


Nanomedicines Targeting Ferroptosis to Treat Stress-Related Diseases

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Abstract: Ferroptosis, a unique form of regulated cell death driven by iron-dependent lethal lipid peroxidation, is implicated in various stress-related diseases like neurodegeneration, vasculopathy, and metabolic disturbance. Stress-related diseases encompass widespread medical disorders that are influenced or exacerbated by stress. These stressors can manifest in various organ or tissue systems and have significant implications for human overall health. Understanding ferroptosis in these diseases offers insights for therapeutic strategies targeting relevant pathways. This review explores ferroptosis mechanisms, its role in pathophysiology, its connection to stress-related diseases, and the potential of ferroptosis-targeted nanomedicines in treating conditions. This monograph also delves into the engineering of ferroptosis-targeted nanomedicines for tackling stress-related diseases, including cancer, cardio-cerebrovascular, neurodegenerative, metabolic and inflammatory diseases. Anyhow, nanotherapy targeting ferroptosis holds promise by both promoting and suppressing ferroptosis for managing stress-related diseases.

Keywords: ferroptosis, stress-related diseases, lipid peroxidation, nanoparticles, nanomedicine, targeted therapy

Introduction

Cell death is crucial for maintaining body development and metabolism balance. It occurs in two forms: accidental cell death (ACD) and regulatory cell death (RCD). ACD is a biologically uncontrolled process, whereas RCD involves strictly structured signaling cascades and molecularly definitive effector mechanisms.¹ Ferroptosis, a newfound modality of RCD featured by iron-dependent lipid peroxidation, has emerged as a crucial player in the pathophysiology of various stress-related diseases. Its association with oxidative damage and cell death makes it a potential target for therapeutic interventions in conditions marked by cellular stress.²

Stress-related diseases are medical conditions that are either caused or exacerbated by chronic or excessive stress.³ Stress, particularly chronic and oxidative stresses, can have a profound impact on the body's physiological processes, leading to a range of health problems. Many diseases are initially caused by stress and are aggravated with the haunting of stress, such as atherosclerosis, senile dementia, and diabetes. It has been shown that there exists a significant crosstalk between ferroptosis and stress. Ferroptosis can be induced or triggered by various stressors through multiple mechanisms.⁴ The dysregulation of ferroptosis pathways can exacerbate cellular damage and death, contributing to the progression of stressful disorders. In these conditions, the imbalance between oxidative stress and the body's antioxidant defense mechanisms can trigger ferroptosis, putting ferroptosis at the crossroad of stress-related diseases. Targeting ferroptosis pathways may offer new therapeutic opportunities for managing stress-related diseases by modulating key regulators of ferroptosis, such as glutathione peroxidase 4 (GPX4) and iron metabolism.^{5–10} In addition, targeting ferroptosis in various diseases holds significant therapeutic implications due to its prominent role in cell death and disease onset. For instance, inducing ferroptosis in cancer can sensitize cancer cells to necrosis and inhibit tumor growth,

especially for chemotherapy-resistant tumor cells.¹¹ Suppression of ferroptosis can mitigate neuronal damage and slow the progression of neurodegenerative diseases.¹² Otherwise, it may be possible to eliminate pathogens and reduce infection-associated stress by inducing ferroptosis in bacteria or viruses.¹³

Nanotechnology represents an emerging branch of science for designing nanomaterials with a nanoscale size and specific function at various microcosmic levels.¹⁴ The manipulation of enabling nanotechnology into biomedical applications is best known as nanomedicine. Nanomedicine can address big medical problems in small ways.^{15,16} Ferroptosis therapy is a relatively new remedial action, and there are several challenges such as insufficient pharmacologic activity and side effects caused by off-target that need to be overcome before access to the clinic.¹⁷ Ferroptosis-targeted nanomedicine can effectively dissolve this dilemma. Likewise, nanomedicines can be engineered to target specific cells or tissues affected by stress-related diseases. Functionalized nanoparticles (NPs) with ligands, antibodies or biomimetic membranes allow for targeted delivery of ferroptosis modulators by recognizing specific markers on diseased cells. They not only protect the therapeutic agents from elimination, but also enhance their stability and bioavailability.¹⁸ Nanomedicines can target ferroptosis pathways in stress-related diseases through rational engineering, leading to expectant and efficient therapeutic interventions for these diseases.

Nanomedicine and nanotechnology bring about an opportunity to fight against stress-related diseases through ferroptosis regulation. Exploring ferroptosis in stress-related diseases offers new perspectives on treatment approaches. This review examines the importance of ferroptosis in stress-related diseases, the spectrum of stress-related diseases, the engineering philosophy of ferroptosis-targeted nanomedicines, and the potential of nanotherapy in this context. It is supposed to bring inspiration for the treatment of stress-related diseases through ferroptosis.

What Do We Know About Ferroptosis and Its Role in Diseases?

Iron is an essential trace element for the human body that is involved in the formation of many proteins, including hemoglobin, myoglobin, and ferritin, as well as various redox reactions in cells.¹⁹ Under normal physiological conditions, the complex and precise mechanisms of iron homeostasis ensure that intracellular iron concentrations remain stable and prevent intracellular iron overload from triggering iron toxicity. Ferroptosis, a newly defined form of cell death, is a non-apoptotic RCD driven by iron-dependent lethal lipid peroxidation.²⁰ This unique programmed cell death is regulated by multiple cellular metabolic pathways (including redox homeostasis, iron metabolism, mitochondrial activity, and the metabolism of amino acids, lipids, and saccharides) as well as a variety of disease-related signaling pathways.²¹ The immanent cause of ferroptosis is the disequilibrium of iron metabolism that results in depletion of intracellular antioxidants, hence the accumulation of lipid peroxides, leading to cell death due to membrane damage. Mechanistically, ferroptosis is caused by various stresses on the cells that incurs iron overload (manifested by increased ferritinophagy) followed by lipid peroxidation with the involvement of reactive oxygen species (ROS), which causes alterations in the structure and function of the cell membrane and the onset of cell death.^{4,22}

Unlike classical apoptosis, there is no cellular shrinkage and chromatin condensation during ferroptosis, but there is mitochondrial wrinkling (decreased cristae and membrane density) and increased lipid peroxides (elevated MDA and 4-hydroxynonenal).²³ Common inhibitors for apoptosis, autophagy, and pyroptosis cannot affect ferroptosis, but ferric ion chelators can, indicating that ferroptosis is a ferric ion-dependent biological process. Initially, ferroptosis was believed to be a new mode of cell death, but recent studies reveal that ferroptosis exists in a shared pathway with other programmed cell deaths.²⁴ Perhaps multiple modes of cell death occur simultaneously, or one of these modes is dominant in some diseases. Ferroptosis, as a fantastic mode of cell death, is closely related to cellular metabolism and stress, including disturbed metabolisms of iron, selenium, amino acids, and lipids as well as aberrant redox.

The occurrence of ferroptosis depends on the outcome of the confrontation between the execution system and defense system for ferroptosis (Figure 1).²⁵ Ferroptosis execution refers to lipid peroxidation in the plasma membrane, mitochondria, endoplasmic reticulum, and lysosomes that results in Fe-dependent cell death, in which acyl-CoA synthetase long-chain family member 4 (ACSL4) and Fe²⁺-mediated Fenton reaction contribute to lipid peroxidation.²⁶ Polyunsaturated fatty acid (PUFA)-containing phospholipids constitute the major source of lipid peroxidation. ACSL4 can facilitate the incorporation of PUFA into membrane phospholipids, thus playing a role in promoting ferroptosis. Fenton reaction is a process that Fe²⁺ catalyze the production of toxic hydroxyl radical ($\cdot\text{OH}$) from hydrogen peroxide. The resultant $\cdot\text{OH}$

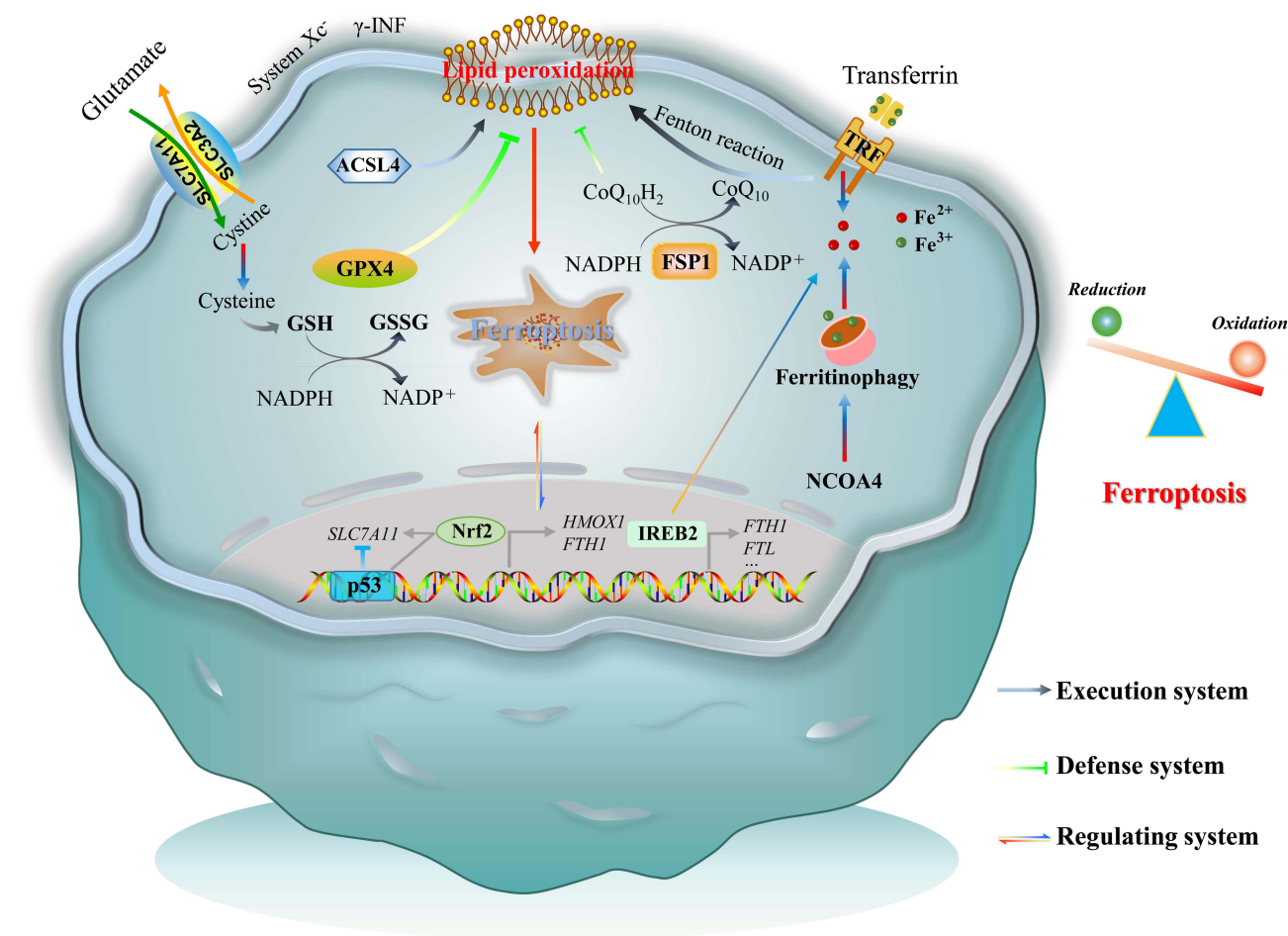


Figure 1 Schematic of ferroptosis. Ferroptosis is the result of a combined confrontation between execution and defense of the body's redox systems, regulated by multiple signaling pathways.

triggers lipid peroxidation of cellular membrane. The defense system of ferroptosis consists of GPX4 and ferroptosis suppressor protein 1 (FSP1).²⁷ GPX4 is able to utilize glutathione (GSH) to protect cells from ferroptosis by reducing toxic lipid peroxides into non-toxic lipid alcohols. GPX4 system represents the most important defense mechanism against ferroptosis in cells. FSP1 is a NADPH-ubiquinone reductase that can abrogate lipid peroxidation by reducing COQ10 and Vitamin K whereby to inhibit ferroptosis.

With the advances in ferroptosis research, it is beginning to be recognized that the regulatory network of ferroptosis plays a broad role in various physiopathologic processes.²⁸ Ferroptosis can be activated under acute or chronic pathologic conditions. Accumulative findings suggest that ferroptosis is strongly associated with stress-related diseases, including metabolic diseases, neurodegenerative diseases, cardiovascular diseases, and carcinoma. Iron is the most abundant trace element in the human body, which plays a crucial role in various physiological functions, such as oxygen transport, energy production, and oxidative metabolism. Ferroptosis stands out from a variety of therapeutic targets in stress-related diseases because it involves fundamental regulation of iron metabolism and oxidative stress pathways. Conventional formulations are associated with a risk of off-target, though nanomedicine can circumvent this problem subtly by virtue of designable targetability. Actually, the progression of some diseases can be interfered with by activating or inhibiting ferroptosis.

Spectrum of Stress-Related Diseases

Stress-related diseases are health conditions that are influenced or exacerbated by chronic or excessive stress.²⁹ Stress refers to any physical or emotional strain or tension on the body, which can be caused by a variety of factors, including

work, relationships, finances, and health problems. When the body is under stress, it responds by releasing hormones such as cortisol and adrenaline,³⁰ which can have both positive and negative effects on the body. Short-term physiological responses help the body manage stress, but chronic or excessive stress can lead to health issues. In a variety of stresses, oxidative stress,³¹ an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants, has been linked to a wide range of diseases due to its ability to cause damage to cells, proteins, and DNA. As the body's anti-oxidative defense mechanisms become overwhelmed and unable to neutralize the ROS produced by stress, our body will undergo pathophysiological changes, resulting in the genesis of stress-related diseases. These diseases can affect various systems of the body, including the cardiovascular, digestive, metabolic, immune, endocrine, nervous, muscular, and dermal systems (Figure 2).

There is a strong relationship between cardiovascular diseases and stress.³² In response to stress, our body releases a hormone called cortisol. This hormone can cause an increase in blood pressure and heart rate, putting additional strain on the heart. Over time, this can lead to the development of conditions such as hypertension, atherosclerosis, and coronary artery disease. In addition, chronic stress can trigger inflammation in the body,³³ which is an additional risk factor for heart disease. Inflammatory reaction can damage the lining of blood vessels, resulting in the buildup of plaque and increasing the risk of heart attack and stroke. It exists a well-established relationship between inflammatory diseases and stress.³⁴ Upon stress, the body releases stress hormones that impact the immune system and inflammatory response. Chronic stress inflicts our bodies in a state of low-grade inflammation.³⁵ This persistent inflammation has been linked to a variety of inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, asthma, and even conditions like psoriasis. Likewise, the released hormones can affect the function of immune cells, breaking the balance in the immune response and increasing the susceptibility to inflammatory conditions. Besides, chronic stress can predispose to the aggravation of inflammatory conditions,³⁶ leading to flare-ups and worsening symptoms. In turn, chronic inflammation amplifies the risk of developing other health problems, including diabetes and cancer. Some research suggests that stress conduces to the development and progression of some types of cancer.³⁷ For example, stress hormones such as cortisol and adrenaline can promote the growth and spread of certain cancer cells.³⁸ Chronic stress can also weaken or disrupt the immune system, which cause deficiency in immunological surveillance, prompting tumor progression and the occurrence of immune diseases.^{39,40} Chronic stress has also been proved to be associated with neurodegenerative

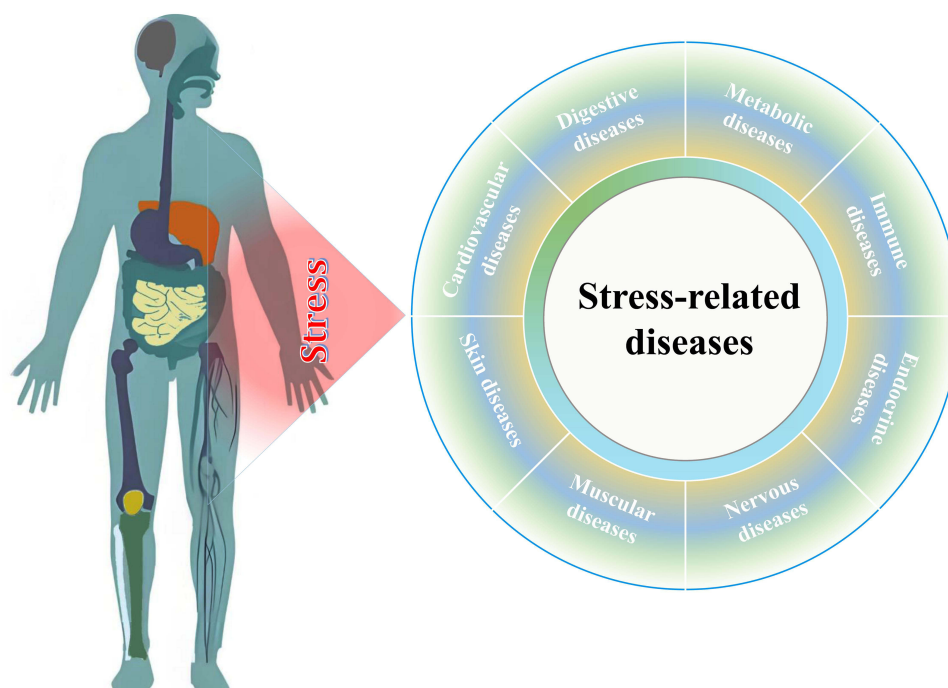


Figure 2 The spectrum of stress-related diseases. Stress can cause hypertension, heart disease, stroke, colitis, rheumatoid arthritis, diabetes, neuritis, Alzheimer's disease, aging, myalgia, systemic lupus erythematosus as well as cancer.

diseases like Alzheimer's and Parkinson's diseases. Prolonged exposure to high levels of stress has detrimental effects on the brain health, including impairing memory and cognitive function, and even contributing to the loss of neurons in certain brain regions.^{41,42} The inflammation developing from chronic stress has been implicated in the genesis and progression of neurodegenerative diseases. Inflammatory responses increase the accumulation of abnormal proteins such as β -amyloid and α -synuclein in neurocytes.⁴³ Otherwise, stress has been implicated in the onset of systemic lupus erythematosus (SLE) and aging.

Understanding the pathophysiological effects of stress on the body is important for developing strategies to manage and mitigate the negative impact of chronic stress on overall health and well-being. Stress can affect individuals differently, with disease severity influenced by factors like genetics, lifestyle, and environment. Many stress-related diseases may have overlapping symptoms with other disease conditions. Nevertheless, accumulative evidence manifests that most diseases originate from chronic stress, followed by inflammation, then lesion, and finally malignancy.

Crosstalk Between Ferroptosis and Stress-Related Diseases

Ferroptosis is defined as a programmed cell death with overlaid accumulation of lipid peroxides, which leads to membrane oxidative damage and cell death. Ferroptosis is suggested to significantly impact stress-related diseases through lipid peroxidation in the cell membrane, a key factor in cellular stress.^{4,22,44} Among the factors of causing cellular stress, lipid oxidation modifications in the lipid bilayer, especially lipid peroxidation, have become a significant regulator in dictating the cell fate. Lipid peroxidation is subject to the modulation of redox homeostasis, which is ultimately modified by ROS and iron metabolism.⁴⁵ Oxidative stress signifies high levels of ROS that likely result in the occurrence of ferroptosis. Oxidative stress and ferroptosis exist crosstalk in a great many of human diseases,⁴⁶ including malignant tumors and vasculopathy. Ferroptosis is essentially involved in the regulation of oxidative stress and inflammatory responses. As known, these cellular pathophysiological processes are implicated in a variety of stress-related diseases.

Most organ damage and degenerative lesions are caused by ferroptosis.⁴⁷ Drug-resistant tumor cells, especially those in a mesenchymal state and prone to metastasis, are very susceptible to ferroptosis.^{48,49} Iron, lipids, ROS, and cysteine in ferroptosis imply a significant connection between cell death, cellular metabolism, and stress. One study found that pro-ferroptotic signaling could accelerate arterial aging via vascular smooth muscle cell senescence, a condition that can be caused by oxidative stress.⁵⁰ It was concluded that the activation of pro-ferroptotic signaling correlated with arterial stiffness in a human study. Another study revealed that ferroptosis was involved in the development of Alzheimer's disease.⁵¹ Mechanistic investigation indicated that NOX4 promoted ferroptosis of astrocytes as a result of oxidative stress-induced lipid peroxidation via mitochondrial metabolic impairment. A parallel study also showed that the loss of ferroportin could worsen memory in Alzheimer's by promoting ferroptosis.⁵² Activation of ferroptosis can contribute to diseases, while its inhibition can also trigger disease development. Tumorigenesis is a paradigm for the restriction of ferroptosis during cell proliferation. In some cases, cancer cells can develop resistance to ferroptosis, allowing them to evade cell death and promote tumor growth and survival.⁵³ Tumor cells can also upregulate antioxidant pathways to counteract the effects of ferroptosis, enabling them to proliferate and resist ferroptotic cell death.⁵⁴ As discussed previously, tumors can be deemed as a chronic stressful disease in addition to genetic and chemical factors. Accordingly, it can be argued that ferroptosis is inextricably linked with the occurrence and development of tumor. Recent studies have shown that ferroptosis may be implicated in the development of other stress-related diseases, including diabetes,⁵⁵ ischemia-reperfusion injury,⁵⁶ fibrosis,⁵⁷ and SLE.⁵⁸ However, more research is required to fully understand the relationship between ferroptosis and these diseases, as well as the potential therapeutic implications of targeting ferroptosis.

Engineering of Ferroptosis-Targeted Nanomedicines

There is no doubt that ferroptosis is associated with the development of many diseases. However, ferroptosis plays a double-edged sword role in the progression of diseases.⁵⁹ In terms of cancer, ferroptosis inhibition promotes unchecked growth of abnormal cells. In this case, activation of ferroptosis is beneficial for managing cancer, especially for metastasis-prone or highly-mutated cancerous cells that are sensitive to ferroptosis. On the other hand, most stress-related diseases highlight inhibition of ferroptosis to halt the disease progression, since ferroptosis mediates or

participates in the evolution of these diseases. Thus, whether ferroptosis is induced or inhibited depends on the type of disease and the role of ferroptosis plays in the disease. Anyway, the medication intended for targeting ferroptosis has shown great promise in addressing refractory diseases.

Physiologically, ferroptosis can be modulated by the use of various chemical agents, natural active ingredients, nanoparticles, or signaling molecules.⁶⁰ The implementation of ferroptotic therapy hinges on the intervention to the execution system, defense system, and regulating system of ferroptosis. Yet, the challenge lies in the ineffective delivery of many regulators to their targets due to undesirable biopharmaceutical properties. Thus, nanomedicine design becomes crucial for precise ferroptotic therapy, leveraging various pathways and compounds. Ferroptosis-targeting nanomedicines can be designed by utilizing various pathways with different medications or molecules. Ferroptosis can be upregulated by inducers (eg, erastin, RSL5 and sorafenib) that act on the execution system or inhibitors (eg, ferrostatin, deferiprone and liproxstatin) that target the defense system through promoting or blocking lipid peroxidation. Likewise, ferroptosis suppression can be implemented to target both the execution and defense systems. The regulating system of ferroptosis consisting of various signaling pathways is also the therapeutic target. Tables 1 and 2 generalizes the commonly used ferroptosis inducers and inhibitors as well as their action mechanisms.

Despite the therapeutic activities, the daunting challenge faced by ferroptotic therapy is the targeting efficiency of ferroptotic medicaments. Many agents demonstrate good regulatory effects on ferroptosis in vitro, but ideal therapeutic outcomes are not frequently gained in vivo, resulting in requirements for the design of targeted delivery systems. Generally, there are three design philosophies available to optimize ferroptotic therapy: i) developing antibody conjugated NPs (ACNPs) to deliver ferroptotic agents; ii) employing nanocarriers to deliver ferroptotic agents; and iii) biomimicking ferroptotic NPs with biomembrane (Figure 3). For small molecule compounds, targeting modification can be achieved by encapsulating them into NPs followed by conjugation with an antibody of ligand.^{18,99} For pure NPs with a ferroptotic activity, they can be camouflaged with autologous biomembrane to improve their targetability.¹⁰⁰ Rational targeting design can capacitate the synergy and attenuation of therapeutic agents, insuring a success of ferroptotic therapy.

Nanotherapy via Promoting Ferroptosis Cancer

The approach to sensitizing ferroptosis is most frequently utilized to treat cancer. Ferroptosis often dysregulates in human cancer. Cancer cells have developed mechanisms to evade ferroptosis,¹⁰¹ contributing to treatment resistance and tumor

Table 1 Representative Inducers of Ferroptosis

Agent Type	Compound	Target	Mechanism	Ref.
Chemicals	Sorafenib	System x_c^-	Inhibit system x_c^- to deplete GSH	[61]
	RSL5	VDACs	Promote production of ROS	[62]
	Erastin	System x_c^- /VDACs	Inhibit system x_c^- and increase ion accumulation	[63]
	RSL3	GPX4	Inhibit the activity of GPX4 via binding selenocysteine	[64]
	Artesunate	GSH	GSH depletion	[65]
Nanoparticles	FSENI	FSP1	Suppress CoQ-FSP1 axis	[66]
	ZnO NPs	Ferritinophagy	Elevate the NCOA4-mediated ferritinophagy	[67]
	Silica NPs	Nrf2	Inhibit Nrf2 through p38	[68]
	CuCP NPs	HMOX1/GSH	Increases intracellular lipid-ROS	[69]
	Silver NPs	GPX4/TfR1	Suppress GPX4 expression and disrupt cellular iron homeostasis	[70]
Biomolecules	Fe ₃ O ₄ NPs	HMOX1	Activate HMOX1 to cause iron overload	[71]
	NEAT1	GSH	Regulating miR-362-3p and MIOX axis	[72]
	LINC00618	System x_c^- /iron	Increase the levels of lipid ROS and iron/decrease the expression of SLC7A11	[73]
	HEPFAL	System x_c^- /iron	Reduce the expression of SLC7A11 and increase the levels of lipid ROS and iron	[74]
	FUNDC2	GPX4/GSH	Regulate mitoGSH via SLC25A11	[75]
	PKCβII	ACSL4	Phosphorylate and activate ACSL4	[76]

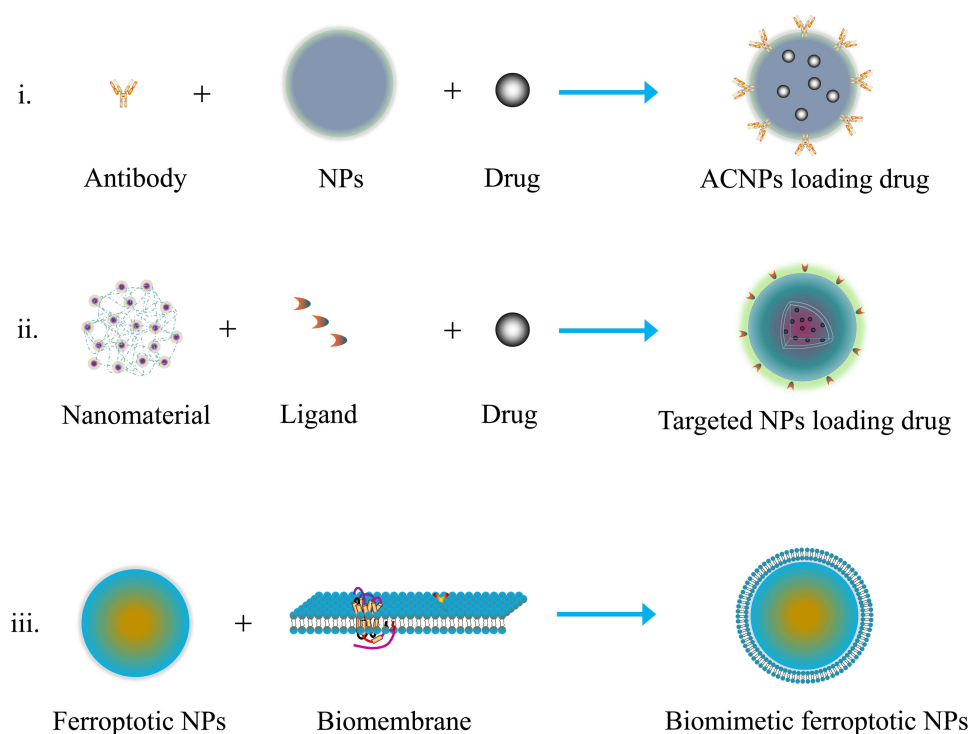
Abbreviations: FSENI, ferroptosis sensitizer I; NEAT1, nuclear paraspeckle assembly transcript 1; LINC00618, a nuclear long non-coding RNA; HEPFAL, a long noncoding RNA; FUNDC2, FUN14 domain-containing 2; PKCβII, protein kinase CβII.

Table 2 Representative Inhibitors of Ferroptosis

Agent Type	Compound	Target	Mechanism	Ref.
Chemicals	Ferrostatin	GPX4/iron	Inhibit lipid peroxidation	[77]
	Liproxstatin-I	GPX4/iron	Improve GPX4 activity and reduce iron accumulation	[78]
	Deferoxamine	Iron	Reduce intracellular iron	[79]
	Ciclopirox olamine	Iron	Reduce intracellular iron	[80]
	Phenoxazine	ROS	Trap radicals to halt oxidation	[81]
	Pioglitazone	ACSL4	Inhibit ACSL4 to prevent ferroptosis execution	[82]
Antioxidants	Vitamin E	ALOX15	Resist LOX PUFA oxygenation	[83]
	Se	CoQ ₁₀	Reduce ubiquinone by sulfide quinone oxidoreductase	[84]
	Taxifolin	GSH	Activate Nrf2 signaling pathway	[85]
	Baicalein	LOX/ACSL/p53	Inhibit LOX, regulate ACSL and decrease p53 acetylation	[86–88]
Nanoparticles	Se NPs	GPX/Nrf2	Restore GPX1/4 antioxidant ability and activate Nrf2	[89,90]
	PDA NPs	ROS/GPX4/iron	Deplete ROS, chelate iron ions, and suppress ubiquitination of GPX4	[91,92]
	Mn ₃ O ₄ NPs	Ferritinophagy/mTOR	Inhibit ferritinophagy-mediated iron mobilization and preserve mTOR activation	[93]
Biomolecules	PHGDH	System x _c [−]	Upregulate the expression of SLC7A11	[94]
	CST I	GPX4	Regulate GPX4 protein stability via OTUB1	[95]
	CoQ ₁₀	FSP1	Reduce lipid peroxyl radicals	[96]
	ENO1	IRP1	Degrade the mRNA of IRP1	[97]
	HIF-1α (protein)	System x _c [−]	Improve the stability of SLC7A11	[98]

Abbreviations: PDA, polydopamine; LOX, lipoygenase; PHGDH, phosphoglycerol dehydrogenase; CST I, cysteine protease inhibitor SN; CoQ10, coenzyme Q10; ENO1, α-enolase I; IRP1, iron regulatory protein I.

survival. Meanwhile, chemotherapy-resistant and metastasis-susceptible cancer cells show increased sensitivity to ferroptosis.¹⁰² Hence, targeting the regulatory network of ferroptosis in cancer can bring about new therapeutic opportunities. However, ferroptosis induction, while inhibiting tumor cells, can also affect the function and activity of immune cells situated in the tumor microenvironment, including T cells, macrophages, neutrophils, and B cells.¹⁰³ The presence of multiple enzymes that regulate ferroptosis also enables the development of ferroptosis-targeted therapies. Cancer treatment based on ferroptosis induction are being actively sought. There have been attempts to use non-targeted NPs to deliver iron, peroxides, and other cytotoxic substances to kill tumor cells.¹⁰⁴

**Figure 3** Design strategies of ferroptosis-targeted nanomedicines.

The most prominent target of ferroptosis is GPX4, which is expressed in most cancer cells and is essential for their survival. Due to GPX4's atypical structure without conventional binding sites, current inhibitors can alter selenocysteine residues in GPX4 and other selenoproteins, raising concerns about their specificity and toxicity.²¹ GPX4 is vital for a variety of peripheral tissues (renal tubular cells), so targeting GPX4 may have side effects unless therapies are intended for the tumor target. Unlike targeting GPX4, the knockout of SLC7A11 gene does not cause major pathological changes and affect the expression of SLC3A2 and/or SLC7A11, so the strategy to block cysteine uptake by inhibiting the system Xc⁻ keeps great promise. Tumor is more sensitive to the inhibition of system Xc⁻ than normal tissues because of its metabolic reprogramming and evolutionary survival mechanism.¹⁰⁵ To prevent excessive peroxidation, tumor cells become more dependent on the detoxification function of system Xc⁻ to withstand oxidative stress. Similar to SLC7A11 subduction, the knockout of FSP1 does not impact the embryo development and cause any overt phenotype in terms of animal experiments,¹⁰⁶ presenting a broad therapeutic window for targeting FSP1. FSP1, highly expressed in many cancer cell lines, is the top gene linked with GPX4 inhibitor resistance.¹⁰⁶ Therefore, FSP1 inhibitors are ideal for treating drug-resistant or differentiated tumors. Other targets toward the execution, defense and regulating systems of ferroptosis can also be opted for the design of ferroptosis-targeted therapy.

Efforts to enhance cancer treatment by boosting ferroptosis have led to the ingenious design of vehicles for targeted delivery of ferroptosis inducers to tumors,¹⁰⁷ even enabling combination therapy. For instance, living bacteria and cancer cell membranes-coated Fe₃O₄ NPs were developed for improving targeted delivery of NPs and the payload sulfasalazine (a ferroptosis inducer) into the tumor tissue in order for synergistic ferroptosis and immunotherapy.¹⁰⁸ Enhanced ferroptosis induced by both Fe₃O₄ NPs and the loaded sulfasalazine effectively suppressed tumor growth and produced immune response through immunogenic cell death (ICD). A nanomedicine composed of pure sorafenib, Ce6 and Fe³⁺ significantly improved the photodynamic therapy of oral cancer via promoting ferroptosis.¹⁰⁹ The carrier-free NPs loading sorafenib, a ferroptosis inducer, and Ce6, a photosensitizer, markedly elevated intracellular ROS and O₂ that induced phototoxicity through the ferroptotic pathway. Ding et al¹¹⁰ constructed pyropheophorbide-a (ppa)-loaded mesoporous Fe₃O₄ NPs with PDA coating and biotin decoration for jointly targeting ferroptosis and apoptosis. The NPs increased ferroptosis sensitivity by depleting GSH and generating hydroxyl radical (OH). In addition, the nanomedicine overcame hypoxia of SDT and promoted ·OH generation through a SOD-like action, thus synergistically improving ferroptosis and apoptosis of tumor cells. Likewise, a diselenide-containing polymer was synthesized to promote tumor ferroptosis by inactivating GPX4 via GSH depletion in the form of self-assembled micelles with a targeting peptide.¹¹¹ The nanoscale micelles can pertinently bind to the active site cysteine of GSH, resulting in a thorough depletion of GSH and inducing ferroptosis. The antitumor effects of NPs were confirmed in vitro and in vivo in the BxPC-3 tumor model. In another study, targeting GPX4 to induce ferroptosis was engineered to actualize an immunogenic translation from “cold” to “hot” of prostate cancer.¹¹² The excellent work developed a transformable self-assembled peptide TEP-FFG-CRApY with alkaline phosphatase (ALP) responsiveness and GPX4 protein targeting. The self-assembled NPs from bioactive peptide were transformed into nanofibers in response to ALP in the endosome and lysosomes after uptake. The in situ formed nanofibers targeted GPX4 and selectively degrade its protein under the light irradiation, thereby inducing cascade ferroptosis. The leaked Fe²⁺ and intracellular Fenton reaction enhanced the ferroptotic effect. Nanoparticles induced immunogenic ferroptosis, leading to increased maturation of dendritic cells and T-cell infiltration in tumors, which stimulated IFN-γ secretion to promote ferroptosis (Figure 4).

Ferroptosis induction based on iron overload has also been explored to fight against cancer. Feng et al¹¹³ developed iron-based NPs as a nanocatalytic medicine to target the niches of cancer stem cells (CSC) and trigger ferroptosis. The NPs effectively accumulated in the microlesions of lung cancer through dextran-mediated TAM targeting via nebulization administration and resulted in a rise in iron level surrounding CSC niches and damage of redox homeostasis, thus enhancing the sensitivity of CSCs to ferroptosis. Carrier-free nanomedicines have also been developed to treat cancer through the ferroptotic pathway. Zhu et al¹¹⁴ engineered ferroptotic nanomedicines with aurantiamide acetate (Aa), scutebarbatine A (SA), and palmitin (P) as self-assembly materials and evaluated their promoting effects on apoptosis and ferroptosis in breast cancer. Intriguingly, the components Aa and P in nanomedicine induced significant mitochondrial apoptosis of cancer cells, while SA and P inhibited triple-negative breast cancer (TNBC) by ferroptosis and upregulating p53. Recently, nanomedicines or NPs pinpointing other targets of ferroptosis have also been reported to ameliorate cancer therapy. For example, Cao et al¹¹⁵ constructed small activating RNA (saRNA) tailored to ALOX15 and loaded it into mesoporous PDA NPs followed by biomimetic modification with macrophage membranes. The resulting hybrid NPs induced ferroptosis in glioblastoma by promoting mitochondrial damage through mediating the expression of ALOX15. Additionally, Tang's group designed a brain-targeting NIR-II ferroptosis nanosystem to enable visualization and

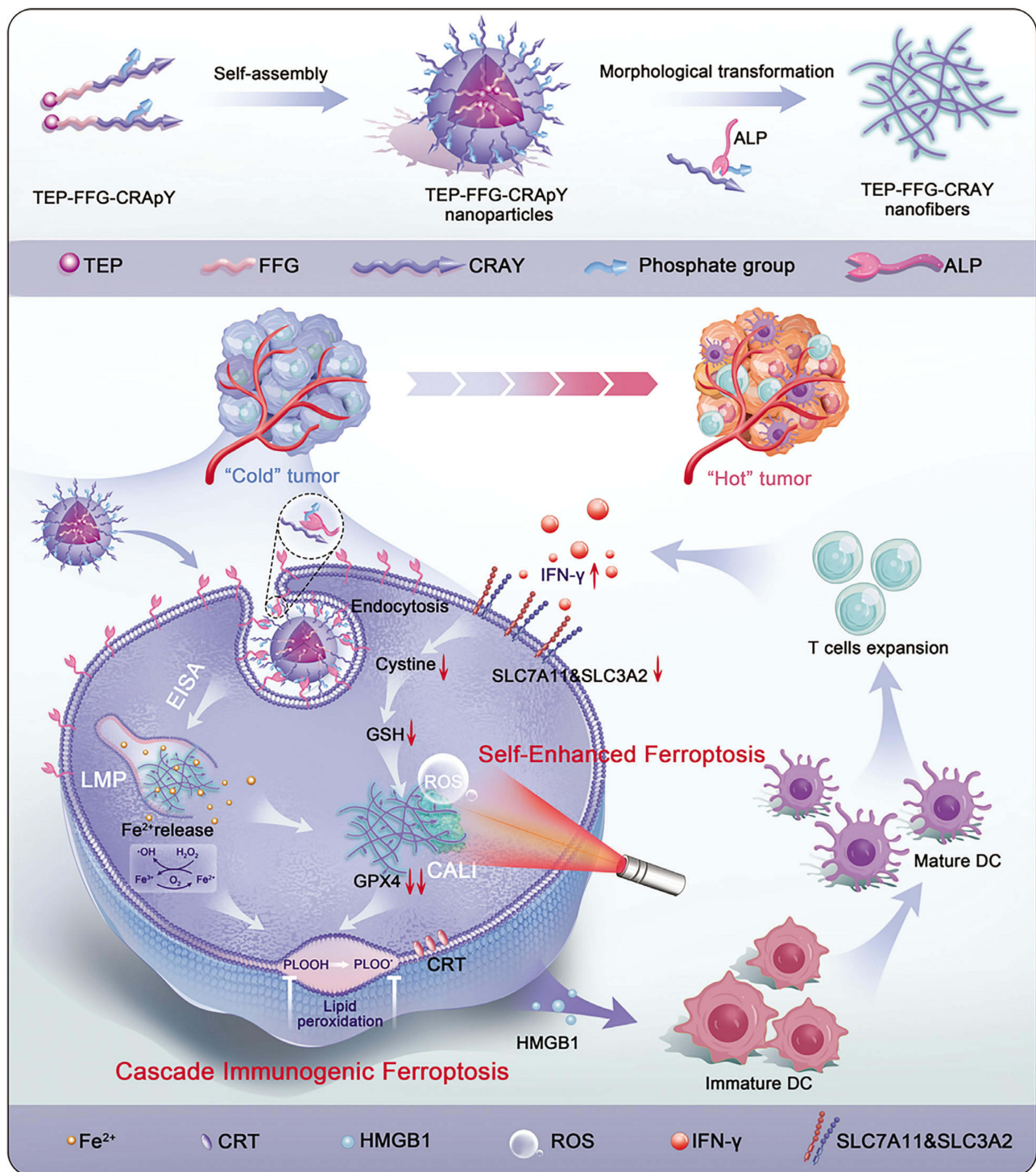


Figure 4 Schematic diagram of self-assembly, morphological transformation, and induction of cascade ferroptosis with TEP-FFG-CRApY in prostate cancer. Reproduced from Wang H, Jiao D, Feng D, et al. Transformable supramolecular self-assembled peptides for cascade self-enhanced ferroptosis primed cancer immunotherapy. *Adv Mater.* 2024;36(21): e2311733, © 2024 Wiley-VCH GmbH.¹¹²

oncotherapy for orthotopic glioblastoma.¹¹⁶ Au(I)-based NIR-II ferroptotic nanoparticles (termed TBTP-Au NPs) released TBTP-Au in the brain that specifically activated HMOX1-regulated ferroptosis of glioma cells, hence greatly prolonging the survival period of glioma-bearing mice. In Fan et al's study,¹¹⁷ MMP-2-sensitive NPs loaded with bispecific antibodies (biABs) were developed for IFN-induced ferroptosis using a dimer of epigallocatechin-3-gallate (EGCG) with hyaluronic acid as a ligand. The self-assembled NPs loaded with B7-H3 \times CD3 biABs displayed uplifted intracranial accumulation and GBM elimination by

boosting ferroptosis and enhancing immune checkpoint blockade. The most prevailing paradigm of ferroptosis induction is programmed for various cancers, and these excellent examples have shed light on negotiating the bottleneck of tumor therapy.

Senescence

The resistance of senescent cells to ferroptosis has been found to be linked with poor healing of chronic wounds.¹¹⁸ Senescent cells are cells that have stopped dividing and entered a state of irreversible cell cycle arrest in response to various stressors, such as DNA damage or oxidative stress.¹¹⁹ Targeting senescent cells with senolytic drugs, which selectively eliminate senescent cells, is proposed as a potential therapeutic strategy for chronic wound healing. As an example, Wei et al¹²⁰ developed a Fe_3O_4 nanosystem (F@GP) with galactose-modified poly (lactic-co-glycolic acid) (PLGA) to induce ferroptosis via the Fenton reaction in the presence of elevated intracellular H_2O_2 levels. After administration, F@GP worked as a chemodynamic therapy that eliminated senescent cells by increasing their sensitivity to ferroptosis, thus deadening cellular senescence, stimulating cell proliferation, promoting re-epithelialization, and accelerating the healing of diabetic wounds in mice. Further, ferroptosis induction can be explored for treating other diseases featured with ferroptotic resistance, such as aging and various age-related diseases.

Infectious Diseases

Infectious diseases are caused by pathogenic microorganisms such as bacteria, viruses, fungi, or parasites. These microorganisms can invade the body and disrupt normal cellular functions, leading to a variety of symptoms and potentially life-threatening complications, including infection-associated stress. Studies have shown that pathogens like bacteria and viruses can manipulate cellular iron metabolism to promote their own survival and replication, including through resistance to ferroptosis.¹²¹ Developing nanomedicines that trigger ferroptosis in pathogens could be a promising strategy to combat infections. A ferroptosis inducer comprising hybrid biomimetic membrane coated NPs made of Fe_3O_4 and cinnamaldehyde (CA) has been developed to mediate bacterial ferroptosis for acute *Staphylococcus aureus* (MRSA) pneumonia treatment.¹²² In this system, Fe_3O_4 can induce ferroptosis, while CA can advance ferroptosis by consuming GSH. To render a lung-targetability, the particles are further camouflaged with erythrocyte membrane and platelet membrane. Under ultrasonic stimulation, the NPs can efficiently release Fe_3O_4 and CA, thus synergistically inducing MRSA death with the characteristics of ferroptosis. Furthermore, the nanomedicine exhibits a capacity of suppressing the quorum sensing, removing biofilms, and reducing strain virulence. The anti-pneumonic effect of NPs by inducing ferroptosis of bacteria has been confirmed in a mouse model of MRSA pneumonia. This study provides pioneering insight into the feasibility of treating infectious diseases via promoting ferroptosis of pathogens.

Nanotherapy via Suppressing Ferroptosis

Stress, whether physical, psychological, or environmental, can trigger cellular responses that lead to ferroptosis activation, contributing to disease development and progression. One key player in the crosstalk between ferroptosis activation and stress-related diseases is oxidative stress.²² Stressors can induce the generation of ROS and disrupt cellular redox balance, resulting in lipid peroxidation and ferroptosis. Chronic stress has been associated with increased oxidative stress and lipid peroxidation,¹²³ which can promote ferroptosis in various tissues and organs. Furthermore, stress-related diseases such as cardiovascular diseases, metabolic disorders and neurodegenerative disorders are characterized by dysregulated iron metabolism, conversely exacerbating ferroptosis. Excessive iron accumulation increases the susceptibility of cells to ferroptosis by providing a source of iron for lipid peroxidation.¹²⁴ In addition, inflammation, another hallmark of stress-related diseases, can also promote ferroptosis.¹²⁵ Inflammatory cytokines/mediators trigger the expression of pro-oxidant enzymes and disrupt cellular antioxidant defenses, leading to ferroptosis activation. Inhibition of ferroptosis has emerged as a potential therapeutic strategy for treating these diseases. One approach to suppress ferroptosis is to target the key regulators of ferroptotic process, such as GPX4 enzyme. Another approach is to modulate iron metabolism by chelation or iron transport inhibition.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterized by the deposition of lipids, immune cells, and fibrous elements in the arterial walls, leading to the formation of plaques. Studies have shown that the interplay between ferroptosis and oxidative stress/inflammation plays a critical role in atherosclerosis.¹²⁶ Oxidized lipids accumulating in atherosclerotic plaques can cause

ferroptotic cell death in vascular cells, as an initiating factor, contributing to plaque instability and progression. In addition, iron overload in these lesions further enhances ferroptosis by boosting lipid peroxidation.¹²⁷ With the growing importance of ferroptosis in atherosclerosis, there is a rising expectation for enhanced arteriosclerosis treatment by inhibiting ferroptosis. Targeting key molecular components in the ferroptotic pathway offers potential to improve therapeutic results. Utilizing iron chelators, antioxidants, lipid peroxidation inhibitors, genetic manipulation, and tailored ferroptosis inhibitors to suppress ferroptosis provide many preferred treatment options for atherosclerosis.

With a deeper understanding of the role of ferroptosis in atherosclerosis, nanomedicines that target ferroptosis may dominate in the future development of medicaments. By leveraging the unique properties, such as targeted delivery, responsiveness, and versatility, practitioners have developed innovative nanomedicines to intervene atherosclerosis. For instance, a broad-spectrum ROS scavenging NPs with intrinsic anti-inflammatory activity was purposed for anti-atherosclerotic treatment.¹²⁸ The NPs were efficiently internalized by macrophages and vascular smooth muscle cells and attenuated ROS-induced inflammation and cell apoptosis in vitro. Increased accumulation in atherosclerotic lesions and inhibited development of atherosclerosis were presented by anti-oxidative NPs in vivo after *i.v.* injection. More importantly, therapy with NPs afforded stabilized plaques except for fewer arterial abnormalities compared with the control. Although ferroptosis has not been related in this report, the broad-spectrum ROS scavenging capability of fabricative NPs lends a notion that the anti-atherosclerotic mechanism of NPs is likely associated with ferroptosis. In another report, Wang et al¹²⁹ contrived macrophage membrane-camouflaged biomimetic NPs for targeting atherosclerosis through a macrophage “homing” effect. The biomimetic NPs loading rapamycin, a mTOR inhibitor with certain anti-inflammatory activity, effectively targeted and accumulated in the atherosclerotic lesions in vivo and significantly retarded the progression of atherosclerosis. Unfortunately, the model drug is not a ferroptotic inhibitor, otherwise the anti-atherosclerosis effect may be more encouraging. Ferroptosis is a promising target for atherosclerosis treatment, and nanomedical research should pay enough attention to this area in the future.

Diabetes and Its Complications

Numerous studies have indicated that ferroptosis plays a pivotal role in the pathophysiology and pathogenesis of diabetes mellitus and its associated complications, including diabetic nephropathy, retinopathy, and neuropathy.¹³⁰ Factors such as oxidative stress, inflammation, and mitochondrial dysfunction, which are common in diabetes, can promote the induction of ferroptosis. Ferroptosis and diabetes are interconnected through mechanisms involving iron metabolism, lipid peroxidation, and cellular stress responses. Ferroptosis as a novel therapeutic target has been widely investigated for diabetes and its complications.¹³¹ Ferroptosis inhibitors show a promise to rescue pancreatic β -cell function and alleviate diabetes and complications thereof.¹³² However, due to the limitations of off-target effects or unsatisfactory pharmacokinetics with ferroptosis inhibitors, nanoformulations are required to be developed.

While there are no direct reports on treating diabetes by inhibiting ferroptosis with nanomedicines, some artificial NPs loaded with antioxidants or therapeutic molecules have demonstrated strong anti-diabetic effects linked to ferroptosis inhibition. In our group, we synthesized selenium nanoparticles (SeNPs) loading herbal extracts (*Folium Mori* and *Puerariae Radix*) for antidiabetic application.¹³³ After treatment for two weeks, the relevant oxidative stress indices were all positively regulated. More importantly, the pancreatic function of model rats was restored to a large extent as manifested by raised islet β cell quantity (Figure 5). Additionally, our latest findings reveal that the antidiabetic effect of selenium-enriched NPs is associated with suppressed ferroptosis (data not shown). Coincidentally, green-synthesized SeNPs incorporating luteolin and diosmin showed significant antidiabetic effect.¹³⁴ The flavonoids-containing SeNPs exhibited good antioxidant activity as examined by catalase (CAT), SOD, and GPX. Nanotherapy for six weeks restored the blood glucose, lipid profile, glycogen, glycosylated hemoglobin, and insulin level in STZ induced-diabetic mice. Antioxidant therapy for diabetes has shown potential, but direct evidence of ferroptosis inhibition in antidiabetic studies is lacking. Yet, research on using nanomedicines to address diabetic complications is actively ongoing.

Hypertensive nephropathy is secondary to diabetes as a causation of chronic kidney disease. Hao et al¹³⁵ communicated a report on inhibition of ubiquitin specific peptidase 1 (USP1) that ameliorated the hypertensive nephropathy through regulating oxidative stress and ferroptosis via nanodelivery. The expression of USP1 in human kidney cells was found to be modulated by angiotensin II. They formulated USP1 inhibitor SJB3-019A into NPs with MIL-100 (Fe-based metal-organic frameworks) and PEGTK (polyethylene glycol-thioketal) as nanomaterials. The nanomedicine exhibited excellent alleviating effects on

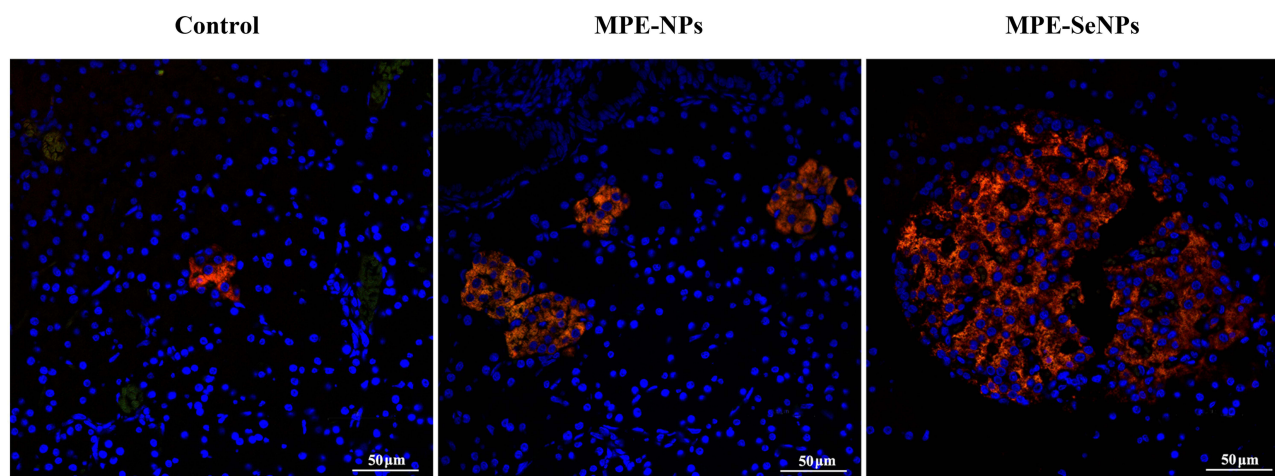


Figure 5 MPE-SeNPs animate β cells in the pancreas islet of diabetic rats after treatment for two weeks compared with MPE-NPs and control groups. Insulin-secreting cells are specifically labeled by Cy3-conjugated antibody. MPE-SeNPs, Folium Mori and Puerariae Radix extracts-loaded selenium NPs; MPE-NPs, selenium-free NPs. Reprinted from Deng W, Wang H, Wu B, Zhang X. Selenium-layered nanoparticles serving for oral delivery of phytochemicals with hypoglycemic activity to synergistically potentiate the antidiabetic effect. *Acta Pharm Sin B*. 2019;9(1):74–86.¹³³

hypertension-induced oxidative stress and ferroptosis in renal cells both in vitro and in vivo. Diabetic osteoporosis (DOP) betokens a serious complication that continues to threaten the bone health of people with diabetes. As a way out, Hao et al¹³⁶ synthesized ferroptosis-suppressing NPs to deliver curcumin, a natural phytochemical, to the bone marrow using tetrahedral framework nucleic acid (tFNA). The nanoformulation could enhance the mitochondrial function by activating the NRF2/GPX4 pathway, thereby inhibiting ferroptosis, promoting osteogenic differentiation of BMSCs in the diabetic context, reducing trabecular loss, and increasing bone formation. In addition to artificial NPs, autogenous nanovesicles secreted by living cells have also been utilized to treat diabetic complications. For example, Cui et al¹³⁷ isolated secretory autophagosomes (SAPs) from human umbilical vein endothelial cells and loaded them into gelatin-methacryloyl (GelMA) hydrogels to fabricate functional wound dressings. SAPs successfully inhibited ferroptosis in high glucose-induced ferroptosis in human dermal fibroblasts, thus improving their proliferation and migration. SAPs inhibited ferroptosis by reducing Fe^{2+} generation through ER stress and increasing Fe^{2+} release via exosomes, showcasing the therapeutic potential of nanomedicines in addressing diabetic complications by targeting ferroptosis.

Ischemia-Reperfusion Injury

Ischemia-reperfusion (IR) injury is a type of tissue damage that occurs when blood flow is restored to a tissue or organ after a period of reduced blood supply (ischemia). This can lead to oxidative stress and inflammation, hence cell death and tissue damage.¹³⁸ In the context of ischemia-reperfusion injury, ferroptosis plays a role in the cell death and tissue damage that occurs during the reperfusion phase.¹³⁹ The accumulation of iron and lipid peroxidation lead to oxidative stress and cell death, exacerbating the damage caused by the initial ischemic insult. In the absence of effective medicines, nanotechnology offers significant therapeutic improvements in IR.

Nanomedicines that can be used for IR therapy involve pure NPs, RNA/enzyme-loaded NPs, anti-ferroptotic agent-loaded NPs, and exosome-like NPs. Polydopamine (PDA) NPs and Cu-based NPs have been reported for anti-ferroptotic applications against IR injury.^{91,140} Drug-free PDA NPs efficiently reduced Fe^{2+} deposition and lipid peroxidation in a myocardial IR injury model, while neutrophil membrane-inspired Cu-based NPs (N-Cu_{5,4}O@DFO NPs) ameliorated IR-induced acute kidney injury through an antioxidant mechanism. Potent antioxidants are preferably chosen to treat IR injury by virtue of suitable formulations. To this end, Wang et al¹⁴¹ developed nano-integrated cascade antioxidants opsonized by albumin to bypass the blood brain barrier (BBB) for treatment of IR injury in the brain. Albumin NPs co-loading CAT and SOD1, integrated with a Se crosslinker, targeted neutrophil and effectively penetrated BBB in vitro and in vivo and alleviated IR injury in the brain via inhibiting neuronal ferroptosis. Besides antioxidative enzyme-loaded NPs, NPs with antioxidative enzyme activity, NPs with antioxidative enzyme activity, such as recombinant human heavy chain ferritin NPs, were discovered meritorious for treating IR diseases like ischemic stroke.¹⁴² Pleiotropic microenvironment remodeling micelles were constructed for targeted delivery of idebenone to the brain to

rescue the ischemic penumbra.¹⁴³ CREKA target peptide-modified micelles accumulated in the damaged brain via binding to microthrombi in the ipsilateral microvessels accompanied with transformation of diselenide bond into hydrophilic seleninic acid upon ROS stimulation. Allosteric transition of NPs synchronously consumed ROS and released drug that prevented oxidative stress-induced neuronal ferroptosis and protected the brain from IR injury. The nose-to-brain route was also utilized to deliver anti-ferroptotic miRNA for cerebral IR injury remedy. Zhao's team prepared anti-CHAC1 exosomes from adipose-derived mesenchymal stem cells (ADSC-Exo) for nose-to-brain delivery of miR-760-3p to treat cerebral IR injury.¹⁴⁴ ADSC-Exo given intranasally improved mouse neurobehavior IR and ferroptosis-related outcomes by targeting CHAC1 in neurons. In addition to cardio-cerebrovascular IR injury, nanomedicines have also been designed for hepatic and intestinal IR injury repair. Qiu et al¹⁴⁵ engineered neutrophil membrane-coated taurine NPs to protect against hepatic IR injury. Nanosized taurine decreased inflammatory cytokines and various oxides, showing good anti-inflammatory and antioxidant properties. The upregulated expression of both SLC7A11 and GPX4 suggested that ferroptosis inhibition may be involved in the mechanism against the hepatic IR injury. Notably, it was reported that a phytomedicine-loaded nanoparticle significantly alleviated intestinal IR injury by ATF3/SLC7A11-mediated ferroptosis.¹⁴⁶ In this study, the researchers synthesized two amphiphilic molecules, DTPA-N10-10 and mPEG-TK-DA, capable of scavenging free radicals and ROS, and then fabricated them into NPs with apigenin-7-O-glucoside (AGL) by self-assembly. The nanomedicine (PDN@AGL) protected intestinal tissues by reducing lipid peroxidation, ROS levels, and suppressing ferroptosis during intestinal IR (Figure 6). Additionally, the ATF3/SLC7A11 pathway was identified as key in mitigating intestinal IR injury.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by the progressive loss of memory and cognitive function. It is believed to be caused by the accumulation of abnormal protein deposits in the brain, leading to the death of nerve cells.¹⁴⁷ Studies have shown that the brains of Alzheimer's patients have higher levels of iron and lipid peroxides, which are key triggers of ferroptosis.¹⁴⁸ This has led researchers to speculate that ferroptosis should be a promising target for management of Alzheimer's disease. In this regard, nanomedicines are also demonstrating a bright therapeutic landscape.

Nawar et al¹⁴⁹ examined the neuroprotective and anti-ferroptotic effects of nanocurcumin and donepezil against AD in AlCl_3 and D-galactose-induced models. Treatment with nanocurcumin alone or in combination with donepezil ameliorated oxidative stress, liver and kidney functions, iron profile and decreased plasma fibrinogen. These indicators forecast a remission of AD possibly related to ferroptosis relief. In another brilliant study, Liu et al¹⁵⁰ artistically engineered an in situ self-assembled phytopolyphenol-coordinated intelligent nanotherapeutic system for multipronged management of ferroptosis-driven AD. Utilizing brain-targeting and mitochondria-targeting features, the triphenylphosphonium-modified quercetin-derived smart nanomedicine efficiently chelated iron through phytopolyphenol-mediated spontaneous coordination. This led to self-assembly into metal-phenolic nanocomplexes, boosting defensive actions against excess iron and free radicals. In addition, the Nrf2 signaling-mediated endogenous defensive system was also reconstituted that restored the iron metabolism homeostasis and enhanced the cytoprotective antioxidant cascades. Nanotherapy improved neurodegenerative symptoms related to brain iron buildup and reversed cognitive decline in AD mice (Figure 7). Although AD intervention via ferroptosis inhibition is in the ascendant phase, these findings suggest that targeting ferroptosis pathways may hold promise as a potential therapeutic approach for treating AD.

Inflammatory Conditions

In recent years, there has been growing interest in targeting ferroptosis as a potential therapeutic strategy for inflammatory conditions or diseases.¹⁵¹ Excessive ferroptosis has been implicated in various inflammatory conditions, including acute lung injury, sepsis, inflammatory bowel disease (IBD), and rheumatoid arthritis. It has been shown that modulating the key regulators of ferroptosis, such as GPX4, iron metabolism, and lipid peroxidation,¹²⁵ can have a protective effect against inflammation. Targeting iron metabolism or lipid peroxidation pathways with nanomedicines shows promise in reducing inflammation linked to ferroptosis.

Different nanotherapeutic agents for IBD have been designed based upon the principle of ferroptosis inhibition. Yang et al¹⁵² fabricated pH-sensitive molybdenum-based polyoxometalate (POM) nanoclusters for IBD treatment by counteracting ferroptosis. POM nanoclusters displayed potent ROS scavenging ability and significantly alleviated the enteric

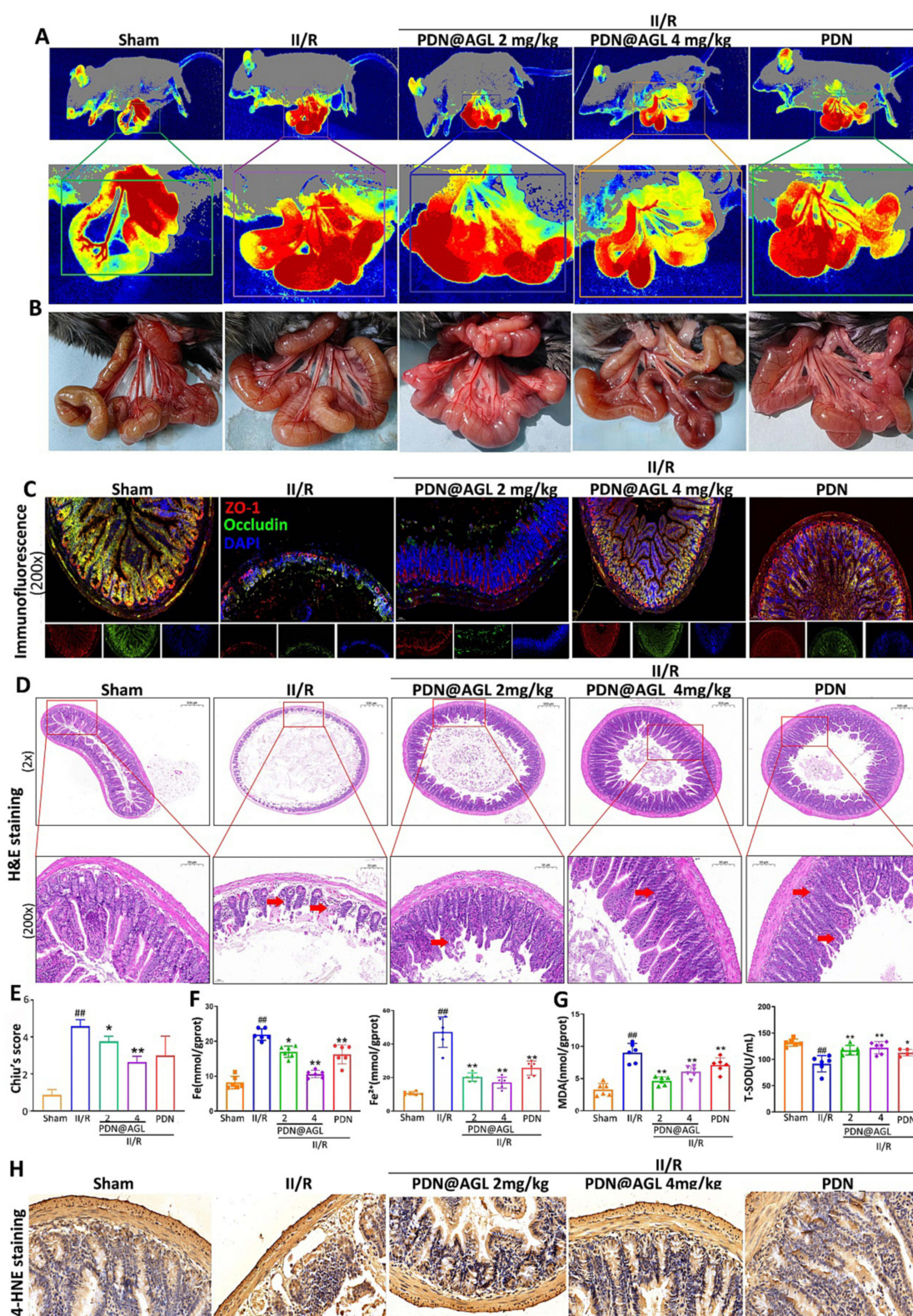


Figure 6 Effects of PDN@AGL on protecting intestinal blood flow, alleviating IR injury and inhibiting ferroptosis in vivo: **(A)** Perfusion of the microcirculation of intestine via laser speckle blood perfusion imaging; **(B)** Representative images of intestine morphologic changes; **(C)** Double fluorescence staining of ZO-1 and occluding of intestine tissues under IR with PDN@AGL; **(D)** H&E staining of intestine tissues under IR with PDN@AGL; **(E)** Chiu's score of small intestine injury; **(F)** Total iron and Fe²⁺ levels in serum under IR injury with PDN@AGL; **(G)** SOD and MDA levels in serum under IR injury with PDN@AGL; and **(H)** 4-HNE immunohistochemical staining of intestine tissues under IR injury with PDN@AGL. Unpaired t-test, *P < 0.05 and **P < 0.01 compared with Sham group, and ###P < 0.01 compared with II/R group. Reproduced from *Journal of Controlled Release*, Volume 366, Zhao X, Wang Z, Wu G, et al, Apigenin-7-glucoside-loaded nanoparticle alleviates intestinal ischemia-reperfusion by ATF3/SLC7A11-mediated ferroptosis, pages 182–193, Copyright 2024, with permission from Elsevier.¹⁴⁶

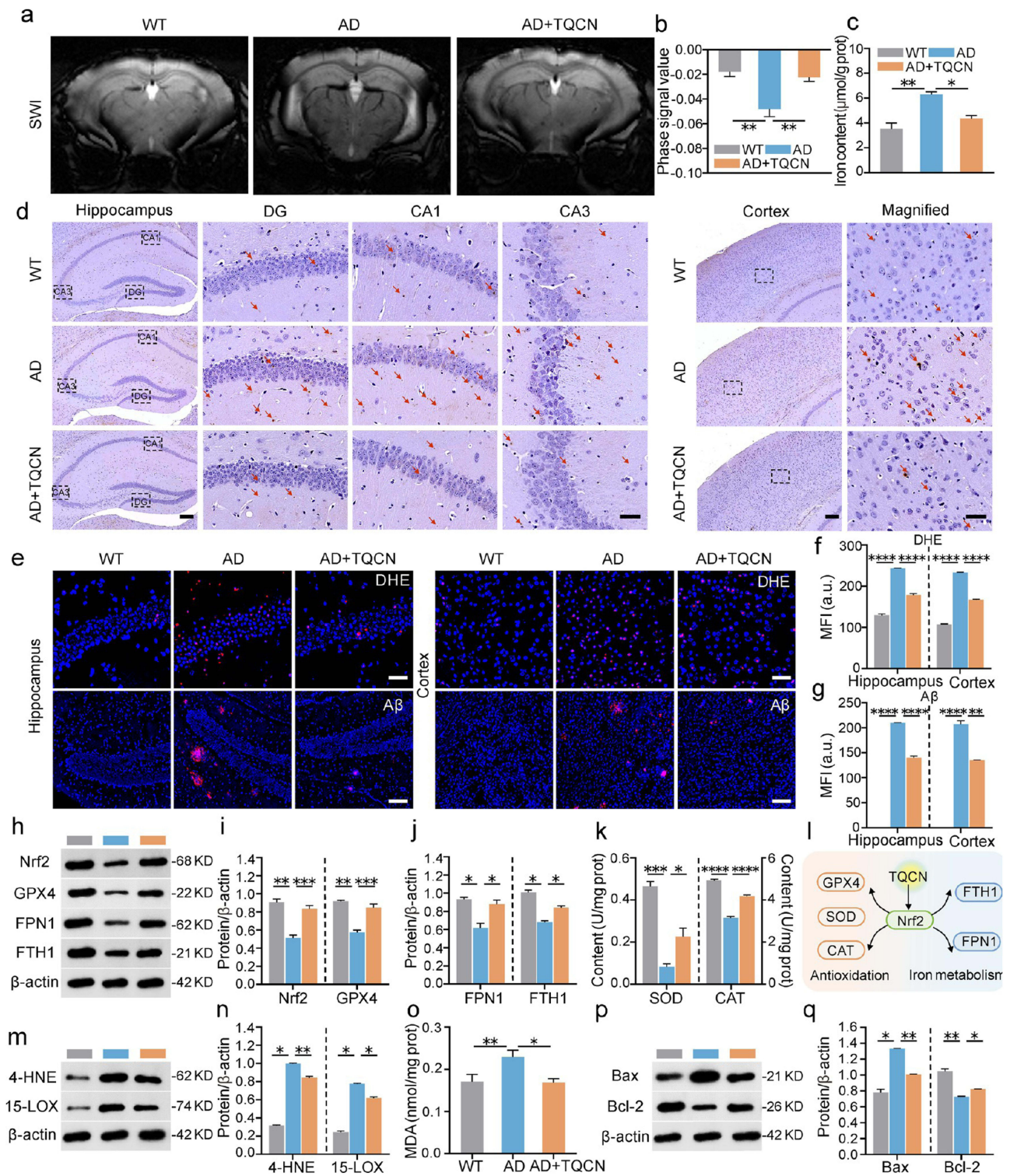


Figure 7 Multipronged anti-AD efficacy of TQCN against ferroptosis: (a) representative SWI images; (b) phase signal value analysis in the hippocampus (n = 5); (c) iron content detection in mouse brain after various treatments; (d) representative images of Perl's Prussian blue staining on brain slices (Red arrows indicate iron-positive plaques); (e) representative confocal fluorescence images; (f and g) quantitative analysis of DHE and Aβ staining; (h–j) representative immunoblots and quantitative analysis for Nrf2, GPX4, FPN1 and FTH1; (k) SOD and CAT activity detection; (l) schematic of Nrf2-mediated defense pathways activated by TQCN; (m and n) representative immunoblots and quantitative analysis for 15-LOX and 4-HNE; (o) MDA content analysis; and (p and q) representative immunoblots and quantitative analysis for Bax and Bcl-2. Student's t-test, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, statistically significant between two groups. Adapted from Liu Y, Zhao D, Yang F, et al. In situ self-assembled phytopolyphenol-coordinated intelligent nanotherapeutics for multipronged management of ferroptosis-driven Alzheimer's disease. *ACS Nano*. 2024;18(11):7890–7906. Copyright American Chemical Society.¹⁵⁰

symptoms and inflammatory indicators in DSS-induced ulcerative colitis (UC) mouse model by attenuating ferroptosis. In the work of Zhu et al¹⁵³ they produced a zero-valence selenium-enriched nanozyme by a hard template method used to reconstruct intestinal barrier against IBD via suppressing ferroptosis and T cells differentiation. In addition, exosomes have also been shown to be useful nanocarriers to tackle IBD via inhibiting ferroptosis.¹⁵⁴ Li et al introduced a groundbreaking study on treating IBD by combining ferroptosis inhibition with macrophage polarization.¹⁵⁵ They developed a nanosystem that targets IBD by polarizing M2 macrophages and inhibiting ferroptosis. CaCO_3 -mineralized liposomes encapsulating ferroptosis inhibitor Fer-1 (CLF) prevent premature release of Fer-1 from liposomes in circulation, while Ca^{2+} is released in the acidic-inflammatory environment that promotes M2 polarization through the $\text{CaSR}/\text{AKT}/\beta$ -catenin pathway. The subsequently released Fer-1 upregulates GSH and GPX4, scavenges ROS, and inhibits ferroptosis in M2 macrophages (Figure 8). CLF improved the targeting efficiency of ferroptotic antagonist in IBD lesions in vivo due to EPR effect and reinforced IBD therapy by elevating the M2/M1 macrophage ratio and suppressing ferroptosis.

Apart from IBD, nanomedicines against ferroptosis have been employed for the treatment of other inflammatory diseases. For instance, Yu et al¹⁵⁶ created supramolecular self-assembly of EGCG-selenomethionine nanodrug for treating osteoarthritis (OA). Through a Mannich condensation reaction between EGCG and selenomethionine, they synthesized polyphenol-based nanodrug in aqueous medium. Molecular biology experiments disclosed that the EGCG-

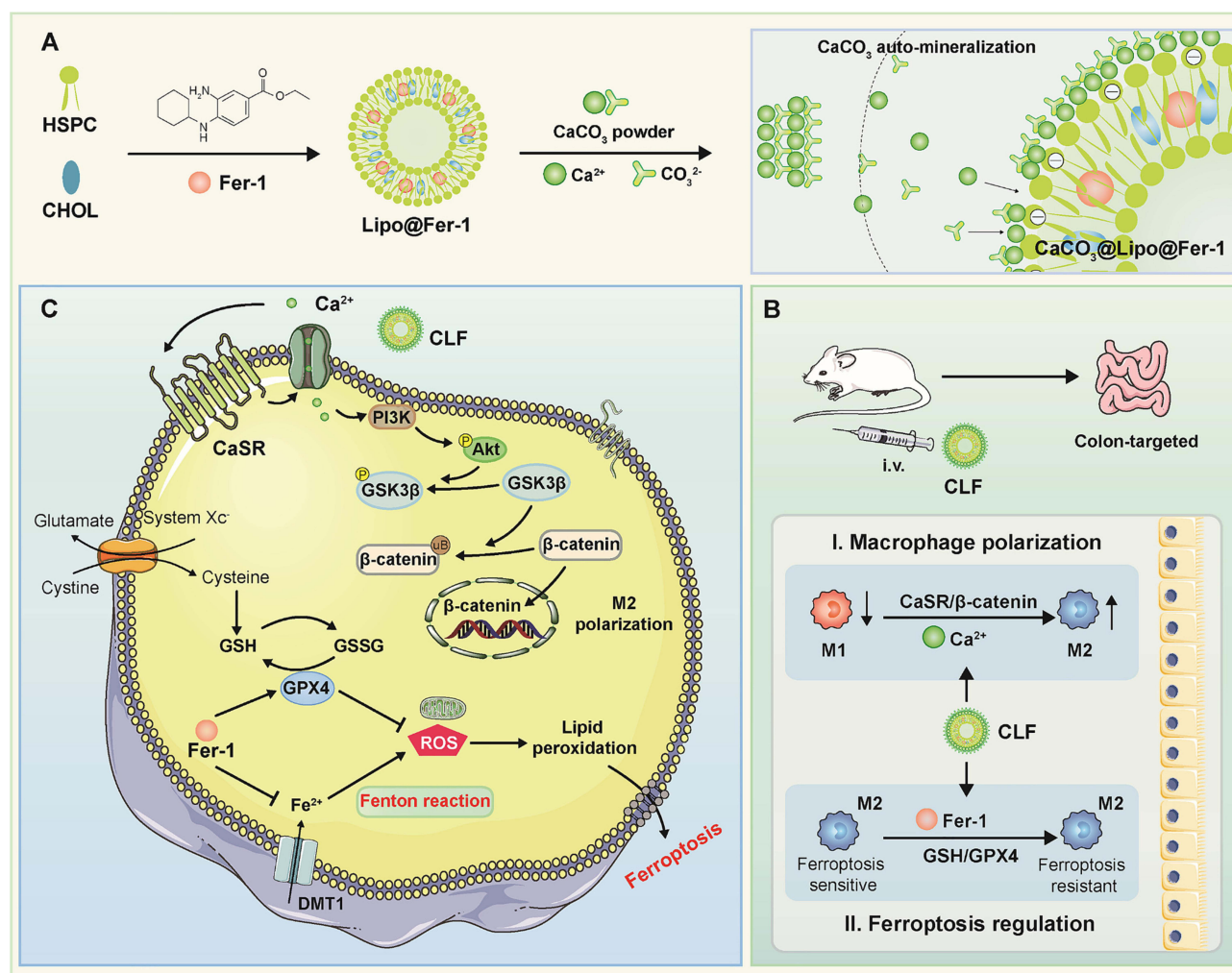


Figure 8 Schematic of the preparation of $\text{CaCO}_3@Lipo@Fer-1$ (CLF) and therapeutic mechanisms in IBD. **(A)** Preparation of CLF mineralized liposome. **(B)** CLF treats IBD by regulating macrophage polarization and inhibiting ferroptosis. **(C)** Mechanisms of CLF promoting polarization and inhibiting ferroptosis of M2 macrophages. Reproduced from *Journal of Controlled Release*, Volume 367, Zhao Y, Yin W, Yang Z, et al, Nanotechnology-enabled M2 macrophage polarization and ferroptosis inhibition for targeted inflammatory bowel disease treatment, pages 339–353, Copyright 2024, with permission from Elsevier.¹⁵⁵

based nanomedicine effectively reduced GPX4 inactivation, abnormal Fe^{2+} accumulation, and lipid peroxidation induced by oxidative stress. It also improved chondrocyte metabolism and addressed various pathological processes related to ferroptosis, highlighting its therapeutic potential for OA. Overall, the development of therapies that specifically target ferroptosis pathways holds great potential for the treatment of inflammatory diseases.

The Future Prospective

Ferroptosis, a burgeoning concept of RCD in the biomedical realm, plays a pleiotropic role in stress-related diseases by contributing to oxidative damage and cell death. Targeting ferroptosis in various diseases presents new therapeutic avenues by regulating key factors like GPX4 and iron levels. Currently, there are 11 completed or ongoing clinical trials on using ferroptosis for treatment, including one focusing on nanomedicine for advanced solid tumors (Carbon nanoparticle-loaded iron, NCT06048367, Clinicaltrials). The growing recognition of ferroptosis in disease pathogenesis is leading to the emergence of specific agonists and antagonists. Ferroptosis is seen as a promising target for future treatment strategies, despite being in the early stages of research. Developing ferroptosis-related nanomedicines hinges on confirming its role in a disease and ensuring targeted delivery to the affected site, thus minimizing side effects. Overcoming these hurdles paves the way for the clinical use of such nanomedicines. Customizable solutions can tackle these challenges effectively.

Engineered nanomedicines targeting ferroptosis in stress-related diseases offer a promising approach for disease management. Utilizing responsive nanocarriers or biomimetic NPs for targeted delivery of ferroptotic agents and combining therapies with other mechanisms allow for efficient interventions against stress-related diseases. Due to the double-edged sword role of ferroptosis in diseases, we can both activate ferroptosis and inhibit ferroptosis upon designing nanomedicines in order to achieve satisfactory treatment outcomes. Targeted nanomedicines allow precise modulation of ferroptotic pathways, mitigating off-target toxicity and side effects. With the advance in nanotechnology, new therapeutic avenues are opened for managing complex stress-related diseases, including but not limited to cancer, neurodegenerative diseases, and inflammatory conditions.

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Disclosure

The authors declare no conflicts of interest.

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