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Nanobiotechnology boosts ferroptosis: opportunities and challenges

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Abstract

Ferroptosis, distinct from apoptosis, necrosis, and autophagy, is a unique type of cell death driven by iron-dependent phospholipid peroxidation. Since ferroptosis was defined in 2012, it has received widespread attention from researchers worldwide. From a biochemical perspective, the regulation of ferroptosis is strongly associated with cellular metabolism, primarily including iron metabolism, lipid metabolism, and redox metabolism. The distinctive regulatory mechanism of ferroptosis holds great potential for overcoming drug resistance—a major challenge in treating cancer. The considerable role of nanobiotechnology in disease treatment has been widely reported, but further and more systematic discussion on how nanobiotechnology enhances the therapeutic efficacy on ferroptosis-associated diseases still needs to be improved. Moreover, while the exciting therapeutic potential of ferroptosis in cancer has been relatively well summarized, its applications in other diseases, such as neurodegenerative diseases, cardiovascular and cerebrovascular diseases, and kidney disease, remain underreported. Consequently, it is necessary to fill these gaps to further complete the applications of nanobiotechnology in ferroptosis. In this review, we provide an extensive introduction to the background of ferroptosis and elaborate its regulatory network. Subsequently, we discuss the various advantages of combining nanobiotechnology with ferroptosis to enhance therapeutic efficacy and reduce the side effects of ferroptosis-associated diseases. Finally, we analyze and discuss the feasibility of nanobiotechnology and ferroptosis in improving clinical treatment outcomes based on clinical needs, as well as the current limitations and future directions of nanobiotechnology in the applications of ferroptosis, which will not only provide significant guidance for the clinical applications of ferroptosis and nanobiotechnology but also accelerate their clinical translations.

Keywords Ferroptosis, Nanobiotechnology, Regulatory mechanism, Drug resistance, Drug delivery, Clinical treatment

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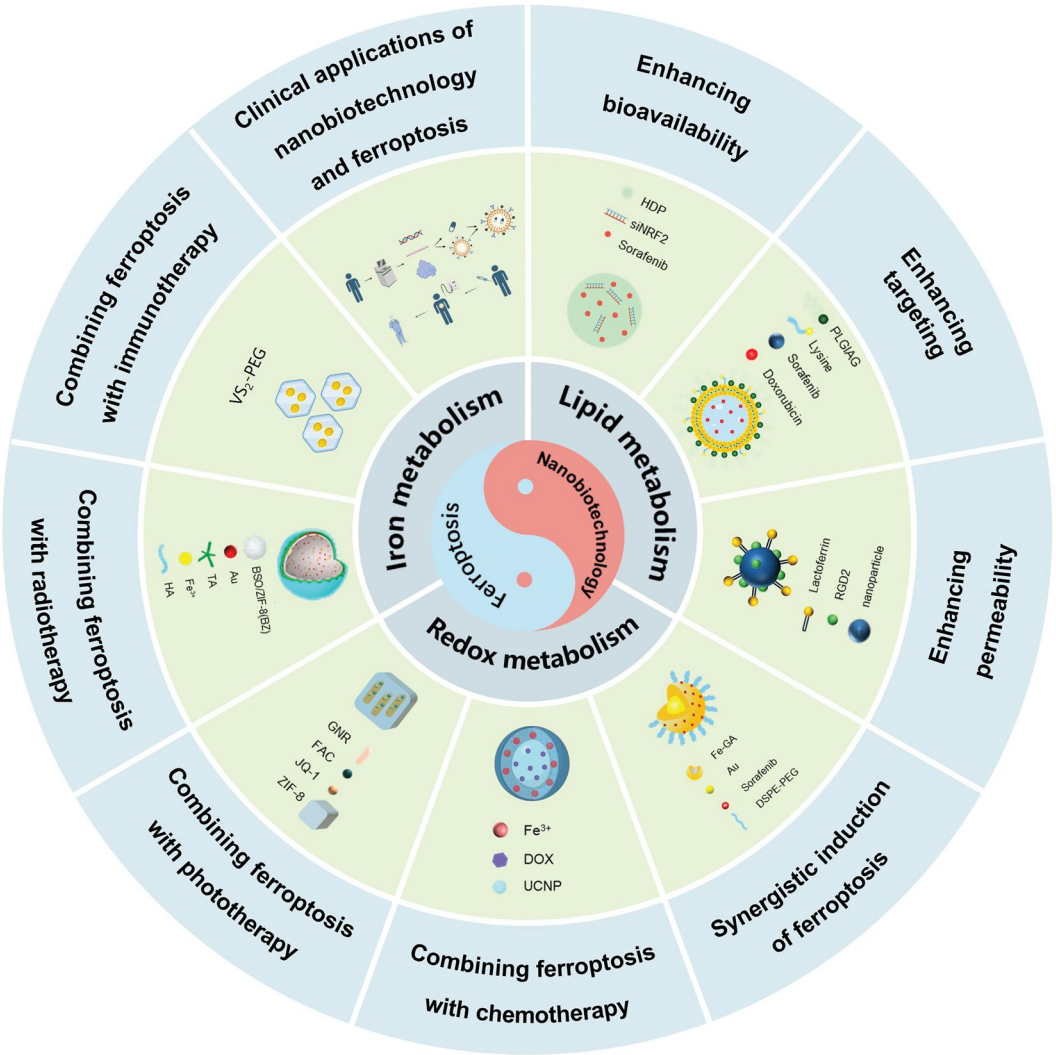
Graphical Abstract



Introduction

Ferroptosis, a form of regulated cell death (RCD), differs from other classic forms of cell death, such as apoptosis, necrosis, and autophagy, is characterized by unique biochemical features, primarily including iron-dependent lipid peroxidation (LPO) and obvious accumulation of reactive oxygen species (ROS) [1, 2]. Cancer, as a disease that is difficult to cure, has long threatened human life and health [3]. Although numerous drugs have been developed for the treatment of cancer, overcoming drug resistance remains a significant challenge in clinical practice [4]. Due to its unique mechanism, ferroptosis represents a highly promising strategy to address the issue of tumor treatment resistance in clinical treatment [5–7]. In addition to cancer, ferroptosis is also associated with other diseases, such as degenerative diseases and tissue injuries [8, 9]. Consequently, utilizing ferroptosis to treat various diseases could be a promising strategy. Although ferroptosis-based drugs have tremendous therapeutic potential, how to improve the targeting of these drugs to lesions to reduce side effects and amplify their efficacy is also an issue that needs to be taken seriously.

Recently, nanobiotechnology, represented by nanodrugs and nanodrug delivery systems (NDDSs), has been growing rapidly, effectively solving various problems in the treatment of diseases, including improving the bioavailability, targeting, and permeability of drugs, as well as prolonging their circulation time in vivo [10–15]. More notably, due to the unique physical and chemical properties of some nanomaterials, these nanomaterials can

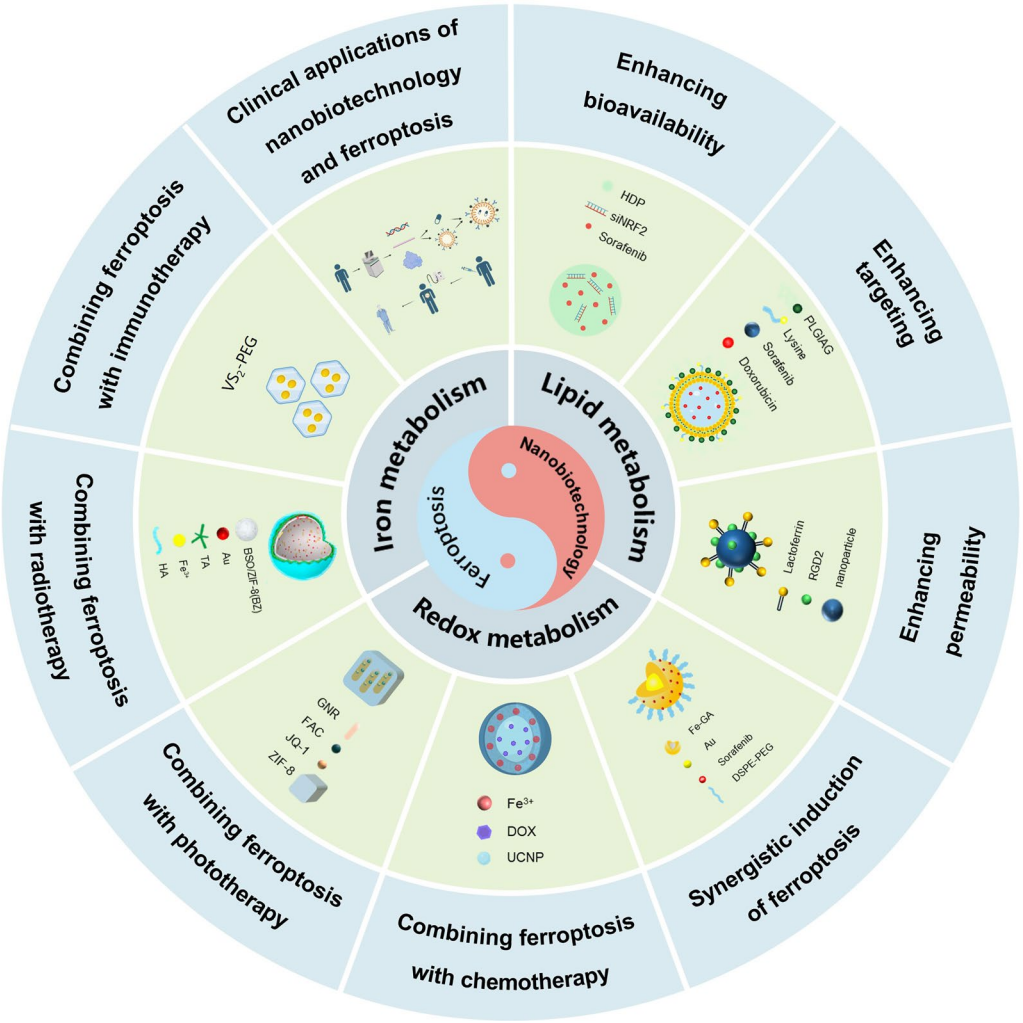


Fig. 1 Schematic illustration of nanobiotechnology enhancing the therapeutic effects of ferroptosis-based drugs

be employed in specific therapeutic scenarios, such as sonodynamic therapy (SDT) and photothermal therapy (PTT), which can be combined with other therapies to enhance treatment efficacy [16–19]. Consequently, taking advantage of nanobiotechnology can not only significantly enhance the therapeutic efficacy of some drugs but also reduce drug side effects, which can achieve desirable therapeutic outcomes.

Herein, we provide a comprehensive overview of ferroptosis, elaborate its main regulatory mechanisms, and provide an in-depth discussion of the various advantages of nanobiotechnology in enhancing ferroptosis-based drugs therapeutic efficacy. Additionally, based on the current medical development context, we explore the clinical applications of nanobiotechnology in treating ferroptosis-related diseases other than cancer and further propose the concept of integrated diagnosis and treatment as well as personalized treatment based on nanobiotechnology and ferroptosis to advance drug development and improve clinical disease treatment. We believe that this review will provide valuable references for the pharmaceutical research and treatment of various diseases (Fig. 1).

Ferroptosis

Background on ferroptosis

It is well known that cell, the fundamental unit constituting living organisms, can lead to the onset of various diseases when their development and proliferation are dysregulated [20]. For a long time, the prevailing view in the scientific community was that there were merely two cell death modalities: regulated apoptosis and unregulated necrosis. However, over the past few decades, several other forms of cell death have been progressively

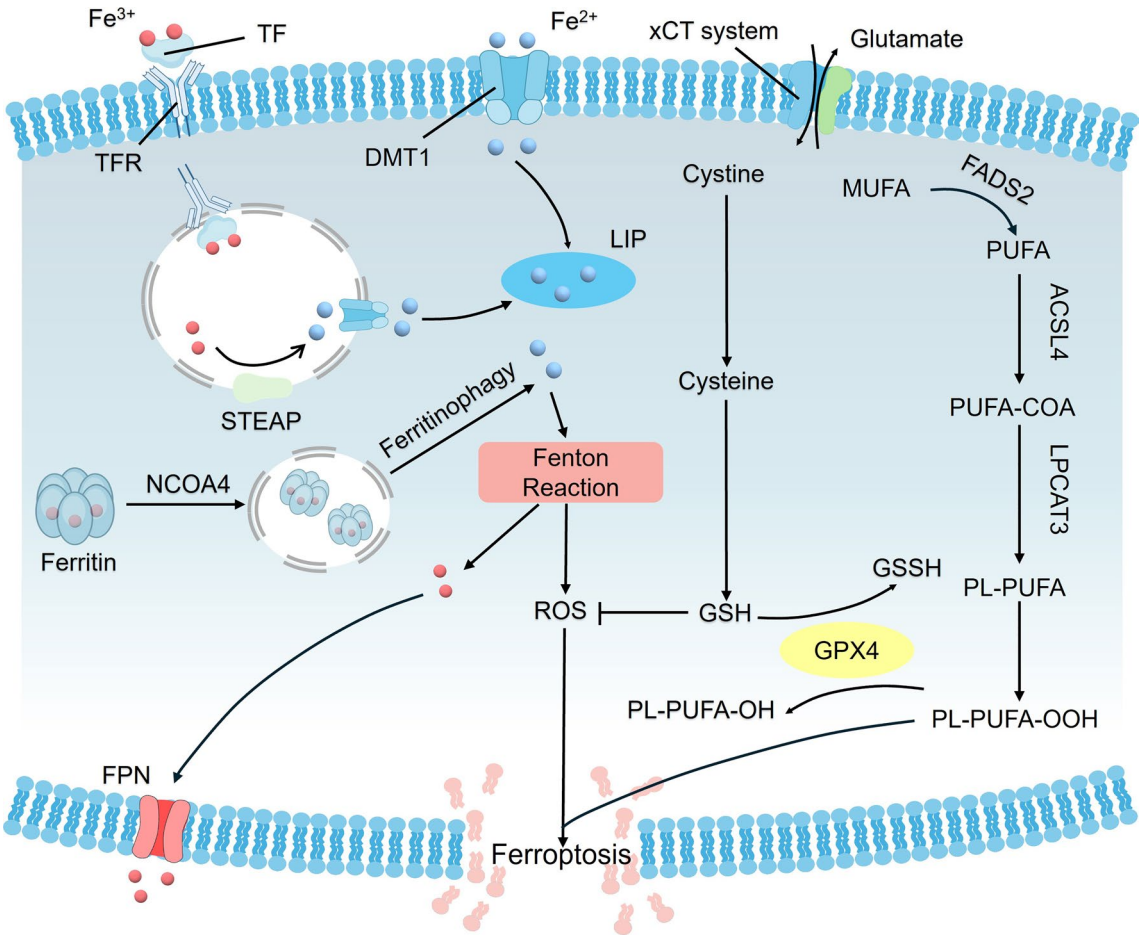


Fig. 2 Schematic illustration of the ferroptosis regulatory network

discovered, including but not limited to pyroptosis, autophagy, ferroptosis, cuproptosis, and disulfidptosis [21]. Ferroptosis, with its unique regulatory mechanisms, is considered to have significant potential in overcoming drug resistance, which has substantially aroused researchers' enthusiasm for its study [6].

In 2003, Dolma et al. used a synthetic lethal chemical screen and found that erastin, a small molecular compound, could induce RAS mutant tumor cells death in a manner distinct from traditional forms of cell death, such as apoptosis and necrosis [22]. In 2008, Yang et al. reported that RSL5 and RSL3 can induce an iron-dependent, non-apoptotic cell death in tumor cells similar to erastin [23]. Concurrently, Seiler et al. demonstrated that the depletion of glutathione peroxidase (GPX4) can lead to the generation of cellular ROS and further induces LPO, which triggers cell death. Interestingly, this mode of death is distinct from classical apoptosis, as evidenced by the absence of Annexin V-positivity, PI-negativity, and caspase-3 activation in GPX4-deficient cells, and Z-VAD, an apoptosis inhibitor, cannot rescue this type of cell death [24]. In 2012, Dixon et al. demonstrated that the cell death triggered by erastin is a consequence of its inhibition of System Xc^-, resulting in a reduction in intracellular cysteine (Cys) levels, which subsequently disrupts the biosynthesis of cellular glutathione (GSH). GSH is essential for the synthesis of GPX4, an intracellular ROS scavenger; the reduction in GSH biosynthesis can lead to the excessive accumulation of ROS within cells, thereby triggering ferroptosis. Additionally, they identified a compound termed ferrostatin-1 (Fer-1) that obviously inhibits cell death caused by RSL3 by scavenging lipid ROS while not affecting other types of cell death and officially termed this iron-dependent form of cell death as ferroptosis [1]. Subsequently, the study of ferroptosis has progressively advanced, with new signal pathways continually being discovered as relevant to the regulation of ferroptosis, the mechanism of ferroptosis is gradually clear.

Ferroptosis regulatory network

Ferroptosis occurs directly because of LPO on the cell membrane. This process is mainly driven by the insertion of substantial polyunsaturated fatty acids (PUFAs) into phospholipids, significantly increasing the susceptibility of phospholipids to peroxidation [25]. The consequential extensive generation of peroxidized lipids and ROS results in the formation of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These compounds further cause the denaturation of proteins and damage the membrane structure, ultimately leading to cell death [26]. At its core, the regulation of ferroptosis is fundamentally about controlling the levels of LPO. The central roles of iron in this process cannot be overlooked; it catalyzes the Fenton reaction, which produces a large number of reactive hydroxyl radicals (·OH). These radicals are potent enough to attack PUFAs within the cellular membrane, triggering LPO. Consequently, the regulatory mechanisms of ferroptosis are primarily divided into three key domains: iron metabolism, lipid metabolism, and redox metabolism (Fig. 2).

Regulating ferroptosis through iron metabolism

Iron is one of the essential trace elements required by the human body and is crucial for maintaining human health [27]. Iron is absorbed in the small intestine, binds as Fe^{3+} to transferrin (TF), and subsequently combines with the transferrin receptor (TFR) on the cell surface. This complex is internalized by the cell through clathrin-mediated endocytosis, leading to the formation of a vesicle. Proton pumps on the vesicle membrane then actively transport H^{+} into the vesicle, causing a reduction in pH. This decrease in pH weakens the binding affinity of Fe^{3+} to TF, resulting in the dissociation of Fe^{3+}. The liberated Fe^{3+} is then converted into Fe^{2+} by the six-transmembrane epithelial antigen of the prostate (STEAP) and further transported into the cytoplasm via divalent metal transporter 1 (DMT1) on the vesicle membrane [28]. Additionally, iron can be absorbed into the cytoplasm via non-transferrin-bound iron (NTBI) pathways, such as DMT1, which facilitates the transport of iron that is not dependent on TF or TFR [29]. Within the cell, a portion of the iron is utilized as Fe^{2+} located in the labile iron pool (LIP). At the same time, the surplus is stored as Fe^{3+} in ferritin, an iron storage protein complex consisting of ferritin light chain (FTL) and ferritin heavy chain (FTH) [30]. Fe^{2+} from LIP is partly transported into the mitochondria, where it participates in the biosynthesis of heme and iron-sulfur clusters within the mitochondrial matrix. The remaining portion can be utilized within the cytoplasm, such as in synthesizing cytoplasmic biomacromolecules and participating the iron-catalyzed Fenton reaction [31, 32]. In addition to iron import, cells can also export iron to maintain better intracellular and systemic iron homeostasis, which is achieved by ferroportin (FPN), the only confirmed protein responsible for iron export in human cells [33].

Because iron is necessary for cell proliferation and survival and plays major roles in numerous enzymatic reactions, including the synthesis of DNA and proteins, it is important for regulating intracellular iron. Iron-regulatory protein 1 (IRP1) and iron-regulatory protein 2 (IRP2) exert their regulatory effects on iron homeostasis at the post-transcriptional level by binding to iron-responsive elements (IREs) located in the 3′UTRs or 5′UTRs of genes associated with iron regulation [28]. Specifically, the 3′ UTRs of the DMT1 and TFR mRNAs contain IRE sequences, while the IREs of FPN and ferritin are located in the 5′ UTRs of their mRNAs. When the intracellular iron concentration is low, the binding of IRPs to IREs is enhanced. For mRNAs with IREs in their 3′ UTR, this increased binding stabilizes the mRNA, promoting the translation of the target proteins. Conversely, for mRNAs with IREs in their 5′ UTRs, the binding of IRPs to IREs inhibits the association of small ribosomal subunits with mRNAs, thereby suppressing translation and reducing protein expression. This process acts as a negative feedback mechanism to increase intracellular iron levels. When iron is abundant, the binding of IRPs to IREs is reduced, leading to the opposite effect [34–36]. In 2016, through RNAi screening, Gao et al. discovered that under conditions that induce ferroptosis (cysteine deprivation and erastin induction), nuclear receptor coactivator 4 (NCOA4) facilitates the lysosomal autophagy of ferritin, leading to the release of stored iron into the cytosolic LIP and the subsequent generation of a substantial amount of ROS through pathways such as the Fenton reaction, which promotes ferroptosis. This process is termed "ferritinophagy" [37, 38]. FPN is currently the only known transporter protein in human cells capable of translocating iron from the intracellular environment to the extracellular space, playing a crucial role in maintaining cellular and systemic iron homeostasis [33]. Specifically, in the liver, when systemic iron levels are elevated, the expression of hepcidin increases. Hepcidin binds to the iron transporter protein on the cell membrane, inducing its ubiquitination and degradation, thereby reducing iron efflux and maintaining systemic iron homeostasis. Conversely, when intracellular iron levels are low in certain cells, such as intestinal epithelial cells and macrophages, hepcidin binds to the membrane-bound iron transporter protein, inhibiting its activity to decrease iron efflux and maintain intracellular iron balance [39–42]. In addition, heme oxygenase-1 (HO-1) catalyzes the degradation of heme into carbon monoxide and biliverdin, which can subsequently be converted into bilirubin and labile Fe^{2+},

thereby participating in the regulation of iron metabolism [43, 44].

Regulating ferroptosis through lipid metabolism

Phospholipid peroxidation at the cell membrane leads to membrane rupture, which is the direct cause of ferroptosis [45]. Therefore, the regulation of phospholipid peroxidation is considered to be crucial for regulating ferroptosis. Phospholipids are composed of various fatty acids, including saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and PUFAs [46]. Compared to SFAs and MUFAs, PUFAs, such as arachidonic acid (AA) and adrenic acid (AdA), are more susceptible to ROS attack due to their multiple C=C double bonds [47]. This vulnerability facilitates chain oxidation reaction catalyzed by metal ions such as Fe^{2+} and Cu^{2+}, continuously generating increased LPOs and leading to severe cellular damage [48]. Furthermore, the intermediate free radicals and the final products, MDA and 4-HNE, can cause severe damage to the membrane structure and intracellular proteins and DNA, leading to cell death [49–51].

PUFAs can be generated through two pathways: on the one hand, cells can internalize PUFAs via specific fatty acid transport proteins (FATPs) [52]; on the other hand, MUFAs can be converted into PUFAs through fatty acid desaturases such as fatty acid desaturase 1 (FADS1), which introduce additional C=C double bonds into the carbon chain of MUFAs [53].

Within cells, free PUFAs can be covalently attached to CoA via the catalysis of acyl-CoA synthetase long-chain family member 4 (ACSL4) [25]. Subsequently, these compounds are esterified into membrane phospholipids by the action of lysophosphatidylcholine acyltransferases (LPCATs) [54]. The peroxidation of PUFAs requires the presence of oxygen, with the lipoxygenase (LOX) enzyme family, a group of iron-containing oxygenases, incorporating oxygen into membrane phospholipids during peroxidation [55]. Overall, the PUFA/ACSL4/LPCAT/LOX axis represents the primary regulatory pathway involved in lipid metabolism during ferroptosis [56]. Additionally, fatty acid desaturase 2 (FADS2) and stearoyl-CoA desaturase 1 (SCD1) are both cellular desaturases, yet they serve contrasting functions in the modulation of ferroptosis. FADS2 is primarily responsible for catalyzing the synthesis of long-chain PUFAs, thereby promoting ferroptosis. In contrast, SCD1 tends to convert SFAs to MUFAs, modifying the lipid composition of membrane lipids by increasing the content of MUFAs to inhibit ferroptosis [57, 58].

In the lipid-mediated regulation of ferroptosis, cholesterol and its derivatives play pivotal roles [59]. Liu et al. revealed that the exposure of cancer cells to 27-hydroxycholesterol (27-HC) enhances metastatic potential. Further analysis revealed that 27-HC promoted the dependence of cancer cells for GPX4, a key enzyme reducing LPO, by augmenting intracellular lipid synthesis and uptake. Consequently, knocking down GPX4 in these cancer cells can induce ferroptosis and significantly inhibits tumor metastasis [60]. In recent studies, 7-dehydrocholesterol (7-DHC) has been demonstrated to inhibit ferroptosis by protecting membrane phospholipids from peroxidation through its high reactivity with peroxyl radicals [61]. These modulations of ferroptosis by cholesterol derivatives underscores the complex interplay between lipid metabolism and cell death pathways, offering novel insights into cancer progression and potential therapeutic targets.

Regulating ferroptosis through redox metabolism

As previously mentioned, the attack of ROS on membrane PUFAs directly triggers ferroptosis. Consequently, intracellular ROS levels serve as another determinant of cellular sensitivity to ferroptosis. In normal cells, ROS levels are maintained within a specific range. However, cells undergo ferroptosis when the balance between ROS production and clearance is disrupted, specifically when ROS generation exceeds clearance capacity.

Since the concept of ferroptosis was proposed, SLC7A11/GSH/GPX4 has been regarded as a classical regulatory pathway of ferroptosis [1]. As a selenoprotein, GPX4, with its selenocysteine binding site activity, can catalyze the oxidation of GSH to glutathione disulfide (GSSG), simultaneously reducing LPOs to alcohols and thereby inhibiting ferroptosis [24]. Solute carrier family 7, membrane 11 (SLC7A11) is one of the active components of the cystine/glutamate antiporter system (System Xc^-), facilitating cystine transport into the cell while exporting glutamate out of the cell. Cystine is a crucial precursor for the intracellular biosynthesis of the reductive substance GSH [1]. Therefore, targeting the SLC7A11/GSH/GPX4 pathway to regulate ferroptosis holds enormous potential for drug development. For instance, erastin and RSL3, which target SLC7A11 and GPX4, respectively, promote ferroptosis and play significant roles in cancer therapy [62]. Notably, SLC7A11 can be regulated by many upstream signals, such as NRF2, P53, and BAP1, which adds diversity to the regulation of ferroptosis [63–65].

In addition to the LPO reduction pathway, which depends on SLC7A11/GSH/GPX4, cells also have reduction pathways that rely on NAD(P)H/FSP1/COQ10 and GCH1/BH4/COQ10 [66]. In 2019, Sebastian et al. generated a cDNA expression library derived from the ferroptosis-resistant MCF7 cell line. They discovered that FSP1 protects cells from ferroptosis in a manner independent

Table 1 Advantages of nanobiotechnology in boosting the development of ferroptosis-related drugs

Nanodrug delivery system	Loaded drug	Disease	Advantages	References
TKPFH NPs	shGPX4 and shMTHFD2	Cancer	Efficient tumor cell uptake and improved lysosomal escape	[75]
Cur-NPs	Curcumin	Intracerebral hemorrhage	Enhancing curcumin bioavailability, improving curcumin delivery to the brain	[76]
SLNART	Artesunate	Esophageal squamous cell carcinoma	Overcoming the poor water solubility and bioavailability of ART, inducing ferroptosis by two pathways	[77]
DOX@Fc-SS-ATRA NPs	doxorubicin	Triple-negative breast cancer	Combining ferroptosis with chemotherapy, enhanced tumor selectivity and stability	[78]
FSRSNs	Shikonin	Cancer	Improving targeting, loading capacity, and bioavailability, decreasing cytotoxicity toward normal cells	[79]
LDM	Dihydroartemisinin and pH-responsive calcium phosphate	Lung cancer	Excellent nebulization properties, enhancing lung lesions drug accumulation	[80]
ARV@PDSA	PROteolysis targeting Chimeras	Cancer	Superior anti-tumor efficacy with a low dose administration and good biocompatibility	[81]
Pa-M/Ti-NCs	TGF-β inhibitor and PD-1 antibody	Cancer	Long circulation, creating an immunogenic microenvironment, ability of magnetic resonance imaging	[82]
Ang-MMsaNPs	Small activating RNA (saALOX15)	Glioblastoma	Reducing the clearance by the mononuclear phagocyte system (MPS), increasing the ability to cross the blood–brain barrier	[83]
RSV-NPs@RBCm	Resveratrol	Colon cancer	Escaping macrophage phagocytosis, having a long circulation effect	[84]
PW-2@HA	Protein transduction domain	Intracellular infections caused by gram-positive bacteria	Improving the resistance of PW-2 to trypsin and proteinase K	[85]
Gi-F-CAA	GPX4 inhibitory peptide	Cancer	Improving tumor endocytosis efficiency by assembly enhanced binding (AEB) effect	[86]
NLC(F)@PC	Fluvastatin	Lung adenocarcinoma	Excellent nebulization properties, enhancing lung lesions drug accumulation	[87]
Fish oil-based microemulsion	PD1/PD-L1 blocking model peptide	Cancer	Sustained drug release manner, enhancing intestinal drug uptake, elevating the oral peptide bioavailability, combining ferroptosis with immunotherapy	[88]
DS@MA-LS	Doxorubicin and sorafenib	Cancer	Prolonging blood circulation, improving targeting, combining ferroptosis with chemotherapy	[89]
BT-EXO-CAP	Capreomycin	Osteosarcoma	Homologous targeting and bone-targeting, decreasing side effects	[90]
Alb/LF NP	DDC/Cu-Fe	Glioma	Combining ferroptosis with immunotherapy, increasing the ability to cross the blood–brain barrier	[91]
UFCL	Ferric ammonium citrate and cisplatin	Triple-negative breast cancer	Maintaining colloidal stability and reducing immunogenicity	[92]
DHM@RSL3	RSL3	Cancer	Enhancing selectivity and decreasing side effects	[93]

Table 1 (continued)

Nanodrug delivery system	Loaded drug	Disease	Advantages	References
Lp-IO	Doxorubicin	Cancer	Traceable magnetic resonance imaging and pH/ROS dual-responsive	[94]
SRF@FeIIITA	Sorafenib	Cancer	Specific to H_2O_2-overloaded cancer cells but minimal in normal cells, combining ferroptosis with imaging-guided photodynamic therapy	[95]
AMSNs	Doxorubicin	Cancer	Ideal water dispersibility, biocompatibility, and tumor homing capacity, combining ferroptosis with chemotherapy, magnetic resonance imaging (MRI)	[96]
Fe/Art-Lip@PFP	Fe/Art-Lip	Cancer	The tumor-targeting effect, enhancing the penetration depth	[97]
OMV@PGZ	Pioglitazone	Reperfusion injury after ischemic stroke	Penetrating the blood–brain barrier	[98]
FeGd-HN@Pt@LF/RGD2	Cisplatin	Brain cancer	Penetrating the blood–brain barrier, magnetic resonance imaging (MRI)	[99]
mPEG-b-PPLGFc@Dox	Doxorubicin	Cancer	Reducing the organ toxicity of Dox, combining ferroptosis with chemotherapy	[100]
NMIL-100@GOx@C	Glucose oxidase	Cancer	Synergistic ferroptosis–starvation anti-tumor therapy	[101]
DEF-HCC-PEG	Deferoxamine	Intracerebral hemorrhage	DEF-HCC-PEG more effectively than the individual therapies individually	[102]
Nanosword-like titanite	Ca, Si, and Fe ions	Antibiosis	Resisting bacterial invasion by a synergistic action of ferroptosis-like bacteria killing, proton disturbance, and physical puncture	[103]
Cu2–xSe/ZIF-8@Era-PEG-FA	Erastin	Triple-negative breast cancer	Combining ferroptosis with immunotherapy, prolonging blood circulation, promoting tumor-specific uptake	[104]
Cu-Hemin-PEG-LA	Hemin and Cu (II)	Liver cancer	Two modes to synergistically induce ferroptosis	[105]
TQCN	Quercetin	Alzheimer's disease	Favorable brain-targeting, mitochondria-locating properties, regulating ferroptosis by multiple pathways	[106]

of GSH, GPX4, ACSL4, and the level of oxidizable fatty acids. Further studies showed that FSP1 disrupts the propagation of LPO by catalyzing the reduction of CoQ10 to CoQ10-H2 (a radical-scavenging antioxidant) using NAD(P)H [67]. Additionally, in 2020, Vanessa A. and colleagues identified GCH1 as a gene that protects against ferroptosis, independent of the glutathione antioxidant reduction system, through a CRISPR/dCas9 overexpression screen using a genome-wide activation library. Specifically, high expression of GCH1 enhances the production of BH4, which acts directly as an antioxidant and promotes de novo synthesis of CoQ10, thereby inhibiting ferroptosis [68].

Advantages of nanobiotechnology in the treatment of ferroptosis-related diseases

The unique regulatory mechanisms of ferroptosis position it as a promising strategy for addressing the issues of tumor drug resistance and recurrence [69–71]. In addition to cancer, ferroptosis has also been linked to other diseases, such as neurodegenerative diseases, cardiovascular and cerebrovascular diseases, and kidney disease, highlighting the exciting potential of ferroptosis-based therapeutic strategies [8, 9]. In recent years, nanobiotechnology has been extensively applied in drug development and clinical treatment, achieving notable success [72–74]. In the following discussion, we explore how

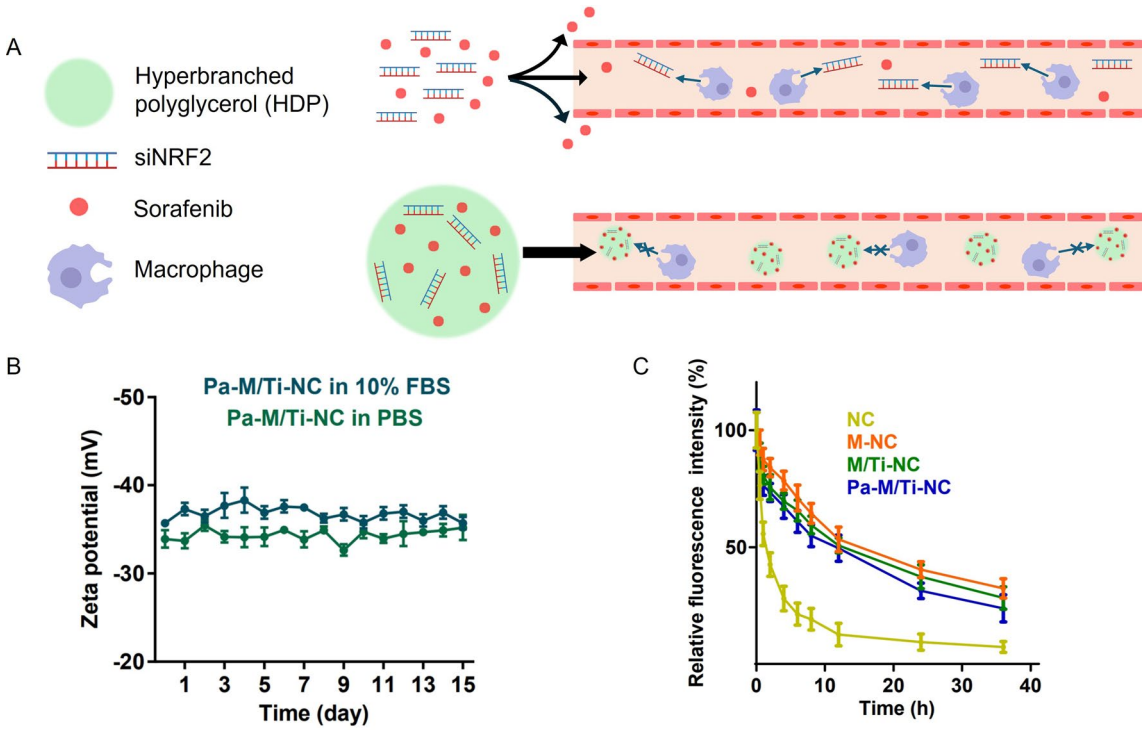


Fig. 3 **A** Schematic representation of NDDSs enhanced the bioavailability of ferroptosis-related drugs. In the absence of a nanoparticle delivery carrier, sorafenib exhibits poor water solubility in blood, and siRNA is easily identified and cleared by macrophages, which decreases their bioavailability. However, the use of NDDSs (depicted as HDP in the diagram), enhances the solubility of drugs, prolongs their circulation time, and increases their bioavailability. **B** The zeta potentials of Pa-M/Ti-NCs in 10% FBS and PBS, little change was found during more than 2 weeks. **C** In vivo pharmacokinetic curves during 36 h after injection of different formulations **B**, **C** Were reproduced from ref. [82] with permission. Copyright 2019, American Chemical Society)

nanobiotechnology enhances the therapeutic efficacy of ferroptosis-based drugs (Table 1).

Enhancing bioavailability

In clinical therapy, bioavailability is a factor that must be considered in drug development [107]. Unfortunately, the therapeutic efficacy of many drugs involved in regulating ferroptosis is limited due to poor water solubility, ease of metabolism, and difficulty accumulating at lesion sites, posing significant challenges to clinical treatment [108, 109]. However, NDDSs can act as "bodyguards" to "escort" these drugs to the designated sites of action, not only significantly enhancing their therapeutic effects but also enriching the clinical drug options, which brings new hope to the treatment of ferroptosis-related diseases [110–112].

Enhancing drug solubility

Although small molecule compounds such as erastin, RSL3, sulfasalazine, sorafenib, and ferrostatin-1 are recognized as effective ferroptosis inducers or inhibitors, their clinical applicational potential is largely limited by their poor water solubility [113–116]. In addition, Traditional Chinese Medicine (TCM), a medical system with thousands of years of history, has significant advantages in regulating ferroptosis, due to the multi-component and multi-target characteristics of active TCM ingredients [111, 117–119]. However, the poor water solubility of most active ingredients in TCM also greatly hinders their clinical applications [120]. Therefore, utilizing nanobiotechnology to address the poor water solubility of active TCM ingredients to enhance their therapeutic effects on ferroptosis-related diseases represents a promising treatment strategy.

Sorafenib has long been used in clinical as a first-line drug for the treatment of hepatocellular carcinoma (HCC) due to its anti-angiogenic effects [121]. Recently, it has been discovered that sorafenib can also induce ferroptosis, which sparks renewed interests in this drug [122]. Tong et al. synthesized an amphiphilic NDDS, hyperbranched polyglycerol (HDP), to co-deliver Sorafenib and NRF2 siRNA (si-NRF2) [123]. This approach not only resolved the poor water solubility of sorafenib but also enhanced its anti-tumor effects through the synergistic action of HDP and

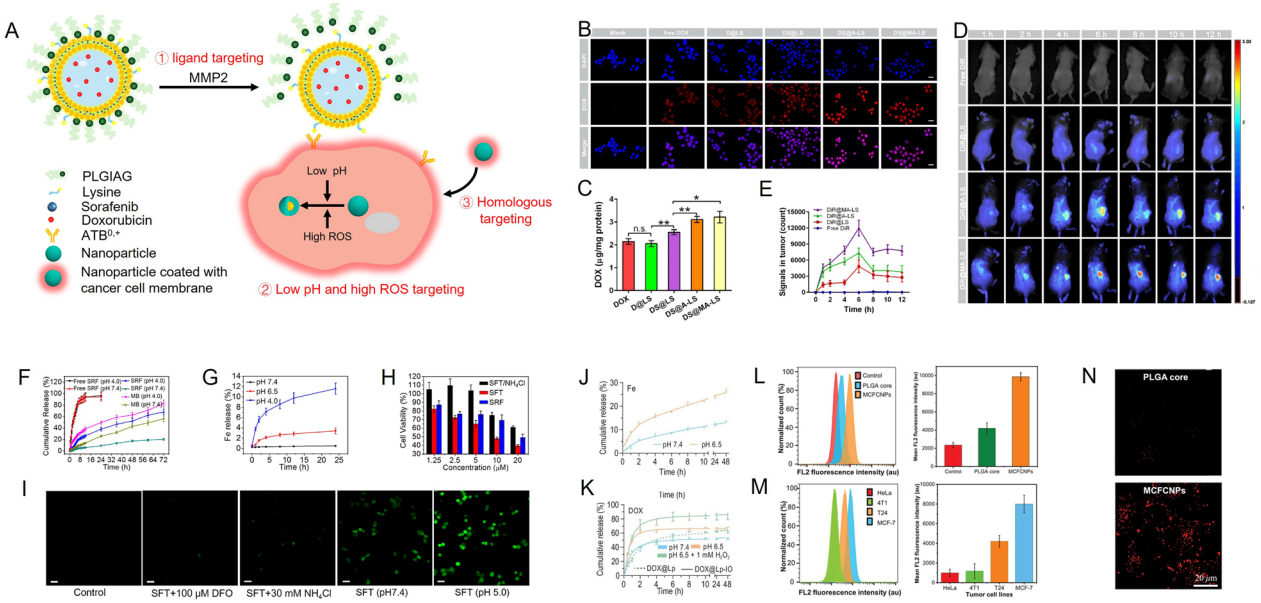


Fig. 4 **A** Schematic representation of nanobiotechnology enhanced the targeting of ferroptosis-related drugs. ① Modifying nanoparticles to specifically target proteins that are overexpressed in tumor tissues for precise tumor targeting. ② Designing nanoparticles that are responsive to low pH and high ROS for precise tumor targeting. ③ Coating nanoparticles with cancer cell membranes for precise tumor targeting. **B**–**E** Enhancing targeting based on overexpressed proteins of tumor tissues (reproduced from ref. [89] with permission. Copyright 2020, American Chemical Society). **F**–**I** Enhancing targeting based on low pH tumor microenvironment (reproduced from ref. [95] with permission. Copyright 2018, American Chemical Society). **J**, **K** Enhancing targeting based on high ROS tumor microenvironment (reproduced from ref. [94] with permission. Copyright 2022, Oxford University Press). **L**–**N** Enhancing targeting based on cell membrane coating (reproduced from ref. [137] with permission. Copyright 2021, John Wiley and Sons)

si-NRF2 (Fig. 3A). Yang et al. encapsulated curcumin in nanoparticles (NPs) to treat intracerebral hemorrhage (ICH) by inhibiting ferroptosis, addressing the issues of poor water solubility and low oral bioavailability of curcumin [76]. Artesunate (ART) is a derivative of artemisinin. Xia et al. discovered that ART induces ferroptosis in esophageal squamous cell carcinoma (ESCC) in a dose-dependent manner, but its poor water solubility hinders its clinical applications. To address this issue, researchers designed a solid lipid nanoparticle (SLN) formulation to encapsulate ART, thereby developing the SLNART strategy [77]. The results showed that the solubility of SLNART in water was significantly greater than that of free ART, and its encapsulation in SLNs also reduced the toxicity of the drug to normal esophageal epithelial cells, demonstrating the significant advantages of nanotechnology in drug delivery.

Prolonging blood circulation

In clinical, the premature clearance of drugs in the bloodstream is a significant issue that affects therapeutic efficacy and involves complex metabolic and immunological mechanisms. On the one hand, drugs in the bloodstream are often cleared or metabolized into inactive forms by the liver and kidneys. On the other hand, once drugs enter the human body as foreign substances, they are often recognized and prematurely cleared by the immune system, greatly reducing their bioavailability [124, 125]. Therefore, prolonging the blood circulation time of drugs is also important for improving their bioavailability.

A common strategy currently employed involves wrapping the drug's surface with cell membranes for biomodification to reduce the rate of clearance by the immune system. For example, Zhang et al. constructed a biomimetic magnetosome coated with leukocyte membranes [82]. The coating of leukocyte membranes prolonged the blood circulation time and facilitated the anchoring of TGF-β inhibitors (Ti) and PD-1 antibodies (Pa) on the membrane of cancer cells. The synergistic effect of immune modulation and ferroptosis greatly enhanced the therapeutic effect on tumor (Fig. 3B, C). Similarly, Cao et al. utilized macrophage membranes (MMs) to coat mesoporous polydopamine (MPDA) loaded with a small activating RNA (saALOX15) (ALOX15 is an essential driver of ferroptosis), which reduces the clearance rate by the mononuclear phagocyte system (MPS) and enhancing the accumulation of NPs in glioblastoma (GBM) [83].

Additionally, chemically modifying nanomedicines to prolong their blood circulation time is also a viable

approach [54]. Proteolysis-targeting chimeras (PROTACs) can selectively degrade intracellular proteins of interest by hijacking the ubiquitin–proteasome system. To this end, Liu et al. encapsulated the BRD4 degrader ARV-771 PROTAC in GSH-responsive poly(disulfide amide) (PDSA) polymers and coated the NPs surface with amphiphilic 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)] (DSPE-PEG) [81]. This strategy not only enhances bioavailability of ARV-771 PROTAC but also improves tumor therapy by inducing ferroptosis through the clearance of GSH.

In recent years, RNA therapy has achieved significant breakthroughs in disease treatment. Unlike traditional gene therapy, RNA therapy directs the synthesis of proteins by directly altering the levels of RNA within cells, avoiding the risks of directly changing DNA, which suggests that we can use this strategy to treat ferroptosis-related diseases [126, 127]. However, RNA is highly susceptible to degradation, so using NDDSs to encapsulate it to prevent premature degradation during blood circulation is a viable approach. Guo et al. encapsulated miR-21-3p in NPs and demonstrated that miR-21-3p can directly target thioredoxin reductase 1 (TXNRD1), leading to a significant decrease in TXNRD1 mRNA and protein levels and further inducing ferroptosis [128]. This study proves the feasibility of combining RNA therapy and nanobiotechnology to treat ferroptosis-related diseases.

Enhancing targeting

With the proposal of "precision medicine," drug development increasingly emphasizes the specificity of drugs for reducing toxic and side effects on normal tissues. Therefore, enhancing the specificity of drugs for treating ferroptosis-related diseases is necessary. Moreover, given that tumor and normal tissues exhibit significant differences in some physicochemical properties, this creates conditions for us to enhance the targeting of drugs [129] (Fig. 4A).

Targeting based on overexpressed proteins

In tumor cells, some proteins, known as tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), are often overexpressed and specifically expressed, respectively. Based on this property of tumor cells, tumor vaccines developed to target these proteins play a crucial role in cancer treatment, suggesting that targeted drug delivery can be achieved by modifying drugs to target these specifically upregulated molecules [130]. Targeting TAAs or TSAs enables the development of highly specific treatments for cancer cells, minimizing the impact on normal cells and potentially leading to more effective and less toxic therapeutic outcomes. For example, Kou et al. designed a liposome loaded with doxorubicin (DOX) and sorafenib (SRF) in which PEG on its surface can be responsively cleaved by matrix metallopeptidase 2 (MMP2), which is highly expressed in tumor tissues, thereby exposing lysine. Lysine can further bind to $ATB^{0,+}$, which is also overexpressed in tumor cells, specifically enhancing the uptake of drugs by tumor cells and the induction effect of DOX and SRF on ferroptosis [89] (Fig. 4B–E).

Targeting based on the tumor microenvironment

Even under conditions of ample oxygen, tumor cells tend to metabolize glucose through anaerobic glycolysis to generate energy rather than through the more efficient process of oxidative phosphorylation [131]. A primary product of anaerobic glycolysis is lactate, whose accumulation in the tumor microenvironment (TME) leads to decreased pH [132]. Furthermore, the rapid proliferation and metabolic activity of tumor cells promote oxidative stress, resulting in the production of a large number of ROS, including hydrogen peroxide (H_2O_2). The abnormal production of lactate and ROS in the TME aids in the design of particular pH- and ROS-sensitive NDDSs. These systems are engineered to respond to the acidic environment and elevated ROS present in tumor tissues, enabling targeted drug release and minimizing damage to healthy tissues. This strategy that exploiting the differences in pH and ROS levels between the TME and normal tissues not only improves the therapeutic index of anticancer drugs but also reduces side effects, offering a promising strategy for precision medicine [133, 134].

In a study by Liu and colleagues, a self-assembling network composed of Fe^{3+} and naturally derived tannic acid (TA, an acid-sensitive reductant) was constructed and attached to SRF nanocrystals to form a core-crown structure SRF@FeIII-TA (SFT) nanostructure [95]. The basic principle of this design is to utilize the relatively stable complex formed by Fe^{3+} and TA under neutral pH conditions. In contrast, a decrease in pH can disrupt this complexation, leading to erosion of the crown layer, thereby rapidly releasing the embedded SRF to initiate ferroptosis. The excess presence of TA causes released and ferroptosis-generated Fe^{3+} to convert to Fe^{2+}, constantly enhancing ferroptosis (Fig. 4F–I).

In designing NDDSs responsive to ROS, Liu and colleagues designed a nanoparticle system named Lp-IO to deliver the chemotherapy drug DOX, achieving specific targeting of the high levels of ROS present in tumor cells [94]. Remarkably, this system utilizes PEG-coated γ-Fe_2O_3 nanoparticles, approximately 3 nm in size, embedded into lipid bilayers. By combining amphiphilic

PEG groups with the lipid bilayer, the permeability of the lipid membrane to H_2O_2 and ·OH is improved, effectively initiating LPO and synergizing with DOX to induce ferroptosis in cancer cells. This innovative approach enhances the targeted delivery and therapeutic efficacy of DOX, leveraging the unique feature of the TME to trigger cell death, specifically in cancer cells (Fig. 4J, K).

Targeting based on cell membrane coating

Homologous targeting based on cell membrane coating involves the use of membranes derived from specific cell types to encapsulate nanoparticles. This technique leverages the inherent homing capabilities and biological functionalities of source cell membranes, facilitating targeted delivery to tissues or cells that share similar markers or environments. Specifically, cancer cell-derived membranes can be used to coat nanoparticles for targeted delivery to the tumor site, exploiting the ability of cancer cells to preferentially interact with and infiltrate their tissue of origin or other tumor sites and enhancing the specificity and efficiency of drug delivery systems, potentially reducing side effects and improving therapeutic outcomes [135, 136].

In the study by Liu and colleagues, a Trojan horse-like nano-AIE (aggregation-induced emission) coated with cancer cell membranes was developed [137]. In simple terms, the coating of NPs with cancer cell membranes provides a form of camouflage that promotes the recognition and uptake of NPs by cancer cells. Compared to normal cells, cancer cells tend to accumulate more lipid droplets (intracellular lipid storage organelles containing large amounts of PUFAs) [138, 139]. Characteristic AIE photosensitizers can effectively aggregate within cancer cells and generate ROS, which act on PUFAs to produce several toxic LPOs, specifically inducing ferroptosis in cancer cells (Fig. 4L–N).

Enhancing permeability

During drug delivery, obstacles such as the blood–brain barrier (BBB) and various biological membranes often prevent effective drugs from reaching lesions in the brain or hindering deep penetration into the core regions of tumor, a significant factor affecting the effects of drugs [140, 141]. The enhanced permeability and retention effect (EPR) is widely utilized in tumor therapy, especially in developing NDDSs. This effect describes the unique

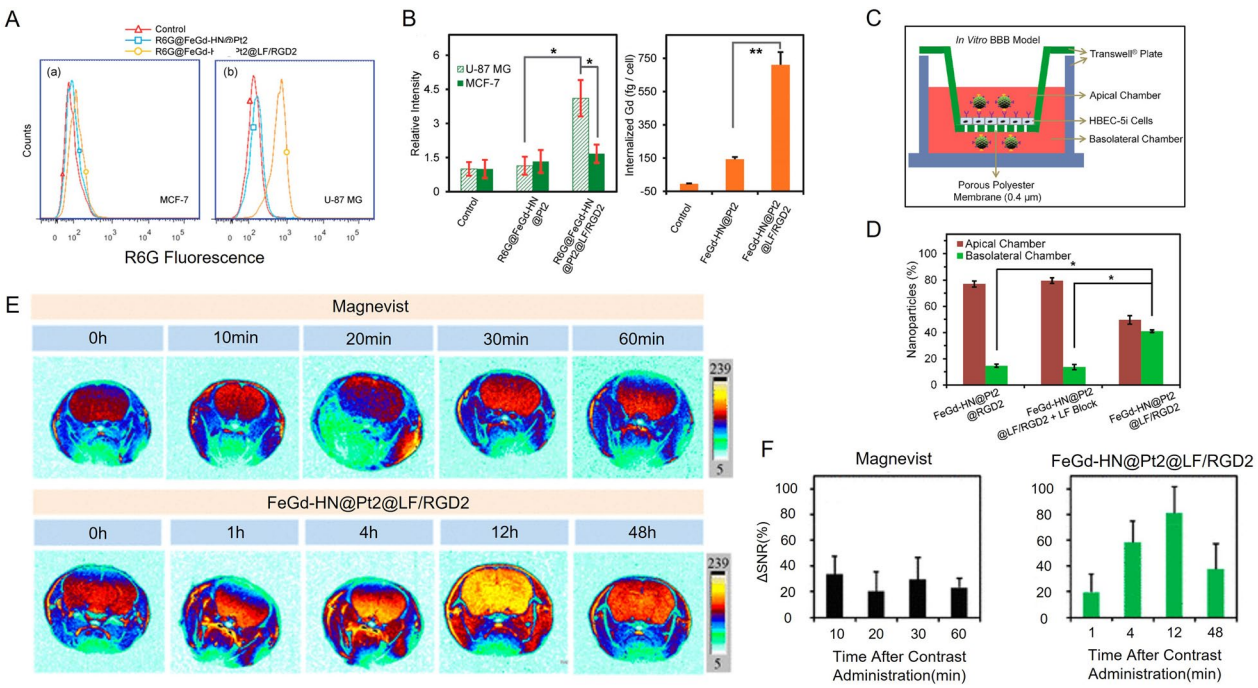


Fig. 5 **A** MCF-7 or U-87 MG cells were coincubated with nanoparticles and analyzed by flow cytometry. The cells without nanoparticle treatment served as control group. **B** Mean fluorescence intensity ratio of nanoparticle-treated cells compared to untreated cells and the amount of nanoparticle internalization in U-87 MG cells measured by ICP. 1 fg = 10^{-15} g. **C** Schematic illustration of the in vitro BBB model. **D** Distribution of FeGd-HN, FeGd-HN@Pt2@LF/RGD2, or FeGd-HN@Pt2@LF/RGD2 plus LF block in the apical or basolateral compartment. Mean ± SD, n = 4; *P < 0.001. **E** T_1-weighted MRI images of mouse normal brains (without tumors) before and after intravenous injection of Magnevist or FeGd-HN@Pt2@LF/RGD2 (C_{Gd} = 5.0 mg/kg mice). **F** Quantitative analysis of the T_1-weighted MRI images in **E** using ΔSNR (reproduced from ref. [99] with permission. Copyright 2018, American Chemical Society)

behavior of nanoscale drug delivery systems in tumor tissues, where these systems can more easily pass through the permeable vascular walls of tumor vessels and remain in tumor tissues for an extended period, unlike normal tissues. This is because, on the one hand, the vascular system of tumor tissues, compared to that of normal tissues, is structurally abnormal and more "leaky," allowing these abnormal vessels to have larger gaps, which enables nanoscale drug delivery systems to pass through the vascular wall into tumor tissues more easily; on the other hand, compared to normal tissues, tumor tissues lack an effective lymphatic drainage system, meaning that once the drug delivery systems penetrate the vascular wall into the tumor tissues, they are more difficult to clear [142]. As a result, the concentration of these nanoscale drug delivery systems in tumor tissues increases, and their retention time prolongs, thereby enhancing the therapeutic effect of the drugs on tumor cells. The EPR effect provides a favorable biological basis for improving tumor treatment efficacy, helping researchers design drug delivery systems that can efficiently penetrate and accumulate in tumor tissues, thus enhancing therapeutic efficacy while reducing toxic impacts on normal tissues.

Enhancing BBB permeability

The blood brain barrier (BBB) is a highly selective permeability barrier between the endothelial cells of blood vessels in the brain. Its primary function is to protect the brain from harmful substances in the blood while also supplying the brain with necessary nutrients [143]. The BBB comprises tightly connected endothelial cells, the basement membrane, astrocytes, and the surrounding microenvironment. This structure ensures high selectivity for substance passage, but it also means that many potential therapeutic drugs cannot cross the BBB to reach the brain's interior [140]. For several brain diseases, such as Alzheimer's disease, Parkinson's disease, and brain cancer, the BBB obviously limits the potential for drug treatment [144, 145]. With the advancement of nanotechnology, it offers new possibilities for designing nanodrugs to overcome the BBB, thereby improving the treatment efficacy for brain diseases [146, 147].

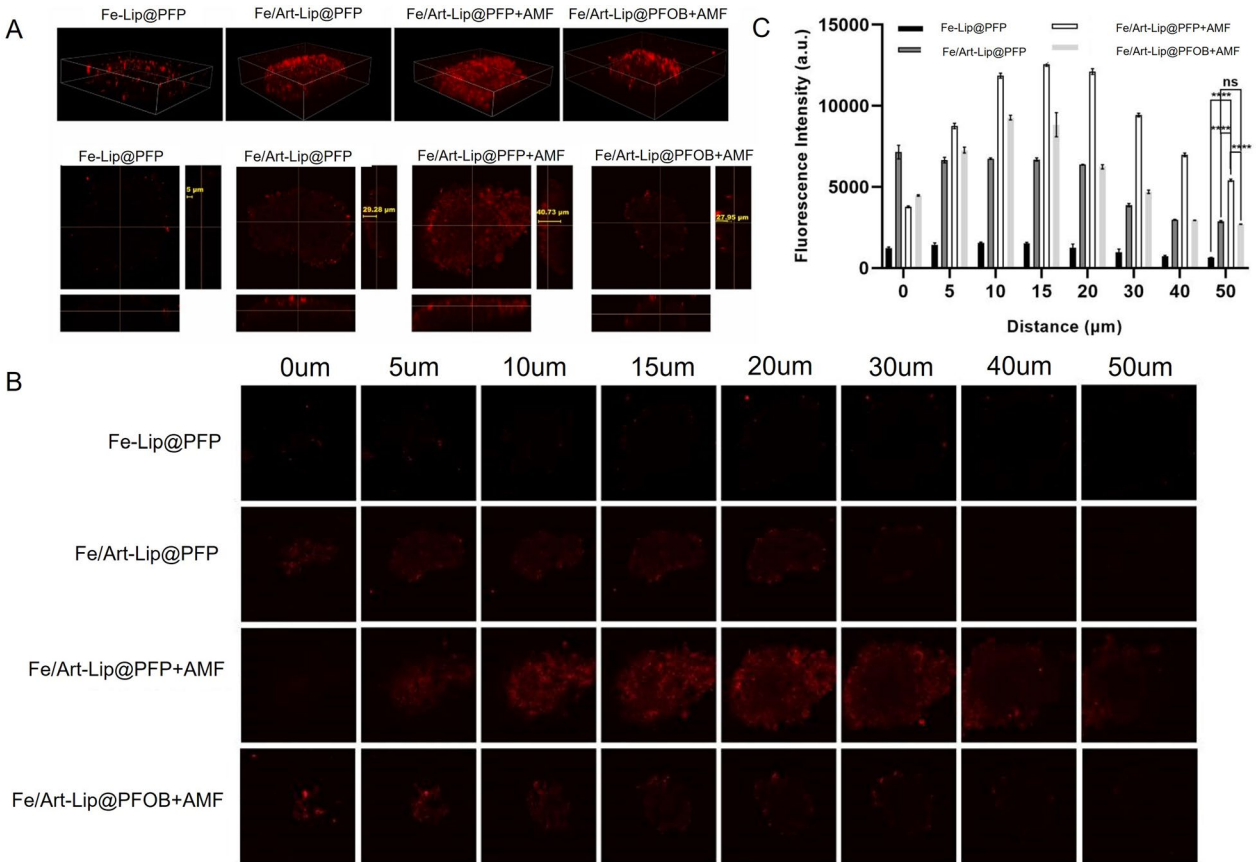


Fig. 6 **A** Multilevel scanning was performed starting from the base of the sphere at 5 or 10 μm intervals for penetration and corresponding fluorescence quantification. **B** 3D reconstruction of the 4T1 spheroid models accepted under different MNDs conditions. **C** Quantitative analysis of the penetration depth of different MNDs (reproduced from ref. [97] with permission. Copyright 2021, Elsevier)

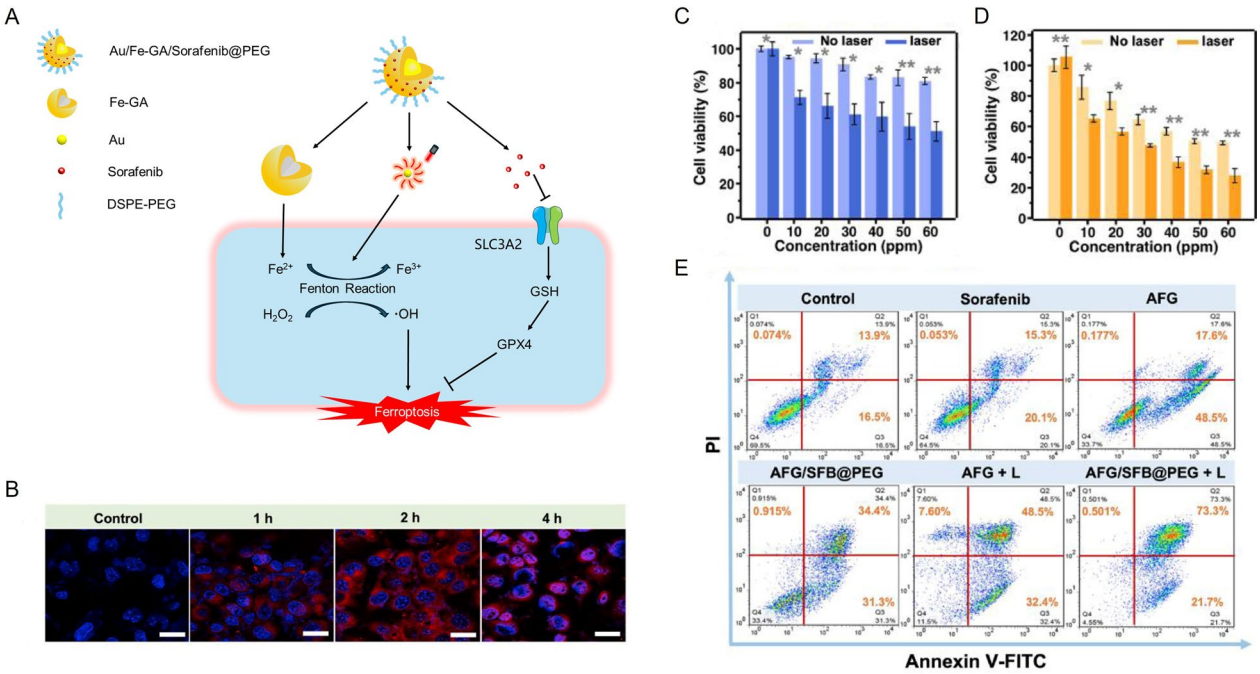


Fig. 7 **A** Schematic representation of nanobiotechnology synergistically induces ferroptosis. Au/Fe-GA and sorafenib synergistically induce ferroptosis by respectively accelerating the Fenton reaction and inhibiting GPX4. **B** CLSM images of the uptake of AFG/SFB@PEG in 4T1 cells at different times. Scale bar = 40 μm. **C**, **D** Cytotoxicity assay of AFG and AFG/SFB@PEG to 4T1 cells with or without laser, the concentration refers to the Fe-GA. **E** Apoptosis analysis of 4T1 cells in different treatment groups using flow cytometry (**B**–**E** Was reproduced from ref. [148] with permission. Copyright 2023, Elsevier

In a study conducted by Shen and colleagues, FeGd-HN@Pt@LF/RGD2 NPs with an average diameter of 6.6 nm loaded with cisplatin (CDDP) were developed [99]. Due to their minimal size, NPs can easily penetrate the BBB. Additionally, leveraging the high expression of lactoferrin (LF) receptors on the brain endothelial cells of the BBB and the overexpression of integrin αvβ3 on the surface of brain tumor cells, the research team coupled LF and RGD2 with NPs. LF can bind to the LF receptor on the BBB and promote drug entry from the blood into the brain through receptor-mediated transcytosis. Moreover, integrin αvβ3 facilitates the absorption of these NPs by tumor cells through endocytosis. Subsequently, the release of Fe^{2+}, Fe^{3+}, and CDDP within tumor cells accelerates the Fenton reaction and results in the production of ROS, which induces ferroptosis in cancer cells. Notably, receptor-mediated transcytosis by LF receptors and integrin αvβ3-mediated endocytosis exploit the physiological mechanisms of the BBB and specific markers of tumor cells, respectively, which provides an effective strategy for drugs to cross the BBB and precisely target brain tumor, effectively overcoming the challenges faced by traditional therapies and enhancing therapeutic efficacy (Fig. 5).

Enhancing deep permeability

The high cellular density, abundant extracellular matrix, and abnormal interstitial pressures within the tumor microenvironment often limit drug effectiveness to the surface layers of tumor, hindering penetration to the core regions, which allows tumor cells in these areas to evade treatment, impacting overall therapeutic outcomes. Therefore, developing new strategies to enhance the deep-tissue penetration of drugs in tumor tissues is crucial for improving the efficacy of cancer treatments, particularly for solid tumor [141].

Wang et al. devised a magnetic nanodroplet (MND) by encapsulating Fe_3O_4 and perfluoropentane (PFP) within liposomes and loading ART into the hydrophobic layer of liposomes [97]. PFP, a low-boiling-point perfluorinated compound, is a liquid at room temperature but can rapidly transition to gas upon mild heating, notably under the mild-temperature magnetic fluid hyperthermia (MHT) conditions described in this study. This rapid phase transition results in substantial microbubble formation. The local pressure produced by this swift phase change assists in disrupting tumor tissue barriers, thereby enhancing the deep penetration of the drug and amplifying the antitumor effects induced by ferroptosis (Fig. 6).

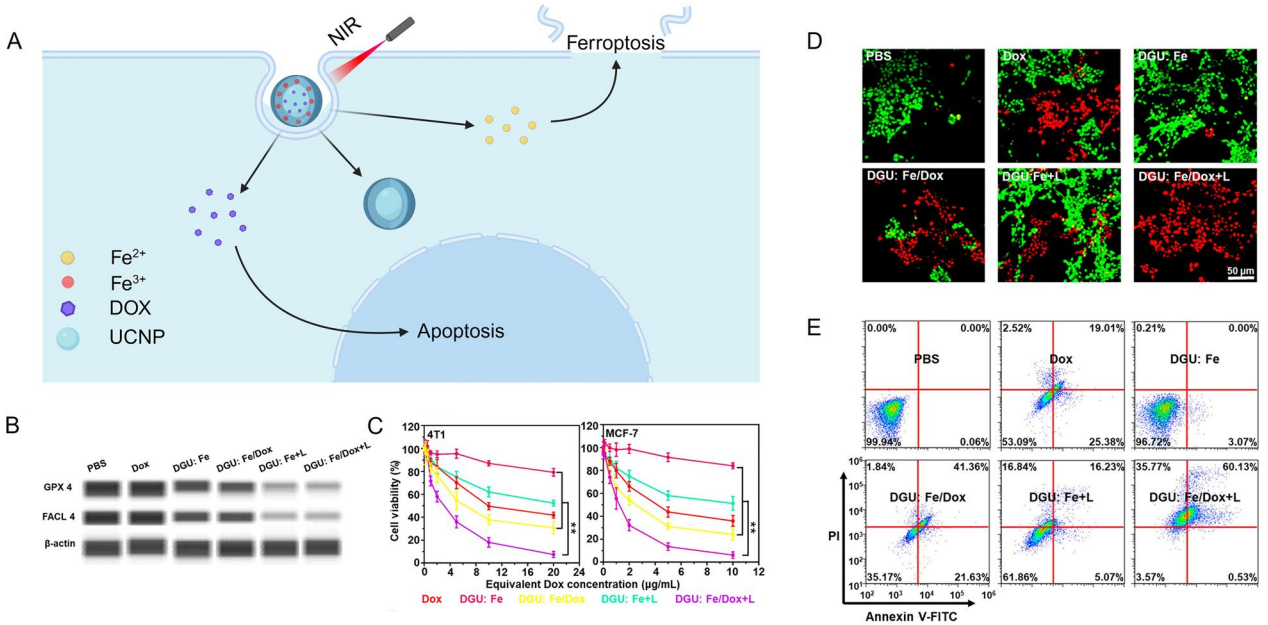


Fig. 8 **A** Schematic representation of nanobiotechnology combines ferroptosis with chemotherapy. Under the action of NIR, UCNPs reduce Fe^{3+} to Fe^{2+}, DOX, and $Fe2^{+}$ respectively promoting cell apoptosis and ferroptosis. **B** Expression levels of ferroptosis-related proteins (GPX4 and FACL4) measured by Western blotting. **C** Cytotoxicity analysis of 4T1 and MCF-7 cells treated with different formulations after 24 h incubation. **D** Live/dead cytotoxicity analysis of 4T1 cells after treatment with different formulations after 24 h incubation. **E** Apoptosis analysis of 4T1 cells after treatment with different formulations after 24 h incubation by flow cytometry (**B**–**E** Were reproduced from ref. [152] with permission. Copyright 2019, American Chemical Society

Synergistically inducing ferroptosis

As previously discussed, ferroptosis represents a cell death modality governed by a complex regulatory network, wherein the intricate interplay among iron metabolism, lipid metabolism, and redox homeostasis forms the basis of its regulatory framework, which suggests a potential strategy to enhance therapeutic outcomes for ferroptosis-related diseases. We can adopt an integral medicine therapeutic concept to treat these diseases by simultaneously targeting these interconnected pathways. Notably, some nanomaterials, such as iron-based nanomaterials and arsenene, can also participate in regulating ferroptosis [105]. Loading ferroptosis-related drugs into these nanomaterials can improve the bioavailability of the drugs, and the intrinsic properties of these nanomaterials can also be utilized in combination with pharmacological drugs to regulate key metabolic pathways of ferroptosis, including increasing cellular iron uptake, depleting GSH levels, and inhibiting the activity of GPX4, thereby enhancing therapeutic effects (Fig. 7A).

Wang et al. designed a nanoreactor named Au/Fe-GA/Sorafenib@PEG [148]. In this nanoreactor, Fe^{2+} is effectively integrated into the structure of the NPs. When these NPs are taken up by cells, they can react with intracellular H_2O_2 to generate a large amount of hydroxyl radicals, directly inducing LPO and cell death. Additionally, the photothermal effect of Au can enhance the activity of Fe^{2+}, accelerating the Fenton reaction by increasing the local temperature, thereby increasing the production of hydroxyl radicals and intensifying LPO and ferroptosis. Furthermore, by binding with SRF, this nanoreactor can not only cause direct oxidative damage through hydroxyl radicals produced by the Fenton reaction but also reduce the synthesis of intracellular GSH by inhibiting SLC3A2 (the heavy chain subunit of System Xc^{-}), further enhancing the inactivation of GPX4 and aggravating ferroptosis. This multifaceted mechanism enhances the effectiveness of ferroptosis treatment strategies (Fig. 7).

Combining ferroptosis with other therapeutic strategies

With today's diverse disease treatment methods, there is hope for achieving comprehensive disease treatment through multimodal approaches in the future. Traditional chemotherapy, phototherapy, radiotherapy, and immunotherapy offer various mechanisms and advantages in cancer treatment. With its unique mechanism, ferroptosis offers potential advantages in overcoming resistance to traditional apoptosis pathways in some cancer cells. Therefore, a strategy that combines ferroptosis-related drugs with other therapeutic strategies has the potential to improve cancer treatment outcomes.

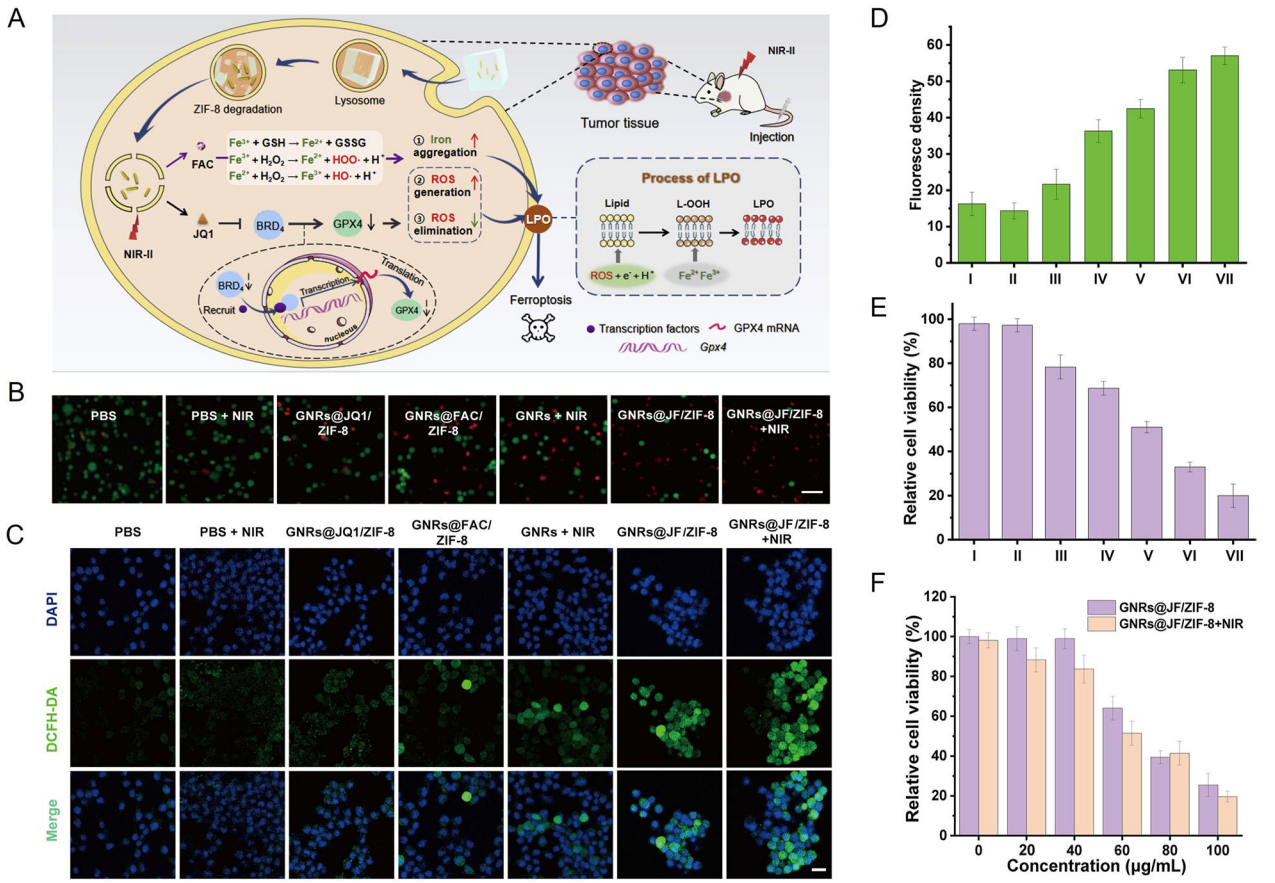


Fig. 9 **A** Schematic representation of nanobiotechnology combines ferroptosis with phototherapy. GNRs, under the effect of NIR, generate high temperature to kill tumor cells and promote the release of drugs. The released FAC and JQ-1 respectively accelerates the Fenton reaction and inhibits GPX4, synergistically inducing ferroptosis. **B** The live/dead cell cytotoxicity analysis of 4T1 cells stained by AM/PI after incubation with various groups (scale bar = 100 mm for all panels). **C** CLSM images of ROS generation after 4T1 cells were treated with different formulations. Scale bar = 25 mm. **D** Quantitative analysis of the ROS intensity in various conditions. **E** Cytotoxicity analysis of 4T1 cells treated with various formulations. **F** Cytotoxicity analysis of 4T1 cells treated with various concentrations of GNRs@JF/ZIF-8 (reproduced from ref. [154] with permission. Copyright 2023, Elsevier)

Combining ferroptosis with chemotherapy

Chemotherapy typically refers to the use of chemical drugs to rapidly inhibit or kill dividing cells, particularly cancer cells. However, these drugs often function by damaging DNA or interfering with the cell division process, affecting both normal and cancerous cells [149]. From another perspective, chemotherapy resistance is a significant barrier in cancer therapy, with many cancer cells able to evade the cytotoxic effects of chemotherapeutic drugs through various mechanisms, such as overexpression of drug efflux pumps, alterations in drug action targets, modifications in cell cycle regulation, and suppression of cell death pathways [150]. Despite significant side effects, chemotherapy remains a widely used treatment for cancer in clinical settings [151]. Ferroptosis, a unique form of cell death, is a novel strategy for circumventing traditional chemotherapy resistance mechanisms. As previously mentioned, since many NDDSs can induce ferroptosis, utilizing these NDDSs to carry chemotherapeutic drugs to combine ferroptosis and chemotherapy is an effective therapeutic strategy (Fig. 8A).

Bao et al. implemented a combined therapy of ferroptosis and chemotherapeutic drugs by designing a delivery system named "Nanolongan" [152]. More specifically, nanolongan employs up-conversion nanoparticles (UCNPs) as the core, which form a stable cross-linked network through coordination between Fe^{3+} and the carboxyl groups in oxidized starch. Concurrently, Dox is encapsulated within the oxidized starch-based gel nanoparticles. With UCNPs as the core component capable of converting near-infrared light (NIR) to ultraviolet light (UV), UCNPs overcome the penetration depth limitation and reduce Fe^{3+} to Fe^{2+}. This valence transition led

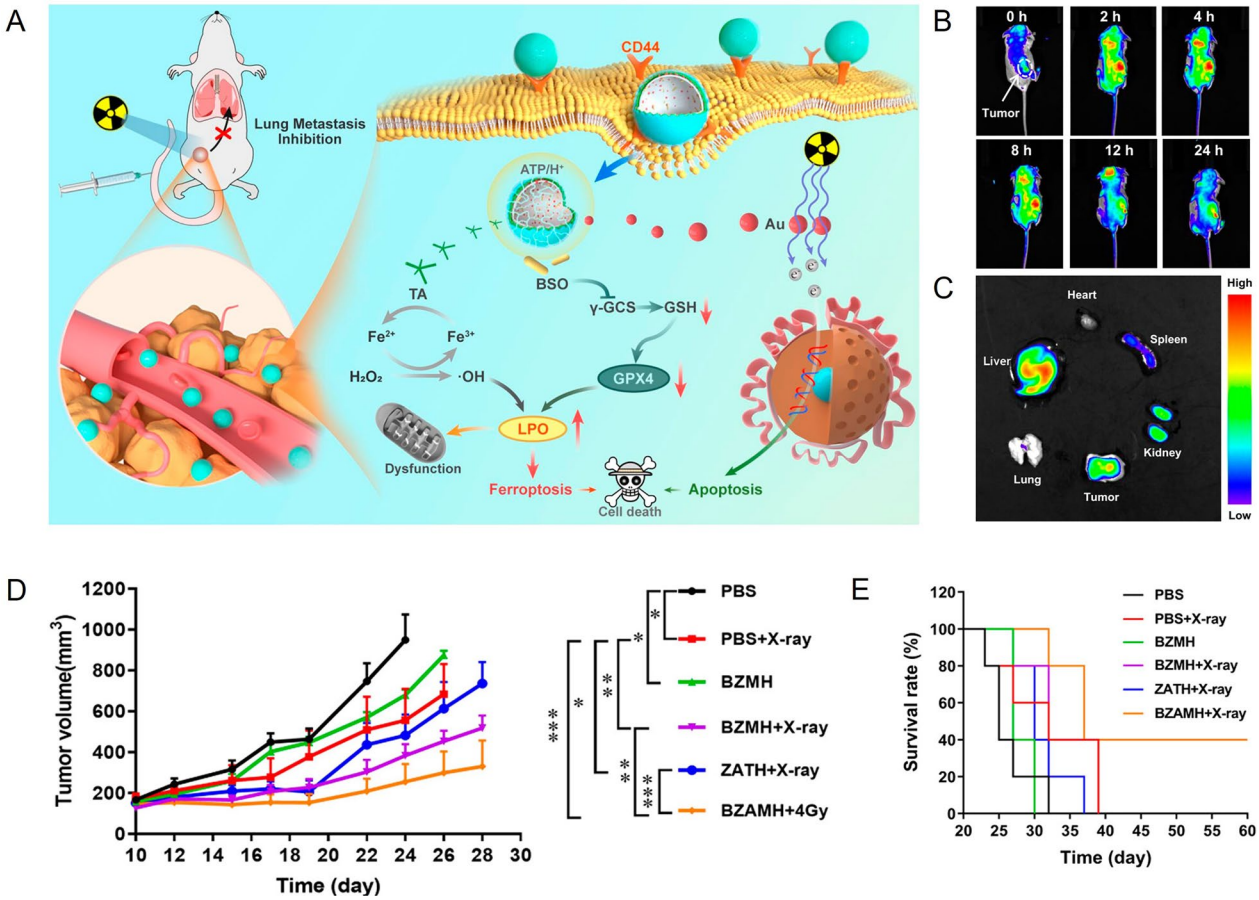


Fig. 10 **A** Schematic representation of the therapeutic mechanism of BZAMH NPs. **B** The fluorescence biodistribution of Cy5.5-labeled BZAMH in 4T1 tumor-bearing mice. **C** The Cy5.5 fluorescent images of tumor and major organs 24 h post-injection. **D** Time-dependent tumor growth curves after various treatments. **E** Survival curves of mice under various treatments (reproduced from ref. [157] with permission. Copyright 2023, American Chemical Society)

to the disintegration of the nanolongan gel network, which rapidly released Fe^{2+} and Dox. In this scenario, Fe^{2+} reacts with intracellular H_2O_2 to produce potent ROS for ferroptosis, while the co-released Dox penetrates the nucleus to induce apoptosis synergistically. In vitro experiments were performed to investigate the effects of nanolongan-induced ferroptosis and apoptosis on 4T1 cells. In a simulated mildly acidic tumor microenvironment (pH = 6.8), GPX4 was inhibited, leading to the fatal accumulation of LPOs (Fig. 8).

Combining ferroptosis with phototherapy

Phototherapy, including PDT and PTT, utilizes a light-activated strategy for cancer treatment. PDT relies on the local activation of photosensitizers within the tumor to induce chemical damage, leading to cell death. On the other hand, PTT employs photothermal agents to convert light energy into heat. A sufficiently high temperature (typically above 42 °C) can induce tumor cell death without causing significant harm to the surrounding healthy tissue [153] (Fig. 9A).

Geng and colleagues reported a "nanomatchbox" structure named GNRs@JF/ZIF-8 [154]. They encapsulated gold nanorods (GNRs) loaded with the bromodomain-containing protein 4 (BRD4) inhibitor (+)-JQ1 (JQ1) and ferric ammonium citrate (FAC) into zeolitic imidazolate framework-8 (ZIF-8). Under near-infrared II (NIR-II) irradiation, GNRs can absorb light energy through the localized surface plasmon resonance effect (LSPR) and convert it into heat, generating high temperature in the TME and inducing a photothermal effect. This photothermal effect not only kills tumor cells but also promotes drug release. ZIF-8 can degrade in acidic environments, releasing JQ-1 and FAC. On the one hand, the FAC-induced Fenton/Fenton-like reactions in the TME can produce iron (Fe^{3+}/Fe^{2+}) and ROS. On the other hand, JQ1 can inhibit the elimination of ROS by downregulating the expression of GPX4, leading to the accumulation

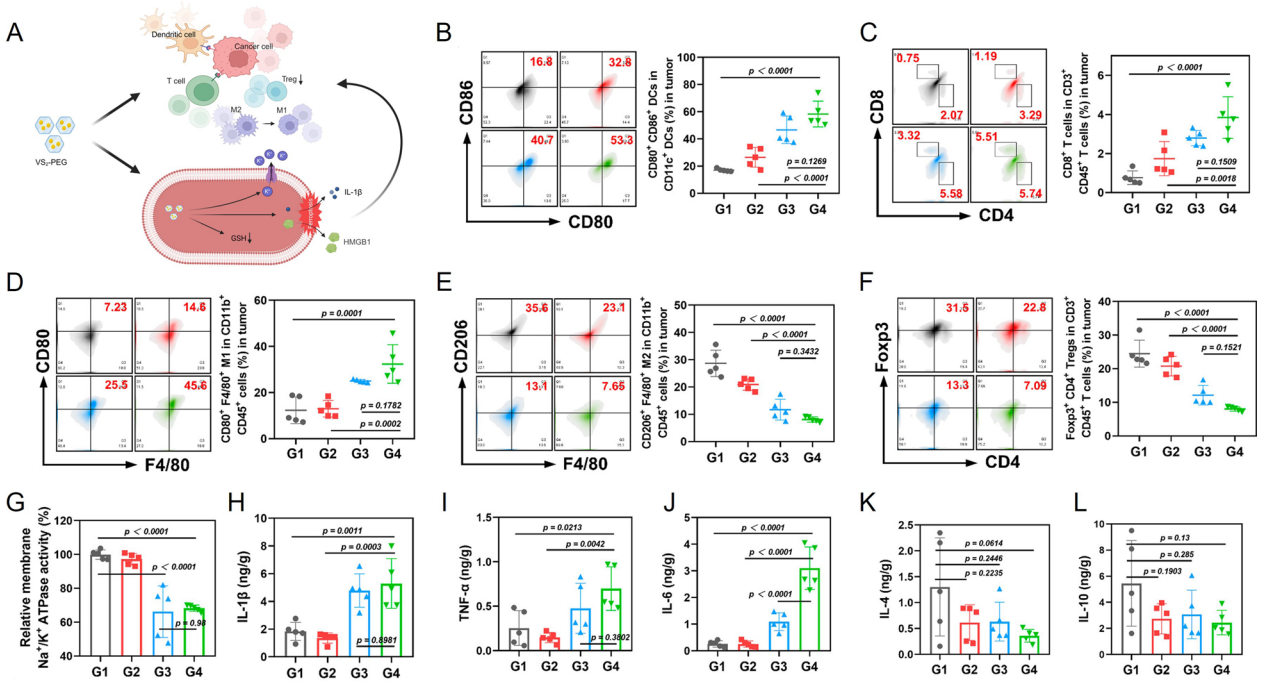


Fig. 11 **A** Schematic representation of nanobiotechnology combines ferroptosis with immunotherapy. VS2-PEG NSs achieve synergistic treatment of ferroptosis and immunotherapy by depleting GSH and regulating the immune microenvironment, which includes enhancing the tumor infiltration of T cells and dendritic cells, and reducing the proportion of Treg cells and M2-type macrophages. **B** DC maturation ($CD80^+$ $CD86^+$) in tumors, gating on $CD11c^+$ cells; **C** $CD8^+$ T cells in $CD3^+$ $CD45^+$ T cells in the tumor; **D** $CD80^+$ $F4/80^+$ M1 macrophages in $CD11b^+$ $CD45^+$ cells in the tumor; **E** $CD206^+$ $F4/80^+$ M2 macrophages in $CD11b^+$ $CD45^+$ cells in the tumor; **F** $Foxp3^+$ $CD4^+$ Tregs in $CD3^+$ $CD45^+$ T cells in the tumor. G1, PBS; G2, α-PD-1; G3, VS2-PEG; and G4, VS2-PEG + α-PD-1. **G**–**L** Detection of Na^+/K^+ ATPase activity, cytokines IL-1β, TNF-α, IL-6, IL-4, and IL-10 in tumors (**A** Was created with Biorender.com; **B**–**I** Were reproduced from ref. [167] with permission. Copyright 2023, American Chemical Society)

of LPOs. Overall, the authors improved the therapeutic effect on tumor by combining PTT with iron-based/BRD4-downregulation (Fig. 9).

Combining ferroptosis with radiotherapy

For decades, radiotherapy has been a primary method in clinical cancer treatment [155]. On the one hand, radiotherapy acts directly on the DNA molecules of tumor cells through high-energy radiation, causing double-strand or single-strand breaks in the DNA. On the other hand, radiotherapy generates a large amount of ROS, indirectly causing DNA strand breaks and damaging proteins, lipids, and other biomolecules, ultimately leading to tumor cell apoptosis [156]. However, the severe side effects and the issue of resistance significantly hinder the clinical efficacy of radiotherapy, necessitating new strategies to improve its clinical application [156]. Based on the antitumor mechanisms and existing issues of radiotherapy, ferroptosis has been considered a feasible approach to enhance the clinical effectiveness of radiotherapy. For instance, both radiotherapy and ferroptosis mediate cellular damage by generating ROS, their combination is expected to enhance therapeutic effects by increasing ROS production and disrupting antioxidant defenses. Additionally, using nanodelivery technology to specifically deliver radiotherapy drugs and ferroptosis inducers to the lesion can reduce the side effects on normal cells during treatment, significantly alleviating patient suffering and improving clinical outcomes (Fig. 10A).

In the study by Zeng et al., researchers developed a multifunctional nanomedicine based on metal–organic frameworks (MOFs) (BZAMH) to enhance ferroptosis and radiotherapy efficacy in triple-negative breast cancer [157]. BSO, a γ-glutamylcysteine synthetase (γ-GCS) inhibitor, suppresses intracellular GSH synthesis, indirectly inactivating GPX4, thereby weakening the antioxidant defenses of tumor cells. The surface decoration of gold nanoparticles enhances the deposition of X-ray radiation doses, inducing a burst of ROS to synergistically promote tumor cell death in the context of weakened antioxidant defenses (Fig. 10).

Combining ferroptosis with immunotherapy

Immunotherapy, involving approaches such as immune checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines, can eradicate cancer cells by activating the

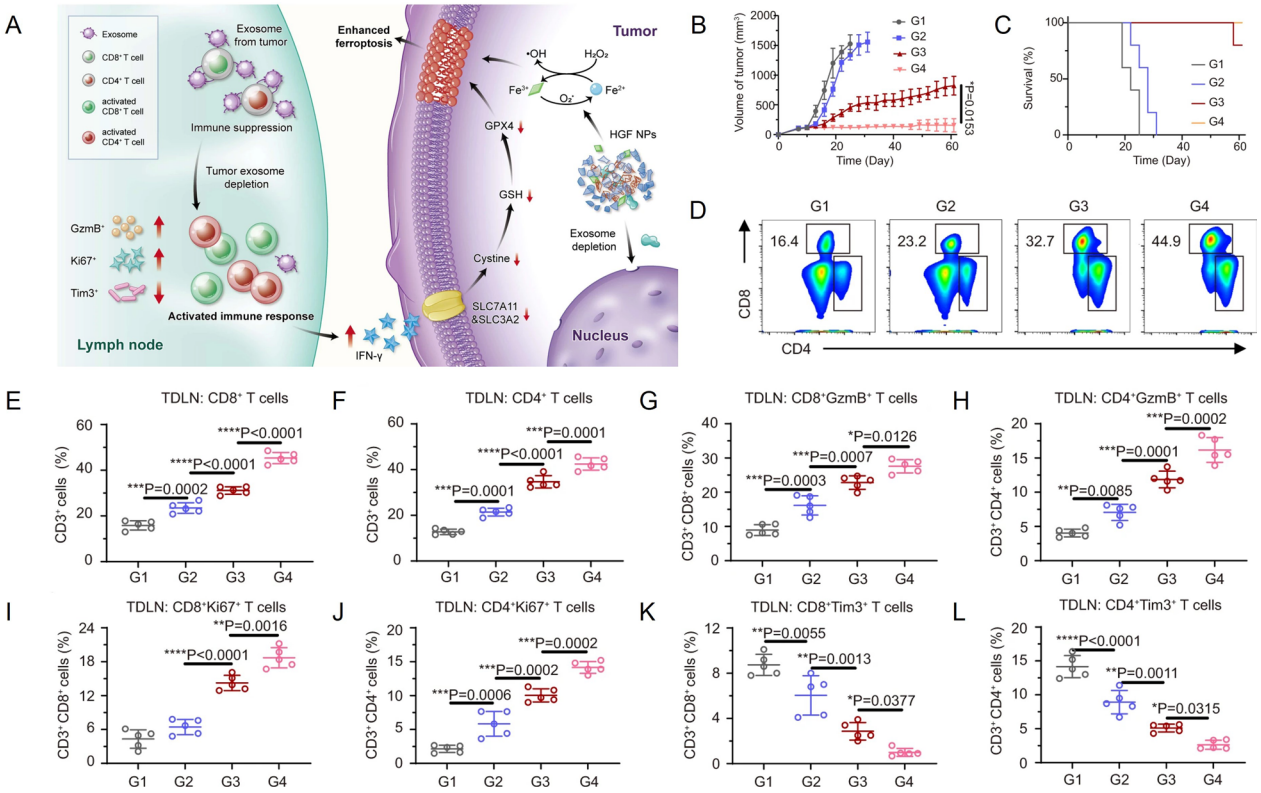


Fig. 12 **A** Schematic representation of the synergistic antitumor effect of the ferroptosis inducer Fe^{3+} and the exosome inhibitor GW4869. **B** Tumor growth curves during treatment. G1, PBS; G2, anti-PD-L1; G3, HGF; G4, HGF^{+} anti-PD-L1. **C** Survival rates of different groups over time. **D**–**F** Quantitative analysis the proportion of $CD8^{+}$ and $CD4^{+}$ T cells in $CD3^{+}$ T cells in the tumor-draining lymph node. **G**–**L** Quantitative analysis the proportion of $GzmB^{+}$ cells, $Ki67^{+}$ cells and $Tim3^{+}$ cells in $CD8^{+}$ and $CD4^{+}$ T cells (reproduced from ref. [168] with permission. Copyright 2021, Springer Nature)

patient's immune system to recognize and destroy them [158, 159]. Immunotherapy can offer long-term antitumor effects; however, its efficacy may be limited in certain cases due to the immunosuppressive nature of the TME or the immune evasion mechanisms of tumor cells [160, 161]. Notably, existing research has shown that ferroptosis can enhance immunogenicity through multiple pathways, demonstrating synergistic effects with immunotherapy, including (1) destroying cell membrane integrity to expose various tumor-associated antigens and activating specific immune responses; (2) mediating the release of pro-inflammatory cytokines, such as IL-33; (3) directly activating T cells through the release of signalling molecules such as high mobility group box 1 (HMGB1), which induces immunogenic cell death (ICD) in cancer cells; and (4) modulating the immune microenvironment, for example, by promoting the conversion of M2 macrophages to M1 macrophages and inhibiting Treg cells [162–165]. Concurrently, Wang et al. demonstrated that immunotherapy enhances the release of interferon-γ (IFN-γ) by $CD8^{+}$ T cells, which downregulates the expression of SLC3A2 and SLC7A11, the subunits of the glutamate-cystine antiporter system Xc^{-}, thereby promoting LPO and ferroptosis in tumor cells [166]. However, tumor cells typically overexpress immunosuppressive molecules such as PD-L1 to evade T cell attacks, which, to some extent, hinders the synergistic effect of ferroptosis with immunotherapy by enhancing immunogenicity. Nowadays, immune checkpoint inhibitor therapy, represented by PD-1/PD-L1 inhibitors, has become a crucial direction in cancer immunotherapy. This suggests that combining ferroptosis with immune checkpoint inhibitor therapy to further enhance tumor treatment efficacy is a feasible approach. In summary, combining ferroptosis with immunotherapy holds great potential for applications (Figs. 11 and 12).

Pei et al. developed PEGylated vanadium disulfide nanosheets (VS_2-PEG NSs) for synergistic therapy involving ferroptosis and immunotherapy [167]. VS_2-PEG NSs deplete GSH and inhibit Na^{+}/K^{+} ATPase activity by degrading vanadate, which induces potassium efflux, inflammasome activation, and IL-1β production, effectively triggering ferroptosis and ICD,

which not only enhances dendritic cells (DCs) and T-cell immune infiltration but also induces a robust anti-tumor immune response by modulating the immune microenvironment, such as reducing the percentage of regulatory T cells (Tregs) and M2-type macrophages. The combination of VS_2-PEG NSs with PD-1 blockade achieved satisfactory therapeutic outcomes (Fig. 11).

Tumor cells typically overexpress PD-L1 on their surface and in secreted exosomes to inhibit T cell activity. In two studies by the Dai's team, researchers constructed two nanomedicine systems (HGF NPs and PFG MPNs) by combining the ferroptosis inducer Fe^{3+} and the exosome inhibitor GW4869. While Fe^{3+} induces ferroptosis and releases DAMPs to promote T cell activation, GW4869 reduces the secretion of tumor-derived exosomes, thereby weakening the immunosuppression of T cells by tumor cells, and enhancing the synergistic therapeutic effects of ferroptosis and immunotherapy [168, 169] (Fig. 12).

Clinical applications of nanobiotechnology in ferroptosis treatment

Nanobiotechnology advances ferroptosis for the treatment of clinical diseases

Many clinical diseases are closely related to ferroptosis, including cancer, neurodegenerative diseases, cardiovascular and cerebrovascular diseases, and kidney diseases. Inducing or inhibiting ferroptosis through nanobiotechnology holds promise as a potential therapeutic strategy for these diseases.

Nanobiotechnology advances ferroptosis for the treatment of cancer

Cancer has always been a focal point in ferroptosis research. On one hand, ferroptosis inducers can induce ferroptosis in tumor cells. On the other hand, ferroptosis can effectively address the issue of drug resistance during cancer treatment. However, ferroptosis inducers often cause damage to immune cells such as T cells [170]. Therefore, utilizing the targeting capabilities of nanobiotechnology to precisely deliver ferroptosis inducers to tumor sites while avoiding damage to normal cells and immune cells will greatly facilitate the clinical application of ferroptosis.

Nanobiotechnology advances ferroptosis for the treatment of neurodegenerative diseases

Studies have shown that ferroptosis is associated with various neurodegenerative diseases. For instance, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are often accompanied by abnormal iron accumulation and oxidative stress in brain tissue, which together lead to neuronal ferroptosis and exacerbate disease symptoms. Nanobiotechnology enables the precise delivery of antioxidants and iron chelators, reducing iron content and oxidative damage in neurons. Additionally, due to the presence of the BBB, conventional drugs often struggle to reach the lesions. Therefore, utilizing nanobiotechnology to improve drug bioavailability and enhance permeability will significantly improve the treatment efficiency for neurodegenerative diseases [171].

Nanobiotechnology advances ferroptosis for the treatment of cardiovascular and cerebrovascular diseases

Multiple studies have established a crucial role of ferroptosis in cardiovascular and cerebrovascular diseases, including atherosclerosis and ischemia–reperfusion-induced organ damage. For example, reports have indicated that ferroptosis is a major pathogenic mechanism in DOX- and ischemia–reperfusion-induced cardiomyopathy [172, 173]. Therefore, inhibiting ferroptosis is a potential therapeutic approach for treating cardiovascular and cerebrovascular diseases. More notably, utilizing nanobiotechnology, it is possible to precisely deliver ferroptosis-related drugs to specific organs and extend their circulation time in the vasculature, thereby enhancing therapeutic efficacy.

Nanobiotechnology advances ferroptosis for the treatment of kidney diseases

Acute kidney injury (AKI) refers to the sudden failure or damage of kidney function, typically leading to extensive cell death and inflammatory responses, and resulting in abnormal renal excretory function [174]. GPX4 has been reported to treat AKI by inhibiting ferroptosis [175]. This suggests that we can utilize nanodrug delivery systems, such as LNPs, combined with mRNA therapy to achieve on-demand and precise treatment for AKI. Additionally, some active components of traditional Chinese medicine, including Ginkgolide B and Baicalein, can also alleviate acute or chronic kidney injury by inhibiting ferroptosis [176, 177]. Enhancing the solubility and targeting of these drugs through nanobiotechnology will greatly improve clinical treatment outcomes.

Personalized treatment of ferroptosis-related diseases by nanobiotechnology

With the continuous maturation of technologies such as genomic sequencing, transcriptomic sequencing, and proteomic analysis, personalized diagnosis and treatment

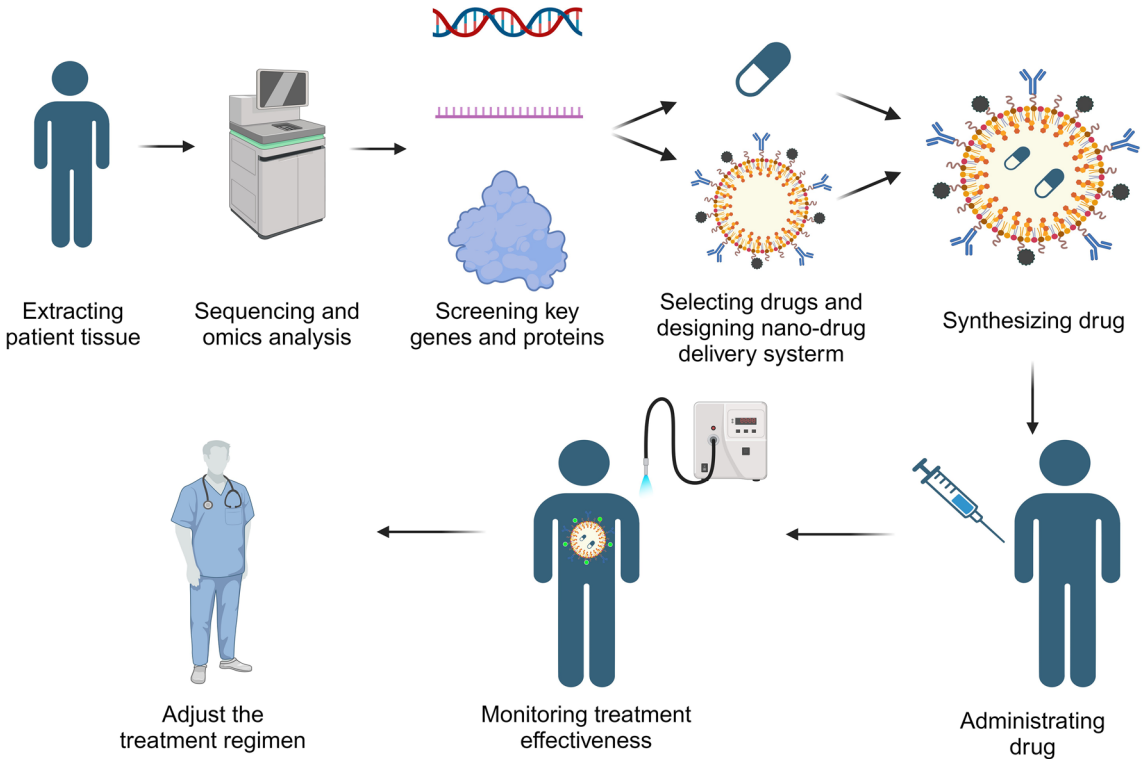


Fig. 13 Nanobiotechnology realizes personalized diagnosis and treatment integration for ferroptosis-related diseases (the figure is created with Biorender.com)

have become future trends in clinical disease treatment. By utilizing these high-throughput biotechnologies, it is possible to delve into patients' pathogenic causes, thereby achieving early prediction of disease risk and accurate interpretation of pathological mechanisms [178, 179]. Notably, due to the complex metabolic regulatory network involved in ferroptosis, the pathogenic factors among patients often differ. Nanodrug delivery systems loaded with therapeutic drugs can be further functionalized by ligands capable of targeting unique biomarkers discovered in individual patients. Such a level of specificity ensures that therapeutic agents are delivered directly to lesions, enhancing the efficacy of treatment and minimizing damage to healthy tissues. Hence, employing these detection and analysis technologies to identify disease biomarkers in patients and then modifying nanodrug delivery systems with ligands that specifically target these biomarkers will improve disease treatment and reduce the side effects caused by previous treatment methods [180]. It is also noteworthy that due to interindividual differences among patients, drug dosages require personalized adjustments to achieve precise delivery and controlled release. Future research on nanomedicine should focus on enhancing targeting specificity and delivery efficiency, developing intelligent response systems, and controlling the spatiotemporal release of drugs. Personalized nanomedicine should be designed based on patient-specific analyses, with dynamic adjustments made according to patient responses and biomarker changes during treatment. In addition, multidisciplinary collaboration is necessary, integrating nanotechnology with medicine to advance the application of nanobiotechnology in clinical practice, thereby significantly improving the efficacy of personalized treatments (Fig. 13).

Integrating diagnosis and treatment of ferroptosis-related diseases by nanobiotechnology

Integrating diagnosis and treatment is a crucial concept in the modern medical system [181]. nanobiotechnology not only enhances the therapeutic effects on ferroptosis-related diseases but also offers an innovative approach to integrating the diagnosis and treatment of these diseases through the physical, chemical, and biological properties of certain nanomaterials [182, 183]. This dual functionality simplifies medical procedures and significantly improves patient outcomes through early intervention and dynamic, personalized treatment [184]. Furthermore, the integration of diagnostic reagents into these nanomaterials represents a new approach to treating ferroptosis-related diseases. Imaging modalities, such as

magnetic resonance imaging (MRI) contrast agents or fluorescent markers, can be incorporated into the design of nanodrug delivery systems [185]. This technology enables clinicians to visualize the distribution of nanodrug delivery systems within the body, assess the efficiency of tumor targeting, and monitor the progression of ferroptosis in real-time. Such real-time feedback is invaluable for adjusting treatment plans to achieve optimal outcomes. Moreover, the development of nanobiotechnology for diagnosing ferroptosis-related diseases has paved the way for personalized medicine, as mentioned earlier. By analyzing an individual patient's genetic makeup, specific biomarkers, and disease characteristics, nanobiotechnology can be customized to match each patient's unique features. In summary, leveraging the multifunctional potential of nanobiotechnology is likely to enhance the precision, effectiveness, and safety of treatments, further advancing the realization of personalized medicine (Fig. 13).

Conclusions

Overall, ferroptosis has demonstrated significant potential in the treatment of various diseases, due to its complex and unique metabolic regulatory network, which plays a crucial role in reversing drugs resistance. Recent years have witnessed the burgeoning potential of nanobiotechnology, highlighting the integration of nanobiotechnology with ferroptosis therapy to enhance the efficacy of ferroptosis-based treatments, including improving the bioavailability of drugs to enhance therapeutic effects, enhancing drug targeting and penetration to increase delivery efficiency and reduce side effects, and synergizing with other treatment modalities. These aspects are important in drug development and clinical therapy.

Despite the promising prospects of nanobiotechnology for improving ferroptosis-based therapeutic outcomes, several challenges warrant attention. The accumulation of certain NDDSs in organs such as the liver and kidneys, due to their difficulty in degradation, can increase metabolic stress on these organs and potentially cause severe adverse reactions. Therefore, the degradability of NDDSs is a critical factor that must be considered in the design of them. Moreover, while some nanomaterials can synergize with immunotherapy by enhancing immunogenicity, they may also provoke severe inflammatory responses, causing significant pain to patients. Thus, avoiding unnecessary immune reactions is a critical issue that nanobiotechnology needs to address. Finally, standardized and large-scale production of these drugs remains a fundamental challenge for their clinical applications, and the difficulty in overcoming this challenge for many nanodrugs significantly limits their clinical translation. Consequently, technological innovation and optimization of production processes are required to reduce costs and achieve standardized and large-scale production.

Given the unresolved issues highlighted above, we propose future directions for nanobiotechnology in the applications of ferroptosis. For instance, developing intelligent nanosystems tailored to specific biological microenvironments (such as pH and enzymatically active biomolecules) could enable more precise drug targeting. Notably, due to the complexity of the ferroptosis regulatory network, there is often variability in genomic and transcriptomic expression among patients. Therefore, integrating genomics and proteomics to design NDDSs targeting specific genes could pave the way for personalized treatment strategies in nanobiotechnology and ferroptosis, enhancing both the efficacy and safety of treatments. Moreover, by leveraging the unique physicochemical properties of certain nanomaterials, the future of nanobiotechnology should aim to integrate multifunctional capabilities (such as imaging, diagnostics, phototherapy, radiotherapy, and electromagnetic therapy) into a unified system, facilitating a one-stop solution for the diagnosis and treatment of diseases such as cancer. Finally, to reduce side effects, lower costs, and achieve standardized and large-scale production, it is also essential to explore further nanomaterials to broaden their applications in the biomedical field.

In summary, the strategy of utilizing nanobiotechnology to enhance the therapeutic effects of ferroptosis-related diseases is promising and worthy of investigation.

Abbreviations

·OH	Hydroxyl radicals
27-HC	27-Hydroxycholesterol
4-HNE	4-Hydroxynonenal
7-DHC	7-Dehydrocholesterol
AA	Arachidonic acid
ACSL4	Acyl-CoA synthetase long-chain family member 4
AdA	Adrenic acid
AKI	Acute kidney injury
ART	Artesunate
BBB	Blood brain barrier
BRD4	Bromodomain-containing protein 4
CDDP	Cisplatin
DCs	Dendritic cells
DMT1	Divalent metal transporter 1
DOX	Doxorubicin
EPR	Enhanced permeability and retention effect
ESCC	Esophageal squamous cell carcinoma
FAC	Ferric ammonium citrate
FADS2	Fatty acid desaturase 2
FATPs	Fatty acid transport proteins
Fer-1	Ferrostatin-1
FPN	Ferroportin
FTH	Ferritin heavy chain
FTL	Ferritin light chain
GPX4	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
HCC	Hepatocellular carcinoma
HDP	Hyperbranched polyglycerol
HMGB1	High mobility group box 1

HO-1	Heme oxygenase-1
ICD	Immunogenic cell death
ICH	Intracerebral hemorrhage
IREs	Iron-responsive elements
IRP1	Iron-regulatory protein 1
IRP2	Iron-regulatory protein 2
LF	Lactoferrin
LIP	Labile iron pool
LOX	Lipoxygenase
LPCATs	Lysophosphatidylcholine acyltransferases
LPO	Lipid peroxidation
LSPR	Localized surface plasmon resonance effect
MDA	Malondialdehyde
MMP2	Matrix metallopeptidase 2
MND	Magnetic nanodroplet
MPDA	Mesoporous polydopamine
MRI	Magnetic resonance imaging
MUFAs	Monounsaturated fatty acids
NCOA4	Nuclear receptor coactivator 4
NDDSs	Nanodrug delivery systems
NIR	Near-infrared light
NPs	Nanoparticles
NTBI	Non-transferrin-bound iron
Pa	PD-1 antibodies
PDSA	Poly (disulfide amide)
PFP	Perfluoropentane
PROTACs	Proteolysis-targeting chimeras
PTT	Photothermal therapy
PUFAs	Polyunsaturated fatty acids
RCD	Regulated cell death
ROS	Reactive oxygen species
SCD1	Stearoyl-CoA desaturase 1
SDT	Sonodynamic therapy
SFAs	Saturated fatty acids
si-NRF2	NRF2 siRNA
SLC7A11	Solute carrier family 7, membrane 11
SLN	Solid lipid nanoparticle
SRF	Sorafenib
STEAP	Six-transmembrane epithelial antigen of the prostate
System Xc^-	Cystine/glutamate antiporter system
TA	Tannic acid
TAAs	Tumor-associated antigens
TCM	Traditional Chinese Medicine
TF	Transferrin
TFR	Transferrin receptor
Ti	TGF-β inhibitors
TME	Tumor microenvironment
Tregs	Regulatory T cells
TSAs	Tumor-specific antigens
TXNRD1	Thioredoxin reductase 1
UV	Ultraviolet light

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors declare full consent for publication.

Competing interests
The authors declare no competing interests.

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