The diagram was generated using MedPeer (www.medpeer.cn).
Abbreviations: ATP7A/B: ATPase copper transporting alpha/beta; CTR1: Copper transporter 1; Cu: Copper; DLAT: Dihydrolipoamide S-acetyltransferase; DMT1: Divalent metal transporter 1; FDX1: Ferredoxin 1; STEAP: Six-transmembrane epithelial antigen of prostate; TCA: Tricarboxylic acid.

small-molecule copper ionophores and FDX1-targeting agents, the cuproptosis pathway is emerging as a promising target for precision cancer therapy and metabolic disease intervention.

4.2. The relationship between cuproptosis and cancer

Copper plays a dual role in tumor biology. On one hand, it can induce tumor cell death through cuproptosis, contributing to antitumor effects. On the other hand, it can promote tumor growth and metastasis via cuproplasia, a copper-dependent pro-tumor process.[158] This dual behavior is influenced by factors such as tumor type, copper homeostasis status, and the surrounding microenvironment. As a result, copper-related pathways are increasingly being recognized as promising targets for precision cancer therapy.[148,159,160]

4.2.1. Activation of cuproptosis in tumors

The activation of cuproptosis in tumors is primarily driven by the disruption of cellular copper homeostasis, leading to mitochondrial copper overload. Notably, tumors with high mitochondrial respiratory activity—such as certain lung and breast cancers—tend to be more susceptible to cuproptosis, whereas those with lower metabolic activity are relatively resistant.[161,162] In addition, copper overload can be artificially induced using nanomaterials or copper ionophores, such as elesclomol and disulfiram, further enhancing this pathway.[163,164] Studies have also shown that silencing FDX1 or supplementing with lipoylation

precursors, such as lipoic acid, can effectively block cuproptosis in tumor cells, supporting the specificity of this activation mechanism.[165,166]

4.2.2. Tumor-suppressive effects of cuproptosis

Cuproptosis exerts antitumor effects mainly through the direct elimination of cancer cells and by reshaping the TME to enhance immune responses. Cu^+-induced oligomerization of lipoylated TCA cycle proteins, together with the resulting proteotoxic stress, can selectively trigger tumor cell death. This effect is particularly evident in chemoresistant or highly metabolic tumors.[167,168] Notably, this process is independent of apoptosis, necrosis, and ferroptosis, and is not blocked by inhibitors targeting BCL-2, caspases, or GPX4, suggesting a potential way to overcome resistance to conventional therapies.[160,169] Beyond its direct cytotoxicity, cuproptosis can also stimulate antitumor immunity. Copper-induced mitochondrial damage leads to the release of DAMPs, including mitochondrial DNA and ROS, which promote dendritic cell maturation and enhance $CD8^+$ T cell infiltration. At the same time, PD-L1 expression is reduced, helping to relieve the immunosuppressive microenvironment.[165,170] In multiple solid tumor models, including colon, gastric, and lung cancers, copper-based nanotherapeutics that induce cuproptosis have been shown to significantly inhibit tumor growth and prolong survival. These approaches also exhibit synergistic effects when combined with PD-1 blockade.[161] Preclinical studies further suggest that cuproptosis-related gene signatures may serve as prognostic biomarkers, with higher cuproptosis activity often associated with better clinical outcomes.[165,171] Taken together, targeting cuproptosis is emerging as a promising intersection between cancer immunotherapy and metabolic intervention.

4.2.3. Pro-tumor effects of cuproptosis

For cuproptosis, the boundary between antitumor proteotoxicity and pro-tumor "cuproplasia" hinges tightly on specific copper thresholds and cellular metabolic context. In malignancies characterized by elevated mitochondrial respiration, excess copper rapidly overcomes defense systems to trigger catastrophic protein aggregation. In contrast, in copper-insensitive or highly glycolytic tumors, sub-lethal copper accumulation fails to induce cuproptosis but instead activates pro-survival pathways (e.g., mitogen-activated protein kinase/AKT), thereby driving cuproplasia, angiogenesis, and metastasis. As a cofactor for multiple enzymes, copper promotes tumor cell proliferation, angiogenesis, invasion, and metastasis, particularly in copper-enriched TME.[158] When copper levels remain below cytotoxic thresholds, or when the cuproptosis pathway is suppressed, copper can instead activate signaling pathways such as mitogen-activated protein kinase, PI3K/AKT, and hypoxia-inducible factor 1-alpha, thereby supporting metabolic reprogramming and the maintenance of cancer stem-like properties.[146,170] This dual role is highly context-dependent. In tumors with elevated copper levels, such as breast and liver cancers, cuproptosis tends to dominate. In contrast, in tumors with lower copper sensitivity—such as prostate cancer or certain gliomas—cuproplasia may contribute more to disease progression.[158,161] Tumor cells can also evade cuproptosis by upregulating copper-binding proteins, such as metallothioneins, or by reducing FDX1 expression, allowing them to exploit copper for survival and metastasis.[148,160] These findings highlight the importance of tumor-specific context and suggest that therapeutic strategies targeting cuproptosis need careful stratification to avoid unintended pro-tumor effects.[166]

In summary, the relationship between cuproptosis and cancer is complex and context-dependent. While its activation relies heavily on mitochondrial copper metabolism, its tumor-suppressive or tumor-promoting effects are shaped by tumor type and microenvironmental conditions.[148] Targeting this pathway—through copper ionophores, nanomedicine, or combination immunotherapies—has shown promising translational potential, offering new avenues to address drug resistance and tumor recurrence.[146,164]

4.3. Antitumor strategies targeting cuproptosis

Cuproptosis, a recently identified mitochondria-dependent form of PCD, is emerging as a promising target in cancer therapy. By artificially inducing intracellular—particularly mitochondrial copper overload, the FDX1–Cu^+–lipoylated TCA protein axis can be activated, leading to selective killing of tumor cells. This approach not only helps overcome resistance to conventional chemotherapy but may also help remodel the TME.[146,148] Current strategies to induce cuproptosis involve small-molecule copper ionophores, copper-based nano-delivery systems, and combination therapies. These approaches have shown notable antitumor activity and acceptable safety profiles in various solid tumor models, including lung, breast, and CRCs.[158,163,164,172]

4.3.1. Small-molecule copper carriers

Small-molecule copper ion carriers are currently the most classic and effective means of inducing cuproptosis. Their core mechanism works by boosting copper uptake into cells or by blocking copper efflux, thereby rapidly raising mitochondrial Cu^{2+} levels. Once reduced to Cu^+ by FDX1, the copper directly binds to lipoylated TCA cycle proteins such as DLAT. This causes protein oligomerization,

proteotoxic stress, and destabilization of iron–sulfur clusters, ultimately leading to mitochondrial respiratory failure and tumor cell death.[163] Drugs like elesclomol and disulfiram have been shown in multiple studies to activate this pathway specifically. They are particularly effective against tumors with high mitochondrial respiration (such as lung cancer and breast cancer), offering strong selective killing while sparing normal cells with much lower toxicity.[171] Beyond acting on their own, these copper carriers can also powerfully reverse chemotherapy resistance. By triggering cuproptosis, they downregulate key resistance-related pathways (such as PI3K/AKT and hypoxia-inducible factor 1-alpha) and restore tumor cells' sensitivity to platinum-based drugs and targeted therapies.[168,169] Preclinical data further show that disulfiram combined with copper supplementation effectively suppresses tumor growth and prolongs survival in animal models. This low-cost, readily translatable strategy offers real promise for treating advanced, drug-resistant cancers.[163,168]

4.3.2. Copper-based nanomaterial delivery systems

To address the limitations of small-molecule copper carriers—such as uneven *in vivo* distribution, systemic toxicity, and poor tumor targeting—copper-based nanomaterial delivery systems have emerged as a leading strategy for inducing cuproptosis. These carriers enable TME-responsive release of copper ions, triggered by pH, ROS, light, or heat. They can precisely deliver copper to the mitochondria of tumor cells, efficiently activating cuproptosis while minimizing exposure to normal tissues.[148,164,166] Beyond copper delivery, these nanomaterials can be integrated with PDT, sonodynamic therapy, or chemotherapeutic drugs to create multifunctional platforms that further amplify proteotoxic stress and mitochondrial damage.[160,162] For example, Liu *et al.*[173] developed a biomimetic system (CuX–P) consisting of MXene nanosheets loaded with DSF/Cu^{2+} and coated with PD-1-overexpressing T cell membranes. This "patch-like" design allows specific binding to PD-L1 on the tumor surface, promoting endocytosis. It creates a positive feedback loop that continuously blocks and consumes PD-L1 while enhancing the accumulation of CuX–P in tumors, thereby triggering cuproptosis. When combined with laser-induced photothermal therapy, the system strongly activates antitumor immunity in mouse models of triple-negative breast cancer, offering a promising new approach for cuproptosis–photothermal–immunotherapy combination.[173] Multiple studies have confirmed that copper-based nanodrugs significantly upregulate cuproptosis markers (such as DLAT oligomerization and FDX1 activity) in colon, gastric, and liver cancer models. They also release DAMPs to stimulate antitumor immune responses.[161] Compared with traditional chemotherapy, these nano-strategies, showing higher tumor enrichment and lower systemic toxicity, make them a key technological platform for translating cuproptosis research from bench to bedside. Nevertheless, transitioning these sophisticated nanoplatforms from bench to bedside remains constrained by several intrinsic translational challenges. Chief among these are unpredictable *in vivo* biodistribution, manufacturing complexity, and poor batch-to-batch reproducibility. Long-term biosafety concerns regarding heavy metal accumulation (such as iron or copper nano-reactors) in healthy organs, combined with a stringent regulatory approval process for multifunctional materials, further complicate scalability and clinical viability.[174]

4.3.3. Combination therapy strategies

Although inducing cuproptosis alone has clear advantages, combining it with other treatments can further boost efficacy and help overcome tumor heterogeneity. Cuproptosis, combined with ICIs (such as PD-1/PD-L1 antibodies), works synergistically to reshape the TME. The mitochondrial damage caused by cuproptosis releases mitochondrial DNA and ROS, which promote dendritic cell maturation and $CD8^+$ T cell infiltration while downregulating PD-L1 expression. This effectively turns "cold tumors" into "hot tumors".[165,170] In addition, pairing cuproptosis with chemotherapy, targeted therapy, or ferroptosis inducers can create strong metabolic synergy. These combinations simultaneously block tumor energy supply and trigger multiple forms of PCD.[158,167] For drug-resistant tumors, cuproptosis-based combination strategies are especially valuable. Approaches such as knocking down or inhibiting negative regulators of FDX1, supplementing with lipoylation precursors, or using cuproptosis gene signatures to guide patient stratification can markedly improve response rate.[160,168,169] Multiple preclinical studies have shown that these combination regimens can achieve complete tumor regression or significant shrinkage across various solid tumors, providing solid theoretical support for personalized and precise cancer treatment.[148,166]

4.3.4. Clinical translation prospects and challenges

Inducing cuproptosis as an antitumor strategy has moved from basic mechanistic studies into the early stages of clinical translation. Both copper ion carriers and copper-based nanodrugs have demonstrated good safety profiles and solid efficacy in animal models, with several candidates now entering early-phase clinical trials.[158,160,175] Additionally, cuproptosis-related gene signatures are emerging as useful biomarkers for predicting patient sensitivity to these therapies, paving the way for more precise, personalized

treatment.[165,171] However, to avoid overstating therapeutic readiness, it is imperative to categorize current evidence strictly. The overwhelming majority of reported synergisms remain confined to *in vitro* cell cultures or murine xenograft models, with very few candidates successfully transitioning to human clinical evaluation. Translating these metal-dependent approaches into successful clinical practice requires overcoming major physiological barriers, including systemic inflammatory responses (cytokine storms) triggered by mass cell lysis, unpredictable pharmacokinetics of small-molecule metal ionophores, and profound inter-patient tumor heterogeneity. To accurately track the intracellular distribution and structural integrity of these metal-associated delivery platforms *in vivo*, advanced molecular imaging is mandatory. For instance, magnetic resonance imaging utilizing specialized membrane-associated magnetosome proteins offers a highly precise paradigm for the non-invasive, high-resolution tracking of mammalian cells under metal stress, thereby improving translational clarity. Ultimately, mitigating these systemic toxicities will inevitably depend on the discovery of reliable predictive biomarkers and the implementation of rigorous patient stratification protocols. That said, several challenges remain. Key issues include achieving truly tissue-specific activation to avoid copper toxicity in normal cells, improving the *in vivo* stability and biocompatibility of nanomaterials, and overcoming adaptive resistance to cuproptosis within the TME.[148,158,164] In summary, cuproptosis-based antitumor strategies offer a fresh approach to tackling cancer drug resistance and recurrence by precisely regulating copper homeostasis and mitochondrial proteotoxic stress. With continued optimization of small-molecule carriers, nanomaterial platforms, and combination regimens, this field is poised to become an important frontier at the intersection of tumor metabolic therapy and immunotherapy.

5. Pyroptosis, ferroptosis, and cuproptosis in cancer: Their network interactions and therapeutic implications

Growing evidence shows that pyroptosis, ferroptosis, and cuproptosis engage in extensive crosstalk at multiple levels, including molecular regulation, tumor immunity, TME remodeling, and treatment response.[176] Several key intersection points have been identified between ferroptosis and pyroptosis. ROS acts as a DAMP, triggering the NLRP3 inflammasome and initiating pyroptosis. At the same time, these ROS further drive PL-OOH formation in ferroptosis, creating a positive feedback loop that amplifies both pathways.[177] Mitochondrial dysfunction serves as a common trigger for both pyroptosis and ferroptosis, with excessive ROS production playing a central role. For instance, mitochondrial ROS can enhance sensitivity to ferroptosis by activating ACSL.[178] Iron overload, through the Fenton reaction, dramatically amplifies ROS signaling, leading to oxidation of the mitochondrial outer membrane translocase receptor Tom20. This recruits Bax, triggers cytochrome c release, and activates caspase-3/GSDME, ultimately inducing pyroptosis in melanoma cells.[179] Defective mitophagy exacerbates ferritin degradation, iron release, and mitochondrial DNA leakage, thereby amplifying activation of the cGAS–STING pathway and driving ferroptosis.

Meanwhile, the same cGAS–STING signaling pathway can also activate NLRP3, promoting pyroptosis.[180,181] Interestingly, ferroptosis and pyroptosis can also antagonize each other. The BRCC36-mediated deubiquitination of 3-hydroxy-3-methylglutaryl-CoA reductase has been shown to suppress ferroptosis and promote pyroptosis simultaneously.[182] In summary, ferroptosis and pyroptosis interact through ROS-NLRP3 inflammasome activation and mitochondrial dysfunction, with ROS accumulation serving as the core driver that shifts the balance between these two forms of cell death.

Ferroptosis and cuproptosis are tightly interconnected through mitochondrial metabolism and GSH homeostasis. The mitochondrial TCA cycle serves as a major convergence point for both pathways. The key TCA enzyme DLAT, once lipoylated by FDX1, binds Cu^{+} and triggers cuproptosis. Interestingly, blocking the TCA cycle has been shown to protect against cysteine deprivation-induced ferroptosis.[183] However, whether lipoylation of DLAT affects the TCA cycle and, in turn, influences cysteine deprivation-induced ferroptosis remains unclear. GSH acts as a shared regulator that suppresses both ferroptosis and cuproptosis, though through different mechanisms. In ferroptosis, GSH functions as an antioxidant to prevent LPO. In cuproptosis, it serves as a copper chaperone that binds free copper ions, thereby reducing abnormal aggregation of lipoylated proteins.[26,184] This crosstalk was clearly demonstrated in a liver cancer combination therapy study: ferroptosis inducers (sorafenib and erastin) significantly increased lipoylated DLAT aggregation in HCC cells, leading to cuproptosis. This effect was closely linked to the inhibition of mitochondrial matrix protease-mediated FDX1 degradation and the suppression of intracellular GSH synthesis.[185] NRF2, a master antioxidant transcription factor, regulates downstream targets SLC7A11 and GPX4, which inhibit the accumulation of PL-OOH in ferroptosis. Notably, SLC7A11 influences both ferroptosis and cuproptosis by controlling GSH synthesis and copper transport, making it a promising multi-pathway therapeutic target.[186] Similarly, the transcription factor p53

promotes ferroptosis by suppressing the SLC7A11/GSH/GPX4 antioxidant axis, while also promoting cuproptosis by disrupting the stability of Fe-S cluster proteins and lowering GSH levels.[187] In summary, ferroptosis and cuproptosis are not isolated processes. Instead, they form a mutually reinforcing death network linked through the mitochondrial TCA cycle, lipoylation modifications, and GSH metabolism.

Copper ions exhibit higher catalytic efficiency in the Fenton reaction than iron. Copper overload, therefore, sharply elevates intracellular ROS levels, leading to mitochondrial dysfunction. The subsequent release of DAMPs further activates the NLRP3 inflammasome and triggers pyroptosis. This ROS-dependent crosstalk synergistically drives both cuproptosis and pyroptosis, ultimately amplifying the overall cell death signal.[188] Moreover, the combined activation of these two death pathways can reprogram the immunosuppressive TME, significantly increase immune cell infiltration, and elicit a potent systemic immune response. For example, a self-destructive, multi-enzyme-mimetic copper-quinone-GOx nanoparticle system (CQG NPs) was designed to simultaneously induce pyroptosis and cuproptosis in tumor cells. By blocking the NRF2-NQO1 antioxidant pathway, depleting GSH, exhausting glucose, and releasing copper ions, these nanoparticles reshape the immunosuppressive microenvironment, awaken robust systemic antitumor immunity, and effectively combat tumor dormancy and recurrence.[189] The shared key nodes between these pathways include the NRF2 antioxidant axis, mitochondrial dysfunction, and metabolic reprogramming. These interactions have recently been shown to play important roles in tumor progression, heterogeneity, and treatment resistance in solid tumors such as breast cancer.[27] Overall, this crosstalk not only adds greater complexity to the tumor cell death network but also provides a strong theoretical foundation for developing multi-pathway synergistic anticancer strategies.

From the above discussion, it is clear that pyroptosis, ferroptosis, and cuproptosis form a dynamic regulatory network through these shared nodes (Figure 4; Table 1). Under low ROS conditions, NRF2 mainly plays a protective role. However, when ROS levels rise or the TME becomes stressed, the network shifts toward the coordinated induction of cell death. This provides precise entry points for multi-target interventions. In the TME, the crosstalk among these three PCD pathways significantly reshapes the immune landscape. They promote maturation of antigen-presenting cells, cross-priming of $CD8^+$ T cells, and release of DAMPs such as high mobility group box 1 and ATP. This strengthens ICD, helping reverse immunosuppression and trigger systemic antitumor immunity.[168] However, combining RCD induction with ICIs requires addressing critical clinical prerequisites that are currently overlooked. Firstly, the massive release of pro-inflammatory cytokines during widespread pyroptosis or ferroptosis can exacerbate immune-related adverse events, potentially leading to systemic hyper-inflammation. Secondly, mechanisms of adaptive resistance and the optimal treatment sequencing—whether to induce RCD prior to or concurrently with ICI administration—remain unresolved. To optimize these combination regimens, non-invasive predictive biomarkers are urgently required. In this regard, advanced imaging techniques, such as near-infrared fluorescence/Cerenkov luminescence dual-modality *in situ* imaging, offer a powerful framework to compare tumor non-specific and PD-L1-specific dynamics, allowing clinicians to dynamically monitor the TME and precisely guide therapeutic sequencing.[190] It is worth noting that treatment-induced ferroptosis, cuproptosis, and PANoptosis (which carries pyroptotic features) also contribute to cancer therapy-related cardiotoxicity. This highlights the need for precise regulation to balance efficacy and safety.[29] At the therapeutic level, targeting these network interactions shows strong potential for clinical translation. Small-molecule inducers like sorafenib can trigger ferroptosis while cooperating with other pathways.

Meanwhile, TME-responsive nanozyme prodrugs can be specifically activated by GSH/H_2O_2, simultaneously and precisely triggering pyroptosis, cuproptosis, and ferroptosis. This creates an *in situ* tumor–vaccine effect, effectively suppressing both primary tumors and metastases.[191] Nano-delivery systems, plant-derived compounds, and metal ion carriers further amplify the synergistic effects among the three pathways. When combined with chemotherapy or immunotherapy, they help overcome tumor resistance and heterogeneity while reducing toxic side effects.[27,192] While recent literature has explored related intersections—such as highlighting these pathways strictly within the context of breast cancer[27] or primarily evaluating the dual synergy between cuproptosis and ferroptosis[192]—this review distinctly maps the comprehensive triple-pathway crosstalk across a broad spectrum of refractory solid tumors, uniquely emphasizing the clinical translation of smart nano-delivery and natural product interventions. Multiple studies have shown that multi-pathway PCD induction strategies outperform single-pathway targeting in reshaping the TME and enhancing antitumor immune memory. A balanced and insightful synthesis of this evolving field requires acknowledging several intense controversies that remain unresolved. Firstly, it is highly debated whether cuproptosis is universally applicable across all cancer types; accumulated data suggest its efficacy

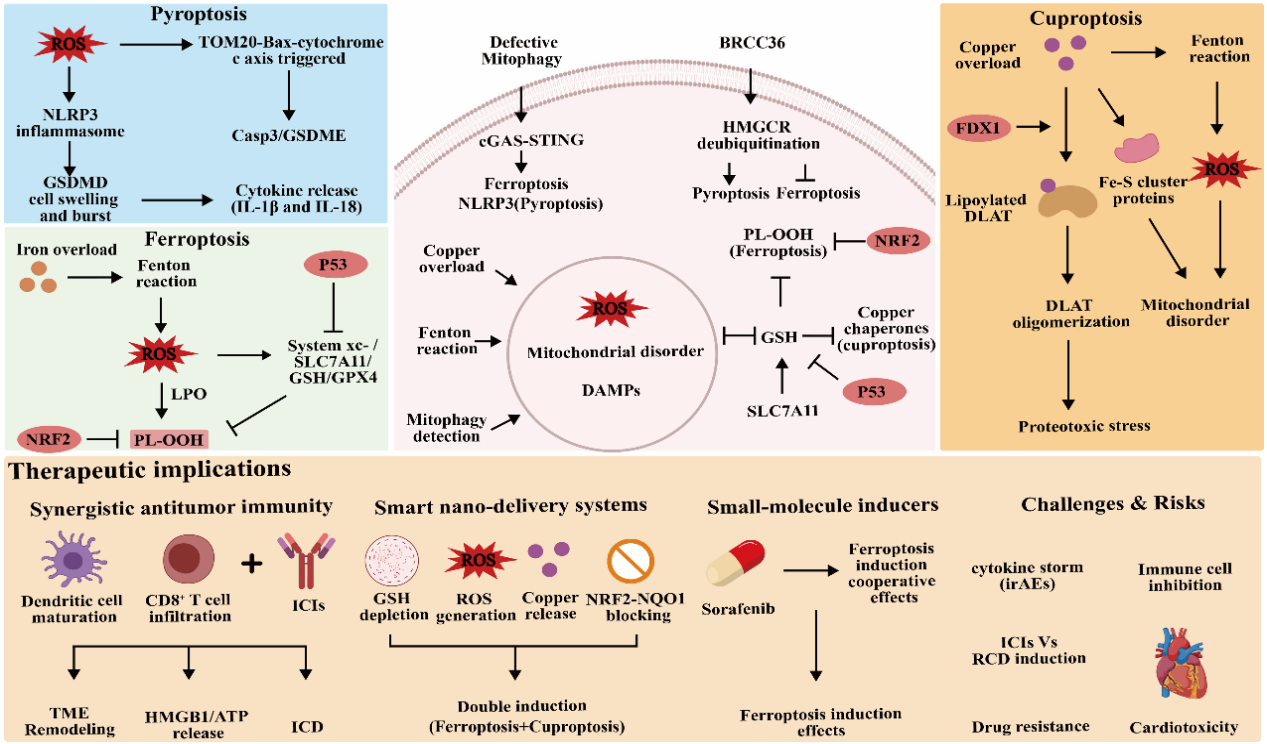


Figure 4. Network interactions among pyroptosis, ferroptosis, and cuproptosis, and their therapeutic implications. The schematic diagram illustrates the crosstalk regulatory mechanisms among three RCD pathways—pyroptosis, ferroptosis, and cuproptosis—along with their potential clinical applications. Top left: mechanisms of pyroptosis and ferroptosis. Pyroptosis is driven by ROS-induced NLRP3 inflammasome activation or the TOM20-Bax-cytochrome c axis, leading to Casp3/GSDME and GSDMD cleavage, cell swelling, and cytokine (IL-1β and IL-18) release. Ferroptosis is triggered by iron overload and Fenton reaction-mediated ROS accumulation and lipid peroxidation (PL-OOH), which is counteracted by the NRF2 and System Xc^-/SLC7A11/GSH/GPX4 axis, while P53 acts as a negative regulator of System Xc^-. Top right: mechanisms of cuproptosis. Copper overload leads to FDX1-mediated lipoylated DLAT oligomerization and proteotoxic stress, or interferes with Fe–S cluster proteins, inducing mitochondrial disorder and Fenton-like ROS generation. Top center: cross-talk network. Mitochondrial disorder, ROS generation, and DAMPs release serve as central hubs connecting these pathways. Key regulators like GSH, SLC7A11, P53, NRF2, cGAS–STING, and BRCC36 mediate the complex regulatory feedback loop among pyroptosis, ferroptosis, and cuproptosis. Bottom: therapeutic implications of targeting RCDs. Strategies include leveraging synergistic antitumor immunity (e.g., TME remodeling and ICD induction via dendritic cell maturation and $CD8^+$ T cell infiltration combined with ICIs), smart nano-delivery systems (e.g., double induction of ferroptosis and cuproptosis), and small-molecule inducers (such as Sorafenib). Associated clinical challenges and risks, such as cytokine storm, drug resistance, and cardiotoxicity, are also highlighted. Arrows indicate activation or promotion; T-bars indicate inhibition. The diagram was generated using MedPeer (www.medpeer.cn).

Abbreviations: Bax: BCL2-associated X protein; BRCC36: BRCA1/BRCA2-containing complex subunit 3; Casp3: Caspase-3; cGAS: Cyclic GMP-AMP synthase; DAMP: Damage-associated molecular pattern; DLAT: Dihydrolipoamide S-acetyltransferase; FDX1: Ferredoxin 1; Fe–S: Iron–sulfur; GPX4: Glutathione peroxidase 4; GSDMD: Gasdermin D; GSDME: Gasdermin E; GSH: Glutathione; ICD: Immunogenic cell death; ICI: Immune checkpoint inhibitor; IL: Interleukin; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; NRF2: Nuclear factor erythroid 2-related factor 2; P53: Tumor protein p53; PL-OOH: Phospholipid hydroperoxide; RCD: Regulated cell death; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11; STING: Stimulator of interferon genes; System Xc^-: Cystine/glutamate antiporter; TME: Tumor microenvironment; TOM20: Translocase of outer mitochondrial membrane 20.

may be strictly restricted to malignancies possessing high baseline mitochondrial respiration, leaving highly glycolytic tumors largely resistant. Secondly, the role of ferroptosis in tumor immune regulation remains double-edged; while some studies demonstrate that ferroptotic cancer cells activate T-cell responses, conflicting evidence indicates that accumulated lipid peroxides actively suppress local dendritic cell and macrophage functions within the TME. Finally, the context-dependent threshold at which pyroptosis switches from a tumor-suppressive immunogenic trigger to a pro-tumor chronic inflammatory driver remains poorly defined, posing a significant challenge for clinical dosing and safety margin determination. In summary, the network interactions among pyroptosis, ferroptosis, and cuproptosis provide a brand-new framework for precision cancer treatment.

Table 1. Comprehensive comparison of pyroptosis, ferroptosis, and cuproptosis

Parameter	Pyroptosis	Ferroptosis	Cuproptosis
Major molecular regulators	Gasdermin (GSDM) family proteins (e.g., GSDMD, GSDME, and GSDMC); caspases (e.g., caspase-1, 4, 5, 11, 3, and 8); NLRP3 inflammasome and granzymes (GZMA, GZMB)	System Xc^- (SLC7A11/SLC3A2), glutathione (GSH), and GPX4; ACSL4, LPCAT3, ALOX, and POR; iron metabolism regulators such as TFR1, DMT1, and FTH1/FTL	FDX1 and lipoylated tricarboxylic acid (TCA) cycle proteins (e.g., DLAT); copper transporters such as CTR1 and ATP7A/B; glutathione (GSH) and metallothioneins (MTs)
Morphological hallmarks	Cell swelling and rupture; formation of 10–20 nm pores in the plasma membrane	Mitochondrial shrinkage; reduced or absent mitochondrial cristae and increased membrane density	High-molecular-weight aggregates of lipoylated proteins; mitochondrial membrane depolarization and structural fragmentation
Specific biomarkers	Massive release of pro-inflammatory cytokines (e.g., IL-1β and IL-18); release of damage-associated molecular patterns (DAMPs); cleaved N-terminal fragment of GSDM	Abnormal intracellular accumulation of free ferrous iron (Fe^{2+}); fatal accumulation of peroxides of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs)	Mitochondrial copper overload; disruption and loss of Fe–S cluster proteins; DLAT oligomerization
Representative inducers/drugs	Traditional chemotherapeutic agents and the allosteric inhibitor SHP099; natural compounds (e.g., astragaloside IV, curcumin, cucurbitacin B); nanomaterials (e.g., photo-chemodynamic nanoplatform $Na_2S_2O_8$-IR780 NP)	Erastin, RSL3, ML162, sorafenib, and fenbendazole; bioactive natural products (e.g., alkannin, resveratrol, gambogenic acid, manoalide)	Small-molecule copper ionophores (e.g., elesclomol and disulfiram); copper-based nanomaterial delivery systems (e.g., CuX–P)
Therapeutic pros & cons	Pros: Triggers strong immunogenic cell death (ICD), remodels the tumor microenvironment (TME) via DAMP release, and robustly activates antitumor immunity Cons: May foster chronic inflammation in certain cancer types or microenvironments, paradoxically recruiting immunosuppressive cells to promote tumor progression or causing normal organ damage	Pros: Bypasses conventional apoptosis resistance (especially in mesenchymal-like or dedifferentiated cancer cells) and synergizes with radiotherapy, chemotherapy, and immune checkpoint inhibitors (ICIs) Cons: Highly context-dependent; its products may trigger chronic inflammation to promote tumor progression in specific microenvironments, alongside risks of systemic toxicity	Pros: Operates independently of apoptosis or ferroptosis pathways, selectively targets chemoresistant or highly metabolic tumors, releases DAMPs, and helps overcome multidrug resistance Cons: Copper also has pro-tumor effects (cuproplasia); tumors can evade death and promote growth/metastasis by upregulating copper-binding proteins like MTs
Current clinical development status	Highly regarded as an emerging immunotherapy strategy, increasingly combined with nano-delivery systems to safely manage its "double-edged sword" potential. Challenges remain regarding low GSDME expression in cancer cells, tissue-specific differences, and unwanted chronic inflammatory side effects	Nano-delivery systems are heavily utilized to overcome the *in vivo* instability and off-target toxicity of ferroptosis inducers. Clinical translation is hindered by a lack of standardized biomarkers, tumor heterogeneity, and the need for more precise patient stratification	Has transitioned from basic mechanistic research to early stages of clinical translation, with several candidates entering early-phase clinical trials. Key challenges include achieving true tissue-specific activation to avoid copper toxicity in normal cells and overcoming adaptive resistance

Abbreviations: ACSL4: Acyl-CoA synthetase long-chain family member 4; ALOX: Arachidonate lipoxygenase; ATP7A/B: ATPase copper transporting alpha/beta; CTR1: Copper transporter 1; CuX–P: Copper-based nanoplatform; DAMP: Damage-associated molecular pattern; DLAT: Dihydrolipoamide S-acetyltransferase; DMT1: Divalent metal transporter 1; FDX1: Ferredoxin 1; Fe: Iron; Fe–S: Iron–sulfur; FTH1: Ferritin heavy chain 1; FTL: Ferritin light chain; GPX4: Glutathione peroxidase 4; GSDM: Gasdermin; GSDMC: Gasdermin C; GSDMD: Gasdermin D; GSDME: Gasdermin E; GSH: Glutathione; GZMA: Granzyme A; GZMB: Granzyme B; ICD: Immunogenic cell death; ICI: Immune checkpoint inhibitor; IL: Interleukin; LPCAT3: Lysophosphatidylcholine acyltransferase 3; MT: Metallothionein; $Na_2S_2O_8$-IR780 NP: Sodium persulfate–IR780 nanoparticle; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; POR: Cytochrome P450 oxidoreductase; PUFA-PL: Polyunsaturated fatty acid-containing phospholipid; SHP099: Src homology 2 domain-containing phosphatase 2 inhibitor; SLC3A2: Solute carrier family 3 member 2; SLC7A11: Solute carrier family 7 member 11; System Xc^-: Cystine/glutamate antiporter; TCA: Tricarboxylic acid; TFR1: Transferrin receptor 1; TME: Tumor microenvironment.

6. Conclusion

Pyroptosis, ferroptosis, and cuproptosis have emerged as three major forms of non-apoptotic PCD, offering exciting new targets for cancer therapy. These pathways exploit distinct yet interconnected mechanisms—NLRP3/GSDMD-mediated pore formation in pyroptosis, iron-driven LPO in ferroptosis, and copper-dependent protein lipidation and TCA cycle disruption in cuproptosis—to target the metabolic weaknesses of tumor cells. Within the TME, they form a complex crosstalk network through shared hubs like ROS, the NRF2/SLC7A11/GPX4 axis, and the NLRP3 inflammasome. This network drives ICD, releasing DAMPs and pro-inflammatory cytokines. The result is a reshaping of the immunosuppressive microenvironment, boosting $CD8^+$ T cell infiltration, reversing multidrug resistance (including to paclitaxel, cisplatin, and epidermal growth factor receptor–tyrosine kinase inhibitors), and working synergistically with ICIs to turn "cold" tumors "hot". Advanced nano-delivery systems further amplify these effects by enabling tumor-specific targeting, controlled release, and multimodal synergy. They can trigger multiple death pathways at once while reducing systemic toxicity. When combined with natural compounds such as curcumin or chelerythrine and immune modulators, these platforms show strong potential for a new paradigm: reprogramming cell death networks while activating antitumor immunity.

That said, several challenges remain. Most current research still leans heavily toward non-cancer diseases, leaving cancer-specific mechanisms under-validated. Issues such as insufficient targeting specificity, off-target effects, and inflammatory side effects (including nanoparticle-induced lung inflammation and cytokine storms) persist. We also lack well-validated biomarkers (e.g., cuproptosis-related gene and pyroptosis-related gene signatures) for prospective use, and tumor heterogeneity continues to affect treatment sensitivity. Long-term biocompatibility and safety of nanocarriers are additional hurdles to clinical translation.

Looking ahead, bridging the gap from bench to bedside will require adopting next-generation biological and computational methodologies. Future research priorities must shift toward: (i) integrating single-cell sequencing and spatial transcriptomics to precisely map RCD sensitivity profiles across heterogeneous tumor landscapes, thereby resolving spatial tumor heterogeneity; (ii) utilizing artificial intelligence-assisted target discovery and deep learning algorithms to identify novel, highly specific small-molecule agonists of gasdermins or FDX1; and (iii) establishing multi-omics prognostic models that combine cell death-related gene signatures for precision oncology approaches, ultimately identifying the specific patient cohorts most likely to derive maximal clinical benefit from RCD-targeted combination protocols. Addressing these directions through multicenter clinical trials, better tumor-normal cell discrimination models, and highly biocompatible "nano–traditional Chinese medicine" platforms will help bridge the gap from bench to bedside. Ultimately, the optimized integration of pyroptosis, ferroptosis, and cuproptosis could usher in a new era of networked, personalized, and low-toxicity cancer treatment—greatly improving patient outcomes and quality of life.

Acknowledgments

None.

Funding

The work was supported by the Sichuan Provincial Administration of Traditional Chinese Medicine under the Traditional Chinese Medicine Research Special Project (2024MS414) and by the Fundamental Research Funds for the Central Universities, Southwest Minzu University (ZYN2025026).

Conflict of interest

The authors declare no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

During the preparation of this work, the authors used generative AI and AI-assisted technologies solely to improve language presentation, grammar, and structural scannability. After using these services, the authors reviewed, edited, and revised the content to ensure scientific accuracy and take full responsibility for the final contents of the peer-reviewed manuscript.

References

1. Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263.

   doi: 10.3322/caac.21834

2. Galluzzi L, Vitale I, Aaronson SA, *et al*. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* 2018;25(3):486-541.

   doi: 10.1038/s41418-017-0012-4

3. Guo D, Guo Y, Zhu C, *et al*. Programmed cell death network in cancer drug resistance: a framework for therapeutic intervention. *Drug Resist Updat.* 2026;86:101387.

   doi: 10.1016/j.drup.2026.101387

4. Zhang Y, Huang Q, Xu Q, Jia C, Xia Y. Pimavanserin tartrate induces apoptosis and cytoprotective autophagy and synergizes with chemotherapy on triple negative breast cancer. *Biomed Pharmacother.* 2023;168:115665.

   doi: 10.1016/j.biopha.2023.115665

5. Liu W, Jin W, Zhu S, Chen Y, Liu B. Targeting regulated cell death (RCD) with small-molecule compounds in cancer therapy: a revisited review of apoptosis, autophagy-dependent cell death and necroptosis. *Drug Discov Today.* 2022;27(2):612-625.

   doi: 10.1016/j.drudis.2021.10.011

6. Yang D, Peng D, Zhou Y, *et al*. Alpha-momorcharin, a type I ribosome inactivating protein, induced apoptosis of hepatocellular carcinoma SK-HEP-1 cells through mitochondrial pathway. *Nat Prod Res.* 2023;39(5):1128-1138.

   doi: 10.1080/14786419.2023.2295915

7. Yang Y, Chen Y, Wu JH, *et al*. Targeting regulated cell death with plant natural compounds for cancer therapy: a revisited review of apoptosis, autophagy-dependent cell death, and necroptosis. *Phytother Res.* 2023;37(4):1488-1525.

   doi: 10.1002/ptr.7738

8. Zeng M, Wang Y, Tao X, *et al*. Novel perspectives in the management of colorectal cancer: mechanistic investigations into the reversal of drug resistance via active constituents derived from herbal medicine. *Phytother Res.* 2024;38(12):5962-5984.

   doi: 10.1002/ptr.8363

9. Zhang J, Wu Y, Li Y, *et al*. Natural products and derivatives for breast cancer treatment: from drug discovery to molecular mechanism. *Phytomedicine.* 2024;129:155600.

   doi: 10.1016/j.phymed.2024.155600

10. Xu L, Xie Y, Gou Q, *et al*. HER2-targeted therapies for HER2-positive early-stage breast cancer: present and future. *Front Pharmacol.* 2024;15.

    doi: 10.3389/fphar.2024.1446414

11. Sun Q, Mattatall GV, Vivekanantha P, *et al*. Magnetic resonance imaging of mammalian cells individually expressing membrane-associated magnetosome proteins I, L, B, and E. *Mol Imaging.* 2024;23.

    doi: 10.1177/15353508241289765

12. Zhang Y, Yi S, Luan M. Advances in non-apoptotic regulated cell death: implications for malignant tumor treatment. *Front Oncol.* 2025;15.

    doi: 10.3389/fonc.2025.1519119

13. Dou L, Fang Y, Yang H, Ai G, Shen N. Immunogenic cell death: a new strategy to enhancing cancer immunotherapy. *Hum Vaccin Immunother.* 2024;20(1).

    doi: 10.1080/21645515.2024.2437918

14. Chen J, Wei Z, Fu K, *et al*. Non-apoptotic cell death in ovarian cancer: treatment, resistance and prognosis. *Biomed Pharmacother.* 2022;150:112929.

    doi: 10.1016/j.biopha.2022.112929

15. Chen Z, Li X, Luo M, Mao W, Huang S, Zhou X. Advances in drug design strategies for phototherapy based on tumor cell death mechanisms. *J Asian Nat Prod Res.* 2026;28(1):1-33.

    doi: 10.1080/10286020.2025.2530748

16. Wan S, Wang X, Chen W, *et al*. Exposure to high dose of polystyrene nanoplastics causes trophoblast cell apoptosis and induces miscarriage. *Part Fibre Toxicol.* 2024;21(1).

    doi: 10.1186/s12989-024-00574-w

17. Unnisa A, Greig NH, Kamal MA. Inhibition of caspase 3 and caspase 9 mediated apoptosis: a multimodal therapeutic target in traumatic brain injury. *Curr Neuropharmacol.* 2023;21(4):1001-1012.

    doi: 10.2174/1570159x20666220327222921

18. Ning Q, Liu J, Liu S, Zou Q, Li K, Li Z. TRx0237 induces apoptosis and enhances anti-PD-1 immunotherapeutic efficacy in anaplastic thyroid cancer. *Int Immunopharmacol.* 2025;155:114610.

    doi: 10.1016/j.intimp.2025.114610

19. Lan T, He S, Luo X, *et al*. Disruption of NADPH homeostasis by total flavonoids from Adinandra nitida Merr. ex Li leaves triggers ROS-dependent p53 activation leading to apoptosis in non-small cell lung cancer cells. *J Ethnopharmacol.* 2024;332:118340.

    doi: 10.1016/j.jep.2024.118340

20. Chen Y, Li X, Yang M, Liu S. Research progress on morphology and mechanism of programmed cell death. *Cell Death Dis.* 2024;15(5).

    doi: 10.1038/s41419-024-06712-8

21. Li Y, Guo B. GSDMD-mediated pyroptosis: molecular mechanisms, diseases and therapeutic targets. *Mol Biomed.* 2025;6(1).

doi: 10.1186/s43556-025-00249-8

22. Broz P. Pyroptosis: molecular mechanisms and roles in disease. *Cell Res.* 2025;35(5):334-344.

doi: 10.1038/s41422-025-01107-6

23. Dixon SJ, Lemberg KM, Lamprecht MR, *et al*. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell.* 2012;149(5):1060-1072.

doi: 10.1016/j.cell.2012.03.042

24. Dong L, He J, Luo L, Wang K. Targeting the interplay of autophagy and ROS for cancer therapy: an updated overview on phytochemicals. *Pharmaceuticals.* 2023;16(1):92.

doi: 10.3390/ph16010092

25. Shi R, Fan H, Yu X, Tang Y, Jiang J, Liang X. Advances of podophyllotoxin and its derivatives: patterns and mechanisms. *Biochem Pharmacol.* 2022;200:115039.

doi: 10.1016/j.bcp.2022.115039

26. Tsvetkov P, Coy S, Petrova B, *et al*. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science.* 2022;375(6586):1254-1261.

doi: 10.1126/science.abf0529

27. Jing Z, Huang W, Mei J, *et al*. Advances in novel cell death mechanisms in breast cancer: intersecting perspectives on ferroptosis, cuproptosis, disulfidptosis, and pyroptosis. *Mol Cancer.* 2025;24(1).

doi: 10.1186/s12943-025-02445-0

28. Wang S, He H, Qu L, Shen Q, Dai Y. Dual roles of inflammatory programmed cell death in cancer: insights into pyroptosis and necroptosis. *Front Pharmacol.* 2024;15.

doi: 10.3389/fphar.2024.1446486

29. Yang F, Zhang G, An N, *et al*. Interplay of ferroptosis, cuproptosis, and PANoptosis in cancer treatment-induced cardiotoxicity: mechanisms and therapeutic implications. *Semin Cancer Biol.* 2024;106-107:106-122.

doi: 10.1016/j.semcancer.2024.09.003

30. Zhang C, Shao J, Tang X, *et al*. The real-world treatment characteristic and efficacy of immune checkpoint inhibitors in non-small cell lung cancer: data from a retrospective cohort study. *Int Immunopharmacol.* 2024;134:112152.

doi: 10.1016/j.intimp.2024.112152

31. Xiang T, Li L, Li J, *et al*. Chromodomain y-like (CDYL) inhibition ameliorates acute kidney injury in mice by regulating tubular pyroptosis. *Acta Pharmacol Sin.* 2024;45(12):2598-2610.

doi: 10.1038/s41401-024-01345-1

32. Liu Y, Li X, Sun T, Li T, Li Q. Pyroptosis in myocardial ischemia/reperfusion and its therapeutic implications. *Eur J Pharmacol.* 2024;971:176464.

doi: 10.1016/j.ejphar.2024.176464

33. Zhang Y, Jiao Y, Li X, *et al*. Pyroptosis: a new insight into eye disease therapy. *Front Pharmacol.* 2021;12.

doi: 10.3389/fphar.2021.797110

34. Bai Y, Pan Y, Liu X. Mechanistic insights into gasdermin-mediated pyroptosis. *Nat Rev Mol Cell Biol.* 2025;26(7):501-521.

doi: 10.1038/s41580-025-00837-0

35. Wang P, Ma J, Zhang R. Inflammasomes as potential therapeutic targets in atherosclerotic cardiovascular disease. *EMIDDT.* 2022;22(14):1378-1389.

doi: 10.2174/1871530322666220407090916

36. Lu L, Zhang Y, Tan X, *et al*. Emerging mechanisms of pyroptosis and its therapeutic strategy in cancer. *Cell Death Discov.* 2022;8(1).

doi: 10.1038/s41420-022-01106-1

37. Zhou K, Gu X, Tan H, *et al*. Identification pyroptosis-related gene signature to predict prognosis and associated regulation axis in colon cancer. *Front Pharmacol.* 2022;13.

doi: 10.3389/fphar.2022.1004425

38. Feng L, Wu Y, Yang Y, *et al*. QBT improved cognitive dysfunction in rats with vascular dementia by regulating the NRF2/xCT/GPX4 and NLRP3/caspase-1/GSDMD pathways to inhibit ferroptosis and pyroptosis of neurons. *Int Immunopharmacol.* 2024;142:113070.

doi: 10.1016/j.intimp.2024.113070

39. Zhou N, Zhang Y, Jiao Y, *et al*. Discovery of a novel pyroptosis inhibitor acting though modulating glutathionylation to suppress NLRP3-related signal pathway. *Int Immunopharmacol.* 2024;127:111314.

doi: 10.1016/j.intimp.2023.111314

40. Gao L, Dong X, Gong W, *et al*. Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis. *Br J Pharmacol.* 2021;178(17):3533-3552.

doi: 10.1111/bph.15499

41. Shi J, Zhao Y, Wang K, *et al*. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature.* 2015;526(7575):660-665.

doi: 10.1038/nature15514

42. Wu X, Yao J, Hu Q, *et al*. Emodin ameliorates acute pancreatitis-associated lung injury through inhibiting the alveolar macrophages pyroptosis. *Front Pharmacol.* 2022;13.

doi: 10.3389/fphar.2022.873053

43. Yang Z, Li H, Wu H, Zhou Y, Du J, Hu Z. Omega-3 polyunsaturated fatty acids alleviate hyperuricemic nephropathy by inhibiting renal pyroptosis through GPR120. *Biochem Pharmacol.* 2024;230:116575.

doi: 10.1016/j.bcp.2024.116575

44. He W, Wan H, Hu L, *et al*. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. *Cell Res.* 2015;25(12):1285-1298.

doi: 10.1038/cr.2015.139

45. He G, Chen K, Wang H, *et al*. Fudosteine attenuates acute lung injury in septic mice by inhibiting pyroptosis via the TXNIP/NLRP3/GSDMD pathway. *Eur J Pharmacol.* 2022;926:175047.

doi: 10.1016/j.ejphar.2022.175047

46. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci.* 2017;42(4):245-254.

doi: 10.1016/j.tibs.2016.10.004

47. Shi J, Zhao Y, Wang Y, *et al*. Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature.* 2014;514(7521):187-192.

doi: 10.1038/nature13683

48. Taabazuing CY, Okondo MC, Bachovchin DA. Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. *Cell Chem Biol.* 2017;24(4):507-514.e4.

doi: 10.1016/j.chembiol.2017.03.009

49. Anthony DA, Andrews DM, Watt SV, Trapani JA, Smyth MJ. Functional dissection of the granzyme family: cell death and inflammation. *Immunol Rev.* 2010;235(1):73-92.

doi: 10.1111/j.0105-2896.2010.00907.x

50. Zhang Z, Zhang Y, Xia S, *et al*. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature.* 2020;579(7799):415-420.

doi: 10.1038/s41586-020-2071-9

51. Wang Y, Gao W, Shi X, *et al*. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature.* 2017;547(7661):99-103.

doi: 10.1038/nature22393

52. Hou J, Zhao R, Xia W, *et al*. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. *Nat Cell Biol.* 2020;22(10):1264-1275.

doi: 10.1038/s41556-020-0575-z

53. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol.* 2015;15(6):388-400.

doi: 10.1038/nri3839

54. Zhang J, Ren Z, Hu Y, *et al*. High HPK1(+)PD-1(+) TIM-3(+)CD8(+) T cells infiltration predicts poor prognosis to immunotherapy in NSCLC patients. *Int Immunopharmacol.* 2024;127:111363.

doi: 10.1016/j.intimp.2023.111363

55. Zhou Z, He H, Wang K, *et al*. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science.* 2020;368(6494).

doi: 10.1126/science.aaz7548

56. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. *Ann Afr Med.* 2019;18(3):121.

doi: 10.4103/aam.aam_56_18

57. Khandia R, Munjal A. Interplay between inflammation and cancer. *Adv Protein Chem Struct Biol.* 2020;119:199-245.

doi: 10.1016/bs.apcsb.2019.09.004

58. Ruan J, Wang S, Wang J. Mechanism and regulation of pyroptosis-mediated in cancer cell death. *Chem Biol Interact.* 2020;323:109052.

doi: 10.1016/j.cbi.2020.109052

59. Jiang M, Qi L, Li L, Li Y. The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer. *Cell Death Discov.* 2020;6(1).

doi: 10.1038/s41420-020-00349-0

60. Hou J, Hsu J, Hung M. Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity. *Mol Cell.* 2021;81(22):4579-4590.

doi: 10.1016/j.molcel.2021.09.003

61. Gao H, Yao Y, Li W, *et al*. Caspase-6/gasdermin C-mediated tumor cell pyroptosis promotes colorectal cancer progression through CXCL2-dependent recruitment of myeloid-derived suppressor cells. *Adv Sci.* 2025;12(20).

doi: 10.1002/advs.202411375

62. Qiu A, Lin J, Hu H, *et al*. Organelles and cancer cell pyroptosis: overview and perspectives. *Cell Death Dis.* 2025;17(1).

doi: 10.1038/s41419-025-08371-9

63. Li Z, Mo F, Wang Y, *et al*. Enhancing gasdermin-induced tumor pyroptosis through preventing ESCRT-dependent cell membrane repair augments antitumor immune response. *Nat Commun.* 2022;13(1).

doi: 10.1038/s41467-022-34036-8

64. Fu C, Ji W, Cui Q, *et al*. GSDME-mediated pyroptosis promotes anti-tumor immunity of neoadjuvant chemotherapy in breast cancer. *Cancer Immunol Immunother.* 2024;73(9).

doi: 10.1007/s00262-024-03752-z

65. Peng X, Na R, Zhou W, *et al*. Nuclear translocation of gasdermin D sensitizes colorectal cancer to

chemotherapy in a pyroptosis-independent manner. *Oncogene.* 2022;41(47):5092-5106.

doi: 10.1038/s41388-022-02503-7

66. Gagnon M, Tian S, Geyer S, *et al*. Distribution of clonal hematopoiesis of indeterminate potential (CHIP) is not associated with race in patients with plasma cell neoplasms. *Blood Cancer J.* 2022;12(7).

doi: 10.1038/s41408-022-00706-5

67. Li S, Yue M, Xu H, *et al*. Chemotherapeutic drugs-induced pyroptosis mediated by gasdermin E promotes the progression and chemoresistance of pancreatic cancer. *Cancer Lett.* 2023;564:216206.

doi: 10.1016/j.canlet.2023.216206

68. Kahaer G, Pan S, Yang C, Xie W, Lu Y. Dual function of gasdermin E: pyroptosis-mediated pan-cancer suppression versus HCC-specific oncogenic activity. *Front Immunol.* 2025;16.

doi: 10.3389/fimmu.2025.1626311

69. Li M, Jiang P, Yang Y, *et al*. The role of pyroptosis and gasdermin family in tumor progression and immune microenvironment. *Exp Hematol Oncol.* 2023;12(1).

doi: 10.1186/s40164-023-00464-5

70. He S, Huang Q, Cheng J. The conflicting role highlights the complexity of GSDMs in cancer. *Front Immunol.* 2025;16.

doi: 10.3389/fimmu.2025.1531695

71. Hou Y, Li W, Yang J, *et al*. Is pyroptosis a brake or an accelerator in the fate of the tumor? *Cell Death Dis.* 2025;16(1).

doi: 10.1038/s41419-025-07866-9

72. Hu Y, Liu Y, Zong L, *et al*. The multifaceted roles of GSDME-mediated pyroptosis in cancer: therapeutic strategies and persisting obstacles. *Cell Death Dis.* 2023;14(12).

doi: 10.1038/s41419-023-06382-y

73. Min R, Bai Y, Wang N, Liu X. Gasdermins in pyroptosis, inflammation, and cancer. *Trends Mol Med.* 2025;31(9):860-875.

doi: 10.1016/j.molmed.2025.04.003

74. Xu Z, Zhao Y, Zhang Y, *et al*. Prediction of immunotherapy response of bladder cancer with a pyroptosis-related signature indicating tumor immune microenvironment. *Front Pharmacol.* 2024;15.

doi: 10.3389/fphar.2024.1387647

75. Zhang Y, Luo M, Liao Z, *et al*. Pyroptosis in cancer: a dual regulator of tumor cell fate and immune activation. *Cancer Biol Med.* 2026:1-22.

doi: 10.20892/j.issn.2095-3941.2025.0826

76. Xi R, Cao Y, Fu N, *et al*. Allosteric inhibition of the tyrosine phosphatase SHP2 enhances the anti-tumor immunity of interferon α through induction of caspase-1-mediated pyroptosis in renal cancer. *Int Immunopharmacol.* 2024;143:113498.

doi: 10.1016/j.intimp.2024.113498

77. Hu C, Li Q, Gong S, *et al*. Astragaloside IV: a potential nemesis for gastric cancer. *Front Pharmacol.* 2025;16.

doi: 10.3389/fphar.2025.1636341

78. Xi Y, Zeng S, Tan X, Deng X. Curcumin inhibits the activity of ubiquitin ligase SMURF2 to promote NLRP3dependent pyroptosis in nonsmall cell lung cancer cells. *Int J Oncol.* 2025;66(3).

doi: 10.3892/ijo.2025.5727

79. Yuan R, Zhao W, Wang Q, *et al*. Cucurbitacin B inhibits non-small cell lung cancer in vivo and in vitro by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis. *Pharmacol Res.* 2021;170:105748.

doi: 10.1016/j.phrs.2021.105748

80. Chen X, Yang M, Zhang H, *et al*. Cucurbitacin B induces oral squamous cell carcinoma pyroptosis via GSDME and inhibits tumour growth. *Transl Oncol.* 2025;58:102422.

doi: 10.1016/j.tranon.2025.102422

81. Mi L, He T, Li R, *et al*. Cucurbitacin B in cancer: a comprehensive review of its targets and molecular mechanisms. *Biochem Pharmacol.* 2025;242:117240.

doi: 10.1016/j.bcp.2025.117240

82. Shi J, Tian H, Peng L, *et al*. A nanoplatform reshaping intracellular osmolarity and redox homeostasis against colorectal cancer. *J Control Release.* 2022;352:766-775.

doi: 10.1016/j.jconrel.2022.10.045

83. Gurianov DS, Antonenko SV, Telegeev GD. Nuclear localization of BCR and cortactin indicates their potential role in regulation of actin branching in nucleus. *Exp Oncol.* 2021;43(1):73-76.

doi: 10.32471/exp-oncology.2312-8852.vol-43-no-1.15811

84. Zhou Q, Meng Y, Li D, *et al*. Ferroptosis in cancer: from molecular mechanisms to therapeutic strategies. *Signal Transduct Target Ther.* 2024;9(1).

doi: 10.1038/s41392-024-01769-5

85. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol.* 2021;22(4):266-282.

doi: 10.1038/s41580-020-00324-8

86. Liu H, Yao Q, Wang X, *et al*. The research progress of crosstalk mechanism of autophagy and apoptosis in diabetic vascular endothelial injury. *Biomed Pharmacother.* 2024;170:116072.

doi: 10.1016/j.biopha.2023.116072

87. Stockwell BR. Ferroptosis turns 10: emerging

mechanisms, physiological functions, and therapeutic applications. *Cell.* 2022;185(14):2401-2421.

doi: 10.1016/j.cell.2022.06.003

88. Zhang M, Li J, Hu W. The complex interplay between ferroptosis and atherosclerosis. *Biomed Pharmacother.* 2024;178:117183.

doi: 10.1016/j.biopha.2024.117183

89. Wang M, Zeng G, Xiong B, *et al*. ALOX5 promotes autophagy-dependent ferroptosis by activating the AMPK/mTOR pathway in melanoma. *Biochem Pharmacol.* 2023;212:115554.

doi: 10.1016/j.bcp.2023.115554

90. Zou Y, Li H, Graham ET, *et al*. Cytochrome P450 oxidoreductase contributes to phospholipid peroxidation in ferroptosis. *Nat Chem Biol.* 2020;16(3):302-309.

doi: 10.1038/s41589-020-0472-6

91. Ghosh MK, Mukhopadhyay M, Chatterjee IB. NADPH-initiated cytochrome P450-dependent free iron-independent microsomal lipid peroxidation: specific prevention by ascorbic acid. *Mol Cell Biochem.* 1997;166(1-2):35-44.

doi: 10.1023/a:1006841228483

92. Zhang Y, Xin L, Xiang M, *et al*. The molecular mechanisms of ferroptosis and its role in cardiovascular disease. *Biomed Pharmacother.* 2022;145:112423.

doi: 10.1016/j.biopha.2021.112423

93. Li J, Zhou Y, Liu J, *et al*. Metal-phenolic networks with ferroptosis to deliver NIR-responsive CO for synergistic therapy. *J Control Release.* 2022;352:313-327.

doi: 10.1016/j.jconrel.2022.10.025

94. Xie L, Fefelova N, Pamarthi SH, Gwathmey JK. Molecular mechanisms of ferroptosis and relevance to cardiovascular disease. *Cells.* 2022;11(17):2726.

doi: 10.3390/cells11172726

95. Costa I, Barbosa DJ, Benfeito S, *et al*. Molecular mechanisms of ferroptosis and their involvement in brain diseases. *Pharmacol Ther.* 2023;244:108373.

doi: 10.1016/j.pharmthera.2023.108373

96. Jin X, Tang J, Qiu X, *et al*. Ferroptosis: emerging mechanisms, biological function, and therapeutic potential in cancer and inflammation. *Cell Death Discov.* 2024;10(1).

doi: 10.1038/s41420-024-01825-7

97. Hsieh H, Yu M, Tseng H, Wu Y, Tsai M. Molecular mechanisms and novel therapeutics targeting ferroptosis in gastric cancer: a literature review. *J Cancer.* 2025;16(15):4270-4283.

doi: 10.7150/jca.119757

98. Li Z, Lu Y, Zhen Y, *et al*. Avicularin inhibits ferroptosis and improves cognitive impairments in Alzheimer's disease by modulating the NOX4/NRF2 axis. *Phytomedicine.* 2024;135:156209.

doi: 10.1016/j.phymed.2024.156209

99. Huang H, Yang G, Yang Y, Yan J, Tang X, Pan Q. TFAP2a is a novel regulator that modulates ferroptosis in gallbladder carcinoma cells via the NRF2 signalling axis. *Eur Rev Med Pharmacol Sci.* 2020;24(9):4745-4755.

doi: 10.26355/eurrev_202005_21163

100. Zhang S, Duan S, Xie Z, *et al*. Epigenetic therapeutics targeting NRF2/KEAP1 signaling in cancer oxidative stress. *Front Pharmacol.* 2022;13.

doi: 10.3389/fphar.2022.924817

101. Zheng X, Li H, Lin J, *et al*. METTL3-mediated m6A modification promotes chemoresistance of intrahepatic cholangiocarcinoma by up-regulating NRF2 to inhibit ferroptosis in cisplatin-resistant cells. *J Chemother.* 2024;37(7):596-606.

doi: 10.1080/1120009x.2024.2421700

102. Singh M, Arora HL, Naik R, *et al*. Ferroptosis in cancer: mechanism and therapeutic potential. *Int J Mol Sci.* 2025;26(8):3852.

doi: 10.3390/ijms26083852

103. Yapici FI, Bebber CM, von Karstedt S. A guide to ferroptosis in cancer. *Mol Oncol.* 2024;18(6):1378-1396.

doi: 10.1002/1878-0261.13649

104. Jiang M, Qiao M, Zhao C, Deng J, Li X, Zhou C. Targeting ferroptosis for cancer therapy: exploring novel strategies from its mechanisms and role in cancers. *Transl Lung Cancer Res.* 2020;9(4):1569-1584.

doi: 10.21037/tlcr-20-341

105. Zhao H, Ao L, Sorina, *et al*. Ferroptosis and gastric cancer: from molecular mechanisms to clinical implications. *Front Immunol.* 2025;16.

doi: 10.3389/fimmu.2025.1581928

106. Dou J, Liu X, Yang L, Huang D, Tan X. Ferroptosis interaction with inflammatory microenvironments: mechanism, biology, and treatment. *Biomed Pharmacother.* 2022;155:113711.

doi: 10.1016/j.biopha.2022.113711

107. Gao W, Tan J, Yu C. Ferroptosis in the tumor microenvironment: mechanisms, advances, and therapeutic perspectives. *Front Oncol.* 2025;15.

doi: 10.3389/fonc.2025.1650219

108. Shen G, Liu J, Wang Y, Deng Z, Deng F. Ferroptosis in cancer and inflammatory diseases: mechanisms and therapeutic implications. *MedComm.* 2025;6(9).

doi: 10.1002/mco2.70349

109. Wang J, Guo D, Jiang S, Wu W, Gao X. Targeting ferroptosis in cancer: from mechanistic insights to therapeutic approaches. *Mol Biomed.* 2026;7(1).

doi: 10.1186/s43556-026-00416-5

110. Mouawad N, El Jaafari N, El Sibai M, Abi-Habib RJ. Harnessing ferroptosis for cancer therapy: mechanisms and therapeutic strategies (review). *Oncol Rep.* 2025;55(1):1-17.

doi: 10.3892/or.2025.9029

111. Chen Q, Liu F, Zhang Y, *et al*. Ferroptosis in cancer toward molecular insights and clinical translation in pancreatic cancer. *Mol Cancer.* 2026;25(1).

doi: 10.1186/s12943-025-02567-5

112. Tang Y, Leng J, Luo Y, Luo F. Focusing on ferroptosis in alveolar bone loss during periodontitis: from mechanisms to therapies. *Int Immunopharmacol.* 2025;156:114683.

doi: 10.1016/j.intimp.2025.114683

113. Liu X, Zhang Y, Wu X, *et al*. Targeting ferroptosis pathway to combat therapy resistance and metastasis of cancer. *Front Pharmacol.* 2022;13.

doi: 10.3389/fphar.2022.909821

114. Li Q, Peng F, Yan X, *et al*. Inhibition of SLC7A11-GPX4 signal pathway is involved in aconitine-induced ferroptosis in vivo and in vitro. *J Ethnopharmacol.* 2023;303:116029.

doi: 10.1016/j.jep.2022.116029

115. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. *Cell Res.* 2020;31(2):107-125.

doi: 10.1038/s41422-020-00441-1

116. Pourhabib Mamaghani M, Mousavikia SN, Azimian H. Ferroptosis in cancer: mechanisms, therapeutic strategies, and clinical implications. *Pathol Res Pract.* 2025;269:155907.

doi: 10.1016/j.prp.2025.155907

117. Li Q, Yuan H, Zhao G, *et al*. DDX39B protects against sorafenib-induced ferroptosis by facilitating the splicing and cytoplasmic export of GPX4 pre-mRNA in hepatocellular carcinoma. *Biochem Pharmacol.* 2024;225:116251.

doi: 10.1016/j.bcp.2024.116251

118. Li Y, Wang X, Chen Y, Tan Q, Liu X, Tan C. Clusterin is upregulated by erastin, a ferroptosis inducer and exerts cytoprotective effects in pancreatic adenocarcinoma cells. *Anti-Cancer Drugs.* 2023;35(3):227-236.

doi: 10.1097/cad.0000000000001561

119. Chen Y, Liao X, Jing P, *et al*. Linoleic acid-glucosamine hybrid for endogenous iron-activated ferroptosis therapy in high-grade serous ovarian cancer. *Mol Pharmaceutics.* 2022;19(9):3187-3198.

doi: 10.1021/acs.molpharmaceut.2c00333

120. Qin L, Zhong Y, Li Y, Yang Y. TCM targets ferroptosis: potential treatments for cancer. *Front Pharmacol.* 2024;15.

doi: 10.3389/fphar.2024.1360030

121. Yu H, Kou Q, Yuan H, *et al*. Alkannin triggered apoptosis and ferroptosis in gastric cancer by suppressing lipid metabolism mediated by the c-fos/SREBF1 axis. *Phytomedicine.* 2025;140:156604.

doi: 10.1016/j.phymed.2025.156604

122. Peng L, Hu X, Liu Z, Liu W, Huang Q, Wen Y. Therapeutic potential of resveratrol through ferroptosis modulation: insights and future directions in disease therapeutics. *Front Pharmacol.* 2024;15.

doi: 10.3389/fphar.2024.1473939

123. Mi L, Xing Z, Zhang Y, *et al*. Unveiling gambogenic acid as a promising antitumor compound: a review. *Planta Med.* 2024;90(05):353-367.

doi: 10.1055/a-2258-6663

124. Ni Y, Liu J, Zeng L, *et al*. Natural product manoalide promotes EGFR-TKI sensitivity of lung cancer cells by KRAS-ERK pathway and mitochondrial Ca2+ overload-induced ferroptosis. *Front Pharmacol.* 2023;13.

doi: 10.3389/fphar.2022.1109822

125. Liu X, Zhang Y, Gao H, *et al*. Induction of an MLKL mediated non-canonical necroptosis through reactive oxygen species by tanshinol A in lung cancer cells. *Biochem Pharmacol.* 2020;171:113684.

doi: 10.1016/j.bcp.2019.113684

126. Zhang W, Wang F, Hu C, Zhou Y, Gao H, Hu J. The progress and perspective of nanoparticle-enabled tumor metastasis treatment. *Acta Pharm Sin B.* 2020;10(11):2037-2053.

doi: 10.1016/j.apsb.2020.07.013

127. Su C, Xue Y, Fan S, *et al*. Ferroptosis and its relationship with cancer. *Front Cell Dev Biol.* 2025;12.

doi: 10.3389/fcell.2024.1423869

128. Zhu W, Liu X, Yang L, He Q, Huang D, Tan X. Ferroptosis and tumor immunity: in perspective of the major cell components in the tumor microenvironment. *Eur J Pharmacol.* 2023;961:176124.

doi: 10.1016/j.ejphar.2023.176124

129. Alu A, Han X, Ma X, Wu M, Wei Y, Wei X. The role of lysosome in regulated necrosis. *Acta Pharm Sin B.* 2020;10(10):1880-1903.

doi: 10.1016/j.apsb.2020.07.003

130. Lin C, Sun J, Yang Y, *et al*. Peptide-based nanoassembly enhances ferroptosis in cancer to overcome paclitaxel resistance. *J Control Release.* 2025;384:113895.

doi: 10.1016/j.jconrel.2025.113895

131. Jiang M, Liu L, Wang Z, *et al*. Kanglaite alleviates lung squamous cell carcinoma through ferroptosis. *Int Immunopharmacol.* 2025;144:113616.

doi: 10.1016/j.intimp.2024.113616

132. Mu M, Chen B, Li H, *et al*. Augmented the sensitivity of photothermal-ferroptosis therapy in triple-negative breast cancer through mitochondria-targeted nanoreactor. *J Control Release.* 2024;375:733-744.

doi: 10.1016/j.jconrel.2024.09.042

133. Deng K, Tian H, Zhang T, *et al*. Chemo-photothermal nanoplatform with diselenide as the key for ferroptosis in colorectal cancer. *J Control Release.* 2024;366:684-693.

doi: 10.1016/j.jconrel.2024.01.024

134. Peng H, Jiang Q, Mao W, *et al*. Fe-HCOF-PEG2000 as a hypoxia-tolerant photosensitizer to trigger ferroptosis and enhance ROS-based cancer therapy. *Int J Nanomedicine.* 2024;19:10165-10183.

doi: 10.2147/IJN.S479848

135. Zhang Y, Song Q, Zhang Y, *et al*. Iron-based nanovehicle delivering FIN56 for hyperthermia-boosted ferroptosis therapy against osteosarcoma. *Int J Nanomedicine.* 2024;19:91-107.

doi: 10.2147/ijn.s441112

136. Mu M, Liang X, Zhao N, *et al*. Boosting ferroptosis and microtubule inhibition for antitumor therapy via a carrier-free supermolecule nanoreactor. *J Pharm Anal.* 2023;13(1):99-109.

doi: 10.1016/j.jpha.2022.09.003

137. Wu M, Ling W, Wei J, *et al*. Biomimetic photosensitizer nanocrystals trigger enhanced ferroptosis for improving cancer treatment. *J Control Release.* 2022;352:1116-1133.

doi: 10.1016/j.jconrel.2022.11.026

138. Tian H, Zhou L, Wang Y, Nice EC, Huang C, Zhang H. A targeted nanomodulator capable of manipulating tumor microenvironment against metastasis. *J Control Release.* 2022;348:590-600.

doi: 10.1016/j.jconrel.2022.06.022

139. Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease. *Signal Transduct Target Ther.* 2022;7(1):378.

doi: 10.1038/s41392-022-01229-y

140. Pan Z, Huang L, Gan Y, Xia Y, Yu W. The molecular mechanisms of cuproptosis and small-molecule drug design in diabetes mellitus. *Molecules.* 2024;29(12):2852.

doi: 10.3390/molecules29122852

141. Li S, Bu L, Cai L. Cuproptosis: lipoylated TCA cycle proteins-mediated novel cell death pathway. *Signal Transduct Target Ther.* 2022;7(1).

doi: 10.1038/s41392-022-01014-x

142. Cobine PA, Brady DC. Cuproptosis: cellular and molecular mechanisms underlying copper-induced cell death. *Mol Cell.* 2022;82(10):1786-1787.

doi: 10.1016/j.molcel.2022.05.001

143. Zou Y, Wu S, Xu X, *et al*. Cope with copper: from molecular mechanisms of cuproptosis to copper-related kidney diseases. *Int Immunopharmacol.* 2024;133:112075.

doi: 10.1016/j.intimp.2024.112075

144. Tang D, Chen X, Kroemer G. Cuproptosis: a copper-triggered modality of mitochondrial cell death. *Cell Res.* 2022;32(5):417-418.

doi: 10.1038/s41422-022-00653-7

145. Hao D, Luo W, Yan Y, Zhou J. Focus on cuproptosis: exploring new mechanisms and therapeutic application prospects of cuproptosis regulation. *Biomed Pharmacother.* 2024;178:117182.

doi: 10.1016/j.biopha.2024.117182

146. Xie J, Yang Y, Gao Y, He J. Cuproptosis: mechanisms and links with cancers. *Mol Cancer.* 2023;22(1).

doi: 10.1186/s12943-023-01732-y

147. Wang D, Tian Z, Zhang P, *et al*. The molecular mechanisms of cuproptosis and its relevance to cardiovascular disease. *Biomed Pharmacother.* 2023;163:114830.

doi: 10.1016/j.biopha.2023.114830

148. Guo Z, Chen D, Yao L, *et al*. The molecular mechanism and therapeutic landscape of copper and cuproptosis in cancer. *Signal Transduct Target Ther.* 2025;10(1).

doi: 10.1038/s41392-025-02192-0

149. Zhang T, Wang Y. Multi-omic insight into the molecular mechanism of cuproptosis-related genes in the pathogenesis of Parkinson's disease. *NPJ Parkinsons Dis.* 2026;12(1).

doi: 10.1038/s41531-025-01250-2

150. Li Y, Han Y, Shu Q, Kan Y, Wang Z. Cuproptosis and copper as potential mechanisms and intervention targets in Alzheimer's disease. *Biomed Pharmacother.* 2025;183:117814.

doi: 10.1016/j.biopha.2025.117814

151. Liu N, Chen M. Crosstalk between ferroptosis and cuproptosis: from mechanism to potential clinical application. *Biomed Pharmacother.* 2024;171:116115.

doi: 10.1016/j.biopha.2023.116115

152. Luo C, Wu X, Zhang S, *et al*. Cuproptosis: a novel therapeutic mechanism in lung cancer. *Cancer Cell Int.* 2025;25(1).

doi: 10.1186/s12935-025-03864-1

153. Wang Y, Zhang L, Zhou F. Cuproptosis: a new form of programmed cell death. *Cell Mol Immunol.* 2022;19(8):867-868.

doi: 10.1038/s41423-022-00866-1

154. Tralongo P, Ballato M, Fiorentino V, *et al*. Cuproptosis: a review on mechanisms, role in solid and hematological tumors, and association with viral infections. *Mediterr J Hematol Infect Dis.* 2025;17(1):e2025052.

doi: 10.4084/mjhid.2025.052

155. Fang X, Ji Y, Li S, *et al*. Paeoniflorin attenuates cuproptosis and ameliorates left ventricular remodeling after AMI in hypobaric hypoxia environments. *J Nat Med.* 2024;78(3):664-676.

doi: 10.1007/s11418-024-01781-7

156. Wang Q, Chen H, Lv Z, *et al*. The molecular mechanism of cuproptosis and research progress in pancreatic diseases. *Ann Med.* 2025;58(1).

doi: 10.1080/07853890.2025.2608490

157. Zhang X, Peng Z, Wang Q, Zhang W, Bu Q, Sun D. Copper oxide nanoparticles induce pulmonary inflammation via triggering cellular cuproptosis. *Toxicology.* 2025;514:154131.

doi: 10.1016/j.tox.2025.154131

158. Tang D, Kroemer G, Kang R. Targeting cuproplasia and cuproptosis in cancer. *Nat Rev Clin Oncol.* 2024;21(5):370-388.

doi: 10.1038/s41571-024-00876-0

159. Zhang P, Yang H, Zhu K, *et al*. SLC31A1 identifying a novel biomarker with potential prognostic and immunotherapeutic potential in pan-cancer. *Biomedicines.* 2023;11(11):2884.

doi: 10.3390/biomedicines11112884

160. Jiang D, Zhuang L, Koong AC, Gan B. Cuproptosis in cancer: from molecular mechanisms to therapeutic intervention. *Trends Cancer.* 2026;12(3):275-286.

doi: 10.1016/j.trecan.2025.12.002

161. Huang X, Shen J, Huang K, Wang L, Sethi G, Ma Z. Cuproptosis in cancers: function and implications from bench to bedside. *Biomed Pharmacother.* 2024;176:116874.

doi: 10.1016/j.biopha.2024.116874

162. Springer C, Humayun D, Skouta R. Cuproptosis: unraveling the mechanisms of copper-induced cell death and its implication in cancer therapy. *Cancers.* 2024;16(3):647.

doi: 10.3390/cancers16030647

163. Hu J, Zhu J, Chen T, Zhao Y, Xu Q, Wang Y. Cuproptosis in cancer therapy: mechanisms, therapeutic application and future prospects. *J Mater Chem B.* 2024;12(47):12191-12206.

doi: 10.1039/d4tb01877j

164. Mao L, Lu J, Wen X, *et al*. Cuproptosis: mechanisms and nanotherapeutic strategies in cancer and beyond. *Chem Soc Rev.* 2025;54(13):6282-6334.

doi: 10.1039/d5cs00083a

165. Cong Y, Li N, Zhang Z, Shang Y, Zhao H. Cuproptosis: molecular mechanisms, cancer prognosis, and therapeutic applications. *J Transl Med.* 2025;23(1).

doi: 10.1186/s12967-025-06121-1

166. Qin W, Sheng H, Hu X, Burden RE, Martin SL, Wu H. Cuproptosis in cancer: emerging mechanism and therapeutic opportunities. *Trends Pharmacol Sci.* 2026;47(4):386-402.

doi: 10.1016/j.tips.2026.02.004

167. Wang Y, Chen Y, Zhang J, *et al*. Cuproptosis: a novel therapeutic target for overcoming cancer drug resistance. *Drug Resist Updat.* 2024;72:101018.

doi: 10.1016/j.drup.2023.101018

168. Zhang C, Huang T, Li L. Targeting cuproptosis for cancer therapy: mechanistic insights and clinical perspectives. *J Hematol Oncol.* 2024;17(1).

doi: 10.1186/s13045-024-01589-8

169. Wu T, Wang S, Liu Y, Bai X, Shi C. Roles and mechanisms of cuproptosis for reversing cancer therapeutic resistance. *Int J Pharm.* 2025;685:126267.

doi: 10.1016/j.ijpharm.2025.126267

170. Hao Q, Gan Y, Zhou X. Tackling cuproptosis: from metabolic rewiring to therapeutic exploitation in cancer. *Cell Mol Immunol.* 2026;23(3):239-260.

doi: 10.1038/s41423-026-01387-x

171. Boaru DL, Leon-Oliva DD, Castro-Martinez PD, *et al*. Cuproptosis: current insights into its multifaceted role in disease, cancer, and translational/therapeutic opportunities. *Biomed Pharmacother.* 2025;190:118422.

doi: 10.1016/j.biopha.2025.118422

172. Chen S, Zhang S, Yuan Y, *et al*. Prognostic value of cuproptosis-related genes signature and its impact on the reshaped immune microenvironment of glioma. *Front Pharmacol.* 2022;13.

doi: 10.3389/fphar.2022.1016520

173. Liu T, Zhou Z, Zhang M, *et al*. Cuproptosis-immunotherapy using PD-1 overexpressing T cell membrane-coated nanosheets efficiently treats tumor. *J Control Release.* 2023;362:502-512.

doi: 10.1016/j.jconrel.2023.08.055

174. Guo K, Ren S, Zhang H, *et al*. Biomimetic gold nanorods modified with erythrocyte membranes for imaging-guided photothermal/gene synergistic therapy. *ACS Appl Mater Interfaces.* 2023;15(21):25285-25299.

doi: 10.1021/acsami.3c00865

175. Feng Q, Huo C, Wang M, Huang H, Zheng X, Xie M. Research progress on cuproptosis in cancer. *Front Pharmacol.* 2024;15.

doi: 10.3389/fphar.2024.1290592

176. Du O, Yan Y, Yang H, *et al*. ALPK1 signaling pathway activation by HMGB1 drives microglial pyroptosis and ferroptosis and brain injury after acute ischemic stroke. *Int Immunopharmacol.* 2025;149:114229.

doi: 10.1016/j.intimp.2025.114229

177. Beltrán-Visiedo M, Soler-Agesta R, Sarosiek KA, Green DR, Galluzzi L. Regulation of inflammatory processes by caspases. *Nat Rev Mol Cell Biol.* 2025;26(11):884-901.

doi: 10.1038/s41580-025-00869-6

178. Liu X, Luo Q, Zhao Y, Ren P, Jin Y, Zhou J. The ferroptosis-mitochondrial axis in depression: unraveling the feedforward loop of oxidative stress, metabolic homeostasis dysregulation, and neuroinflammation. *Antioxidants.* 2025;14(5):613.

doi: 10.3390/antiox14050613

179. Zhou B, Zhang J, Liu X, *et al*. Tom20 senses iron-activated ROS signaling to promote melanoma cell pyroptosis. *Cell Res.* 2018;28(12):1171-1185.

doi: 10.1038/s41422-018-0090-y

180. Wang Z, Hu X, Cui P, *et al*. Progress in understanding the role of cGAS-STING pathway associated with programmed cell death in intervertebral disc degeneration. *Cell Death Discov.* 2023;9(1).

doi: 10.1038/s41420-023-01607-7

181. Chen Y, Fang Z, Yi X, Wei X, Jiang D. The interaction between ferroptosis and inflammatory signaling pathways. *Cell Death Dis.* 2023;14(3).

doi: 10.1038/s41419-023-05716-0

182. Wang H, Shu L, Lv C, *et al*. BRCC36 deubiquitinates HMGCR to regulate the interplay between ferroptosis and pyroptosis. *Adv Sci.* 2024;11(11).

doi: 10.1002/advs.202304263

183. Gao M, Yi J, Zhu J, Minikes AM, *et al*. Role of mitochondria in ferroptosis. *Mol Cell.* 2019;73(2):354-363.e3.

doi: 10.1016/j.molcel.2018.10.042

184. Badgley MA, Kremer DM, Maurer HC, *et al*. Cysteine depletion induces pancreatic tumor ferroptosis in mice. *Science.* 2020;368(6486):85-89.

doi: 10.1126/science.aaw9872

185. Wang W, Lu K, Jiang X, *et al*. Ferroptosis inducers enhanced cuproptosis induced by copper ionophores in primary liver cancer. *J Exp Clin Cancer Res.* 2023;42(1).

doi: 10.1186/s13046-023-02720-2

186. Zhou X, Peng S. The cross-talk and interplay between ferroptosis and cuproptosis in tumor and therapeutics. *Cell Oncol.* 2026;49(1).

doi: 10.1007/s13402-025-01138-6

187. Xiong C, Ling H, Hao Q, Zhou X. Cuproptosis: p53-regulated metabolic cell death? *Cell Death Differ.* 2023;30(4):876-884.

doi: 10.1038/s41418-023-01125-0

188. Guo H, Ouyang Y, Yin H, *et al*. Induction of autophagy via the ROS-dependent AMPK-mTOR pathway protects copper-induced spermatogenesis disorder. *Redox Biol.* 2022;49:102227.

doi: 10.1016/j.redox.2021.102227

189. Qiao L, Zhu G, Jiang T, *et al*. Self-destructive copper carriers induce pyroptosis and cuproptosis for efficient tumor immunotherapy against dormant and recurrent tumors. *Adv Mater.* 2023;36(8).

doi: 10.1002/adma.202308241

190. Zhang L, Zhao L, Lin X, *et al*. Comparison of tumor non-specific and PD-L1 specific imaging by near-infrared fluorescence/Cherenkov luminescence dual-modality in-situ imaging. *Mol Imaging.* 2024;23.

doi: 10.1177/15353508241261473

191. Wang Y, Zhao H, Sun K, *et al*. Conductive coordination nanozyme prodrugs precisely trigger pyroptosis, cuproptosis and ferroptosis for in situ cancer vaccination. *Signal Transduct Target Ther.* 2026;11(1).

doi: 10.1038/s41392-026-02607-6

192. Chauhan P, Pandey P, Singh A, *et al*. Exploring the synergetic role of cuproptosis and ferroptosis and their implication in advancing cancer therapeutics. *Discov Oncol.* 2025;16(1).

doi: 10.1007/s12672-025-03150-6