Acta Pharmaceutica Sinica B 2025;15(12):6307−6341



Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Ferroptosis meets cancer immunotherapy: Overcoming the crosstalk challenges through advanced drug delivery strategies



Lu Gan[a,b,†], Xincheng Lin[a,b,†], Ziqiao Zhong[a,b,†], Yichun Zheng[a,b], Xinyi Chen[a,b], Jun Chen[a,b], Xiao Yue[a,b], Yingshan Liu[a,b], Xin Pan[c], Chuanbin Wu[a,b,d], Ying Huang[a,b,*], Wenhao Wang[c,*]

[a]*State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Jinan University, Guangzhou 511443, China*
[b]*College of Pharmacy, Jinan University, Guangzhou 511443, China*
[c]*School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China*
[d]*Jiangmen Wuyi Hospital of Traditional Chinese Medicine, Affiliated Jiangmen Traditional Chinese Medicine Hospital of Jinan University, Jiangmen 529031, China*

Received 27 April 2025; received in revised form 16 July 2025; accepted 25 August 2025

KEY WORDS

Cancer;
Ferroptosis;
Immunotherapy;
Immune cells;
Crosstalk challenges;
Tumor targeted delivery;
Immunostimulatory active pharmaceutical ingredients co-delivery;
Stimuli-responsive delivery

Abstract The integration of ferroptosis induction with cancer immunotherapy has emerged as a promising approach in oncology, offering dual mechanisms to overcome therapeutic resistance and tumor heterogeneity. Nevertheless, the dynamic and complicated crosstalk between ferroptosis processes and immune regulation in tumor microenvironments presents both opportunities and challenges. By inducing lipid peroxidation in tumor tissues, ferroptotic tumor cell death can stimulate immunogenicity. Nevertheless, excessive lipid peroxidation may paradoxically impair the functionality of multiple immune cells, thereby presenting crosstalk challenges in therapeutic strategies. To address these crosstalk challenges, several advanced drug delivery strategies have been proposed, such as immunostimulatory active pharmaceutical ingredients co-delivery, tumor-targeted delivery, and stimuli-responsive delivery. These drug delivery strategies demonstrate dual therapeutic efficacy by synergistically potentiating ferroptosis induction in malignant cells while concurrently mitigating immunotoxicity and even augmenting

*Corresponding authors.
E-mail addresses: huangy2007@163.com (Ying Huang), whwang97@yeah.net (Wenhao Wang).
†These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.09.043
2211-3835 © 2025 The Authors. Published by Elsevier B.V. on behalf of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

antitumor immunity. This review offers detailed insights into the crosstalk between ferroptosis and tumor immunity, along with a guiding overview of the three delivery strategies. The current obstacles and translational potential were thoroughly analyzed, providing valuable perspectives for future research.

© 2025 The Authors. Published by Elsevier B.V. on behalf of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Cancer is a class of diseases characterized by uncontrolled cellular proliferation and dysregulated differentiation, leading to the formation of localized masses, invasion of adjacent tissues, and metastasis to distant organs *via* the bloodstream or lymphatic system[1]. According to the latest data from the International Agency for Research on Cancer, approximately 20 million new cancer cases and nearly 10 million cancer-related deaths were reported globally in 2022, with lung, breast, colorectal, and prostate cancers being the most prevalent types[2]. Current therapeutic approaches encompass surgical resection, radiotherapy, chemotherapy, and immunotherapy. Among these, immunotherapy has emerged as a revolutionized approach due to its advantages in immune persistence, specificity, broad applicability, and synergistic potential, distinguishing it from conventional treatments[3].

Specifically, immunotherapy operates by modulating or enhancing the patient's immune system to recognize and eliminate malignant cells. Key mechanisms of immunotherapy include alleviating immunosuppression (*e.g.*, blockade of immune checkpoints such as PD-1/PD-L1 and CTLA-4), activating immune effector cells, and remodeling the tumor microenvironment (*e.g.*, targeting regulatory T cells or tumor-associated macrophages)[4,5]. Current immunotherapeutic strategies include immune checkpoint inhibitors (*e.g.*, pembrolizumab and ipilimumab), adoptive cell therapies (*e.g.*, CAR-T and tumor-infiltrating lymphocyte therapy), cytokines (*e.g.*, IL-2 and IFN-α), bispecific antibodies, and cancer vaccines[6]. Recent advancements have introduced novel approaches such as T-cell immunoreceptors with Ig and ITIM domains inhibitors and personalized neoantigen vaccines into clinical trials[7].

The high specificity of cancer immunotherapy arises from immune recognition of tumor-specific antigens, necessitating antigen release to stimulate immune cell maturation and differentiation[8,9]. Therefore, to amplify therapeutic efficacy, combination strategies integrating tumor ablation with immunotherapy have been proposed, such as chemo-immunotherapy, radio-immunotherapy, photo-immunotherapy, and ferroptosis-immunotherapy. While chemo-immunotherapy leverages chemotherapeutic agents to enhance tumor antigen release and immune activation, radio- and photo-immunotherapy employ physical modalities (radiation or laser ablation) to achieve similar effects[10-13]. These therapies possess distinct advantages and have made significant contributions to the ongoing fight against cancer in humans.

In recent years, ferroptosis-immunotherapy has emerged as a promising strategy to address therapeutic resistance and tumor heterogeneity in malignant cancers. Ferroptosis, an iron-dependent form of regulated cell death, is characterized by lipid peroxide (LPO) accumulation and suppression of glutathione peroxidase 4 (GPX4) activity[14]. Ferroptosis-immunotherapy combines ferroptosis inducers with immunotherapeutic agents to simultaneously trigger tumor cell ferroptosis and potentiate antitumor immune responses[15]. The core mechanism involves ferroptosis-induced tumor cell lysis, which releases tumor-associated antigens and damage-associated molecular patterns (DAMPs), thereby eliciting immunogenic cell death (ICD) and synergizing with immunotherapeutic agents such as immune checkpoint inhibitors or cellular therapies to achieve durable antitumor effects[16-19]. For instance, representative agents such as Erastin (Er)[20], Sorafenib[21], and the GPX4 inhibitor RSL3[22] induce lipid peroxidation through mechanisms involving glutathione (GSH) depletion and GPX4 activity inhibition. Meanwhile, pharmacological agents, including Artesunate[23], statins[24,25], and ammonium ferric citrate, promote ferroptosis by disrupting intracellular iron homeostasis to facilitate ROS generation *via* the Fenton reaction. Besides, IFN-γ released by $CD8^+$ T cells during the anti-tumor immune response induces ferroptosis in tumor cells, demonstrating the interaction and mutual influence between ferroptosis and immune responses[26-28]. Unlike apoptosis induced by chemotherapy or radiotherapy, ferroptosis circumvents apoptotic resistance mechanisms and effectively eliminates therapy-resistant cancer stem cells, which are often drivers of recurrence and metastasis[29,30]. Moreover, ferroptosis inducers exhibit selectivity for tumor cells with dysregulated lipid metabolism or elevated iron-related protein expression, minimizing off-target toxicity[31]. Critically, ferroptosis-induced ICD activates dendritic cells (DCs), enhances antigen presentation, and synergizes with immunotherapy to amplify systemic antitumor immunity, positioning ferroptosis-immunotherapy as a highly promising therapeutic paradigm.

However, although ferroptosis-immunotherapy demonstrates significant therapeutic potential, the interplay between ferroptosis and immune responses is complex and bidirectional. On one hand, ferroptosis in tumor cells stimulates immune activation, while ferroptosis in immune cells has been demonstrated to impair immunological responses[26,32-34]. Conversely, immune cells can modulate tumor cell sensitivity to ferroptosis through either enhancement or suppression mechanisms, thereby influencing therapeutic outcomes of ferroptosis-immunotherapy[35,36]. Consequently, precision drug delivery strategies can selectively enhance ferroptosis in tumor cells while minimizing potential damage to immune cells, which constitutes a prerequisite for optimizing the efficacy of combined ferroptosis-immunotherapy regimens. Current research has documented multiple drug delivery strategies for ferroptosis-immunotherapy, primarily including immunostimulatory active pharmaceutical ingredients (ISAPIs) co-delivery, tumor-targeted delivery, and stimuli-responsive delivery. These strategies have demonstrated remarkable anti-tumor efficacy through distinct mechanisms. Immune-stimulating API co-delivery enables immunomodulatory targeting through coordinated delivery of ferroptosis inducers and immune-activating agents, facilitating tumor eradication and sustained anti-tumor immunity. Tumor-targeted delivery achieves preferential tumor

accumulation *via* either enhanced permeability and retention (passive targeting) or ligand-receptor interactions (active targeting), effectively inhibiting tumor progression. Stimuli-responsive delivery utilizes endogenous/exogenous physical triggers (*e.g.*, pH, redox, ion, or light) to achieve spatiotemporal control of drug release, thereby minimizing systemic toxicity while enhancing therapeutic precision. Each strategy exhibits unique advantages in oncology applications. This review will provide a comprehensive analysis of their mechanisms, clinical applications, and future development directions in ferroptosis-immunotherapy.

To investigate the development of ferroptosis-immunotherapy and its drug delivery strategies, a literature survey was conducted based on the Web of Science by the search query, "ferroptosis AND immunity AND drug delivery systems". The results revealed that approximately 321 publications in this field were published over the past 6 years. The first paper in this field was published in 2019, indicating that the field is emerging and gaining significant attention. Notably, the year 2024 was the peak of the number of publications, and "article" was the main publication type. The number of citations related to ferroptosis-immunotherapy and its drug delivery strategies has been steadily increasing in recent years, with a count of nearly 3981 citations for the year 2024. The papers published by the researchers from China accounted for 291. Additionally, the top 5 journals that have published papers on ferroptosis-immunotherapy and its drug delivery strategies include *Chemical Engineering Journal*, *Advanced Healthcare Materials*, *ACS Nano*, *Advanced Science* and *Journal of Nanobiotechnology*. A majority of these journals pertain to the field of materials science, likely since numerous ongoing studies are centered on the development of novel materials for constructing drug delivery systems aimed at ferroptosis-immunotherapy. This observation signifies a growing emphasis and interest in this field. Thus, it is necessary to summarize and analyze the current publications on ferroptosis-immunotherapy and its drug delivery strategies, enabling the scientific community to gain the latest development direction and research focus in this field.

2. The interplay between ferroptosis and tumor immunity

Ferroptosis differs from apoptosis, necrosis and autophagy in morphology, biochemistry and genetics. It cannot be inhibited by inhibitors of apoptosis, pyroptosis, or autophagy, but can be inhibited by iron chelators and antioxidants[37]. In addition, ferroptotic cells also typically display hallmark features including decreased cell volume, mitochondrial shrinkage, and compromised cell membrane integrity. Besides, it's noteworthy that ferroptosis inducers exhibit better selectivity compared to chemotherapy drugs capable of inducing ICD in tumor cells to activate immune responses. These inducers can overcome drug resistance and hold potential for synergistic therapeutic strategies. Ferroptosis inducers typically target tumor cells selectively, as these cells are characterized by high fatty acid content and increased sensitivity to ferroptosis[38,39]. In contrast, their impact on normal cells is relatively minimal, thereby reducing collateral damage to healthy tissues. Additionally, certain tumor cells develop resistance to conventional chemotherapeutic agents, such as apoptosis inducers. However, ferroptosis inducers may circumvent this resistance through alternative signaling mechanisms, including the inhibition of GPX4[40]. Furthermore, the combination of ferroptosis inducers with immune-stimulatory agents, such as immune checkpoint inhibitors, can markedly potentiate anti-tumor immune responses. Representative ferroptosis inducers and their therapeutic mechanisms are summarized in Table 1[12,40-55].

Ferroptosis is a form of regulated cell death induced by iron-dependent lipid peroxidation[56]. Its defining characteristic is the abnormal accumulation of intracellular iron ions, particularly Fe^{2+}, along with excessive production of LPO, which ultimately leads to structural damage of the cell membrane and subsequent

Table 1 Ferroptosis inducers and their therapeutic mechanisms.

Type of ferroptosis inducers	Representative drug	The therapeutic mechanism	Ref.
Micromolecule	Erastin and its derivatives, sorafenib, sulfasalazine	Decrease intracellular GSH levels by inhibiting the key protein SLC7A11 of the system Xc^-, blocking the uptake of cystine, thereby weakening the antioxidant activity of GPX4 and eventually triggering lipid peroxidation	41−44
	RSL3, dGPX4, FIN56, ML162, ML210, cisplatin	Inhibit or degrade GPX4 to make it inactive or reduce its content, leading to the inability to reduce lipid peroxides, thereby triggering lipid peroxidation of cell membranes	45−47
	iFSP1	Inhibit FSP1 activity and reduce coenzyme Q10 production	48
	Artemisinin, Artesunate, Palatinib, FINO2, tBOOH	Induction of lipid peroxidation *via* iron or PUFA overload	49,50
	Fentomycin-1	Activation of lysosomal iron leading to phospholipid oxidative degradation	50
Macromolecule	Lipoxygenase	Direct oxidation of PUFA generating lipid peroxides	12
Nano-composites	High-density lipoprotein-like nanoparticles	Reduce TXNRD1 expression and the cells' utilization of selenium to diminish the synthesis of selenoproteins such as GPX4. Enhance ACSL4-dependent PUFA membrane phospholipid synthesis to provide critical substrates for ferroptosis	40
	Ruthenosomes	Targeting mitochondria and inducing ferritin autophagy to release iron ions, driving lipid peroxidation and ferroptosis	51
	Iron nanoparticles	Direct induction of lipid peroxidation through surface catalysis	52,53
	Gold nanoparticles	Generate local high heat through surface plasmon resonance effect, or produce ROS through surface catalysis, thereby indirectly promoting ferroptosis	54,55

GPX4, glutathione peroxidase 4; PUFA, polyunsaturated-fatty-acid; ACSL4, long-chain-fatty-acid-CoA ligase 4.

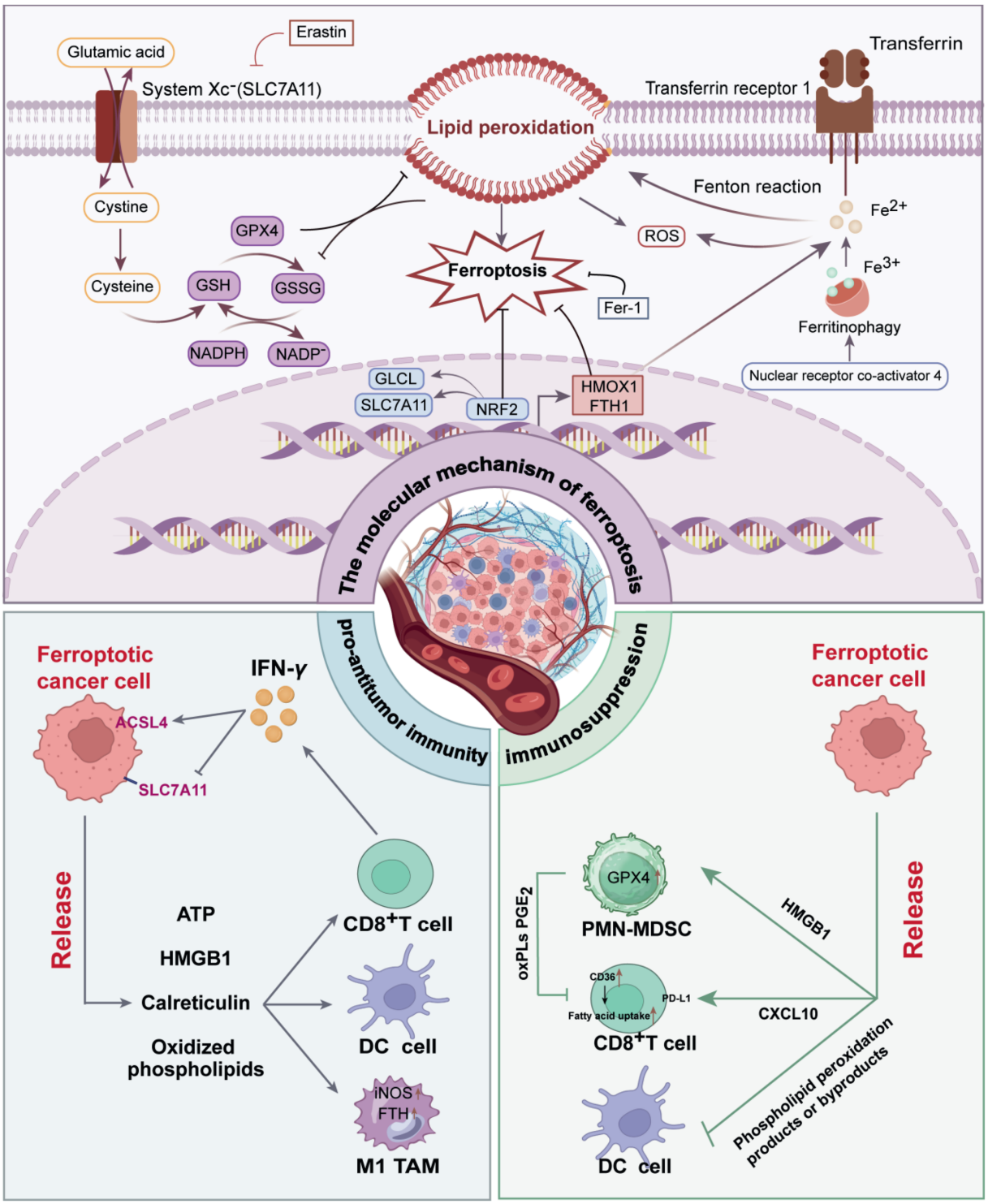


Figure 1 The top section illustrates the molecular mechanism underlying ferroptosis. The bottom-left section shows ferroptosis involved in antitumor immunity. And the bottom-right section depicts ferroptosis involved in immunosuppression.

cell death[57]. The System−GSH−GPX4 signaling axis plays a central role in this process (Fig. 1). System Xc^-, also known as the cystine/glutamate antiporter, facilitates the cellular uptake of cystine, which is essential for the synthesis of GSH. GSH serves as a crucial cofactor for GPX4, an enzyme that protects cells from oxidative stress by neutralizing LPO. Inhibition of System Xc^-, such as by erastin, results in reduced GSH levels and impaired GPX4 activity, thereby promoting LPO and initiating ferroptosis[58]. Additionally, iron overload is a key driver of ferroptosis. Iron enters the cell *via* transferrin receptor-mediated uptake and is subsequently reduced to Fe^{2+} *in vivo*. Fe^{2+} catalyzes the conversion of hydrogen peroxide into highly reactive hydroxyl

radicals through the Fenton reaction, further accelerating lipid peroxidation. Moreover, the degradation of iron storage proteins, such as ferritin, *via* a selective autophagic process termed ferritinophagy, contributes to elevated Fe^{2+} levels, thereby enhancing ferroptotic cell death[59] (Fig. 1).

The tumor microenvironment (TME) constitutes a multifaceted ecosystem consisting of tumor cells, immune cells, stroma cells, and other cells. These components not only coexist but also engage in intricate interactions that significantly influence tumor growth and progression[60,61]. Compared with apoptosis, necrosis and autophagy, ferroptosis exerts a more complex influence on immune regulation, exhibiting a bidirectional interaction with the immune system. On one hand, ferroptosis in cancer cells may initiate or modulate immune responses in the TME (Fig. 1). On the other hand, the susceptibility of immune cells in the TME to ferroptosis varies significantly, and different immune cell types can either promote or suppress ferroptosis in cancer cells[32] (Fig. 1). This distinct characteristic highlights the unique role of ferroptosis in immune regulation as compared to apoptosis, necrosis and autophagy. Subsequently, we would classify the interaction between tumor ferroptosis and immune cells to elucidate this intricate relationship more comprehensively.

2.1. *The effect of tumor ferroptosis on immune cells*

The impact of tumor ferroptosis on the immune system is highly complex, with even contradictory research findings reported. Ferroptosis may serve as a form of ICD, which is driven by stress stimuli and can induce adaptive immunity against dead cell antigens[26,33]. Not only do cell death-related antigens activate immune responses, but ICD is also accompanied by the release of a multitude of DAMPs during ferroptosis. These DAMPs, including calreticulin exposed on the cell surface, high-mobility group protein 1 (HMGB1) secreted by tumor cells, adenosine triphosphate (ATP) released by cells, and heat shock proteins (such as HSP70 and HSP90), among others, can bind to pattern recognition receptors on antigen-presenting cells (APCs) and enhance the efficiency of macrophage phagocytosis of ferroptotic cancer cells, thereby activating immune responses[33,62]. In addition to the aforementioned conventional DAMPs, ferroptosis tumor cells further release a subset of their characteristic DAMPs. For instance, the oxidized phospholipids (PL), such as 1-stearoyl-2-15-HpETE-*sn*-glycero-3-PE, located on the cell surface of ferroptotic cancer cells, can be recognized by Toll-like receptor 2 (TLR2) on macrophages, promoting their engulfment[63]. Wen et al.[64] investigated the HMGB1 release mechanism of ferroptotic cancer cells, where HMGB1 was a DAMP that could be released by ferroptotic cells in an autophagy-dependent manner. Mechanistically, inhibition of autophagy-mediated histone deacetylase promoted HMGB1 acetylation, leading to HMGB1 release during ferroptosis. HMGB1 induced macrophage inflammation and released TNF through the AGER pathway. Additionally, it was reported that HMGB1 could upregulate cyclooxygenase 2 (COX2) and transferrin expression *via* the RAS−JNK/p38 pathway, promoting erastin-induced ferroptosis[65]. These interactions not only drive macrophages to polarize towards the M1 phenotype but also promote T-cell infiltration and activity within tumors. They can even trigger vaccine-like responses, activating antitumor immunity[65]. Conversely, inhibiting ferroptosis results in reduced T cell infiltration and activity in the TME, ultimately dampening T cell-mediated antitumor responses.

However, it is noteworthy that some studies have suggested that ferroptotic cancer cells may hinder DCs maturation, thereby affecting their antigen-presenting capacity[34]. PL peroxidation products generated by the 12/15-lipoxygenase reaction in ferroptotic cancer cells, or other lipid peroxidation by-products, such as 4-hydroxynonenal, appear to impair DCs maturation and function[66,67]. The interaction between ferroptotic cancer cells and DCs may depend on the stage of ferroptosis. It has been reported that during the early stages of ferroptosis, cancer cells trigger DC maturation; however, in the later stages, although DCs can effectively engulf these late-stage ferroptosis cells, their ability to promote DC maturation is reduced[33]. Overall, the impact of ferroptosis on antitumor immune responses is dual-edged. While it exhibits characteristics of ICD by releasing DAMPs to induce immune cell maturation, it also affects immune cell function and immune responses due to its unique properties, such as the production of PL peroxidation products.

2.2. *The effect of immune cells on tumor ferroptosis*

Immune cells within the TME can influence the sensitivity of cancer cells to ferroptosis by enhancing or inhibiting it. For instance, Wang et al.[35] discovered that activated $CD8^+$ T cells during tumor immunotherapy could enhance ferroptosis-specific lipid peroxidation levels within tumor cells, thereby increasing their sensitivity to ferroptosis. Further research revealed that the Interferon-gamma (IFN-γ) released by $CD8^+$ T cells has a dual impact on cancer cell ferroptosis. On one hand, IFN-γ downregulates the expression of solute carrier family 3 member 2 (SLC3A2) and solute carrier family 7 member 11 (SLC7A11) on the tumor cell surface through the JAK−STAT1 pathway. SLC3A2 and SLC7A11 are two subunits of the glutamate−cysteine antiporter System Xc^-, which impairs tumor cell cystine uptake, thereby enhancing lipid peroxidation and ferroptosis[26,36]. On the other hand, IFN-γ upregulates the expression of long-chain-fatty-acid-CoA ligase 4 (ACSL4), promoting the synthesis of ACSL4-mediated polyunsaturated-fatty-acid-PL (PUFA-PL) (especially those containing arachidonic acid). Therefore, IFN-γ promotes ferroptosis by inhibiting the cell's defense against it and amplifying the metabolic activities driving the process. However, despite IFN-γ enhancing tumor cell ferroptosis, studies have also shown that it promotes tumor dormancy, and edits tumor cell immunosuppression, leading to tumor evasion and recurrence[68].

In the TME, tumor-associated macrophages (TAMs) primarily exhibit an immunosuppressive M2 phenotype[69]. An extensive tumor immunological study aims to clear M2 TAMs and/or convert them into a more anti-tumor M1 phenotype. Recent studies have shown that M1 TAMs exhibit greater resistance to ferroptosis compared to M2 TAMs[70]. The elevated levels of inducible nitric oxide synthase in M1 TAMs can produce more nitric oxide radicals (NO·), which can inhibit 15-lipoxygenase, resulting in a resistance to ferroptosis comparable to GPX4[70]. Additionally, NO· has membrane diffusibility, which can confer ferroptosis resistance to cells surrounding M1 macrophages[70]. Exosomes secreted by adipose tissue macrophages containing miR-140-5p can target SLC7A11 in cardiomyocytes, inhibiting reduced glutathione synthesis and inducing ferroptosis in cardiomyocytes, providing a new therapeutic strategy for obesity-induced cardiac damage[71,72]. Furthermore, studies have found that TAM-secreted TGF-β1 regulates the expression of hepatic leukemia factor in triple-negative breast cancer through SMAD3, which transactivates gamma-glutamyl transferase 1 (GGT1)[73].

GGT1 catalyzes the decomposition of extracellular glutathione, providing cysteine for intracellular glutathione synthesis, enhancing GPX4 activity and the tumor cell's resistance to ferroptosis.

Moreover, other immune cells also have a significant impact on ferroptosis. For example, in a glioblastoma mouse model driven by PDZ-binding motifs, neutrophils transfer myeloperoxidase (MPO) into tumor cells through direct cell contact or close contact, inducing tumor cell lipid peroxidation and promoting ferroptosis[74].

In summary, ferroptosis and the immune response in the TME have complex interactions, which can both enhance anti-tumor immunity and suppress immune reactions. In practical therapeutic applications, how to utilize the positive effects of ferroptosis on the immune response while avoiding its negative impacts has become an important topic in tumor cell ferroptosis therapy.

3. Delivery strategies for ferroptosis-immunotherapy therapy

The analysis above shows that ferroptosis has a complex interaction with the immune response in the TME. It is crucial for tumor treatment to enhance the synergy between ferroptosis therapy and immunotherapy, avoiding the interference of ferroptosis with the immune response. It is of great importance to develop drug delivery strategies for the combination of ferroptosis and immunotherapy.

Therefore, many drug delivery strategies loaded with ferroptosis inducers have been developed, and ISAPIs co-delivery strategy, tumor targeted delivery strategy and stimuli-responsive delivery strategy have become mainstream.

3.1. ISAPIs co-delivery

As previously discussed, several studies have manifested that inducing ferroptosis is capable of activating the anti-tumor innate immune response and further augmenting the therapeutic efficacy of ferroptosis[62,75,76]. However, as research advances, it has become increasingly evident that ferroptosis may not only be inadequate in activating innate immunity in the early stage of ferroptosis (characterized by the intact membrane) but could also potentially impair immune cells to a certain extent. For example, $CD8^+$ T cells are susceptible to ferroptosis, and the IFN-γ released by them may upregulate PD-L1 expression in tumor cells and induce inflammatory immunosuppression. Consequently, to compensate for the insufficiency of the immune system in ferroptosis-immune therapy, one of the most straightforward and simplistic strategies is to incorporate ISAPIs into the ferroptosis induction system, thereby positively eliciting an effective, long-lasting, and profound anti-tumor immune response[77].

To achieve that end, an increasing number of immune-stimulating agents have emerged, effectively enhancing the immune activation effect induced by ferroptosis: (1) Augment the innate immune response. During the advanced stage of ferroptosis, antigen presentation was insufficient. To overcome this deficiency, agonists of STING and TLR, as well as blockers of indoleamine 2,3-dioxygenase (IDO) and CD73, among others, can be encapsulated to enhance the intensity of the anti-tumor immune response by strengthening the functions of macrophages, DCs, or natural killer (NK) cells[78-80]. (2) Enhance adaptive immunity: The direct or indirect negative impacts of ferroptosis on tumor-specific effector T cells can be counterbalanced by the addition of T-cell-associated immune checkpoint inhibitors (such as PD-1 monoclonal antibodies or CTLA-4 antibodies)[81]. (3) Inhibit the formation of immunosuppressive microenvironment: IDO blockers, TGF-β blockers and COX2/PEG inhibitors are employed to block immunosuppressive signals, inhibit tumor fibrosis, angiogenesis and alleviate hypoxia to improve the immune microenvironment[82] (Fig. 2).

However, in recent years, with the advancement of ferroptosis-immunotherapy, the uncontrolled release and long-term stability of ISAPIs have gradually emerged as crucial issues. Although a simple injection of ISAPI can exert an immediate effect, it frequently leads to a series of side effects, such as pain at the injection site and an inflammatory factor storm due to the instantaneous high concentration. For instance, after the TLR agonist TLR-7/8 is injected into the body, it can rapidly disseminate from the blood throughout the entire body, thereby causing potent side effects[83-85]. In addition, the majority of the ISAPIs under investigation are proteins or nucleic acids, which are prone to degradation and clearance by the internal environment, further restricting the persistence of their efficacy. Hence, the development of delivery systems capable of achieving the stable release of ISAPIs has emerged as a research focus. The drug delivery system can optimize the druggability of ISAPIs and broaden the range of disease applications. At present, the development of delivery systems for the co-delivery of ferroptosis inducers and ISAPIs has manifested the following significant characteristics: (1) Synergistically augment anti-tumor effects: Integrating a ferroptosis inducer and an ISAPI into a single drug delivery system enables more precise control and synergistic effects compared to two separate injections. (2) Enhance the efficiency of antigen delivery: By designing the size, shape, and spatial structure of the delivery system to simulate the traits of pathogens, it can effectively enhance the antigen uptake capacity of APCs, thereby laying a foundation for further improving the efficacy of immunotherapy[86]. (3) Prolonging the biological activity of immune-stimulating agents: The delivery system can provide physical or chemical protection for immune-stimulating agents, effectively counteracting the impairment to their activity caused by the complex internal environment, thereby offering more stable immune support for tumor treatment[87]. Based on the mechanism of ISAPIs in the drug delivery system, we have classified them into two types: cargoes with immune-stimulating effects and vectors with intrinsic immune activation functions. We systematically review the structural characteristics, mechanisms, and applications of these two types of delivery systems in tumor therapy.

3.1.1. Cargoes with immune-stimulating effects

Firstly, it is feasible to design the immunostimulatory materials as the cargoes within the drug delivery system, encapsulate them along with ferroptosis inducers, and precisely deliver them to the TME. Based on numerous studies, the cargoes with immune-stimulating effects can be categorized into two major types: macromolecules (such as proteins, nucleic acids, etc.) and small-molecule drugs. Subsequently, we will expound on the mechanism of such ISAPIs and explore the crucial role of the drug delivery system in optimizing their therapeutic efficacy, both of which are summarized in Table 2[21,88-96].

3.1.1.1. Protein and nucleic acid macromolecular immune-stimulating cargoes. Protein ISAPIs are predominantly monoclonal antibodies targeting immune checkpoints, which are a set of molecules expressed on immune cells or cancer cells and regulate immune activation, playing a crucial role in preventing the

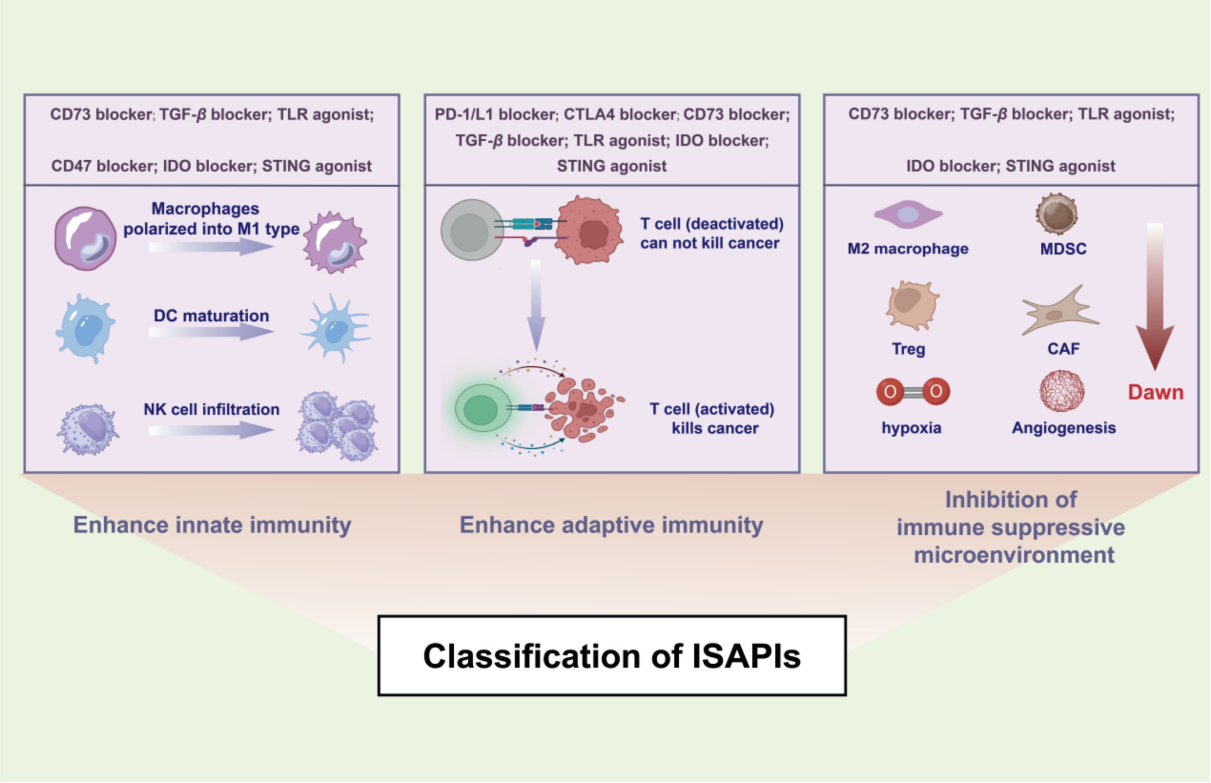


Figure 2 Classification of ISAPIs.

Table 2 Immune-stimulating cargoes and their application.

Immune-stimulating cargo	Ferroptosis inducer	Drug delivery system	Tumor model	Ref.
aPD-1	Withaferin A	Hydrogel	Melanoma	88
aPD-L1	Fe^{3+}	Metal nanocomplex	Lymphoma	89
	Ultrasmall iron nanoparticles	Ultrasmall iron nanoparticles	Breast cancer	90
aTGF-β	Sorafenib	Hybrid metal nanoparticles	Colon tumor	21
PEP20 (CD47 inhibitory peptide)	Hemin (H)	Biomimetic nanoparticles	Breast cancer	91
Pol (I:C) (TLR3 agonists)	AIEgens	Polymer nanoparticle	Breast cancer	92
Indoximod (Ido blocker)	Quinone methide and Fe^{3+}	Polymer nanoparticle	Breast cancer	93
DNA (STING agonists)	DHA	Iron-based metal−organic framework	Lewis lung cancer	94
Mn^{2+} (STING agonists)	MnO_2, GOx	Hybrid metal nanoparticles	Breast cancer	95
R848 (TLR7/8 agonists)	Fe-TCPP	Iron-based metal−organic framework	Melanoma	96

IDO, indoleamine 2, 3-dioxygenase; DHA, dihydroartemisinin; GOx, glucose oxidase; TLR, Toll-like receptor.

occurrence of autoimmune reactions[97]. For example, immune checkpoints such as the typical protein ISAPIs can be classified into activated and suppressed ones. It is well-known that numerous tumor cells employ suppressed immune checkpoints, including PD-1, PD-L1/2, CTLA-4, CD73 and so on, to achieve the effect of tumor immune escape[98-103]. Owing to their high specificity, a substantial number of clinically validated pharmaceutical products have been successfully developed and commercialized. Such as PD-1 antibodies, namely nivolumab, Pembrolizumab, Cemiplimab, Toripalimab, and Carfilzomib; PD-L1 antibodies, including Atezolizumab, Avelumab, and Durvalumab; and CTLA-4 monoclonal antibodies, for instance, ipilimumab, etc[102,104,105]. In addition, CD73 is also a classical immune checkpoint. CD73, as Ecto-5′-Nucleotidase, is the critical enzyme that catalyzes adenosine monophosphate (AMP) to generate extracellular adenosine[106,107]. However, adenosine is an immunosuppressive molecule that influences both innate and adaptive immunity, as well as the TME[108,109]. Consequently, aCD73, as an emerging star of immune checkpoint monoclonal antibodies, has been extensively developed, such as oleclumab developed by AstraZeneca and ulileldimab developed by Celestia, both which are in the clinical stage.

In addition to immune checkpoint monoclonal antibodies, there are other immunotherapy protein drugs, such as anti-TGF-β and anti-CD47 antibodies, as ISAPIs. TGF-β exerted negative impacts on the innate and adaptive immune system, as well as the TME[110-114]. Luspatercept is a drug targeting TGF-β and has received marketing approval for addressing the pathological processes associated with TGF-β. CD47, also known as integrin-associated protein I (IAP), is the "self" marker of almost all tumor cells, representing the "don't eat me" signal. CD47 can bind to the SIRPα on the surface of macrophages, effectively avoiding

macrophage phagocytosis[115,116]. Hence, multiple CD47-targeting antibodies have advanced into late-stage clinical trials as well.

Although a wide range of antibody-based ISAPIs continues to emerge as one of the most promising frontiers in new drug development, their therapeutic potential is often hindered by inadequate stability issues such as denaturation, fragmentation, and enzymatic hydrolysis. These limitations are further exacerbated by suboptimal controlled-release properties, which reduce therapeutic efficacy and increase the risk of systemic toxicity[117,118]. For instance, intravenous administration of monoclonal antibodies yields low response rates (overall response rate <30%) in most cancer patients, largely due to inefficient delivery[119]. Consequently, the pharmacological activity of biologic drugs critically depends on developing safe and efficient delivery systems—such as hydrogels, metal nanoparticles, and biomimetic nanoparticles—to overcome these challenges.

Hydrogel is a high-molecular system that contains a considerable quantity of water and has a three-dimensional network structure, which has been employed for the delivery of protein drugs. It is reported that hydrogel formed through cross-linking hyaluronic acid and dextran is capable of maintaining the therapeutic concentration of bevacizumab for at least three months[120]. Cheng et al.[88] developed an injectable hydrogel (Gel@WA-cRGD + aPD-L1) based on β-cyclodextrin, Ca^{2+}, and oxidized sodium alginate. The porous network of the hydrogel was designed to deliver both aPD-L1 and the ferroptosis-inducing prodrug WA-cRGD (Fig. 3A−C). The prodrug conjugation of cRGD ligands could facilitate the preferential uptake by tumor cells while preventing their accidental uptake by immune cells, so as to lower the cytotoxic impact on splenic immune cells. *In vivo* imaging of Cy5-loaded hydrogels in mice demonstrated prolonged fluorescence retention compared to free Cy5, indicating the hydrogel's potential for controlled drug release (Fig. 3D). In a bilateral B16F10 postoperative tumor model, the treatment significantly inhibited tumor growth over 60 days and markedly enhanced the infiltration of mature DCs and M1 macrophages in distant tumors, both with a 21% increase compared to the control group.

In ferroptosis therapy, metal nanoparticles are widely utilized, often incorporating iron and other elements to enhance the therapeutic efficacy of ferroptosis. This "self-supplying iron/self-inducing ferroptosis" feature bypasses complex drug-loading processes, significantly streamlining nanocarrier fabrication while controlling iron ion release through a TME-responsive strategy. Furthermore, antibodies can be engineered through various modification and functionalization strategies, enabling their self-assembly into nanostructured particles with enhanced stability and controlled release properties. Nie et al.[89] fabricated aPD-L1 to spermidine-grafted glucan (APP-SPM-DEX) through the EDC/NHS reaction, and subsequently complexed it with sodium tripolyphosphate and Fe^{3+} nanomorph, ultimately constructing a spermidine-immune peptide−metal nanocomplex (APP-Fe NC) for regulating the TME. They discovered that aPD-L1-Fe NC induced more significant cytotoxicity to mouse lymphoma cells than aPD-L1-SPM-DEX and free Fe^{3+}. Similarly, in the *in vivo* anti-lymphoma experiments, the tumor weight was decreased by 25.4%, 35.8%, and 73.6%, respectively, in the aPD-L1-SPM-DEX, free Fe^{3+}, and aPD-L1-Fe NC groups compared to the control group (Fig. 3E). All these imply that immunotherapy drugs alone might not yield a significant therapeutic effect, while the combination of ferroptosis and immunotherapy will achieve the optimal anti-tumor effect (Fig. 3F). Similarly, Shen et al.[90] implemented ^{131}I modification on aPD-L1 to acquire ^{131}I-APD-L1, which was co-assembled with the ultrasmall iron nanoparticles (USINPs) functionalized with fluorobenoborate. These nanoparticles not only serve as direct ferroptosis inducers but also prolong blood circulation time and enhance tumor accumulation, offering significant advantages. The combined ferroptosis-immune-radiation therapy effectively inhibits the progression of breast cancer. Zhou et al.[21] loaded the ferroptosis inducer sorafenib and aTGF-β onto Fe_3O_4/Gd_2O_3 hybrid nanoparticles. aTGF-β could be specifically released in tumor tissues and synergize with iron particles and sorafenib to mediate ferroptosis, thereby promoting DCs maturation, M1 macrophage infiltration, and T cell activation to remodel the TME.

Leveraging their cell-membrane-mimicking structures, biomimetic nanoparticles have emerged as strategic vectors for the co-delivery of ferroptosis inducers and ISAPIs, where the nanoparticles' natural tropism enhances tumor accumulation while their biomimetic cloak minimizes immune clearance, thereby creating a synergistic platform for dual-modality therapy. He et al.[91] employed BSA coated with the M1 macrophage cell membrane as a delivery carrier (MP@CH/BSA NP), loaded Ce6 as a photosensitizer, and heme as well (Fig. 3G and H). They aimed to upregulate the expression of heme oxidase-1, thereby inducing heme degradation and Fe^{2+} release, promoting the Fenton reaction and ferroptosis. Interestingly, the study revealed that laser irradiation significantly enhances hemin release, achieving rates twice as high as those measured under unirradiated conditions (Fig. 3I). The CD47 inhibitory peptide PEP20 was recoupled to the macrophage cell membrane, which was expected to block the CD47−SIRRPα interaction in the TME. Additionally, after drug treatment, the secretion of IFN-γ in the tumor could be significantly increased, thus down-regulating the expression of Xc^- in the system, which could significantly sensitize ferroptosis (Fig. 3J−L).

While protein-based ISAPIs dominate current ferroptosis-immunotherapy paradigms, nucleic acid ISAPIs have also gradually gained a position due to their distinctive immune regulatory function. Nevertheless, because of its susceptibility to degradation by nuclease in serum and electrostatic repulsion with the cell membrane, its cellular uptake efficiency is low, thereby restricting its practical application[121,122]. Currently, one of the most prevalent nucleic acid ISAPIs is polyinosinolate Poly(I:C), which is a TLR agonist. Poly(I:C) is a synthetic double-stranded RNA molecule. Since its structure is similar to that of viral double-stranded RNA, it can simulate the natural immune response of the host induced by viral infection and is regarded as a potent interferon inducer[123-125]. Nucleic acid-based immune stimulants typically have a short half-life. According to reports, loading the nucleic acid immune stimulant CpG ODN into a nanodelivery system can significantly extend its elimination half-life by approximately 7 h. Moreover, this approach enhances its ability to promote the maturation of BMDCs and boost the secretion of TNF-α and IL-6[126]. Wang et al.[92] developed a nanoplatform through a self-assembly strategy by complexing negatively charged Poly(I:C) with positively charged aggregation-induced emission luminogens (AIEgens) MTCN-3. The resulting complex was further encapsulated in the amphiphilic polymer DSPE-Hyd-PEG-Folate, denoted as M@P (Fig. 3M). Upon light irradiation, MTCN-3 generated ROS and heat, leading to lysosomal dysfunction and subsequently triggering pyroptosis and ferroptosis in tumor cells. Following M@P injection, the nanoplatform actively targeted the tumor site in mice within 6 h and continued to accumulate for up to 24 h. In a breast cancer mouse model, treatment significantly increased the

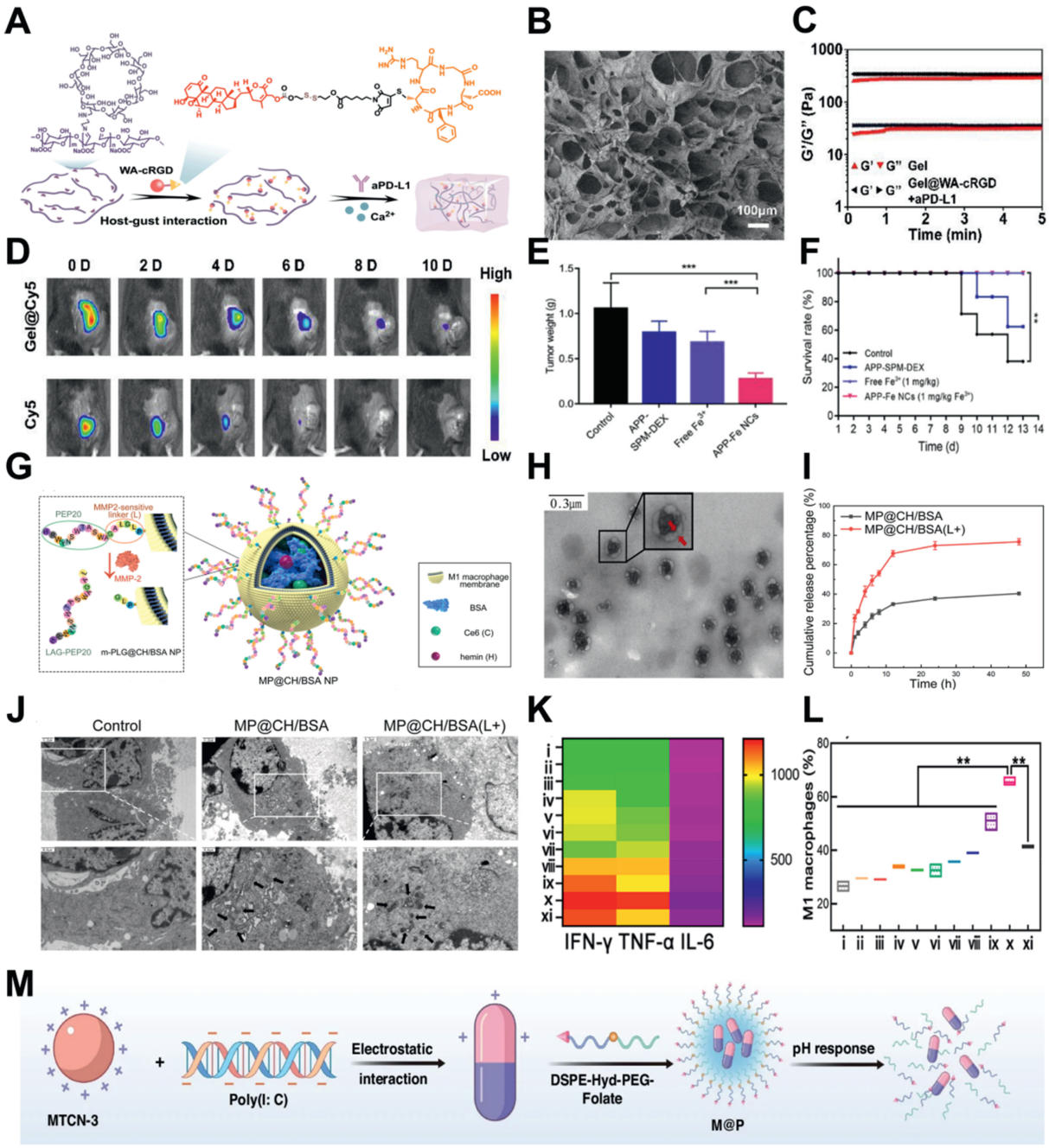


Figure 3 Protein and nucleic acid macromolecular immune-stimulating cargoes and their application in ferroptosis-immunotherapy. (A) Schematic illustration of the synthesis procedure for Gel@WA-cRGD + aPD-L1, a carrier designed for co-delivering aPD-L1and WA-cRGD. (B) SEM image of hydrogel with a porous network. Scale bar = 100 μm. (C) Rheology behavior of Gel and Gel@WA-cRGD + aPD-L. (D) Fluorescence imaging showing the different drug release behavior between free Cy5 and Gel@Cy5 *in vivo*. The unit of fluorescence intensity is a. u. Reprinted with the permission from Ref. 88. Copyright © 2023 Elsevier. (E) Tumor weight, and (F) survival rate of mice from each treatment group. Reprinted with the permission from Ref. 89. Copyright © 2023 American Chemical Society. (G) Schematic illustration of MP@CH/BSA coupled with PEP20 peptide and co-loaded with Ce6 and heme. (H) TEM images of MP@CH/BSA. Scale bar = 0.3 μm. (I) Laser-triggered release of hemin from MP@CH/BSA NP. (J) Representative bio-TEM images of 4T1 cells treated with fresh medium, MP@CH/BSA NP or MP@CH/BSA NP (L+). Scale bar = 1.2 μm in original view above and 0.6 μm in enlarged view below. (K) A heat map showing concentrations of IFN-γ, TNF-α, and IL-6 in 4T1 tumor-bearing mice subjected to different treatment regimens. The unit of concentration intensity is pg/mL. (L) Percentages of M1 macrophages in tumors. Reprinted with the permission from Ref. 91. Copyright © 2022 Elsevier. (M) Illustration of the synthesis procedure for M@P. Reprinted with the permission from Ref. 92. Copyright © 2025 Springer Nature.

proportion of mature DCs cells from 26.4% to 45.3%, while the levels of pro-inflammatory cytokines, including IL-6, IL-18, IL-1α, IL-1β, TNF-α, and IFN-γ, were markedly elevated.

In recent years, RNA interference (RNAi) technology based on small interfering RNA (siRNA) has shown significant advantages in the field of anti-tumor therapy. While siRNA is not traditionally considered an ISAPI, it can exhibit adjuvant-like effects under certain conditions[127]. siRNA specifically degrades target mRNA and precisely regulates gene expression at the post-transcriptional level. Studies have demonstrated the successful development of various siRNA-based delivery systems, including liposomes, polymeric micelles, dendritic macromolecules, and other carriers, to achieve the downregulation of PD-L1, VEGF, or TGF-β[128-131]. These systems have effectively inhibited tumor growth and metastasis. Although research on siRNA technology in ferroptosis-related immunotherapy has not yet been reported, its precise gene regulation capabilities and promising therapeutic effects provide new insights for the development of novel ferroptosis-immunotherapy combination strategies.

Although antibody and nucleic acid ISAPIs show strong therapeutic potential in immunotherapy because of their highly specific immune activation ability, which can accurately identify specific targets through antibody−antigen and other reactions. However, due to its macromolecular structure, the development of such ISAPI faces many challenges, such as: (1) Complex and costly development and production: complex structure and strict quality control requirements lead to high production costs. (2) Poor stability: easy to be affected by environmental conditions (such as temperature, pH), needs to be stored at low temperatures, which increases the difficulty of transportation and storage[132]. These factors limit the clinical transformation and wide application of such ISAPIs. In contrast, small molecule ISAPI is similar to a large molecule in immune response mechanism, but its simple structure and stronger stability make it more flexible and operable in clinical application, and provide a broader prospect for the popularization and development of immunotherapy.

3.1.1.2. Small-molecule ISAPIs. In recent years, small-molecule immunomodulators have made significant progress in the field of immunotherapy. These drugs target specific immune regulatory sites, such as IDO, Cyclic GMP−AMP synthase (cGAS)-stimulator of interferon genes (STING), and TLR, allowing for precise modulation of immune responses and thereby exerting therapeutic effects. Next, we will classify small-molecule immunomodulators based on their mechanisms, with a focus on the mechanisms of IDO inhibitors, STING agonists, and TLR agonists, as well as their remarkable efficacy in ferroptosis-immunotherapy delivery systems.

Studies have demonstrated that the enhancement of tryptophan−kynurenine (Trp−Kyn) metabolic pathway activity is associated with local immunosuppression in the TME, facilitating the immune escape of cancer cells[133-135]. Small molecule inhibitors targeting IDO, governing the Trp−Kyn metabolic axis, have emerged as promising immunotherapeutic agents, given IDO's pivotal role in tumor immune evasion through local tryptophan depletion and kynurenine-mediated immunosuppressive signaling. Hence, targeting IDO *via* small molecules might be a potential protocol for cancer therapy. Huang et al.[93] fabricated a multifunctional nanoplatform featuring self-driven release of IDO inhibitor, indoximod (IND), and enhancement of oxidative stress. They initially devised an IND prodrug based on the release of ROS and esterase in response and chelated it with Fe^{3+} and polydopamine to form nanoparticles (Fig. 4A and B). In a tumor-specific high-ROS microenvironment, the IND prodrug undergoes activation to generate IND, thereby inhibiting the conversion of Trp into Tyn and concomitantly generating quinone (QM) as a by-product (Fig. 4C). QM further augments oxidative stress by elevating ROS and depleting GSH, and collaborates with iron ions to facilitate the ferroptosis process (Fig. 4D). Additionally, the intensification of oxidative stress significantly expedited the self-driven release of the prodrug, achieving efficient drug delivery. This design amplifies the therapeutic effect through multiple mechanisms, offering an innovative strategy for the combination of ferroptosis and immunotherapy.

Within the realm of small-molecule ISAPIs, the cGAS−STING signaling axis also serves as a pivotal biosensor mechanism, orchestrating cytoplasmic surveillance of extranuclear DNA through a precisely coordinated molecular cascade. Specifically, cGAS, a DNA receptor in the cytoplasm, recognizes DNA from the nucleus or mitochondria and catalyzes the production of cyclic dinucleotides (CDNs, *e.g.*, 2′,3′-cGAMP)[136]. As a second messenger, the CDNs are capable of binding to and activating STING, a key protein in the innate immune system, that exists in the endoplasmic reticulum in the form of a symmetric dimer. The activated STING forms polymers that recruit and activate downstream molecules, TBK1 and IRF3. Subsequently, TBK1 phosphorylates IRF3, inducing the dimer to enter the nucleus and initiating the expression of type I interferons (such as IFN-β), which triggers the interferon immune response[137]. Subsequently, the production of IFN can enhance the maturation of DCs and promote the expression of chemokines CXCL9 and CXCL10, facilitating the migration of T cells to the TME. Furthermore, the activation of STING not only polarizes TAM towards anti-tumor M1 macrophages but also reprograms M2-TAM to the M1 phenotype[138-141]. In conclusion, with respect to the activation of the STING pathway, not only can an increase in the release of DNA activate cGAS, but also the activation of CDNs is capable of activating STING. Hence, cGAS−STING pathway activators are often incorporated into delivery systems to enhance the efficacy of ferroptosis-based immunotherapy.

CDNs are a natural and direct agonist for STING. However, its high molecular weight and strong polarity restrict its ability to penetrate the cell membrane. Meanwhile, its phosphodiester bond is prone to enzymatic hydrolysis, leading to poor metabolic stability and thereby limiting its clinical application[142]. To overcome these shortcomings, non-nucleotide STING agonists, including Mn^{2+}, STING agonist-4, have emerged as a research focus. In ferroptosis-immunotherapy, ferroptosis might impact the normal functionality of immune cells, resulting in mitochondrial dysfunction and the release of intracellular DNA. Nevertheless, this process can be ingeniously exploited to further activate the STING pathway and enhance its immunogenicity, thereby offering novel concepts and potential breakthroughs for the synergistic application of ferroptosis and immunotherapy. Li et al.[94] administered an iron-based metal-organic frameworks (MOF) encapsulating Dihydroartemisinin (DHA), denoted as DHA@MIL-101, into the TAM (Fig. 4E). The construction of the MOF enhances the solubility and bioavailability of DHA and ingeniously exploits the disparity in the content of basic iron ions between cancer cells and macrophages to achieve the reprogramming of TAM. It has been experimentally verified that TAM can phagocytose the drug-carrying MOFs and exert a certain ferroptosis effect (Fig. 4F). The ROS and LPO produced will damage intracellular DNA, and their

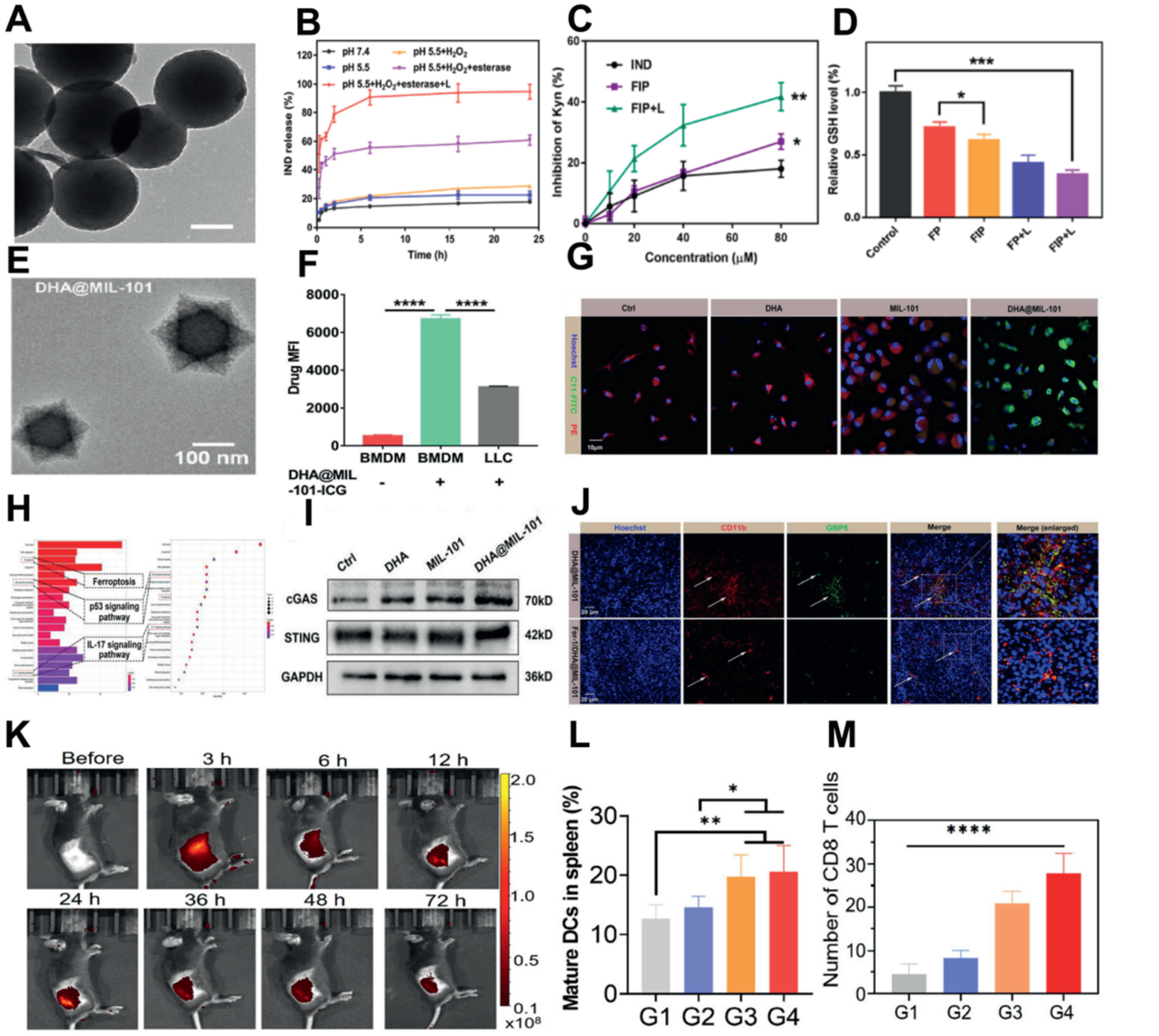


Figure 4 Small molecule immune-stimulating cargoes and their application in ferroptosis-immunotherapy. (A) TEM image of nanoparticles. Scale bar = 100 nm. (B) Release profile of IND under different conditions. H_2O_2: 100 μmol/L, esterase: 100 U/mL. (C) Kyn inhibition rate in 4T1 cells after different treatments. (D) The GSH level in 4T1 cells after different treatments. Reprinted with the permission from Ref. 93. Copyright © 2023 Elsevier. (E) TEM images of DHA@MIL-101. Scale bar = 100 nm. (F) The uptake of DHA@MIL-101-ICG in TAM and lung cancer cells (LLC). The unit of fluorescence intensity is a.u. (G) The LPO generation in TAM was observed with laser confocal microscopy. Scale bar = 10 μm. (H) The Kyoto Encyclopedia of Genes and Genomes functional enrichment analysis was conducted. The DEGs were mainly enriched in the ferroptosis and DNA damage-associated signaling pathways. (I) The expression of cGAS/STING was detected by WB. (J) Multiple immunofluorescence staining examined molecules of M1, GBP5. Scale bar = 20 μm. Reprinted with the permission from Ref. 94. Copyright © 2023 Wiley. (K) Improved tumor enrichment of Fe-MOF-RP was monitored by fluorescence imaging *in vivo*. The unit of fluorescence intensity is a.u. (L) DC maturation expressed on $CD11c^+$ cells. (M) Proportion of $CD8^+$ T cells after different treatments. Reprinted with the permission from Ref. 96. Copyright © 2024 American Chemical Society.

fragments mediate the activation of cGAS/STING, thereby generating an anti-lung cancer immune effect (Fig. 4G−I). By employing the DNA damage inhibitor Wortmannin and the ferroptosis inhibitor Fer-1, the study demonstrates that ferroptosis-induced DNA damage in TAMs is essential for activating the STING pathway, which subsequently enhances polarization and phagocytic function (Fig. 4J). Mn^{2+} has also been encompassed in the studies of STING activation. Mn^{2+}, as an essential trace element, is capable of enhancing the enzyme activity of cGAS[143]. Nevertheless, as a hydrophilic ion, Mn^{2+} possesses a high clearance rate *in vivo* and poor membrane permeability; thus, free Mn^{2+} injections fail to yield a curative effect[144]. Hu et al.[145] successively modified MnO_2 and glucose oxidase (GOx) on the Hafnium oxide (HfO_2) core to form HfO_2@MnO_2@GOx (HMG) nanoparticles. The shell layer of MnO_2 can consume GSH, which not only elevates intracellular ROS content by the Fenton-like reaction of Mn^{2+} but also directly binds to cGAS, enhances the binding affinity of cGAS to cell membrane DNA, promotes its enzymatic activity, and generates cGAMP in the presence of trace cell membrane DNA. In addition, HMG nanoparticles, whether

administered intravenously or intraperitoneally, possess effective antitumor properties in tumor-bearing mice.

TLRs, a class of evolutionarily conserved pattern recognition receptors strategically localized at plasma membranes and endolysosomal compartments, can identify pathogen-associated molecular patterns through leucine-rich repeat (LRR) domains while amplifying DAMPs signals[80]. R848 is a small imidazoline−quinoline compound possessing dual agonist activity towards TLR7 and TLR8, which is strikingly distinct from some nucleic acid agonists (such as CpG ODN)[146-148]. Through binding to TLR7/8, R848 is capable of triggering a MyD88-dependent signaling pathway, effectively activating DCs and significantly enhancing both innate and adaptive immune responses[149]. R848 can induce the polarization of TAM from the immunosuppressive M2 phenotype to the M1 phenotype with anti-tumor activity, subsequently promoting the secretion of pro-inflammatory cytokines (such as IL-6, IL-12) and chemokines, and enhancing the anti-tumor immune response[150]. Nevertheless, the direct administration of R848 as a free drug presents a significant issue of a sharp increase in blood concentration. Significant differences in the delivery behavior between free R848 and R848 encapsulated in nanoparticles have been well-documented. Within 4 h after administration, the serum concentration of the drug in the free group was considerably higher than that in the polylactic acid nanoparticle group, even 4−5 times greater. This concentration fluctuation might result in systemic toxicity, which could potentially restrict its clinical application[151]. Fan et al.[96] devised a light-triggered nanozyme, namely Fe-TCPP-R848-PEG (Fe-MOF-RP). Utilizing Fe-TCPP MOF as the core architecture, the immunoagonist R848 was encapsulated within the nanozyme, and PEG was modified on the surface, thereby significantly optimizing its pharmacokinetic properties. The PEG modification not only endows Fe-MOF with excellent biocompatibility but also enhances its tumor-accumulation ability, prolongs the drug's blood circulation time, and markedly improves its selective enrichment in tumor tissues (Fig. 4K). In contrast to the PBS group, Fe-MOF-RP in combination with laser irradiation significantly elevated the expression levels of co-stimulatory molecules ($CD80^+$ and $CD86^+$) and MHC I in DCs. Additionally, the proportion of $CD8^+$ T cells and memory T cells also increased significantly, indicating that it can effectively enhance the tumor-specific immune response (Fig. 4L and M).

Cargoes possessing immunostimulating capacity are capable of augmenting the activity of immune cells and enhancing the immune system's response to tumors. Nevertheless, at high dosages or when employed inappropriately, these cargoes can give rise to the overactivation of immune cells, triggering cytokine storms or other toxic reactions. Hence, precise dose control and release strategies are indispensable to prevent an uncontrolled immune response or toxic accumulation, thereby guaranteeing the safety and efficacy of the treatment. Additionally, carrier design is particularly crucial when co-delivering immune-stimulating cargo along with ferroptosis inducers. A sophisticated carrier system is requisite to ensure the synergistic release of the two, guarantee the balanced release of drugs in the tumor area and avoid the unbalanced drug release influencing the therapeutic effect, so as to optimize the combined therapeutic effect of ferroptosis and immunotherapy.

3.1.2. Vectors with intrinsic immune activation functions

Vectors with intrinsic immune activation functions refer to carriers that can actively trigger immune responses without the need for additional exogenous immunostimulants. These systems leverage the intrinsic immunoactivating properties of their constituent materials, such as chitosan-based carriers or bacterial membrane vesicles, or rely on specific physicochemical characteristics, including surface charge and structural morphology, to directly activate immune cells such as DCs and macrophages or to activate key immune signaling pathways[152-154]. In the following sections, we will provide a detailed discussion of the underlying immunoactivation mechanisms and highlight innovative applications of these systems in enhancing the immunotherapeutic synergy of ferroptosis-based cancer treatments.

Chitosan is a type of natural polymeric material. Due to its immunomodulatory effect, chitosan has been extensively utilized in immunotherapy and ferroptosis research. Studies have indicated that highly deacetylated chitosan can induce mitochondrial stress, facilitate the generation of mitochondrial ROS and the release of DNA, activate the cGAS−STING signaling pathway and the NLRP3 inflammasome, and further promote the maturation of DCs by inducing type I interferon[155]. Moreover, it enhances the antigen-specific Th1 response in a type I IFN receptor-dependent manner[156,157]. Meng et al.[158] constructed an injectable hydrogel delivery system consisting of chitosan hydrochloride and oxidized dextran (CH-OD) for loading the FDA-approved ferroptosis inducer salazopyridine (SSZ), attaining both tumor cell elimination and anti-tumor immune activation. Experiments have manifested that both CH and CH-OD can prominently facilitate the polarization of bone marine-derived macrophages (BMDMs) towards the M1 phenotype, demonstrating their inherent immunostimulatory capacity. Moreover, the SSZ-loaded CH-OD system (CH-OD-SSZ) further significantly augments this ability. This is attributed to the fact that SSZ induces ferroptosis in H22 liver cancer cells, releasing DAMPs, thereby amplifying the immune activation effect. Nevertheless, due to the restricted immunostimulating capability of chitosan, the Day 60 survival rate after CH-OD-SSZ treatment was merely 25% in model mice. When combined with aPD-1, the survival rate of mice escalated significantly to 58%. Therefore, even though chitosan has emerged as one of the core materials in ferroptosis-immunotherapy research on account of its immunoregulatory capacity, biocompatibility, and degradability, its inherent immunostimulatory ability is inadequate and thus difficult to fulfill the requirement for sufficient activation of the immune system in complex treatment scenarios. To surmount this limitation, the introduction of an immune adjuvant as extra functional cargo based on chitosan can conspicuously enhance its immune activation effect, concurrently endowing it with greater therapeutic flexibility and efficiency[159].

At present, the natural membrane self-adjuvant delivery system is the most widely used carrier for such research. For example, bacterial outer membrane vesicles (OMV), which are natural nanovesicles secreted by Gram-negative bacteria with a particle size of 20 to 250 nm, are an excellent adjuvant carrier platform[160]. Because OMV contains peptidoglycan, LPS and flagellin, it is a natural TLR agonist with a strong ability to activate innate immune signaling pathways[161]. Kim et al.[162] demonstrated that OMV derived from *Escherichia coli* with the ΔmsbB mutation can effectively inhibit the growth of colon cancer, breast cancer and melanoma in mice, and significantly improve the release of anti-tumor cytokines IL-12, p40, IFN-γ and CXCL10. Moreover, due to the specific phospholipid bilayer nanostructure, similar to liposomes, OMV usually acts as a drug delivery carrier and the drugs that induce ferroptosis can be modified on the OMV surface by covalent coupling or electrostatic adsorption, or embedded in the lipid bilayer membrane by co-

incubation, electroporation, etc[163]. For example, Sun et al.[164] fixed *Escherichia coli* OMV with Fe^{2+} by electrostatic interaction and loaded with STING agonist-4, along with DSPE-PEG-FA modification, to achieve a functional design of OMV/SaFeFA. The introduction of OMV and STING agonist-4 significantly increased the maturity of DCs by 84%, while the levels of $CD8^+$ T cells and $CD4^+$ T cells were respectively elevated by twofold and 80%.

Furthermore, researchers are vigorously investigating the crucial role of the physical and chemical properties of materials (such as surface charge, morphological characteristics, etc.) in the regulation of immune cells. For instance, by exposing positively charged primary amine groups on the surface of the carrier, it can not only effectively facilitate the maturation of DCs as an immune adjuvant, but also activate the immune response of CTLs[152]. Researchers are also endeavoring to develop novel delivery systems that control immune activation through modulation of their morphological properties. Hu et al.[153] developed an innovative, aspecific tetrapod spiky-like iron-palladium (FePd) nanocrystal, which significantly augmented the ferroptosis of cancer cells while inducing macrophages to release pro-inflammatory cytokines, further amplifying the activation effect of the immune system. In addition, He et al.[154] also endeavored to achieve more precise immune regulation by designing chiral nanocarriers to precisely regulate the phenotypic differentiation of macrophages. Looking forward, by optimizing the surface design and functional modification of materials, not only can their ability to regulate immune cells be enhanced, but also more efficient and safer immune regulatory systems can be developed. These technologies will offer a novel direction for the study of tumor therapy and other immune-related diseases and promote the further advancement of immunotherapy.

The utilization of carrier materials possessing immune-activating capacities not only circumvents intricate ISAPI loading procedures but also simplifies carrier design. Such self-adjuvant vectors can discharge immune activation signals more uniformly and sustainably, thereby augmenting the immune response while reducing the dependence on complex controlled release mechanisms and enhancing the efficacy of therapy. Nevertheless, despite the remarkable advancements made in theory and experimentation with this approach, due to the technical demands and cost limitations of its production process, achieving large-scale industrial transformation remains challenging, which has emerged as a bottleneck in clinical application.

Overall, compared to the traditional method of separately administering ferroptosis inducers and ISAPIs, co-encapsulating both agents within a single delivery system enables more precise control over drug spatiotemporal distribution and synergistic effects. This co-delivery strategy ensures the concurrent arrival of both drugs at the target site (*e.g.*, tumor tissue or specific cells) and their simultaneous release at the lesion site in a predetermined optimal ratio. Consequently, it maximizes the synergistic effect between ferroptosis-induced immunogenic cell death and ISAPI-activated anti-tumor immune responses, thus avoiding issues associated with separate injections, such as uneven drug distribution, temporal mismatch in action, and disproportionate dosing[83]. However, given variations across tumor types, disease stages, and individual patients, the optimal combination of inducers and ISAPIs may require personalized selection. Therefore, implementing personalized treatment is paramount, requiring thorough evaluation of the patient's specific disease profile (*e.g.*, tumor characteristics) and physiological status (*e.g.*, immune function, organ function) to formulate a tailored therapeutic regimen.

3.2. Tumor targeted delivery

As a novel therapeutic approach, ferroptosis has demonstrated an indispensable role in anti-tumor treatment. Nevertheless, the non-specific distribution of ferroptosis inducers *in vivo* constitutes an important limiting factor in ferroptosis therapy. The systemic circulation of ferroptosis agents following intravenous administration may induce off-target cytotoxicity, particularly affecting critical immune components, including $CD8^+$ T cells, NK cells, and DCs. Furthermore, tumor heterogeneity often leads to reduced susceptibility to ferroptosis, while ferroptosis-inducing agents can simultaneously trigger T cell apoptosis and cause damage to non-tumor tissues, thereby constraining the therapeutic potential of ferroptosis-based cancer treatment. Consequently, enhancing tumor-specific drug targeting represents a crucial strategy for improving anti-tumor efficacy[16,165].

Targeted drug delivery is an advanced technology that can achieve a more efficient accumulation of drug in the target tissues and cells through the heterogeneity of different tissues. Inspired by the targeted technology, many researchers have worked on the targeted drug delivery of ferroptosis inducers. Many targeted delivery strategies have been developed, including enhanced permeability and retention effect (EPR effect), receptor-mediated targeted and bionic materials-mediated targeted, etc.

With the development of nanotechnology and biomaterials, nanomaterials have proved to be feasible carriers for achieving targeted delivery. On the one hand, the nanomaterial, through a suitable size, can effectively penetrate the tumor tissue and accumulate in the deep tumor cells. It is also not easy to clean up. Therefore, the application of nanomaterials improves the bioavailability of drugs[166]. On the other hand, through surface modification of nanomaterials, the targeting can be enhanced, which mediates the endocytosis of nanomaterials by tumor cells and then increases the intracellular drug concentration. All these advantages indicate that nanomaterials are excellent carriers for targeted delivery strategies[167].

Based on the different targeting mechanisms, drug targeting systems can be divided into passive and active targeted delivery.

3.2.1. Passive targeted delivery

Passive targeted drug delivery is a typical strategy in which the drug can accumulate in tumor tissues through the EPR effect. The materials widely used for passive targeting are mainly nanomaterials, including metal-based nanomaterials, liposomes, polymers, supramolecular nanoplatforms, and so on. Up to now, there are several reviews describing passive targeting-based nano-delivery systems for tumor therapy, and here we take metal-based nanomaterials as an example for a brief analysis[168-170].

Metal-based nanomaterials are a class of nanoscale metal materials. Powerful catalytic, imaging, and photothermal conversion capabilities broaden their applications in tumor diagnosis and treatment. Common metal-based nanomaterials include monolithic and metal oxide nanoparticles, metal-organic frameworks (MOFs), metal-phenolic networks (MPNs), and nano-enzymes.

For example, Huang et al.[171] reported Fe-MnO_2 nanosheets for loading DHA (Fig. 5A), which improved the DHA targeting and therapeutic effect. DHA is an excellent ferroptosis inducer, in which the endoperoxide bridge can be broken under the catalysis of Fe^{2+}, generating ROS to trigger ferroptosis[172,173]. However, the

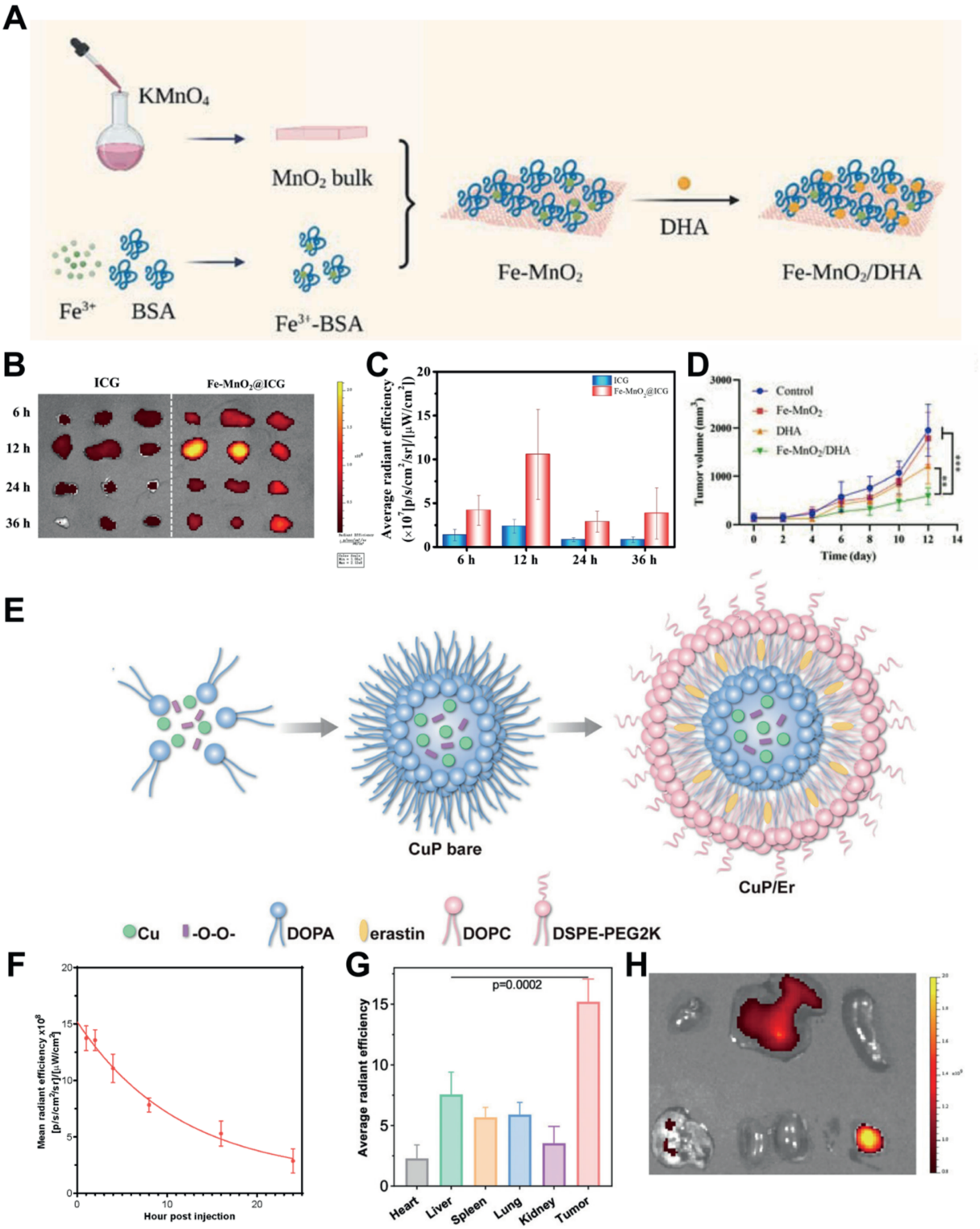


Figure 5 Passive targeted drug delivery system and its application to ferroptosis therapy. (A) Preparation process of Fe-MnO_2/DHA. Tumor fluorescence images (B) and quantitative analysis (C) in the ICG group and Fe-MnO_2@ICG group at different time points. The unit of fluorescence intensity is a.u. (D) Tumor growth curves in different treatment groups. Reprinted with the permission from Ref. 171. Copyright © 2023 Elsevier. (E) Schematic showing the synthesis of CuP/Er. (F) Time-dependent Ce6 fluorescence intensities in the plasma after CuP-Ce6/intravenous injection. The unit is $\times 10^8$ [p/s/cm^{2}sr]/[μW/cm^2]. (G) Average radiant efficiency of different organs after i.v. injection of CuP-Ce6/Er to 4T1 tumor-bearing mice. The unit is $\times 10^8$ [p/s/cm^2 sr]/[μW/cm^2]. (H) Fluorescence intensity of tumors and major organs *ex vivo*. Color bar represents radiant efficiency([p/s/cm^2/sr]/[μW/cm^2]). Reprinted with the permission from Ref. 176. Copyright © 2024 Wiley.

poor targeting ability of DHA and low Fe^{2+} content in tumor cells limit the therapeutic effect. Therefore, the research carried out by Huang et al. suggested that the nanosheet group had stronger fluorescence in the tumor (Fig. 5B and C) and an anti-tumor effect (Fig. 5D) compared to the free drug group. The combination of Fe-nanomaterials and DHA enhanced the accumulation of DHA while providing a source of Fe for DHA activation. Erastin also suffered the same dilemma. Erastin is an inducer that is widely applied in ferroptosis therapy. It acts by inhibiting the Xc^- system, thereby reducing the cellular uptake of cystine[174]. This inhibition ultimately leads to the induction of ferroptosis and lipid peroxidation. Nevertheless, the administration of free Erastin is associated with a plethora of adverse reactions, such as cerebral infarction, glomerular abnormalities, splenomegaly, and anemia, etc[175]. To address this difficulty, Li et al.[176] reported a core-shell nanoparticle (Cu/Er NCP) for targeted delivery of erastin (Fig. 5E). These nanoparticles enhance the stability of Erastin. It's worth noting that the half-life of Cu/Er NCP *in vivo* is up to 8 h (Fig. 5F). The prolongation of systemic circulation time creates favorable conditions for the accumulation of drugs in tumors. In the *in vivo* distribution experiment, the fluorescence intensity at the tumor site was the highest. Specifically, it was 2.7 times and 4.3 times that of the spleen and kidney, respectively (Fig. 5G and H). These results indicated that the nanoparticles conferred the targeting ability of the drug delivery system to achieve efficient accumulation at the tumor site.

Although nanomaterials can accumulate and remain in tumor tissues through the EPR effect, there are still some challenges in their practical application: (1) Tumor factors. Tumors of different sizes have different vascular distributions and permeabilities. Large tumors often hinder the accumulation and penetration of nanoparticles due to the formation of blood clots. In addition, pericytes and extracellular matrix (ECM) form a "wall" outside the tumor blood vessels, which hinders the penetration of nanoparticles and even leads to reflux. Finally, the tumor microenvironment often has a high interstitial fluid pressure (IFP), and a high IFP reduces the pressure difference between the inside and outside of the blood vessels, reducing the driving force for the penetration of nanoparticles into the tissue and affecting drug accumulation[177]. (2) Nanomaterial factors. Particle size, charge, and surface wettability are important factors affecting tumor accumulation. Small particle size can lead to too low retention, while large particle size can cause insufficient permeability. Moreover, positively charged or hydrophobic nanoparticles are more easily cleared by the reticuloendothelial system (RES)[178]. Therefore, in view of the disadvantages of passive targeting strategies, the development of active targeting delivery systems is urgently needed.

3.2.2. Active targeted delivery

Active targeted drug delivery entails the surface modification of nanosystems through the incorporation of specific proteins, small-molecule peptides, antibodies, and small molecules. These modifications facilitate the recognition and binding to specific molecular markers and proteins expressed on tumor cell surfaces, thereby enabling selective drug accumulation within tumor tissues. A list of common targeting materials has been provided in Table 3[179-189].

An active targeted drug delivery system has the following advantages: 1. Higher target activity. Passive targeting realizes accumulation in tumors *via* systemic circulation and EPR effects, which tend to result in insufficient drug content in tumor cells. The long-term retention in the tumor microenvironment may cause the drug to be cleared. In contrast, active targeting improves the targeting "initiative" by recognizing and binding to specific molecules and receptors on the surface of tumor cells[190]. 2. Higher biosafety. The normal cell surface is characterized by specific receptors of low quality and quantity. Therefore, the affinity of the active targeted drug delivery system to normal cells is weak, which greatly reduces the accumulation and absorption of drugs in normal tissues, thus improving the safety of drugs. Due to the different mechanisms of active targeted drug delivery systems,

Table 3 Categories of common targeting materials in active targeted delivery.

Strategy	Material	Advantage	Disadvantage	Ref.
Receptor-mediated targeted delivery	CD44 targeting materials (HA)	Easy to modify, amphiphilic property, good biocompatibility, long blood circulation times, evasion of MPS clearance	Insufficient targeting capacity, tough purification process	179,180
	Integrin targeting materials (cRGD, iRGD and fibronectin)	Good permeability, tumor vascular inhibition	Immunogenicity, rapid blood clearance, and significant MPS accumulation	181−183
	TfR targeting materials (ferritin)	Small size enhancing drug stability, ease of production and modification	Immunogenicity, low drug loading efficacy and insufficient targeting	184,185
	FR targeting materials (FA)	Favorable pharmacokinetic properties, convenient availability and low cost	Inconsistent folate attachment,	186,187
Bionic materials-mediated targeted delivery	Tumor cell membrane	Unlimited proliferation, evasion of MPS clearance and enhancing the immune response	Difficult isolation and purification, immunogenicity, and susceptible to contamination	188
	Immunocyte membrane	Inflammatory response, evasion of MPS clearance	Limited membrane source, susceptible to contamination	189

HA, hyaluronic acid; MPS, mononuclear phagocyte system; cRGD, cyclic RGDs; iRGD, linear RGDs; TfR, transferrin receptor; FA, folate.

they can be divided into receptor-mediated targeted delivery and cell membrane-based targeted delivery.

3.2.2.1. Receptor-mediated targeted delivery. The receptor-mediated targeted delivery is a key component of the active targeted drug delivery system. It targets a specific or overexpressed receptor on the tumor cells surface, facilitating the drug delivery to the tumor cells through the modification of the ligand and the specific reaction between the receptor and the ligand. Many receptors are often differentiated or overexpressed on the surface of the tumor cell membrane. This provides the possibility to design correlative ligands according to the structure of the receptor and implement precision therapy. CD44, integrin, transferrin receptor (TfR) and folate receptor (FR) are all typical examples of the receptor-mediated targeted delivery system.

CD44: CD44 is a type-I transmembrane single-chain glycoprotein, widely distributed on the cell membrane of lymphocytes, tumor cells, endothelial cells, and other cells. It has been shown that CD44 is overexpressed on the surface of tumor cells. Based on this, many CD44-targeting drug delivery platforms have been developed. Hyaluronic acid (HA), a naturally occurring polysaccharide, binds to the hyaluronic acid-binding sites on CD44, forming a complex that is subsequently internalized by tumor cells. Consequently, HA is frequently employed as a surface coating for targeted drug delivery systems to enhance their specificity and efficacy[191].

Wang et al.[192] combined palmityl palmitate with cetyltrimethylammonium bromide to construct core−shell nanoparticles (PNDH) for targeted delivery of ferroptosis inducer cisplatin, while using HA as the surface coating to improve tumor targeting. In the presence of HA, the tumor recognition efficiency was enhanced approximately twofold. Chi et al.[193] reported "core-shell" magnetic nanoparticles (FMMHG/Sor) modified with HA, comprising an Fe_3O_4 core and a mesoporous organic silica shell (Fig. 6A). By loading ferroptosis inducer sorafenib into the nanoparticle, dual-pathway ferroptosis therapy was achieved. HA modification significantly promoted cell uptake, with a cellular uptake rate of 72.3%. However, after pretreatment with free HA, cell uptake was less than 20%, further demonstrating the active targeting ability of HA (Fig. 6B). Thanks to the modification of HA, FMMHG/Sor exerted effective anti-tumor effects. No significant increase in tumor volume was observed at the end of the study. HA-coated targeted delivery platforms can be used not only for small-molecule drug delivery, but also for macromolecular drug delivery. For example, Fan et al.[194] assembled anti-B7-H3 antibody (biAbs), epigallocatechin-3-gallate dimer (dEGCG) and HA to form S-biAb/dEGCG@NPs for the treatment of glioblastoma (GBM) (Fig. 6C). The intracranial accumulation of S-biAb/dEGCG@NPs was 12.3 times higher than that of free biAb. Tumor-bearing mice in the S-biAb/dEGCG@NP group survived significantly longer due to efficient drug accumulation (Fig. 6D). The above results indicate that S-biAb/dEGCG@NPs have a better therapeutic effect due to their better penetration and targeting. In conclusion, the HA-coated ferroptosis inducer delivery platform effectively improves ferroptosis efficiency. However, CD44 is mentioned to be widely distributed in normal tissues. HA-mediated targeting systems inevitably lead to accumulation in normal tissues and organs. Therefore, the development of more efficient targeting ligands still needs to be explored.

Integrin: Integrins are a family of cell surface receptors that can be activated by anchoring ligands, triggering endocytosis. Moreover, it has been found that certain tumor cell membranes overexpress integrin $\alpha_V\beta_3$. These characteristics make the selective delivery of ferroptosis inducers possible. Integrin $\alpha_V\beta_3$ is usually poorly expressed in most cells but can be upregulated in tumor cells and endothelial cells within the tumor microenvironment[195]. Thus, integrin $\alpha_V\beta_3$ has a higher selectivity compared to CD44. The integrin-mediated targeted delivery system is suitable for precise delivery to tumors[196,197]. The arginine−glycine−aspartate (RGD) peptide is a three-amino acid sequence[195]. According to the different structure of RGDs, RGD peptides can be divided into linear RGDs (iRGD) and cyclic RGDs (cRGD). Kapp et al.[198] demonstrated that RGD peptides bind to $\alpha_V\beta_3$ through a bidentate salt bridge, which is involved in the interaction of the guanidinium moiety on arginine and the α-subunit Asp218 in $\alpha_V\beta_3$. Furthermore, the electrostatic interaction present between RGD and metal ions in integrins also contributes to targeting[199]. All of these characteristics set up integrin as an ideal target for cancer therapy.

cRGD contains the thiol group, which enables it to form a disulfide bond with drugs that also possess the thiol group. Under the targeting effect of cRGD, the drug successfully entered the tumor cells, exerting its curative effect. For example, Cheng et al.[88] reported sodium alginate hydrogels loaded with WA-cRGD and aPD-L1. After intratumoral injection, WA is internalized by B16 cells *via* the interaction with cRGD-integrin receptors and subsequently released by the cells. As shown in Fig. 6E, the GPX4 activity in the WA-cRGD group was 25% lower than that in the WA group, which indicates that cRGD enhances tumor endocytosis of WA and brings a more significant ferroptosis inhibition. Furthermore, flow cytometry experiment results reaffirm the necessity for WA delivery with cRGD. As shown in Fig. 6F, the tumor cell death rate in the WA-cRGD group was 20% higher than that in the WA group. To sum up, the modification of cRGD significantly improved the tumor targeting of WA, promoted the accumulation of WA, and induced more intense ferroptosis. In addition, the application of iRGD in tumor-targeted drug delivery also achieved promising results. Sun and his colleagues[200]prepared iRGD-modified ultrasmall single-crystal Fe nanoparticles (iRGD-bcc-USINPs). iRGD−integrin interaction promotes the iRGD bcc-USINPs, internalized by tumors, and iron single crystals were released to induce ferroptosis in the acidic tumor microenvironment (Fig. 6G). According to the tracking of nanoparticles *in vivo*, the modification of iRGD resulted in a doubling of cellular uptake (Fig. 6H).

Except for RGD peptides, which are directly used to modify drug carriers, RGD-enriched substances can also be utilized to modify drug carriers for targeting properties. Fibronectin (FN) is a typical example. FN is an ECM protein that contains an RGD sequence[201]. Xu et al.[202] utilize this characteristic of FN to achieve targeted delivery of the metal polyphenol network. Under the interaction of FN, the metal polyphenol network enters the tumor cells and releases Fe^{2+} to induce ferroptosis. The *in vivo* anti-tumor experiments showed that DOX-TAF@FN has a significant inhibition of tumor and has a significant difference with DOX-TAF@BSA, which reflects the excellent targeting of FN (Fig. 6I).

In conclusion, constructing a delivery system including the "missiles" RGD peptides offers a new approach to the precise delivery of ferroptosis inducers. Unfortunately, cRGD-modified delivery systems were shown to be highly immunogenic[182,203]. In addition, the susceptibility degradation of RGD peptides by proteases may reduce their stability *in vivo*[204]. This brings challenges to the clinical application of RGD peptides. For the

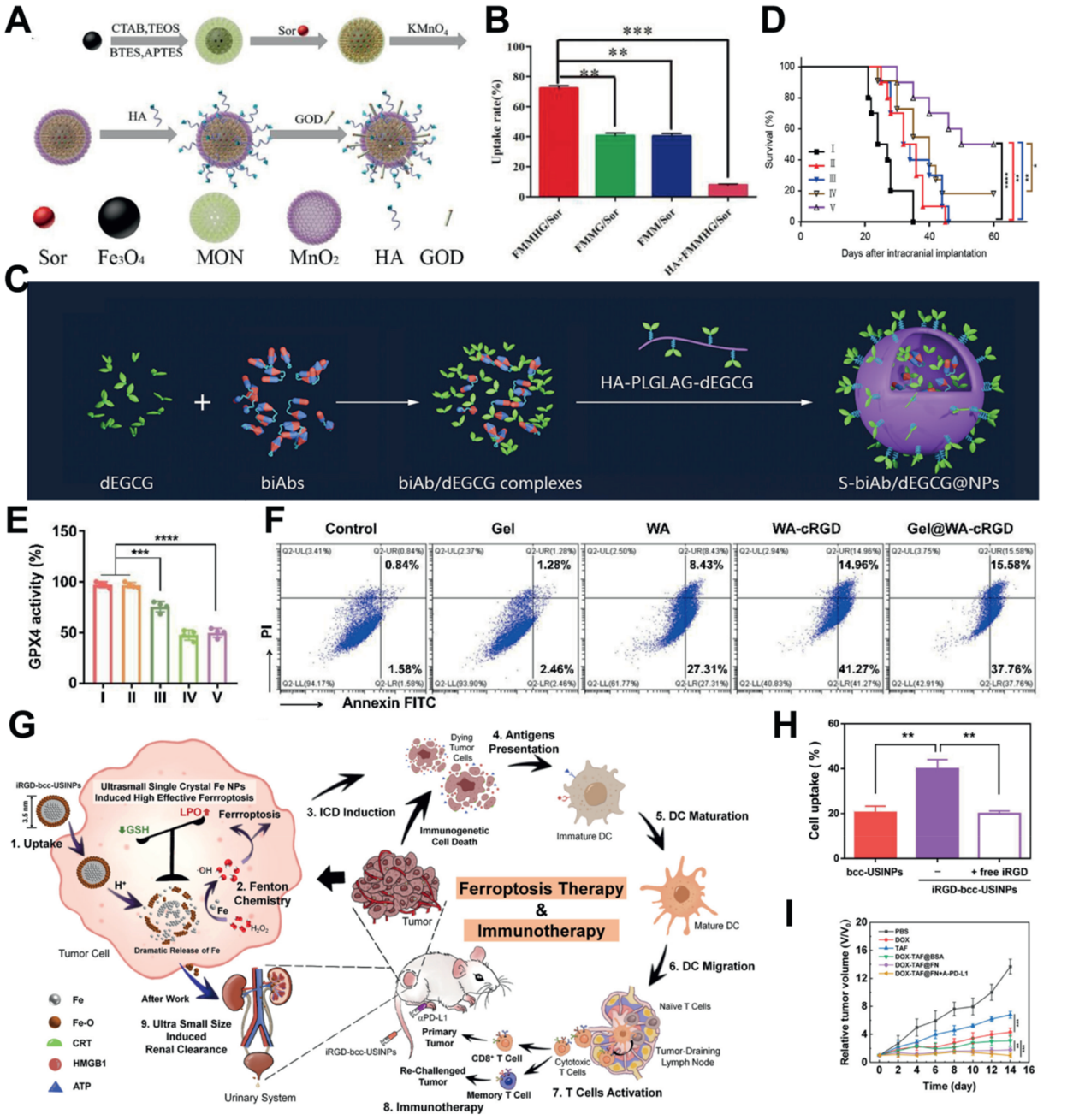


Figure 6 CD44 and integrin-mediated active targeted delivery systems in ferroptosis therapy. (A) Schematic diagram of dual-responsive FMMHG/Sor preparation. (B) The quantified results of cellular uptake of FMMHG/Sor, FMMG/Sor, FMM/Sor and HA + FMMHG/Sor in A549 cells. Reprinted with the permission from Ref. 193. Copyright © 2022 Elsevier. (C) The synthesis route schematic diagram of S-biAb/dEGCG@NP. (D) Survival curves of mice given different treatments. (I) Control, (II) biAbs, (III) biAb/dEGCG complexes, (IV) biAb/dEGCG@NPs, and (V) S-biAb/dEGCG@NPs. Reprinted with the permission from Ref. 194. Copyright © 2023 American Chemical Society. (E) Changes in the GPX4 activity in B16F10 cells after different treatments, including (I) Control, (II) Gel, (III) WA, (IV) WA-cRGD, (V) Gel@WA-cRGD. (F) Flow cytometry analysis of tumor cell death after different treatments. The unit of fluorescence intensity is a.u. Reprinted with the permission from Ref. 88. Copyright © 2023 Elsevier. (G) The Schematic diagram of ferroptosis in tumor cells induced by bcc-USINPs and subsequently the anti-tumor immune reaction. (H) Cell uptake in bcc-USINPs, iRGD-bcc-USINPs and iRGD-bcc-USINPs + free iRGD. Reprinted with the permission from Ref. 200. Copyright © 2021 American Chemical Society. (I) Relative tumor volume in tumor-bearing mice as a function of time during treatment. Reprinted with the permission from Ref. 202. Copyright © Reproduced from 2022 American Chemical Society.

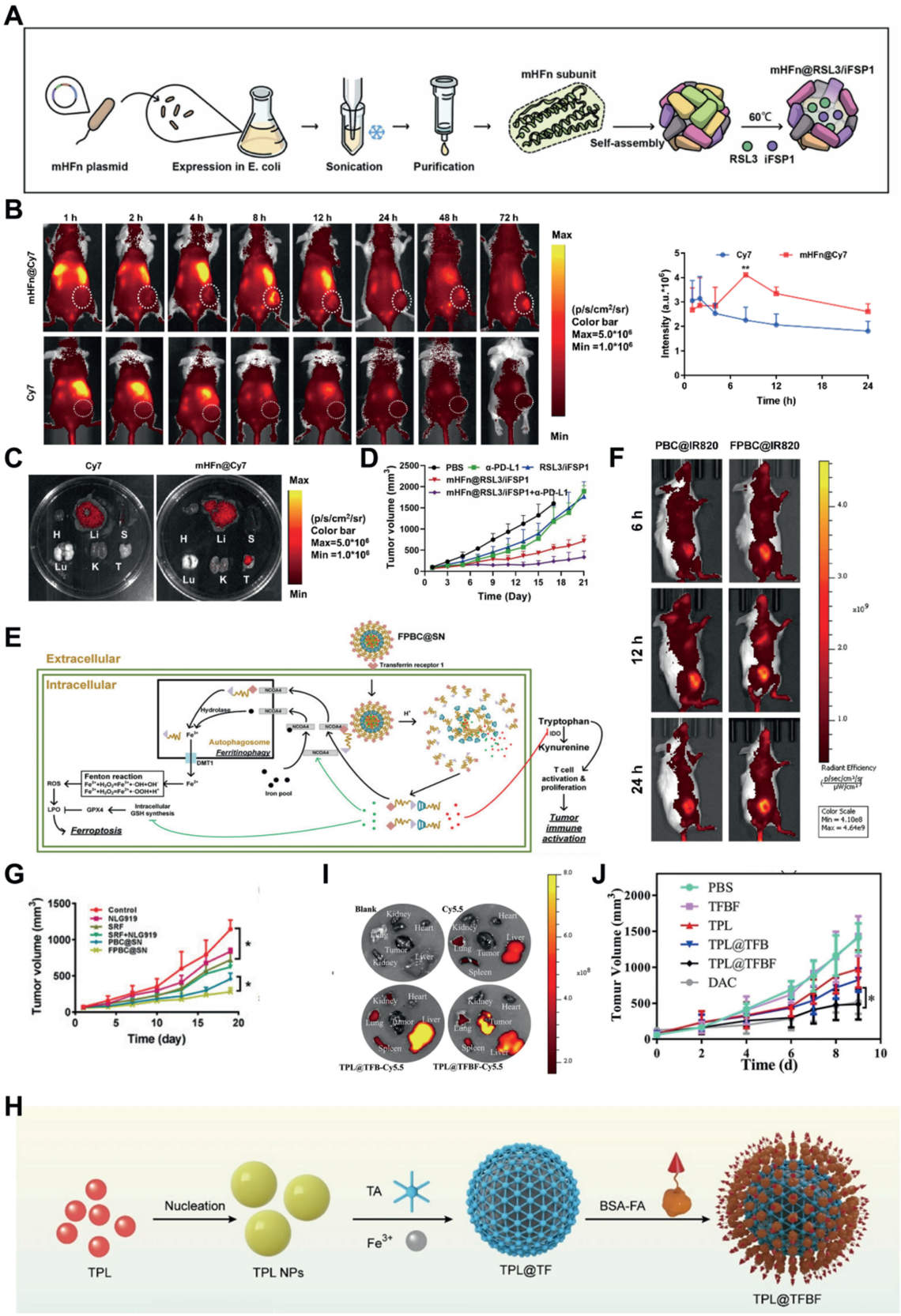


Figure 7 TfR and FR-mediated active targeted delivery systems in ferroptosis therapy. (A) Schematic diagram for the preparation process of mHFn@RSL3/iFSP1 nanocage. (B) *In vivo* biodistribution and fluorescence intensity quantification of mHFn@Cy7 in CT26 tumor-bearing BALB/c mice in CT26 tumors at predetermined time points. The unit is $\times 10^6$ p/s/cm^2/sr. (C) *Ex vivo* imaging of CT26 tumor-bearing BALB/c mice at 72 h post-free Cy7 or mHFn@Cy7 administration. The unit is $\times 10^6$ p/s/cm^2/sr. (D) MC38 tumor growth curves in different treatment

development of RGD peptide-targeting systems, finding a balance between targeting ability, immunogenicity, and instability is still a challenge.

TfR: TfR is a kind of surface receptor of nucleated cells, which can bind to ferritin and maintain the homeostasis of intracellular iron level[205]. However, the extreme deficiency of iron ions in the tumor limits its growth and differentiation. Several studies have shown that TfR1 is highly expressed in a wide range of tumor cells (pancreatic, rectal, lung, bladder, etc.) to improve intracellular iron ion levels[205,206]. As a result, TfR-mediated ferroptosis inducer delivery strategy progressively becomes a new trend in targeted therapy of cancer. Ferritin is a protein nanocage composed of heavy chain ferritin (HFn) and light chain ferritin. As a major iron-storage protein in the body, ferritin can bind to TfR1 on the cell surface through its heavy chain. After entering the cytoplasm, ferritin releases iron ions to promote cell growth and development[184,207,208]. In addition, ferroptosis therapy is highly dependent on the intracellular iron level in tumor cells. Based on the TfR targeting ability and abundant iron ions, ferritin is considered an excellent carrier for the targeted delivery of ferroptosis inducers.

Cheng et al.[209] constructed murine heavy chain ferritin (mHFn) by genetic engineering for targeted delivery of the ferroptosis inducers RSL3 and iFSP1 (Fig. 7A). *In vivo* and *ex vivo* imaging demonstrated that the high affinity of mHFn to TfR1 allowed the delivery system to be retained in the tumor cell for a longer time after intravenous injection (Fig. 7B and C). The long retention improved the drug's antitumor effect. In the *in vivo* antitumor experiments, the tumor volume in the mHFn@RSL3/iFSP1 group was only half of that in the free RSL3/iFSP1 group (Fig. 7D). The encapsulation of mHFn enables RSL3/iFSP1 to improve targeting capacity while reducing the possibility of being cleared. Zuo et al.[210] reported a ferritin-coated sorafenib to achieve targeted therapy for breast cancer (Fig. 7E). Ferritin enhanced the uptake of sorafenib in tumor cells, and the ferritin-modified group had higher fluorescence intensity (Fig. 7F) and tumor inhibition (Fig. 7G).

In conclusion, ferritin as the ligand could target tumor cells, and after the carrier was internalized into tumor cells, the ferroptosis inducer was released and triggered ferroptosis, which is an excellent candidate for targeted delivery of ferroptosis inducers.

FR: FR is a glycosylphosphatidylinositol-linked membrane glycoprotein, which is characterized by high affinity to folate (FA)[211]. However, different forms of folate have different affinities for FR. Therefore, it is necessary to make structural modifications to folic acid to improve targeting efficiency. FR-mediated targeted delivery systems combine folic acid or analogues with a ferroptosis inducer and finally form a complex. Upon binding to FR, the cytomembrane was invaginated and the intracellular inclusion was produced. Finally, the complex is released from the inclusion under the ionic pump function. Therefore, drug delivery systems targeting FR also provide new solutions for the delivery of ferroptosis drugs.

Wang et al.[212] constructed a BSA-FA functionalized iron-containing metal-organic framework (TPL@TFBF) (Fig. 7H). With the help of FA, TPL@TFBF targeted melanoma cells and released Triptolide (TPL), Fe^{3+} and TA, triggering ferroptosis and pyroptosis. In the *ex vivo* fluorescence imaging, we observed significant fluorescence from TPL@TFBF-Cy5.5 in the tumor tissues compared to other groups (Fig. 7I). This result demonstrated significant tumor targeting of FA. *In vivo* anti-tumor experiments demonstrated the significant advantages of the FA-modified delivery system. TPL@TFB group showed that the tumor growth inhibition is 41.74%, whereas FA modification significantly increased the tumor inhibition of TPL@TFBF (65.58%) (Fig. 7J).

Although receptor-mediated targeting preparation improves the targeting performance against tumors, there are still some challenges in clinical application and industrialization. Firstly, animal tumor model tends to be established in a short time, whereas primary tumor in humans tends to form in several years. The variability of species and formation time often leads to heterogeneity of receptors and differences in expression levels; therefore, equivalence for clinical application remains a factor to be considered[213]. In addition, the modifying proportion of the ligand is also an important factor. The lower modification often leads to limited targeting efficiency, while the higher modification may affect the release of the drug from the carrier and reduce the efficacy[214]. Finally, possible off-target effects. Although these specific receptors are overexpressed in tumor cells, they also have low expression in normal cells. Therefore, exploring the toxicity of receptor-mediated targeted delivery systems in normal cells is also a matter that needs to be addressed[215].

3.2.2.2. Bionic materials-mediated targeted delivery. With the development of bionic technology, the cytomembrane has brought a new perspective for drug delivery. The cytomembrane-mediated targeting strategy utilizes the cytomembrane to wrap and deliver drugs to tumor cells by virtue of the natural properties of the cytomembrane, such as homologous targeting, chemotaxis, adhesion and so on. Second, the cell membrane is derived from the body, which confers high biosafety and avoids recognition and clearance by the immune system. Thus, membrane-based biomimetic carriers usher in a new era for the delivery of ferroptosis inducers. Therefore, cell membrane-based biomimetic carriers bring out a new era for the delivery of iron death inducers.

Many biomolecules on the tumor cytomembrane (such as galactan-3, calreticulin, and Thomson-Friedenlein antigen, etc.) are involved in cell communication and adhesion, which behavior promotes aggregation for tumor cell[216]. Depending on these functional biomolecules, the tumor cell membrane, as the "coat" of the drug delivery system, can effectively deliver drugs to the tumor cell. Guo et al.[217] structured a ferroptosis inducer prodrug cisplatin delivery platform, covered gastric cancer cytomembrane "coat" (CMnMPt) to target gastric cancer cells *in vivo*. *In vivo* experiments showed that CMnMPt nanoparticles at the tumor site had double fluorescence intensity compared to MnMPt

groups. Reprinted with the permission from Ref. 209. Copyright © 2024 Elsevier. (E) Scheme of *in vivo* FPBC@SN behavior and related pathways of ferritinophagy-cascade. (F) Biodistribution images of PBC@IR820 and FPBC@IR820 at different time points *in vivo*. The unit is $\times 10^9$ [p/sec/cm^2/sr]/[μW/cm^2]. (G) Tumor growth curves in different treatment groups. Reprinted with the permission from Ref. 210. Copyright © 2021 Wiley. (H) Schematic diagram of the synthesis process of TPL@TFBF. (I) Fluorescence images of tumor-bearing mice *in vitro* after different treatments. The unit of fluorescence intensity is a.u. (J) The tumor growth curves of mice in different treatment groups. Reprinted with the permission from Ref. 212. Copyright © 2023 Springer Nature.

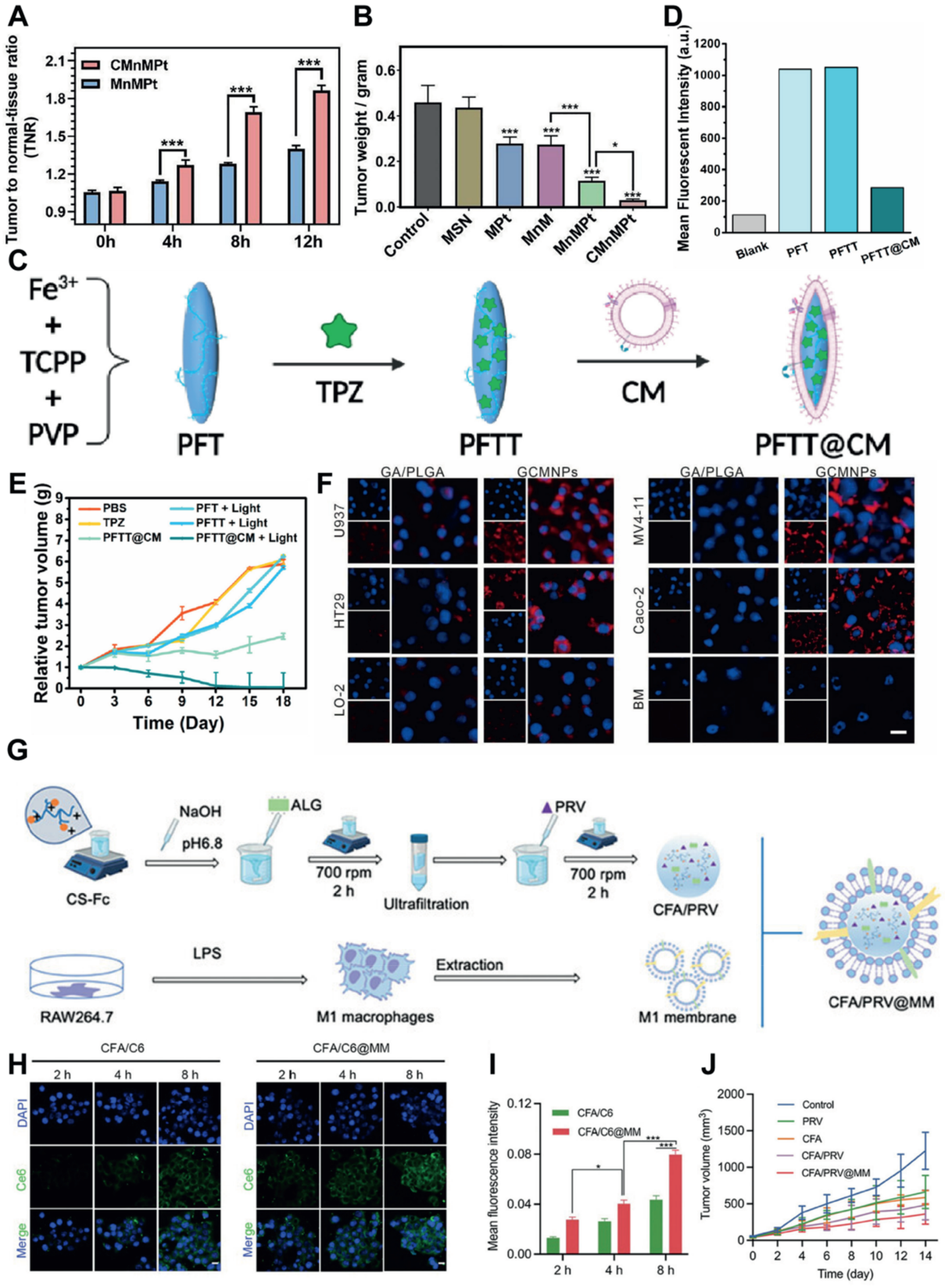


Figure 8 Cell membrane-modified delivery systems and their application in ferroptosis treatment. (A) The MRI signal of the tumor to normal-tissue ratio at 0, 4, 8 and 12 h after being treated with MnMPt or CMnMPt. (B) The weight of excised tumors in mice treated with Control, MSN, MPt, MnM, MnMPt or CMnMPt. Reprinted with the permission from Ref. 217. Copyright © 2023 Elsevier. (C) Synthesis of the tumor cell membrane-coated drug delivery system PFTT@CM. (D) Mean fluorescence intensity analysis of RAW 264.7 after incubating with PFT, PFTT,

nanoparticles (Fig. 8A) and the tumor inhibition also increased nearly 20% (Fig. 8B). In addition, evscaping the recognition and uptake by immune cells is also a key factor. Pan et al.[218] designed a drug delivery system (PFTT@CM), consisting of tiaprazine (TPZ), ferroptosis inducer PFT, and cancer cell membrane (Fig. 8C), and researched the uptake behavior of RAW 264.7 cells to the drug delivery system. The result suggested that the uptake rate of PFTT nanoparticles by RAW 264.7 cells was 3.69 times higher than PFTT@CM (Fig. 8D). With precise targeting, PFTT@CM completely suppressed tumor growth within 18 days (Fig. 8E).

Immune cells are a family of cells that are associated with the immune response, including macrophages, NK cells, leukocytes, neutrophils and others. A variety of receptors with different functions are distributed on the immune cell membrane, and these receptors provide specialized biological functions for immune cells. For example, CD47 and CD45 send out the "don't eat me" signal, while the chemokine receptor and Toll receptor have inflammatory chemotactic properties[219,220]. The inflammatory features of the tumor microenvironment provide a new insight for the application of immune cell membranes to target drug delivery. For example, Gao et al.[221] designed a macrophage membrane-encapsulated chlorella (M-Chl). The cell membrane could interact with the inflammatory factors of solid tumor tissues *via* the inflammatory cytokines-related receptors. This specific substrate recognition drives the targeted accumulation and retention of M-Chl in the tumor sites. Second, immune cell membranes inherit cell markers, such as adhesion molecules and chemokine receptors[220,222]. For bionic nanocarriers, these markers are involved in the recognition of tumors, contributing greatly to the successful delivery of drugs inside tumor cells. Li et al.[223] developed white cell membrane-encapsulated ferroptosis drug glycyrrhetinic acid (GA) nanoparticles (GCMNPs) for the treatment of leukemia and colorectal tumors. Compared to normal cells (LO-2) and bone marrow (BM) cells, GCMNPs exhibited intense red fluorescence in colorectal cancer and leukemia cells (Fig. 8F), demonstrating the ability of GCMNPs to selectively target tumor cells without affecting normal cells. Yang et al.[224] prepared a nanogel (chitosan-Fc polymer crosslink with sodium alginate to form CFA nanogels) for encapsulating the ferroptosis inducer pravastatin (PRV), then wrapped with macrophage membranes (MM) to form CFA/PRV@MM (Fig. 8G). In cellular uptake experiments, CFA/PRV@MM showed significantly higher fluorescence intensity than CFA/PRV (Fig. 8H and I). The enhanced cellular uptake could be attributed to MM-induced tumor accumulation and endocytosis. With the help of MM, CFA/PRV@MM demonstrated the superior tumor inhibition effect (Fig. 8J).

Although the cell membrane-based targeted drug delivery system has active targeting capacity, which improves the therapeutic effect. However, bio-nanotechnology is still in its infancy, faced with certain challenges in clinical application and industrialization. The limited membrane source is the first problem to be solved. The immune cells are limited-proliferation cells. Many cultured cells are still required to obtain cell membranes, which is unrealistic for industrialization. Second, isolation and purification are still a major challenge. For cancer cell membranes, the nucleus and genetic material should be strictly removed to eliminate potential carcinogenicity[225]. In addition, the expression of major histocompatibility complex (MHC) molecules on the membranes derived from immune cells brings immunogenicity issues[226]. All these issues will bring potential risks to the subsequent clinical application. Third, membrane separation is usually achieved by fragmentation and centrifugation, but the specific conditions have not been clearly demonstrated[227,228]. Further, we also need to define standard quality control criteria for cell membranes to ensure integrity without microorganisms. Otherwise, the quality and purity of the generated cell membranes cannot be guaranteed[226].

3.2.3. Perspectives of tumor targeted delivery

Compared to the traditional drug delivery route, the targeted drug delivery strategy significantly increases the drug deposition in tumor cells and greatly improves the drug delivery efficiency and therapeutic effect. Passive or active targeting strategies can promote the delivery of drugs to the tumor, which makes the antitumor effect and side effects of patients take a turn for the better. However, the targeted delivery technology is immature, and there are many existing issues that need to be solved. For example, there are limited FDA-approved targeting materials and a single method for evaluating targeting ability. In addition, the safety of the materials is an important factor that we need to evaluate. Apart from examining short-term toxicity, such as organ toxicity and routine blood analysis, the long-term toxicity of targeting materials is rarely systematically evaluated[229]. Finally, the human tumor tends to take a long time to develop compared to animal models. Therefore, the tumor and microenvironment are often more complex, which requires us to further evaluate the efficacy of the ferroptosis inducer.

3.3. Stimuli-responsive delivery strategy

In ferroptosis-immunotherapy, the targeting strategy of the drug delivery system elevates the effective concentration of the drug at the tumor site. However, controlled release strategies, playing a crucial role in ensuring drug safety and efficacy by preventing the premature release of ferroptosis inducers, are essential to minimize their toxicity to immune cells such as T cells and macrophages. Among these, stimuli-responsive delivery strategies have demonstrated unparalleled therapeutic function. The core objective of this controlled drug release is to precisely deliver drugs to the lesion area and precisely regulate the timing and dose of drug release through external or endogenous stimulation signals, thereby achieving the "on-off" control of drug release[230,231]. Through this strategy, it can effectively prevent the toxic side effects that might be induced by the release of large doses of drugs

and PFTT@CM, using RAW 264.7 without any treatment as a blank group. The unit of fluorescence intensity is a.u. (E) Tumor volume growth curves were presented in the different treatment groups. Reprinted with the permission from Ref. 218. Copyright © 2022 Elsevier. (F) Cellular uptake of GA/PLGA (left) and GCMNPs (right) in U937, MV4−11, HT29, Caco-2, LO-2 and BM cells after 30 min of incubation. The nucleus was stained with DAPI (blue). The GCMNPs were labeled with Nile red (red). Scale bar = 10 μm. Reprinted with the permission from Ref. 223. Copyright © 2022 Elsevier. (G) The preparation process of CFA/PRV@MM. (H) Time-dependent cellular uptake of CFA/C6 and CFA/C6@MM in 4T1 cells and (I) fluorescence semi-quantitative analysis of C6 signal. Scale bar in (H) = 10 μm. The unit of fluorescence intensity in (I) is a.u. (J) Average tumor growth curves after 14 days of different treatments. Reprinted with the permission from Ref. 224. Copyright © 2024 Wiley.

Table 4 Stimuli-responsive delivery system for ferroptosis-immunotherapy.

Stimuli-responsive delivery system		Advantage	Disadvantage	Ref.
Endogenous	pH-stimuli-responsive	Controlled release triggered by tumor acidity; Neutralizing the acidic environment	Tumor pH heterogeneity; Acid interference from inflammation or metabolic variations	233−235
	REDOX-stimuli-responsive	Disrupting the equilibrium of GSH and ROS; Enhancing ferroptosis efficiency	Limited specificity in tumors with normal redox levels; Complex synthesis of redox-sensitive linkers/carriers; Variable redox heterogeneity within tumors	236,237
	Enzyme-stimuli-responsive	High specificity; Rapid response by fast enzymatic catalysis	Unable to directly eliminate abnormal enzymes; Variability in enzyme activity across tumor types/individuals; Inflammation-triggered leakage	238
	Multi-stimuli-responsive	Synergistic release control; Adaptability to heterogeneity	Insufficient conditions within the TME; Design complexity; High validation costs	239
Exogenous	Light-stimuli-responsive	Synergistic therapeutic action with PTT/PDT; Remotely controlled activation	Risks of cutaneous injury during treatment; Toxicological risks from photosensitizers	240,241
	Ultrasound- stimuli-responsive	Synergistic therapeutic action with SDT; Deep tissue penetration	Device reliance; Tissue damage risks; Carrier stability demands	242,243

GSH, glutathione; TME, tumor microenvironment; PTT, photothermal therapy; PDT, photodynamic therapy; SDT, sonodynamic therapy.

within a short period, reduce the frequency of administration, and enhance patient compliance[232]. Such systems can respond to endogenous (such as low pH, high concentrations of ROS and GSH in the TME, specific overexpressed enzymes, etc.) or exogenous (such as light, ultrasound, etc.) stimuli to trigger the release of drugs, thereby achieving efficient treatment in the tumor area. Hence, based on the origin of response conditions, we will categorize them into endogenous stimulus-responsive delivery strategy and exogenous stimulus-responsive delivery strategy and introduce the characteristics of corresponding delivery systems and their application in ferroptosis-immunotherapy. Table 4[233-243] lists the advantages and disadvantages of each stimuli-responsive delivery system.

3.3.1. Endogenous stimuli-responsive delivery strategy

Compared to the physiological homeostasis of normal tissues, the TME exhibits significant pathological heterogeneity. These distinct pathological features provide a strategic opportunity for the design and development of tumor-stimuli drug delivery systems.

Endogenous stimuli-responsive delivery strategy facilitates precise drug delivery by exploiting the characteristics of the tumor-specific microenvironment[244]. These systems can be activated in response to the stimulation of specific tumor pathological markers and only exert a therapeutic effect in tumor tissue while remaining "inactive" in normal tissue, thereby ensuring biosafety[245]. Given that the specificity of the TME is closely associated with the occurrence and development of tumors, this strategy can not only alleviate the abnormal TME but also achieve the specific release of drugs, attaining the effect of "one stone, two birds" and significantly enhancing ferroptosis and immunotherapy. Based on the different abnormal characteristics of the TME, endogenous stimulus-responsive delivery systems can be classified into pH-stimuli-responsive, REDOX-stimuli-responsive, enzyme-stimuli-responsive and multi-stimuli-responsive drug delivery strategies. The following will focus on the features of the corresponding delivery systems and their application in ferroptosis and immunotherapy.

In solid tumors, in accordance with the Warburg effect, irrespective of the availability of oxygen, tumor cells have a greater propensity to undertake energy metabolism *via* anaerobic glycolysis, namely lactic acid metabolism, which leads to the accumulation of lactic acid[246]. Simultaneously, ion exchange proteins on the tumor cell membrane are constantly transporting H^+ from inside the cell to the exterior to prevent self-acidosis. Consequently, the TME assumes a weakly acidic state with a pH ranging from 6 to 7[247]. This acidic milieu can impact the activity of T cells, NK cells, and DCs, thereby suppressing immune function[248,249]. The slightly acidic environment of tumors can serve as an ideal stimulus for responsive drug delivery systems, which can enhance anti-tumor therapy by precisely controlling drug release. pH-sensitive chemical bonds, such as Schiff base bonds[250], hydrazone bonds [251,252], amido bonds[253], acetal bonds[254], ester bonds[255] and so on, can typically be incorporated into the material structure to construct acid-responsive carriers[256,257]. The Schiff base bond is formed through the nucleophilic addition reaction between aldehydes and amines. In an acidic environment, C═N will undergo protonation and become unstable, readily breaking, and thereby decomposing into the original carbonyl and amino groups[258]. Zhang et al.[75] employed the reaction between 1,3,5-benzenetricarboxaldehyde and *p*-phenylenediamine to polymerize a COF layer on the surface of MOF,

into which arachidonic acid (AA) was subsequently loaded. In the TME solution, the COF layer was gradually dissociated and AA was gradually released. The iron-based MOF converts H_2O_2 and O_2 into OH and O_2^- with a strong oxidizing capacity through the activity of peroxidase and natural oxidase, and possesses a strong GSH scavenging ability. The occurrence of ferroptosis promotes the immune response, and $CD8^+$T cells secrete IFN-γ, which further activates ACSL4 and promotes the phosphatidylation of AA, thereby exacerbating ferroptosis. After treatment, the survival rate of the breast cancer mice reached 100 percent within 50 days. In the design of pH-stimuli-responsive delivery systems, in addition to utilizing pH-sensitive chemical bonds, the intelligent regulation of "ionizable functional groups" has emerged as a crucial strategy. Functional groups such as amino[259], carboxyl[260], and sulfonic acid groups can undergo protonation/deprotonation, leading to charge reversal or hydrophilicity−hydrophobicity transitions, thereby precisely driving structural reconstruction of the carrier and controlled drug release[260]. Despite these, the imidazole group has garnered significant attention due to its unique protonation properties, enabling it to absorb protons under mildly acidic conditions (pH 6.0−6.5), thereby inducing a hydrophilicity−hydrophobicity transition[261]. Zuo et al.[210] fabricated a pH-sensitive nanoparticle FPBC@SN and loaded Sorafenib and IDO inhibitor NLG919 to inhibit breast cancer. In an acidic milieu, the benzimidazole within the nanoparticles can be protonated and subsequently transformed from hydrophobic to hydrophilic, leading to the disintegration of the nanoparticles. Sorafenib successfully upregulates the expression of nuclear receptor coactivator 4 to facilitate ferritin autophagy and promote the liberation of endogenous iron ions. Simultaneously, the application of NLG919 also effectively reduced the Kyn/Trp ratio and elicited a potent anti-tumor immune response. An increasing amount of evidence indicates that lactic acid in the TME can suppress anti-tumor immunity by impeding the function and metabolism of related immune cells, thereby playing a role in promoting tumor growth[233]. Therefore, the pH-stimuli-responsive delivery system can not only trigger drug release *via* H^+ protonation in the TME but also enhance the proliferation and activation of immune cells by neutralizing the acidic environment, thereby augmenting the efficacy of immunotherapy.

The REDOX-stimuli-responsive delivery system, designed to exploit the aberrant ROS and GSH levels in tumors, can achieve controlled drug delivery while disrupting this equilibrium. Within the TME, ROS (including superoxides and H_2O_2) and GSH exist at high concentrations, maintaining this balance[262]. Notably, TME H_2O_2 levels can reach ∼100 μmol/L-100-fold higher than in normal tissues, inducing oxidative DNA damage (*e.g.*, elevated 8-OHdG). Unrepaired damage contributes to malignant transformation[263]. While ROS promotes tumor development, it can also cause cellular damage. Consequently, tumor cells upregulate antioxidant systems like the GSH/GSSG pair. GSH, a major intracellular antioxidant, neutralizes ROS to protect tumor cells from oxidative stress and enhance survival[236]. Elevated GSH levels are further linked to increased cancer cell proliferation and resistance to apoptosis[237], allowing tumors to safeguard growth through ROS/GSH dynamics.

ROS-stimuli-responsive delivery systems can specifically react to ROS through changes in chemical structure or physical properties. Functional groups such as thioether[264,265], borate ester[266], and selenide[267] play a crucial role in these transformations, making such systems widely applicable in anti-tumor ferroptosis-immunotherapy. Ma et al.[266] utilized polyvinyl alcohol (PVA) as the gel matrix and incorporated TSPBA (borate ester bonds as crosslinker/ROS-sensor) to construct a hydrogel with ROS-stimuli−responsive properties (Fig. 9A and B). Loaded with Rhodamine B and FITC, it demonstrated H_2O_2−triggered sol−gel transition and drug release. After seven days, the cumulative release of Rhodamine B and FITC was approximately three times higher than that in PBS (Fig. 9C and D). In mouse models of breast cancer, the release of CuS nanoparticles loaded with iFSP1 inhibited GPX4 and FSP1 and enhanced LPO, thereby inducing ferroptosis (Fig. 9E). Simultaneously, hydrogel-loaded SSO blocked CD36 on immunosuppressive cells, remodeling the TME (Fig. 9F). This strategy promoted ferroptosis, DC maturation, and T-cell responses (Fig. 9G). The consumption of GSH is also an important strategy for enhancing ferroptosis-immunotherapy. The levels of GSH in tumor cells can reach 2−10 mol/L, approximately 100−1000 times that of the extracellular matrix (2−10 μmol/L) and 7−10 times that of normal tissue[268]. GSH is capable of reducing various metal-based nanomaterials, such as MnO_2 and MOFs, leading to the disintegration of the carrier structure and facilitating drug release. Furthermore, as a widely studied structural motif, disulfide bonds can be reduced to thiol groups under the action of GSH. Consequently, numerous disulfide-rich carriers have been designed for responsive drug delivery systems[269,270]. Dai et al.[271] developed a nanoreactor, ssPPELap@Fe-TA, where ssPPE is a polyphosphate ester containing disulfide bonds. This nanoreactor is capable of consuming GSH, leading to the inactivation of GPX4, and simultaneously triggering the rapid release of the loaded drug, β-lapachone. Experimental results demonstrate that, in mouse CT26 colon cancer cells, the levels of GSH and GPX4 significantly decreased following treatment. Furthermore, the therapeutic outcomes revealed that the proportion of DCs increased from 23.4% to 45.0%, and the IL-6 level was elevated by approximately 3.6-fold compared to the PBS control group. These findings highlight the promising potential of ssPPELap@Fe-TA in cancer therapy. REDOX−stimuli−responsive delivery systems sensitize ferroptosis by disrupting the equilibrium between ROS and GSH, thereby augmenting the efficacy of immunotherapy. Nevertheless, excessive REDOX reactions might result in unanticipated side effects, and this uncertainty could be a major challenge for future clinical transformation.

Enzyme-stimuli-responsive drug delivery systems are also commonly used in ferroptosis-immunotherapy. Studies have demonstrated that the pathology of the tumor is associated with the dysfunction or dysregulation of enzyme expression, matrix metalloproteinases (MMP)[272], hyaluronidase (HAase)[273], esterasem[19,274], oxidoreductase[275] and so on. Among these, the most typical is the overexpression of MMP, which can participate in numerous pathological processes related to tumor initiation, progression, invasion, and metastasis by modulating signal transduction[276]. Based on this characteristic, it is of considerable significance to utilize enzymes as a responsive point to design and develop an anti-tumor drug delivery system, which is conducive to the controlled release of drugs at the tumor site. Xu et al.[277] conjugated hemoglobin (Hb) with the photosensitizer Ce6 to construct a two-in-one nanoplatform loaded with Sorafenib (SRF@Hb-Ce6), and subsequently integrated amphiphilic MMP2-responsive peptide into the framework of the nanoplatform to guarantee drug-specific release. Under the influence of MMP, 70% of the drug could be released within 120 min (Fig. 9H and I). After laser irradiation at 150 mW/cm^2, the PDT generated by the photosensitizer enhanced ferroptosis by recruiting immune cells to

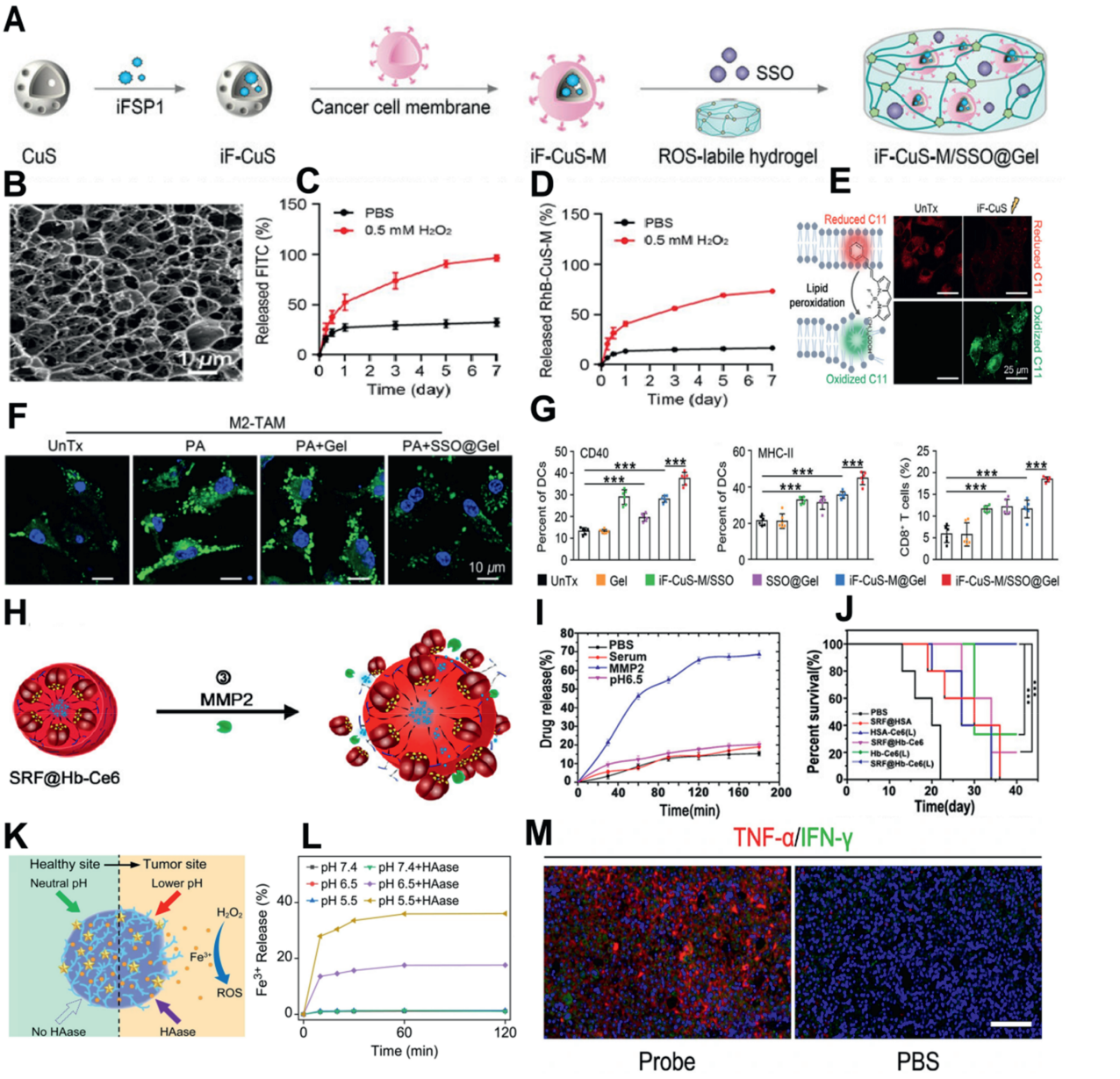


Figure 9 Endogenous stimuli-responsive delivery strategy and their application in ferroptosis-immunotherapy. (A) A scheme for the assembly of the ROS-stimuli-responsive composite hydrogel. (B) The cryo-SEM image of the composite hydrogel. Scale bar = 1 μm. Cumulative releasing curves of (C) FITC and (D) RhB-CuS-M from the composite hydrogel in the absence or presence of 0.5 mmol/L H_2O_2. (E) The LPO levels in 4T1 cells. Scale bar = 25 μm. (F) Fluorescence imaging of free fatty acid uptake by M2-TAMs in the absence or presence of SSO (300 μmol/L) from Hydrogel. Scale bar = 10 μm. (G) The ratios of $CD40^+$ cells, $MHC\text{-}II^+$ cells and $CD8^+$ T cells after different treatments. Reprinted with the permission from Ref. 266. Copyright © 2023 Wiley. (H) Schematic illustration showing the dissociation of Sorafenib@Hb-Ce6 under MMP2. (I) Drug release in different environments (PBS, serum, MMP2, pH 6.5). (J) Survival rates of mice in different treatment groups. Reprinted with the permission from Ref. 277. Copyright © 2020 American Chemical Society. (K) Schematic illustration of the dual-stimuli triggered peroxidase-like activity of FeIIITA@HA. (L) Fe^{3+} release kinetics of nanoprobes recorded under different conditions. (M) The TNF-α/IFN-γ staining images of the tumor slices after 10 days of treatment. Scale bar = 100 μm. Ref. 239. Copyright © 2023 Springer Nature.

secrete IFN-γ. The results indicated that Sorafenib@Hb-Ce6 exhibited an excellent therapeutic effect *in vivo*, and the survival rate of breast cancer mice reached 100% within 40 days (Fig. 9J). Although the activity and quantity of enzymes do not undergo significant alterations before and after catalysis, it appears that enzyme-stimuli-responsive delivery systems are unable to directly eliminate abnormal enzymes. Nevertheless, due to the high specificity of enzymes, such delivery systems can still effectively exploit the characteristics of enzymes to achieve precise drug release, thereby exerting a significant therapeutic effect. However, the species-specific differences in esterase activity (*e.g.*, between preclinical models and humans) lead to inconsistent therapeutic outcomes with identical formulations, posing a major translational challenge for advancing enzyme-responsive delivery systems[238].

Given that the physiological environment of healthy tissues is highly complex, this may result in the accidental activation of the

drug delivery system. For instance, acidic characteristics are not exclusive to the TME. The site of infection also possesses an acidic environment due to the accumulation of lactic acid, which might also trigger the release of active drugs and give rise to adverse toxicity[234,235]. By leveraging the multi-stimuli-responsive properties of certain materials or incorporating multiple materials, it is anticipated that the controlled drug release can be optimized. HA can not only bind to CD44 on the surface of cancer cells to exert a targeted effect, but also serve as a degradation site in response to stimulation by being degraded by hyaluronidase in the TME[278]. Zhang et al.[239] employed Fe^{3+}, TA and HA to design and fabricate a novel pH/HAase double-stimulated smart nanoprobe, FeIIITA@HA (Fig. 9K and L). The precise diagnosis and treatment of squamous cell carcinoma were achieved. At the tumor site, HA gradually undergoes degradation under the action of HAase. Subsequently, FeIIITA is internalized by tumor cells, and the acidic state of the cellular lysosome further triggers protonation, leading to the release of Fe^{3+} from the nanoprobe and triggering ferroptosis. The dual-stimuli-responsive delivery system enables a gradual release, significantly enhancing the specificity of tumor treatment (Fig. 9M).

A controlled release delivery strategy exploiting the characteristics of the TME can be employed to regulate the microenvironment, exert a certain therapeutic effect, and does not require reliance on external stimulation, thereby being more conducive to delivery. Nevertheless, the conditions within the microenvironment are insufficient, and the response is inadequate. Some stimuli-response conditions sometimes exhibit a non-specific distribution. Even with the use of multi-responsive delivery strategies, complete prevention of drug leakage cannot be guaranteed. Additionally, as the complexity of the carrier increases, the design and manufacturing challenges of the system also grow accordingly. Not only that, but due to the heterogeneity of the tumor, it is challenging to ensure the complete activation of the material at the tumor site, making the realization of precisely controlled release highly difficult. In preclinical research, it is necessary to simultaneously optimize the two response thresholds and the synergy effect.

3.3.2. Exogenous stimuli-responsive delivery strategy

In contrast to endogenous stimuli-responsive delivery, exogenous stimuli-responsive delivery requires external stimuli and responsive carriers. However, it offers advantages for precise tumor treatment, as it's non-invasive and controllable. This review will focus specifically on exogenous stimulus-responsive delivery strategies related to photothermal therapy (PTT), photodynamic therapy (PDT), and sonodynamic therapy (SDT). These three modalities utilize either light or ultrasound as external stimuli to enhance ferroptosis while concurrently activating antitumor immunity through the generation of photothermal effects or ROS. Detailed discussions of each approach will follow in subsequent sections.

Light is increasingly used in responsive drug delivery systems for tumor treatment. Given the spatiotemporal controllability of light, the light-stimuli-responsive drug delivery strategy exhibits higher selectivity and specificity in achieving on-demand drug release and activation[240]. Specific wavelengths of light (namely, ultraviolet, visible, and near-infrared) can modify the stability or structural degradation of responsive materials in light-stimuli-responsive drug delivery systems to release drugs at precise locations[279]. Besides the significant function of responsive drug release, light-responsive delivery systems are also closely associated with PTT and PDT. For PTT, materials with photothermal conversion capability can promote the ICD of cancer cells by generating high temperatures in the local tumor under the influence of light, which can significantly sensitize ferroptosis and immunotherapy. Chen et al.[241] developed MetaCell, a cellular Trojan horse, which utilizes living neutrophils to incorporate heat-sensitive liposomal bimetallic Fe-Cu-MOFs (Lip@Fe-Cu-MOFs). When the NIR laser stimulates the tumor area, a significant difference in inflammation is observed between the normal tissue and the tumor area. These differences facilitate the enhanced recruitment of MetaCell to the tumor site. Subsequently, Fe-Cu-MOFs, which possess significant photothermal conversion ability, can elevate the temperature and control the release of heat-sensitive liposomes for drug release. Experimental results indicate that Lip@Fe-Cu-MOF (500 μg/mL) can increase to ∼50 °C after 5 min of irradiation with 808 nm light (1.5 W/cm^2), and 44.36% of the drug can be released within 1 h. Not only that, but there are multiple options for the utilization of light, and a second type of near-infrared light (NIR-II) can be employed for this purpose. This is because it exhibits greater tissue penetration and lower phototoxicity in comparison to NIR-I[280]. For instance, Yue utilizes NIR-II to activate dual-enzyme modified semiconductor polymer nanopreparations (SPHGA) to achieve controlled ferroptosis/immunotherapy/PPT therapy[281]. Under 1064 nm laser irradiation, the nanoparticles undergo photothermal conversion and structural disruption, releasing a ferroptosis inducer, Hb and an immune adjuvant, adenosine deaminase, to precisely regulate tumor suppression. In a subcutaneous bilateral 4T1 breast cancer mouse model, the ability to completely suppress the tumor and prevent recurrence was demonstrated. For PDT, the photosensitizer needs to be activated under the light to generate ROS, which can not only enable responsive delivery but also sensitize ferroptosis. Besides directly exerting cytotoxicity on tumor cells, PDT also demonstrates immunomodulatory properties, inducing ICD[282]. Wang et al.[283] have developed a multifunctional nanoplatform (CMArg@Lip), where the hydrophilic NO donor Arg is enveloped in a ROS-stimuli-responsive liposome through a hydrophobic interaction, and the hydrophobic photosensitizer Ce6 and the NRF2 inhibitor ML385 are located within the lipid bilayer of the nanoplatform. Under 650 nm light stimulation, Ce6 generates ROS and induces liposome depolymerization, facilitating the release of encapsulated drugs. CMArg@Lip has exhibited potent anti-tumor effects by disrupting the powerful antioxidant capacity of cancer cells, promoting the ICD of cancer cells, and activating the STING pathway.

Ultrasound-stimuli-responsive delivery strategies are intimately associated with sonodynamic therapy (SDT)[284]. Likewise, SDT has demonstrated remarkable potential in inducing ICD and activating anti-tumor immunity[243]. Ding et al.[242] fabricated a semiconductor polymer nanotherapeutic agent (SPC_{Fe}/siP). SPC_{Fe}/siP integrates PD-L1 siRNA, ferroptosis-inducing Fe_3O_4 nanoparticles, and a semiconductor polymer sonosensitizer within a singlet oxygen ($^1O_2$)-cleavable nanosystem. After the injection of the nanomedicine and subsequent ultrasound irradiation, SPC_{Fe}/siP generates $^1O_2$ *via* the SDT effect of the semiconductor polymer, leading to precise and efficient liberation of Fe_3O_4 nanoparticles and PD-L1 siRNA from SPC_{Fe}/siP. This ultrasound-activated ferroptosis immunotherapy using SPC_{Fe}/siP effectively suppressed the growth of orthotopic glioma in mouse models.

Among the exogenous stimulus-responsive delivery strategies, the utilization of light sources for photoresponsive delivery systems is currently the most extensively developed. However, among

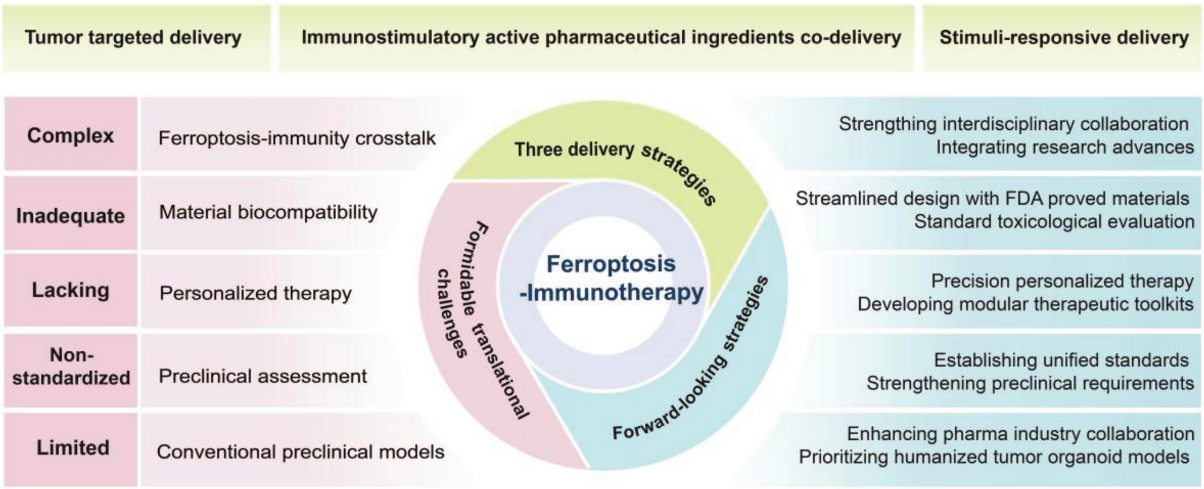


Figure 10 Conclusion and perspectives of ferroptosis-cancer immunotherapy. The upper section lists the three delivery strategies, the left section outlines the formidable challenges, and the right section presents the corresponding forward-looking strategies.

several distinct types of light, such as ultraviolet, visible, and near-infrared light, short and medium-wave ultraviolet (200−320 nm) tend to induce more severe skin damage[285]. A considerable number of studies have demonstrated that even UVA with a wavelength of 337 nm can also cause harm to DNA[279,286]. In contrast, near-infrared light exhibits more prominent advantages in related clinical applications and is more conducive to clinical transformation.

It is noteworthy that light/ultrasound-triggered drug release typically relies on metal-based sensitizers, which may pose potential biosafety risks[287]. For successful clinical translation, it is imperative to employ biocompatible materials or regulatory-approved sensitizers, such as FDA-certified ICG and iron oxide nanoparticles authorized for PTT in the European Union[288]. However, systems enabling stimulus-triggered release without added sensitizers simplify preparation, will enhance safety, and improve clinical potential. This aligns with approaches like light-triggered Fe^{2+} release from ferrihydrite below 480 nm. Yang et al.[289] employed visible blue light at 450 nm for the release of Fe^{2+}. Firstly, they fabricated PEG-coated ferrihydrite nanoparticles (PEG-Fns), which released 60−170 μmol/L Fe^{2+} within 90 min after blue light irradiation, significantly higher than the Fe^{2+} in normal cells (2.4 ± 0.4 μmol/L)[290]. Besides the release of Fe^{2+}, PEG-Fns possesses photofenton activity and is capable of generating ·OH under blue light irradiation. The formation of Fe^{2+} and ·OH initiates potent ferroptosis and PDT effects. The results of the *in vivo* study in mice demonstrated that this approach can induce the polarization of TAM from the tumor-promoting M2 type to the tumor-suppressing M1 type, and effectively alleviate lung metastasis. Therefore, the future direction should focus on developing light-responsive systems that do not require the introduction of photosensitizers.

Compared to conventional injections, both endogenous and exogenous stimulus-responsive delivery systems enable precise drug release control to prevent burst release effects and prolong plasma half-life. While externally stimulated therapies, including PTT, PDT, and SDT, enhance tumor inhibition, endogenous systems such as pH-responsive carriers reduce immunotoxicity *via* tumor microenvironment pH normalization and impair tumor progression through redox balance disruption, synergistically boosting antitumor responses. However, clinical translation remains challenged by tumor microenvironment heterogeneity, limiting release precision, alongside complex manufacturing scale-up, high quality-control expenses, and deficient regulatory frameworks.

3.4. *Combination strategy*

In this review, we categorize the delivery strategies for ferroptosis-immunotherapy into three functional modules: co-delivery strategies, targeting strategies and stimuli-responsive release strategies. Each of these strategies independently contributes to the enhancement of ferroptosis or immune activation, thereby improving antitumor efficacy. Importantly, rather than relying on a single approach, recent studies commonly favor the integration of multiple strategies to maximize therapeutic efficacy. For example, combining targeting strategies with co-delivery has been widely explored: cRGD-mediated tumor targeting has been integrated with the co-delivery of aPD-L1 to simultaneously enhance delivery efficiency and immune activation[88]. Similarly, biomimetic nanocarriers can serve dual roles by providing active targeting capabilities while functioning as ISAPIs themselves[217]. Moreover, stimuli-responsive strategies are often merged with co-delivery approaches; for instance, pH-sensitive nanocarriers have been developed to co-deliver NLG919, achieving precise release within the acidic tumor environment to boost immune responses[210]. However, it inevitably introduces greater complexity to the design and manufacturing processes, posing significant challenges for clinical translation.

4. Conclusions and perspectives

Ferroptosis-cancer immunotherapy shows remarkable advantages in cancer treatment. However, it is noteworthy that the crosstalk between ferroptosis and immunity is highly complex. Some studies have shown that ferroptosis in tumor cells may have negative effects on immune cells, such as excessive LPO, potentially impairing the function of DCs. Therefore, precise drug delivery strategies that can achieve ferroptosis-cancer

immunotherapy while mitigating immune damage have been developed: (1) Immunostimulatory active pharmaceutical ingredients co-delivery directly stimulates the immune system and enhances synergistic effects, thereby augmenting anti-tumor efficacy while mitigating the side effects of ferroptosis on the immune. (2) Tumor-targeted delivery systems selectively accumulate therapeutic agents in malignant cells while preserving immune cell viability. (3) Stimuli-responsive release strategies utilize TME-specific cues to achieve controlled release at the lesion site or incorporate auxiliary therapies (*e.g.*, photo-, thermo-, or sonotherapy) to amplify therapeutic effects. Thus, implementing precise and efficient delivery strategies to enhance ferroptosis in tumor cells while minimizing immune system damage is essential for improving the efficacy of ferroptosis-cancer immunotherapy.

However, formidable challenges persist during the transition from preclinical studies to clinical applications. In this section, we systematically analyze the underlying challenges hindering clinical translation and propose forward-looking strategies to overcome these obstacles (Fig. 10). (1) Complex mechanistic crosstalk between ferroptosis and antitumor immunity. It's widely believed that tumor cell ferroptosis, as ICD can activate APCs, subsequently initiating $CD8^+$T cell responses. Activated $CD8^+$ T cells can secrete IFN-γ that sensitizes ferroptosis through dual pathways. However, critical knowledge gaps persist: T cells exhibit heightened ferroptosis susceptibility due to absent p53 suppressors, and the dose-response relationship between T-cell infiltration depth and ferroptosis sensitivity remains unquantified[291]. Critically, LPO accumulating on ferroptotic tumor cell membranes lacks cellular selectivity and may directly damage neighboring immune cells, compromising antitumor immunity. Additionally, the specificity of ferroptosis inducers and their efficacy in distinct tumor subtypes requires further validation. Therefore, future efforts should focus on developing more inhibitors of reductive systems (*e.g.*, targeting the system Xc^-/GSH/GPX_4 axis) to reduce tumor ferroptosis resistance rather than directly enhancing LPO, integrating ISAPIs to directly potentiate immunity, simultaneously enhancing tumor-specific drug accumulation *via* targeting strategies, alongside achieving controlled release at the lesion site. Furthermore, interdisciplinary collaboration to integrate research advances across fields is essential, such as employing high-throughput screening to identify specific ferroptosis-inducing agents, leveraging single-cell sequencing and metabolomics to decode ferroptosis-immune crosstalk. (2) Biocompatibility concerns persist in ferroptosis-immunotherapy delivery systems. Although the three strategies enhance tumor-specific accumulation and spatiotemporal drug control, their complex material designs raise critical biosafety challenges. The core dilemma lies in the necessity for multi-functional modifications, such as targeting ligands, responsive linkers or photo/ultrasound-sensitive components, to achieve precise drug delivery. These modular additions may compromise biocompatibility through: (a) heterogeneous surface modifications destabilizing carriers, causing off-target organ accumulation; (b) interference with immune cell metabolic homeostasis; (c) insufficient toxicological analysis of multi-excipient formulations. Future investigations should focus on streamlined modular design with biocompatible materials with FDA-approved, incorporating systematic toxicology assessments of long-term biodistribution, immunogenicity, and metabolic stability. (3) The Lack of personalized therapeutic strategies targeting ferroptosis modulation with immunotherapy continues to limit synergistic efficacy in tumor treatment. Future research could propose a precision medicine framework that leverages patient-specific tumor genetic profiles and tumor microenvironment biomarkers, such as $CD8^+$ T-cell infiltration density and M2 macrophage prevalence to develop modular therapeutic toolkits, optimizing treatment regimens. (4) The development of standardized multidimensional evaluation frameworks for assessing therapeutic outcomes in oncology remains a formidable challenge. While the Response Evaluation Criteria in Solid Tumors (RECIST) provides an internationally recognized, quantitative framework for evaluating therapeutic efficacy in clinical trials, significant discrepancies exist in preclinical research due to inconsistent evaluation criteria across institutions and experimental designs. To address this limitation, future efforts should establish unified standards and protocols, strengthen preclinical quality requirements, foster interdisciplinary collaboration, and ensure scientific validity and practicality of strategies. (5) A persistent translational bottleneck also stems from the limited conventional preclinical models. Drug candidates demonstrating efficacy in rodent models frequently exhibit suboptimal therapeutic outcomes during clinical translation phases due to interspecies disparities in drug metabolism and tumor microenvironmental dynamics. To bridge this preclinical-clinical divide, next-generation model systems—such as humanized tumor organoid models-must be prioritized to enhance clinical correlation. Harness cutting-edge technologies to improve data quality, leveraging big data and AI for real-time monitoring and analysis of treatment responses to optimize therapeutic strategies. Foster interdisciplinary collaboration and deepen research through partnerships across the pharma industry.

Acknowledgments

This work was supported by National Natural Science Foundation of China (No. 82073774), Science and Technology Projects in Guangzhou (No. 202102070001), Jinan University Scientific and Technological Association Youth Science and Technology Talent Cultivation Program (No. 21624223, China), "Master Mentor Plan" of Jinan University (No. YDXS2406), the Outstanding Innovative Talents Cultivation Funded Programs for Doctoral Students of Jinan University (No. 2024CXB026, China) and Special Funds for the Cultivation of Guangdong College Students' Scientific and Technological Innovation ("Climbing Program" Special Funds) (No. pdjh2025bk037, China).

Author contributions

Lu Gan, Xincheng Lin and Ziqiao Zhong: Writing − original draft. Yichun Zheng, Xinyi Chen and Jun Chen: Visualization. Xiao Yue and Yingshan Liu revised the manuscript. Wenhao Wang, Ying Huang, Xin Pan and Chuanbin Wu: Writing − review & editing, Supervision, Conceptualization. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov* 2022;**12**:31−46.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209−49.
3. Yang Z, Gao D, Zhao J, Yang GJ, Guo M, Wang Y, et al. Thermal immuno-nanomedicine in cancer. *Nat Rev Clin Oncol* 2023;**20**: 116−34.
4. Qin S, Xu LP, Yi M, Yu SN, Wu KM, Luo SX. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. *Mol Cancer* 2019;**18**:1−14.
5. Nishinakamura H, Shinya S, Irie T, Sakihama S, Naito T, Watanabe K, et al. Coactivation of innate immune suppressive cells induces acquired resistance against combined TLR agonism and PD-1 blockade. *Sci Transl Med* 2025;**17**:eadk3160.
6. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science* 2018;**359**:1361−5.
7. Shigemori K. *Radiation-induced inflammatory responses in carcinogenesis and cardiac disease*. Oxford (United Kingdom): University of; 2022.
8. Li R, Hao YH, Pan W, Wang W, Min YZ. Monophosphoryl lipid A-assembled nanovaccines enhance tumor immunotherapy. *Acta Biomater* 2023;**171**:482−94.
9. Wang SX, He ZK, Wang X, Li HM, Liu XS. Antigen presentation and tumor immunogenicity in cancer immunotherapy response prediction. *eLife* 2019;**8**:e49020.
10. Diaz LA, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab *versus* chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* 2022;**23**:659−70.
11. Kumagai S, Koyama S, Nishikawa H. Antitumour immunity regulated by aberrant ERBB family signalling. *Nat Rev Cancer* 2021;**21**: 181−97.
12. Yang ZJ, Zhu YJ, Dong ZL, Li W, Yang NL, Wang XW, et al. Tumor-killing nanoreactors fueled by tumor debris can enhance radiofrequency ablation therapy and boost antitumor immune responses. *Nat Commun* 2021;**12**:4299.
13. Fang L, Zhao ZT, Wang J, Zhang PC, Ding YP, Jiang YY, et al. Engineering autologous tumor cell vaccine to locally mobilize antitumor immunity in tumor surgical bed. *Sci Adv* 2020;**6**: eaba4024.
14. Freitas-Cortez MA, Masrorpour F, Jiang H, Mahmud I, Lu Y, Huang A, et al. Cancer cells avoid ferroptosis induced by immune cells *via* fatty acid binding proteins. *Mol Cancer* 2025;**24**:40.
15. Zhang XY, Ge HY, Ma YL, Song LL, Ma YS, Tian GL, et al. Engineered anti-cancer nanomedicine for synergistic ferroptosis-immunotherapy. *Chem Eng J* 2023;**455**:140688.
16. Chung CH, Lin CY, Chen CY, Hsueh CW, Chang YW, Wang CC, et al. Ferroptosis signature shapes the immune profiles to enhance the response to immune checkpoint inhibitors in head and neck cancer. *Adv Sci* 2023;**10**:2204514.
17. Feng QS, Qi FG, Fang WM, Hu P, Shi JL. Ferroptosis to pyroptosis regulation by iron-based nanocatalysts for enhanced tumor immunotherapy. *J Am Chem Soc* 2024;**146**:32403−14.
18. Zheng SY, Guan XY. Ferroptosis: promising approach for cancer and cancer immunotherapy. *Cancer Lett* 2023;**561**:216152.
19. Dai XM, Zhang J, Bao XW, Guo YX, Jin YZ, Yang CJ, et al. Induction of tumor ferroptosis-dependent immunity *via* an injectable attractive pickering emulsion gel. *Adv Mater* 2023;**35**:2303542.
20. Zhang QP, Sun TT, Yu F, Liu W, Gao J, Chen JY, et al. PAFAH2 suppresses synchronized ferroptosis to ameliorate acute kidney injury. *Nat Chem Biol* 2024;**20**:835−46.
21. Zhou R, Liu YT, Wang ZJ, Lv JY, Liao WJ, Shen ZY, et al. Nanoparticle-based MRI-guided tumor microenvironment heating *via* the synergistic effect of ferroptosis and inhibition of TGF-β signaling. *Adv Healthcare Mater* 2023;**12**:2300176.
22. Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, et al. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. *Nature* 2017;**551**:247−50.
23. Roh JL, Kim EH, Jang H, Shin D. Nrf2 inhibition reverses the resistance of cisplatin-resistant head and neck cancer cells to artesunate-induced ferroptosis. *Redox Biol* 2017;**11**:254−62.
24. Mishima E, Nakamura T, Zheng J, Zhang W, Mourão ASD, Sennhenn P, et al. DHODH inhibitors sensitize to ferroptosis by FSP1 inhibition. *Nature* 2023;**619**:E9−18.
25. Gu YL, Li YZ, Wang JX, Zhang LL, Zhang JF, Wang YX. Targeting ferroptosis: paving new roads for drug design and discovery. *Eur J Med Chem* 2023;**247**:115015.
26. Liao P, Wang WM, Wang WC, Kryczek I, Li X, Bian YJ, et al. $CD8^+$ T cells and fatty acids orchestrate tumor ferroptosis and immunity *via* ACSL4. *Cancer Cell* 2022;**40**:365-78.e6.
27. Zheng YC, Sun LQ, Guo JM, Ma J. The crosstalk between ferroptosis and anti-tumor immunity in the tumor microenvironment: molecular mechanisms and therapeutic controversy. *Cancer Commun* 2023;**43**:1071−96.
28. Ping Y, Shan JQ, Qin HM, Li F, Qu J, Guo R, et al. PD-1 signaling limits expression of phospholipid phosphatase 1 and promotes intratumoral $CD8^+$ T cell ferroptosis. *Immunity* 2024;**57**:2122−39.e9.
29. Luo YL, Bai XY, Zhang L, Hu QQ, Zhang N, Cheng JZ, et al. Ferroptosis in cancer therapy: mechanisms, small molecule inducers, and novel approaches. *Drug Des Dev Ther* 2024;**18**:2485−529.
30. Wu MM, Zhang X, Zhang WJ, Chiou YS, Qian WC, Liu XT, et al. Cancer stem cell regulated phenotypic plasticity protects metastasized cancer cells from ferroptosis. *Nat Commun* 2022;**13**:1371.
31. Liang C, Zhang XL, Yang MS, Dong XC. Recent progress in ferroptosis inducers for cancer therapy. *Adv Mater* 2019;**31**:1904197.
32. Lei G, Zhuang L, Gan BY. The roles of ferroptosis in cancer: tumor suppression, tumor microenvironment, and therapeutic interventions. *Cancer Cell* 2024;**42**:513−34.
33. Efimova I, Catanzaro E, Van der Meeren L, Turubanova VD, Hammad H, Mishchenko TA, et al. Vaccination with early ferroptotic cancer cells induces efficient antitumor immunity. *J Immunother Cancer* 2020;**8**:e001369.
34. Wiernicki B, Maschalidi S, Pinney J, Adjemian S, Vanden Berghe T, Ravichandran KS, et al. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor immunity. *Nat Commun* 2022;**13**: 3676.
35. Wang WM, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, et al. $CD8^+$ T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* 2019;**569**:270−4.
36. Conche C, Finkelmeier F, Pešić M, Nicolas AM, Böttger TW, Kennel KB, et al. Combining ferroptosis induction with MDSC blockade renders primary tumours and metastases in liver sensitive to immune checkpoint blockade. *Gut* 2023;**72**:1774−82.
37. Hou W, Xie YC, Song XX, Sun XF, Lotze MT, Zeh IIIHJ, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy* 2016;**12**:1425−8.
38. Little JL, Wheeler FB, Fels DR, Koumenis C, Kridel SJ. Inhibition of fatty acid synthase induces endoplasmic reticulum stress in tumor cells. *Cancer Res* 2007;**67**:1262−9.
39. Dierge E, Debock E, Guilbaud C, Corbet C, Mignolet E, Mignard L, et al. Peroxidation of *n*-3 and *n*-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. *Cell Metab* 2021;**33**:1701-15.e5.
40. Lamperis SM, McMahon KM, Calvert AE, Rink JS, Vasan K, Pandkar MR, et al. CRISPR screen reveals a simultaneous targeted mechanism to reduce cancer cell selenium and increase lipid oxidation to induce ferroptosis. *Proc Natl Acad Sci U S A* 2025;**122**: e2502876122.
41. Su YW, Zhao B, Zhou LF, Zhang ZY, Shen Y, Lv HH, et al. Ferroptosis, a novel pharmacological mechanism of anti-cancer drugs. *Cancer Lett* 2020;**483**:127−36.

42. Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu HR, Brown LM, et al. Imidazole ketone erastin induces ferroptosis and slows tumor growth in a mouse lymphoma model. *Cell Chem Biol* 2019;**26**:623−33.e9.
43. Montesdeoca N, Johannknecht L, Efanova E, Heinen-Weiler J, Karges J. Ferroptosis inducing Co(III) polypyridine sulfasalazine complex for therapeutically enhanced anticancer therapy. *Angew Chem Int Ed* 2024;**63**:e202412585.
44. Tang QQ, Wang YY, Yan B, Zhang J, Wang T, Fang Y, et al. Intracellular magnetic hyperthermia sensitizes sorafenib to orthotopic hepatocellular carcinoma *via* amplified ferroptosis. *ACS Nano* 2024;**18**:29804−19.
45. Zhang Y, Luo MY, Cui XH, O'Connell D, Yang YF. Long noncoding RNA NEAT1 promotes ferroptosis by modulating the miR-362-3p/MIOX axis as a ceRNA. *Cell Death Differ* 2022;**29**:1850−63.
46. Luo TL, Zheng QZ, Shao LH, Ma TY, Mao LQ, Wang M. Intracellular delivery of glutathione peroxidase degrader induces ferroptosis *in vivo*. *Angew Chem Int Ed* 2022;**134**:e202206277.
47. Akiyama H, Zhao R, Rahhal A, Nishida Y, Ayoub E, Ostermann LB, et al. Therapeutic targeting of ferroptosis pathway in combination with mitochondrial oxidative stress induction in acute myeloid leukemia. *Blood* 2021;**138**:1162.
48. Miao HX, Meng HY, Zhang YS, Chen T, Zhang L, Cheng WJ. FSP1 inhibition enhances olaparib sensitivity in BRCA-proficient ovarian cancer patients *via* a nonferroptosis mechanism. *Cell Death Differ* 2024;**31**:497−510.
49. Tang L, Cao YQ, Yin Y, Liu HN, Feng JW, Fu C, et al. Dual-targeting nanozyme combined with aPD-L1-based immunotherapy for combating cancer recurrence and metastasis. *Mater Today* 2024;**73**: 79−95.
50. Faust D, Wenz C, Holm S, Harms G, Greffrath W, Dietrich C. Cell−cell contacts prevent t-BuOOH-triggered ferroptosis and cellular damage *in vitro* by regulation of intracellular calcium. *Arch Toxicol* 2024;**98**:2953−69.
51. Meng CT, Li SJ, Ma YN, Yu HW, Song JQ, Zhi JC, et al. Assembling ruthenium complexes to form ruthenosome unleashing ferritinophagy-mediated tumor suppression. *ACS Nano* 2025;**19**: 10207−19.
52. Kudarha R, Dhas N, Mutalik S. Distinct features of iron based metal organic frameworks (MOFs) for ferroptosis mediated cancer therapy: a comprehensive review. *Coord Chem Rev* 2023;**494**:215330.
53. Bae C, Hernández Millares R, Ryu S, Moon H, Kim D, Lee G, et al. Synergistic effect of ferroptosis-inducing nanoparticles and x-ray irradiation combination therapy. *Small* 2024;**20**:2310873.
54. Li K, Lin CC, Li MH, Xu K, He Y, Mao YL, et al. Multienzyme-like reactivity cooperatively impairs glutathione peroxidase 4 and ferroptosis suppressor protein 1 pathways in triple-negative breast cancer for sensitized ferroptosis therapy. *ACS Nano* 2022;**16**: 2381−98.
55. Du YQ, Zhang R, Yang JN, Liu SK, Zhou JL, Zhao RX, et al. A "closed-loop" therapeutic strategy based on mutually reinforced ferroptosis and immunotherapy. *Adv Funct Mater* 2022;**32**:2111784.
56. Lei P, Walker T, Ayton S. Neuroferroptosis in health and diseases. *Nat Rev Neurosci* 2025;**26**:1−15.
57. Li J, Cao F, Yin Hl, Huang Zj, Lin Zt, Mao N, et al. Ferroptosis: past, present and future. *Cell Death Dis* 2020;**11**:88.
58. Pope LE, Dixon SJ. Regulation of ferroptosis by lipid metabolism. *Trends Cell Biol* 2023;**33**:1077−87.
59. Dixon SJ, Olzmann JA. The cell biology of ferroptosis. *Nat Rev Mol Cell Biol* 2024;**25**:424−42.
60. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018;**24**:541−50.
61. De Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. *Cancer Cell* 2023;**41**: 374−403.
62. Yu B, Choi B, Li WG, Kim DH. Magnetic field boosted ferroptosis-like cell death and responsive MRI using hybrid vesicles for cancer immunotherapy. *Nat Commun* 2020;**11**:3637.
63. Luo X, Gong HB, Gao HY, Wu YP, Sun WY, Li ZQ, et al. Oxygenated phosphatidylethanolamine navigates phagocytosis of ferroptotic cells by interacting with TLR2. *Cell Death Differ* 2021; **28**:1971−89.
64. Wen QR, Liu J, Kang R, Zhou BR, Tang DL. The release and activity of HMGB1 in ferroptosis. *Biochem Biophys Res Commun* 2019;**510**: 278−83.
65. Ye FH, Chai WW, Xie M, Yang MH, Yu Y, Cao LZ, et al. HMGB1 regulates erastin-induced ferroptosis *via* RAS−JNK/p38 signaling in HL-60/NRASQ61L cells. *Am J Cancer Res* 2019;**9**:730.
66. Rothe T, Gruber F, Uderhardt S, Ipseiz N, Rössner S, Oskolkova O, et al. 12/15-lipoxygenase-mediated enzymatic lipid oxidation regulates DC maturation and function. *J Clin Investig* 2015;**125**:1944−54.
67. Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, et al. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015;**161**: 1527−38.
68. Aqbi HF, Wallace M, Sappal S, Payne KK, Manjili MH. IFN-γ orchestrates tumor elimination, tumor dormancy, tumor escape, and progression. *J Leukoc Biol* 2018;**103**:1219−23.
69. Xia YQ, Rao L, Yao HM, Wang ZL, Ning PB, Chen XY. Engineering macrophages for cancer immunotherapy and drug delivery. *Adv Mater* 2020;**32**:2002054.
70. Kapralov AA, Yang Q, Dar HH, Tyurina YY, Anthonymuthu TS, Kim R, et al. Redox lipid reprogramming commands susceptibility of macrophages and microglia to ferroptotic death. *Nat Chem Biol* 2020;**16**:278−90.
71. Dar HH, Anthonymuthu TS, Ponomareva LA, Souryavong AB, Shurin GV, Kapralov AO, et al. A new thiol-independent mechanism of epithelial host defense against Pseudomonas aeruginosa: inos/no· sabotage of theft-ferroptosis. *Redox Biol* 2021;**45**:102045.
72. Mikulska-Ruminska K, Anthonymuthu TS, Levkina A, Shrivastava IH, Kapralov AA, Bayır H, et al. NO· represses the oxygenation of arachidonoyl PE by 15LOX/PEBP1: mechanism and role in ferroptosis. *Int J Mol Sci* 2021;**22**:5253.
73. Li HY, Yang PH, Wang JH, Zhang J, Ma QY, Jiang YJ, et al. HLF regulates ferroptosis, development and chemoresistance of triple-negative breast cancer by activating tumor cell-macrophage crosstalk. *J Hematol Oncol* 2022;**15**:2.
74. Yee PP, Wei Y, Kim S-Y, Lu T, Chih SY, Lawson C, et al. Neutrophil-induced ferroptosis promotes tumor necrosis in glioblastoma progression. *Nat Commun* 2020;**11**:5424.
75. Zhang H, Cao Y, Li WY, Zhang SP, Song SY, Wang YH, et al. Ferroptosis-induced immunomodulation with biometabolic MOF@ COF nanovaccine for self-boosting anti-tumor immunotherapy. *Chem Eng J* 2024;**493**:152675.
76. Xu QB, Zhan GT, Zhang ZL, Yong TY, Yang XL, Gan L. Manganese porphyrin-based metal-organic framework for synergistic sonodynamic therapy and ferroptosis in hypoxic tumors. *Theranostics* 2021;**11**:1937.
77. Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. *Immunity* 2010;**33**:492−503.
78. Dhanak D, Edwards JP, Nguyen A, Tummino PJ. Small-molecule targets in immuno-oncology. *Cell Chem Biol* 2017;**24**:1148−60.
79. Pham T, Roth S, Kong J, Guerra G, Narasimhan V, Pereira L, et al. An update on immunotherapy for solid tumors: a review. *Ann Surg Oncol* 2018;**25**:3404−12.
80. Kaur A, Baldwin J, Brar D, Salunke DB, Petrovsky N. Toll-like receptor (TLR) agonists as a driving force behind next-generation vaccine adjuvants and cancer therapeutics. *Curr Opin Chem Biol* 2022;**70**:102172.
81. Hendry S, Byrne DJ, Wright GM, Young RJ, Sturrock S, Cooper WA, et al. Comparison of four PD-L1 immunohistochemical assays in lung cancer. *J Thorac Oncol* 2018;**13**:367−76.
82. Shou MY, Zhou HY, Ma L. New advances in cancer therapy targeting TGF-β signaling pathways. *Mol Ther Oncolytics* 2023;**31**:100755.
83. Batista-Duharte A, Portuondo D, Perez O, Carlos IZ. Systemic immunotoxicity reactions induced by adjuvanted vaccines. *Int Immunopharmacol* 2014;**20**:170−80.

84. Lynn GM, Laga R, Darrah PA, Ishizuka AS, Balaci AJ, Dulcey AE, et al. *In vivo* characterization of the physicochemical properties of polymer-linked TLR agonists that enhance vaccine immunogenicity. *Nat Biotechnol* 2015;**33**:1201−10.
85. Tomai MA, Vasilakos JP. TLR-7 and-8 agonists as vaccine adjuvants. *Expert Rev Vaccines* 2011;**10**:405−7.
86. Bachmann MF, Jennings GT. Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns. *Nat Rev Immunol* 2010; **10**:787−96.
87. Roth GA, Picece VC, Ou BS, Luo W, Pulendran B, Appel EA. Designing spatial and temporal control of vaccine responses. *Nat Rev Mater* 2022;**7**:174−95.
88. Cheng Z, Xue CC, Liu MH, Cheng ZM, Tian G, Li MH, et al. Injectable microenvironment-responsive hydrogels with redox-activatable supramolecular prodrugs mediate ferroptosis-immunotherapy for postoperative tumor treatment. *Acta Biomater* 2023;**169**:289−305.
89. Nie TQ, Liu HY, Fang ZW, Zheng YL, Zhang RH, Xu XJ, et al. Tumor microenvironment mediated spermidine-metal-immunopeptide nanocomplex for boosting ferroptotic immunotherapy of lymphoma. *ACS Nano* 2023;**17**:10925−37.
90. Shen JJ, Feng K, Yu J, Zhao YX, Chen RF, Xiong HH, et al. Responsive and traceless assembly of iron nanoparticles and 131I labeled radiopharmaceuticals for ferroptosis enhanced radio-immunotherapy. *Biomaterials* 2025;**313**:122795.
91. He ZJ, Zhou H, Zhang Y, Du XY, Liu SJ, Ji JB, et al. Oxygen-boosted biomimetic nanoplatform for synergetic photo-therapy/ferroptosis activation and reversal of immune-suppressed tumor microenvironment. *Biomaterials* 2022;**290**:121832.
92. Wang ZC, Tang YQ, Li Q. A self-assembling nanoplatform for pyroptosis and ferroptosis enhanced cancer photoimmunotherapy. *Light Sci Appl* 2025;**14**:16.
93. Huang P, Yang Y, Wang WY, Li ZM, Gao NS, Chen HJ, et al. Self-driven nanoprodrug platform with enhanced ferroptosis for synergistic photothermal-IDO immunotherapy. *Biomaterials* 2023;**299**: 122157.
94. Li LG, Yang XX, Xu HZ, Yu TT, Li QR, Hu J, et al. A dihydroartemisinin-loaded nanoreactor motivates anti-cancer immunotherapy by synergy-induced ferroptosis to activate cGAS/STING for reprogramming of macrophage. *Adv Healthcare Mater* 2023;**12**:2301561.
95. Hu HL, Zheng ST, He CX, Zheng YF, Wei QM, Chen SW, et al. Radiotherapy-sensitized cancer immunotherapy *via* cGAS−STING immune pathway by activatable nanocascade reaction. *J Nanobiotechnol* 2024;**22**:234.
96. Fan ZJ, Wu SC, Deng HP, Li GL, Huang LH, Liu HX. Light-triggered nanozymes remodel the tumor hypoxic and immunosuppressive microenvironment for ferroptosis-enhanced antitumor immunity. *ACS Nano* 2024;**18**:12261−75.
97. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. *Cell* 2021; **184**:5309−37.
98. Hurov K, Lahdenranta J, Upadhyaya P, Haines E, Cohen H, Repash E, et al. BT7480, a novel fully synthetic bicycle tumor-targeted immune cell agonist™ (Bicycle TICA™) induces tumor localized CD137 agonism. *J Immunother Cancer* 2021;**9**:e002883.
99. Fang J, Chen F, Liu D, Gu FY, Chen ZG, Wang YJ. Prognostic value of immune checkpoint molecules in breast cancer. *Biosci Rep* 2020; **40**:BSR20201054.
100. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;**12**:252−64.
101. Zhang XW, Schwartz J-CD, Guo XL, Bhatia S, Cao EH, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity* 2004;**20**:337−47.
102. Han YY, Liu DD, Li LH. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* 2020;**10**:727.
103. Azuma M, Ito D, Yagita H, Okumura K, Phillips JH, Lanier LL, et al. B70 antigen is a second ligand for CTLA-4 and CD28. *Nature* 1993; **366**:76−9.
104. Yamaguchi H, Hsu JM, Sun LL, Wang SC, Hung MC. Advances and prospects of biomarkers for immune checkpoint inhibitors. *Cell Rep Med* 2024;**5**:101621.
105. Zhang H, Dai ZY, Wu WT, Wang ZY, Zhang N, Zhang LY, et al. Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer. *J Exp Clin Cancer Res* 2021;**40**:184.
106. Minor M, Alcedo KP, Battaglia RA, Snider NT. Cell type-and tissue-specific functions of ecto-5′-nucleotidase (CD73). *Am J Physiol Cell Physiol* 2019;**317**:C1079−92.
107. Xu Y, Liu D, Zhang WZ, Liu ZN, Liu JJ, Zhang WL, et al. Discovery of novel 5-(pyridazin-3-yl) pyrimidine-2,4(1*H*,3*H*)-dione derivatives as potent and orally bioavailable inhibitors targeting ecto-5′-nucleotidase. *J Med Chem* 2024;**67**:18491−511.
108. Vijayan D, Young A, Teng MW, Smyth MJ. Targeting immunosuppressive adenosine in cancer. *Nat Rev Cancer* 2017;**17**:709−24.
109. Yu M, Guo G, Huang L, Deng LB, Chang CS, Achyut BR, et al. CD73 on cancer-associated fibroblasts enhanced by the A2B-mediated feedforward circuit enforces an immune checkpoint. *Nat Commun* 2020;**11**:515.
110. Zaiatz-Bittencourt V, Finlay DK, Gardiner CM. Canonical TGF-β signaling pathway represses human NK cell metabolism. *J Immunol* 2018;**200**:3934−41.
111. Brandes ME, Mai U, Ohura K, Wahl SM. Type I transforming growth factor-beta receptors on neutrophils mediate chemotaxis to transforming growth factor-beta. *J Immunol* 1991;**147**:1600−6.
112. Kulkarni AB, Huh C-G, Becker D, Geiser A, Lyght M, Flanders KC, et al. Transforming growth factor beta 1 null mutation in mice causes excessive inflammatory response and early death. *Proc Natl Acad Sci U S A* 1993;**90**:770−4.
113. Gorelik L, Flavell RA. Immune-mediated eradication of tumors through the blockade of transforming growth factor-β signaling in T cells. *Nat Med* 2001;**7**:1118−22.
114. Wu TQ, Wang WF, Shi GH, Hao MG, Wang YY, Yao MF, et al. Targeting HIC1/TGF-β axis-shaped prostate cancer microenvironment restrains its progression. *Cell Death Dis* 2022;**13**:624.
115. Willingham SB, Volkmer J-P, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, et al. The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors. *Proc Natl Acad Sci U S A* 2012;**109**:6662−7.
116. Chao MP, Alizadeh AA, Tang C, Myklebust JH, Varghese B, Gill S, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate Non-Hodgkin lymphoma. *Cell* 2010;**142**: 699−713.
117. Richter WF, Bhansali SG, Morris ME. Mechanistic determinants of biotherapeutics absorption following SC administration. *AAPS J* 2012;**14**:559−70.
118. Frokjaer S, Otzen DE. Protein drug stability: a formulation challenge. *Nat Rev Drug Discov* 2005;**4**:298−306.
119. Wang DG, Wang TT, Yu HJ, Feng B, Zhou L, Zhou FY, et al. Engineering nanoparticles to locally activate T cells in the tumor microenvironment. *Sci Immunol* 2019;**4**:eaau6584.
120. Yu Y, Lau LCM, Lo AC-y, Chau Y. Injectable chemically crosslinked hydrogel for the controlled release of bevacizumab in vitreous: a 6-month *in vivo* study. *Transl Vis Sci Technol* 2015;**4**:5.
121. Hanagata N. Structure-dependent immunostimulatory effect of CpG oligodeoxynucleotides and their delivery system. *Int J Nanomed* 2012;**7**:2181−95.
122. Ngamcherdtrakul W, Reda M, Nelson MA, Wang R, Zaidan HY, Bejan DS, et al. In situ tumor vaccination with nanoparticle co-delivering CpG and STAT3 siRNA to effectively induce whole-body antitumor immune response. *Adv Mater* 2021;**33**:2100628.
123. Dai J, Wu M, Wang Q, Ding SY, Dong XQ, Xue LR, et al. Red blood cell membrane-camouflaged nanoparticles loaded with AIEgen and Poly (I:C) for enhanced tumoral photodynamic-immunotherapy. *Natl Sci Rev* 2021;**8**:nwab039.
124. Dauletbaev N, Cammisano M, Herscovitch K, Lands LC. Stimulation of the RIG-I/MAVS pathway by polyinosinic: polycytidylic acid

upregulates IFN-β in airway epithelial cells with minimal costimulation of IL-8. *J Immunol* 2015;**195**:2829−41.
125. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-κB by toll-like receptor 3. *Nature* 2001;**413**:732−8.
126. Wei JJ, Wu D, Zhao SS, Shao Y, Xia YF, Ni DW, et al. Immunotherapy of malignant glioma by noninvasive administration of TLR9 agonist CpG nano-immunoadjuvant. *Adv Sci* 2022;**9**:2103689.
127. Yi YF, Yu M, Feng C, Hao HS, Zeng WW, Lin CC, et al. Transforming "cold" tumors into "hot" ones *via* tumor-microenvironment-responsive siRNA micelleplexes for enhanced immunotherapy. *Matter* 2022;**5**:2285−305.
128. Liu B, Cao W, Qiao GL, Yao SY, Pan SJ, Wang LR, et al. Effects of gold nanoprism-assisted human PD-L1 siRNA on both gene down-regulation and photothermal therapy on lung cancer. *Acta Biomater* 2019;**99**:307−19.
129. Li B, Niu HR, Zhao XY, Huang XY, Ding Y, Dang K, et al. Targeted anti-cancer therapy: co-delivery of VEGF siRNA and phenethyl isothiocyanate (PEITC) *via* cRGD-modified lipid nanoparticles for enhanced anti-angiogenic efficacy. *Asian J Pharm Sci* 2024;**19**:100891.
130. Shamshiripour P, Rahnama M, Nikoobakht M, Rad VF, Moradi AR, Ahmadvand D. Extracellular vesicles derived from dendritic cells loaded with VEGF-A siRNA and doxorubicin reduce glioma angiogenesis *in vitro*. *J Control Release* 2024;**369**:128−45.
131. Yang MM, Qin C, Tao LL, Cheng G, Li JJ, Lv FN, et al. Synchronous targeted delivery of TGF-β siRNA to stromal and tumor cells elicits robust antitumor immunity against triple-negative breast cancer by comprehensively remodeling the tumor microenvironment. *Biomaterials* 2023;**301**:122253.
132. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* 2021;**5**: 951−67.
133. Holmgaard RB, Zamarin D, Li Y, Gasmi B, Munn DH, Allison JP, et al. Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. *Cell Rep* 2015;**13**:412−24.
134. Brenk M, Scheler M, Koch S, Neumann J, Takikawa O, Häcker G, et al. Tryptophan deprivation induces inhibitory receptors ILT3 and ILT4 on dendritic cells favoring the induction of human $CD4^+$ $CD25^+$ $Foxp3^+$ T regulatory cells. *J Immunol* 2009;**183**:145−54.
135. Cheong JE, Sun L. Targeting the IDO1/TDO2−KYN−AhR pathway for cancer immunotherapy−challenges and opportunities. *Trends Pharmacol Sci* 2018;**39**:307−25.
136. Liu S, Yang B, Hou YX, Cui KG, Yang XZ, Li XX, et al. The mechanism of STING autoinhibition and activation. *Mol Cell* 2023; **83**:1502−18.e10.
137. Wang Y, Li SR, Hu MY, Yang YC, McCabe E, Zhang L, et al. Universal STING mimic boosts antitumour immunity *via* preferential activation of tumour control signalling pathways. *Nat Nanotechnol* 2024;**19**:856−66.
138. Doshi AS, Cantin S, Prickett LB, Mele DA, Amiji M. Systemic nanodelivery of low-dose STING agonist targeted to $CD103^+$ dendritic cells for cancer immunotherapy. *J Control Release* 2022;**345**:721−33.
139. Benoit-Lizon I, Jacquin E, Vargas TR, Richard C, Roussey A, Dal Zuffo L, et al. CD4 T cell-intrinsic STING signaling controls the differentiation and effector functions of TH1 and TH9 cells. *J Immunother Cancer* 2022;**10**:e003459.
140. Jing W, McAllister D, Vonderhaar EP, Palen K, Riese MJ, Gershan J, et al. STING agonist inflames the pancreatic cancer immune microenvironment and reduces tumor burden in mouse models. *J Immunother Cancer* 2019;**7**:1−18.
141. Lee SJ, Yang H, Kim WR, Lee YS, Lee WS, Kong SJ, et al. STING activation normalizes the intraperitoneal vascular-immune microenvironment and suppresses peritoneal carcinomatosis of colon cancer. *J Immunother Cancer* 2021;**9**:e002195.
142. Xian SY, Chen XN, Ren SH, Chen XL, Wang HX. Ionizable STING-activating nanoadjuvants enhance tumor immunogenicity and potentiate immunotherapy efficacy in solid tumors. *Cancer Res* 2024; **84**:3044−57.
143. Liu JP, Zhan JZ, Zhang Y, Huang L, Yang J, Feng J, et al. Ultrathin clay nanoparticles-mediated mutual reinforcement of ferroptosis and cancer immunotherapy. *Adv Mater* 2024;**36**:2309562.
144. Li ZY, Li XH, Lu YJ, Zhu XD, Zheng WX, Chen K, et al. Novel photo-STING agonists delivered by erythrocyte efferocytosis-mimicking pattern to repolarize tumor-associated macrophages for boosting anticancer immunotherapy. *Adv Mater* 2024;**36**:2410937.
145. Hu H, Zheng S, He C, Zheng Y, Wei Q, Chen S, et al. Radiotherapy-sensitized cancer immunotherapy *via* cGAS−STING immune pathway by activatable nanocascade reaction. *J Nanobiotechnol* 2024;**22**:234.
146. Wang B, Van Herck S, Chen Y, Bai XY, Zhong ZF, Deswarte K, et al. Potent and prolonged innate immune activation by enzyme-responsive imidazoquinoline TLR7/8 agonist prodrug vesicles. *J Am Chem Soc* 2020;**142**:12133−9.
147. Turco V, Pfleiderer K, Hunger J, Horvat NK, Karimian-Jazi K, Schregel K, et al. T cell-independent eradication of experimental glioma by intravenous TLR7/8-agonist-loaded nanoparticles. *Nat Commun* 2023;**14**:771.
148. Zhang YY, Ya SN, Huang JN, Ju YY, Fang XY, Ouyang XT, et al. Spatial isolation of single copper (i) sites for cascade enzyme-like catalysis and simultaneous ferroptosis/cuproptosis boosted immunotherapy. *Explorations* 2025;**5**:20240275.
149. Rodell CB, Arlauckas SP, Cuccarese MF, Garris CS, Li R, Ahmed MS, et al. TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. *Nat Biomed Eng* 2018;**2**:578−88.
150. Phuengkham H, Song C, Lim YT. A designer scaffold with immune nanoconverters for reverting immunosuppression and enhancing immune checkpoint blockade therapy. *Adv Mater* 2019;**31**:1903242.
151. Bahmani B, Gong H, Luk BT, Haushalter KJ, DeTeresa E, Previti M, et al. Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors. *Nat Commun* 2021;**12**:1999.
152. Li YJ, Lei NJ, Yao XH, Zhang Y, Dong Y, Yi JM, et al. Hijacking endogenous iron and GSH *via* a polyvalent ferroptosis agonist to enhance tumor immunotherapy. *Adv Funct Mater* 2023;**33**:2303195.
153. Hu RZ, Dai C, Dai XY, Dong CH, Huang H, Song XR, et al. Topology regulation of nanomedicine for autophagy-augmented ferroptosis and cancer immunotherapy. *Sci Bull* 2023;**68**:77−94.
154. He YD, Zhang XG, Meng FH, Wang JJ, Li Y, Zhang Y, et al. Biomimetic chiral nanotopography for manipulating immunological response. *Adv Funct Mater* 2024;**34**:2313157.
155. Qiu NS, Xu C, Zhang Z, Wang R, Wei XY, Xie YL, et al. Autologous tumoral esterase-driven therapeutic polymers sequentially orchestrated antigen-induction, STING activation and anti-angiogenesis for systemic cancer immune therapy. *Biomaterials* 2025;**320**:123260.
156. Carroll EC, Jin L, Mori A, Munoz-Wolf N, Oleszycka E, Moran HB, et al. The vaccine adjuvant chitosan promotes cellular immunity *via* DNA sensor cGAS−STING-dependent induction of type I interferons. *Immunity* 2016;**44**:597−608.
157. Turley JL, Moran HB, McEntee CP, O'Grady K, Muñoz-Wolf N, Jin L, et al. Chitin-derived polymer deacetylation regulates mitochondrial reactive oxygen species dependent cGAS−STING and NLRP3 inflammasome activation. *Biomaterials* 2021;**275**:120961.
158. Meng JS, Yang X, Huang J, Tuo Z, Hu Y, Liao ZY, et al. Ferroptosis-enhanced immunotherapy with an injectable dextran-chitosan hydrogel for the treatment of malignant ascites in hepatocellular carcinoma. *Adv Sci* 2023;**10**:2300517.
159. Zhou H, Wang W, Cai ZD, Jia ZY, Li YY, He W, et al. Injectable hybrid hydrogels enable enhanced combination chemotherapy and roused anti-tumor immunity in the synergistic treatment of pancreatic ductal adenocarcinoma. *J Nanobiotechnol* 2024;**22**:353.
160. Kaparakis-Liaskos M, Ferrero RL. Immune modulation by bacterial outer membrane vesicles. *Nat Rev Immunol* 2015;**15**:375−87.
161. Li M, Zhou H, Yang C, Wu Y, Zhou XC, Liu H, et al. Bacterial outer membrane vesicles as a platform for biomedical applications: an update. *J Control Release* 2020;**323**:253−68.

162. Kim OY, Park HT, Dinh NTH, Choi SJ, Lee J, Kim JH, et al. Bacterial outer membrane vesicles suppress tumor by interferon-γ-mediated antitumor response. *Nat Commun* 2017;**8**:626.
163. Chen X, Li PZ, Luo B, Song C, Wu MC, Yao YZ, et al. Surface mineralization of engineered bacterial outer membrane vesicles to enhance tumor photothermal/immunotherapy. *ACS Nano* 2024;**18**: 1357−70.
164. Sun Y, Ma YY, Shangguan SJ, Ruan YH, Bai TJ, Xue PP, et al. Metal ions-anchored bacterial outer membrane vesicles for enhanced ferroptosis induction and immune stimulation in targeted antitumor therapy. *J Nanobiotechnol* 2024;**22**:474.
165. Deng ZH, Li BH, Yang MY, Lu LS, Shi XJ, Lovell JF, et al. Irradiated microparticles suppress prostate cancer by tumor microenvironment reprogramming and ferroptosis. *J Nanobiotechnol* 2024;**22**: 225.
166. Ding L, Liang ML, Li CC, Ji XT, Zhang JF, Xie WF, et al. Design strategies of tumor-targeted delivery systems based on 2D nanomaterials. *Small Methods* 2022;**6**:2200853.
167. Wu JR, Hernandez Y, Miyasaki KF, Kwon EJ. Engineered nanomaterials that exploit blood−brain barrier dysfunction for delivery to the brain. *Adv Drug Deliv Rev* 2023;**197**:114820.
168. Li JM, Wang QL, Xia GY, Adilijiang N, Li Y, Hou ZQ, et al. Recent advances in targeted drug delivery strategy for enhancing oncotherapy. *Pharmaceutics* 2023;**15**:2233.
169. Subhan MA, Yalamarty SSK, Filipczak N, Parveen F, Torchilin VP. Recent advances in tumor targeting *via* EPR effect for cancer treatment. *J Personalized Med* 2021;**11**:571.
170. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F, et al. Tumor targeting *via* EPR: strategies to enhance patient responses. *Adv Drug Deliv Rev* 2018;**130**:17−38.
171. Huang DD, Xu DF, Chen WX, Wu RM, Wen YJ, Liu AL, et al. Fe-MnO_2 nanosheets loading dihydroartemisinin for ferroptosis and immunotherapy. *Biomed Pharmacother* 2023;**161**:114431.
172. Rodriguez M, Bonnet-Delpon D, Bégué JP, Robert A, Meunier B. Alkylation of manganese (II) tetraphenylporphyrin by antimalarial fluorinated artemisinin derivatives. *Bioorg Med Chem Lett* 2003;**13**: 1059−62.
173. Fu FQ, Wang WH, Wu LJ, Wang WH, Huang ZW, Huang Y, et al. Inhalable biomineralized liposomes for cyclic Ca^{2+}-burst-centered endoplasmic reticulum stress enhanced lung cancer ferroptosis therapy. *ACS Nano* 2023;**17**:5486−502.
174. Zhao YC, Li YQ, Zhang RF, Wang F, Wang TJ, Jiao Y. The role of erastin in ferroptosis and its prospects in cancer therapy. *OncoTargets Ther* 2020;**13**:5429−41.
175. Zhao J, Xu B, Xiong QQ, Feng YF, Du HH. Erastin-induced ferroptosis causes physiological and pathological changes in healthy tissues of mice. *Mol Med Rep* 2021;**24**:1−8.
176. Li YY, Liu J, Chen YM, Weichselbaum RR, Lin WB. Nanoparticles synergize ferroptosis and cuproptosis to potentiate cancer immunotherapy. *Adv Sci* 2024;**11**:2310309.
177. Sun R, Xiang JJ, Zhou Q, Piao Y, Tang JB, Shao SQ, et al. The tumor EPR effect for cancer drug delivery: current status, limitations, and alternatives. *Adv Drug Deliv Rev* 2022;**191**:114614.
178. Dai LL, Liu JJ, Luo Z, Li MH, Cai KY. Tumor therapy: targeted drug delivery systems. *J Mater Chem B* 2016;**4**:6758−72.
179. Hou XY, Zhong D, Chen HY, Gu ZW, Gong QY, Ma XL, et al. Recent advances in hyaluronic acid-based nanomedicines: preparation and application in cancer therapy. *Carbohydr Polym* 2022;**292**: 119662.
180. Luo ZJ, Dai Y, Gao HL. Development and application of hyaluronic acid in tumor targeting drug delivery. *Acta Pharm Sin B* 2019;**9**: 1099−112.
181. Wang C, Li Y, Chen BB, Zou MJ. *In vivo* pharmacokinetics, biodistribution and the anti-tumor effect of cyclic RGD-modified doxorubicin-loaded polymers in tumor-bearing mice. *Colloid Surf B-Biointerfaces* 2016;**146**:31−8.
182. Wang XY, Wang H, Jiang K, Zhang YY, Zhan CY, Ying M, et al. Liposomes with cyclic RGD peptide motif triggers acute immune response in mice. *J Control Release* 2019;**293**:201−14.
183. Li GH, Wang MK, Ding TH, Wang J, Chen T, Shao QW, et al. cRGD enables rapid phagocytosis of liposomal vancomycin for intracellular bacterial clearance. *J Control Release* 2022;**344**:202−13.
184. Khoshnejad M, Parhiz H, Shuvaev VV, Dmochowski IJ, Muzykantov VR. Ferritin-based drug delivery systems: hybrid nanocarriers for vascular immunotargeting. *J Control Release* 2018; **282**:13−24.
185. He JY, Fan KL, Yan XY. Ferritin drug carrier (FDC) for tumor targeting therapy. *J Control Release* 2019;**311-312**:288−300.
186. Kesharwani P, Halwai K, Jha SK, Al Mughram MH, Almujri SS, Almalki WH, et al. Folate-engineered chitosan nanoparticles: next-generation anticancer nanocarriers. *Mol Cancer* 2024;**23**:244.
187. Sudimack J, Lee RJ. Targeted drug delivery *via* the folate receptor. *Adv Drug Deliv Rev* 2000;**41**:147−62.
188. Wu ML, Le WJ, Mei TX, Wang YC, Chen BD, Liu ZM, et al. Cell membrane camouflaged nanoparticles: a new biomimetic platform for cancer photothermal therapy. *Int J Nanomed* 2019;**14**:4431−48.
189. Wang YM, Xu XY, Chen XY, Li JS. Multifunctional biomedical materials derived from biological membranes. *Adv Mater* 2022;**34**: 2107406.
190. Behera A, Padhi S. Passive and active targeting strategies for the delivery of the camptothecin anticancer drug: a review. *Environ Chem Lett* 2020;**18**:1557−67.
191. Ouyang QH, Zhao Y, Xu KY, He YC, Qin M. Hyaluronic acid receptor-mediated nanomedicines and targeted therapy. *Small Methods* 2024;**8**:2400513.
192. Wang WH, Wang WH, Jin SW, Fu FQ, Huang ZW, Huang Y, et al. Open pocket and tighten holes: inhalable lung cancer-targeted nanocomposite for enhanced ferroptosis-apoptosis synergetic therapy. *Chem Eng J* 2023;**458**:141487.
193. Chi H, Zhu G, Yin YL, Diao H, Liu ZC, Sun SB, et al. Dual-responsive multifunctional "core−shell" magnetic nanoparticles promoting Fenton reaction for tumor ferroptosis therapy. *Int J Pharm* 2022;**622**:121898.
194. Fan RR, Chen CL, Mu M, Chuan D, Liu H, Hou H, et al. Engineering MMP-2 activated nanoparticles carrying B7-H3 bispecific antibodies for ferroptosis-enhanced glioblastoma immunotherapy. *ACS Nano* 2023;**17**:9126−39.
195. Qin W, Chandra J, Abourehab MA, Gupta N, Chen ZS, Kesharwani P, et al. New opportunities for RGD-engineered metal nanoparticles in cancer. *Mol Cancer* 2023;**22**:87.
196. Chen K, Chen XY. Integrin targeted delivery of chemotherapeutics. *Theranostics* 2011;**1**:189.
197. Pachane BC, Selistre-de-Araujo HS. The role of $\alpha v\beta 3$ integrin in cancer therapy resistance. *Biomedicines* 2024;**12**:1163.
198. Kapp TG, Rechenmacher F, Neubauer S, Maltsev OV, Cavalcanti-Adam EA, Zarka R, et al. A comprehensive evaluation of the activity and selectivity profile of ligands for RGD-binding integrins. *Sci Rep* 2017;**7**:39805.
199. Asati S, Pandey V, Soni V. RGD peptide as a targeting moiety for theranostic purpose: an update study. *Int J Pept Res Therapeut* 2019; **25**:49−65.
200. Liang H, Wu XY, Zhao GZ, Feng K, Ni KY, Sun XL. Renal clearable ultrasmall single-crystal Fe nanoparticles for highly selective and effective ferroptosis therapy and immunotherapy. *J Am Chem Soc* 2021;**143**:15812−23.
201. Patten J, Wang K. Fibronectin in development and wound healing. *Adv Drug Deliv Rev* 2021;**170**:353−68.
202. Xu Y, Guo YQ, Zhang CC, Zhan MS, Jia L, Song SL, et al. Fibronectin-coated metal−phenolic networks for cooperative tumor chemo-/chemodynamic/immune therapy *via* enhanced ferroptosis-mediated immunogenic cell death. *ACS Nano* 2022;**16**:984−96.
203. Wang XY, Meng NN, Wang SL, Lu LW, Wang H, Zhan CY, et al. Factors influencing the immunogenicity and immunotoxicity of

cyclic RGD peptide-modified nanodrug delivery systems. *Mol Pharm* 2020;**17**:3281−90.
204. Javid H, Oryani MA, Rezagholinejad N, Esparham A, Tajaldini M, Karimi-Shahri M. RGD peptide in cancer targeting: benefits, challenges, solutions, and possible integrin−RGD interactions. *Cancer Med* 2024;**13**:e6800.
205. Trinder D, Baker E. Transferrin receptor 2: a new molecule in iron metabolism. *Int J Biochem Cell Biol* 2003;**35**:292−6.
206. Lodhi MS, Khan MT, Bukhari SMH, Sabir SH, Samra ZQ, Butt H, et al. Probing transferrin receptor overexpression in gastric cancer mice models. *ACS Omega* 2021;**6**:29893−904.
207. Zhang JL, Cheng DF, He JY, Hong JJ, Yuan C, Liang MM. Cargo loading within ferritin nanocages in preparation for tumor-targeted delivery. *Nat Protoc* 2021;**16**:4878−96.
208. Li L, Fang CJ, Ryan JC, Niemi EC, Lebrón JA, Björkman PJ, et al. Binding and uptake of H-ferritin are mediated by human transferrin receptor-1. *Proc Natl Acad Sci U S A* 2010;**107**:3505−10.
209. Cheng JM, Yu QL, Li JX, Xu ZY, Li JH, Guan LY, et al. Intrinsic tumor-targeted murine Ferritin nanocage co-delivers GPX4 and FSP1 inhibitors for synergistic ferroptosis-immunotherapy. *Nano Today* 2024;**58**:102411.
210. Zuo TT, Fang TX, Zhang J, Yang J, Xu R, Wang ZH, et al. pH-Sensitive molecular-switch-containing polymer nanoparticle for breast cancer therapy with ferritinophagy-cascade ferroptosis and tumor immune activation. *Adv Healthcare Mater* 2021;**10**:2100683.
211. Sudimack J, Lee RJ. Targeted drug delivery *via* the folate receptor. *Adv Drug Deliv Rev* 2000;**41**:147−62.
212. Wang SM, Guo QY, Xu RB, Lin P, Deng GY, Xia XH. Combination of ferroptosis and pyroptosis dual induction by triptolide nano-MOFs for immunotherapy of Melanoma. *J Nanobiotechnol* 2023;**21**:383.
213. Wang WH, Zhong ZQ, Huang ZW, Hiew TN, Huang Y, Wu CB, et al. Nanomedicines for targeted pulmonary delivery: receptor-mediated strategy and alternatives. *Nanoscale* 2024;**16**:2820−33.
214. Sebak AA, El-Shenawy BM, El-Safy S, El-Shazly M. From passive targeting to personalized nanomedicine: multidimensional insights on nanoparticles' interaction with the tumor microenvironment. *Curr Pharm Biotechnol* 2021;**22**:1444−65.
215. Rios de la Rosa JM, Pingrajai P, Pelliccia M, Spadea A, Lallana E, Gennari A, et al. Binding and internalization in receptor-targeted carriers: the complex role of CD44 in the uptake of hyaluronic acid-based nanoparticles (siRNA delivery). *Adv Healthcare Mater* 2019;**8**:1901182.
216. Patra P, Rengan AK. Cancer cell membrane cloaked nanocarriers: a biomimetic approach towards cancer theranostics. *Mater Today Commun* 2022;**33**:104289.
217. Guo WH, Chen ZA, Li ZH, Huang HL, Ren YX, Li ZY, et al. Cancer cell membrane biomimetic mesoporous silica nanotheranostics for enhanced ferroptosis-mediated immuogenic cell death on gastric cancer. *Chem Eng J* 2023;**455**:140868.
218. Pan WL, Tan Y, Meng W, Huang NH, Zhao YB, Yu ZQ, et al. Microenvironment-driven sequential ferroptosis, photodynamic therapy, and chemotherapy for targeted breast cancer therapy by a cancer-cell-membrane-coated nanoscale metal-organic framework. *Biomaterials* 2022;**283**:121449.
219. Dash P, Piras AM, Dash M. Cell membrane coated nanocarriers-an efficient biomimetic platform for targeted therapy. *J Control Release* 2020;**327**:546−70.
220. Lopes J, Lopes D, Pereira-Silva M, Peixoto D, Veiga F, Hamblin MR, et al. Macrophage cell membrane-cloaked nanoplatforms for biomedical applications. *Small Methods* 2022;**6**:2200289.
221. Gao C, Kwong CH, Wang QF, Kam H, Wei JW, Chen Q, et al. Surface-engineered chlorella alleviated hypoxic tumor microenvironment for enhanced chemotherapy and immunotherapy of first-line drugs. *Mater Today* 2022;**58**:57−70.
222. Wang D, Wang SY, Zhou ZD, Bai DA, Zhang QZ, Ai XZ, et al. White blood cell membrane-coated nanoparticles: recent development and medical applications. *Adv Healthcare Mater* 2022;**11**:2101349.
223. Li Q, Su R, Bao X, Cao KX, Du YY, Wang NY, et al. Glycyrrhetinic acid nanoparticles combined with ferrotherapy for improved cancer immunotherapy. *Acta Biomater* 2022;**144**:109−20.
224. Yang N, Pan XH, Zhou XW, Liu ZY, Yang J, Zhang J, et al. Biomimetic nanoarchitectonics with chitosan nanogels for collaborative induction of ferroptosis and anticancer immunity for cancer therapy. *Adv Healthcare Mater* 2024;**13**:2302752.
225. Zeng SY, Tang QL, Xiao MN, Tong XY, Yang T, Yin DH, et al. Cell membrane-coated nanomaterials for cancer therapy. *Mater Today Bio* 2023;**20**:100633.
226. Oroojalian F, Beygi M, Baradaran B, Mokhtarzadeh A, Shahbazi MA. Immune cell membrane-coated biomimetic nanoparticles for targeted cancer therapy. *Small* 2021;**17**:2006484.
227. Ferreira-Faria I, Yousefiasl S, Macário-Soares A, Pereira-Silva M, Peixoto D, Zafar H, et al. Stem cell membrane-coated abiotic nanomaterials for biomedical applications. *J Control Release* 2022;**351**:174−97.
228. Lee N-H, You S, Taghizadeh A, Taghizadeh M, Kim HS. Cell membrane-cloaked nanotherapeutics for targeted drug delivery. *Int J Mol Sci* 2022;**23**:2223.
229. Wu ZX, Chen JR, Wang BQ, Wen Q, Fu SZ. Nanoparticle-Based drug delivery strategies for targeted therapy to hypoxic solid tumors. *Chem Eng J* 2024;**502**:158081.
230. Yang C, Ming H, Li BW, Liu SS, Chen LH, Zhang TT, et al. A pH and glutathione-responsive carbon monoxide-driven nano-herb delivery system for enhanced immunotherapy in colorectal cancer. *J Control Release* 2024;**376**:659−77.
231. Ding X, Wang TY, Bai SW, Yang M, Peng N, Qiu T, et al. A dual heat shock protein down-regulation strategy using PDA/Cu/ICG/R controlled by NIR "switch" enhances mild-photothermal therapy effect. *Adv Healthcare Mater* 2023;**12**:2300929.
232. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. *Nat Rev Drug Discov* 2023;**22**:387−409.
233. Peralta RM, Xie B, Lontos K, Nieves-Rosado H, Spahr K, Joshi S, et al. Dysfunction of exhausted T cells is enforced by MCT11-mediated lactate metabolism. *Nat Immunol* 2024;**25**:2297−307.
234. Pucino V, Certo M, Bulusu V, Cucchi D, Goldmann K, Pontarini E, et al. Lactate buildup at the site of chronic inflammation promotes disease by inducing $CD4^+$ T cell metabolic rewiring. *Cell Metab* 2019;**30**:1055-74.e8.
235. Chai MY, Gao YF, Liu J, Deng YY, Hu DF, Jin Q, et al. Polymyxin b-polysaccharide polyion nanocomplex with improved biocompatibility and unaffected antibacterial activity for acute lung infection management. *Adv Healthcare Mater* 2020;**9**:1901542.
236. Zhao CX, Zhang TT, Xue ST, Zhang PT, Wang F, Li YX, et al. Adipocyte-derived glutathione promotes obesity-related breast cancer by regulating the SCARB2−ARF1−mTORC1 complex. *Cell Metab* 2025;**37**:692−707.e9.
237. Yeh CC, Hou MF, Wu SH, Tsai SM, Lin SK, Hou LA, et al. A study of glutathione status in the blood and tissues of patients with breast cancer. *Cell Biochem Funct* 2006;**24**:555−9.
238. Fontaine SD, Hann B, Reid R, Ashley GW, Santi DV. Species-specific optimization of PEG∼ SN-38 prodrug pharmacokinetics and antitumor effects in a triple-negative BRCA1-deficient xenograft. *Cancer Chemother Pharmacol* 2019;**84**:729−38.
239. Zhang PS, Cui YY, Wang J, Cheng JW, Zhu LC, Liu C, et al. Dual-stimuli responsive smart nanoprobe for precise diagnosis and synergistic multi-modalities therapy of superficial squamous cell carcinoma. *J Nanobiotechnol* 2023;**21**:4.
240. Li JC, Cui D, Jiang YY, Huang JG, Cheng PH, Pu KY. Near-infrared photoactivatable semiconducting polymer nanoblockaders for metastasis-inhibited combination cancer therapy. *Adv Mater* 2019;**31**:1905091.
241. Chen KR, Zhou AW, Zhou XY, He JL, Xu YR, Ning XH. Cellular Trojan Horse initiates bimetallic Fe−Cu MOF-mediated synergistic cuproptosis and ferroptosis against malignancies. *Sci Adv* 2024;**10**:eadk3201.

242. Ding MB, Zhu AN, Zhang YJ, Liu JS, Lin L, Wang XY, et al. Neutrophil-based Trojan horse containing polymer nano-therapeutics for sono-activatable ferroptosis-immunotherapy of orthotopic glioma. *Nano Today* 2024;**57**:102398.
243. Liang S, Yao JJ, Liu D, Rao L, Chen XY, Wang ZH. Harnessing nanomaterials for cancer sonodynamic immunotherapy. *Adv Mater* 2023;**35**:2211130.
244. Zhang M, Guo XL, Wang MF, Liu KH. Tumor microenvironment-induced structure changing drug/gene delivery system for overcoming delivery-associated challenges. *J Control Release* 2020;**323**: 203−24.
245. Zhu L, Torchilin VP. Stimulus-responsive nanopreparations for tumor targeting. *Integr Biol* 2013;**5**:96−107.
246. Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* 2011;**11**: 325−37.
247. Corbet C, Feron O. Tumour acidosis: from the passenger to the driver's seat. *Nat Rev Cancer* 2017;**17**:577−93.
248. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* 2007;**109**:3812−9.
249. Feng Q, Bennett Z, Grichuk A, Pantoja R, Huang T, Faubert B, et al. Severely polarized extracellular acidity around tumour cells. *Nat Biomed Eng* 2024;**8**:787−99.
250. Liu J, He SS, Luo YL, Zhang Y, Du XJ, Xu C, et al. Tumor-microenvironment-activatable polymer nano-immunomodulator for precision cancer photoimmunotherapy. *Adv Mater* 2022;**34**: 2106654.
251. Xia CY, Yin S, Xu SS, Ran GY, Deng M, Mei L, et al. Low molecular weight heparin-coated and dendrimer-based core-shell nanoplatform with enhanced immune activation and multiple anti-metastatic effects for melanoma treatment. *Theranostics* 2019;**9**:337.
252. Ju YM, Wang ZY, Ali Z, Zhang HC, Wang YZ, Xu N, et al. A pH-responsive biomimetic drug delivery nanosystem for targeted chemo-photothermal therapy of tumors. *Nano Res* 2022;**15**:4274−84.
253. Li YM, Yang JH, Xu B, Gao F, Wang W, Liu WG. Enhanced therapeutic siRNA to tumor cells by a pH-sensitive agmatine−chitosan bioconjugate. *ACS Appl Mater Interfaces* 2015;**7**:8114−24.
254. Li ZZ, Liu QL, Wang GR, Bai R, Li SM, Liu T, et al. An oxidative stress nanoamplifier to enhance the efficacy of cisplatin in head and neck cancer. *Angew Chem Int Ed* 2025;**64**:e202421481.
255. Zhang L, Shen Y, Zhang TT, Jiang XH, Wang LG, Wang B, et al. pH responsive and zwitterionic micelle for enhanced cellular uptake and antitumor performance. *Biomater Adv* 2025;**167**:214082.
256. Han XX, Li YY, Xu Y, Zhao X, Zhang YL, Yang X, et al. Reversal of pancreatic desmoplasia by re-educating stellate cells with a tumour microenvironment-activated nanosystem. *Nat Commun* 2018;**9**:3390.
257. Wang XH, Shan MY, Zhang SK, Chen X, Liu WT, Chen JZ, et al. Stimuli-responsive antibacterial materials: molecular structures, design principles, and biomedical applications. *Adv Sci* 2022;**9**: 2104843.
258. Ding HT, Tan P, Fu SQ, Tian XH, Zhang H, Ma XL, et al. Preparation and application of pH-responsive drug delivery systems. *J Control Release* 2022;**348**:206−38.
259. Işıklan N, Polat S. Synthesis and characterization of thermo/pH-sensitive pectin-graft-poly(dimethylaminoethyl methacrylate) coated magnetic nanoparticles. *Int J Biol Macromol* 2020;**164**: 4499−515.
260. Wang Z, Deng XP, Ding JS, Zhou WH, Zheng X, Tang GT. Mechanisms of drug release in pH-sensitive micelles for tumour targeted drug delivery system: a review. *Int J Pharm* 2018;**535**:253−60.
261. Xu YB, Zi YX, Lei JF, Mo XY, Shao ZL, Wu YY, et al. pH-Responsive nanoparticles based on cholesterol/imidazole modified oxidized-starch for targeted anticancer drug delivery. *Carbohydr Polym* 2020;**233**:115858.
262. Ovais M, Mukherjee S, Pramanik A, Das D, Mukherjee A, Raza A, et al. Designing stimuli-responsive upconversion nanoparticles that exploit the tumor microenvironment. *Adv Mater* 2020;**32**:2000055.
263. Valavanidis A, Vlachogianni T, Fiotakis C. 8-Hydroxy-2′-deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis. *J Environ Sci Health Part C Toxicol Carcinogen* 2009;**27**:120−39.
264. Gupta MK, Meyer TA, Nelson CE, Duvall CL. Poly (PS-*b*-DMA) micelles for reactive oxygen species triggered drug release. *J Control Release* 2012;**162**:591−8.
265. Cheng YY, Jiao XY, Xu TL, Wang WQ, Cao Y, Wen YQ, et al. Free-blockage mesoporous anticancer nanoparticles based on ROS-responsive wetting behavior of nanopores. *Small* 2017;**13**:1701942.
266. Ma J, Guo DX, Ji XY, Zhou YF, Liu C, Li Q, et al. Composite hydrogel for spatiotemporal lipid intervention of tumor milieu. *Adv Mater* 2023;**35**:2211579.
267. Liu JY, Pang Y, Zhu ZY, Wang DL, Li CT, Huang W, et al. Therapeutic nanocarriers with hydrogen peroxide-triggered drug release for cancer treatment. *Biomacromolecules* 2013;**14**:1627−36.
268. Zhong XY, Wang XW, Cheng L, Tang YA, Zhan GT, Gong F, et al. GSH-depleted PtCu3 nanocages for chemodynamic-enhanced sonodynamic cancer therapy. *Adv Funct Mater* 2020;**30**:1907954.
269. Fan ZJ, Liu HX, Xue YH, Lin JY, Fu Y, Xia ZH, et al. Reversing cold tumors to hot: an immunoadjuvant-functionalized metal-organic framework for multimodal imaging-guided synergistic photo-immunotherapy. *Bioact Mater* 2021;**6**:312−25.
270. Zhao JY, Wang DD, Zhang X, Di YD, Yang S, Yan LS. Preparation of disulfide/trisulfide core-cross-linked polycarbonate nanocarriers for intracellular reduction-triggered drug release. *ACS Macro Lett* 2024;**13**:1433−41.
271. Dai X, Zhu YQ, Su M, Chen JB, Shen S, Xu CF, et al. Rigid shell decorated nanodevice with Fe/H_2O_2 supply and glutathione depletion capabilities for potentiated ferroptosis and synergized immunotherapy. *Adv Funct Mater* 2023;**33**:2215022.
272. Wijewantha N, Sane S, Eikanger M, Antony RM, Potts RA, Lang L, et al. Enhancing anti-tumorigenic efficacy of eugenol in human colon cancer cells using enzyme-responsive nanoparticles. *Cancers* 2023; **15**:1145.
273. Zhang MZ, Xu CL, Wen LQ, Han MK, Xiao B, Zhou J, et al. A hyaluronidase-responsive nanoparticle-based drug delivery system for targeting colon cancer cells. *Cancer Res* 2016;**76**:7208−18.
274. Dong HN, Pang L, Cong HL, Shen YQ, Yu B. Application and design of esterase-responsive nanoparticles for cancer therapy. *Drug Deliv* 2019;**26**:416−32.
275. Janczy-Cempa E, Mazuryk O, Kania A, Brindell M. Significance of specific oxidoreductases in the design of hypoxia-activated prodrugs and fluorescent turn off−on probes for hypoxia imaging. *Cancers* 2022;**14**:2686.
276. Ye YQ, Kuang XW, Xie ZZ, Liang L, Zhang Z, Zhang YC, et al. Small-molecule MMP2/MMP9 inhibitor SB-3CT modulates tumor immune surveillance by regulating PD-L1. *Genome Med* 2020;**12**: 1−19.
277. Xu T, Ma YY, Yuan QL, Hu HX, Hu XK, Qian ZY, et al. Enhanced ferroptosis by oxygen-boosted phototherapy based on a 2-in-1 nanoplatform of ferrous hemoglobin for tumor synergistic therapy. *ACS Nano* 2020;**14**:3414−25.
278. Bourguignon LY, Bikle D. Selective hyaluronan−CD44 signaling promotes miRNA-21 expression and interacts with vitamin D function during cutaneous squamous cell carcinomas progression following UV irradiation. *Front Immunol* 2015;**6**:224.
279. Zhong ZQ, Gan L, Feng ZY, Wang WH, Pan X, Wu CB, et al. Hydrogel local drug delivery systems for postsurgical management of tumors: *status Quo* and perspectives. *Mater Today Bio* 2024;**29**: 101308.
280. Tang HL, Xu XJ, Chen YX, Xin HH, Wan T, Li BW, et al. Reprogramming the tumor microenvironment through second-near-infrared-window photothermal genome editing of PD-L1 mediated by supramolecular gold nanorods for enhanced cancer immunotherapy. *Adv Mater* 2021;**33**:2006003.
281. Liu Y, Lu RJ, Li M, Cheng DL, Wang FS, Ouyang XM, et al. Dual-enzyme decorated semiconducting polymer nanoagents for second

near-infrared photoactivatable ferroptosis-immunotherapy. *Mater Horiz* 2024;**11**:2406−19.
282. Choi J, Sun I-C, Hwang HS, Yoon HY, Kim K. Light-triggered photodynamic nanomedicines for overcoming localized therapeutic efficacy in cancer treatment. *Adv Drug Deliv Rev* 2022;**186**:114344.
283. Wang WM, Gao Y, Xu JJ, Zou TH, Yang B, Hu SB, et al. A NRF2 regulated and the immunosuppressive microenvironment reversed nanoplatform for cholangiocarcinoma photodynamic-gas therapy. *Adv Sci* 2024;**11**:2307143.
284. Bai X, Kang J, Wei SL, Wang Y, Liu YS, Yuan B, et al. A pH responsive nanocomposite for combination sonodynamic-immunotherapy with ferroptosis and calcium ion overload *via* SLC7A11/ACSL4/LPCAT3 pathway. *Explorations* 2025;**5**:20240002.
285. Che DN, Xie GH, Cho BO, Shin JY, Kang HJ, Jang SI. Protective effects of grape stem extract against UVB-induced damage in C57BL mice skin. *J Photochem Photobiol, B* 2017;**173**:551−9.
286. Kielbassa C, Roza L, Epe B. Wavelength dependence of oxidative DNA damage induced by UV and visible light. *Carcinogenesis* 1997; **18**:811−6.
287. Yue YF, Li BW, Wang DD, Wu CZ, Li ZY, Liu B. Optimizing photosensitizers with type I and type II ROS generation through modulating triplet lifetime and intersystem crossing efficiency. *Adv Funct Mater* 2025;**35**:2414542.
288. Hu K, Xie L, Zhang YD, Hanyu M, Yang ZM, Nagatsu K, et al. Marriage of black phosphorus and Cu^{2+} as effective photothermal agents for PET-guided combination cancer therapy. *Nat Commun* 2020;**11**:2778.
289. Yang YC, Tian Q, Wu SQ, Li YX, Yang K, Yan Y, et al. Blue light-triggered Fe^{2+}-release from monodispersed ferrihydrite nanoparticles for cancer iron therapy. *Biomaterials* 2021;**271**:120739.
290. Tenopoulou M, Kurz T, Doulias P-T, Galaris D, Brunk UT. Does the calcein-AM method assay the total cellular 'labile iron pool'or only a fraction of it?. *Biochem J* 2007;**403**:261−6.
291. Tyurin V, Balasubramanian K, Winnica D, Tyurina Y, Vikulina A, He R, et al. Oxidatively modified phosphatidylserines on the surface of apoptotic cells are essential phagocytic 'eat-me' signals: cleavage and inhibition of phagocytosis by Lp-PLA2. *Cell Death Differ* 2014; **21**:825−35.