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REVIEW

Metal-Based Nanomedicines for Inducing Programmed Cell Death to Enhance the Efficacy of Cancer Immunotherapy

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Abstract: Metal ions exert indispensable functions in various physiological processes, and metal ion homeostasis is needed in cells. Intracellular metal ion homeostasis is regulated by their efflux and influx across the cell membrane. Dysregulation of intracellular metallic ions can trigger programmed cell death (PCD). In recent years, metallic ions as potent immunomodulators and enhancers for cancer immunotherapy through modulating the immunosuppressive tumor microenvironment and triggering an immunostimulatory response have been extensively explored. The review focuses on the mechanism of PCD and immunomodulatory effects for various metal ions including iron, copper, calcium, zinc, and manganese, and provides a systematic overview of nanoparticles for delivering metallic ions or constructed of metals to realize PCD and enhance cancer immunotherapy. Finally, the prospect and challenges of clinic translation of metal-based nano-drug delivery systems in cancer therapy are outlined, and especially restriction of large-scale manufacturing and safety concern for clinic translation are further discussed.

Keywords: metal ions, programmed cell death, cancer immunotherapy, immunomodulators, nanomedicine

Introduction

Cancer is a major health concern worldwide and a leading cause of mortality, and decreases average life expectancy in all countries.[1] There were 18.5 million new cancer cases and 10.4 million cancer deaths estimated to occur globally in 2023, and there will be anticipated 30.5 million cases and 18.6 million deaths from cancer globally in 2050.[2] Currently, chemotherapy, surgery, radiotherapy, targeted therapy and immunotherapy are the mainly therapeutic tactics for cancer. In recent years programmed cell death (PCD) has emerged as a potent approach to induce cell suicide, and it has drawn widespread attention as a research hotspot for cancer treatment. PCD is provoked by endogenous and exogenous factors that disturb cellular homeostasis and trigger cell suicide under dedicated molecular pathways,[3,4] and multiple types of PCD such as ferroptosis, cuproptosis, calcicoptosis, apoptosis, pyroptosis, necroptosis, and PANoptosis have been elucidated and serve as targets for cancer therapy. Metal ions have essential effects on cell homeostasis, and increasing researches on the relationship of metal ions and tumor treatment have shown that several metal ions can induce PCD and provide novel insight for cancer therapy.[5,6]

PCD has been demonstrated to be related to modulate the immunosuppressive tumor microenvironment (TME) and trigger an immunostimulatory response.[7,8] Cancer immunotherapy that harnesses the patient's immune system to combat cancer cells has revolutionized cancer therapy. Over the past decades, cancer immunotherapy mainly including immune checkpoint inhibitors, vaccines, and immune cell therapies has been successfully implemented in the clinic and emerged as a novel therapeutic paradigm in solid and hematological malignancies.[9] However, despite substantial achievements of cancer immunotherapy, patients experience low response, and a substantial proportion fail to achieve clinical benefit from cancer immunotherapy.[10,11] As a prominent immune checkpoint blockade therapy, anti-programmed cell death protein 1

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(PD-1) and anti-programmed cell death ligand 1 (PD-L1) monoclonal antibodies have a low response rate of approximately 10–30%.[12,13] Therapeutic potential of the combination of PCD and immunotherapy was proposed as a promising approach to improve the efficacy of caner immunotherapy.[14,15] Metal ions, their targets and induced PCD, and mechanism of modulating immune response are summarized in Table 1. However, clinical utility of metal ions for eliciting PCD is prominently restricted by insufficient selectivity and targeting ability, toxicity, and dysregulation of systemic ion metabolism.[16] Hence, the targeting delivery of metal ions to malignant cells is urgently needed to enhance therapeutic efficacy while minimizing adverse systemic effects.

The past few decades have witnessed significant advancements of nanotechnology, and multiple nanopharmaceuticals such as Doxil, Abraxane, Marqibo, and Onivyde are approved and marketed for carcinoma therapy.[17] Nanoparticles can improve the solubility of hydrophobic drugs, stability of unstable agents, modulate the pharmacokinetics and biodistribution of loaded drug, realize passive targeting and active targeting via surface modification, reverse drug resistance, and minimize toxicity.[17–19] A nanoparticle-based delivery system can achieve targeted delivery of metal ions, strengthening their PCD potency and minimizing off-target toxicity. Metal ions can be engineered into therapeutic nanostructures either by directly forming nanoscale particles or by being strongly coordinated into fabricated nanocarriers. This nanoformulation strategy not only enables passive tumor accumulation via the enhanced permeability and retention (EPR) effect but also allows further surface modification for active targeting. Therefore, the nanoparticles function not merely as delivery vehicles but as integral components that modulate biodistribution, prolong systemic circulation, and reduce off-target toxicity, ultimately leading to enhanced therapeutic efficacy.

This review introduces the mechanism of PCD triggered by metal ions, the potency of PCD to modulate an immunosuppressive TME and induce an immunostimulatory response, and nanoformulations for integrating PCD and cancer immunotherapy. Relevant studies were retrieved from PubMed through title/abstract searches using combinations of "metal", "nanoparticle", and "immunotherapy". As depicted in Scheme 1, the review focuses on ferroptosis, cuproptosis, calcicoptosis, and other PCD triggered by zinc and manganese. The interplay between PCD and cancer immunotherapy is discussed, and potential tactics to boost immunotherapy via PCD are presented. The review analyzes advantages and challenges in nanomedicine-loaded metal ions to trigger PCD and promote potency of immunotherapy, explores future research orientations, and proposes strategies to address existing challenges. Moreover, we expect to offer some rewarding suggestions and enlightenments for cancer immunotherapy.

Nanoparticles for Ferroptosis and Cancer Immunotherapy

Ferroptosis was first identified in 2012 by Dixon et al as a PCD pattern and is characterized by iron-driven lipid peroxidation.[20] Ferroptosis has emerged as an important modulator in a scope of pathophysiological incidences encompassing oncology, ischemic organ injury, stroke, acute kidney injury, chronic kidney disease, cardiomyopathy, and neurodegenerative diseases.[21] The importance of ferroptosis has piqued research interest of scholarly community, especially in cancer treatment. Despite the need to elucidate the physiological and pathological roles of ferroptosis, its mechanism of induction and function have been gradually revealed.

Regulation Mechanism of Ferroptosis

Ferroptosis is mediated by several primary pathways, encompassing iron metabolism, lipid peroxidation, and antioxidant mechanisms (Figure 1).[22] It is crucial to determine if interactions among the aforementioned pathways affect cellular susceptibility to ferroptosis, posing profound implications for overall fitness.

Iron is indispensable in physiological processes, is acquired by cells via intestinal absorption and degradation of erythrocytes, and plays a pivotal character in the pathway of ferroptosis. Extracellular ferric ion (Fe^{3+}) preliminarily binds to transferrin (TF) to be internalized into cells via endocytosis by transferrin receptor 1 (TFR1).[23] Fe^{3+} is reduced to Fe^{2+} after being transferred into the endosome by six-transmembrane epithelial antigen of prostate 3 (STEAP3), and then Fe^{2+} is liberated into the cytoplasm by divalent metal transporter 1 (DMT1). If the Fe^{2+} is not utilized, it can be preserved in mitochondria and cytoplasm in the form of a labile iron pool (LIP) or sequestered within a ferritin complex.[24,25] Ferroportin is the sole protein responsible for exporting iron from the intracellular compartment to extracellular matrix, and it exerts a vital role in ferroptosis.[26] Under pathological conditions, dysregulation in genes

Table 1 Summary of Metal Ions, Their Molecular Targets, Induced Types of PCD, and Mechanisms of Immune Modulation

Metal Ion	Target	Induced PCD	Mechanism of its Enhanced Cancer Immunotherapy
Fe	Fenton reaction and generating ROS.	Ferroptosis	Induction of cell death for M2 macrophages, Treg cells and myeloid-derived suppressor cells and reversal of their immunosuppressive function; release of oxidation products and DAMPs; recovery of $CD8^+$ T cell function; recruitment of antigen-presenting cells; release of immunomodulatory signals; mediating DCs maturation.
Cu	DLAT, Fe-S cluster proteins.	Cuproptosis	Enhancement of anticancer immunity via cGAS-STING pathway, activating tumor antigen-presentation and promoting DCs maturation; downregulation of WNT and PD-L1, enhancing infiltration and cytotoxicity $CD8^+$ T cells; induction of ICD; elicitation of macrophages to M1 polarization; activation of $CD8^+$ T cells and natural killer cells via major histocompatibility complex-I pathway.
Ca	Calcium/calmodulin-dependent protein phosphatase, necrosome complex, mitochondria.	Calcicoptosis	Stimulation of cytotoxic lymphocytes proliferation; activation of T lymphocyte-associated transcription factors; release of DAMPs; facilitation of exposure of calreticulin to deliver pro-phagocytic signals to myeloid cells; repolarization of TAMs to M1 phenotype and inhibition of M2 polarization.
Zn	Bax, Smad2, PIAS1, lysosome, ERK1/2, MTF1, CaMKKb/AMPK	Apoptosis, lysozincrosis, autophagy, necroptosis, ferroptosis and pyroptosis	Enhancement of an array of immune cells activity; alleviation of immunosuppressive TME via inhibiting release of inflammatory molecular and inflammatory response; enhancement of presentation and recognition of antigen; suppression of immune checkpoint protein expression; activation of cGAS-STING; release of DAMPs and interferon γ.
Mn	System Xc^- and excitatory amino acid transporter, Fenton and Haber-Weiss reactions, iron homeostasis, hypoxia-inducible factor-1 α /p53/SLC7A11, nuclear translocation of Yes-associated protein/transcriptional co-activator with PDZ-binding motif, histone deacetylase, histone acetyltransferase, p53- and p38-mitogen-activated protein kinases, mitogen and stress response kinase-1, STING-tumor necrosis factor.	Ferroptosis, apoptosis, necroptosis	Activation and functional regulation of immune cells, cGAS-STING pathway.

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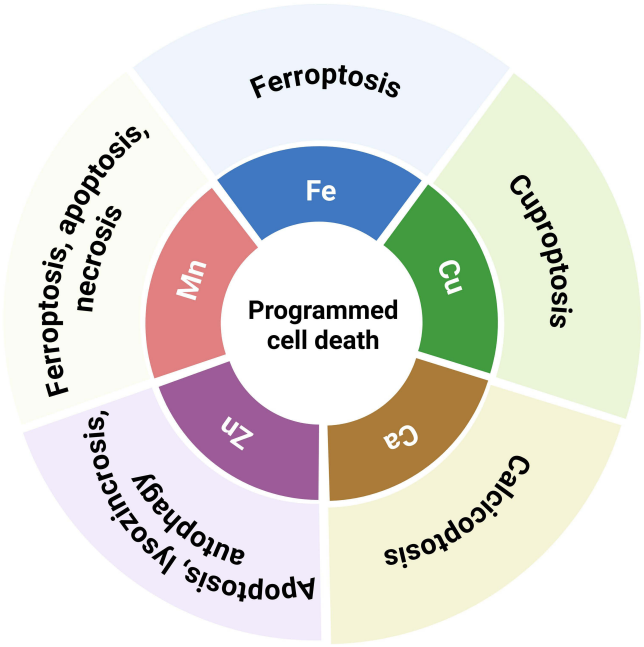

Scheme 1 Metal ion-induced programmed cell death.

encoding iron metabolism, particularly reduction in ferritin heavy chain 1 expression coupled with overexpression of TFR1, could trigger a substantial accumulation of intracellular iron to elicit a surge in reactive oxygen species (ROS) via the Fenton reaction.[25,27,28] The elevated oxidative microenvironment can ultimately result in susceptibility of vulnerable cells to ferroptosis.[25] Also, ferritinophagy which is regulated by nuclear receptor coactivator-4 (NCOA4) can activate ferroptosis by increasing intracellular iron density due to its involvement in ferritin breakdown.[29]

In addition, polyunsaturated fatty acids (PUFA) are essential components for cell membranes, and they are perceived as key stimuli for lipid peroxidation, which is a crucial process responsible for the onset of ferroptosis.[30] PUFA undergoes esterification with long-chain acyl-coenzyme A (CoA), which is facilitated by acyl-CoA synthetase long-chain family member 4 (ACSL4), leading to the production of PUFA-CoAs. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) which is responsible for delivery of PUFA-CoAs into cell membrane phospholipids, plays a pivotal role in the subsequent peroxidation.[31] Once integrated into phospholipids, the PUFA-CoA-integrated phospholipids are subjected to enzymatic oxidation by lipoxygenases (LOX) or autoxidation, and a cascade of biological reactions is initiated to generate the iron-dependent lipid peroxides that are a hallmark of ferroptosis.[27,32] Once LOX, LPCAT3, and ACSL4 enzymes are overly active, lipid peroxidation occurs, resulting in oxidation of PUFA and accumulation of lipid peroxides. As displayed in Figure 1, eventually excessive lipid peroxides synergize with intracellular overloaded iron to cause a Fenton reaction, resulting in increased ROS levels, loss of structural integrity of the lipid bilayer, cytotoxicity, and death.[27]

System Xc^-, a ubiquitous amino acid antiporter in phospholipid bilayers, regulates the exchange of cystine and glutamate at a stoichiometric ratio of 1:1 and is essential for cellular uptake of cystine.[33,34] Within cells, cystine is converted into cysteine, which is an indispensable precursor for biosynthesis of glutathione (GSH).[35] GSH is an endogenous antioxidant responsible for scavenging ROS via glutathione peroxidases (GPXs). Therefore, inhibition of this antiporter can lead to depletion of intracellular GSH and an increase of glutamate, which participates in ROS production after conversion into glutamine by glutaminase enzyme.[36–38] GPX4 possesses the potency to degrade a range of lipid peroxides and block the detrimental cascade of lipid peroxidation, exerting a pivotal role in ferroptosis. A dramatic decline in the activity of GPX4 results in overproduced ROS and elevated oxidative stress, inducing ferroptotic cell death by the active ROS and lipid peroxides (Figure 1).[39] Furthermore, p53 as a cancer suppressor protein can

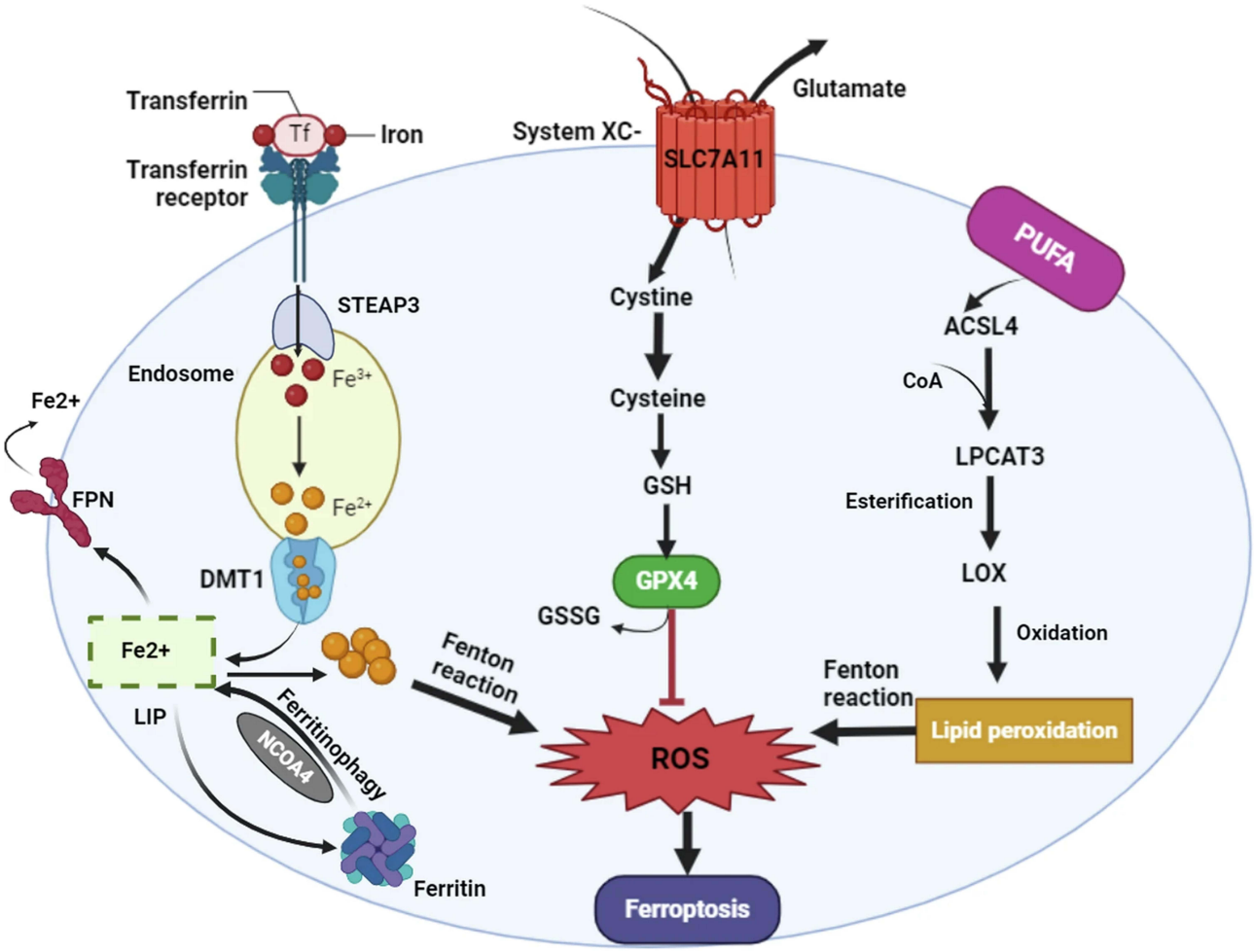

Figure 1 Summary of the metabolic pathway of ferroptosis. The intricate modulation of ferroptosis is regulated via several primary pathways, encompassing iron metabolism, lipid peroxidation, and antioxidant mechanisms.

mediate cystine uptake by inhibiting the light chain SLC7A11 of the antiporter, influencing GPX4 activity and triggering ferroptosis.[15]

Interplay Between Ferroptosis and Cancer Immunotherapy

Ferroptosis has been identified as an important player in regulation of immunosuppressive microenvironments and differentiation of immune cells, and its role in immunotherapy is becoming increasingly evident.

Macrophages are important in tumor immunosuppression by supporting tumor development and progression and resistance to therapy. They can polarize into three phenotypes: unactivated M0, classically activated M1, and alternatively activated M2 macrophages. M1 macrophages show high expression of iron-sequestering proteins such as ferritin and low expression of iron-exporting proteins such as FPN, store iron, and are resistant to ferroptosis, helping to fight cancer cells. On the contrary, M2 macrophages promote tumor cell proliferation and immune evasion by releasing iron, and they are susceptible to ferroptosis owing to high FPN and low ferritin expression.[40] M2 macrophages can be repolarized into the M1 phenotype by ferroptosis inducers, and iron can promote M1 polarization under certain conditions.[41,42] Similarly, Treg cells and myeloid-derived suppressor cells have an immunosuppressive role and antagonize ferroptosis through high expression of GPX4 or other proteins. Induction of ferroptosis in these cells may induce cell death and reverse their immunosuppressive function.[42]

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Ferroptosis is accompanied by release of oxidation products, and damage-associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1) can trigger inflammatory and immune responses during cell death.[43,44] HMGB1 is one of the key elements required for activation of the innate and adaptive immune systems by binding to pattern recognition receptors.[45] Recovery of $CD8^+$ cytotoxic T cell function within the TME is an important factor determining response to cancer immunotherapy, and ferroptosis is a key metabolic regulator of $CD8^+$ T cells activity.[46] Ferroptotic cells liberate lipid cytokines as "find me" signals, which recruit antigen-presenting cells and other immune cells to the site.[44] LOXs not only oxygenate esterified PUFAs as ferroptotic signals but also contribute to the release of oxidized lipid mediators as immunomodulatory signals from ferroptotic cancer cells, enhancing anti-tumor immunity.[44] Arachidonate 15-lipoxygenase-derived lipid mediators mediate dendritic cells (DCs) maturation and regulate adaptive immune responses.[47]

Immune cells have an anti-tumor immunity function by releasing cytokines that trigger ferroptosis in cancer cells. For example, interferon γ released by $CD8^+$ T cells and transforming growth factor-β released by macrophages decrease the expression of the antiporter system Xc^-, followed by impaired uptake of cystine in cancer cells, promoting lipid peroxidation and ferroptosis in tumor cells.[48,49]

Nanoparticles for Ferroptosis to Enhance Cancer Immunotherapy

Overload of iron can elicit tissue damage encompassing myocarditis that can progress to heart failure and neurological and neurodegenerative diseases.[50,51] Hence, the targeted delivery of iron is indispensable to protect healthy tissues. Ferroptosis has been broadly applied as a novel strategy to enhance the efficacy of cancer immunotherapy. PD-1 and its ligand PD-L1 have emerged as important immune checkpoints in tumor treatment. Although neutralization of the negative immune checkpoints with anti-PD-1 or anti-PD-L1 antibodies has generated impressive progress in treatment of several types of cancer, such therapy is limited by a low response rate.[12,13] As summarized in Table 2, various nanoparticles for delivery of iron ion have been designed and fabricated, aiming to augment the immune response against anti-PD-1 or anti-PD-L1 therapy by modulating activating immune cells.

Cholesterol oxidase is responsible for catalysis of cholesterol to H_2O_2, and cholestenone enhances lipid peroxidation and ROS levels, promoting ferroptosis immune therapy.[52] A novel nanozyme composed of iron metal-organic framework (MOF) for delivery of cholesterol oxidase and polyethylene glycosylation (Figure 2) [52] and catalytic hydrogel-loaded dimethyl maleic anhydride-modified cholesterol oxidase and a metalloporphyrin compound hemin with peroxidase-like activity[53] were developed for integrated ferroptosis and immunotherapy. In combination with PD-1 or PD-L1 inhibitor, the nanodrug delivery system exerted a synergistic therapeutic effect.

Jingbo Ma et al synthesized a multifunctional nanocomposite of sonosensitizer HMME, Fe^{3+}, and tannic acid, and the nanocomposite consolidated the function of HMME for producing ROS and Fe^{3+} for induction of ferroptosis and ROS.[54] More importantly, the nanocomposite could potentiate efficacy of immunotherapy by recruiting additional T cells and natural killer cells and promoting DCs maturation, and its combination with anti-PD-1 antibody could eradicate tumors. A hydrazide/Cu^{2+}/Fe^{2+}/indocyanine green coordinated nanoplatform was developed, the hydrazide-metal-sulfonate coordination significantly potentiated $CD8^+$ T cell infiltration into tumor, and the nanoplatform and antibody against PD-1 synergistically eliminated the primary tumor and inhibited distant tumor metastasis and recurrence.[55] A metal-coordinated carrier-free nanodrug was prepared by co-assembly of a natural product of ursolic acid, sorafenib, Fe^{3+}, low-molecular weight protamine, and epithelial cell adhesion molecule aptamer. The nanodrug induced immunogenic cell death (ICD) and augmented the immune response against PD-L1 via increasing infiltration of cytotoxic T cells to suppress tumor growth and distant metastasis.[56] A tannic acid-Fe^{3+}-coated 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(PEG2000] (ammonium salt) micelle loaded with doxorubicin and anti-PD-L1 antibody enhanced anti-tumor immunity by activating $CD4^+$ and $CD8^+$ T cells and reducing the ratio of regulatory T cells to $CD4^+$ T cells.[57]

Postoperative recurrence and metastasis especially brain metastasis dramatically deteriorate the survival rates for breast cancer sufferers. A core-shell nanoparticle of Fe MOF-encapsulated hollow mesoporous organosilica nanoparticles was proposed to deliver doxorubicin to prevent recurrence and metastasis.[58] The nanosuspension synergistically improved doxorubicin chemotherapy, achieved remarkable ferroptosis by doxorubicin and iron ions, and significantly activated immune response including stimulating DCs, recruiting T cells, and facilitating antigen presentation. When

Table 2 Iron-Based Nanomedicines for Triggering Ferroptosis to Enhance Cancer Immunotherapy

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Iron MOF	Cholesterol oxidase	Iron MOF, PEG	220	Enhancement of ROS levels and inducement of LPO via depleting cholesterol and generating hydrogen peroxide, thereby promoting ferroptosis.	iv	Notable biosafety and synergistic therapeutic efficacy of the Fe MOF and PD-1 checkpoint blockade.	[52]
Hydrogel	Cholesterol oxidase	Oxydextran, hemin-chitosan		Trigger of ferroptosis by combination of cholesterol oxidase and hemin, hence increased potency of anti-PD-L1 therapy.	iv	Inhibition of primary tumor growth and distant metastases.	[53]
Self-assembly	HMME, Fe^{3+}	Tannic acid, cholesterol, DSPE-PEG2000, lecithin	73–83	Inducing apoptosis, ferroptosis, and ICD, and reshaping the TME and recruiting T cell infiltration.	iv	Almost eradication of tumors by integration of the self-assembly and PD-1 blockade.	[54]
Self-assembly	Cu^{2+}, Fe^{2+}, indocyanine green	3,3′-dithiobis(propionohydrazide)	60	Photodynamic therapy and ferroptosis.	iv	Elimination of primary tumors and inhibition of distant tumor growth, lung metastasis and tumor recurrence by this self-assembly and PD-1 antibody.	[55]
Self-assembly	Sorafenib, Fe^{3+}	Ursolic acid, low-molecular weight protamine, epithelial cell adhesion molecule aptamer	137.1	Ferroptosis, chemotherapy and chemodynamic therapy.	iv	Significant suppression of tumor growth and distant metastasis by this self-assembly and anti-PD-L1.	[56]
Micelle	Fe^{3+}, doxorubicin	Tannic acid, DSPE-PEG	18.17	Apoptosis and ferroptosis-mediated ICD.	iv	Considerable inhibition of tumor growth and improvement of anti-tumor immunity in combination with anti-PD-L1 antibody.	[57]
Nanosuspension	Doxorubicin	Fe MOF, mesoporous organosilica nanoparticles	150	Ferroptosis, chemotherapy, ICD.	it	Inhibition of postoperative recurrence and brain metastasis in integration with PD-1 antibody.	[58]
Core-shell nanoparticle	Cholesterol derivative of dihydroartemisinin, pyropheophorbide-iron	2-dioleoyl-snglycero-3-phosphate, 1,2-dioleyl-*sn*-glycero-3-phosphocholine, cholesterol, DSPE-PEG 2000, Zn-pyrophosphate	90	Ferroptosis, immunostimulatory effect.	iv	Sensitization of non-immunogenic colorectal tumors to anti-PD-L1 therapy.	[59]
MOF	Triptolide	Tannic acid, Fe^{3+}, folic acid modified bovine serum albumin	200	Ferroptosis, pyroptosis, release of large amounts of DAMPs.	iv	Effective inhibition of primary tumor and metastasis, and this effects were further enhanced by combination with PD-L1 antibody.	[60]
MOF	Glucose oxidase	MnO_2, iron-based MOF, PEG	245	Ferroptosis, release of tumor immune-associated antigens.	iv	Synergistic treatment of this MOF with aptamer-PD-L1.	[61]
Hybrid nanoparticle	Sorafenib, antibody against transforming growth factor-β	Fe_3O_4/Gd_2O_3 hybrid nanoparticles, arginine-glycine-aspartic dimer	15.4	Ferroptosis, release of DAMPs, promotion of DCs maturation, recruitment of $CD8^+$ T cells.	iv	Inhibition of tumor growth and lung metastasis, and enhancement of anti-PD-1 efficacy.	[62]

(*Continued*)

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Table 2 (Continued).

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Nanoparticle	Glucose oxidase	Cyclic arginine glycyl aspartate peptide, anisamide, polydopamine, Fe_3O_4 nanoparticle	150	Ferroptosis, photothermal therapy, ICD.	iv	Combined with PD-L1 antibody, favorable synergistic effectiveness against colorectal cancer.	[63]
Magnetic nanoparticle	Sulfasalazine	Mesoporous magnetic nanoparticles, platelet membrane	268.9	Ferroptotic cell death, repolarization of macrophages from M2 to M1 phenotype.	iv	The magnetic nanoparticles jointly with immunotherapy effectively inhibited the metastasis tumor growth.	[64]
Ultrasmall Fe nanoparticle	None	Fe core, iron oxide shell, iRGD peptide	3.8	Ferroptosis and ICD.	iv	Promotion of maturation of DCs and adaptive T cell response. Combined with anti-PD-L1 antibody, the nanoparticle significantly potentiated immune response and developed strong immune memory.	[65]
Ultrasmall Fe nanoparticle	^{131}I-labeled antibody against PD-L1	Ultrasmall iron nanoparticles, dopamine-fluorophenylboronic acid, bovine serum albumin	150	Ferroptosis, radiotherapy, ICD.	iv	Significant inhibitory effect on both primary and metastatic tumor growth.	[66]
Nanocrystal	None	Iron-palladium nanocrystal, polyvinylpyrrolidone	110	Autophagy-augmented ferroptosis, photothermal therapy, ICD.	iv	The nanocrystal synergized with PD-L1 antibody in suppressing both primary and distant tumors.	[67]

Abbreviations: iv, intravenous injection; it, intratumoral injection.

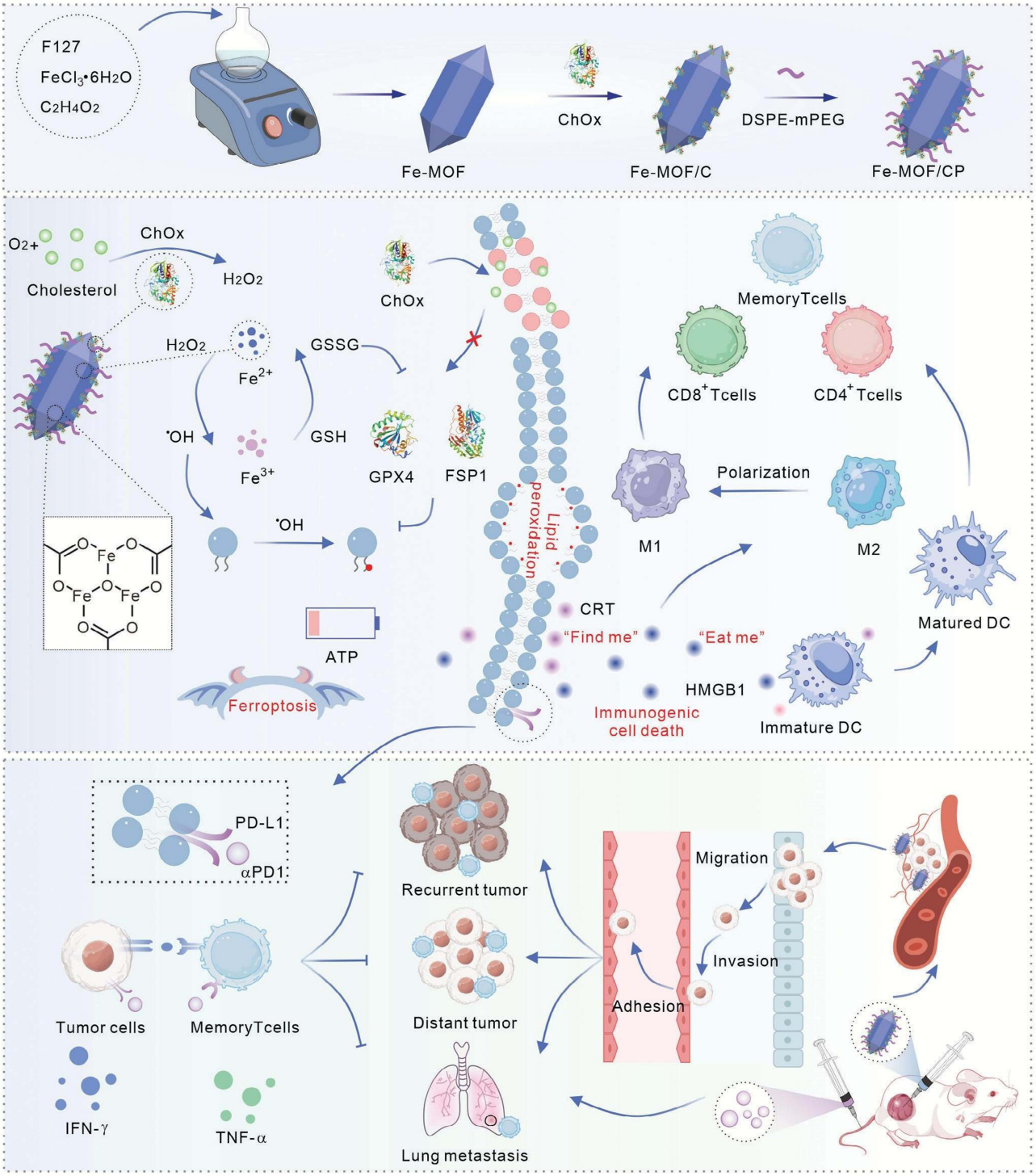

Figure 2 A novel nanozyme composed of iron metal-organic framework nanoparticles delivering cholesterol oxidase and polyethylene glycosylation for integrated ferroptosis and immunotherapy. The nanozyme depleted cholesterol, produced excessive H_2O_2, and enhanced ROS and lipid peroxides levels to promote ferroptosis. Concurrently, the nanozyme augmented immunogenic cell death by reducing PD-L1 expression, promoting DCs maturation and M1 macrophage polarization, revitalizing exhausted $CD8^+$ T cells and priming $CD8^+$ T cells. In combination with PD-1 inhibitor the nanozyme exerted a synergistic therapeutic effect.

used in conjunction with the PD-1 antibody, the nanosuspension could inhibit postoperative recurrence and brain metastasis of breast cancer. Zn-pyrophosphate core-shell nanoparticles for co-delivering a cholesterol derivative of dihydroartemisinin and pyropheophorbide-iron sensitized non-immunogenic colorectal tumor to anti-PD-L1 checkpoint blockade immunotherapy.[59]

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A MOF was formed through the coordination between tannic acid and Fe^{3+} to deliver triptolide and was functionalized by folic acid-modified bovine serum albumin.[60] The nanoplatform triggered a potent systemic anti-tumor immune response by inducing ferroptosis and pyroptosis, and its combination with antibody against PD-L1 enhanced immunotherapy. Combined with aptamer-PD-L1 checkpoint blockade, iron-based MOF nanoparticles modified by MnO_2, glucose oxidase, and polyethylene glycol (PEG) strengthened the tumor treatment efficiency.[61]

Fe_3O_4/Gd_2O_3 hybrid nanoparticles conjugated to arginine-glycine-aspartic dimers for loading sorafenib and antibody against transforming growth factor-β achieved cumulative ferroptosis through Fe_3O_4/Gd_2O_3 hybrid nanoparticle-mediated Fenton reaction and sorafenib-mediated GSH synthesis blocking, and increased the potency of anti-PD1 therapy.[62] Polydopamine, cyclic arginine glycyl aspartate, and anisamide-modified Fe_3O_4 nanoparticles enhanced cellular ferroptosis induced by Fe^{2+}-mediated Fenton reaction via introducing glucose oxidase as a catalyzer for generation of H_2O_2, and in combination with antibody against PD-L1 the nanoparticles exhibited favorable synergistic effectiveness against colorectal cancer.[63] A biomimetic platelet membrane camouflaged with Fe_3O_4 nanoparticles for delivery of sulfasalazine triggered ferroptotic cell death, and the biomimetic nanoparticles induced an anticancer immune response and efficiently repolarized immunosuppressive M2 macrophages to anti-tumor M1 phenotype, drastically enhancing the efficacy of PD-1 inhibitor.[64]

Ultrasmall body-centered cubic Fe nanoparticles with an Fe core approximately 2 nm in size and an iron oxide shell less than 0.7 nm were synthesized and further modified by the CRGDKGPD (iRGD) peptide. These nanoparticles could efficiently induce immunogenetic promotion of DCs maturation and adaptive T cell response. Combined with anti-PD-L1 antibody, the ultrasmall Fe nanoparticle-triggered ferroptosis significantly potentiated immune response and developed strong immune memory.[65] Ultrasmall iron nanoparticles were functionalized by fluorophenylboronic acid to generate nitrogen-boronate complex with bovine serum albumin and ^{131}I-labeled antibody against PD-L1. The ultrasmall nanoparticles were responsive to an increase of adenosine triphosphate in tumor owing to a relatively stronger affinity of ribose structure in adenosine triphosphate to fluorophenylboronic acid. The ICD caused by radiopharmaceutical therapy and ferroptosis combined with antibody against PD-L1 exhibited a strong anti-tumor immunity.[66]

A tetrapod spiky-like iron-palladium nanocrystal was engineered with decylamine as a coordinating ligand for co-reduction of Fe and Pd species, and the surface of nanocrystal was modified with polyvinylpyrrolidone to improve its biosafety and biocompatibility. The nanocrystal induced lipid peroxide accumulation, promoted ferroptosis, and effectively triggered the release of inflammatory cytokines (tumor necrosis factor-α, interleukin-6, and interleukin-1β) in macrophages, strengthening immunotherapy with antibody against PD-L1.[67]

Researches have reported synergism of iron nanoparticle-mediated ferroptosis and A2 adenosine receptor blocker,[68] CD47 blocking antibody,[69] or cytotoxic T lymphocyte-associated protein 4 (CTLA-4) check point inhibitor[70–72] for cancer immunotherapy.

Nanoparticles for Cuproptosis and Cancer Immunotherapy

In 2022, Tsvetkov et al discovered excessive copper-induced cell death as a distinct type of PCD from other modalities, and it was termed cuproptosis.[73] Cuproptosis is featured by excessive accumulation of copper in cells, followed by mitochondrial dysfunction and toxic protein stress, ultimately leading to cell death. Tumor cells demonstrate increased metabolism processes and energy consumption, which are intricately associated with mitochondrial function. This indicates opportunities for cuproptosis as a novel target for eradication of tumor cells.

Mechanism of Cuproptosis

Copper is indispensable for regulation of redox-active enzymes, which are involved in various metabolism processes, signaling pathways, and biological functions.[74] Intracellular copper homeostasis is tightly mediated by transporters, efflux protein, and enzymes responsible for conversion of Cu^{2+} to Cu^{+}, and their coordinated processes maintain a precise balance of copper in cells. Disruption of copper homeostasis can lead to detrimental dysfunction of cells. Inadequate copper blunts normal metabolic activity, while excess copper produces cytotoxicity and ultimately results in cell death.

The copper ionophore elesclomol translocates Cu^{2+} into cells dependent on mitochondrial respiration and disrupts copper homeostasis mediated by solute carrier family 31 member 1 (SLC31A1) which is previously called copper

transporter protein 1 (CTR1) as copper import protein, and ATPase copper transporting α/β (ATP7A/B) as copper export protein (Figure 3).[75] Accumulated copper in cells can directly combine with dihydrolipoamide *S*-acetyltransferase (DLAT), a lipoylated protein involved in the tricarboxylic acid cycle, to generate protein oligomers. Copper ions can undermine the synthesis of Fe-S cluster proteins, which are a crucial family of functional mitochondrial proteins involved in multiple process including cell energy metabolism, electron transfer, and substrate synthesis.[76] These steps synergistically result in proteotoxic stress response and ultimately lead to cuproptosis.

Additional metabolic pathways mediating cuproptosis have been identified, among which ferredoxin 1 plays a pivotal role in protein lipoylation through integration into lipoic acid synthase and facilitation of its functional interplay with glycine cleavage system protein H.[77] On the other hand, the ferredoxin 1 gene is responsible for encoding a small iron-sulfur protein that converts Cu^{2+} to more toxic Cu^{+}. However, Cu^{+} ions undermine the structure and function of iron-sulfur clusters, resulting in their degradation (Figure 3). GSH, a cellular protector, can reduce the concentration of free Cu^{2+} and inhibit cuproptosis by binding to Cu^{2+} and generating a complex. The combination of GSH and Cu^{2+} is beneficial for maintenance of intracellular copper ion balance, and ferredoxin 1-mediated Cu^{2+} reduction reduces the detrimental influence of Cu^{+} on iron-sulfur cluster proteins, defending cells against copper-induced injury.[78] Recent studies demonstrate that tumor suppressor p53 is also involved in modulation of cuproptosis. P53 is responsible for regulating transcription of GSH reductase to modulate biosynthesis and recycle GSH, and also is responsible for mediating the expression of genes linked to iron-sulfur proteins, regulating cellular GSH and iron-sulfur levels.[79] Pathways mediating cuproptosis are illustrated in Figure 3.

Relationship Between Cuproptosis and Cancer Immunotherapy

Cuproptosis is believed to be closely associated with immune cell infiltration and has an important role in reprogramming the immunosuppressive microenvironment. The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) is demonstrated as a critical regulator of cancer immunity and facilitates various immune effector responses, and a cGAS-STING-mediated immune supportive microenvironment can hamper malignancy occurrence.[80,81] Cuproptosis has been reported to enhance anticancer immunity through the cGAS-STING pathway, activating tumor antigen-presentation. The cGAS-STING signaling in DCs is triggered by cuproptosis-stimulated cancer cells, followed by release of inflammatory factors. In addition, combined cuproptosis inducers and PD-1 inhibitor synergistically

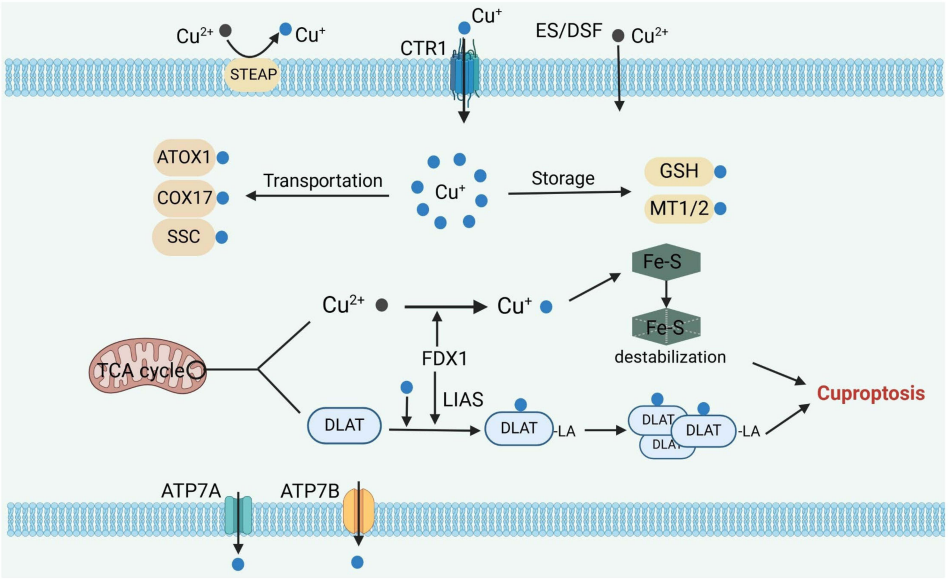

Figure 3 Pathways mediating cuproptosis. Elesclomol binds to Cu^{2+} and transports it into intracellular compartments. Cu^{+} is primarily transported into cells via solute SLC31A1 previously called CTR1, while ATP7A/B are responsible for exporting copper ion. Excess intracellular copper primarily leads to cuproptosis through mitochondrial protein toxicity stress mediated by FDX1. This FDX1 reduces Cu^{2+} to Cu^{+}, promotes lipidation and aggregation of enzymes involved in the mitochondrial tricarboxylic acid cycle particularly DLAT, and degrades iron-sulfur cluster proteins. (reproduced with permission from Xiaojie Zhang et al (2024). Copyright 2024 Springer Nature).

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increases the circulating levels of $CD45^+CD8^+$ T cells, enhancing immunotherapy efficacy.[82] Cuproptosis also significantly stimulates mitochondrial DNA release to activate innate immunity via cGAS-STING signaling in vivo. Subsequently, secretion of type I interferon and expression of interferon-β are upregulated and DCs maturation is promoted. In addition, cuproptosis-associated innate immunity activates T-cell immunity.[83] In vivo cuproptosis enhances infiltration of $CD8^+$ T cells into tumor tissue, and cuproptosis potentiates the cytotoxicity of $CD8^+$ T cells, which is realized by downregulating the WNT signaling pathway and PD-L1 expression.[84] Cuproptosis triggered by a mitochondria-targeted copper dithiocarbamate induces immunogenic death of cancer cells, leading to the release of DAMPs. The released DAMPs effectively elicit macrophages to M1 polarization and their migration towards target cell antigens, and secretion of relevant cytokines. The copper dithiocarbamate promotes antigen processing and presentation in cancer cells through the major histocompatibility complex-I pathway, activating $CD8^+$ T cells and natural killer cells.[85]

Nanoparticles for Cuproptosis to Enhance Cancer Immunotherapy

Copper overload in tissues leads to damages, including hepatotoxicity, nephrotoxicity, neurotoxicity, hemolysis, and cytotoxicity.[86] Nanotechnology provides a potent approach to enhance anti-tumor immune response by regulating cuproptosis, overcoming the obstacles of current cancer immunotherapy and minimizing off-target toxicity. Nanodrugs for inducing cuproptosis to boost cancer immunotherapy are presented in Table 3.

As depicted in Figure 4, a biomimetic cuproptosis amplifier was fabricated by Cu^{2+}-regulated coordinative self-assembly of near-infrared II (1000–1700 nm) ultrasmall polymer dots and doxorubicin, followed by camouflaging of cancer cytomembrane. Overexpressed GSH in the TME reduced Cu^{2+} to Cu^+, resulting in disassembly of the amplifier, photothermal therapy, chemotherapy, and cuproptosis. Cuproptosis elicited significant DCs maturation and infiltration of CD^{4+} and CD^{8+} T cells through ICD and reshaped the immunosuppressive TME via downregulated Tregs. The amplifier together with anti-PD-L1 antibody elicited a powerful anti-tumor immune response.[87]

A sodium alginate hydrogel incorporating elesclomol-Cu and galactose was developed to trigger persistent cuproptosis, and the hydrogel abrogated radiation-induced PD-L1 upregulation, significantly enhancing the sensitization of cancer to radiotherapy and immunotherapy.[88] A hydrogel composed of glycyrrhizic acid, copper ions, and celastrol was fabricated for synergistic cuproptosis and apoptosis, and the hydrogel repolarized tumor-associated macrophages (TAMs) into M1 phenotype, induced T cell proliferation and infiltration, activated antigen presentation, and upregulated PD-L1 expression. Upon co-administration with PD-L1 antibody, the hydrogel synergistically alleviated both primary and metastatic tumors.[89]

Yiming Xu et al decorated lung cancer cytomembrane onto glucose oxidase-loaded copper-layered double hydroxide nanoparticles to generate an intelligent biomimetic nanodrug. The nanodrug significantly induced cuproptosis and PD-L1 upregulation in lung cancer cells and sensitized the therapeutic potency of antibody against PD-L1.[90] An *Escherichia coli* and Cu_2O nanoparticle microbial nanohybrid was fabricated by electrostatic interaction through simple mixing, and the nanohybrid reversed the immunosuppressive microenvironment by inducing DCs maturation and T cell activation. Upon synergism with PD-1 antibody, the nanohybrid inhibited relapse and metastasis of colon tumors.[91]

Tumor-targeting peptides RGD coated hollow mesoporous copper sulfide nanoparticle for delivery of the nitric oxide donor L-Arginine induced cuproptosis, promoted immune cell infiltration and activation, and converted "cold" tumors into "hot" ones. In addition, their combination with antibody against PD-L1 significantly enhanced the immunotherapy response rate in triple-negative breast cancer.[92] A Cu^{2+}-based MOF loaded with the copper ionophore elesclomol and surface modified with PEG polymer was developed for cuproptosis induction to increase anticancer immune response, and combing the MOF with PD-L1 antibody reshaped the immunosuppressive TME to an immunogenic milieu, significantly inhibiting tumor growth.[93]

A ROS-sensitive polymer was designed and used to encapsulate elesclomol and copper. The micelle triggered cuproptosis, promoted DCs maturation and $CD8^+$ cell infiltration, and reprogrammed the TME. Moreover, the micelle dramatically increased PD-L1 expression and effectively enhanced the response rate to anti-PD-L1 therapy.[94] Copper oxide nanoparticles were encapsulated into the PEG-modified copper ionophore elesclomol, and the nanodrug triggered an immune response and reshaped the immunosuppressive microenvironment by increasing the number of tumor-infiltrating lymphocytes and secretion of inflammatory cytokines. In addition, combining the nanoparticles and anti-

Table 3 Copper-Based Nanomedicines for Inducing Cuproptosis to Boost Cancer Immunotherapy

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Self-assembly	Doxorubicin	Near-infrared II ultrasmall polymer dots, tumor cell membranes	122	Cuproptosis, ICD, photothermal therapy and chemotherapy.	iv	Elicitation of boosted immune response, promotion of T cells infiltration, and enhanced anti-tumor effects on primary and distant tumors together with PD-L1 antibody.	[87]
Hydrogel	Elesclomol-Cu, galactose	Sodium alginate	None	Cuproptosis, radio-immunotherapy.	it	Downregulation of PD-L1, sensitization of tumor to radiotherapy and immunotherapy, and prolonged survival of mice bearing both local and metastatic tumors in combination of PD-L1 antibody.	[88]
Hydrogel	Cu^{2+}, celastrol	Glycyrrhizic acid	None	Chemo-dynamic therapy, apoptosis, cuproptosis.	it	Co-administration with PD-L1 antibody, mitigation of both primary and metastasis tumors.	[89]
Nanoparticle	Glucose oxidase	Copper-layered double hydroxide nanoparticle, lung cancer cell membrane	93.93	Cuproptosis, cancer starvation, upregulation of PD-L1.	iv	Sensitization of efficacy of PD-L1 antibody, and substantial inhibition of both subcutaneous and lung metastasis tumors.	[90]
Nanohybrid	None	*Escherichia coli* and Cu_2O nanoparticles	~1600	Ferroptosis, cuproptosis, photothermal therapy, immunosuppression reversion.	iv	Reversal of cancer immunosuppression by triggering DCs maturation and T cell activation.	[91]
Hollow mesoporous nanoparticle	L-Arginine	RGD peptide, hollow mesoporous CuS nanoparticle	300	Mild photothermal therapy, cuproptosis, generation of peroxynitrite anions, ICD.	iv	Promotion of immune cell infiltration and activation, and conversion of "cold" tumors into "hot" ones.	[92]
MOF	Copper ionophore elesclomol	Cu^{2+}-based MOF, PEG	171.9	Cuproptosis, ICD.	iv	Conversion of immunosuppressive tumor to immunogenic one and effective inhibition of tumor growth by combined MOF and PD-L1 antibody.	[93]
Nanoparticle	Elesclomol and Cu	ROS-sensitive polymer PHPM	62.8	Cuproptosis, increment of PD-L1 expression in tumor cells, transformation of immune "cold tumors" into "hot tumors".	iv	Reprogramming TME and triggering an effective anti-tumor immune response together with PD-L1 antibody.	[94]
Nanoparticle	Copper ionophore elesclomol	Copper oxide nanoparticles, PEG	112	Cuproptosis, ICD, release of DAMPs.	iv	Remodeling immunosuppressive TME and significant inhibition of tumor growth in combination with PD-1 antibody.	[95]
Nanoparticle	Copper, erastin	1,2-dioleoyl-*sn*-glycero-3-phosphocholine, 1,2-dioleoyl-*sn*-glycero-3-phosphate, cholesterol,DSPE-PEG2000	146.8	Ferroptosis, cuproptosis, ICD.	iv	Co-administration with PD-L1 antibody, potent regression of tumor and prevention of tumor metastasis.	[96]
Nanoparticle	Celastrol, Cu	DSPE-PEG2000	110	Cuproptosis, ICD.	iv	Combing with PD-L1 antibody, effective eradication of metastatic tumors in lung metastasis model.	[97]

(*Continued*)

Table 3 (Continued).

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Nanoparticle	Copper	Aloe emodin, PEG2000-DSPE-folic acid	120	Cuproptosis, photodynamic immunotherapy	iv	Induction of DCs maturation, promotion of lymphocyte infiltration, transformation of "cold tumors" into "hot tumors", and significant enhancement of immune checkpoint blockade efficacy.	[98]
MOF	Pyruvate dehydrogenase kinase 1 siRNA	Poly (2-(N-oxide-N,N-diethylamino)ethyl methacrylate), copper-based MOF	147.4	Cuproptosis, ICD, upregulation of membrane-associated PD-L1 expression and soluble PD-L1 secretion.	ih	Conversion of immunosuppressive TME to immune-activating environment and inhibition of metastatic lung tumor growth.	[99]
Nanoparticle	Disulfiram	Cu^{2+}-chitosan shell and low molecular weight heparin-tocopherol succinate core	186.9	Cuproptosis, activation of cGAS-STING pathway to increase innate and adaptive immunity, reversal of immunosuppressive TME.	ih	Collaborated with PD-L1 antibody, provocation of more powerful anti-tumor immunity to inhibit occurrence of lung metastasis.	[100]

Abbreviations: iv, intravenous injection; it, intratumoral injection; ih, inhalation.

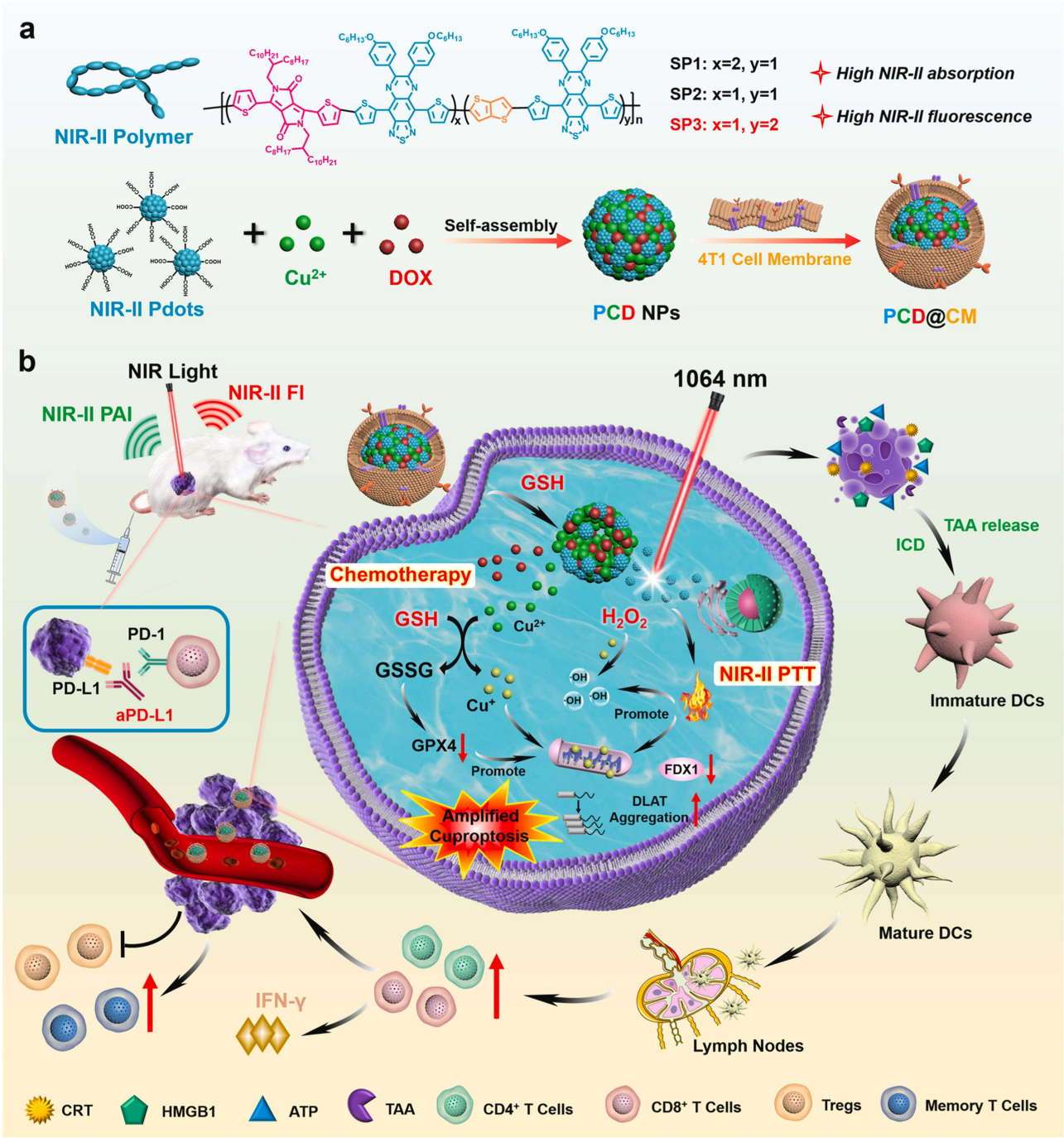

Figure 4 Schematic illustration of the biomimetic self-assembly of cuproptosis amplifier for synergistic tumor immunotherapy. (**a**) Preparation of the near-infrared II semiconducting polymer and the biomimetic cuproptosis amplifier (PCD@CM). (**b**) Near-infrared-II fluorescence/photoacoustic imaging-mediated chemotherapy and photothermal amplified cuproptosis, provoking anti-tumor immunotherapy combined with immune checkpoint blockade mediated by anti-PD-L1 antibody. ↓, downregulation; ↑, upregulation. (reproduced with permission from Yeneng Dai et al (2024). Copyright 2024 Elsevier).

PD-1 therapy substantially increased the anticancer potency.[95] A novel bifunctional nanoparticle comprising a core of 1,2-dioleoyl-sn-glycero-3-phosphocholine, cholesterol, PEG-coated copper ions and peroxide, and an erastin shell was constructed for synergistic cuproptosis and ferroptosis. Erastin of anti-Warburg potency sensitized cancer cells to cuproptosis, resulting in ICD, enhanced antigen presentation, increased proliferation and infiltration of T cells, and upregulated PD-1 expression. When combined with PD-L1 antibody, the nanoparticles supported T cells to mediate cancer regression and prevent metastasis.[96]

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Self-amplified cuproptotic nanoparticles have been produced using the natural product celastrol as a versatile copper ionophore and scavenger for GSH to amplify cuproptosis, and the celastrol-copper complex was encapsulated by PEG. The self-amplified cuproptotic nanoparticles evoked ICD to trigger a potent immune response, and their combination with antibody against PD-L1 effectively eradicated metastatic tumors in an animal model.[97] Aloe emodin, a natural compound found in a plant, was chelated to copper ions and self-assembled into nanoparticles under modification with PEG and folic acid conjunction. The nanoparticles elicited maturation of DCs, infiltration of lymphocytes, transformation of "cold tumors" into "hot tumors", and potently increased the efficacy of immune checkpoint blockade.[98]

An inhalable poly (2-(*N*-oxide-*N,N*-diethylamino) ethyl methacrylate)-coated copper-based MOF loaded with pyruvate dehydrogenase kinase 1 siRNA, which blocks the copper efflux protein ATP7B, was fabricated to trigger cuproptosis and promote immunotherapy. The nanodrug triggered ICD and upregulated membrane-associated PD-L1 expression and soluble PD-L1 secretion, demonstrating synergism with the PD-L1 antibody.[99] Another inhalable nanoparticle was composed of a Cu^{2+}-chitosan shell and a low-molecular-weight heparin-tocopherol succinate core and was loaded with disulfiram, which chelated with Cu^{2+} to suppress ATP generation and Cu^{+} transporter ATP7B expression. The inhalable nanoparticles enhanced cuproptosis and activated the cGAS-STING pathway to increase innate and adaptive immunity, and strong anticancer immunity was realized by combing with PD-L1 antibody.[100]

Nanoparticles for Calcicoptosis and Cancer Immunotherapy

Calcium overload is generally featured by excessive accumulation of Ca^{2+} in cytoplasm or mitochondria. Under endoplasmic reticulum (ER) stress, the capability of cells to manipulate Ca^{2+} homeostasis is undermined. Ca^{2+} is sustainably released from the ER, which is the primary intracellular calcium ion pool, and cytosolic Ca^{2+} concentration is increased, followed by transport of Ca^{2+} into mitochondria, leading to mitochondrial Ca^{2+} overload.[101] In some conditions, Ca^{2+} overload can cause cell death through a distinct mechanism defined as calcicoptosis, which offers a novel strategy for cancer treatment.

Mechanism of Calcicoptosis

ER Ca^{2+} channel protein transmembrane and coiled-coil domains 1 (TMCO1) exert an important function in regulating calcium overload and maintaining calcium homeostasis, and inhibiting TMCO1 expression disrupts intracellular calcium homeostasis.[102] Participation of calcium in signaling among organelles determines the fate of cells and influences cell survival or programmed death.

During ER stress such as excessive misfolded protein, DNA damage, oxidative stress, and pro-apoptotic signals, Ca^{2+} is liberated into cytoplasm to activate dependent proteases approaching the ER. The activated proteases can trigger and release Caspase-12 into cytoplasm and activate the calcium/calmodulin-dependent protein phosphatase, which is responsible for dephosphorylation of the pro-apoptotic protein Bad, followed by release of cytochrome C to induce apoptosis.-[103] A previous study has uncovered a synergistic effect between cellular oxidative stress and calcium overload, ultimately leading to cell death.[104] Figure 5 schematically illustrates the mechanism of calcicoptosis.

Necroptosis, which is responsive to death stimuli such as tumor necrosis factor α and Fas ligand, also depends on calcium homeostasis. Upon reorganization of the ligand by the receptor on cell membrane, receptor-interacting protein kinase (RIPK)-1 forms a necrosome complex with RIPK3 and mixed lineage kinase domain-like protein (MLKL). The necrosome triggers mitochondria to produce ROS, leading to cell death.[105] The formation of a necrosome complex results in increased cytosolic calcium, followed by trimerization of MLKL and its translocation to the cell membrane. The MLKL enables influx of calcium into the cell and intensifies necroptosis in a feedback manner through interaction with the transient receptor potential melastatin 7 channel.[106] Calcium acts as a modulator of necrosome complex proteins and cell death.

Necrosis which is featured by rapid disintegration of cytoarchitecture, release of cellular contents, and an inflammatory reaction is also triggered by calcium overload.[107,108] Increased intracellular calcium concentration is induced by activation of transient receptor potential cation channel subfamily V member 1 to trigger cell death mainly through a necrotic pathway.[109] The release of Ca^{2+} from ER into the cytoplasm and their accumulation in mitochondria lead to Ca^{2+}

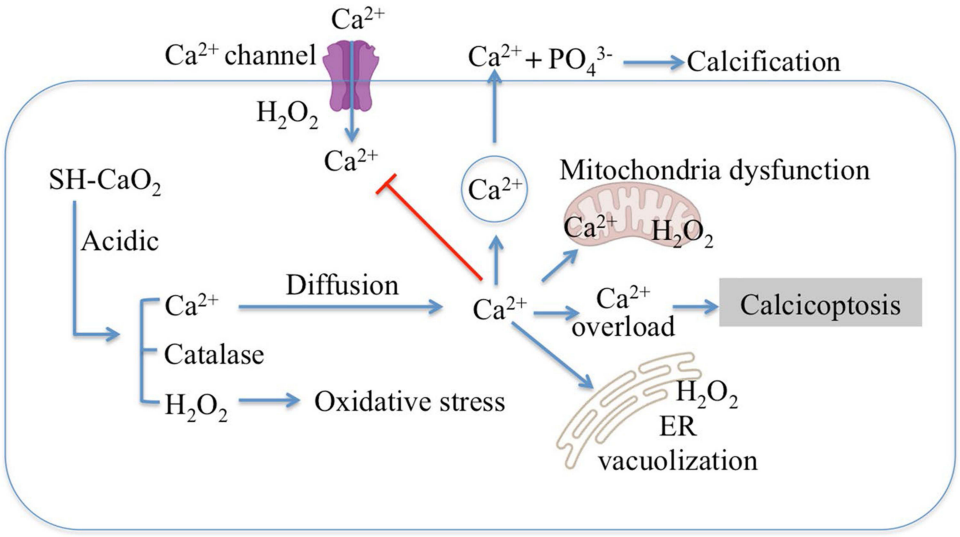

Figure 5 Schematic illustration of the mechanism of calcicoptosis. Under endoplasmic reticulum stress, Ca^{2+} is sustainably released from the endoplasmic reticulum, which is the primary intracellular calcium ion pool, and cytosolic Ca^{2+} concentration is increased and transported into mitochondria, leading to mitochondrial Ca^{2+} overload. In some conditions, Ca^{2+} overload can cause cell death through a distinct mechanism defined as calcicoptosis, which offers a novel strategy for cancer treatment. (reproduced with permission from Jie Gu et al (2024). Copyright 2024 Springer Nature).

overload and opening of mitochondrial permeability transition pores, resulting in swelling, mitochondrial rupture, and release of their contents to induce necrosis.[110]

Calcium ions also exert an important character in regulation of other PCD such as ferroptosis, pyroptosis, autophagy, and paraptosis.[110] Precise regulation of calcium signaling in cells is a powerful tool in cancer therapy.

Relationship Between Calcicoptosis and Cancer Immunotherapy

The regulation of intracellular calcium ions plays an essential role in immune cell activation, and targeting increased intracellular calcium ions can significantly stimulate the proliferation of cytotoxic lymphocytes.[111] Moreover, activation of T lymphocyte-associated transcription factors, for example, nuclear factor of activated T cells, nuclear factor kappa-B, and c-Jun N-terminal kinase, are heavily dependent on excessive accumulation of intracellular calcium ions.[112,113] Necroptosis is dependent on calcium homeostasis and triggers cells to release DAMPs that promote an anti-tumor immune response.[114] HMGB1 is liberated from cells undergoing necrosis triggered by calcium overload, acting as a DAMP to activate macrophages and DCs in the TME.[115] Further, calcium overload facilitates the exposure of calreticulin localized in ER to deliver intensive pro-phagocytic signals to myeloid cells.[116,117] Previous researches have demonstrated that the concentration of calcium ion in macrophages might be closely associated with their phenotype.

Increase in cytoplasmic calcium ions can activate p38 and nuclear factor kappa-B for repolarizing TAMs to the M1 phenotype and stimulate transcription factor EB for reprograming the metabolism of TAMs.[118] Excessive ROS and lipid peroxidation triggered by calcium overload through the ROS/p38-MAPK/diacylglycerol-O-acyltransferase 1 pathway are also speculated to inhibit M2 macrophage polarization.[119]

Nanoparticles for Calcicoptosis to Enhance Cancer Immunotherapy

Hypercalcemia results in clinical manifestations such as nausea, renal dysfunction, nephrocalcinosis, vascular calcification, and cardiac arrhythmias.[120] Therefore, the targeted delivery with nanomedicine can enhance efficacy and minimize toxicity. Nanoparticles for delivering Ca^{2+} or calcium-based nanovehicles to strengthen cancer immunotherapy are illustrated in Table 4.

Calcium carbonate-based nanoparticles are the most widely used vehicle for calcium overload therapy. pH-responsive and catalase-delivered calcium carbonate nanoparticles have been constructed to reshape the TME for enhanced immune checkpoint blockade. $CaCO_3$ nanoparticles reacted with protons in an acidic TME to reprogram it, and the released Ca^{2+} led to overload in cancer cells, followed by liberation of DAMP signals and repolarization of M2 TAMs to the M1

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Table 4 Calcium-Based Nanomedicines for Inducing Calcicoptosis to Strengthen Cancer Immunotherapy

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Nanoparticle	Catalase	Calcium carbonate nanoparticle	187	Normalization of pH and relieve of hypoxia in TME, Ca^{2+} overload triggered release of DAMPs, enhanced tumor antigen presentation by DCs, repolarization of M2 TAMs to M1 phenotype.	it	Together with PD-1 antibody, effective evocation of local and systemic anti-tumor immune responses, and inhibition of treated and distant tumors growth.	[121]
Hydrogel	Bufalin	$CaCO_3$ nanoparticles, alginate hydrogel	None	Direct anticancer efficacy, Ca^{2+} overload-triggered pyroptosis, upregulation of PD-L1.	it	Potential evocation of higher immune response, promotion of DCs maturation, $CD8^+$ T cell maturation and infiltration, and generation of a synergistic effect together with PD-1 antibody.	[122]
Core-shell nanostructure	None	Cu_2O core, $CaCO_3$ shell, hyaluronic acid	167.6	Photothermal, photodynamic, chemodynamic and calcium-overload mediated therapy	iv	Reprogramming macrophages from M2 to M1 phenotype and initiating a vaccine-like immune effect, which intensifies immune responses for anti-CD47 antibody to inhibit distant metastasis and recurrence.	[123]
Nanoparticle	Doxorubicin, erianin	$CaCO_3$ nanoparticle, poly($_{D,L}$-lactide-*co*-glycolide)−PEG	120	Calcium overload, chemotherapy, metabolic remodeling, ferroptosis, apoptosis, ICD.	iv	Reversal of unfavorable TME and enhancement of PD-L1 antibody immunotherapy.	[124]
Nanoparticle	Carbonic anhydrase inhibitor	$CaCO_3$ nanoparticles, 1, 2-dioleoyl-*sn*-glycero-3-phosphate sodium, 1,2-Dipalmitoyl-*sn*-glycero-3-phosphorylcholine, cholesterol, DSPE-PEG5000	115.5	Reversal of acidic tumor microenvironment and the increase of intracellular H^+, calcium overload, radiotherapy-induced ICD and DCs maturation, repolarization of macrophages from M2 to M1 phenotype.	iv	Combined with PD-L1 antibody, effective inhibition the growth of distant/orthotropic tumors.	[125]
Nanoparticle	Curcumin	$CaCO_3$ and MnO_2 nanoparticles, B16F10 cell membrane	392.70	Neutralization of protons and attenuation of cellular acidity, ICD, calcium overload, relief of hypoxia, activation of cGAS-STING pathway, induction of macrophage polarization and DCs maturation	iv	Enhanced anti-tumor responses of antibody against PD-1.	[126]
Colloidosome	Catalase, PD-1 antibody	$CaCO_3$ nanoparticle, sodium n-octanoate, poly($_{D,L}$-lactide-*co*-glycolide) acid	100	Modulation of tumor acidity and hypoxia, reversal of tumor immunosuppression.	it	Significant potentiation of both immune checkpoint blockade and CAR-T cell immunotherapies toward solid tumors.	[127]
Self-assembly	Ca^{2+}, GSK2837808A	Hyaluronic acid-catechol, PEG-polyphenol, and PEG-IR780	122.4	Suppression of aerobic glycolysis and creation of high-glucose and low-lactate conditions, calcium overload, release of DAMPs for activation and tumor infiltration of $CD8^+$ T cell.	iv	Combining with CTLA-4 antibodies, effective inhibition of both primary and distant tumors.	[128]

MOF	Ca^{2+}	Zr, tetrakis-(4-carboxyphenyl)-porphyrin	~200	Calcium overload, photodynamic therapy, ICD, release of tumor-associated antigen, promotion of DCs maturation and $CD8^+$ T cells activity.	iv	Co-administrated with PD-1 antibody, prominent elimination of primary tumor and obvious antimetastasis effect.	[129]
Core-shell nanoparticle	None	TiO_2 core, CaP shell, poly (acrylic acid)	Diameter 73.40, length 57.73	Calcium overload, sonodynamic therapy, ICD, enhanced T-cell recruitment and infiltration.	iv	In conjunction with PD-1 antibody, elicitation of systemic anti-tumor immunity, regression of distant tumors and lung metastasis.	[130]
Nanoparticle	None	Calcium hydroxide nanoparticle, layer of silica, PEG, anti-CD205 antibody	245.2	Activation of nuclear factor of activated T cells and the nuclear factor kappa-B by elevated cytosolic calcium, and promotion of expression of costimulatory, antigen-presenting and pro-inflammatory molecules.	it	Enhanced anti-tumor immune response and augmented efficacy for radiotherapy, chemotherapy and immunotherapy.	[131]
Nanoparticle	CaO_2	Mesoporous silica nanoparticles, mitochondrial photosensitizer N770	462.7	Calcium overload, phototherapy, alleviation of immunosuppressive microenvironment, ICD.	iv	Together with PD-L1 antibody, eradication of orthotopic and distant tumors, and potentiation of systemic anti-tumor immunity.	[132]
Nanoparticle	None	CaO_2 nanoparticle, ultrasmall CuS-MnO_2, hyaluronate acid	180	Calcium overload, photodynamic therapy, ICD, elicitation of adequate DAMPs, reprogramming tumor immunosuppression by transforming TAMs to M1 phenotype.	iv	Combined with PD-L1 antibody, effective increment of matured DCs, M1 macrophages and $CD8^+$ T cells in tumor, and vigorous immune memory against tumor metastasis.	[133]
Nanoparticle	None	Manganese-doped calcium sulfide nanoparticles, PEG	80	Calcium overload-regulated pyroptosis and cGAS-STING pathway, inhibition of energy metabolism, mitochondrial dysfunction, activation of DCs, H_2S enhanced innate and adaptive immune responses.	it	Integrated with PD-1 immunotherapy, activation of a strong anti-tumor immune response and synergistic anti-tumor effect.	[134]
Nanoparticle	None	Calcium sulfide nanoparticles, poly(acrylic acid), zinc protoporphyrin	127.5	Ca^{2+} overload, Ca^{2+}-dependent cell death, activation of anti-tumor immunity, suppression of antideath effect.	iv	Co-administrated with PD-1 antibody, marked eradication of primary tumor and distant metastases, and fabrication of immunological memory to arrest tumor metastasis and recurrence.	[135]

Abbreviations: iv, intravenous injection; it, intratumoral injection.

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phenotype, enhancing tumor antigen presentation by DCs. Consequently, the $CaCO_3$ nanoparticles triggered a T cell-regulated immune response that can combine with antibody against PD-1 to stimulate local and systemic immune responses, suppressing growth of both primary and metastatic tumors.[121] A calcium carbonate nanoparticle hydrogel was loaded with the anticancer drug bufalin as an inhibitor of Na^+/K^+-ATPase to increase intracellular Ca^{2+} level. The resulting pyroptosis enhanced the efficacy of PD-1 antibody to induce an inflammatory TME, achieving synergistic potency in stimulating an immune response.[122] A core-shell Cu_2O and $CaCO_3$ nanocomposite that was responsive to acidic pH and H_2S sulfuration was used for photothermal, photodynamic, chemodynamic, and calcium-overload-mediated therapy, reprogrammed TAMs of the M2 phenotype to that of M1, and initiated a T cell-regulated immune response. Combined CD47 blockade and the nanocomposite induced a strong immune response, effective ablation of the primary tumor, and inhibition of cancer recurrence and metastasis.[123] Zheng et al used a modified double emulsion method to encapsulate doxorubicin and erianin into $CaCO_3$ nanoparticles. The multifunctional nanoparticles effectively elicited calcium overload and oxidative stress damage to activate hybrid ferroptosis and apoptosis pathways and led to prominent ICD. Additionally, the $CaCO_3$ nanoparticles synergistically amplified the potency of anti-PD-L1 antibody.[124] $CaCO_3$ nanoparticles were utilized to deliver a carbonic anhydrase inhibitor that improved the sensitivity of cancer to radiotherapy and further were modified with liposomes. The nanoparticles induced cellular calcium overload, strengthened ICD triggered by radiotherapy and DCs maturation, and repolarized macrophages from pro-tumor M2 to anti-tumor M1 phenotype, amplifying systemic anti-adaptive immunity. With PD-L1 antibody, the efficacy of $CaCO_3$ nanoparticles plus radiotherapy was increased, resulting in longer survival time.[125] A pH-sensitive nanoparticle for co-delivery of curcumin as a Ca^{2+} enhancer, $CaCO_3$ and MnO_2 were encapsulated by a cancer cell membrane, and the released Ca^{2+} triggered calcium overload and ROS production in mitochondria and ER, leading to ICD. In addition, the nanoparticle repolarized macrophages and induced DCs maturation via antigen presentation and enhanced immune responses of the anti-PD1 antibody.[126] Calcium carbonate nanoparticles encapsulating catalase assembled colloidosomes could activate strong anticancer immunity to significantly amplify the efficacy of co-loaded antibody against PD-1 and dramatically reinforce the therapeutic outcome of epidermal growth factor receptor-expressing CAR-T cells.[127]

Hyaluronic acid-catechol, PEG-polyphenol, and PEG-IR780 self-assembled into nanoparticles for carrying Ca^{2+} and lactate dehydrogenase A inhibitor GSK2837808A. Satisfying glucose nutrition required by $CD8^+$ tumor-infiltrating lymphocytes and destabilizing regulatory T were realized by inhibiting lactate dehydrogenase A, and further $CD8^+$ T cell activation and tumor infiltration were promoted by the released DAMPs triggered by Ca^{2+} overload in mitochondrion and amplified mitochondrial dysfunction. Cooperating with CTLA-4 antibodies further enhanced therapeutic efficacy.[128]

Yu et al constructed a mineralized porphyrin MOF encapsulating calcium phosphate for amplified cell damage caused by calcium overload and photodynamic therapy. The MOF could induce cell immunogenic death to liberate tumor-associated antigen, promote DCs maturation and enhance anticancer activity of $CD8^+$ T cells, and co-administration with PD-1 antibody demonstrated prominent elimination of primary tumor and obvious inhibition for metastasis.[129] A transformable TiO_2 core and CaP shell nanosonosensitizer combining ROS generation and intracellular calcium overload substantially strengthened ICD, T cell recruitment, and infiltration into the immunogenic cold tumor. In combination with PD-1 antibody, the nanosonosensitizer regulated sonodynamic therapy-triggered systemic anticancer immunity.[130]

Calcium hydroxide nanoparticles coated with a layer of silica and further conjugated with anti-CD205 antibody were designed for targeted delivery to DCs. The elevated cytosolic calcium triggered nuclear factor of activated T cells and the nuclear factor kappa-B signaling pathway, followed by enhanced anticancer immune response and increased efficacy of anti-PD-L1 antibody.[131]

The mitochondrial photosensitizer N770 conjugated mesoporous silica nanoparticles for delivery of CaO_2 achieved phototherapy, and calcium overload triggered ER stress and mitochondrial damage, and relieved the immunosuppressive microenvironment. Moreover, mesoporous silica nanoparticles together with antibody against PD-L1 significantly potentiated systemic anti-tumor immunity.[132] Bovine serum albumin-templated ultrasmall CuS-MnO_2 nanoparticles were adhered to the surface of CaO_2 nanoparticles via surface electrostatic interaction, and the nanoparticles were wrapped with hyaluronate acid. A large mass of O_2 and Ca^{2+} produced by CaO_2 nanoparticles strengthened photodynamic therapy and Ca^{2+} overload separately, amplifying ICD. Combing the nanoparticles with antibody against PD-L1 achieved enhanced immunotherapy efficacy and long-term protection.[133]

PEG-decorated manganese-doped calcium sulfide nanoparticles rapidly liberated Ca^{2+}, Mn^{2+}, and H_2S responding to a TME, and the released H_2S was a crucial synergist for Ca^{2+} in pyroptosis-triggered calcium overload by disrupting intracellular calcium homeostasis and interfering with oxidative phosphorylation pathways (Figure 6). Via activation of calcium overload-regulated pyroptosis and the cGAS-STING pathway, manganese-doped calcium sulfide nanoparticles stimulated both innate and adaptive anticancer immune response and boosted the efficacy of anti-PD-1 therapy.[134] A porous poly(acrylic acid) stabilized CaS nanoparticles delivering zinc protoporphyrin as a messenger amplifier resulted in Ca^{2+}-dependent tumor immunogenic death and triggered release of tumor-associated antigens as an in situ vaccine to activate the immune response. Integration of CaS nanoparticles and anti-PD-1 antibody fabricated immune memory to produce long-term immunity against tumor metastasis and recurrence.[135]

Zinc-Based Nanoparticles and Cancer Immunotherapy

Zinc ions exert an essential character in a vast array of physiological and cellular processes, including activation of matrix metalloproteinases, cell proliferation, development, metabolism, DNA biosynthesis and transcription, and PCD. Zinc ions also are involved in protection from oxidation stress, inflammation response, and immune regulation.[5] Transportation of zinc ions across cytomembranes is regulated by the cooperation of zinc transporter proteins, known as zinc transporter family or Zrt/Irt-like proteins (ZIPs). ZIPs are responsible for influx of zinc ions from the extracellular compartment or intracellular organelles into cytoplasm, while zinc transporters take charge of zinc ion efflux from

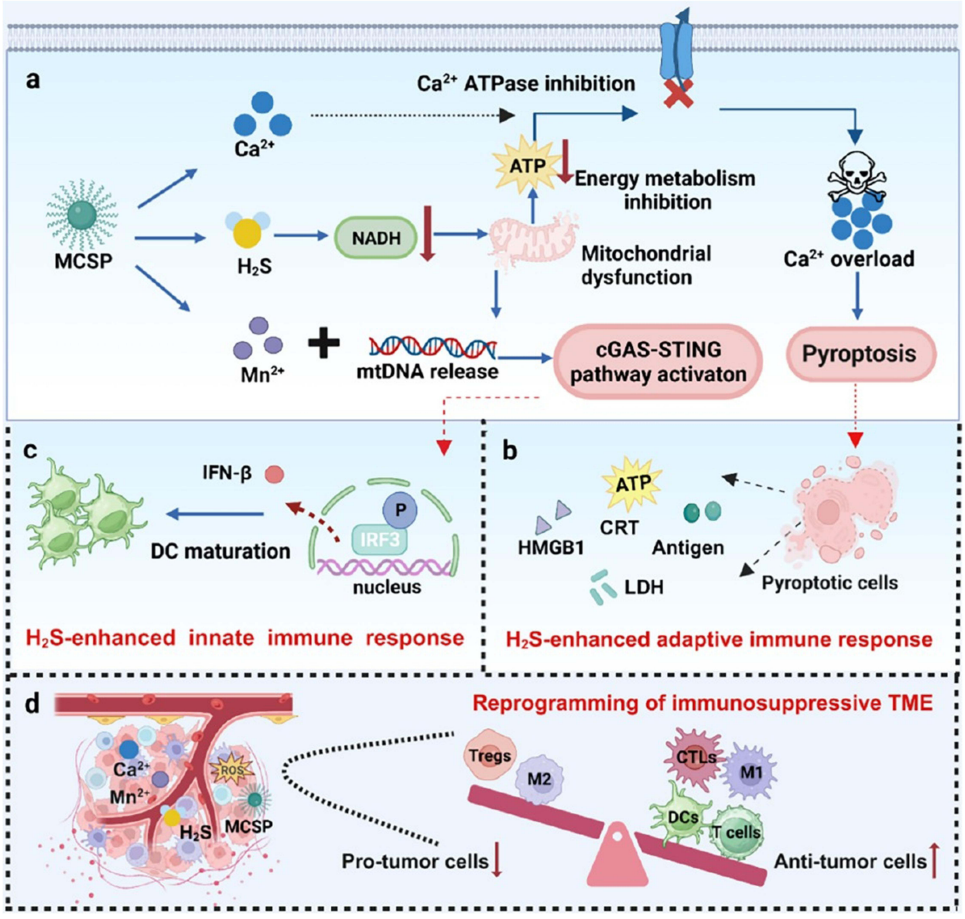

Figure 6 Schematic illustration of the underlying therapeutic mechanism of manganese-doped calcium sulfide nanoparticles for cancer cell pyroptosis and cGAS-STING pathway activation. (**a**) The mechanism of pyroptosis and activation of the cGAS-STING signaling pathway triggered by manganese-doped calcium sulfide nanoparticles. (**b**) H_2S strengthened the adaptive immune response. (**c**) H_2S amplified the innate immune response. (**d**) Reshaping of the immunosuppressive tumor microenvironment.[134] ↓, downregulation; ↑, upregulation; ✖, inhibition. (Reprinted with permission from Lin Liu et al (2024). Copyright (2024) American Chemical Society).

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cytoplasm to extracellular compartment or intracellular organelles.[136] Given their essential characters in physiological and cellular processes, it necessitates stringent control of zinc ions homeostasis.

Zinc Triggered PCD

Zinc ion-elicited apoptosis is regulated by promotion of B-cell lymphoma-2 associated X protein (Bax) expression which triggers the liberation of cytochrome C and activation of caspase 3, eventually leading to apoptosis.[137] An increase in the ratio of Bax to B-cell lymphoma-2 contributes to deterioration of hypoxia inducible factor-1α followed by decreased expression of the inhibitor of survivin, ultimately triggering apoptosis.[138] Also zinc ions can strengthen the expression of Smad2 and PIAS1 as transcription activator 1, followed by activation of P21 gene expression and promotion of apoptosis.[139] ZIP9, a zinc transporter protein and membrane androgen-binding receptor, is revealed to be associated with apoptosis via activating G protein.[140]

In cancer development, lysosomal function is usually upregulated to satisfy the enhanced energy requirement for rapidly proliferating tumor cells.[141] Transient receptor potential mucolipin 1, a cation channel with dual permeability to calcium and zinc ions, is upregulated in certain cancer cells and can be activated to trigger lysozincrosis via release of zinc ions from lysosomes, mitochondrial swelling and impairment, and energy depletion.[142] Moreover, normal cells expressing low level of transient receptor potential mucolipin 1 are not susceptible to lysozincrosis, indicating its possibility for cancer therapy.

Autophagy, a conserved catabolic process, is triggered in response to stress such as energy deprivation, hypoxia, infection, and ER stress and results in degradation of intracellular components.[143] Multiple studies consistently indicated that zinc triggers autophagy; however, the mechanisms are still poorly clarified. Extracellular-signal-regulated kinase 1/2 (ERK1/2), metal responsive transcription factor-1 (MTF1), and calcium/calmodulin-dependent protein kinase kinase-B/AMP-activated protein kinase (CaMKKb/AMPK) are involved in induction of autophagy by zinc.[143] Zinc ions are also responsible for triggering necroptosis,[144] ferroptosis[145] and pyroptosis.[146] The mechanism for Zn^{2+} induced PCD is summarized in Figure 7.

Zinc Triggered PCD and Cancer Immunotherapy

Zinc ions can enhance the activity of an array of immune cells, including T cells, B cells, and natural killer cells; can polarize macrophages into the M1 phenotype; and alleviate the immunosuppressive state of microenvironment through inhibiting release of inflammatory molecular and inflammatory response. Zinc ions can enhance tumor antigen presentation and recognition of antigen by immune cells and suppress immune checkpoint protein expression to reinforce an anticancer immune response.[147]

Zinc ions have emerged as an immunologic adjuvant to activate the cGAS-STING signaling pathway in initiation of anticancer immunity and transformation of a "cold" tumor into a "hot" one.[148] Zinc ion-modulated ferroptosis increases the potency of immune cells such as T cells or macrophages, which is related to the release of DAMPs and interferon γ.[145] Excess zinc ion-triggered tumor cell pyroptosis also resulted in liberation of mass DAMPs.[147] Autophagy and necroptosis also lead to the liberation of DAMPs, activation of immune cells, and antigen presentation.[149] Therefore, the combination of zinc ions and cancer immunotherapy can enhance the response rate.

Zinc-Based Nanoparticles Enhance Cancer Immunotherapy

Overexposure of zinc can damage the nervous system,[150] and the targeted delivery of zinc is highlighted to reduce its toxicity. Nanoparticles for delivering Zn ions or zinc-based nanovehicles to boost cancer immunotherapy are shown in Table 5.

Sun et al fabricated an erythrocyte membrane-decorated zinc-phenolic nanocapsule for delivery of mitoxantrone and antibody against PD-L1 to treat triple-negative breast cancer with limit immune response. The zinc-phenolic nanocapsule triggered cancer cell pyroptosis, activated the cGAS-STING pathway, and amplified the efficacy of anti-PD-L1 antibody, achieving sustained immune response.[151] Zhu et al synthesized ferritin heavy chain siRNA and hyaluronic acid warped arginine-stabilized zinc peroxide to induce Fe^{2+} overload and ferroptosis, and the liberated Zn^{2+} induced mitochondrial dysfunction and oxidative stress to further boost ferroptosis. The nanoagent-regulated ferroptosis exerted a potent

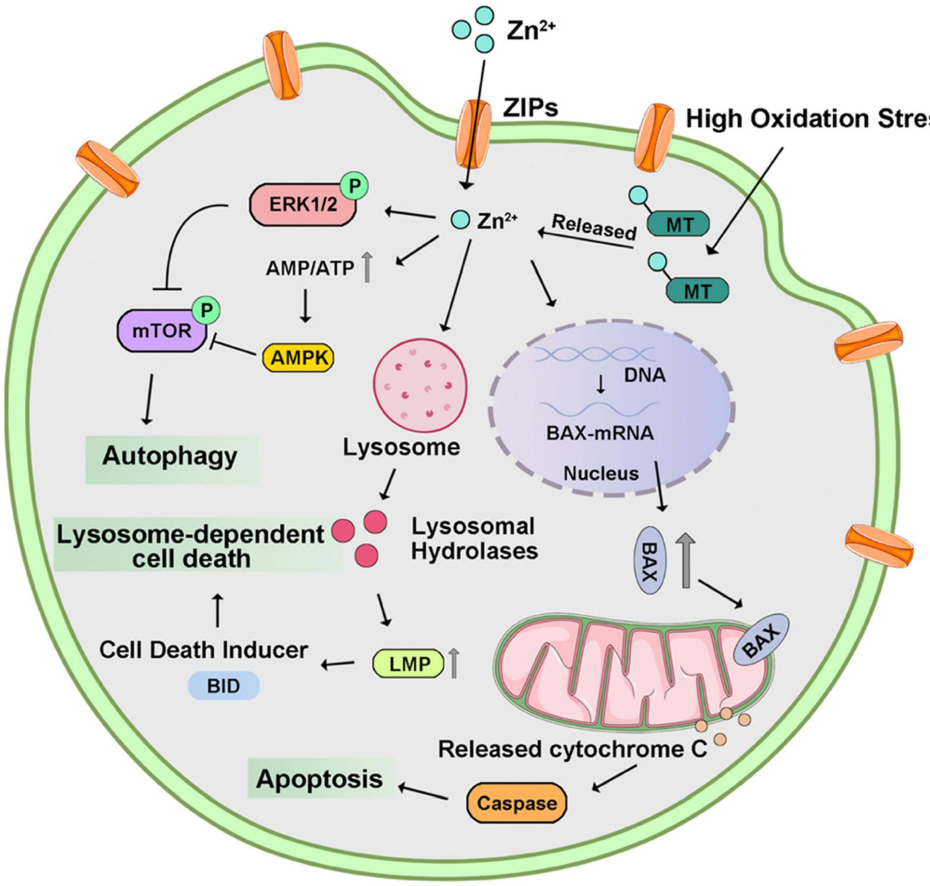

Figure 7 Schematic illustration of a representative signaling pathway for zinc ion-induced PCD. (reproduced with permission from Yawen You et al (2025). ↑, upregulation. Copyright 2025 Royal Society of Chemistry).

immunogenic response for T-cell activation and infiltration, and integration of the nanoagent with anti-PD-1 antibody resulted in prominent anticancer efficacy in vivo.[152] A polydopamine-coated zinc-copper bimetallic nanoplatform was introduced to spontaneously liberate Cu^{2+}, Zn^{2+}, and H_2O_2 in the acidic TME, leading to irreversible cuproptosis and cGAS-STING pathway activation. The zinc-copper bimetallic nanoplatform induced DCs maturation, T cell activation, and PD-L1 expression, sensitizing triple-negative breast cancer to antibody against PD-L1 therapy.[153] Lu et al fabricated hyaluronic acid-modified zinc peroxide-iron nanocomposites to reshape the TME and simultaneously trigger pyroptosis and ferroptosis, significantly enhancing the anticancer immune response to anti-PD-1 antibody.[154] Bioactive zinc-nickel hydroxide nanosheets initiated zinc overload-regulated pyroptosis, and the released Ni^{2+} amplified pyroptosis through concurrently inducing paraptosis, inhibiting autophagic flux, and triggering release of endogenous zinc ions. The nanosheets triggered liberation of DAMPs from cancer cells, followed by stimulation of DCs maturation, increase in $CD8^+$ T cell infiltration, and transformation of macrophages to M1 phenotype, strengthening the therapeutic potency of the antibody against PD-1.[155]

A bovine serum albumin nanocluster was constructed via an ion diffusion approach for co-delivery of zinc and sulfur to enhance cancer immunotherapy as demonstrated in Figure 8. The released zinc ions in a low pH TME prominently enhanced the cGAS-STING pathway. H_2S produced by the nanocluster further facilitated production of ROS by zinc ions via specifically inhibiting catalase in hepatocellular carcinoma cells, leading to further activation of cGAS-STING by the accumulated ROS. The nanocluster promoted infiltration of $CD8^+$ T cells into the tumor and cross-presentation of DCs, and integration of the nanocluster and PD-L1 antibody resulted in a significant inhibiting effect on tumor growth and potent immune response.[156]

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Table 5 Zinc-Based Nanomedicines to Boost Cancer Immunotherapy

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Nanocapsule	Mitoxantrone, anti-PD-L1 antibody	Zinc-phenolic nanocapsule, tannic acid, 8-arm-PEG–OH, erythrocyte membrane	~160	Pyroptosis, STING activation	iv	Infiltration of cytotoxic T cells, inhibition of suppressive immune cells proliferation, increment of memory T cells in tumor and spleen, and effective inhibition of metastatic tumor growth.	[151]
Nanocomplex	Ferritin heavy chain siRNA	Arg-stabilized zinc peroxide, hyaluronic acid	~190	Ferroptosis, enhanced lipid peroxidation production, inhibition of mitochondrial function, ICD, activation and infiltration of T-cell.	iv	Induction of a strong antitumour immune response, and potentiation of anti-PD-1 antibody efficacy.	[152]
Nanoparticle	None	Zinc-copper bimetallic nanoparticle, polyvinylpyrrolidone, polydopamine	177.2	Photothermal therapy, cuproptosis, cGAS-STING activation, reversal of immunosuppressive TME, and upregulation of PD-L1.	it	Co-administrated with PD-L1 antibody, markedly bolstered anti-tumor immunity and inhibition of tumor growth and metastasis.	[153]
Nanoparticle	None	Zinc peroxide-iron nanocomposite, hyaluronic acid, polyvinylpyrrolidone	220	Reshaping tumor stromal microenvironment, pyroptosis, ferroptosis, ICD.	iv	In combination with PD-1 antibody, prevention of T cells exhaustion and activation of immune response, and potentiation of PD-1 antibody efficacy.	[154]
Nanosheet	None	Zinc-nickel hydroxide nanosheet	Diameter 200, thickness 11 nm	Zinc overload-mediated pyroptosis, paraptosis, ICD.	it	Activation of immune response, and significant augmentation of PD-1 antibody efficacy.	[155]
Nanocluster	ZnS	Bovine serum albumin	100	cGAS/STING activation, apoptosis, promotion of $CD8^+$ T cells infiltration and DCs cross-presentation.	iv	Facilitation of systemic immune responses, a potential to prevent tumor relapse and metastases. Combined with PD-L1 antibody, significant inhibition of tumor growth.	[156]

Abbreviations: iv, intravenous injection; it, intratumoral injection.

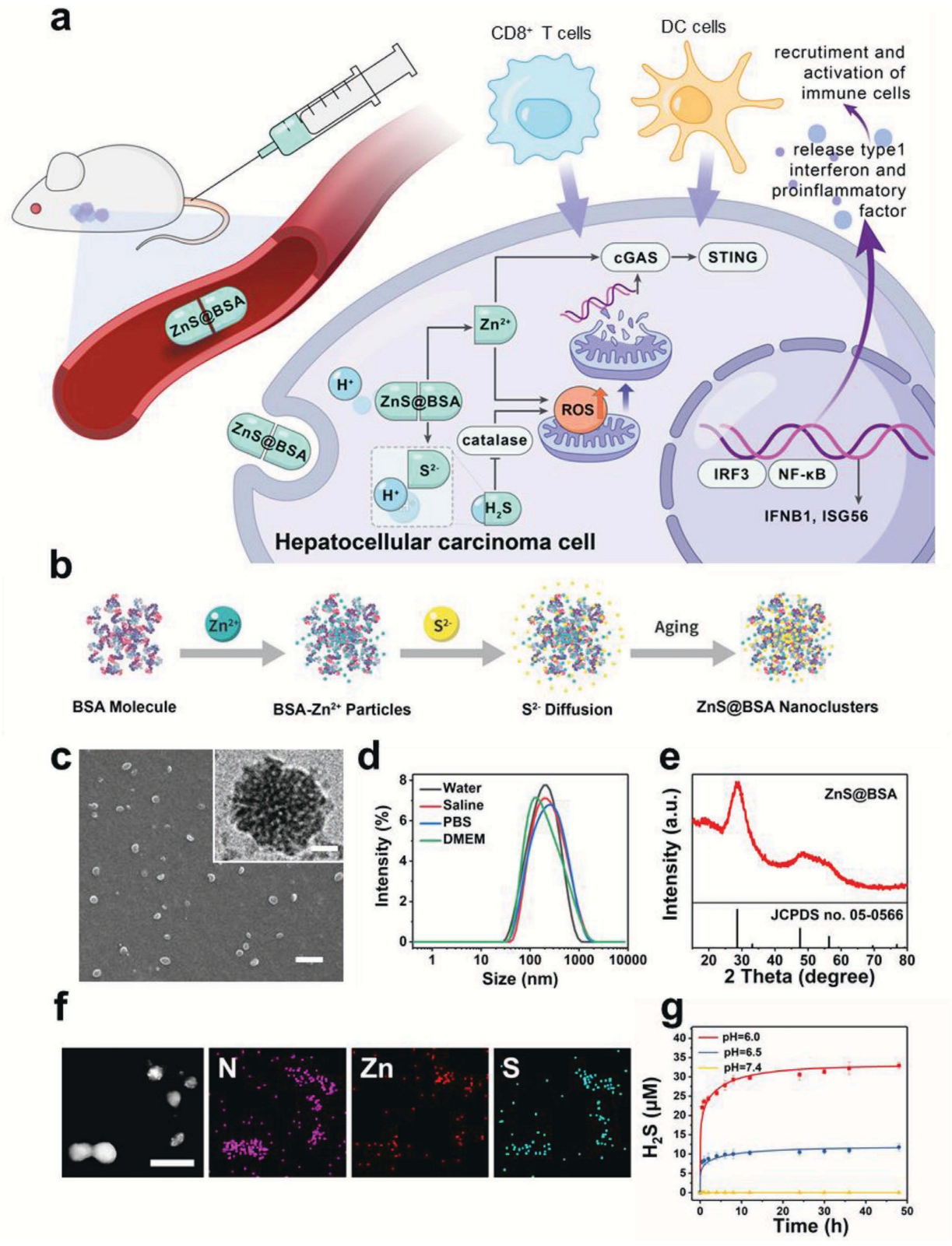

Figure 8 Schematic and characteristics of a bovine serum albumin nanocluster for co-delivery of zinc and sulfur. (**a**) The therapeutic process of the nanoclusters. (**b**) The synthesis routine of the nanoclusters. (**c**) Scanning electron microscopy image of the nanoclusters. Scale bar: 1 μm. Inset: High-resolution transmission electron microscopy image. Scale bar: 20 nm. (**d**) Hydrodynamic size of the nanoclusters in different solutions. (**e**) X-ray diffraction pattern of the nanoclusters. (**f**) Element mapping of the nanoclusters. Scale bar: 200 nm. (**g**) Release profile of H_2S from nanoclusters in solutions with different pH of 7.4, 6.5, and 6.0 (n = 3, mean ± standard deviation). ↑, upregulation; ↑, the following step. (reproduced with permission from Xiujun Cai et al (2021). Copyright 2021 John Wiley and Sons).

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Manganese-Based Nanoparticles and Cancer Immunotherapy

Manganese, an indispensable trace element in the human body, participates in a vast array of physiologic processes such as serving as a cofactor for various enzymes, development, metabolism, hematopoiesis, protein and vitamin synthesis, endocrine regulation, protection from ROS, and redox homeostasis.[5,157] In recent decades, manganese has been used as an inducer for PCD and enhancer for immune function.

Manganese-Dependent Cell Death

Manganese ions downregulate system Xc^- and excitatory amino acid transporter, and cystine as a precursor for GSH biosynthesis is reduced, leading to depletion of GSH and its synthesis.[158,159] Blocking the biosynthesis of GSH resulted in excessive accumulation of ROS followed by lipid peroxidation overproduction, and ultimate cell death.[160,161] Manganese ions catalyze Fenton-like and Haber-Weiss reactions that produce ROS and exhaust GSH, similar to the iron-triggered Fenton reaction.[157] Manganese ions catalyze a Fenton-like reaction in the presence of H_2O_2 to generate ·OH. Manganese ions also increase mitochondrial H_2O_2 by fostering superoxide dismutase 2 activity, and releasing oxidoreductases from the Krebs cycle through triggering permeability transition.[162,163]

Cellular uptake of manganese and iron ions is competitive, and several transporters responsible for iron ions transportation, such as DMT1, TFR, ferroportin, and ferritin, also deliver manganese ions.[164–166] Manganese ions disturb iron homeostasis through over-expression of TfR and upregulation of iron uptake in the brain, leading to significantly increased cellular levels of labile iron rather than total cellular iron levels.[167–169]

Manganese ions trigger ferroptosis in dopaminergic neurons by regulating the hypoxia-inducible factor-1 α /p53/SLC7A11 signaling pathway.[170] Manganese ions drive ferroptosis in oral squamous cell carcinoma cells via nuclear translocation of Yes-associated protein/transcriptional co-activator with PDZ-binding motif and subsequent ACSL4 activation.[171]

Manganese ions at high concentration trigger cytochrome C liberation from mitochondria and caspase-8 regulated apoptosis in B cells. In neuronal cells, manganese ion-induced apoptosis is facilitated by transcriptional activation of caspase 3, which is induced by phosphorylation of zinc finger transcription factor SP-1.[172] Manganese ions can inhibit the acetylation of histone H3 and H4 by augmenting the activity of histone deacetylase and decreasing that of histone acetyltransferase, which eventually triggers apoptosis.[173] Manganese ions induce apoptosis through p53- and p38-mitogen-activated protein kinases and the mitogen and stress response kinase-1 signaling pathway.[174,175]

Manganese ions trigger necrosis through ROS-induced lysosomal membrane permeabilization and release of cathepsin D into the cytosol, and also via ROS-triggered DNA damage, translocation of apoptosis-inducing factor from mitochondria to the nucleus, and parthanatos.[176] Manganese ions also induce necroptosis in macrophages infected with *Mycobacterium tuberculosis* through the STING-tumor necrosis factor signaling pathway.[177]

Manganese-Regulated Cancer Immunotherapy

Manganese ions exert vital roles in activation and functional regulation of immune cells including T cells, macrophages, and natural killer cells, and they play a role in cancer immunotherapy.[147] Manganese ions potently enhance the affinity of cGAS to its agonist DNA substrates, and cGAS is activated by combination with DNA, leading to enzymatic production of cGAMP and activation of STING downstream signaling.[178,179] The activated cGAS-STING pathway leads to generation of type I interferons and a vast array of pro-inflammatory cytokines, resulting in enhanced immune surveillance, cytotoxicity of natural killer cells and macrophages, and activation and proliferation of T cells.[80,180] Manganese ions modulate the function and upregulate the expression of costimulatory molecules on the membrane of antigen-presenting cells, boost T cell infiltration and survival in the TME, and enhance the strength of natural killer cells and their release of cytokines.[147]

Although the mechanisms of manganese ions regulated tumor immunotherapy are not fully elucidated, previous studies have explored their clinical value. In a Phase I clinical trial, patients were administered different dose of manganese chloride intranasally or by inhalation in combination with PD-1 antibodies and chemotherapy. After a median

follow-up of 11.8 months, the combined protocol exhibited manageable side effects and prominent potency across various tumor types including ovarian, breast, and pancreatic cancers, achieving a disease control rate of 90.9%.[80]

Manganese-Based Nanoparticles Enhance Cancer Immunotherapy

Clinical application of manganese is significantly hindered by its neurotoxicity and non-specific distribution,[181] and targeted delivery is of great importance to minimize neurotoxicity. As presented in Table 6, an array of nanoagents delivering manganese ions or manganese-based nanovehicles have been introduced to amplify the immune response and have been integrated with immunotherapy for cancer treatment.

A manganese-phenolic network platform was based on doxorubicin carrying PEG-poly(lactic-*co*-glycolic acid) nanoparticles and further modified by manganese-tannic acid. Manganese triggered a Fenton-like reaction and enhanced anti-tumor immunity by amplifying the cGAS-STING pathway, and integrated therapy of the nanodrug with CTLA-4 blocking antibody exerted superior treatment efficacy to monotherapy.[182] Sun et al fabricated hollow mesoporous silica-coated MnO nanoparticles with conjugated iRGD peptide and applied them for cGAS-STING pathway-amplified immunotherapy, a Fenton-like reaction, and T_1-weighted magnetic resonance imaging. Integrated MnO nanoparticles and anti-PD-1 antibody enhanced tumor inhibition and activated the immune response.[183] PEG-coated manganese molybdate nanoparticles depleted highly accumulated GSH in a tumor and inhibited GPX4 expression, triggering ferroptosis. The manganese molybdate nanoparticles induced release of DAMPs, promoted DCs maturation and T cell infiltration, and reversed the immunosuppressive microenvironment, reprogramming "cold" tumors to "hot" ones. Integration with antibody against PD-L1 further enhanced anti-tumor efficacy and inhibited metastasis.[184] As illustrated in Figure 9, a hydrogen peroxide/ultrasound-propelled mesoporous manganese oxide nanomotor was fabricated to load mitochondrial sonosensitizers into mesoporous channels, and their surface was dual-functionalized with silk fibroin and chondroitin sulfate. Mn^{2+} ions regulated a Fenton-like reaction that decomposed excess H_2O_2 in the TME into oxygen and toxic hydroxyl radicals. The nanomotor effectively depleted intracellular GSH to downregulate GPX4, a vital regulator for ferroptosis, leading to accumulation of LPO as the hallmark for ferroptosis. The integrated Mn^{2+} and ultrasound promoted maturation of DCs and T cell-mediated immune response. Integration of the manganese oxide nanomotor and PD-L1 checkpoint inhibitor potently restrained primary tumor growth and prevented tumor recurrence by potentiating systemic anticancer immunity and providing long-term immune memory.[185] Risedronate-manganese nano-belts were fabricated via coordination-driven self-assembly and exerted an outstanding Fenton-like catalytic property and amplified radiotherapy-regulated oxidative stress. The released Mn^{2+} further activated the cGAS-STING pathway, boosting the efficacy of anti-PD-L1 antibody against primary and metastatic tumors.[186] Ultrathin manganese-based layered double hydroxide nanosheets delivering cytokine interferon γ were synthesized to strengthen ferroptosis and systemic anti-tumor immunity. Manganese ion-induced ferroptosis was further boosted by the loaded interferon γ-triggered downregulation of SLC7A11, which is responsible for uptake of cystine into cells for GSH biosynthesis. The released manganese ions activated the cGAS-STING signaling pathway and stimulated DCs maturation and T cell infiltration. Endogenous interferon γ secreted by activated $CD8^+$ T cells promoted a cascade of immunogenic ferroptosis, forming a closed-loop treatment. Integrated nanosheets and antibody against PD-L1 achieved a potent abscopal effect on inhibition of both primary and distant tumors.[187]

A dendrobium polysaccharide hydrogel embedded with Mn^{2+}-pectin microspheres induced apoptosis in cancer cells, activating the cGAS-STING signaling pathway and initiating a cascade of anti-tumor immune responses. The hydrogel generated a synergistic potency with anti-PD1 antibody to inhibit metastasis and abscopal brain tumor proliferation.[188] A PEG-modified Mn^{2+}-based MOF delivering paclitaxel induced pronounced apoptosis and promoted maturation of DCs and infiltration of T lymphocytes by activating the cGAS-STING pathway, enhancing the potency of anti-PD-L1 antibody.[189] Alginate microspheres embedded in a Pluronic F-127 matrix as a vehicle for Mg^{2+} and Mn^{2+} formed a hybrid hydrogel that elicited apoptosis and converted a "cold tumor" to a "hot tumor", augmenting the therapeutic efficacy of antibody against PD-L1.[190] Zhou et al developed manganese-enriched zinc peroxide nanoparticles for synergistic anticancer immunotherapy. The nanoparticles elicited apoptosis, activated the STING pathway, and decreased the immunosuppressive TME. Integrated with PD-1 checkpoint blockage, the nanoparticles demonstrated potent inhibition of tumor growth and metastasis.[191] A tumor cell membrane containing multienzyme-mimicking manganese oxide

Table 6 Manganese-Based Nanomedicines to Amplify Cancer Immunotherapy

Carrier Type	Payload	Composition	Particle Size (nm)	Mechanism of Action	Administration	Outcome	Ref.
Nanoparticle	Doxorubicin	PEG-poly(lactic-*co*-glycolic acid), manganese-tannic acid network	70	Chemotherapy, chemodynamic therapy, ICD, amplifying STING signal.	iv	Remarkable promotion of DCs maturation and $CD8^+$ T cell infiltration. Combined with CTLA-4 antibody, significant inhibition of tumor growth and lung metastasis.	[182]
Nanoparticle	None	MnO nanoparticle, hollow mesoporous silica, iRGD peptide	132	Activation of cGAS-STING pathway, immunotherapy, Fenton-like reaction.	iv	Synergized with PD-1 antibody, high elicitation of cytotoxic T lymphocyte infiltration and restriction of melanoma progression and metastasis.	[183]
Nanoparticle	None	Manganese molybdate nanoparticle, DSPE-PEG5000	30	Ferroptosis, ICD, release of DAMPs, promotion of DCs maturation, T cells infiltration, and reversal of immunosuppressive microenvironment.	it	In combination with PD-L1 antibody, enhanced anti-tumor effect and inhibition of metastases.	[184]
Hydrogel embedding nanoparticle	None	Chitosan/alginate hydrogel, mesoporous manganese oxide, regenerated silk fibroin, chondroitin sulfate	212.3	Ferroptosis, sonodynamic therapy, chemodynamic therapy, ICD and reversion of immunosuppressive TME.	oral	Together with PD-L1 antibody, simultaneous suppression of primary and distal tumors.	[185]
Nanobelt	None	Risedronate-manganese nanobelt	Length 180, width 5	Fenton-like catalytic activity, ICD, inhibition of hypoxia-inducible factor-1α/vascular endothelial growth factor axis and activation of cGAS/STING pathway.	iv	Synergized with PD-L1 antibody, inhibition of both in situ and metastatic tumor growth.	[186]
Nanosheet	Interferon γ	Ultrathin manganese-based layered double hydroxide nanosheets	Diameter 58, thickness 2.28	Ferroptosis, ICD, facilitation of DCs maturation and priming T cells.	iv	Potent abscopal effect in growth inhibition of primary and distant tumors	[187]
Hydrogel embedding microsphere	Mn^{2+}	Dendrobium polysaccharide, polyvinyl alcohol, pectin	~80	ICD, activation of cGAS-STING, induction of M1 polarization for macrophages, DCs maturation, antigen presentation and T cell-mediated tumor cell killing.	implantation	Significant inhibition of residual tumor growth and metastasis. Combined with PD-1 antibody, superior therapeutic potency in inhibiting metastasis and abscopal brain tumor.	[188]
MOF	Paclitaxel	Mn^{2+} based MOF, PEG	77.44	ICD, normalization of tumor blood vessels, alleviation of hypoxia, activation of cGAS-STING, promotion of DCs maturation and cytotoxic T lymphocytes infiltration.	iv	Integrated with PD-L1 antibody, enhanced tumor suppression and prolonged survival in mice.	[189]
Microsphere-encapsulated hydrogel	Mg^{2+}, Mn^{2+}	Pluronic F-127 hydrogel, alginate microspheres		Apoptosis, increment of T cells and natural killer cells infiltration, hindrance of myeloid-derived suppressor cells recruitment, modulation of immune checkpoints expression and reshaping TME.	it	Augment of immune checkpoint blockade efficacy. In conjunction with PD-L1 antibody, potential to reduce tumor recurrence.	[190]

Nanoparticle	Mn^{2+}	ZnO_2 nanoparticle, polyvinylpyrrolidone	30–50	ICD, activation of STING pathway, priming T cell maturation and expansion, downregulation of Tregs and polarization of M2 macrophages to the M1.	iv	In combination with PD-1 antibody, superior efficacy in inhibiting tumor growth and preventing lung metastasis.	[191]
Nanoparticle	None	Manganese oxide nanoparticle, 4T1 cells membrane	159.31	Apoptosis, ICD, promotion of DCs maturation and M1 repolarization for macrophages, reversal of immunosuppressive TME, and hypoxia relief.	iv	Together with PD-1 antibody, a robust tumor-specific T cell-mediated anti-tumor response, inhibition of primary and metastatic tumors, and induction of a long-term immune memory.	[192]
Nanoparticle	Peroxydisulfate	Mn_2Al_1 layered double hydroxide nanoparticles	80	Necroptosis, ICD, activation of STING pathway.	it	Potent activity in inhibiting tumor growth and lung metastasis. Combined with PD-L1 antibody, significant inhibition of distant tumors.	[193]

Abbreviations: iv, intravenous injection; it, intratumoral injection.

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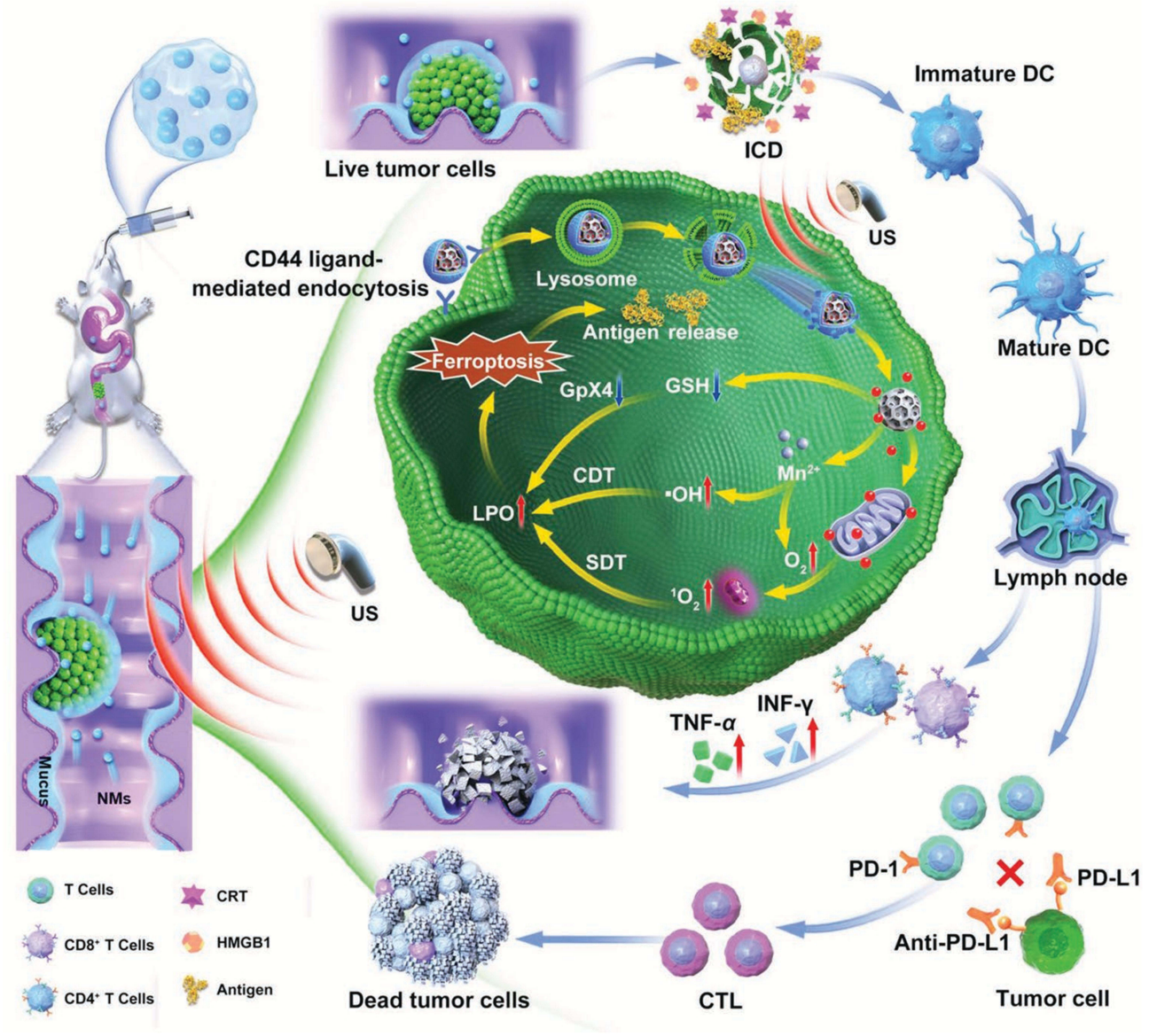

Figure 9 Schematic illustration of a hydrogen peroxide/ultrasound-propelled mesoporous manganese oxide nanomotor to achieve efficient mucus-traversing ability, deep tumor penetration, high anti-tumor efficacy, and potentiation of anti-tumor immunity. ↓, downregulation; ↑, upregulation; ✖, blockade. (reproduced with permission from Yingui Cao et al (2022). Copyright 2022 John Wiley and Sons).

nanozymes induced apoptosis in cancer cells, and the released Mn^{2+} ions promoted maturation of DCs and M1 repolarization of macrophages by activating the STING pathway. With the support of PD-1 checkpoint blockade, robust anti-tumor immune response and long-term immune memory were achieved, and the growth of primary tumor and metastasis was prominently inhibited.[192]

An in situ vaccine was fabricated by intercalating peroxydisulfate, a precursor of $SO_4^{\cdot-}$, into manganese layered double hydroxide nanoparticles. Mn^{2+} mediated peroxydisulfate degradation through Fenton-type advanced oxidation in the tumor to produce in situ $SO_4^{\cdot-}$, which elicited necroptotic cell death and adaptive immunity. The in situ vaccine activated the STING pathway to further enhance anticancer immunity. When integrated with anti-PDL1 antibody, remarkable inhibition of distant tumors was realized.[193]

Perspectives

Cancer is responsible for high morbidity and mortality rates and is a prominent health burden worldwide. In recent decades, immunotherapy has emerged as a vital treatment for cancer following chemotherapy, surgical treatment, radiotherapy, and targeted therapy. Patients can benefit from a range of immunotherapeutic approaches including immune checkpoint inhibitors, CAR-T cell therapy, antibody-drug conjugate, cytokine therapy, and vaccination. Despite its great potential, cancer immunotherapy is confronted with significant challenges, and low response rates are a considerable hurdle. Excessive intracellular accumulation of several metal ions, such as Fe^{2+}, Cu^{2+}, Ca^{2+}, Zn^{2+}, and Mn^{2+}, is important for regulating PCD through various signaling pathways. PCD is capable of reprogramming the immunosuppressive TME and inducing immunostimulatory responses,[7,8] indicating it as a viable option to enhance the potency of cancer immunotherapy. With advancement of nanotechnology, metal ions are used more extensively in cancer therapy, and efficacy of immunotherapy has been increased. However, issues in academic investigation and clinical application remain to be solved.

The precise mechanisms and signaling pathway for metal ion-mediated PCD and enhanced immune response by PCD have not been fully elucidated, and in-depth molecular mechanism study should be performed. The metabolism and long-term safety of metal ions and metal-based nanomaterials are unknown, and further investigation is required. Moreover, optimization of material formulations and development of more biocompatible nanomaterials are needed. One key limitation of this review is insufficient assessment of metabolism and long-term safety of the proposed nanodrugs.

Tumor heterogeneity has emerged as a mediator for the efficacy of immunotherapy.[194] However, this characteristic spatially and temporally evolves, and it is relatively complex and insufficiently characterized.[195] The influential factors affecting response to immunotherapy are complicated rather other only induction of PCD. Integrated strategies to overcome or minimize the detrimental impacts of tumor heterogeneity on immunotherapy and triggers of PCD for achievement of personalized treatment are promising research directions.

Additionally, in design of nanomaterials delivering metal ions or metal-based nanovehicles, druggability should be considered. The pharmaceutical industry operates on the "keep it simple, stupid" principle, and complicated manufacturing processes and standardization issues restrict up-scaling of nanodrugs from laboratory to industry scale.

In 2025, Clinicaltrials.gov retrieved no ongoing or completed clinic trials about metal ions and cancer immunotherapy. This is likely due to challenges in large-scale manufacturing and concerns regarding the safety of nanoparticle-based systems. Comprehensive preclinical data on safety and efficacy in large-scale animal tumor xenograft models are essential for successful clinical translation. To improve the prospect of clinical translation, simple and biocompatible nanosystems for loading metal ions and metal-based nanodrugs should be fabricated. Controlled clinical trials are needed to define the limitations and effectiveness of nanomaterials for metal ions in cancer immunotherapy.

Conclusion

In conclusion, there are challenges for cancer immunotherapy, and leverage of PCD induced by metal ions to amplify efficacy of immunotherapy has demonstrated encouraging achievements in scientific research. Simpler and safer nanocarriers are expected for personal treatment based on research in PCD and tumor heterogeneity, and translation of such methods into clinic is expected to be realized in the near future, along with patients benefit from immunotherapy.

Abbreviations

ACSL4, acyl-CoA synthetase long-chain family member 4; ATP7A/B, ATPase copper transporting α/β; Bax, B-cell lymphoma-2 associated X protein; BID, BH3 interacting domain death agonist; CaMKKb/AMPK, calcium/calmodulin-dependent protein kinase kinase-B/AMP-activated protein kinase; CAR-T, chimeric antigen receptor T; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; CoA, coenzyme A; CTLA-4, cytotoxic T lymphocyte-associated protein 4; CTR1, copper transporter protein 1; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; DLAT, dihydrolipoamide S-acetyltransferase; DMT1, divalent metal transporter 1; ER, endoplasmic reticulum; ERK1/2, extracellular-signal-regulated kinase; Fe^{3+}, ferric ion; GSH, glutathione; GPXs, glutathione peroxidases; HMGB1, high mobility group box 1; ICD, immunogenic cell death; iRGD, CRGDKGPD peptide; LIP, labile iron

pool; MLKL, mixed lineage kinase domain-like protein; LMP, lysosomal membrane permeabilization; LOX, lipoxygenases; LPCAT3, Lysophosphatidylcholine acyltransferase 3; MOF, metal-organic framework; MT, metallothionein; MTF1, metal responsive transcription factor-1; mTOR, mammalian target of the rapamycin; NCOA4, nuclear receptor coactivator-4; PCD, programmed cell death; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PEG, polyethylene glycol; PUFA, polyunsaturated fatty acids; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; TAMs, tumor-associated macrophages; TF, transferrin; TFR1, transferrin receptor 1; TMCO1, transmembrane and coiled-coil domains 1; TME, tumor microenviroment; SLC31A1, solute carrier family 31 member 1; STEAP3, six-transmembrane epithelial antigen of prostate 3; ZIPs, Zrt/Irt-like proteins.

Ethics Approval

This article does not contain any studies with human participants.

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The authors have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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