

Nanomaterial-Driven Regulated Cell Death: Mechanistic Insights and Novel Strategies for Tumor Therapy

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Abstract: The rapid development of nanomaterials (NMs) and nanotechnology has profoundly impacted the biomedical field. Due to their unique physicochemical properties, NMs can interact with biological molecules, including proteins and DNA, to induce regulated cell death (RCD). Recent studies have demonstrated that NMs trigger RCD by promoting reactive oxygen species generation, activating signaling proteins, and disrupting intracellular ion homeostasis. Among the various forms of RCD, necroptosis, pyroptosis, ferroptosis, and cuproptosis have garnered significant research attention. Increasing evidence suggests that these emerging RCD pathways are crucial for tumor proliferation and migration, tumor microenvironment (TME) remodeling, and drug resistance mitigation. Accordingly, leveraging NM-driven RCD's effects in designing multifunctional drug delivery systems holds great promise for cancer therapy. NMs can also serve as versatile drug carriers in synergistic treatments with targeting agents, photothermal/photodynamic therapy, and immunomodulators, thereby overcoming the limitations of conventional treatments. Collectively, this review systematically summarizes recent advancements in NM-induced RCD in cancer cells and discusses the diverse roles of RCD in tumor pathology. We highlight the innovative potential of NMs in inducing RCD through precise targeting and synergistic therapy, offering novel strategies to overcome tumor resistance and reshape the immunosuppressive TME.

Keywords: nanomaterials, regulated cell death, cuproptosis, tumor drug resistance, tumor microenvironment

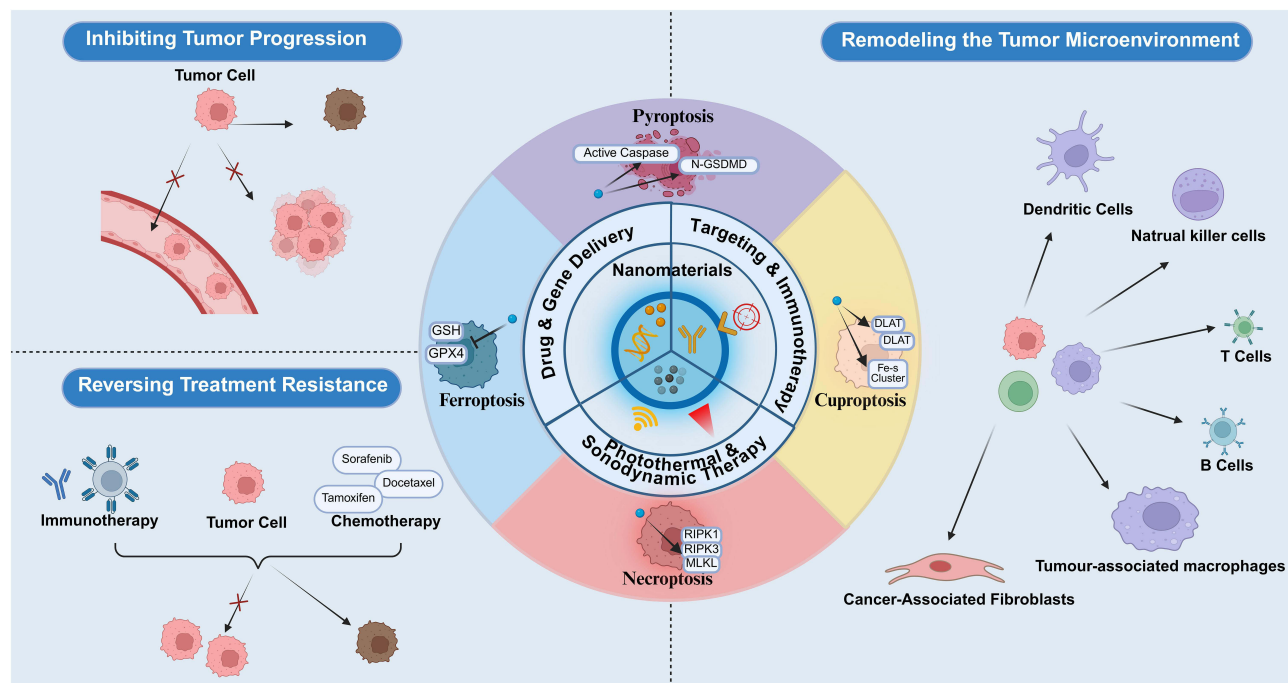
Introduction

Regulated cell death (RCD) refers to forms of cell death induced by activating one or more signal transduction modules.¹ Currently, the primary known types of RCD include autophagic cell death, apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis.² RCD may be initiated when cells fail to adapt to microenvironmental disturbances.³ In recent years, necroptosis, ferroptosis, cuproptosis, and pyroptosis have become research hotspots considering their important role in tumor proliferation and migration,² tumor microenvironment (TME) remodeling,⁴ and tumor drug resistance mechanisms.^{5,6} For example, tumor-associated macrophages (TAMs) in the TME have been reported to transfer ceruloplasmin mRNA to human fibrosarcoma HT1080 cells via extracellular vesicles, leading to reduced intracellular iron content and lipid peroxidation, and thereby inhibiting ferroptosis.⁷ In addition, induction of copper metabolic dysregulation and disruption of Fe-S cluster proteins in cervical cancer cells has been shown to trigger cuproptosis, thereby overcoming cisplatin resistance.⁸

Nanomaterials (NMs) are materials with at least one nanometer-sized dimension (1–100 nm), with a high specific surface area and adjustable optical, electronic, and surface modification capabilities.⁹ By modifying the physical and chemical properties of NMs, such as their shape, structure, and adsorption capacity, researchers can design functional materials with important applications in energy, the environment, and medicine.¹⁰ Traditional cancer treatments like surgery, radiotherapy, and chemotherapy remain challenged by insufficient specificity, systemic toxicity, and drug



Graphical Abstract



resistance. To overcome these limitations, nanomaterial-guided therapeutic strategies have emerged as a promising approach for precise and low-toxicity interventions.^{11,12} As Nanomaterials can precisely target tumors and enhance drug accumulation, thereby reducing damage to healthy tissues.^{13,14} Moreover, by delivering immune stimulatory factors (eg, antigens, adjuvants, and immune checkpoint inhibitors), nanomaterials can directly modulate immune cells, thus enhancing anti-tumor immune responses and reducing systemic toxicity.¹⁵

Notably, a growing body of evidence indicates a close association between nanomaterials and RCD.^{16,17} For example, Si nanoparticles (NPs) induce ferroptosis through two mechanisms: by promoting the accumulation of iron ions, triggering the generation of reactive oxygen species (ROS) and lipid peroxidation; and by depleting glutathione (GSH) and inhibiting glutathione peroxidase-4 (GPX4) activity, which aggravate lipid peroxidation and eventually lead to cell death.¹⁸ ZnO NPs have been reported to increase the levels of necroptosis-related proteins (RIP3, MLKL) and pyroptosis-related proteins (GSDMD, caspase-1) by upregulating Z-DNA-binding protein 1 (ZBP1) expression, thereby triggering necroptosis and pyroptosis simultaneously.¹⁹ These findings suggest that nanomaterial-guided RCD represents a novel direction and strategy for tumor therapy. Indeed, a significant body of research has confirmed this. For example, biomimetic copper-doped polydopamine nanoparticles (PC NPs) can synergize with radiotherapy to inhibit tumor growth. PC NPs can release Cu^{2+} in acidic microenvironments to trigger ferroptosis. Moreover, when combined with radiotherapy, the key ferroptosis protein FDX1 is downregulated most significantly.²⁰ Gao et al designed an Fe-MOF @Erastin@Herceptin nanoplatform that could target HER2-positive breast cancer through trastuzumab modification. By releasing Fe^{3+} and the ferroptosis inducer Erastin, lipid peroxidation and ferroptosis are triggered, resulting in precise ferroptosis therapy for HER2-positive breast cancer.²¹

This review systematically synthesizes the advancements in research concerning NM-induced novel RCD in tumors, with a primary focus on elucidating the key molecular mechanisms involved in the regulation of necroptosis, pyroptosis, cuproptosis, and ferroptosis. Furthermore, the article provides an in-depth analysis of the pivotal role that novel RCD plays in modulating tumor cell growth, invasion, and migration, as well as in reshaping the tumor microenvironment and counteracting tumor drug resistance. Notably, while the therapeutic strategy of integrating NMs with RCD demonstrates

considerable potential, challenges persist regarding the molecular mechanisms of action, pharmacokinetics, and standardized production processes. This review aspires to furnish a theoretical foundation and novel insights for anti-tumor therapies based on NMs, facilitating their more reliable clinical translation.

Nanomaterial-Induced RCD in Tumor Cells: Mechanistic Insights

Necroptosis

Necroptosis is characterized by increased cell size, organelle swelling, and perforation of cell membranes. The most important molecular feature is the formation of necrosomes, which are complexes of receptor-interacting protease 1 (RIP1), receptor-interacting protease 3 (RIP3), and mixed lineage kinase domain-like (MLKL). Many signaling molecules, such as tumor necrosis factor (TNF), lipopolysaccharide, and interferon-gamma (IFN- γ), can induce necroptosis.²² Among them, the most widely reported mechanism is triggered when TNF binds to tumor necrosis factor receptor 1 to form tumor necrosis factor receptor type 1-associated death domain protein (TRADD), which then recruits FAS-associated death domain protein (FADD) and eventually forms RIPK3-MLKL necrosomes to induce necroptosis.²³

NMs have been reported to activate various signaling molecules to induce cell necroptosis. Ag NPs induced necroptosis of human pancreatic ductal adenocarcinoma cells (PANC-1 cells) by increasing the protein levels of RIP1, RIP3, and MLKL.²⁴ Zn NPs induced necroptosis in human breast cancer cells (MCF-7 cells) through a similar mechanism. Moreover, the expression of RIPK1, RIPK3, and MLKL was further enhanced after autophagy inhibitor 3-MA treatment.²⁵ In another study, graphene oxochloroquine nanoconjugates increased the expression of autophagy receptor protein p62 by inducing autophagosome accumulation in human lung adenocarcinoma cells (A549 cells). In addition, the nanoconjugates recruited RIPK1 and promoted the assembly of the RIPK1-RIPK3-MLKL complex on autophagosomes to initiate necroptosis.²⁶ These studies suggest that the level of autophagy may regulate cancer cell necroptosis. An increased level of ZBP1 is also one of the hallmarks of necroptosis. In one study, ZBP1 promoted RIPK3-mediated activation of MLKL in the nucleus, disrupting the nuclear membrane and DNA leakage into the cytoplasm.²⁷ Ag NPs were reported to induce necroptosis in human breast cancer cells (MDA-MB-231 cells) by upregulating ZBP1 expression.²⁸ NMs can also induce cell death by slowing the degradation of necrotizing proteins. A trastuzumab/graphene oxide complex reduced RIPK3 and RIPK1 cleavage by inhibiting the expression of caspase-8 in Osteosarcoma cells. The complex also promoted the formation of complex II containing FADD, TRADD, and RIPK1 by downregulating the cellular inhibitor of apoptosis (cIAP) protein. Together, these two pathways led to necroptosis in cells.²⁹ Similarly, tracheal perfusion of C57 mice with 2 mg/kg Si NPs activated FLICE inhibitory protein in testicular tissue, which competitively bound to caspase-8 and inhibited its cleavage of RIPK3 and RIPK1, ultimately triggering necroptosis.³⁰ We summarized the signaling pathways involved in the induction of necroptosis by NMs and presented them in [Figure 1](#).

Pyroptosis

The classic pyroptosis pathway is mediated by inflammasomes that recognize pathogen-associated molecular patterns and host-derived danger-associated molecular patterns (DAMPs). This leads to the recruitment and activation of caspase-1, which then cleaves gasdermin-D (GSDMD) to form pores in the cell membrane, causing the cell to swell and leak its cellular contents.³¹ An atypical pathway involves caspases-11/4/5, which directly cleave GSDMD in response to lipopolysaccharide and trigger pyroptosis.³² Studies have increasingly suggested that NMs and NP-associated molecular patterns act as novel danger signals of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome.^{33,34} A novel drug delivery system using the homing effect of cancer cell membranes to deliver the composite drug Ca@GOx to mitochondria induced mitochondrial Ca²⁺ overload and generated ROS, thus triggering pyroptosis in tumor cells.³⁵ Other caspases can also initiate pyroptosis. In cancer cells with high expression of gasdermin-E (GSDME), such as SH-SY5Y neuroblastoma cells and MeWo melanoma cells, chemotherapeutic agents such as cisplatin and paclitaxel activate caspase-3 to cleave GSDME, releasing the N-terminal domain, which forms pores in the membrane.³⁶ In melanoma cells, iron ions act as redox enzyme sensitizers, enhancing ROS signaling initiated by chemotherapeutic agents such as sulfasalazine. This promotes oxidation of the mitochondrial outer membrane protein Tom20, which then releases cytochrome c and activates caspase-3 to cleave

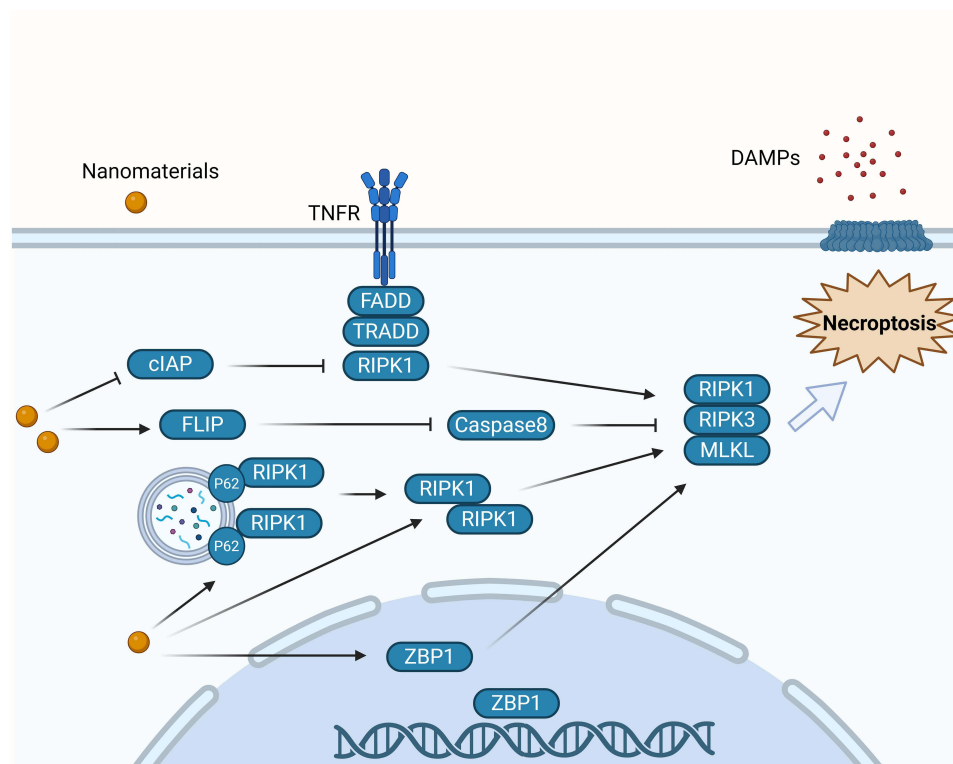


Figure 1 Molecular mechanism of nanomaterial-induced Necroptosis. Nanomaterials downregulate cIAPs and inhibit caspase-8, promoting necroptosis through the formation of complex II (TRADD–FADD–RIPK1) and stabilization of RIPK1/RIPK3. Additionally, nanomaterials upregulate FLICE inhibitory protein (FLIP), which interferes with caspase-8 activation and further enhances necrosome assembly. Nanomaterials also increase p62 expression and autophagosome accumulation, facilitating the recruitment of RIPK1–RIPK3–MLKL complexes to autophagosomes. In the nucleus, nanomaterials elevate ZBP1 levels, which activate RIPK3 and MLKL, ultimately leading to necroptosis.

GSDME, inducing pyroptosis.³⁷ GSDME levels largely constrain the efficiency of caspase-3-mediated pyroptosis. A biomimetic NP loaded with decitabine increased the cytochrome c content in the cytoplasm after internalization in the cell, thereby activating caspase-3. Decitabine inhibited DNA methylation, upregulated GSDME expression, enhanced caspase-3 cleavage of GSDME, and promoted pyroptosis in cancer cells.³⁸ We summarized the signaling pathways involved in the induction of pyroptosis by NMs and presented them in [Figure 2](#).

Ferroptosis

The morphological characteristics of the mitochondria are important indicators by which ferroptosis is distinguished from other forms of RCD. Electron microscopy revealed mitochondrial shrinkage, degradation, and loss of cristae, as well as increased membrane density after ferroptosis was induced in cells. The accumulation of ROS and lipid peroxides (LPOs) is widely considered the primary cause of ferroptosis. NMs generate toxic hydroxyl radicals ($\bullet\text{OH}$) via Fenton reactions involving iron ions, which produce high levels of ROS that cause lipid peroxidation of the cell membrane and ultimately induce ferroptosis.³⁹ For example, body-centered cubic Fe NPs efficiently catalyzed Fenton reactions under acidic conditions (pH 5.5), generated ROS, and induced LPO accumulation in HepG2 liver cancer cells, leading to ferroptosis (shown in [Figure 3](#)).⁴⁰ GSH reduces toxic lipid peroxides (L-OOH) to alcohols (L-OH). Thus, inhibiting this process is an effective means of inducing ferroptosis.⁴¹ Zhang et al encapsulated imidazole ketone erastin (a system Xc^- inhibitor) in polyethylene glycol NPs to reduce GSH synthesis by inhibiting the amino acid antiporter system Xc^- and successfully induced ferroptosis.⁴² Similarly, Gao et al used nanopolymer micelles to deliver RSL3 (a GPX4 inhibitor) to cancer cells. This reduced the activity of GPX4, weakened the GSH reduction reaction, and induced ferroptosis.⁴³

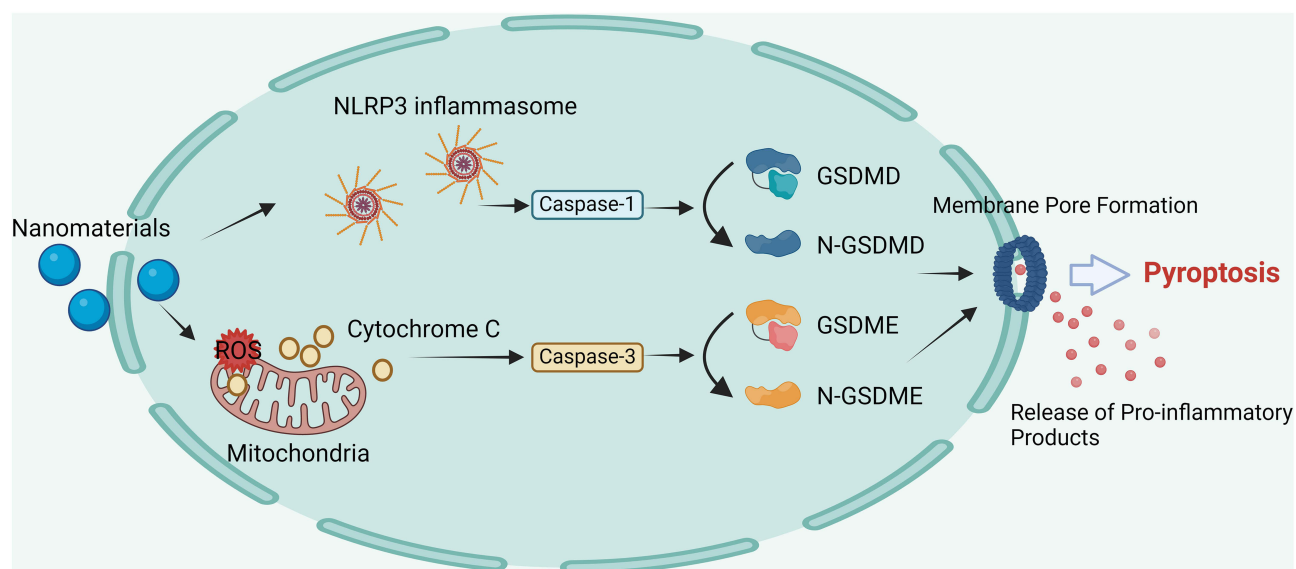


Figure 2 Molecular mechanism of nanomaterial-induced pyroptosis. Nanomaterials activate the NLRP3 inflammasome, leading to caspase-1 activation and cleavage of GSDMD into N-GSDMD, which forms membrane pores and promotes the release of pro-inflammatory products. Additionally, nanomaterials induce mitochondrial ROS accumulation and damage, triggering Cytochrome C release and caspase-3 activation, which cleaves GSDME into N-GSDME. These processes collectively result in pyroptosis through membrane pore formation and the release of pro-inflammatory products.

Cuproptosis

The morphological features of cuproptosis include cell membrane rupture, mitochondrial shrinkage, and chromatin fragmentation. Ferredoxin 1 (FDX1), lipoic acid synthase (LIAS), and dihydrolipoamide S-acetyltransferase (DLAT) are key proteins involved in cuproptosis. FDX1 is a crucial upstream regulator of cuproptosis. FDX1 reduces Cu^{2+} to Cu^{+} and regulates protein lipoylation. Lipoic acid, synthesized by LIAS, is a necessary substrate for protein lipoylation. After Cu^{+} accumulates within a cell, it binds to lipoylated proteins (particularly DLAT) and induces their oligomerization, which also lowers the levels of Fe-S cluster proteins in the mitochondria. Together, these effects lead to protein toxicity stress and ultimately cuproptosis.⁴⁴ Su et al discovered that CuO NPs increased Cu^{2+} levels in HTR8/SVneo human trophoblast cells, leading to DLAT oligomerization that triggered cuproptosis.⁴⁵ Moreover, CuO NPs were shown to activate the p53 pathway and deplete GSH, causing apoptosis and ferroptosis. Further research has indicated that GSH depletion is a common regulatory mechanism for both ferroptosis and cuproptosis.⁴⁶ Supplementing tumor cells with GSH can simultaneously inhibit ferroptosis and cuproptosis through the following mechanisms: (1) as an antioxidant, GSH prevents LPO, and (2) as a copper chaperone, GSH binds to copper, reducing the aggregation of lipoylated proteins.⁴⁷ Additionally, p53 regulates cuproptosis by upregulating the expression of ferredoxin reductase and influencing electron transfer in the mitochondrial respiratory chain, thereby affecting two key steps in the cuproptosis pathway, Fe-S clustering and GSH biosynthesis.⁴⁸ These findings indicate crosstalk between different programmed cell death mechanisms, and regulating a single signaling molecule can affect multiple cell death pathways. The mechanism of ferroptosis and cuproptosis caused by NMs is demonstrated in Figure 4. A detailed summary of NM-induced RCD, including NMs' characteristics, experimental conditions, and molecular mechanisms, is provided in Table 1.

Integrating RCD Into Tumor Biology

Tumor Cell Proliferation, Invasion, and Metastasis

RIPK1-RIPK3-MLKL Pathway

Necroptosis is closely associated with malignant tumor phenotypes. Necroptosis defects and the low expression of related molecules often contribute to tumor initiation and progression.⁵⁵ In colorectal cancer (CRC) cells, tumor necrosis factor receptor-associated factor 6 promoted the polyubiquitination and subsequent degradation of RIPK1, consequently suppressing the assembly of the RIPK1-RIPK3-MLKL necroptotic complex and facilitating tumor cell proliferation.⁵⁶

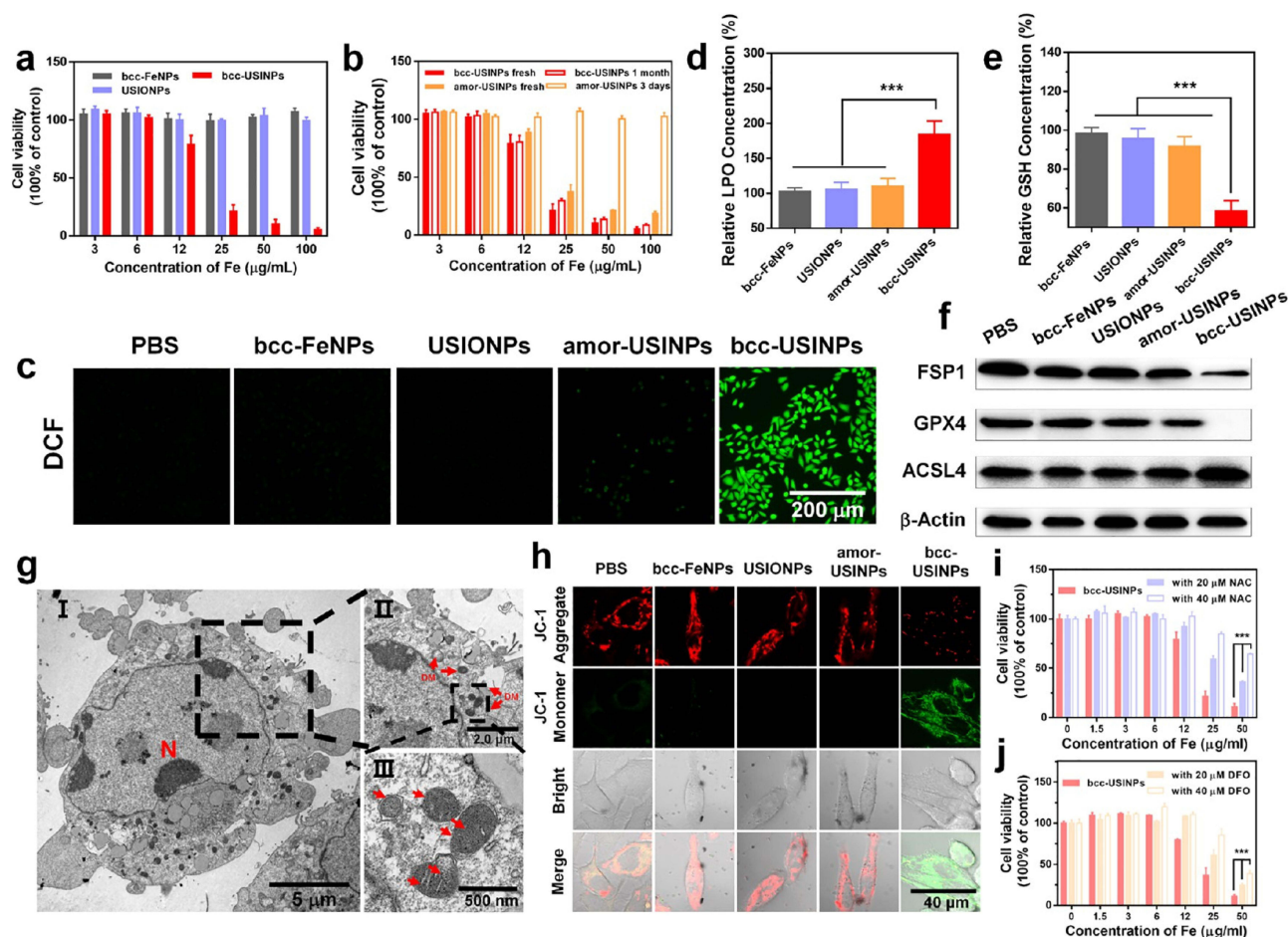


Figure 3 In vitro assessment of the cytotoxicity and ferroptosis of bcc-USINPs. (a) Relative cell viability of HepG2 cells after being incubated with 15 nm bcc-Fe NPs, USIONPs, and bcc-USINPs for 24 h. (b) Comparative cytotoxicity of fresh prepared bcc-USINPs, 1-month air-exposed bcc-USINPs, fresh prepared amor-USINPs, and 3-day air-exposed amor-USINPs for HepG2 cells after 24 h incubation. (c) Fluorescence microscope images of HepG2 cells after incubation with PBS, bcc-Fe NPs, USIONPs, amor-USINPs, and bcc-USINPs at a concentration of 20 $\mu\text{g/mL}$ for 4 h and subsequently stained with ROS fluorescence probe DCFH-DA. Scale bar: 200 μm . (d and e) Relative (d) LPO content and (e) GSH content of HepG2 cells treated with different nanoparticles (20 $\mu\text{g/mL}$). (f) Expression of FSP1, GPX4, and ACSL4 in HepG2 cells after being incubated with bcc-Fe NPs, USIONPs, amor-USINPs, or bcc-USINPs at a concentration of 20 $\mu\text{g/mL}$ for 12 h. (g) Bio-TEM image of the cross section of HepG2 cell (I) and its local view (II, III) after being incubated with bcc-USINPs for 4 h. N indicates nucleus, DM indicates damaged mitochondrion. (h) CLSM images of HepG2 cells after incubation with different nanoparticles and stained with JC-1. Green fluorescence was emitted by cytosolic JC-1 monomers, which indicates $\Delta\psi\text{m}$ dissipation. The JC-1 aggregates in healthy mitochondria emitted red fluorescence. Scale bar: 40 μm . (i and j) Relative cell viability of HepG2 cells after being incubated with (i) bcc-USINPs + NAC and (j) bcc-USINPs + DFO. *** $P < 0.001$ indicates statistical significance.⁴⁰ Copyright © 2021, American Chemical Society.

Erigeron breviscapus enhanced the phosphorylation of RIPK3 and MLKL in CRC, leading to ROS generation and necrosome formation, which significantly suppressed tumor proliferation.⁵⁷ RIP3 expression levels were shown to determine CRC tumor cell sensitivity to necroptosis.⁵⁸ Studies have confirmed that abnormal DNA methylation leads to RIP3 deficiency and necroptosis defects in many tumor cell types, thereby enhancing malignant proliferation and tumor cell survival.⁵⁵ Interestingly, Vucur et al reported that chronic activation of necroptosis in hepatocytes promoted hepatocarcinogenesis in mice, potentially by increasing the levels of cytokines and chemokines released by cells.⁵⁹ Liu et al summarized the role of necroptosis in tumors and proposed that low-level, chronic necroptosis enhanced the infiltration of immunosuppressive cells in the tumor microenvironment by continuously releasing immunosuppressive molecules such as CXCL1, thereby promoting tumor growth. In contrast, high levels of necroptosis induced the release of immunostimulatory cytokines, which exerted anti-tumor effects.⁶⁰ Tumor necrosis is often associated with tumor invasiveness and metastasis, and necroptosis cells are frequently found near necrotic areas in solid tumors.⁶¹ In one study, compared with pancreatic ductal adenocarcinoma (PDAC) patients without metastasis, those with early liver metastasis exhibited increased MLKL expression and enhanced necroptotic signaling. Specifically, MLKL-driven necroptosis recruited macrophages, strengthened the tumor's CD47 “don't eat me” signal, and induced macrophages to

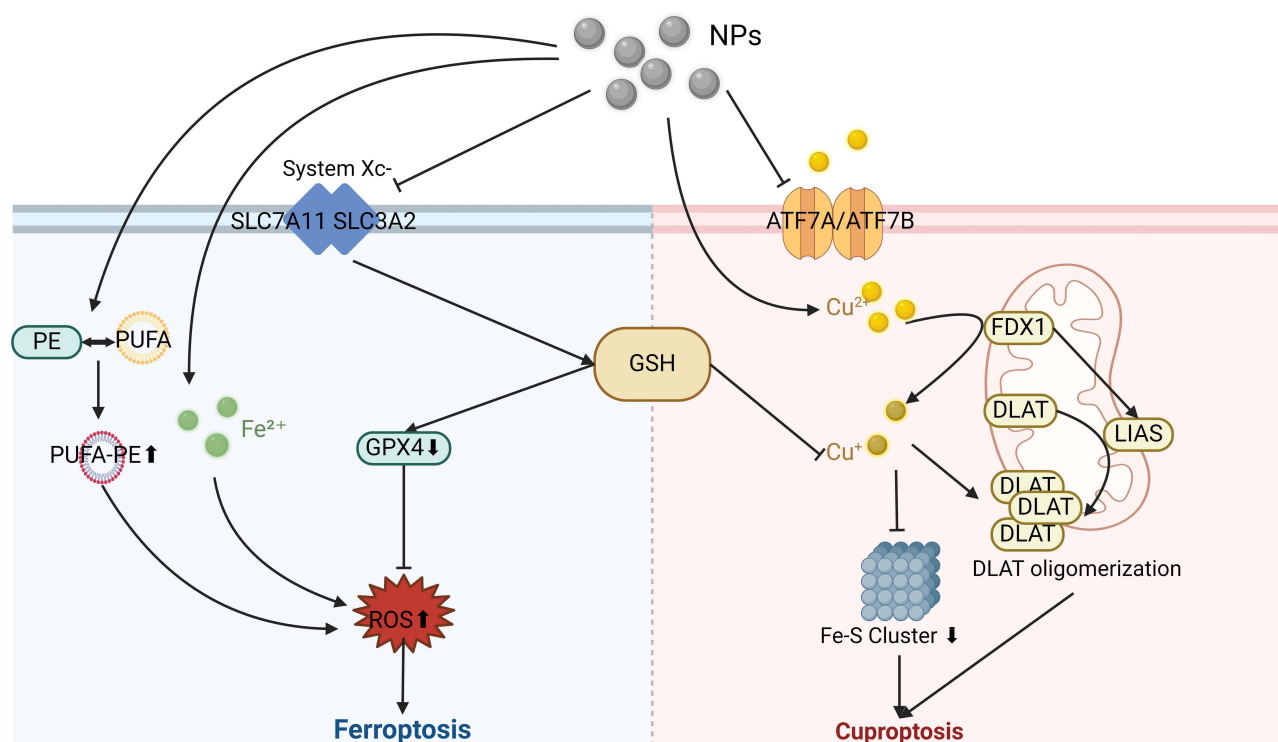


Figure 4 Molecular mechanism of nanomaterial-induced ferroptosis and cuproptosis. Nanomaterials deliver Fe^{2+} into the cell, which generates toxic $\cdot\text{OH}$ via the Fenton reaction, producing large amounts of ROS and causing Ferroptosis. By inhibiting system Xc^- conveying cystine into cells, nanomaterials also down-regulate GSH and GPX4 levels to generate ROS; this result can also be achieved by inducing the binding of PUFA to PE. On the other side, nanomaterials can deliver excess Cu^{2+} to the cell, which is converted by FDX1 to the more toxic Cu^+ . This ultimately leads to Cuproptosis by promoting DLAT oligomerization and reducing the synthesis of the Fe-S Cluster. During this process, Cu^{2+} overload can be facilitated by inhibiting the Cu^{2+} transporter ATPases ATP7A and ATP7B or down-regulating GSH level.

form extracellular traps, which facilitated the epithelial-mesenchymal transition (EMT) and extracellular matrix degradation and ultimately promoted PDAC liver metastasis.⁶² Additionally, tumor cells can express amyloid precursor protein, which was shown to interact with death receptor 6 to induce necroptosis in endothelial cells, creating channels that allowed tumor cells to extravasate and migrate.⁶³

NLRP3/GSDMD Pathway

The NLRP3 inflammasome is a key molecule that recognizes pyroptosis signals, and it has a double-edged role in tumor cell invasion, proliferation, and metastasis.⁶⁴ In hepatocellular carcinoma (HCC), significant downregulation or loss of NLRP3 expression promoted tumor progression.⁶⁵ He et al also reported that the virulence factor CagA produced by *Helicobacter pylori* enhanced gastric cancer cell invasion and migration by activating the NLRP3 inflammasome and inducing ROS production.⁶⁶ However, in some instances, NLRP3 activation instead promotes cancer growth. IL-1 β secretion induced by NLRP3 activation was shown to be crucial in the proliferation, invasion, and migration of breast cancer cells and gastric cancer cells.^{67,68} In an animal study, tumor growth and metastatic capacity were lower in *NLRP3*-knockout mice injected with breast tumor cells (PyT8) than in wild-type mice.⁶⁹ Another group of pyroptosis effector proteins, the gasdermin family, has also gained attention for its role in tumor progression.⁷⁰ Xu et al found that higher GSDMD expression in non-small cell lung cancer was closely associated with increased tumor size and accelerated late-stage metastasis.⁷¹ The EGFR/Akt signaling pathway is involved in tumor cell proliferation, migration, and angiogenesis.⁷² In non-small cell lung cancer, GSDMD downregulation inhibited tumor proliferation by promoting apoptosis and suppressing EGFR/Akt signaling.⁷³ In contrast, in both in vitro and in vivo models of gastric cancer, GSDMD downregulation activated the STAT3 and PI3K/PKB signaling pathways, which facilitated the S/G2 phase transition and significantly promoted tumor proliferation.⁷⁴ Similarly, high expression of GSDMB and GSDME was

Table I Nanomaterial-Induced Regulated Cell Death Under in vitro and in vivo Conditions

RCD	NMs	Size +Coating	Cell Line	Dose and Incubation Time	Animal Model	Administration	Molecular Mechanism	Reference
Necroptosis	Ag NPs	2.6 nm, 18 nm coating: formvar	PANC-1	2.6 nm Ag NPs at 0.5, 1.5, 2.5, 3.5, 5 µg/mL for 24 h; 18 nm Ag NPs at 5, 10, 25, 50, 100 µg/mL for 24 h	-	-	Upregulate MLKL, RIP1 and RIP3 protein level	[24]
	Zn NPs	63.7 ± 6.5 nm	MCF-7, MCF-10A	10 µmol/mL	-	-	Upregulate MLKL, RIP1 and RIP3 protein level	[25]
	Si NPs	57.66 nm	-	-	C57 male mice (6–7 week)	Tracheal perfusion (2 µg/g every 3 days for 45 days)	Upregulate MLKL, RIP1 and RIP3 protein level	[30]
	Gold and silver alloy	10-20 nm	MDA-MB-231, LNCaP	30,40, and 50 µg/mL for 23 h	-	-	Trigger the ZPBI-dependent necroptotic pathway	[28]
Pyroptosis	Ca@GOx	154.4±0.42 nm	4T1 cells	0.2 µg/mL for 24h	Female mice (6–8 week)	Intravenous injection (0.25 mg/kg)	1. Induce mitochondrial Ca ²⁺ overload 2. Upregulate ROS	[35]
	ZnO NPs	In water: 206.9 nm In medium: 951.3 nm In serum: 49.69 nm	EpH4-Ev cells	16 µg/mL for 24 h	ICR mice (12–15-day, 50–60 g)	Intravenous injection (1, 3 and 5 mg/kg)	Trigger the caspase-1/GSDMD signaling pathway by upregulating ZBP1	[19]
	CM NAs	50 nm	4T1, B16F10, CT26, and MC38	1 µg/mL Ce6 and 0.5 µg/mL MTO for 4 h	C57BL/6 mice and BALB/c mice (5–6 week)	Intravenous injection (a dose of 6 mg/kg Ce6 and 3 mg/kg MTO)	Trigger the caspase-3/GSDME signaling pathway	[49]
	Biomimetic nanoparticle	114 nm	4T1 cells	ICG 40µg/mL DCT 7.6µg/mL for 24h	Female BALB/c mice (6 week)	Intravenous injection (ICG: 1 mg/kg, DCT: 0.19 mg/Kg)	ICG: 1. Upregulate cytoplasmic Ca ²⁺ 2. Induce the release of cytochrome c and the activation of caspase-3 DCT: Trigger the caspase-3/GSDME signaling pathway	[38]

Ferroptosis	IRGD-bcc-USINPs	3.8±0.8 nm	HTR8/SVneo cells and human endometrial stromal cells	500 µg/mL for 6d	Adult female and male Sprague–Dawley rats, (10–12 week)	Intravenous injection (1 mg/kg, 10 mg/kg, 1 mg/kg for 3 times)	Upregulate ROS and LPO through Fenton reaction	[40]
	Si NPs	50 nm	The human umbilical vein endothelial cell	6.25, 12.5, 25, 50, 100 µg/mL for 24 h	-	-	1. Upregulate ROS and LPO 2. Upregulate the intracellular iron level 3. Deplete GSH	[18]
	PEG-PLGA NPs	80 nm	DLBCL	10 mg/mL for 24h	NCG mice (6 week)	Intraperitoneal injection (23 mg/kg every day for 14 days)	1. Upregulate ROS and LPO 2. Deplete GSH	[42]
	①ZVI@Ag ②ZVI@CMC	①97.1±19.3 nm ②78.8±19.8 nm	Human lung cancer cell lines, LLC, MRC-5, IMR-90, HUVEC	5 and 10 µg/mL for 24h	BALB/c nude mice, NOD/SCID mice (5–6week) and C57BL/6 mice (6 week)	Intratymoral injection (25 mg/kg for 60 days)	1. Inhibit Nrf2-dependent cytoprotective pathway 2. Trigger AMPK/mTOR signaling pathway	[50]
Cuproptosis	CuO NPs	100 nm	PHTR8/SVneo cells and human endometrial stromal cells	500 µg/mL for 6d	Adult female and male Sprague–Dawley rats (10–12week)	Intrauterine injection (20 µL at concentrations of 200, 500, and 1000 µg/mL)	Upregulate the intracellular Cu ²⁺ level	[45]
	ZCA NSs	2 nm	CT26 colon cancer cells and normal HUVEC	50 µg/mL for 6 h	Female Balb/c mice (4–6 week)	Intratumor injection (5 mg/kg for 10min)	Upregulate the intracellular Cu ²⁺ level	[51]
	CS/NPs	108.2 nm	MCF-7 and 4T1 cell	0.58, 1.16, 2.90, 5.80, 11.60 µg/mL DOX for 4h	Female BALB/c and BALB/c-Nude mice, (6 week and weigh 16–22 g)	Vein injection (4.5 mg/kg every other day for 15 days)	1. Upregulate the intracellular Cu ²⁺ level 2. Damage mitochondria	[52]
	HMME-RGD @C3F8 NBs	220nm	HepG2 cells and HepG2 cells	2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25 µg/mL for 12h	Male BALB/c Nude mice (6 week)	Vein injection (5 mg/kg for 12h)	Upregulate the intracellular Cu ²⁺ level	[53]

(Continued)

Table 1 (Continued).

RCD	NMs	Size +Coating	Cell Line	Dose and Incubation Time	Animal Model	Administration	Molecular Mechanism	Reference
Cross interactions	R-CM@MSN@BC	141.62 nm coating: Erythrocyte membrane	HIBEpic cells	5,10,20,50,100 µg/mL for 24 h	Male C57BL/6 and Balb/c nude mice (4–6 week)	Vein injection (5 mg/kg for 48h)	1.Upregulate ROS, causing Necroptosis 2.Necroptosis resulted in the release of DAMPs, causing Immunogenic Cell Death	[54]
	CuO NPs	100 nm	PHTR8/SVneo cells and human endometrial stromal cells	500 µg/mL for 2d, 4d and 6d	Adult female and male Sprague–Dawley rats (10–12week)	Intrauterine injection (20 µL at concentrations of 200, 500, and 1000 µg/mL)	1.Upregulate the intracellular Cu ²⁺ level, causing Cuproptosis 2.Reduce GPX4 activity and Upregulate ROS and LPO through the Fenton reaction, causing Ferroptosis	[45]

shown to promote the proliferation and invasion of breast cancer cells, bladder cancer cells, and colorectal cancer cells.^{75,76}

SLC Family Signaling

A growing body of evidence suggests that activating ferroptosis suppresses tumor cell proliferation. The expression of tumor suppressor genes such as *P53* and BRCA1-associated protein 1 induces ferroptosis by inhibiting SLC7A11 (the light chain of system Xc⁻) transcription and by deubiquitination, respectively, thereby restraining tumor cell proliferation.^{77,78} Consequently, tumors have developed mechanisms for evading ferroptosis, including reducing ROS levels and decreasing lipid peroxidation, which then promotes proliferation.^{79–81} SLC7A11 and SLC3A2 form system Xc⁻, a crucial signaling complex in the ferroptosis pathway, which primarily regulates ferroptosis by modulating glutamate-cysteine exchange. Upregulated integrin ITGB3 increased SLC7A11 expression in platelet-derived extracellular vesicles from nasopharyngeal carcinoma patients, inhibiting ferroptosis and promoting invasion and distant metastasis of nasopharyngeal carcinoma cells, whereas *SLC7A11* knockdown significantly reduced nasopharyngeal carcinoma cell adhesion, colony formation, and migration.⁸² In gastric cancer, ubiquitin-mediated degradation of stearyl-CoA desaturase, a lipid metabolism enzyme, increased lipid peroxidation, induced ferroptosis, and suppressed tumor migration.⁸³ The EMT is a key process in cancer metastasis that enhances tumor cell motility and invasiveness by downregulating epithelial genes and upregulating mesenchymal genes.⁸⁴ There are multiple interactions between ferroptosis-related molecular signals and the EMT.⁸⁵ For example, in pancreatic ductal adenocarcinoma, SMAD4 increased ferroptosis susceptibility by downregulating GPX4 expression and also promoted cancer cell invasion and migration by facilitating the EMT through the TGF-β1 signaling pathway.⁸⁶ Additionally, Bi et al reported that metadherin increased ferroptosis susceptibility by inhibiting GPX4 and SLC3A2 and by positively regulating the EMT, thereby promoting invasion and migration in triple-negative breast cancer (TNBC) and endometrial cancer.⁸⁷

FDX1/DLAT Signaling

Several cuproptosis-related genes (CRGs) have been shown to be closely associated with tumor progression and metastasis. For example, *FDX1*, a key gene regulating cuproptosis, suppressed colorectal cancer growth and invasion by delaying the EMT progression.⁸⁸ Wang et al also demonstrated that FDX1 overexpression reduced HCC proliferation, and in vivo experiments showed a decrease in pulmonary metastases.⁸⁹ Moreover, FDX1 downregulation activated the PI3K/AKT signaling pathway, inducing mitophagy of damaged mitochondria to maintain metabolic stability, and ultimately promoted HCC progression. DLAT is an upstream regulator of cuproptosis. Peng et al found that silencing *DLAT* caused gastric cancer cells to arrest in the G0/G1 phase, effectively inhibiting their proliferation.⁹⁰ Notably, increasingly more research has focused on the association between CRGs and tumor development, suggesting that targeting CRGs such as *LIAS*, *CTR1*, *ATP7A*, and *ATP7B* using gene therapy holds promise for cancer treatment.⁹¹

Tumor Microenvironment

The TME is a multifaceted ecosystem comprising tumor cells, immune cells, stromal cells, and other components. These elements interact in a complex manner to collectively influence tumor growth and progression. Immune cells are critical in the TME. CD8⁺ T cells and regulatory T cells primarily exhibit anti-tumor effects, while myeloid-derived suppressor cells (MDSCs) exert immunosuppressive functions, promoting tumor development. Additionally, CD4⁺ T cells, B cells, neutrophils, macrophages, and monocytes often play dual roles in tumor progression and immunity.⁹²

Dual Role of RIPK3/RIP3

Necroptosis leads to the release of intracellular contents, generating DAMPs that alter cell communication, cell fate decisions, and immune responses in the TME.^{93,94} The level of the necroptosis-related molecule RIPK3 is closely associated with anti-tumor immunity. In HT-29 colorectal cancer cells and SNU-620 gastric cancer cells, necroptosis led to upregulated RIPK3 expression, which activated the NF-κB signaling pathway and promoted the secretion of inflammatory cytokines such as IL-1β and CCL4. This mechanism enhanced the activity of dendritic cells (DCs) and CD8⁺ T cells in the TME and ultimately promoted tumor antigen presentation and tumor-killing effects.⁹⁵ Moreover, RIPK3 was shown to promote IFN-β release, which facilitated CD4⁺ T cell activation and infiltration into tumor sites,

further shaping an anti-tumor TME.⁹⁶ Conversely, RIPK3 downregulation activated the PPAR pathway, promoting the polarization of TAMs toward the M2 phenotype and ultimately fostering tumor growth.⁹⁷ Notably, the role of necroptosis signaling molecules in the TME is more complex than previously thought. In PDAC and colitis-associated colorectal cancer, high RIP3 expression activated CXCL1 signaling, which recruited MDSCs and TAMs for a pro-tumorigenic TME.^{98,99}

Immune Cells and Signals of Ferroptosis

Immune cells in the TME regulate tumor ferroptosis by releasing various signaling molecules.¹⁰⁰ For example, activated CD8⁺ T cells release IFN- γ , which downregulates SLC3A2 and SLC7A11 expression in system Xc⁻; this reduces cystine uptake in tumor cells and ultimately promotes lipid peroxidation and ferroptosis.¹⁰¹ In contrast, TAMs in the TME inhibited ferroptosis by transferring ceruloplasmin mRNA via extracellular vesicles to human fibrosarcoma HT1080 cells, which reduced intracellular iron levels and lipid peroxidation.⁷ Ferroptosis also occurs in immune cells, which affects tumor progression. Ma et al found that CD8⁺ T cells upregulated CD36 expression, increasing arachidonic acid uptake, which in turn triggered ferroptosis and reduced the number of CD8⁺ T cells in the TME, ultimately promoting tumor progression.¹⁰² Similarly, ferroptosis in MDSCs led to the production of prostaglandin E2 and oxidized arachidonic acid-phosphatidylethanolamine, thereby suppressing CD8⁺ T cells and promoting a tumor-supportive TME.¹⁰³ Moreover, cancer-associated fibroblasts (CAFs) in the TME could release exosomes containing lncRNA FTX, which, upon being taken up by oral squamous cell carcinoma (OSCC) cells, led to the demethylation of the flap endonuclease-1 promoter, thereby inhibiting ferroptosis and facilitating tumor invasion and migration.¹⁰⁴ Interestingly, ferroptosis also activates anti-tumor immunity. In TAMs, APOC1 downregulation increased intracellular iron levels and ROS, which induced ferroptosis and subsequently promoted the polarization of other TAMs into the M1 phenotype, thereby inhibiting hepatocellular carcinoma growth.¹⁰⁵

Immune Cells and Signals of Pyroptosis

Pyroptotic tumor cells release tumor-associated antigens,¹⁰⁶ which activate anti-tumor immune responses. Some pyroptosis-derived factors also act as DAMPs,^{107,108} which either promote inflammation or suppress immune responses. For example, IL-1 β and TNF- α released from pyroptotic cells induced IL-8 production in an NF- κ B-dependent manner, recruiting MDSCs to the TME and suppressing tumor immunity.¹⁰⁹ Blocking IL-1 β converted an immunosuppressive TME into an anti-tumor immune environment by increasing CD8⁺ T-cell infiltration and inhibiting neutrophils and MDSCs.¹¹⁰ The gasdermin family is also important in tumor immunity.^{34,111} It was found that IFN- γ in the TME induced GSDMB expression in tumor cells; granzyme A produced by NK (Natural Killer) cells and cytotoxic T lymphocytes killed the GSDMB-positive tumor cells via the cell pyroptosis pathway.¹¹² In addition, granzyme B secreted by NK cells was shown to induce tumor cell pyroptosis and enhance anti-tumor immunity by directly cleaving GSDME.¹¹³ TAMs are abundant in the TME, and because they primarily exhibit an immunosuppressive M2 phenotype, the TME is usually in an immunosuppressed state. However, inflammatory factors released by pyroptotic tumor cells were shown to promote the release of INF- γ from NK cells and T cells, which in turn promoted the polarization of TAMs toward the immunoreactive M1 phenotype.¹¹⁴ TAMs also increased the number of CD8⁺ T cells, CD4⁺ T cells, and NK cells in the TME, while significantly decreasing the number of neutrophils, MDSCs, and monocytes.¹¹⁵ These changes in immune cell populations ultimately remodel the immunosuppressive TME into an immunogenic TME with anti-tumor effects.^{116,117}

Interactions Between CRGs, Immune Cells, or CAFs

Cuproptosis influences immune cell infiltration into the TME. In hepatocellular carcinoma, increased expression of CRGs such as *DLAT*, *GLS*, and *CDKN2A* correlated with the activation of the TGF- β -mediated immunosuppressive pathway, whereas their downregulation was associated with increased numbers of T memory and macrophage FCN1+ cells, suggesting that downregulation of these genes enhanced anti-tumor immunity.¹¹⁸ Similarly, in bladder cancer, high cuproptosis activity correlated with reduced immune cell infiltration, including decreased levels of CD4⁺ T cells, CD8⁺ T cells, DCs, and NK cells.¹¹⁹ Notably, different cuproptosis signals generated the opposite immune response. For example, in colorectal cancer, upregulation of the CRG *DLAT* increased the number of CD8⁺ GZMK⁺ T cells, activating anti-tumor immunity. However, *COX17* expression promoted tumor growth by increasing the level of exhausted CD8⁺

PDCD1⁺ T cells and generating immunosuppressive CD4⁺ CXCL13⁺ T cells. Studies on non-immune cells in the TME have focused on cancer-associated fibroblasts (CAFs), which are implicated in angiogenesis, tumor metabolism, and connective tissue proliferation and contribute to cancer immune evasion.¹²⁰ In studies of colon adenocarcinomas, high expression of FDX1 inhibited tumor growth and metastasis, which was closely related to the low level of infiltrating CAFs.¹²¹ In contrast, Li et al found that extensive proliferation of CAFs in oral squamous cell carcinoma significantly increased the expression of the CRGs *GLS* and *MTF1*, which in turn affected tumor cell copper homeostasis.¹²² Moreover, CAFs released exosomes containing downregulated miR-148b-3p, resulting in the upregulation of *ATP7A* expression in OSCC, ultimately inhibiting cuproptosis and promoting the malignant phenotype of the tumor.¹²³

Treatment Resistance

Although drug therapy has made significant progress in slowing tumor development, progression, and metastasis, cancer drug resistance seriously reduces the effectiveness of drug therapy.⁴ It has been demonstrated that novel types of RCD and their molecular signaling influence tumor drug resistance through both direct and indirect effects. Here, we examine this finding with respect to chemotherapy and immunotherapy.

Chemotherapy Resistance

One mechanism by which tamoxifen kills breast cancer cells is ferroptosis. Downregulation of the long non-coding RNA LINC00152 inhibited the expression of the ferroptosis signals GPX4 and SLC7A11, increased intracellular iron ions, and reversed tamoxifen resistance in breast cancer.¹²⁴ Similarly, reduced androgen receptor expression was found to inhibit GPX4 expression, increasing the intracellular redox imbalance and causing ferroptosis, which increased the sensitivity of glioblastoma to temozolomide.¹²⁵ Cuproptosis was found to alter prostate cancer resistance to docetaxel. Wen et al induced DLAT expression in prostate cancer, which led to mTOR phosphorylation and inhibition of cellular autophagy; this, in turn, caused cancer cells to remain in the G2/M phase, which enhanced the killing effect of docetaxel on tumor cells and effectively reversed tumor resistance.¹²⁶ Under specific circumstances, RCD may also promote tumor resistance. For example, inflammatory factors secreted by ovarian cancer cells, such as IL-6 and IL-8, induced pyroptosis of omental adipocytes. The free fatty acids released during pyroptosis of omental adipocytes were then taken up by ovarian cancer cells to activate the STAT3/CPT1B pathway, which increased phospholipid biosynthesis and the mitochondrial membrane potential, thus resisting apoptosis induced by chemotherapeutic agents.¹²⁷ Under hypoxic conditions, HSP90 α inhibited MLKL activation by binding to necrosomes. This attenuated necroptosis was triggered by sorafenib, which ultimately led to the emergence of tumor resistance.¹²⁸ Notably, RCD also acts on other TME components to indirectly affect tumor resistance. For example, cisplatin and paclitaxel were shown to promote the secretion of miR-522 by CAFs. MiR-522 entered gastric cancer cells and reduced the accumulation of lipid peroxides and ferroptosis by inhibiting the expression of ALOX15, enhancing acquired chemoresistance in gastric cancer cells.¹²⁹

Immunotherapy Resistance

Increasingly more studies are focusing on the effects of RCD on tumor immune resistance. Ferroptosis is an important mechanism by which CD8⁺ T cells achieve anti-tumor effects. CD8⁺ T cells inhibited the expression of system Xc⁻ in tumor cells by secreting IFN- γ , reducing the ability of the cells to scavenge lipid peroxides; IFN- γ then upregulated the expression of intracellular ACSL4, which accelerated the formation of lipid peroxidation, further promoting ferroptosis.¹³⁰ Carnitine palmitoyl transferase 1A is a key enzyme in lipid metabolism and forms a positive feedback loop with the transcription factor c-Myc, which was shown to activate the NRF2/GPX4 antioxidant system and enhance the tolerance of cancer stem cells to ferroptosis. Because this tolerance impaired the killing effect of ferroptosis induced by CD8⁺ T cells, the efficacy of immunotherapy was reduced.¹³¹ Similarly, overexpression of the tyrosine kinase receptor TYRO3 in TNBC inhibited CD8⁺ T cell-induced ferroptosis. At the same time, TYRO3 overexpression also upregulated the vascular endothelial growth factor signaling pathway and promoted the polarization of macrophages from the M1-type to the M2-type, further inhibiting anti-tumor immune responses.¹³² In contrast, activation of necroptosis and cuproptosis reverses tumor immune resistance by promoting infiltration of CD8⁺ T cells. In the TME, ZBP1-dependent fibroblast necroptosis promoted CD8⁺ T cell recruitment, which enhanced anti-tumor immunity and, therefore,

is a potential target for reversing drug resistance.¹³³ Microsatellite-stable colon cancer has been considered resistant to immunotherapy. However, recent studies have reported that inducing cuproptosis in Microsatellite-stable colon cancer inhibited WNT signaling and thus downregulated the expression of the immunosuppressive receptor PD-L1 by tumor cells, enhancing immune attack by CD8⁺ T cells and effectively slowing tumor progression.¹³⁴

Anti-Tumor Design Strategies Using Nanomaterials

Due to the intrinsic or acquired resistance of cancer cells, conventional anti-tumor drugs often yield unsatisfactory clinical outcomes. The introduction of NMs has opened new possibilities for improving these outcomes. Because of their unique physicochemical properties and biological behaviors, NMs can directly induce RCD in cancer cells. Moreover, as drug carriers or conjugated to tumor-targeting molecules, they can further enhance therapeutic efficacy.¹³⁵

Suppressing Tumor Proliferation Combined with Photothermal or Photodynamic Therapy

NMs have shown great potential for inhibiting tumor cell proliferation and invasion. For example, researchers developed a disulfide-crosslinked polypeptide nanogel system, STP-NG/SHK, targeting the VIM protein on a tumor surface, which significantly enhanced tumor specificity. The system induced RIP1- and RIP3-dependent necroptosis, effectively suppressing osteosarcoma cell proliferation and reducing pulmonary metastasis.¹³⁶ Ferroptosis has also demonstrated strong tumor-suppressive effects. Li et al designed a nanoplatfrom, MPDA/Fe/RSL3@M-gy1, carrying both iron ions and the GPX4 inhibitor RSL3, and coated it with macrophage membranes to enhance targeting.¹³⁷ The system significantly induced ferroptosis in castration-resistant prostate cancer cells, which effectively suppressed their proliferation under low androgen conditions. Similarly, diethyl dithiocarbamate-ferrous oxide NPs increased intracellular ROS levels and inhibited the GSH-GPX4 antioxidant system, triggering ferroptosis in cisplatin-resistant A549 cancer cells, thereby successfully suppressing cancer cell proliferation.¹³⁸ Research on pyroptosis has further expanded the scope of therapeutic strategies for cancer. Elisa et al developed the CXCR4-targeted self-assembling nanomicelles T22-PE24-H6 and T22-DITOX-H6 that activated the caspase-3/GSDME-dependent pyroptotic pathway, thereby inhibiting head and neck squamous cell carcinoma proliferation while minimizing systemic toxicity due to their high targeting efficiency.¹³⁹ In another study, a self-assembled nanocomposite system comprising the photosensitizer chlorin e6 and the photochemical drug mitoxantrone induced pyroptosis through combined photothermal and photodynamic therapy, which effectively suppressed tumor growth while avoiding damage to normal tissues.⁴⁹ In recent years, nanotherapeutic strategies targeting cuproptosis have advanced rapidly. To overcome the suppression of sonodynamic therapy (SDT) efficacy by GSH in the TME, researchers combined HMME-RGD@C3F8 NBs, nanobubbles loaded with the sonosensitizer HMME and the tumor-targeting peptide RGD, with the cuproptosis inducer Elesclomol-Cu. This approach not only directly induced cuproptosis in tumor cells but also enhanced SDT efficacy by increasing Cu²⁺ consumption to deplete GSH.⁵³ All these NMs leveraged precise targeting and activation of specific RCD pathways to suppress tumor cell proliferation and invasion, suggesting high clinical potential.

Activating Anti-Tumor Immune Responses by Releasing DAMPs

NMs modulate different aspects of the immune microenvironment through multiple mechanisms, including the release of DAMPs, polarization of immune cells, and activation of CD8⁺ T cells. These mechanisms collectively establish a multilayered immune regulatory network, providing various approaches for tumor therapy. For example, an R-CM@MSN@BC nanocomposite induced necroptosis in cholangiocarcinoma cells, releasing DAMPs that enhanced antigen presentation, which promoted M1 macrophage infiltration and reduced the activity of immunosuppressive cells, ultimately boosting anti-tumor immune responses.⁵⁴ Similarly, metabolism-aiming Cu_{2-x}S nanoagents induced ICD in 4T1 cells via cuproptosis, releasing DAMPs that promoted the conversion of M2 macrophages to the M1 phenotype, significantly reducing the tumor size and inhibiting metastasis.¹⁴⁰ Another research focus is antigen uptake enhancement to promote DC maturation and activate anti-tumor immunity. The CaO₂-core-driven nanoplatfrom CTFAP released oxygen synergistically with sonodynamic therapy and Fenton reactions to induce ferroptosis, which significantly

enhanced DC antigen uptake and strengthened anti-tumor immunity.¹⁴¹ Similarly, Zhong et al developed the nanoliposome GM@LR that co-delivered a GSDME-expressing plasmid and manganese carbonate into TNBC cells.¹⁴² The treatment upregulated GSDME expression while increasing DC infiltration and antigen uptake within tumors. Recent studies highlighted interactions between CD8⁺ T cells and novel RCD pathways.¹³⁰ For example, zero-valent iron NPs inhibited NRF2-mediated cytoprotective mechanisms and activated the AMPK/mTOR signaling pathway to induce ferroptosis, significantly enhancing CD8⁺ T cell cytotoxicity and promoting M1 macrophage polarization for dual modulation of the tumor immune microenvironment.⁵⁰ Similarly, Cu-substituted ZnAl ternary layered double hydroxide nanosheets in combination with sonodynamic therapy induced cuproptosis by activating ICD, promoting DC maturation, and enhancing CD8⁺ T cell activity, thereby reversing immune suppression and inhibiting tumor growth and metastasis.⁵¹ The detailed mechanisms are illustrated in Figure 5.

Overcoming Tumor Drug Resistance by Modulating Key Signals

Chemoresistance is a major challenge in conventional cancer treatment. The use of NMs can improve drug delivery efficiency and alter tumor cell responses to anticancer drugs to reverse chemoresistance. For example, a near-infrared-activated photothermal therapy system combining fluorescent carbon nanodots with irinotecan successfully overcame breast cancer apoptosis resistance. The CD-PEG-BT/IT complex, upon near-infrared activation, locally released heat and drugs, which induced necroptosis through the TNF- α and RIPK1 pathways, upregulated pro-apoptotic genes and downregulated anti-apoptotic genes, thus promoting apoptosis.¹⁴³ Both cuproptosis and ferroptosis have shown promise

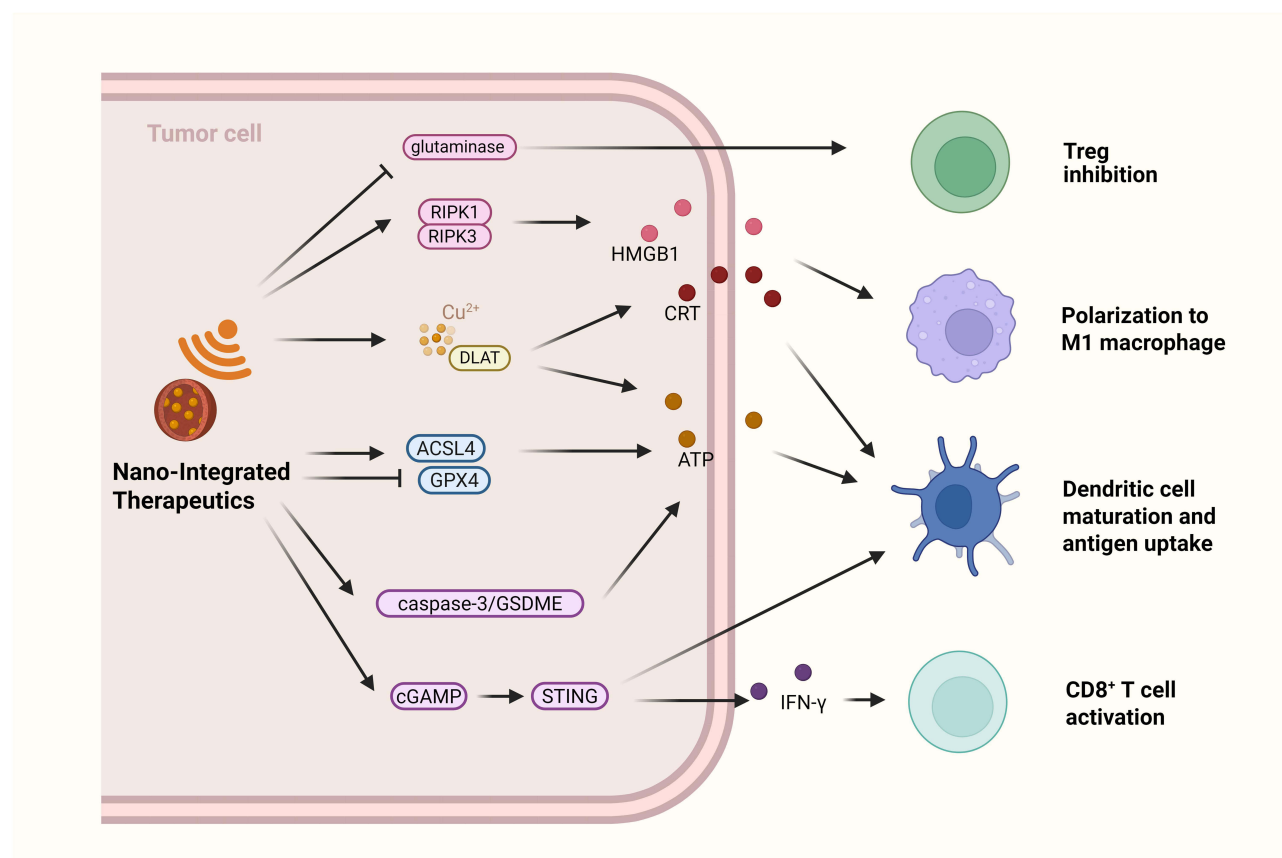


Figure 5 Activation of Anti-tumor Immune Responses by Release of DAMPs in Nano-Integrated Therapy. Nano-integrated therapy inhibits glutamine metabolism to reverse T cell exhaustion and restore anti-tumor function. It also induces necroptosis, leading to the release of HMGB1 and calreticulin (CRT), which promotes macrophage polarization toward the M1 phenotype. Cuproptosis-based and ferroptosis-based strategies trigger immunogenic cell death, accompanied by the release of HMGB1, CRT, and ATP, thereby enhancing antigen uptake and presentation. Moreover, nanomaterials upregulate the cGAS–STING signaling pathway through cGAMP accumulation, promoting DC maturation and CD8⁺ T cell activation; pyroptosis can further amplify anti-tumor immunity by facilitating DAMPs release and remodeling the immune microenvironment.

in overcoming resistance. Tsai et al designed iron-platinum alloy NPs that generated high levels of ROS via the Fenton reaction, inducing cell death and inhibiting the proliferation and migration of tyrosine kinase inhibitor-resistant lung cancer cells.¹⁴⁴ PAB@MIL-53 NPs enhanced drug efficacy by increasing ROS production, depleting GSH, and reducing P-gp expression, thereby preventing drug efflux and reversing multidrug resistance.¹⁴⁵ Similarly, Lu et al synthesized an ellagic acid-copper nanoplatfom combined with doxorubicin to form CS/NPs, which increased intracellular copper concentrations, reduced ATP-dependent P-gp expression, and overcame doxorubicin resistance in breast cancer cells.⁵² In response to radiotherapy resistance, nanocapsules synthesized by Liao et al released copper ions under controlled ionizing radiation, inducing cancer cell death and thus reversing tumor radioresistance.¹⁴⁶ The NM-based strategies for inducing various forms of RCD in tumor therapy are summarized in Table 2.

Anti-Tumor Activity Influenced by Physicochemical Properties of NMs

A significant focus in NM-based anti-tumor therapy is the meticulous design of their physicochemical properties, as these attributes profoundly affect cytotoxicity, circulation, biodistribution, and the initiation of various forms of RCD.

Particle size is particularly influential. Numerous studies have indicated that smaller NMs tend to exhibit enhanced cytotoxicity and RCD induction, attributed to their more efficient cellular penetration, nuclear localization, and ROS generation.^{147–149} Nonetheless, accumulating evidence indicates that the relationship between particle size and biological outcomes is highly context-dependent, varying according to the type of NMs and the tumor cell environment. For example, research on Au NPs has shown that particles of intermediate size (~50 nm) achieve the highest cellular uptake, outperforming both smaller and larger particles.^{150–152} This observation is believed to result from a balance between membrane wrapping energy and receptor-ligand binding kinetics.^{153–156} Importantly, nanoparticles of varying sizes can activate distinct RCD pathways. For instance, larger graphene oxide particles have been reported to activate phospholipase C signaling, leading to pyroptosis.¹⁵⁷ Similarly, Si NPs with diameters less than 20 nm are capable of directly penetrating the cell membrane, leading to necroptosis. In contrast, particles measuring 50 nm are internalized via endocytosis and predominantly trigger caspase-mediated apoptosis.¹⁵⁸

The shape of NMs is another critical factor, as it affects not only the rate of internalization but also the type of RCD that occurs.¹⁵⁹ Rod-shaped NMs are internalized more rapidly and exhibit higher uptake compared to their spherical counterparts, likely due to the increased contact area provided by their longitudinal axis with the cell membrane.^{159,160} Additionally, surface modification of NMs can enhance their functionality through various strategies. For instance, ligand modification can improve tumor targeting and facilitate cellular uptake, thereby augmenting cytotoxicity and the induction of RCD.^{161–164} The formation of a protein corona can sometimes mitigate toxicity by decelerating internalization or neutralizing reactive surface groups.¹⁶⁵ Hydrophilic modifications, such as PEG or hyaluronic acid, are known to extend blood circulation, enhance biodistribution, and improve the biocompatibility of NMs.^{166–168} The surface charge of NMs is also a critical determinant of their biological interactions. Cationic NMs typically exhibit greater cytotoxicity, which is likely attributable to their interactions with lysosomal membranes, resulting in a “proton sponge effect” and facilitating endosomal escape.^{169,170} Studies involving gold AuNPs have demonstrated that cationic particles can induce apoptosis at low concentrations (10 µg/mL) via mitochondrial stress and activation of the p53/caspase-3 pathway. Conversely, neutral particles necessitate higher concentrations (≥ 25 µg/mL) to primarily induce necrotic cell death.¹⁷¹

Challenges and Future Directions

By triggering RCD pathways, NMs unlock novel therapeutic possibilities in oncology.¹⁷² Organic NMs (eg, lipid nanoparticles, metal–organic frameworks) exhibit excellent biocompatibility, degradability, and stimulus-responsive properties. They enable precision delivery of drugs or immunomodulators while inducing ferroptosis or immunogenic cell death ICD within the TME, thereby enhancing anti-tumor immune responses.^{173,174} Inorganic NMs (eg, metal oxides) leverage photothermal, photodynamic, or magnetothermal effects to achieve precise tumor targeting while synergizing with RCD to amplify cytotoxic effects against tumor cells.^{175–177} Despite their potential, challenges remain in understanding the molecular mechanisms, pharmacokinetics, and standardization required for clinical translation.

Currently, the effects of physicochemical properties of NMs (eg, particle size, shape, surface modifications) on RCD induction remain insufficiently understood.¹⁵⁸ Variations in NM properties, such as size and shape, critically determine

Table 2 Nanomaterial-Based Strategies for Inducing Regulated Cell Death in Tumor Therapy

Anti-Tumor Strategy	RCD	NMs	Size+Coating	Target	Tumor Type	Molecular Mechanism	Reference
Inhibit tumor proliferation and migration	Necroptosis	STP-NG/SHK	75 nm coating: carbon	Vimentin	Osteosarcoma	1.Load shikonin into tumor cells 2.Upregulate RIP1 and RIP3	[136]
	Ferroptosis	MPDA/Fe/RSL3@M-gyI	171.8 ± 25.89 nm coating: macrophage membrane	Prostate-specific membrane antigen	Castration-resistant Prostate cancer	1.Load iron ions and ferroptosis inducer RSL3 2.Upregulate LPO and ROS	[137]
		DE-FeO NPs	157.8 nm	ALDH1A1	Glioma stem cells (GSCs) radioresistant GSCs	1.Load ALDH1A1 inhibitor DE 2.Inhibit GSH and GPX4 3.Upregulate ROS	[138]
	Pyroptosis	①T22-PE24-H6 ②T22-DITOX-H6	①60 nm ②38 nm; 90 nm	CXCR4	Head and neck squamous cell carcinoma	1.Activate the caspase-3/GSDME-dependent pathway 2.Upregulate tumor-infiltrating macrophages in nanotoxin-treated animals.	[139]
Activate anti-tumor immune response	Necroptosis	R-CM@MSN@BC	141.62 nm coating: Erythrocyte membrane	GLS1	Cholangiocarcinoma	1.Release ce6 and combine with photodynamic therapy 2.Release the GLS1 inhibitor BPTES 3.Promote M1-type macrophage polarization 4.Inhibit T-cell depletion	[54]
	Ferroptosis	CTFAP	118 nm coating: PEG	-	4T1 cell	1.Release oxygen to mediate the Fenton reaction 2.Combined with sonodynamic therapy 3.Promote DC maturation and upregulate IFN- γ	[141]
	Cuproptosis	MACuS	12 nm	GLUT-1	4T1 cell	1.Combined with photodynamic therapy 2.Upregulate ROS and Inhibit GSH 3.Promote the transformation of M2-type macrophages into M1 type	[140]
	Pyroptosis	GM@LR	108 nm	-	Triple-negative breast cancer	1.Upregulate the proportion of DCs in the tumor 2.Activate caspase-3 3.Activate the cGAS-STING signal	[142]

(Continued)

Table 2 (Continued).

Anti-Tumor Strategy	RCD	NMs	Size+Coating	Target	Tumor Type	Molecular Mechanism	Reference
Reverse tumor resistance	Necroptosis	CDs-PEG-BT/IT	8 nm	-	Breast cancer	1.Reverse resistance to apoptosis 2.Combined with near-infrared-triggered photothermal treatments 3.Activate of TNF- α and RIPK1 signaling pathways 4. Upregulate proapoptotic genes	[143]
	Ferroptosis	FePt NPs	6 nm	Mesenchymal drug-tolerant “persister” cells	TKI-resistant mesenchymal-state lung cancer	1.Reverse resistance to TKI 2.Activate the Fenton reaction and upregulate LPO	[144]
		PAB@MIL-53	254.4 nm coating: RBC membranes	-	MCF-7 and MCF-7/ADR cells	1.Reduce the drug efflux ability of tumor cells 2.Upregulate ROS and Inhibit GSH 3.Inhibit P-gp	[145]
	Cuproptosis	PWCu nanocapsules	1–1.6 nm	Residual cancer cells with acquired resistance to radiation therapy	Experimental cognate mouse tumor (4T1, CT26, B16-F10 and Hepa 1–6) and mice-bearing xenografted human tumor (HeLa, A549, MDA-MB-231 and HCT116)	1.Reverse resistance to radiotherapy 2.Controlled release of copper ions under conditions of ionizing radiation 3.Upregulate FDX1 and LIAS	[146]

their interactions with cellular membranes, internalization pathways, and activation of RCD signaling cascades. This intrinsic heterogeneity poses a fundamental constraint on the precision engineering of NMs for therapeutic use. In addition, the interplay between RCD and the TME remains unclear.⁴ The induction of RCD does not necessarily lead to the formation of a tumor-suppressive TME. For example, downregulating NRF2-related genes can enhance ferroptosis, but under certain conditions, this may paradoxically promote tumor progression.^{178,179} These findings highlight the need for more precise regulation of RCD pathways in therapy design. Current studies primarily focus on the activation of DCs and promotion of CD8⁺ T cells following DAMP release during NM-induced RCD. However, the effects on immunosuppressive cells, such as Tregs and MDSCs, have not been systematically evaluated. Likewise, the role of non-immune stromal cells in the TME, such as CAFs, remains poorly understood. The lack of studies in these areas indicates that therapeutic strategies based on NM-driven RCD still face uncertainties in both efficacy assessment and safety risks.

Equally important, the biodistribution, circulation, and clearance of NMs are critical determinants of the efficiency and safety of RCD induction. Different administration routes can lead to entirely distinct pharmacokinetic profiles and toxicity responses.^{180–182} The clinical translation of NMs remains hindered by insufficient data on their long-term toxicity, immunological side effects, and in vivo accumulation.^{180,182} Future research should focus on establishing standardized evaluation models and optimizing NM designs (eg, TME-responsive nanoplatfoms) to enhance targeting specificity and long-term biosafety, thereby promoting their potential for clinical translation. Beyond these limitations, relying on a single RCD pathway is inadequate for complete tumor eradication and often leads to therapeutic resistance. Consequently, multimodal combination strategies represent a critical direction for future research. For example, photothermal and photodynamic therapies can directly kill tumor cells through localized heating or ROS generation, while simultaneously promoting necroptosis. The combined activation of ferroptosis and cuproptosis can induce severe oxidative stress and metabolic disruption, thereby amplifying cytotoxic effects. Moreover, RCD induction can upregulate immune checkpoint molecules such as PD-L1 on tumor cells, and combining this approach with immune checkpoint inhibitors can significantly enhance anti-tumor immune responses.^{183,184} Overall, therapeutic strategies integrating NMs and RCD remain in the early stages of exploration. The number of clinical studies demonstrating positive outcomes remains very limited,^{172,185,186} underscoring the urgent need for substantial research efforts to achieve successful clinical translation.

Conclusion

This review summarizes recent advances in using NMs to induce novel forms of RCD in tumors, including necroptosis, pyroptosis, ferroptosis, and cuproptosis. NMs regulate key signaling molecules and cellular metabolism to trigger these RCD types. For example, the RIPK1-RIPK3-MLKL complex mediates necroptosis, while NLRP3 inflammasome activation and GSDMD/GSDME cleavage induce pyroptosis. Excessive ROS and Fe³⁺ or Cu²⁺ accumulation drive ferroptosis and cuproptosis. RCD plays dual roles in tumor progression. On the one hand, it releases DAMPs to activate anti-tumor immunity, promoting DC maturation, CD8⁺ T cell recruitment, and M1 macrophage polarization, thereby inhibiting tumor growth and metastasis. On the other hand, specific cytokines and immunosuppressive signals induced by RCD may facilitate immune evasion and tumor progression. Understanding the context-dependent effects of RCD in specific tumor types and microenvironments is essential for precision therapy. Although NMs exhibit potential in cancer therapy, their in vivo distribution, metabolism, and long-term biological safety remain inadequately characterized. The impact of NMs on immunosuppressive and stromal cells within the TME is also insufficiently understood. Furthermore, the physicochemical properties of NMs, such as particle size, morphology, and surface functionalization, play a crucial role in determining their interactions with cell membranes, cellular uptake mechanisms, and the activation of RCD signaling pathways. However, inconsistencies and variability in current research findings present significant obstacles to the rational design of NMs and NM-based composites. Future research should prioritize optimizing the physicochemical properties and delivery strategies of NMs, as well as elucidating interactions among RCD, the TME, and metabolic signaling, to achieve precise therapeutic outcomes and facilitate clinical translation.

Abbreviations

NMs, Nanomaterials; RCD, regulated cell death; TME, tumor microenvironment; TAMs, tumor-associated macrophages; ROS, reactive oxygen species; GPX4, glutathione peroxidase-4; GSH, glutathione; ZBP1, Z-DNA-binding protein 1; ICD, immunogenic cell death; RIP1, receptor-interacting protease 1; RIP3, receptor-interacting protease 3; MLKL, mixed lineage kinase domain-like protein; TNF, tumor necrosis factor; IFN- γ , interferon gamma; TRADD, tumor necrosis factor receptor type 1-associated death domain protein; FADD, FAS-associated death domain protein; DAMPs, danger-associated molecular patterns; NLRP3, NOD-like receptor family pyrin domain-containing 3; GSDMD, gasdermin-D; GSDME, gasdermin-E; LPO, lipid peroxides; FDX1, ferredoxin 1; LIAS, lipoic acid synthase; DLAT, dihydrolipoamide S-acetyltransferase; PDAC, pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma; EMT, epithelial-mesenchymal transition; TNBC, triple-negative breast cancer; CRGs, cuproptosis-related genes; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; NK, natural killer; DCs, dendritic cells; SDT, sonodynamic therapy; OSCC, oral squamous cell carcinoma; PEG, polyethylene glycol; CRT, calreticulin.

Consent for Publication

All authors read and agreed to submit the manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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