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Review paper

Mechanisms and therapeutic targets of ferroptosis: Implications for nanomedicine design

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ABSTRACT

Ferroptosis is a nonapoptotic form of cell death and differs considerably from the well-known forms of cell death in terms of cell morphology, genetics, and biochemistry. The three primary pathways for cell ferroptosis are system Xc^-/glutathione peroxidase 4 (GPX4), lipid metabolism, and ferric metabolism. Since the discovery of ferroptosis, mounting evidence has revealed its critical regulatory role in several diseases, especially as a novel potential target for cancer therapy, thereby attracting increasing attention in the fields of tumor biology and anti-tumor therapy. Accordingly, broad prospects exist for identifying ferroptosis as a potential therapeutic target. In this review, we aimed to systematically summarize the activation and defense mechanisms of ferroptosis, highlight the therapeutic targets, and discuss the design of nanomedicines for ferroptosis regulation. In addition, we opted to present the advantages and disadvantages of current ferroptosis research and provide an optimistic vision of future directions in related fields. Overall, we aim to provide new ideas for further ferroptosis research and inspire new strategies for disease diagnosis and treatment.

1. Introduction

1.1. Historical outline of ferroptosis

Cell death is the terminal phase of a cell's life that frequently occurs in normal tissues to maintain tissue function and morphology [1]. Programmed cell death refers to an active extinction process determined by genes that play an important role in the maintenance of internal environmental homeostasis, including apoptosis, necrosis, autophagy, etc. [2]. Novel forms of programmed cell death with unique biological processes and pathophysiological characteristics have been identified. In 2003, Dolma et al. [3] discovered erastin, a compound with a quinazolinone skeleton that selectively kills engineered tumorigenic primary human foreskin fibroblasts expressing small T and mutant rat sarcoma (*RAS*) genes. Erastin was found to induce cell death in the absence of non-apoptosis. In 2008, Yang and Stockwell [4] discovered two compounds, oncogenic-*RAS*-selective lethal small molecule 3 (RSL3) and RSL5, which had similar properties to erastin. RSL3 and RSL5 were reported to induce iron-dependent non-apoptotic cell death in a series of engineered cell lines derived from primary human fibroblasts. Further, cell death was found to be inhibited by iron chelators, such as deferoxamine (DFO) mesylate (DFOM) and antioxidants (vitamin E). Besides, the death of erastin-treated cells involves characteristic morphological, biochemical, and genetic phenomena; hence, in 2012, these investigators formally named this form of cell death as ferroptosis.

The concept of ferroptosis has been unraveled through more than one decade of research. Ferroptosis is an individual form of programmed cell death associated with iron-dependent lipid peroxidation (LPO) that involves genetic, metabolic, and protein regulators, triggers, and execution mechanisms that possess limited overlap with other forms of programmed cell death [5]. Studies on ferroptosis were officially launched in 2012 and have extensively focused on its regulatory mechanisms. Subsequently, multiple regulatory factors related to ferroptosis, such as glutathione peroxidase 4 (GPX4), polyunsaturated fatty acids (PUFAs), acyl-CoA synthetase long-chain family member 4 (ACSL4), ferroptosis suppressor protein 1 (FSP1), and nuclear receptor coactivator 4

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(NCOA4) and absent in melanoma 2 (AIM2) [6], were successfully identified. Zhou and Bao [7] established a manually collected and managed database of ferroptosis-related markers, regulators, and diseases that further promoted in-depth research on ferroptosis. More detailed timelines can be found in other reviews [8–11].

Following the discovery of ferroptosis, numerous significant papers were published [12–22]. However, the number of publications on ferroptosis has grown continuously worldwide over the last decade (Fig. 1). In fact, the number of publications has recently grown at an alarming pace, indicating that ferroptosis research has attracted global attention and has remarkable potential for exploration as a therapeutic target.

The first paper on the use of nanoparticles to activate ferroptosis was published in 2016. The primary aim of the study was to design ultrasmall poly(ethylene glycol) (PEG)-coated silica nanoparticles functionalized with melanoma-targeting peptides. Specifically, the nanoparticles consist of the latest generation of cornell dots (C′ dots), while surface is functionalized with a 14 mer peptide analogue, alpha-melanocyte stimulating hormone (αMSH). When the αMSH-PEG-C′ dots induced the death of MCF10A human mammary epithelial cells, the accumulation of reactive oxygen species (ROS) was observed and the inhibitors of ferroptosis were found to block cell death. Based on these findings, αMSH-PEG-C′ dots could trigger the ferroptosis of amino-acid-starved MCF10A human mammary epithelial cells [23].

1.2. Characteristics of ferroptosis

Ferroptosis has unique morphological, biochemical, and genetic features compared to other programmed cell death pathways, such as apoptosis, autophagy, necroptosis, and pyroptosis.

1.2.1. Morphological features

Morphologically, the classical characteristics of apoptosis, autophagy, necroptosis, and pyroptosis are not observed in ferroptotic cells [24]. Ferroptosis is characterized by the presence of shrunken mitochondria with condensed densities, reduction or disappearance of mitochondrial cristae, and rupture of the outer mitochondrial membranes [25]. The barrier function of the cytomembrane is impaired by peroxidation of membrane lipids [26]. Moreover, nuclear morphology remains unchanged and chromatin condensation does not occur [27].

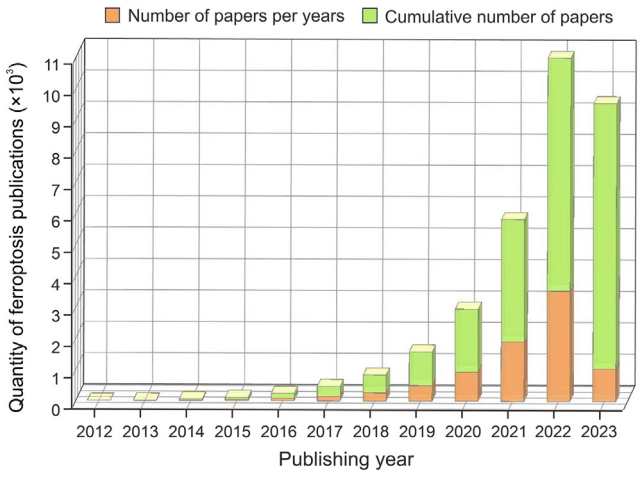

Fig. 1. Annual growth in the number of published papers on ferroptosis (Statistics from the Web of Science; access date: March 20, 2023).

1.2.2. Biochemical features

Ferroptosis is a highly iron-dependent process of cell death. Intracellular iron levels (also known as labile iron pools (LIPs)) are regulated by various pathways, such as transferrin and ferritin (Fn). By disturbing their expression, the ion levels in ferroptotic cells increase significantly and then disrupt cellular redox homeostasis and LPO [28,29]. Beyond iron, LPO compounds accumulate during this type of cell death [30].

1.2.3. Genetic features

The abnormal expression of certain genes is considered as a biomarker of ferroptosis. For instance, positive expression of ACSL4 leads to cells being susceptible to oxidative stress, resulting in ferroptosis [31]. Prostaglandin endoperoxide synthase 2 is associated with the upregulation of oxidative stress-associated genes [32]. The positive expression of transferrin receptor 1 (TFR1) and NCOA4 can trigger ferroptosis, which is ascribed to an increase in intracellular iron levels, resulting in iron accumulation [33]. In contrast, the negative expression of light chain subunit solute carrier family 7 member 11 (SLC7A11) suppresses ferroptosis [34]. Nuclear factor erythroid 2-related factor 2 (Nrf2), FSP1, and Fn heavy chain 1 are downregulated during ferroptosis [35].

The main morphological, biochemical, and genetic features of different types of cell death compared with those of ferroptosis are summarized in Table 1 [36–43]. Biotransmission electron microscopy diagrams of the different cell death pathways are also presented to highlight the fact that ferroptosis is vastly different from other classical death pathways (Fig. 2) [44–48].

1.3. Outline of the current review

The discovery of ferroptosis has not only advanced the definition and our understanding of cell death but has also shed light on new opportunities for the treatment of different diseases. Before the successful application of ferroptosis-targeting therapy, the detailed activation and defense mechanisms must be determined to facilitate therapeutic discovery and development.

This review aimed to systematically summarize the activation and defense mechanisms of ferroptosis, highlight the therapeutic targets, and discuss the design of nanomedicines for ferroptosis regulation. We also opted to discuss the status quo of nanoparticle-based ferroptosis regulation research and propose future directions in related fields.

2. Activation mechanisms of ferroptosis

2.1. System Xc^-/GPX4 pathway

System Xc^- is an amino acid transporter on the cell membrane that consists of SLC7A11 and solute carrier family 3 member 2 subunits [49]. System Xc^- can mediate the efflux of glutamate and uptake of cystine, with cystine being rapidly converted to cysteine after intracellular entry. Simultaneously, nicotinamide adenine dinucleotide phosphate (NADPH) is converted to the oxidized form NADPH ($NADP^+$). Together with glutamate, the generated cysteine is used to synthesize γ-glutamicysteine, which is facilitated by glutamic-cysteine ligase. The intermediate, γ-glutamicysteine, rapidly undergoes further enzymatic transformation, combining with glycine under the catalysis of GSH synthetase to form GSH [50]. GSH, an antioxidant tripeptide composed of glutamate, cysteine, and glycine (the three aforementioned substrates), is an important scavenger of free radicals and oxidants. In fact, GSH is recognized as a mandatory cofactor for GPX4. GPX4 is a central inhibitor of ferroptosis that reduces lipid peroxide to nontoxic lipid alcohol to suppress ferroptosis, which is

Table 1
Characteristics of ferroptosis, apoptosis, autophagy, necroptosis, and pyroptosis.

Item	Ferroptosis	Apoptosis	Autophagy	Necroptosis	Pyroptosis	Refs.
Morphological features	Mitochondrial shrinkage with increased mitochondrial membrane densities, reduced or vanished mitochondria crista, and rupture of outer mitochondrial membrane	Cytoplasmic shrinkage, blebbing of the plasma membrane, chromatin condensation, and the formation of apoptotic bodies	Formation of double-membraned autolysosomes	Rupture of the plasma membrane, translucent cytoplasm, and swelled organelles	Cell membrane rupture and cell contents flowed out, cell swollen, and bubble-like protrusions	[36,37]
Biochemical features	Iron accumulation and LPO	Caspases activation	Autophagic flux	Drop in ATP levels	Dependent on caspase-1 and proinflammatory cytokine releases	[38,39]
Genetic features	Positive: *PTGS2*, *ACSL4*, *TFR1*, and *NCOA4*; Negative: *SLC7A11*, *Nrf2*, *FSP1*, and *FTH1*	Positive: *Bax*, *Bak*, *Bad*, *Bim*, and *Bid*; Negative: *Bcl-2*, *Bcl-xl*, and *Mcl-1*	Positive: *ATG5*, *ATG7*, *LC3*, and *Becn1*; Negative: *mTOR*	Positive: *RIP1*,*RIP3*, and *MLKL*; Negative: *AURKA* and *ESCRT-III*	Positive: *caspase-1*, *IL-18*, and *IL-1β*; Negative: *ESCRT-III* and *GPX4*	[40–43]

LPO: lipid peroxidation; *PTGS2*: prostaglandin endoperoxide synthase 2; *ACSL4*: acyl-CoA synthetase long-chain family member 4; *TFR1*: transferrin receptor 1; *NCOA4*: nuclear receptor coactivator 4; *SLC7A11*: solute carrier family 7 member 11; *Nrf2*: nuclear factor erythroid 2-related factor 2; *FSP1*: ferroptosis suppressor protein 1; *FTH1*: ferritin (Fn) heavy chain 1; *Bax*: the B cell leukemia-2 (*Bcl-2*) associated X protein; *Bak*: *Bcl-2* antagonist/killer 1; *Bad*: Bcl-2 antagonist of cell death; *Bim*: Bcl-2 interacting mediator of cell death; *Bid*: BH3 interacting domain death agonist; *Bcl-xl*: Bcl-extra long; *Mcl-1*: myeloid cell leukemia-1; *ATG5*: autophagy-related protein 5; *LC3*: microtubule-associated protein 1 light chain 3; *Becn1*: Beclin1; *mTOR*: the mechanistic target of rapamycin pathway; *RIP1*: receptor-interacting serine/threonine kinase 1; *MLKL*: mixed lineage kinase domain like protein; *AURKA*: aurora kinase A; *ESCRT-III*: endosomal sorting complexes required for transport III; *IL-18*: interleukin-18; *GPX4*: glutathione (GSH) peroxidase 4.

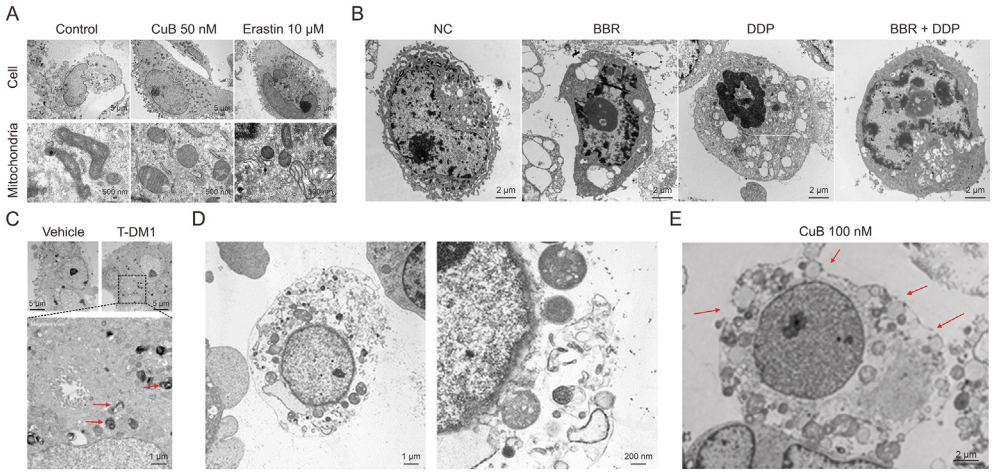

Fig. 2. Typical morphological images of the different cell death pathways: (A) ferroptosis [44], (B) apoptosis [45], (C) autophagy [46], (D) necroptosis [47], and (E) pyroptosis [48]. CuB: cucurbitacin B; NC: blank control group; BBR: berberine; DDP: cisplatin; T-DM1: trastuzumab emtansine. Reprinted from Refs. [44–48] with permission.

accompanied by the oxidation of GSH to oxidized GSH (GSSG) [51]. NADPH is dehydrogenated and oxidated to $NADP^+$ during the reduction of GSSG.

Inhibiting the function of system Xc^- reduces the formation of GSH, which affects the activity of GPX4, thereby leading to lipid peroxide accumulation and ultimately resulting in ROS-mediated ferroptosis. System Xc^- inhibition can be achieved using SLC7A11 inhibitors (such as erastin [52], sorafenib [53], or sulfasalazine [53]). According to prior studies, blocking GPX4 (e.g., using RSL3 [53], ML162 [54], or ML210 [55]) and inducing GPX4 degradation (e.g., using FIN56 [18,56] or palladium pyrithione complex (PDPT) [57]) can directly influence the activity of GSH peroxidase, which is another significant ferroptosis activation pathway. The system Xc^-/GPX4 pathway [53,58] is illustrated in Fig. 3. Overall, SLC7A11 and GPX4 are important targets of ferroptosis in this pathway.

2.2. Lipid metabolic pathway

PUFAs are essential fatty acids in the human body that are obtained through the diet. PUFAs play vital roles in human health and regulate the immune system, metabolism, excretion, reproduction, and other physiological functions *in vivo*. Studies [59–62] have found that the oxidation of long-chain PUFAs can lead to ferroptosis through non-enzymatic oxidation by free radicals or enzymatic oxidation by lipoxygenase. The oxidation of PUFAs is one of the unique fingerprints of ferroptosis.

In the biological matrix, PUFAs, such as linoleic and arachidonic acids (AAs), can generate PUFA coenzyme A (PUFA-CoA) through ACSL4 [63–65], as depicted in Fig. S1. The generated PUFA-CoA is used as a substrate in combination with phosphatidylethanolamine (PE) via lysophosphatidylcholine acyltransferase 3 (LPCAT3) to yield phospholipids (PLs) containing PUFAs (PUFA-PE). PUFA-PE is vulnerable to the free radicals generated by arachidonate lipoxygenases (ALOXs) or cytochrome P450 oxidoreductase (POR), leading to its peroxidation. The continuous accumulation of peroxidized PUFA-PE (PUFA-PE-OOH) impairs lipid membranes and organelles, thereby contributing to ferroptosis [66,67].

ALOXs are oxidoreductases whose catalytic centers contain iron and play an indispensable role in ferroptosis induced by lipid metabolism. ALOXs are important targets for the regulation of ferroptosis [68]. In particular, POR mediates the conversion of O_2 to H_2O_2, accompanied by the oxidation of NADPH. The generated H_2O_2

can undergo a Fenton reaction with intracellular Fe^{2+} to yield a large amount of hydroxyl radicals (•OH.), which expedites the production of PUFA-PE-OOH and boosts the activation of ferroptosis. Consequently, iron chelators [68] (such as DFO and DFOM), ferrostatin-1 [69], POR inhibitors [34], and LPO inhibitors (e.g., liproxstatin-1) [70] can reduce the formation of PUFA-PE-OOH by attenuating the content of Fe^{2+} *in vivo* or inhibiting the catalytic activity of ALOXs or POR, thereby preventing ferroptosis. The introduction of ACSL3 hinders ferroptosis, which might be due to the inhibition of PUFA-PE generation induced by ACSL3. ALOXs and POR are two significant targets of ferroptosis in the lipid metabolic pathway.

2.3. Iron metabolic pathway

Iron is an important trace element for the maintenance of human health. Iron is replenished through food; however, the non-heme iron in food is mainly insoluble Fe^{3+}, which must be reduced to Fe^{2+} for absorption, distribution, transport, storage, utilization, metabolism, and excretion by organisms. This process is known as iron metabolism [21].

Upon entry into the blood, Fe^{3+} binds to transferrin and is recognized by TFR1 in the cell membrane. Six-transmembrane epithelial antigen of prostate 3 (STEAP3) reduces Fe^{3+} to Fe^{2+}. Under the action of divalent metal transporter 1, an iron metabolism regulator in the zinc-iron regulatory protein family, Fe^{2+} is transported into the cytoplasmic LIP and a portion is stored in Fn. Fe^{2+} can also emancipate itself from Fn, converging back to LIP. Surplus Fe^{2+} is transferred out of the cell by the membrane protein, ferroportin (FPN). When Fe^{2+} accumulates excessively or Fn is markedly degraded, it reacts with hydrogen peroxide to produce a Fenton reaction, generating a large amount of •OH, which induces LPO and leads to ferroptosis [71]. Concurrently, as delineated in the lipid metabolic pathway, the free radicals generated by the Fenton reaction can also act on the lipid metabolic pathway, promoting PUFA-PE peroxidation and ultimately inducing ferroptosis [65].

In the iron metabolic pathway, TFR1 and STEAP3 are the key targets that regulate ferroptosis [18]. The sensitivity of ferroptosis

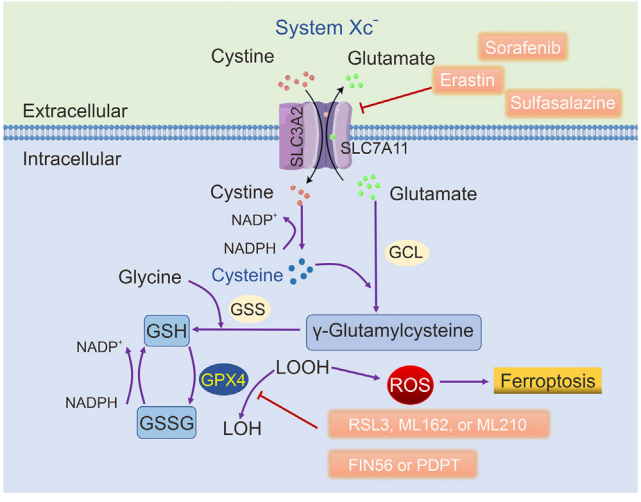

Fig. 3. The system Xc^-/GPX4 pathway is used to activate ferroptosis. SLC3A2: solute carrier family 3 member 2; SLC7A11: solute carrier family 7 member 11; $NADP^+$: oxidized form of nicotinamide adenine dinucleotide phosphate (NADPH); GCL: glutamate cysteine ligase; GSS: glutathione (GSH) synthetase; GPX4: GSH peroxidase 4; GSSG: oxidized GSH; LOH: lipid alcohol; LOOH: lipid hydroperoxide; ROS: reactive oxygen species; PDPT: palladium pyrithione complex.

can be increased by the upregulation of *TFR1* and *STEAP3* gene expression and downregulation of Fn expression [71]. Consequently, the expression of TFR1 can be downregulated by the TFR1 inhibitor, ferristatin II, while the uptake of iron ions in cells is hindered, thereby inhibiting ferroptosis activation [72]. From another standpoint, a large amount of Fe^{2+} is released *in vivo* owing to the lysosome-mediated degradation of Fn, triggering the Fenton reaction, which induces ferroptosis [73]. Fe^{2+} can be released and enriched in large amounts from heme through the catalytic action of overactivated heme oxygenase 1 (HMOX1), thereby generating a large amount of ROS [74]. Notably, nitrogen-fixing protein 1 (NFS1), a cysteine-desulfurizing enzyme, can dissociate sulfur from cysteine and generate iron-sulfur clusters with iron; simultaneously, a large amount of Fe^{2+} *in vivo* is consumed. However, a decrease in iron content *in vivo* leads to an iron-hunger effect, which expedites the generation of Fe^{2+}. As the generation and accumulation of Fe^{2+} continue to increase, •OH is constantly generated, thereby initiating ferroptosis [75]. The iron metabolic pathways [76] are shown in Fig. S2.

2.4. Other pathways

In addition to the three classic pathways for ferroptosis, other pathways can induce ferroptosis, such as the P53/SLC7A11, P53-spermidine/spermine N1-acetyltransferase 1 (SAT1)-ALOX15, sulfur transfer, voltage-dependent ion channels (VDACs) mitochondria, glutamine metabolism, P62-Kelch-like ECH-associated protein 1 (Keap1)-Nrf2, mevalonate (MVA), FSP1-coenzyme Q10 (CoQ10)-NAD(P)H, and autophagy-related protein 5/7 (ATG5/7)-NCOA4 pathways, etc.. As all activation pathways fundamentally culminate in ferroptosis by fostering intracellular ROS generation and stimulating LPO, other pathways may have interconnections or synergies with the three classical pathways. Nevertheless, besides the classical activation pathways, unmentioned proteins (such as P53, FSP1, NCOA4, ATG5/7, etc.) or pathways (such as the P62-Keap1-Nrf2 pathway and VDACs mitochondria pathway) are also implicated in activated-ferroptosis. Other pathways leading to ferroptosis [77–84] are shown in Fig. S3.

2.4.1. P53/SLC7A11 pathway

P53 is a protein that inhibits cancer cells and plays an essential role in tumor formation. P53 can impede the expression of SLC7A11, which mediates the uptake of cystine and efflux of glutamate, leading to abatement in GSH production and a decrease in cellular antioxidant capacity. A large accumulation of lipid hydroperoxide (LOOH) can ultimately activate ferroptosis [80].

2.4.2. P53-SAT1-ALOX15 pathway

SAT1, a transcriptional target of P53 and an important rate-limiting enzyme in polyamine catabolism, is activated or upregulated due to the activation of P53. The overexpression of SAT1 enhances cellular LPO and ferroptosis under ROS stress [85]. ALOX15 is a downstream effector of P53-induced SAT1 and plays a critical role in this pathway. According to Ou et al. [77], an ALOX15-specific inhibitor (PD146176) completely eliminated ferroptosis induced by SAT1 and ROS.

2.4.3. Sulfur transfer pathway

Under oxidative stress, methionine is converted into cysteine via the sulfur transfer pathway. Initially, methionine is demethylated and transformed into the intermediate, homocysteine. Thereafter, this intermediate enters the cell across the membrane and combines with serine in the cell to generate cysteine and α-ketobutyric acid. The generated cysteine combines with glutamate and glycine to yield GSH, whose antioxidant activity can be exploited *in vivo*.

GSH generation can be reduced by inhibiting the sulfur transfer pathway, which increases the accumulation of lipid peroxides and induces ferroptosis [81].

2.4.4. VDACs mitochondria pathway

VDACs are ion channels located in the outer membrane of the mitochondria that mediate and regulate the transport of molecules (such as adenosine triphosphate (ATP) and metabolites) and ions between the mitochondria and cytoplasm. Altering the permeability of VDACs by introducing excessive Ca^{2+} or glutamate can induce mitochondrial metabolic disorders and excessive ROS generation, ultimately leading to the activation of ferroptosis [81].

2.4.5. Glutamine metabolic pathway

Glutamate is an important amino acid that regulates ferroptosis and serves as a vital metabolite of glutamine. The cellular uptake of glutamine occurs with the aid of the amino acid transporter, solute carrier family 1 member 5 (ASCT2/SLC1A5), which undergoes a deamination reaction within the mitochondria that is orchestrated by the enzyme, glutaminase, resulting in the generation of glutamate. Glutamate generation can be attenuated by impeding its metabolism, which results in a decline in the biosynthesis of GSH and the subsequent induction of ferroptosis [83].

2.4.6. P62-Keap1-Nrf2 pathway

P62 is an autophagic receptor protein whose Keap1-interacting region domain can degrade Keap1, thereby reducing Keap1-mediated ubiquitination of Nrf2 and activating the antioxidant activity of Nrf2. By suppressing P62, unmasked Keap1 plays an instrumental role in promoting the ubiquitination of Nrf2, subsequently impairing the antioxidant capacity of cells and accumulating a large amount of ROS, which ultimately leads to ferroptosis [78].

2.4.7. MVA pathway

The MVA pathway generates certain substances, including CoQ10 and squalene. Statins can reduce the antioxidant activity of cells and accelerate the activation of ferroptosis by blocking the biosynthesis of GPX4 and CoQ10. Researchers have revealed that squalene cannot induce but can inhibit ferroptosis. Squalene synthase (SQS) agonists (such as the ferroptosis inducer FIN56) can promote ferroptosis to a certain extent. In particular, FIN56 can not only induce ferroptosis by inducing the degradation of GPX4 but also target the binding and activation of the protein, SQS, which can consume CoQ10 and inhibit the production of the antioxidant substance, ubiquinol (CoQH2), ultimately decreasing cellular antioxidant activity and leading to ferroptosis [86].

2.4.8. FSP1-CoQ10-NAD(P)H pathway

FSP1, formerly known as apoptosis-inducing factor mitochondria-associated 2, is a GSH-independent ferroptosis suppressor that directly engages NAD(P)H to catalytically drive the reduction of CoQ10 in the cell membrane, yielding CoQH2 with antioxidant activity. A consequential reduction in CoQH2 biosynthesis ensues by hampering the activity of FSP1, resulting in debilitated cellular antioxidant capacity, increased ROS generation, and the promotion of ferroptosis [79,87].

2.4.9. ATG5/7-NCOA4 pathway

Ferroptosis is promoted by the upregulation of autophagy-related *ATG5/7* gene expression, facilitating an increase in intracellular iron levels and the intensification of LPO. NCOA4 is a selective autophagic cargo receptor that binds Fn and translocates to lysosomes to induce Fn degradation. Fn degradation results in Fe^{2+} enrichment in cells, which eventually causes ferroptosis induced by the Fenton reaction [84].

Overall, the activation of ferroptosis is primarily regulated by the intricate interplay of the system Xc^-/GPX4, lipid metabolic, and iron metabolic pathways, accompanied by an assemblage of supplementary pathways, such as the P53/SLC7A11, P53-SAT1-ALOX15, sulfur transfer, VDACs mitochondria, glutamine metabolism, P62-Keap1-Nrf2, MVA, FSP1-CoQ10-NAD(P)H, and ATG5/7-NCOA4 pathways, etc.. These regulatory pathways synergistically intertwine, harmonize, and conjoin to elicit intracellular ferroptosis.

3. Defense mechanisms of ferroptosis

During therapeutic discovery and development, targets for both activation and defense mechanisms should be considered. As the activation mechanisms have been summarized, we now present the defense mechanisms. Three ferroptosis defense mechanisms have been comprehensively studied: GPX4-GSH, FSP1-CoQH2, and dihydroorotate (DHO) dehydrogenase (DHODH)-CoQH2.

3.1. GPX4-GSH system

In the system Xc^-/GPX4 pathway, GPX4 and GSH are the key regulatory targets of ferroptosis. The intracellular GSH content can be potentiated by activating or overexpressing system Xc^- and indirectly activating the activity of GPX4. Activated GPX4 uses GSH to reduce lipid peroxides to non-toxic lipid alcohols, thereby eliminating lipid peroxides and inhibiting ferroptosis [34,88]. Conversely, the knockout of the *SLC7A11* gene or the administration of GPX4 inhibitors (such as RSL3, ML162, or ML210) or GPX4 degradation agents (such as FIN56 or PDPT) is not conducive to hampering ferroptosis. Consequently, the upregulation of SLC7A11 expression, activation of GPX4, or augmentation of GSH production assumes a protective role against ferroptosis [28,89,90]. The mechanism by which ferroptosis is prevented by the GPX4-GSH system [34,91–93] is shown in the blue box in Fig. 4.

3.2. FSP1-CoQH2 system

Cells can undergo ferroptosis via the FSP1-CoQ10-NAD(P)H pathway, in which the FSP1-CoQH2 system exerts a defensive effect on the activation of ferroptosis, as shown in the red box in Fig. 4. FSP1, a GSH-independent ferroptosis inhibitor, acts as an oxidoreductase that facilitates the transformation of CoQ10 into CoQH2, even in the absence of GPX4. CoQH2, a lipophilic antioxidant, exerts its elemental activity by trapping free radicals and inhibiting the formation of lipid peroxides. Intracellular FSP1 exploits NAD(P)H to catalyze the regeneration of CoQ10 while continuously generating the antioxidant, CoQH2, thereby clearing ROS in cells and preventing ferroptosis [93]. The augmentation of *FSP1* gene expression amplifies cellular antioxidant processes to deter ferroptosis. Hadian [91] discovered a highly effective endogenous ferroptosis inhibitor, guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1), which is independent of GPX4. GCH1, a rate-limiting enzyme, plays a significant role in the biosynthesis of the antioxidant, tetrahydrobiopterin (BH4). Upregulating the expression of GCH1 promotes the production of the antioxidant, BH4, thereby preventing the accumulation of lipid peroxides and impeding ferroptosis.

3.3. DHODH-CoQH2 system

Gan and co-workers [92] discovered a new type of ferroptosis defense system in the mitochondria that is independent of the GSH

pathway. This system is mediated by mitochondrial DHODH, a flavin-dependent enzyme that resides in the inner mitochondrial membrane. The primary function of this system is to catalyze the oxidation process that transforms DHO into orotate, which is accompanied by the electron transfer and reduction reaction of CoQ10, thereby generating abundant CoQH2. LPO and ferroptosis in the mitochondria are impeded by the regulation of CoQH2 production in the inner mitochondrial membrane, as shown in the purple box in Fig. 4. Consequently, DHODH can serve as a regulatory factor for the activation and defense of ferroptosis and is a prominent anti-tumor target. Although the DHODH-CoQH2 system can cooperate with mitochondrial GPX4 to resist LPO and ferroptosis, it is independent of the classical cytoplasmic GPX4 and FSP1 pathways. Moreover, in cells with low GPX4 expression, the DHODH inhibitor, brequinar (BQR), was found to markedly attenuate DHODH activity and the production of CoQH2, thereby boosting ferroptosis. However, for GPX4 high-expression cells, BQR enhanced the susceptibility to ferroptosis inducers and failed to directly induce ferroptosis [94].

Generally, at least three ferroptosis defense systems exist in cells based on their subcellular localizations: the GPX4-GSH system in the cytoplasm and mitochondria, the FSP1-CoQH2 system on the cell membrane, and DHODH-CoQH2 system in the mitochondria. Based on their disparate spatial distributions, the mechanisms and functions of these pathways are unique characteristics. However, as these pathways involve redox systems, underlying interconnections and synergistic interplay may exist for some pathways or protein factors. In the context of countering ferroptosis, these pathways may demonstrate a certain degree of correlation, which warrants further investigation. These three mechanisms form a tripod that works together to prevent ferroptosis.

4. Interplay between ferroptosis and diseases

Ferroptosis has recently become a research hotspot in the field of disease prognosis and therapy and is associated with a variety of diseases, including cancers, neurological diseases, and metabolic diseases [2]. Based on the expertise of the authors, we opted to refrain from discussing ferroptosis regulation in disease management. Therapists have suggested activating ferroptosis to combat cancer and bacterial infections, while inhibiting ferroptosis to treat other diseases, including neurological and inflammatory diseases [2].

4.1. Activating ferroptosis for anticancer and antibacterial therapy

Ferroptosis has been extensively studied in cancers, in which it is activated by diverse pathways to suppress tumor development, thereby prolonging the lives of patients. Ferroptosis bypasses the resistance to most current anticancer drugs (which mostly rely on apoptosis) and potentially enables a new approach to cancer treatment [95]. For example, the overexpression of ACSL4 has been reported to play an essential role in promoting ferroptosis and inhibiting the proliferation of glioma cells [96]. Moreover, when sorafenib and the GPX4-inhibitor, RSL3, are administered to sorafenib-resistant HCT-8 cells, ferroptosis can be activated, ultimately decreasing cancer cell viability [97].

Intracellular bacterial survival is a major factor in chronic or recurrent infections. Ferroptosis has been studied extensively in the field of antibacterial agents. According to previous studies, the iron(III) complexes exhibit promising antimicrobial effects against *Staphylococcus aureus* (*S. aureus*) by triggering ferroptosis (or ferroptosis-like death) [98]. Subsequently, Ma et al. [99] reported that ferroptosis contributes to the suppression of intracellular *S. aureus* and *Escherichia coli* (*E. coli*) in RAW264.7 mouse macrophages. The import of ferrous iron into bacterial vacuoles via FPN was found to be reversed, thereby inducing *in situ* ferroptosis-like bacterial death.

Overall, activating ferroptosis may serve as a remarkable anticancer and antibacterial therapy.

4.2. Suppressing ferroptosis for other disease therapy

The prominent advantages of ferroptosis in the fight against cancer have attracted the attention of researchers in other fields. In contrast to cancer, for idiopathic pulmonary fibrosis (IPF), acute kidney injury (AKI), inflammatory bowel disease (IBD), and Alzheimer's disease (AD), etc., disease deterioration can be controlled by the inhibition of ferroptosis [100,101].

Increased iron levels are typically observed in the lungs of patients with IPF, owing to tracheal fibrosis and alterations in pulmonary function. Substantially large amounts of ROS have been identified in the bronchoalveolar lavage fluid of patients, which can trigger LPO [102]. Disturbances in iron metabolism and LPO characterize ferroptosis. Consequently, suppression of ferroptosis may be a potential therapeutic option for alleviating the symptoms of patients with IPF.

Cheng et al. [103] studied the relationship between ferroptosis and IPF and found a large amount of iron deposition in the lung tissues of patients. Similarly, iron deposition and ferroptosis were observed in alveolar type II (ATII) cells and the fibrotic lung tissue of IPF mice. Upon addition of the ferroptosis inhibitor, DFO, the profibrotic effect of bleomycin (BLM) was significantly alleviated and the Ashcroft score for pulmonary fibrosis decreased from 7 to 4. Further investigation of the mechanism revealed that DFO completely prevented the profibrotic effect of BLM by reducing the ferroptosis of ATII cells.

Ferroptosis alleviates renal tubular injury in ischemia/reperfusion-induced AKI (I/R-AKI). AKI, a syndrome that is as heterogeneous as cancer, is associated with pathogenic factors, including massive production of ROS and iron superloading [104–106]. Hence, a new promising strategy for the prevention and management of AKI is offered by the inhibition of ROS production and normalization of iron metabolism. Thus, the inhibition of ferroptosis contributes to the attenuation of AKI symptoms. A remarkable group of scientists revealed that ferroptosis is closely associated with AKI. In particular, Yang et al. [107] demonstrated that entacapone prevents I/R-AKI by remarkably attenuating LPO and iron accumulation in HK-2 cells.

Gao et al. [108] summarized that some potent ferroptosis inhibitors, including iron chelators, can reduce LPO and alleviate colitis-associated intestinal diseases. Recently, ferroptosis was identified as a major process in the pathophysiology of AD and as a target for AD management. Iron accumulates in the neuronal cells of patients with AD. High levels of intracellular iron serve as the primary route for ferroptosis activation, which ultimately manifests as LPO [109]. The high predominance of PUFAs in the brain tissue renders the central nervous system highly susceptible to LPO. GPX4-deficient mouse models were found to be substantially prone to AD, with pronounced neurological and cognitive deficits. Targeted inhibition of ferroptosis is a novel therapeutic strategy for the management of AD [110,111]. Wang et al. [112] found that forsythoside A could prevent erastin-induced ferroptosis by activating the Nrf2/GPX4 axis, ultimately enabling AD therapy. Researchers also found that iron deposition occurs in Parkinson's disease (PD). Therefore, ferroptosis was proposed as a potential therapeutic strategy for the management of PD. According to Hu et al. [113], DL-3-*n*-butylphthalide can regulate the expression of the iron metabolism-related proteins, TFR, Fn light chain, and transferrin 1, resulting in the inhibition of iron deposition, oxidative stress, and ferroptosis. d-Mannose alleviates osteoarthritis progression by

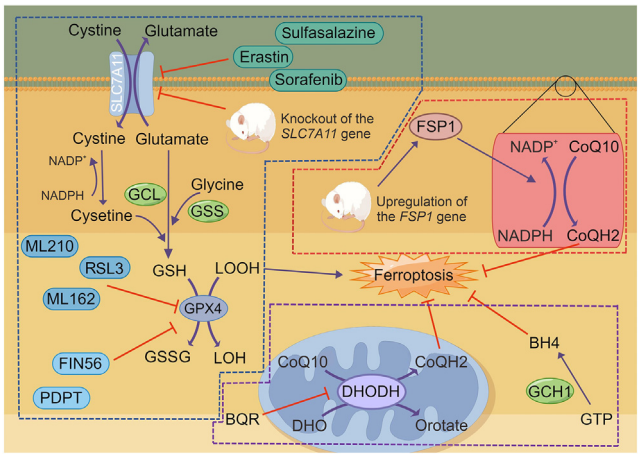

Fig. 4. Mechanisms are used to defend ferroptosis. SLC7A11: solute carrier family 7 member 11; $NADP^+$: oxidized form of nicotinamide adenine dinucleotide phosphate (NADPH); GCL: glutamic cysteine ligase; GSS: glutathione (GSH) synthetase; LOOH: lipid hydroperoxide; GPX4: GSH peroxidase 4; GSSG: oxidized GSH; LOH: lipid alcohol; PDPT: palladium pyrithione complex; FSP1: ferroptosis suppressor protein 1; CoQ10: coenzyme Q10; CoQH2: ubiquinol; BQR: brequinar; DHO: dihydroorotate; DHODH: DHO dehydrogenase; BH4: tetrahydrobiopterin; GCH1: guanosine triphosphate (GTP) cyclohydrolase 1.

inhibiting chondrocyte ferroptosis via hypoxia-inducible factor 2 alpha (HIF-2α) [114]. Dexmedetomidine alleviates myocardial I/R injury in rats by inhibiting ferroptosis, which occurs via the activation of the SLC7A11/GPX4 axis [115]. Liver injury is reported to be a common feature of coronavirus disease 2019 (COVID-19). According to researchers, ferroptosis may also participate in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-associated liver injury. Chen et al. [116] reported that DFO could be a potential drug for the treatment of COVID-19-induced liver injury.

Overall, these diseases can be effectively treated by suppressing ferroptosis.

5. Nanomedicine design based on ferroptosis targets

Nanomedicine is the application of the principles and methods of nanoscience and nanotechnology to medicine to exploit increasingly sensitive and precise medical methods and understand the processes and mechanisms of biological activity at the nanoscopic level [117]. The combination of ferroptosis and nanotechnology has led to significant advances in the diagnosis and management of various diseases. Recently, versatile nanomedicines have been designed based on ferroptosis targets, as summarized below.

5.1. Cystine/GSH/GPX4

5.1.1. Rationale

Two major groups of ferroptosis inducers exist. The first group of inducers, which includes erastin, sulfasalazine, and glutamate, interacts with system Xc^-, promotes intracellular GSH depletion, and indirectly suppresses the expression of GPX4. The second group of inducers, which includes RSL3, directly inhibits GPX4 activity [82]. Selenoperoxidase GPX4 converts LOOHs to lipid alcohols, a process that prevents the generation of Fe^{2+}-dependent toxic lipid ROS [118]. Therefore, the inhibition of GPX4 function leads to LPO, which can induce ferroptosis.

5.1.2. Nanomedicines design

5.1.2.1. Nanomedicines for cancer therapy. RSL3 covalently inactivates GPX4 by conjugating to selenocysteine on its active site, ultimately impeding the function of GPX4 and triggering ferroptotic cell death [106]. Previously, a bioinspired bovine serum albumin (BSA)-Fn complex was reported to enhance ferroptosis therapy as a tumor-targeted delivery platform for RSL3 [119]. All groups achieved a high reduction (63%) in GPX4 activity. In addition, the growth of BSA@RSL3@Fn-processed MDA-MB-231 cells were suppressed. Similarly, Li et al. [120] developed novel self-assembly nanomicelles with superior anti-tumor properties, which were decorated by maltose ligand (maltose-PEG-azobenzene@RSL3). These nanomicelles could inhibit the activity of GPX4 and induce the ferroptosis of HepG2 cells (Fig. 5A) [120].

Besides the ferroptosis inducers that usually trigger a single pathway, erastin can trigger multiple ferroptotic pathways, including the system Xc^-, VDACs, and P53 [82]. Recently, Yu et al. [121] developed folate (FA)-vectorized exosomes (EXO) loaded with erastin (erastin@FA-EXO). The proliferation and migration of MDA-MB-231 cells were found to be significantly inhibited by erastin@FA-EXO. Gai et al. [122] prepared FA-modified liposome (FA-LP) nanoparticles for the targeted co-delivery of erastin and metallothionein one dimensional (1D) pseudogene. Based on the methyl thiazolyl tetrazolium (MTT) assay results, erastin/metallothionein 1D pseudogene (MT1DP)@FA-liposomes (FA-LPs) remarkably reduced the viability of A549 and H1299 cells.

Overall, the direct or indirect suppression of GPX4 activity results in the accumulation of LPO, which can lead to ferroptosis during tumor therapy.

5.1.2.2. Nanomedicines for other disease therapy. Based on compelling evidence, ferroptosis plays an important role in inflammatory therapies. For instance, IBD is a chronic inflammatory disease characterized by oxidative stress in the intestine. This condition is attributed to the excessive iron in the intestine mediating Fenton reactions, generating remarkable amounts of ROS, and resulting in REDOX imbalance [123,124]. Ferroptosis-like features, such as abnormally elevated iron levels, GSH depletion, inactivation of GPX4, and LPO, which are collectively responsible for intestinal cell death and persistent inflammation, are commonly observed in patients with IBD. The potential for the incorporation of ferroptosis into the research landscape of IBD therapeutics could lead to promising therapies for patients. Previously, an oral nano-antioxidant (curcumin (Cur)-nanoceria (CeO_2) (Ce)@mannose modified chitosan (MCS) was developed by encapsulating Cur and Ce into mannose-modified chitosan (Fig. 5B) [101]. The nanoparticles were found to increase the expression of GSH and GPX4 for ROS scavenging, which contributed to the suppression of macrophage-induced inflammation and inhibition of the ferroptosis of intestinal cells [101].

5.2. Lipid metabolism

5.2.1. Rationale

Lipids play essential roles in the apoptotic and non-apoptotic cell death pathways. Ferroptosis is triggered by the excessive iron-dependent peroxidation of PUFA-containing PLs in cellular membranes. This process requires ACSL4, which functions as a restraining enzyme that catalyzes the conversion of long-chain PUFAs, such as arachidonic and eicosapentaenoic acids, to PUFA-CoA, resulting in aggravated LPO and ferroptosis [125].

5.2.2. Nanomedicine design

5.2.2.1. Nanomedicines for cancer therapy. Oleanolic acid activates ferroptosis by promoting the expression of ACSL4, thereby decreasing HeLa cell viability [126]. Zhu et al. synthesized oleanolic acid@Fe-single-atom catalyst (SAC)@erythrocyte membrane (EM) nanoparticles consisting of oleanolic acid-loaded iron SAC-

embedded hollow carbon nanospheres encapsulated in an EM (Fig. 6A) [127]. These researchers found that the nanoparticles could effectively elevate the expression of endogenous ACSL4 and enrich cell membranes with ROS-sensitive PUFAs, ultimately inducing ferroptotic MCF-7 cells death.

Although the regulation of ACSL4 contributes to the predisposition of cancer cells to ferroptosis, this situation is generally complicated by the vulnerability of ACSL4-related pathways to cancer heterogeneity [128]. Therefore, regulating lipid metabolism *in vivo* by delivering exogenous unsaturated fatty acids, which ultimately regulate ferroptosis, is a promising strategy for disease treatment. Sun et al. [129] reported a molecularly self-engineered LPO nanoamplifier for the delivery of FIN56 and AA, simultaneously in the modification with a small amount of disulfide bond-containing lipid-PEG (DSPE-SS-PEG_{2K}). Notably, AA as one of the most important unsaturated fatty acids in cell membrane PLs [130]. AA is catalyzed by ACSL4, LPCAT3, and lipoxygenase enzymes (LOXs) for the occurrence of LPO in tumor cells, which induces ferroptosis [131]. Well as expected, the FIN56-AA-DSPE-SS-PEG_{2K} nanoparticles (FAS NPs) exhibited excellent inhibition of tumor development driven by ferroptosis in xenografted 4T1 mammary tumor-bearing mice (Fig. 6B) [129].

5.2.2.2. Nanomedicines for other disease therapy. The inhibition of ACSL4 markedly prevents ferroptosis and inhibits the progression of inflammation. Wang et al. [100] confirmed that ACSL4 knockout significantly reduced ferroptosis in the kidney tubules of Cdh16Cre-ACSL4F/F mice, suggesting that ACSL4 is a potential target for the prevention and management of AKI. Deng et al. developed Se/albumin nanoparticles (SA NPs) (Fig. 7) [132], which could alleviate cisplatin (DDP)-induced AKI in a murine model. These results suggest that SA NPs could impede DDP-induced AKI by increasing the expression of ACSL4, thereby inhibiting ferroptosis.

5.3. Iron metabolism

5.3.1. Rationale

Iron accumulation increases during ferroptotic cell death. Iron ions can react with the metabolite, H_2O_2, resulting in ROS generation and the subsequent occurrence of ferroptosis [133]. Interfering with the metabolism of intracellular iron by altering Fn levels is an alternative approach.

5.3.2. Nanomedicine design

5.3.2.1. Nanomedicines for cancer therapy. As nanotechnology evolves, various iron-based nanomaterials exhibit extremely attractive therapeutic effects. These nanomaterials have superior benefits in antineoplastic therapy owing to their ability to deliver exogenous iron and activate ferroptosis [134]. Li et al. [135] constructed ferrocene (Fc) polymer micelles (protoporphyrin IX (PpIX) @amphiphilic methoxyl PEG (mPEG)-polylysine (PLys)-Fc micelles (M_{Fc})) that could induce GSH consumption by converting Fc to Fe^{2+} after ultrasonication in the presence of elevated H_2O_2 in the tumor microenvironment, and hence ferroptotic cell death via exogenous iron ions. Upon ultrasound treatment, the PpIX@M_{Fc} micelles combined sonodynamic and chemodynamic therapy (CDT) to activate apoptosis (Fig. 8A) [135].

Zheng et al. [136] used the ultrasonic technology in a similar recent study. These researchers developed a liposomal nanomedicine that encapsulated iron-based Fenton catalysts, gallic acid (GA)-Fe(II) and doxorubicin hydrochloride (DOX). GA-Fe(II) catalyzes the overexpression of H_2O_2 to •OH, thereby further depleting GSH and delivering exogenous iron to induce LPO and ferroptosis of DOX-resistant MCF-7/ADR cancer cells.

The introduction of excessive exogenous iron may cause injuries to human health. Hence, ferroptosis, which affects Fn, functions as an alternative that interferes with intracellular iron metabolism [137]. Zhu et al. fabricated Fn-hijacking nanoparticles (chlorin e6 (Ce6)-PEG-HKN_{15}). Owing to the amphiphilic character of the synthesized conjugates, the nanoparticles were formed via self-assembly in an aqueous solution and could trigger autophagic degradation of Fn and the spontaneous ferroptosis of cancer cells upon laser irradiation (Fig. 8B) [137].

5.3.2.2. Nanomedicines for other disease therapy. Ferroptosis functions as an anti-infectious agent. Xue et al. fabricated nanoswords of Fe-doped titanite, which resulted in an alkaline

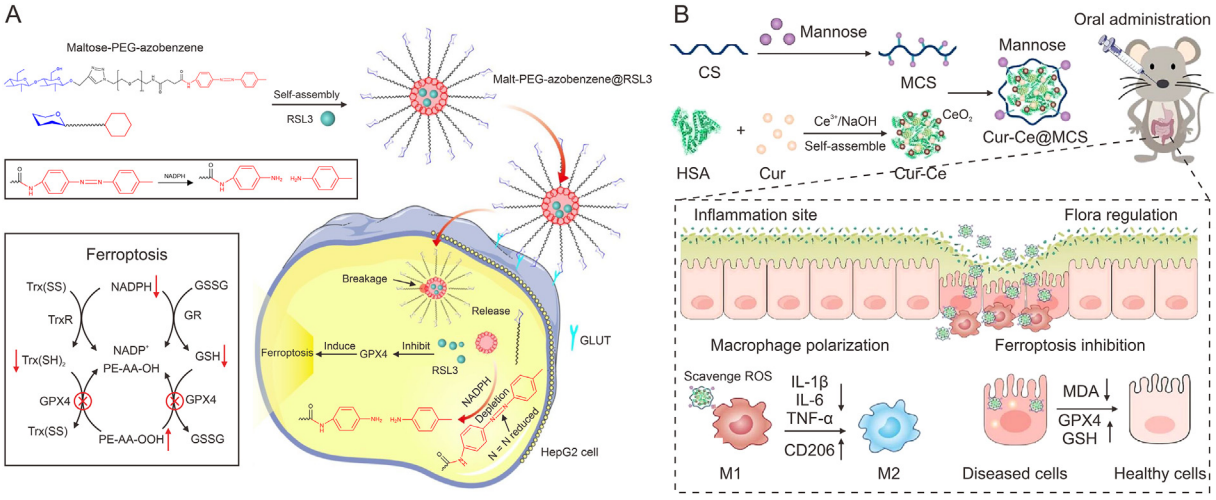

Fig. 5. Nanomedicine design based on cystine/glutathione (GSH)/GSH peroxidase 4 (GPX4) mechanism applied in cancer and inflammatory bowel disease (IBD). (A) Schematic illustration of the design of maltose-poly(ethylene glycol) (PEG)-azobenzene@RSL3 micelles and the mechanisms for triggering ferroptosis after entering the HepG2 cells [120]. (B) Schematic illustration of the preparation processes and the mechanisms of an oral nano-antioxidant encapsulated curcumin (Cur) and nanoceria (CeO_2) (Ce) to mannose modified chitosan (MCS) (Cur-Ce@MCS) for the treatment of IBD [101]. RSL3: a GPX4 inhibitor; Trx: thioredoxin; Trx (SS): oxidized Trx; TrxR: Trx reductase; $Trx(SH)_2$: reduced Trx; NADPH: nicotinamide adenine dinucleotide phosphate; $NADP^+$: oxidized form of NADPH; GSSG: oxidized GSH; GR: GSH reductase; PE-AA-OH: hydroxy-arachidonoyl phosphatidylethanolamine; PE-AA-OOH: hydroperoxy-arachidonoyl phosphatidylethanolamine; GLUT: glucose transporter; CS: chitosan; HSA: human serum albumin; ROS: reactive oxygen species; M1: macrophages M1 phenotype; IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; M2: macrophages M2 phenotype; MDA: malondialdehyde. Reprinted from Refs. [101,120] with permission.

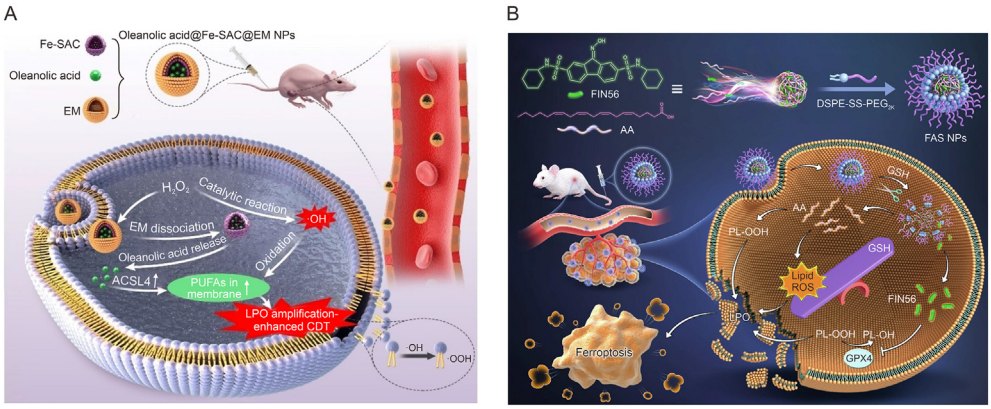

Fig. 6. Nanomedicine design based on lipid metabolism applied in cancer. (A) Schematic illustrating the preparation processes of the oleanolic acid@Fe-single-atom catalysts (SAC)@erythrocyte membrane (EM) nanoparticles and the anticancer mechanisms for chemodynamic therapy (CDT) [127]. (B) Schematic presentation on the fabrication processes of the molecularly self-engineered lipid peroxidation (LPO) nano-amplifier FIN56-AA-DSPE-SS-PEG_{2K} nanoparticles (FAS NPs) and the mechanisms for ferroptosis-driven tumor therapy [129]. ACSL4: acyl-CoA synthetase long-chain family member 4; PUFAs: polyunsaturated fatty acids; AA: arachidonic acid; DSPE-SS-PEG_{2K}: a small amount of disulfide bond-containing lipid-poly(ethylene glycol) (PEG); PL-OOH: phospholipid (PL) hydroperoxides; GSH: glutathione; ROS: reactive oxygen species; GPX4: GSH peroxidase 4; PL-OH: PL alcohols. Reprinted from Refs. [127,129] with permission.

microenvironment (Fig. 9) [138]. These nanoswords can trigger ferroptosis-like bacterial death by disturbing the proton dynamics and altering the membrane permeability, thereby accelerating the influx of Fe^{2+} ions into *S. aureus*.

5.4. Nicotinamide adenine dinucleotide (NADH)/FSP1/CoQ10

5.4.1. Rationale

Generally, ROS mediates redox stimulation, which is a significant factor in triggering ferroptosis. However, tumor cells are typically ferroptosis-insensitive and self-adaptively regulate their metabolic pathways to maintain redox homeostasis [139]. The therapeutic effect of ferroptosis can be augmented by interfering with essential metabolic pathways associated with intracellular redox homeostasis. FSP1, which acts in parallel with GPX4 as a guardian to protect against ferroptosis in the absence of GPX4, has been appealing to scientists [140]. FSP1 is a critical enzyme that reduces CoQ10 to CoQH2, which is a potent antioxidant that prevents LPO by trapping free radicals [91].

5.4.2. Nanomedicine design

5.4.2.1. Nanomedicines for cancer therapy. Yang et al. designed Cu-silk fibrin (SF) rosuvastatin (RSV) nanoparticles (Cu-SF(RSV) NPs), in which RSV was encapsulated in SF nanoparticles (Fig. 10A) [141]. These nanoparticles can overcome ferroptosis resistance by intervening in the metabolic MVA pathway. SF nanoparticles also disrupt the redox homeostasis regulated by the CoQ/FSP1 axis in 4T1 cells.

5.4.2.2. Nanomedicines for other disease therapy. Stroke is a devastating disease of the central nervous system that regularly confers disability or mortality, which studies have revealed is blamed on inflammation, oxidative stress, and an association with ferroptosis [142]. Therefore, Cui et al. developed platelet-derived nanoparticles (PM-GB) to deliver ginkgolide B (GB) with encapsulated platelet membrane (PM). The results showed that PM-GB increases the expression level of FSP1 by nearly four-fold and prevents LPO, thereby inhibiting the occurrence of ferroptosis, which protects neural cells, and promoting motor recovery in middle cerebral artery occlusion model rats (MCAO/R) (Fig. 10B) [142].

5.5. DHODH mediated ferroptosis defense

5.5.1. Rationale

As an iron-containing flavin-dependent enzyme, DHODH is involved in the synthesis of pyrimidines *in vivo* as well as the composition of RNA nucleotides by catalyzing the conversion of DHO-orotate-uridine monophosphate [143]. DHODH is an enzyme localized on the outer surface of the inner mitochondrial membrane. The mitochondria are the primary organelles involved in ROS generation. DHODH plays an essential role in mitochondrial ROS scavenging in parallel with GPX4. Therefore, suppression of DHODH activity can induce ferroptosis stemming from the mitochondria [92].

5.5.2. Nanomedicines design

Li et al. prepared magnetic nanoparticles (MNP) that utilized EXO with excellent biocompatibility and the ability to penetrate the blood-brain barrier and combined an inhibitor of DHODH (BQR) with Fe_3O_4 nanoparticle-mediated Fe^{2+} release for glioblastoma therapy (Fig. 11A) [144].

Owing to the satisfactory effects of ferroptosis treatment, Chen et al. revealed a strategy to block redox systems and enhanced ferroptotic cancer cell death based on a layered double hydroxide (LDH) nanoplatform (siR/iron oxide nanoparticles (IONs)@LDH). This LDH was co-loaded with the ferroptosis-activating agent, iron oxide nanoparticles, and the DHODH small interfering RNA (siRNA) inhibitor against DHODH (Fig. 11B) [145].

Briefly, various nanomedicines have been designed to either trigger or suppress ferroptosis, primarily via interactions with several targets of the pathways mentioned above (Table 2) [101,119–122,127,129,132,135–138,141,142,144,145]. Preliminary studies have demonstrated that the use of ferroptosis as a therapeutic target has ample potential for clinical translation.

6. Reflections and perspectives on future research

6.1. Implications for therapeutic discovery

Ferroptosis is of great significance for the normal physiological metabolism of organisms. The induction of ferroptosis is a potent approach for the treatment of neoplastic diseases. System Xc^-/GPX4, lipid metabolism, and iron metabolism are the main

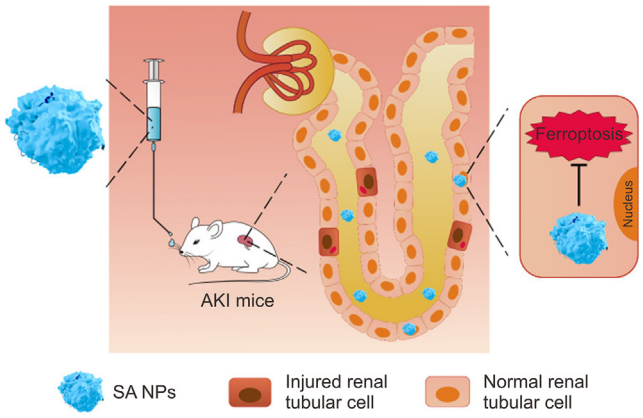

Fig. 7. Schematic illustrating the application of Se/albumin nanoparticles (SA NPs) for inhibiting ferroptosis [132]. AKI: acute kidney injury. Reprinted from Ref. [132] with permission.

pathways that promote the ferroptosis of cells [146]. Among them, the redox of lipid peroxides can be inhibited by introducing SLC7A11 inhibitors (such as erastin [52], sorafenib [53], or sulfasalazine [53]), GPX4 inhibitors, or degradation agents (such as RSL3 [53], ML162 [53], ML210 [55], FIN56 [18] or PDPT [57]), or upregulating the gene expression of some proteins or factors related to ferroptosis (such as *ALOXs*, *POR*, *ACSL4*, *TFR1*, *NCOA4*, or *HMOX1*) [71,74,75,84], thereby leading to ferroptosis (Table 3) [18,52–55,57,60,62,69,71,72,75,77,78,84,92,147]. Therefore, factors or proteins, such as SLCA7A11, GPX4, ALOXs, POR, ACSL4, TFR1, and HMOX1, can be used as targets to design nanomedicines that promote the ferroptosis of cancer cells, thereby exerting therapeutic effects.

The upregulation of ferroptosis is associated with many non-tumor diseases, such as AKI, IBD, IPF, AD, PD, osteoarthritis, myocardial ischemia, COVID-19, etc.. Therefore, scientists have opted to suppress ferroptosis to treat these diseases [84,148–152]. Currently, at least three ferroptosis defense mechanisms have been discovered: GPX4-GSH [34], FSP1-CoQH2 [72,93,153], and DHODH-CoQH2 [92]. By upregulating *SLC7A11* gene expression or downregulating *P53* gene expression to increase GSH biosynthesis; upregulating *ATG5/7* gene expression or introducing PD146176 to activate GPX4 activity [92]; upregulating *FSP1*, *GCH1*, and *DHODH* gene expression to potentiate cellular antioxidant capacity, or introducing iron chelators [68] (e.g., DFO, DFOM), ferrostatin-1 [34], POR inhibitors [93], and LPO inhibitors (e.g., liproxstatin-1) [60], the accumulation of LPO can be reduced, thereby impeding ferroptosis (Table 3). Therefore, the development of novel nanomedicines for targets, such as SLCA7A11, GPX4, FSP1, GCH1, and DHODH, has great research value for the treatment of ferroptosis-related AKI, IBD, IPF, AD, PD, osteoarthritis, myocardial ischemia, and COVID-19.

The agonists and inhibitors used to activate or inhibit ferroptosis for the treatment of various diseases are shown in Fig. 12. For simplicity, some typical diseases are included in this scheme.

6.2. Functions of nanomedicines

The role of nanomedicines in ferroptosis-based therapies must not be underestimated. When ferroptosis-inducing or inhibiting drug molecules are administered via conventional drug delivery systems, they may be rapidly released upon entering the body, which impedes the attainment of accurate target-specific drug delivery. Furthermore, the clinical utility of ferroptosis inhibitors, activators, and gene-based medicines that modulate ferroptosis is impeded by the inherent challenges posed by their limited solubility, stability, permeability, and bioavailability. Nanomedicines may serve as a remarkable avenue for resolving issues shown below [154].

1) Compared with conventional pharmaceuticals, nanomedicines exhibit remarkable biocompatibility, exerting a solubilizing effect while elevating absorption rates, permeability, and cellular uptake [155,156].
2) Nanomedicines can augment drug targeting, regulate drug pharmacokinetics, and achieve sustained or controlled drug release. Targeted nanomedicines can mitigate the deleterious effects of nonspecific distribution by reducing both the dosage and frequency of medication intake, thereby enhancing patient compliance with therapeutic regimens [157,158].
3) Nanomedicines can enhance the stability of active pharmaceutical ingredients, shielding them from degradation by biological fluids until their therapeutic action is exhibited, ultimately enhancing their bioavailability [159].
4) Based on the aforementioned characteristics, nanomedicines are associated with altered bioavailability and heightened effectiveness compared with conventional pharmaceuticals [160].

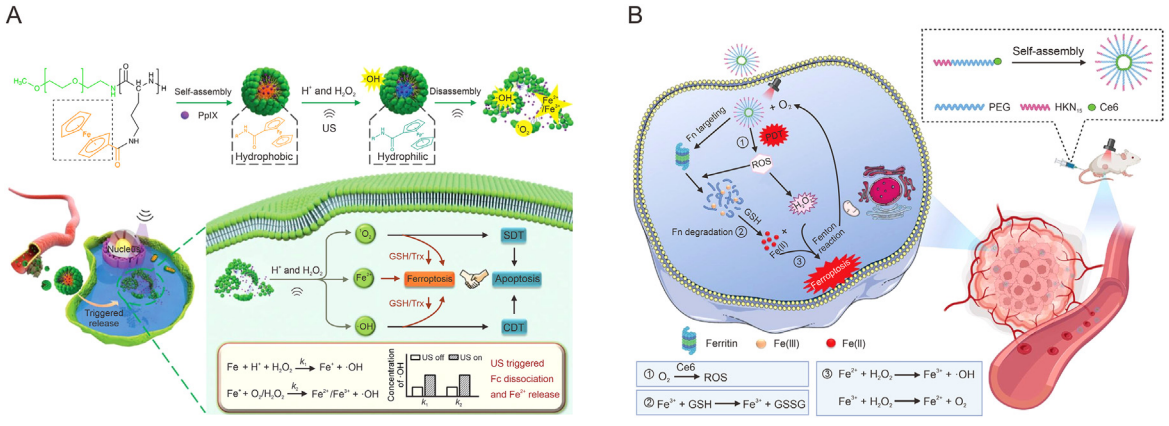

Fig. 8. Nanomedicine design based on iron metabolism applied in cancer. (A) Schematic illustration of the preparation processes of the mechano-responsive leapfrog micelles (protoporphyrin IX (PpIX)@M_{Fc}) and the mechanisms of collaborative sonodynamic therapy (SDT) and chemodynamic therapy (CDT) for apoptotic and ferroptotic cancer therapy [135]. (B) Fabrication procedures and antitumor mechanisms of ferritin (Fn)-targeting nanoparticles (chlorin e6 (Ce6)-poly(ethylene glycol) (PEG)-HKN_{15} nanoparticles (NPs)) for synergistic photodynamic therapy (PDT) and ferroptosis therapy [137]. M_{Fc}: amphiphilic methoxyl PEG (mPEG)-polylysine (PLys)-ferrocene (Fc) micelles; US: ultrasound; GSH: glutathione; Trx: thioredoxin; k_1: first-order dissociation energy; k_2: second-order dissociation energy; ROS: lipid reactive oxygen species; GSSG: oxidized GSH. Reprinted from Refs. [135,137] with permission.

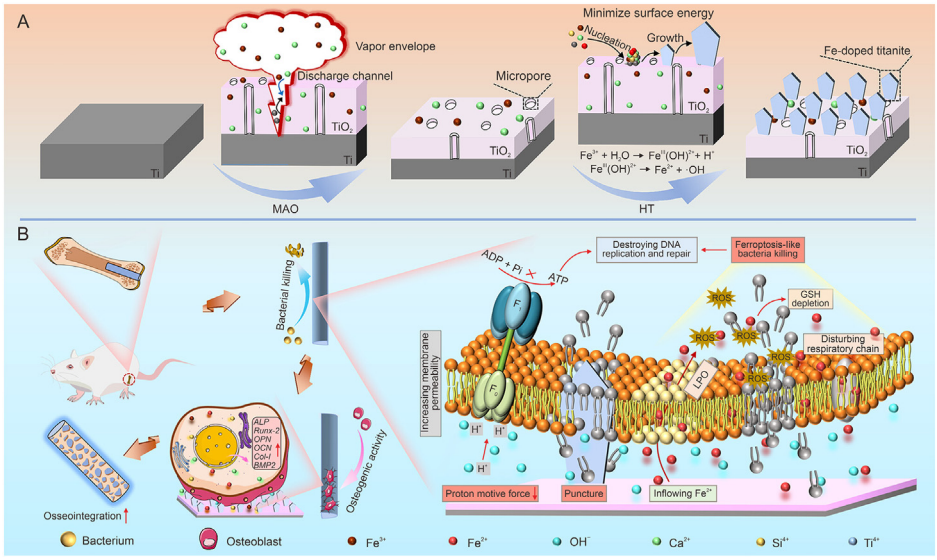

Fig. 9. Preparation of nanoswords (Fe-doped titanite) on implants for killing bacteria and improving osteogenesis [138]. (A) Schematic on the preparation processes of nanoswords. (B) Mechanism of killing bacteria and improving osteogenesis by nanosword. MAO: microarc oxidation; HT: hydrothermal treatment; *ALP*: alkaline phosphatase; *Runx-2*, *OPN*, *OCN*, *Col-1*, and *BMP2*: some typical genes for assessing the osteogenesis ability of osteoblasts; ADP: adenosine diphosphate; ATP: adenosine triphosphate; F1: F1 subunit of the ATP synthase complex; F0: F0 subunit of the ATP synthase complex; LPO: lipid peroxidation; GSH: glutathione; ROS: reactive oxygen species. Reprinted from Ref. [138] with permission.

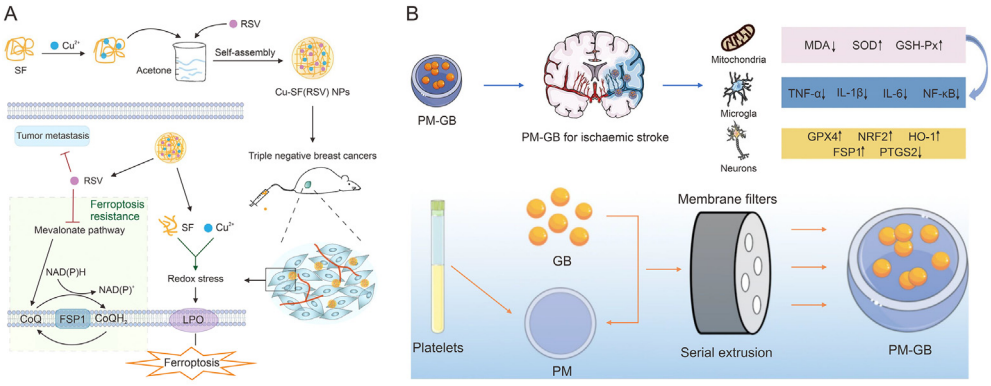

Fig. 10. Nanomedicine design based on nicotinamide adenine dinucleotide (NADH)/ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) mechanism applied in cancer and ischaemic stroke. (A) Schematic on the preparation processes and the antitumor mechanism of the metabolic intervention nanoparticles Cu-silk fibrin (SF) rosuvastatin (RSV) nanoparticles (Cu-SF(RSV) NPs) for triple-negative breast cancer (TNBC) [141]. (B) Schematic mechanism of the anti-inflammatory, antioxidative stress, and ferroptosis inhibition properties of nanoparticles deliver ginkgolide B (GB) with encapsulated platelet membrane (PM) (PM-GB) in ischaemic stroke and the preparation processes [142]. NAD(P)H: NADH phosphate; $NAD(P)^+$: oxidized form of NADPH; CoQ: ubiquinone; CoQH2: ubiquinol; LPO: lipid peroxidation; MDA: malondialdehyde; SOD: superoxide dismutase; GSH-Px: glutathione (GSH) peroxidase; TNF-α: tumor necrosis factor alpha; IL: interleukin; NF-κB: nuclear factor-kappaB; GPX4: GSH peroxidase 4; NRF2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase-1; PTGS2: prostaglandin endoperoxide synthase 2. Reproduced from Refs. [141,142] with permission.

Overall, combined with their potent ferroptosis mechanisms, nanomedicines hold promise as the main driver in ferroptosis-based therapies.

6.3. Future directions

In conclusion, the identification and exploration of ferroptosis have led to a novel methodology for the treatment of various diseases. The identification of numerous new targets can address a range of contemporary drug resistance challenges, highlighting the crucial advancements in medicine and pharmacology. However, such identification was associated with challenges. 1) The activation and defense mechanisms of ferroptosis *in vivo* are extremely complex and intertwined, and comprise many regulatory factors. Current scientific studies have only revealed a small part of the mechanisms of ferroptosis; thus, the complete mechanism has not been fully revealed [161]. 2) The connection between ferroptosis and other forms of cell death, such as apoptosis, pyroptosis, and autophagy, remains incompletely understood, and potential interactions with other cellular mechanisms cannot be dismissed [162,163]. 3) Ferroptosis activators and inhibitors exhibit limited selectivity for inducing cell death. Consequently, direct administration has low targetability and may result in side effects [164,165].

The following perspectives are offered to address the above shortcomings. 1) A follow-up in-depth study is required to elucidate the mechanisms associated with ferroptosis [19,166]. 2) A thorough investigation should be performed to reveal the correlation between ferroptosis and prevalent cell death modalities (apoptosis, pyroptosis, autophagy, etc.), which is essential to mitigate potential interference from alternative mechanisms of ferroptosis or enhance the therapeutic effects of ferroptosis [167]. 3) Nanomedicines encapsulating ferroptosis agonists or inhibitors can be developed by designing intelligent targeted delivery systems to enhance drug selectivity while minimizing potential side effects [168].

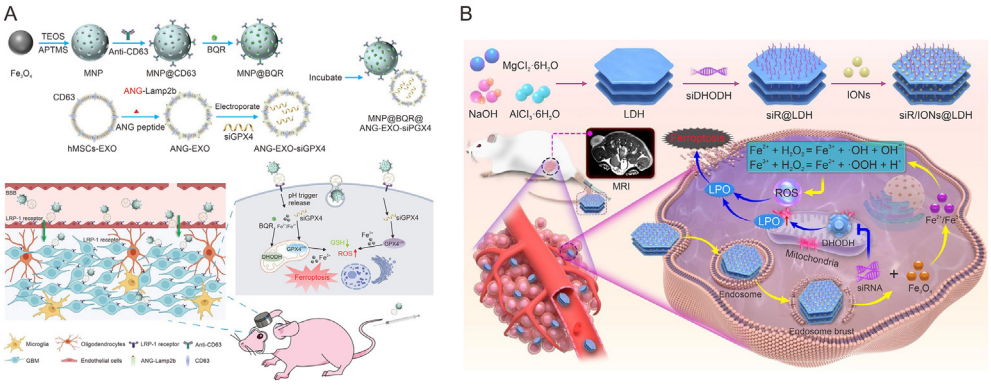

Fig. 11. Nanomedicine design based on dihydroorotate (DHO) dehydrogenase (DHODH) mediated ferroptosis defense mechanism applied in cancer. (A) Schematic illustration of the synthesis of magnetic nanoparticles (MNP)@brequinar (BQR)@angiopep-2 (ANG)-exosome (EXO)-small interfering RNA glutathione peroxidase 4 (siGPX4) (MNP@BQR@ANG-EXO-siGPX4) and the mechanisms underlying the induction of glioblastoma (GBM) cell ferroptosis [144]. (B) Schematic illustration of the construction and theranostic mechanism of the layered double hydroxide (LDH) nanoplatform co-loaded with ferroptosis agent iron oxide nanoparticles (IONs) and the DHODH inhibitor (siR/IONs@LDH) in nanomaterial-mediated tumor ferroptosis therapy [145]. TEOS: silicon tetraacetate; APTMS: (3-Aminopropyl) trimethoxysilane; hMSCs: human mesenchymal stromal cells; BBB: blood-brain barrier; LRP-1: lipoprotein receptor protein 1; $GPX4^{mito}$: GPX4 in mitochondrion; ROS: reactive oxygen species; $GPX4^{cyto}$: GPX4 in cytoplasm; siDHODH: DHODH inhibitor; siR@LDH: a siRNA@layered double hydroxide; MRI: magnetic resonance imaging; LPO: lipid peroxidation. Reprinted from Refs. [144,145] with permission.

Table 2
Summary of nanomedicines targeting ferroptosis.

Mechanisms	Nanomedicines for cancer therapy	Tumor cells	Nanomedicines for other disease therapy	Disease	Refs.
Cystine/GSH/GPX4	BSA@RSL3@Fn, maltose-PEG-azobenzene@RSL3, erastin@FA-EXO, and MT1DP@FA-LPs	MDA-MB-231, HepG2, A549, or H1299 cells	Cur-Ce@MCS	IBD	[101,119–122]
Lipid metabolism	Oleanolic acid@Fe-SAC@EM and FAS NPs	MCF-7 and 4T1 cells	SA NPs	AKI	[127,129,132]
Iron metabolism	PpIX@M_{Fc} micelles, Lipo@GA-Fe(II)@DOX, and Ce6-PEG-HKN_{15}	4T1 and MCF-7/ADR cells	Fe-doped titanite nanoswords	*S. aureus* infection	[135–138]
NADH/FSP1/CoQ10	Cu-SF(RSV)	4T1 cells	PM-GB	Stroke	[141,142]
DHODH mediation	MNP@BQR@ANG-EXO-siGPX4 and siR/IONs@LDH	GBM and 4T1 cells	–	–	[144,145]

–: no data. GSH: glutathione; GPX4: GSH peroxidase 4; BSA@RSL3@Fn: a bioinspired bovine serum albumin (BSA)-ferritin (Fn) complex loaded RSL3; maltose-PEG-azobenzene@RSL3: a novel self-assembly nanomicelles decorated maltose ligand; erastin@FA-EXO: folate (FA)-vectorized exosomes (EXO) loaded with erastin; MT1DP: erastin/metallothionein one dimensional (1D) pseudogene; FA-LPs: FA-liposomes; Cur-Ce@MCS: an oral nano-antioxidant encapsulated curcumin (Cur) and nanoceria (CeO_2) (Ce)to mannose modified chitosan (MCS); IBD: inflammatory bowel disease; oleanolic acid@Fe-SAC@EM: consisted of oleanolic acid-loaded iron single-atom catalyst (Fe-SAC)-embedded hollow carbon nanospheres encapsulated by an erythrocyte membrane (EM); FAS NPs: a molecularly self-engineered lipid peroxidation (LPO) nanoamplifier for the delivery of FIN56 and AA, simultaneously in the modification with DSPE-SS-PEG2K; SA NPs: Se/albumin nanoparticles; AKI: acute kidney injury; PpIX@M_{Fc} micelles: protoporphyrin IX@amphiphilic methoxyl poly(ethylene glycol) (mPEG)-polylysine (PLys)-ferrocene (Fc) micelles; Lipo@GA-Fe(II)@DOX: liposomal nanomedicine encapsulated iron-based Fenton catalyst GA-Fe(II) and doxorubicin hydrochloride (DOX); Ce6-PEG-HKN_{15}: a Fn-hijacking nanoparticle; Fe-doped titanite: nano swords of Fe-doped titanite; *S. aureus*: *Staphylococcus aureus*; NADH: nicotinamide adenine dinucleotide; FSP1: ferroptosis suppressor protein 1; CoQ10: coenzyme Q10; Cu-SF(RSV): encapsulated rosuvastatin (RSV), Cu^{2+}, and silk fibroin (SF); PM-GB: a nanoparticles deliver ginkgolide B (GB) with encapsulated platelet membrane (PM); DHODH: dihydroorotate (DHO) dehydrogenase; MNP@BQR@ANG-EXO-siGPX4: magnetic nanoparticles (MNP)@brequinar (BQR)@angiopep-2 (ANG)-EXO-small interfering RNA glutathione peroxidase 4 (siGPX); siR/IONs@LDH: a layered double hydroxide (LDH) nano platform co-loaded ferroptosis activating agent iron oxide nanoparticles (IONs) and the DHODH inhibitor small interfering RNA (siRNA) against DHODH (siR); GBM: glioblastoma.

Based on the advantages of nanomedicines described above, the development of ferroptosis agonists and inhibitors as nanomedicines can enhance drug solubility, stability, bioavailability, and targeting in clinical applications. This strategy shows considerable promise for addressing diverse medical conditions, including IPF, AKI, IBD, and other ailments. However, many issues regarding ferroptosis-regulating activities remain in the field of nanomedicine. The following viewpoints were discussed: 1) Currently, ferroptosis-based nanomedicines are undergoing preclinical investigations; these therapies have not been fully translated for clinical use [169]. Further concerted efforts are imperative for the continued progress and development of this domain. 2) Although numerous ferroptosis-based nanomedicines have emerged for the treatment of several diseases, their applicability remains limited [170]. Thus, an urgent need exists to develop novel therapeutic strategies for a wider range of diseases. 3) As other forms of programmed cell death (such as apoptosis) have been reported to involve defense mechanisms, drug resistance in ferroptosis-based nanomedicines may become an issue in the future. Combining ferroptosis with other pathways, such as apoptosis, necrosis, pyroptosis, autophagy, and cuproptosis, may lead to improved therapeutic effects and mitigation of drug resistance, thereby serving as a new method for disease management [171]. Similarly, the use of ferroptosis therapy in combination with other therapies, such as chemotherapy [172–174], photothermal therapy [112,175,176], photodynamic therapy [177,178], immunotherapy [179–181], sonodynamic therapy [182,183], and radiotherapy [184–186], for the treatment of cancer is a current and future trend in research and promises to enable the combination of multiple therapies for the precision treatment

Table 3
The site of action and function of multiple small molecule drugs and factors that regulate ferroptosis.

Compounds	Site of action	System	Activity type	Ferroptosis	Refs.
FIN56	GPX4	System Xc^-/GPX4 pathway	GPX4 degradant	Activation	[18]
Erastin	SLC7A11	System Xc^-/GPX4 pathway	SLC7A11 inhibitor	Activation	[52]
RSL3	GPX4	System Xc^-/GPX4 pathway	GPX4 inhibitor	Activation	[53]
ML162	GPX4	System Xc^-/GPX4 pathway	GPX4 inhibitor	Activation	[54]
ML210	GPX4	System Xc^-/GPX4 pathway	GPX4 inhibitor	Activation	[55]
Palladium pyrithione complex	GPX4	System Xc^-/GPX4 pathway	GPX4 degradant	Activation	[57]
Liproxstatin-1	Poly-unsaturated fatty acid-phosphatidyl ethanolamine	Lipid metabolic pathway	LPO inhibitor	Defense	[60]
Oleanolic acid	ACSL4	Lipid metabolic pathway	ACSL4 expression promoter	Activation	[62]
Ferrostatin-1	•OH	Lipid metabolic pathway	Antioxidant	Defense	[69]
STEAP3	Fe^{3+}	Iron metabolic pathway	Metalloreductase	Activation	[71]
Ferristatin II	TFR1	Iron metabolic pathway	TFR1 inhibitor	Defense	[72]
NFS1	Cysteine	Iron metabolic pathway	Cysteine desulfurizing enzyme	Activation	[75]
PD146176	ALOX15	P53-SAT1-ALOX15 pathway	ALOX15-specific inhibitor	Defense	[77]
Nrf2	•OH	P62-Keap1-Nrf2 pathway	Antioxidant	Defense	[78]
NCOA4	Fn	ATG5/7-NCOA4 pathway	Autophagic cargo receptor	Activation	[84]
BQR	DHODH	DHODH-CoQH2 system	DHODH inhibitor	Activation	[92]
GCH1	GTP	FSP1-CoQH2 system	Rate limiting enzyme for generating BH4	Defense	[147]

GPX4: glutathione (GSH) peroxidase 4; SLC7A11: solute carrier family 7 member 11; LPO: lipid peroxidation; ACSL4: acyl-CoA synthetase long-chain family member 4; STEAP3: six-transmembrane epithelial antigen of prostate 3; TFR1: transferrin receptor 1; NFS1: nitrogen-fixing protein 1; ALOX15: arachidonate lipoxygenase 15; SAT1: spermidine/spermine N1-acetyltransferase 1; Nrf2: nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; NCOA4: nuclear receptor coactivator 4; Fn: ferritin; ATG5/7: autophagy-related protein 5/7; BQR: brequinar; DHODH: dihydroorotate (DHO) dehydrogenase; CoQH2: ubiquinol; GCH1: guanosine triphosphate (GTP) cyclohydrolase; FSP1: ferroptosis suppressor protein 1; BH4: tetrahydrobiopterin.

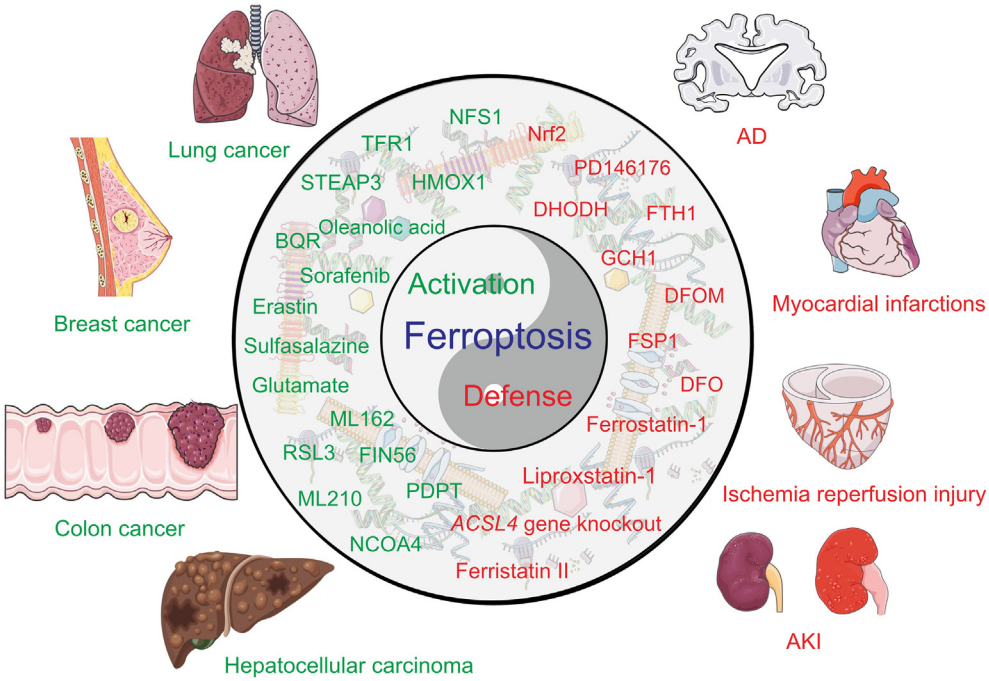

Fig. 12. Yin Yang symbol of agonists or inhibitors activating or inhibiting ferroptosis to treat multiple diseases. NFS1: nitrogen-fixing protein 1; TFR1: transferrin receptor 1; Nrf2: nuclear factor erythroid 2-related factor 2; STEAP3: six-transmembrane epithelial antigen of prostate 3; HMOX1: heme oxygenase 1; DHODH: dihydroorotate (DHO) dehydrogenase; FTH1: ferritin (Fn) heavy chain 1; BQR: brequinar; GCH1: guanosine triphosphate (GTP) cyclohydrolase 1; DFOM: deferoxamine (DFO) mesylate; FSP1: ferroptosis suppressor protein 1; PDPT: palladium pyrithione complex; *ACSL4*: acyl-CoA synthetase long-chain family member 4; NCOA4: nuclear receptor coactivator 4; AD: Alzheimer's disease; AKI: acute kidney injury.

of diseases. 4) Finally, the industrial scale-up and clinical translation of designed and synthesized ferroptosis-based nanomedicines have always been important topics that require attention [187].

Overall, an urgent need exists to solve the above problems, which can be achieved through intensive investigations to lay a good foundation for the development of new, safe, and effective nanomedicines to regulate ferroptosis.

7. Conclusion

This review sought to provide an overview of the history and characteristics of ferroptosis, a non-apoptotic form of cell death. Herein, the activation and defense mechanisms of ferroptosis were systematically described, and multiple targets that regulate ferroptosis were highlighted. We reviewed the current design of nanomedicines that target multiple factors or proteins, such as

SLCA7A11, GPX4, FSP1, GCH1, DHODH, etc., as therapeutic targets. Finally, the existing problems and difficulties that need to be solved in current ferroptosis research were discussed and summarized.

Overall, the development of nanomedicines targeting ferroptosis has remarkable fundamental research and clinical application prospects for the treatment of various diseases, such as tumors, pulmonary fibrosis, muscle ischemia, and neurodegenerative diseases. Further exploration is needed to design new, safe, and effective nanomedicines that regulate ferroptosis. This topic should receive more attention from the scientific community to enable rapid advancements.

CRediT author statement

Meihong Zhang, **Mengqin Guo**, and **Yue Gao:** Writing - Original draft preparation, Investigation; **Chuanbin Wu** and **Xin Pan:** Conceptualization, Project administration; **Zhengwei Huang:** Writing - Reviewing and Editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2024.03.001.

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