





Ferroptosis in Cancer Therapy: Mechanisms, Small Molecule Inducers, and Novel Approaches

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Abstract: Ferroptosis, a unique form of programmed cell death, is initiated by an excess of iron accumulation and lipid peroxidation-induced damage. There is a growing body of evidence indicating that ferroptosis plays a critical role in the advancement of tumors. The increased metabolic activity and higher iron levels in tumor cells make them particularly vulnerable to ferroptosis. As a result, the targeted induction of ferroptosis is becoming an increasingly promising approach for cancer treatment. This review offers an overview of the regulatory mechanisms of ferroptosis, delves into the mechanism of action of traditional small molecule ferroptosis inducers and their effects on various tumors. In addition, the latest progress in inducing ferroptosis using new means such as proteolysis-targeting chimeras (PROTACs), photodynamic therapy (PDT), sonodynamic therapy (SDT) and nanomaterials is summarized. Finally, this review discusses the challenges and opportunities in the development of ferroptosis-inducing agents, focusing on discovering new targets, improving selectivity, and reducing toxic and side effects.

Keywords: ferroptosis inducers, small molecules, PROTACs, PDT, SDT, nanomaterials

Introduction

The latest data released by the International Agency for Research on Cancer (IARC) indicates that there were 20 million new cancer cases globally in 2022, resulting in 9.7 million deaths. This data highlights the increasing global burden of cancer.¹ However, the effectiveness of existing cancer treatments is concerning, as tumor cell resistance is reducing the efficacy of conventional therapies like radiotherapy and chemotherapy.² Additionally, refractory cancers like small cell lung cancer (SCLC),³ triple-negative breast cancer (TNBC),⁴ and pancreatic cancer⁵ present significant challenges in oncology treatment due to their resistance to existing therapies. Ferroptosis, a novel iron-dependent form of programmed cell death first proposed by Dr. Brent R. Stockwell in 2012, is distinct from apoptosis, necrosis, and autophagy.⁶ It is triggered by glutathione (GSH) depletion, decreased activity of glutathione peroxidase 4 (GPX4), failure of lipid oxides to be metabolized by GPX4, and Fe²⁺-mediated oxidation of lipids leading to the generation of reactive oxygen species (ROS) that promote ferroptosis.⁷ Ferroptosis provides a new way of thinking about cancer treatment. Ferroptosis induction therapy has several natural advantages for cancer treatment. Firstly, the unique metabolism of cancer cells, the high load of ROS, and their specific mutations make some of them sensitive to ferroptosis,⁸ eg, clear cell renal cell carcinoma (ccRCC),⁹ pancreatic ductal adenocarcinoma,¹⁰ and TNBC.¹¹ Cancer cells typically require more iron than normal cells to proliferate, and this iron dependence makes them more susceptible to ferroptosis.¹² Cancer cells with a high mesenchymal state were found to be more resistant to a wide range of cancer treatments but were particularly susceptible to ferroptosis inducers.¹³ Also, ferroptosis induction therapy can be used in combination with conventional tumor treatments to enhance their therapeutic effects in certain malignancies.¹⁴

Ferroptosis-inducing therapies have emerged as a crucial strategy in oncology, with ongoing advancements in the development and study of various small molecule drugs targeting ferroptosis-regulating pathways.¹⁵ This review provides an overview of the regulatory mechanisms of ferroptosis and delves into the mechanisms of traditional small molecule ferroptosis inducers and their effects on various tumors. It also highlights the recent progress in inducing

ferroptosis through innovative methods such as PROTACs, PDT, SDT, and nanomaterials. Furthermore, the review addresses the challenges and opportunities in developing ferroptosis-inducing agents, including the exploration of new targets, enhancement of selectivity, and mitigation of toxic and side effects (Figure 1).

Ferroptosis Mechanism

Ferroptosis is a new form of cell death characterized by iron-dependent accumulation of lipid peroxidation to lethal levels.¹⁶ It has been shown that in mammalian cells, ferroptosis is mainly regulated by iron homeostasis, lipid metabolism, and glutathione-dependent redox homeostasis (Figure 2).

Iron Homeostasis

Iron is a trace element essential for maintaining the life of living organisms. It is involved in various metabolic pathways and exists in the human body mainly in Fe^{2+} and Fe^{3+} .¹⁷ Two molecules of Fe^{3+} can bind to a transferrin (TRF) for transport in vivo and transport iron into the cell by binding to the transferrin receptor TFR1 on the cell surface to form the TF- Fe^{3+} -TFR1 complex.¹⁸ Fe^{3+} is reduced to Fe^{2+} by the Six-Transmembrane Epithelial Antigen of Prostate 3 (STEAP3),¹⁹ which accumulates in cells to form the labile iron pool (LIP).²⁰ SLC11A2 regulates this process. Fe^{2+} in LIP participates in the Fenton reaction to generate reactive oxygen species (ROS) substances represented by hydroxyl radicals ($\cdot\text{OH}$).²¹ Accumulated ROS will undergo lipid peroxidation, resulting in loss of cellular function and cellular ferroptosis.²² Autophagic ferritin degradation in lysosomes mediated by nuclear receptor coactivator 4 (NCOA4) can induce ferroptosis by releasing free iron from ferritin.²³ In iron metabolism, the Ferritin Exporter (FE) is the only protein that can translocate iron from the cell, thereby reducing the intracellular Fe^{2+} concentration.²⁴

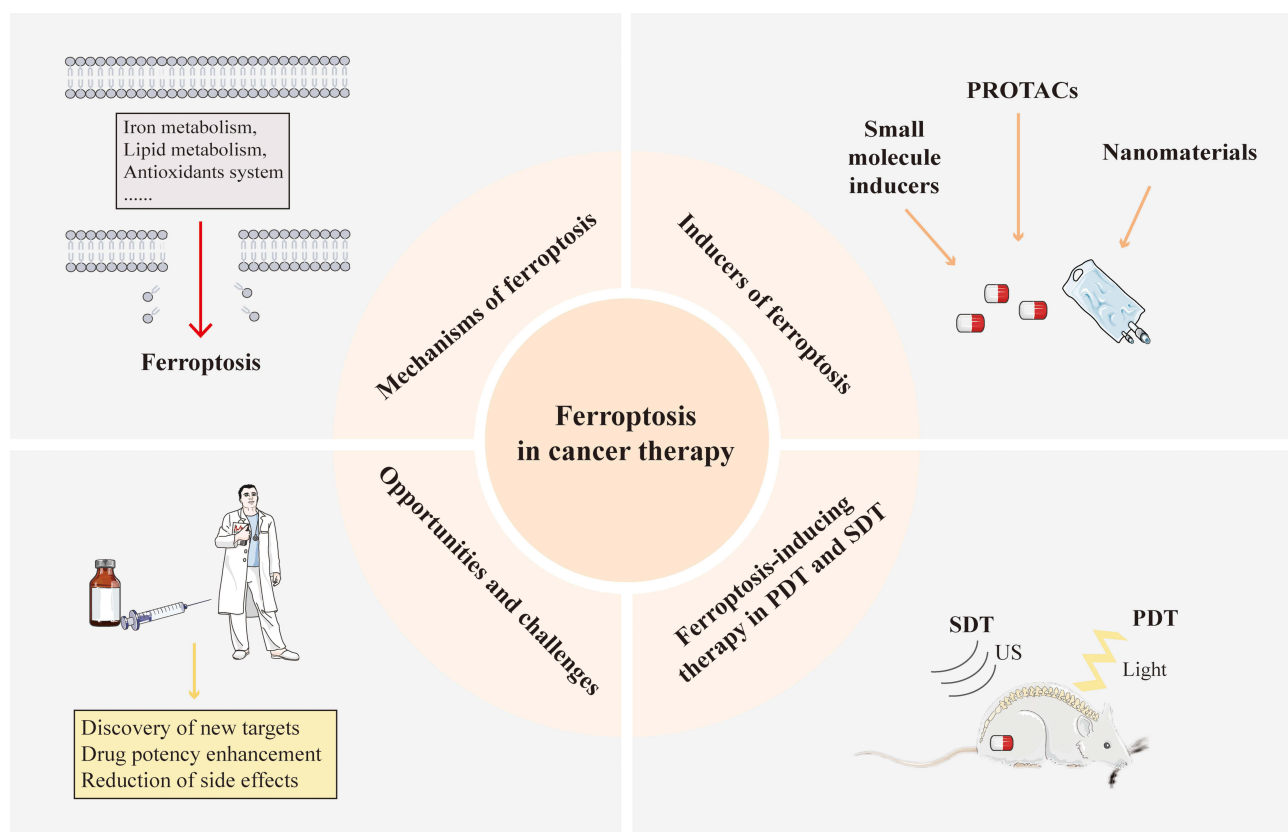


Figure 1 Ferroptosis in cancer therapy.

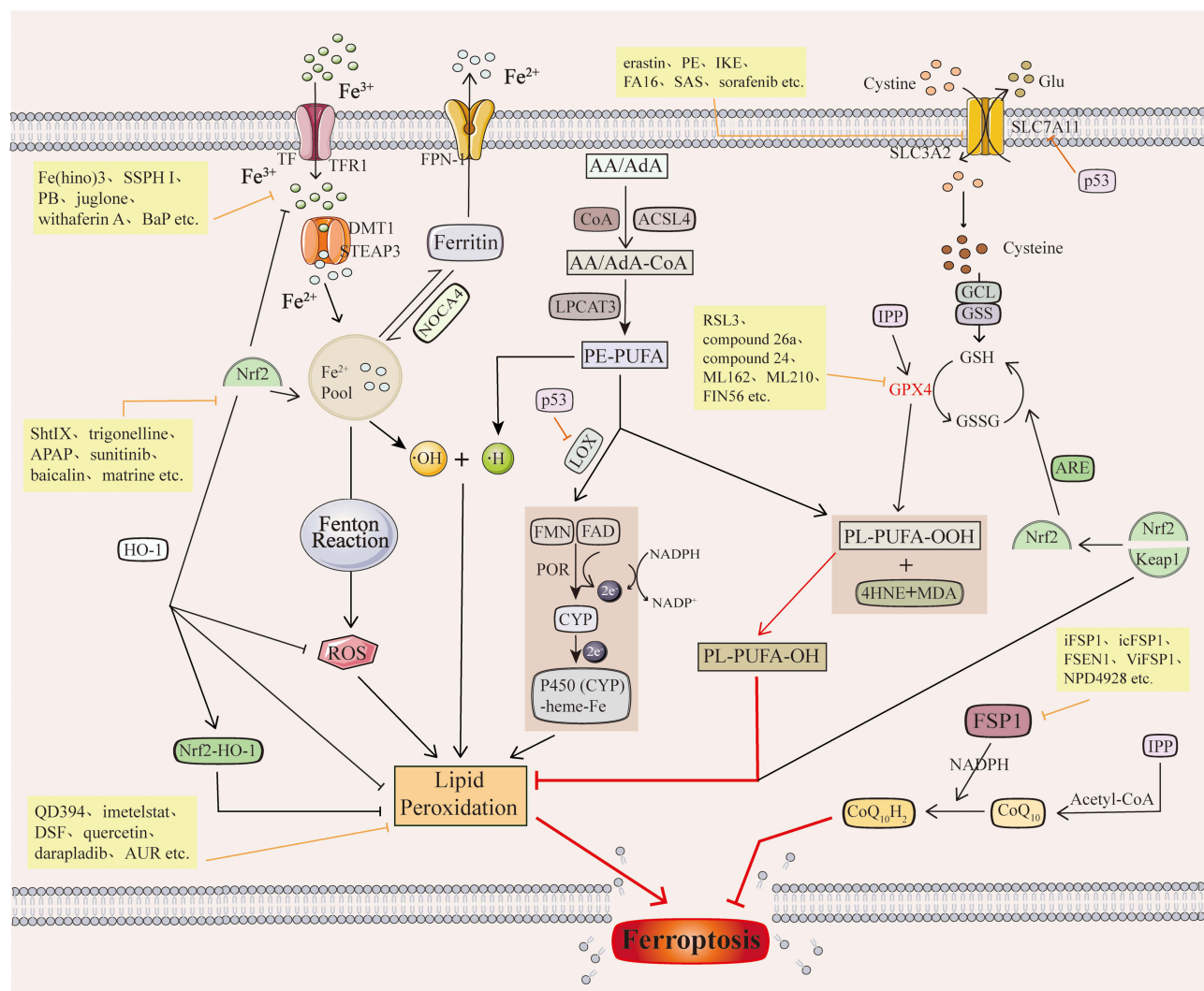


Figure 2 Ferroptosis mechanisms and their associated inducers of ferroptosis.

Abbreviations: TF, Serum Transferrin; TFR1, The membrane protein Transferrin Receptor 1; NCOA4, Nuclear receptor coactivator 4; STEAP3, Six-Transmembrane Epithelial Antigen of Prostate 3; DMT1, Divalent Metal Transporter 1; PE-PUFA, Phosphatidyl Ethanolamine-Polyunsaturated Fatty Acids; LOX, Lipoxygenase; Ferroportin 1, FPN1, Ferritin; Membrane iron transport protein 1; PL-PUFA-OOH, Lipid hydroperoxide; ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; SLC3A2, Recombinant Solute Carrier Family 3, Member 2; MDA, Malondialdehyde; 4HNE, 4-hydroxynonenal; POR, Cytochrome P450 oxidoreductase; FMN, Flavin mononucleotide; FAD, Flavin adenine dinucleotide; SLC7A11, Recombinant Solute Carrier Family 7, Member 11; GCL, Glutamate-cysteine ligase; GSS, Glutathione synthase; GSH, Glutathione; GPX4, Glutathione Peroxidase 4; GSSG, Oxidized glutathione; Glu, Glutamic acid; Nrf2, Nuclear factor E2-related factor 2; tumor suppressor, p53; Keap1, Recombinant Kelch-like ECH Associated Protein 1; ARE, Antioxidant response element; HO-1, Heme oxygenase-1; FSP1, Ferroptosis Inhibitory Protein 1; CoQ10, Coenzyme Q10; CoQ10H2, Panthenol; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; Ipp, Isopentenyl pyrophosphate.

Lipid Metabolism

Lipid metabolism is strongly associated with ferroptosis.²⁵ Lipid peroxidation, a process in which oxygen combines with lipids to form peroxy radicals to produce lipid peroxides, is critical to the onset of ferroptosis.²⁶ Polyunsaturated fatty acids (PUFAs) containing two or more double bonds are involved in the lipid oxidation process of ferroptosis.²⁷ Arachidonic acid (AA) or adrenaline (AdA) was acylated to AA/AdA-CoA by Abstract Long-chain acyl-coenzyme A (CoA) synthase 4 (ACSL4) and then by Lysophosphatidylcholine acyltransferase 3 (LPCAT3) to PE-AA/AdA.²⁸ PE-AA/AdA is involved in downstream ferroptosis's non-enzymatic and enzymatic oxidation reactions.²⁹ Non-enzymatic reactions refer to the reaction of $\cdot\text{OH}$ produced by the Fenton reaction with lipids to form lipid peroxides, which eventually undergo lipid peroxidation, leading to ferroptosis.³⁰ Enzymatic reactions include two kinds. One is that PE-PUFA is catalyzed by lipoxygenase (LOX) to form toxic products such as Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE), which react with DNA bases, proteins, and other nucleophilic molecules to cause severe

harmful effects.³¹ The other is Cytochrome P450 reductase (POR), which promotes lipid peroxidation and leads to ferroptosis.³² Thus, ACSL4, LOX, and LPCAT3 are compelling targets for the action of ferroptosis inducers.

Antioxidant Pathways

The intracellular antioxidant pathway resists the onset of ferroptosis by neutralizing lipid peroxides and is a critical ferroptosis defense system in the body.³³ Inhibiting antioxidant pathways disrupts ferroptosis defenses, leading to the induction of ferroptosis. Described below are a few of the major pathways involved in the induction of ferroptosis.

Xc⁻-GSH-GPX4

The Xc⁻-GSH-GPX4 axis is a central regulatory pathway for ferroptosis.³⁴ The Cystine/Glutamate Antiporter (System Xc⁻) is on the cytoplasmic membrane. It contains solute carrier family 3 member 2 Gene (SLC3A2) and solute carrier family 7 member 11 Gene (SLC7A11, xCT), which is responsible for the transfer of cysteine(Cys) into the cell and glutamate(Glu) out of the cell.³⁵ Cysteine that is moved into the cell by system Xc⁻ can synthesize glutathione (GSH), which has antioxidant properties and strong reducing properties, with glutamate and glycine catalyzed by Glutathione synthetase (GSS) and Glutamate-cysteine ligase (GCL).³⁶ GPX4 converts GSH in cells to oxidized glutathione (GSSG).³⁷ In this process, GSH acts as an electron donor to convert toxic lipid peroxides in the cell to non-toxic Lipid alcohol (PL-PUFA-OH).³⁸ GSH and GPX4 are essential for maintaining intracellular redox balance and inhibiting the occurrence of ferroptosis. Inhibition of GSH synthesis through inhibition of system Xc⁻ and direct inhibition of GPX4 are important mechanisms of action of ferroptosis inducers. Selenocysteine is one of the essential amino acids for the active group of GPX4.³⁹ Thus, selenocysteine is an important target for a variety of GPX4 inhibitors.

FSP1-CoQ10-NAD(P)H Pathway

The FSP1-CoQ10-NAD(P)H pathway and the GSH-GPX4 pathway are two parallel lipid antioxidant pathways.⁴⁰ CoQ10 (ubiquinone) is a lipophilic free radical trapping antioxidant that blocks the propagation of lipid peroxides and inhibits ferroptosis.⁴¹ Its reduced form of CoQ10H2 (panthenol) reduces oxidative stress and inhibits lipid ROS accumulation.⁴² Ferroptosis suppressor protein 1 (FSP1) reduces CoQ10 to CoQ10H2 in response to NADPH and catalyzes the regeneration of CoQ10 via NAD(P)H.⁴³ The FSP1-CoQ10-NAD(P)H pathway exerts antioxidant effects independently of the system Xc⁻-GSH-GPX4 axis and inhibits ferroptosis. Inhibition of FSP1 blocks the antioxidant effects of the FSP1-CoQ10-NAD(P)H pathway, thereby inducing ferroptosis.⁴⁰

Nrf2/ARE-GPX4 Pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a crucial role in cellular antioxidant capacity. Nrf2 regulates the expression of antioxidant and pro-electrical stress genes. It also participates in other important pathways such as lipid metabolism, iron homeostasis and energy metabolism.⁴⁴ Kelch-like ECH-associated protein 1 (Keap1) is an active inhibitor of Nrf2. Under normal conditions, Nrf2 binds to Keap1. Under oxidative stress, Nrf2 is detached from the Keap1 binding site. It rapidly translocates to the nucleus, interacting with the Antioxidant Response Element (ARE) in the promoter region of mRNAs encoding detoxification enzymes and cytoprotective genes to enhance the expression of downstream target genes.⁴⁵ The downstream target genes of Nrf2 include genes related to iron metabolism, genes related to NADPH regeneration, and genes related to GSH metabolism.⁴⁶ Activation of these target genes will effectively maintain the redox homeostasis of the cell. Nrf2 also binds to Heme Oxygenase-1(HO-1) and inhibits the occurrence of lipid peroxidation.⁴⁷ Furthermore, activation of Nrf2 reduces cellular iron uptake, increases iron storage, and limits ROS production.⁴⁸ This shows that Nrf2 plays an important protective role against ferroptosis. Inhibition of Nrf2 is also a very important mechanism of action for ferroptosis inducers.⁴⁹

Mevalonate Pathway

The Mevalonate pathway (MVA pathway) includes the generation of isopentenyl pyrophosphate (IPP), squalene and CoQ10.⁵⁰ Selenocysteine is one of the amino acids in the active center of GPX4, and embedding it in GPX4 requires a special transporter, selenocysteine tRNA.⁵¹ IPP promotes selenocysteine tRNA maturation and GPX4 synthesis. Also,

IPP is a precursor of CoQ10 and can synthesize CoQ10 in the presence of acetyl-coenzyme A (Acetyl-CoA).⁵² Thus, the MVA pathway connects the system Xc⁻-GSH-GPX4 axis and the NADPH-FSP1-CoQ10 pathway.

p53 Gene

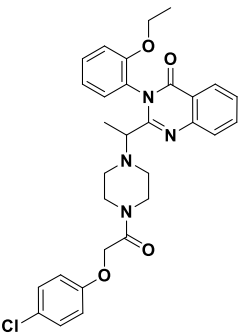
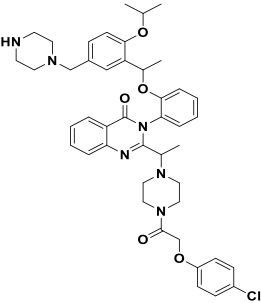
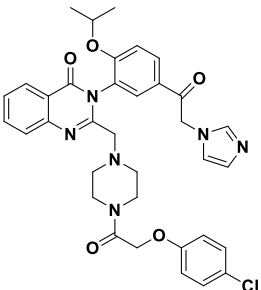
The p53 gene is a classical oncogene. As a transcription factor, p53 activates or represses the transcription of multiple downstream target genes to perform its function.⁵³ The p53 can transcriptionally repress SLC7A11 expression at the transcriptional level, thereby promoting the occurrence of ferroptosis in cells.⁵⁴ Also, p53 releases Arachidonate 12-lipoxygenase (ALOX12). Free ALOX12 oxidizes cell membrane phospholipids' polyunsaturated fatty acid chains, leading to ferroptosis.⁵⁵

Ferroptosis Inducers

Traditional Small Molecular Compounds

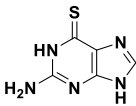
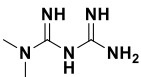
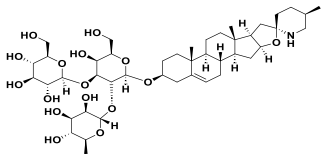
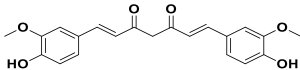
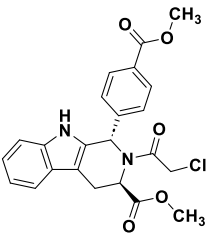
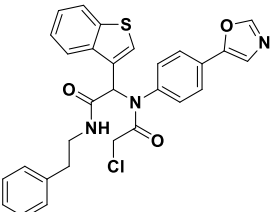
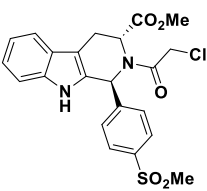
With the increasing research on ferroptosis, more and more inducers targeting ferroptosis have been identified and developed. Traditional small molecular compounds are an essential component of the ferroptosis inducer field. The following section will summarise these ferroptosis inducers in terms of the pathways of action of these drugs (Table 1).

Table 1 Small Molecular Ferroptosis Inducers

Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
Erastin		Quinazolinone derivatives	Inhibition of the expression of SLC7A11	ALL xenograft model; Melanoma xenograft model; Hepatocellular carcinoma xenograft model	[56–58]
Piperazine erastin (PE)		Piperazine fragment-containing derivatives of Erastin	Inhibition of SLC7A11 expression	Fibrosarcoma xenograft model	[59]
Imidazole ketone erastin (IKE)		Carbonyl-containing derivatives of Erastin	Inhibition of SLC7A11 expression	DLBCL xenograft model; Lymphoma xenograft model; CIA mouse model	[60]

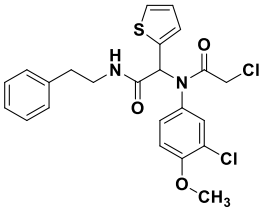
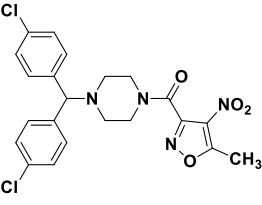
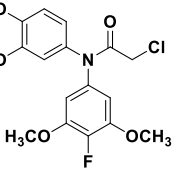
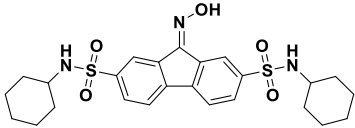
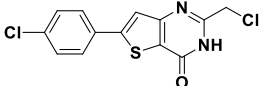
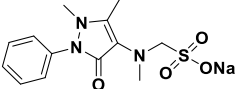
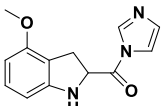
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
6-Thioguanine (6-TG)		Anti-leukemic drug	Suppression system Xc^-	Gastric cancer xenograft model	[68]
Metformin		Antidiabetic medication	Suppression of SLC7A11 expression; Suppression of Nrf2 expression	HI299 cells; A549 cells; Breast cancer xenograft model	[69,70]
Solasone (SS)		Natural product alkaloid	Suppression of SLC7A11 expression in a p53-dependent manner	Nasopharyngeal cancer xenograft model; Pancreatic cancer xenograft model	[71,72]
Curcumin		Natural polyphenols	Upregulation of SLC1A5 expression; Activation of autophagy	Breast cancer Xenograft model; Non-small cell lung cancer xenograft model	[73,74]
RAS-selective lethal 3 (RSL3)		Tetrahydro-β-carboline derivative	Covalent inhibition of GPX4; increased ROS and cellular LAP	Fibrosarcoma xenograft model; Hepatocellular carcinoma xenograft model	[75,76]
Compound 26a		RSL3 derivative	Inhibition of GPX4	Breast Cancer Xenograft Model	[77]
Compound 24		RSL3 derivative	Inhibition of GPX4	A xenograft model of diffuse large B lymphoma	[78]

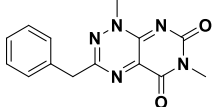
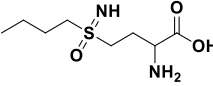
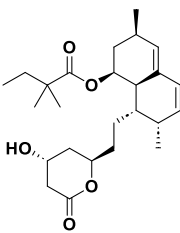
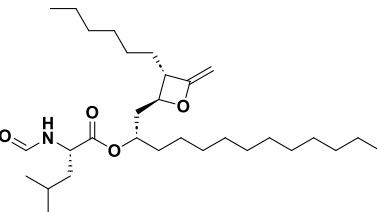
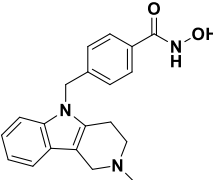
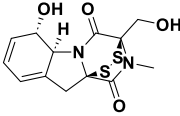
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
ML162		GPX4 covalent inhibitor	Covalent inhibition of GPX4	HRASG12V cell line	[79]
ML210		GPX4 covalent inhibitor	Covalent inhibition of GPX4	HRASG12V cell line	[79]
Compound C18		GPX4 covalent inhibitor	Covalent inhibition of GPX4	TNBC xenograft model	[80]
FIN56		GPX4 inhibitor	Induction of GPX4 degradation; activation of SQS	NCI60 cell line; Glioblastoma xenograft model	[81]
N6F11		GPX4 degradant	Induction of GPX4 degradation	Hs 578T cells; BxPC-3 cells; Hela cells	[82]
Metamizole sodium		COX inhibitor	Inhibition of GPX4-u46c - c10a - c66a enzyme activity		[83]
LOC1886		GPX4 inhibitor	Covalent inhibition of GPX4	G401 cell line	[84]

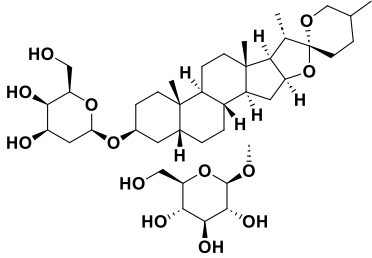
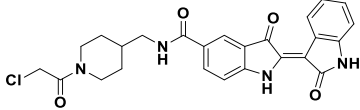
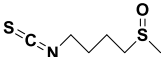
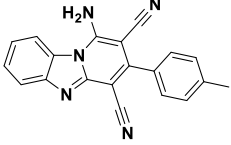
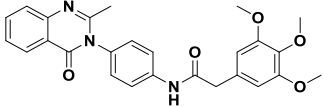
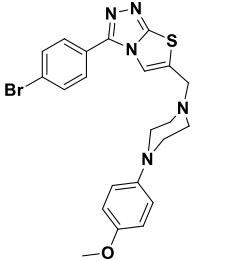
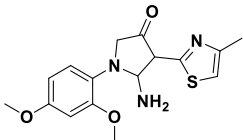
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
CH004		CBS inhibitor	Inhibition of CBS activity	Hepatocellular carcinoma xenograft model	[85]
BSO		GCL inhibitor	Inhibition of GSH synthesis	Breast cancer xenograft model; M14 cells	[86]
Simvastatin		Statin hypolipidemic drug	Mevalonate pathway	LX-2 cells	[87]
Orlistat		Lipase inhibitor	Induction of lipid peroxidation; inhibition of GPX4	Lung cancer xenograft model; Pancreatic cancer xenograft model	[88,89]
Tubastatin A		HDAC6 inhibitor	Inhibition of GPX4	TNBC xenograft model	[90]
Gliotoxin		Mycotoxins	Inhibition of GPX4; Targeted protein SLC7A11	H1975 cells; MCF-7 cells	[91]

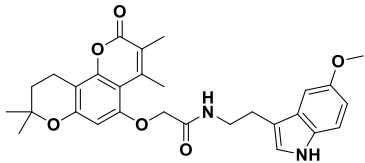
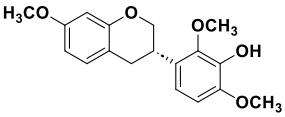
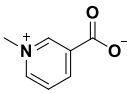
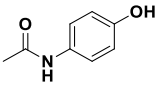
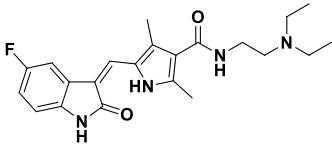
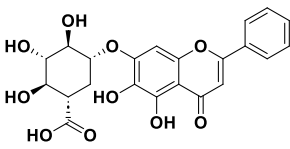
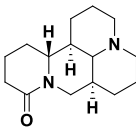
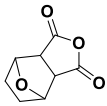
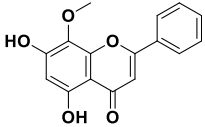
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Table I (Continued).

Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
Timosaponin AIII		Steroidal saponin	Promotes GPX4 ubiquitination and degradation; lipophagy	Non-small cell lung cancer xenograft tumor models	[92]
Compound31		Indirubin derivative	Promotes GPX4 ubiquitination	Colon cancer xenograft tumor model	[93]
Sulforaphane		Natural isothiocyanate	GSH depletion; decreased GPX4 expression	U-937 cells	[94]
iFSP1		Inhibitor targeting FSP1	Inhibition of FSP1	HCC cells	[95]
icFSP1		3-phenylquinazolinone	Inhibition of FSP1	Melanoma xenograft tumor model	[96]
FSENI		Non-competitive inhibitor of FSP1	Inhibition of FSP1	A549 cells; H460 cells	[97]
ViFSP1		FSP1 inhibitor	Inhibition of FSP1	HT-1080 cells; A375 cells; Huh7 cells	[98]

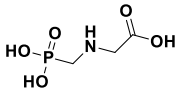
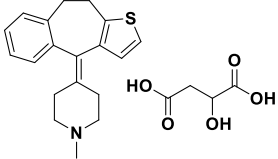
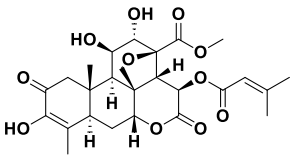
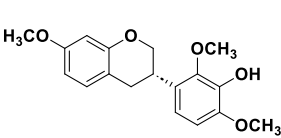
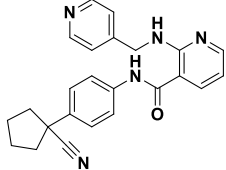
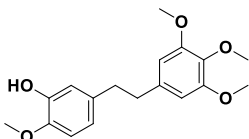
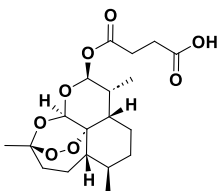
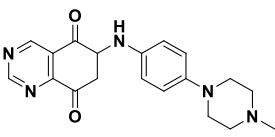
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
NPD4928		FSPI inhibitor	Inhibition of FSPI	PC-3 cells; MKN74 cells; DU145 cells	[99]
ShtIX		Natural novel isoflavonoid	Inhibition of the Nrf2/HO-1 signaling pathway	Non-small cell lung cancer xenograft tumor models	[100]
Trigonelline		Natural alkaloid	Inhibition of Nrf2	Non-small cell lung cancer xenograft tumor models	[101]
APAP		NSAIDs	Inhibition of Nrf2	Non-small cell lung cancer xenograft tumor models	[102]
Sunitinib		Multitargeted tyrosine kinase inhibitor	Inhibition of Nrf2	H9c2 cells	[103]
Baicalin		Natural-derived flavonoid	Downregulation of FTH1; inhibition of Nrf2	Bladder cancer xenograft tumor model; Osteosarcoma xenograft tumor model	[104]
Matrine		Natural alkaloid	Inhibition of x-CT; activation of TFR; inhibition of Nrf2; activation of Piezo1-Ca2+ signaling	Cervical cancer xenograft tumor model; L02 cells	[105]
NCTD		Demethylated analogue of cantharidin	Suppression of NRF2/HO-1/GPX4/xCT Axis	Ovarian cancer xenograft tumor model	[106]
Wogonin		Natural-derived Flavonoid	Suppression of Nrf2/GPX4 axes	Pancreatic cancer xenograft tumor model	[107]

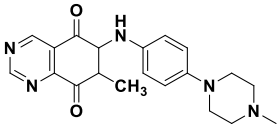
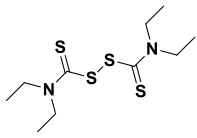
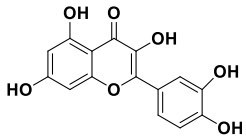
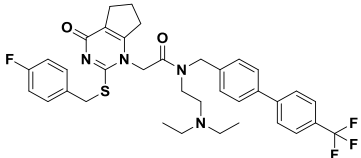
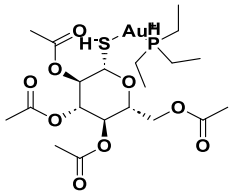
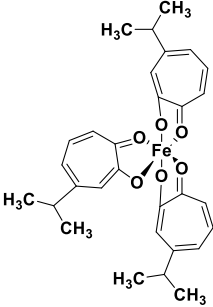
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
Glyphosate		Organophosphorus herbicide	Suppression of Nrf2/GSH/GPX4 axes	Normal mouse model	[108]
Pizotifen malate (PZM)		5-HT ₂ receptor antagonist	Inhibition of Nrf2	Xenograft tumor model of esophageal squamous carcinoma	[109]
Brusatol (Bru)		Bioactive compound	Inhibition of GSH synthesis; inhibition of Nrf2	Xenograft tumor model of esophageal squamous carcinoma	[110]
S-3'-hydroxy-7', 2', 4'-trimethoxyisoxane (ShtlX)		Isoflavans compound	Inhibition of Nrf2/HO-1 pathway	Non-small cell lung cancer xenograft tumor models	[100]
Lapatinib		Tyrosine kinase inhibitor	Targeting ELOVL6/ACSL4; Inhibition of VEGFR2/Nrf2/Keap1 pathway; Inhibition of GSH	HCT116 cells; Glioma xenograft tumor model; Gastric cancer xenograft tumor model	[111]
Erianin		Bioactive natural compound	Blockade of the JAK2/STAT3/SLC7A11 pathway; promotion of N6-Methyladenosine modification of ALOX12/P53 mRNA; inhibition of Nrf2	Hepatocellular carcinoma xenograft tumor model; Kidney cancer xenograft tumor model	[112]
Artesunate		Artemisia extract	Increased lipid peroxidation; inhibition of GSH	Hepatocellular carcinoma xenograft tumor model	[113]
QD394		ROS inducer	Add ROS	PANC-1 cells	[114]

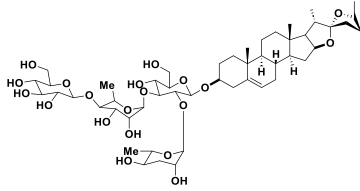
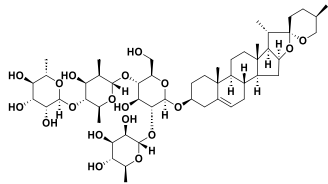
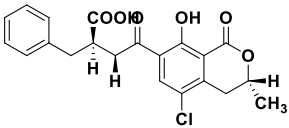
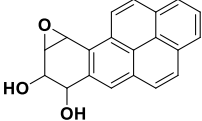
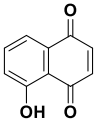
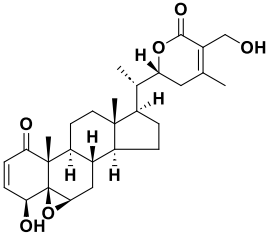
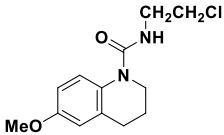
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
QD394-Me		ROS inducer	Add ROS	PANC-1 cells	[114]
Imetelstat		Telomerase inhibitor	Increased synthesis and subsequent oxidation of PUFA phospholipids; lipid phagocytosis	Patients with (AML)	[115]
Disulfiram		ALDH1 inhibitor	Induction of lipid peroxidation	U251 cells; LN229 cells	[116]
Quercetin		Flavonoid compound	Increased ROS generation; increased TFR	MCF-7 cells; MDA-MB-231 cells; HEC-1-A cells	[117]
Darapladib		Lp-PLA2 inhibitor	Inhibition of Lp-PLA2	Hs746T cells; SNU-484 cells	[118]
Auranofin (AUR)		Drug for rheumatoid arthritis	Inhibits TXNRD activity; increases lipid peroxidation	Huh7 cells; HEK293T cells; Normal mouse model	[119]
Fe(hino) ₃		Redox-active complex	Increase in Fe	TNBC xenograft tumor model	[120]

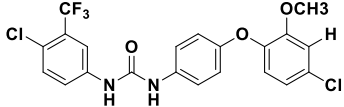
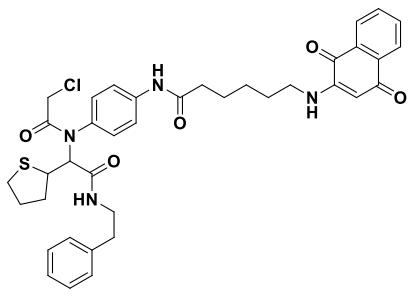
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Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
SSPH I		Natural steroidal saponin	Up-regulation of SLC7A5 expression; up-regulation of TFR and FPN protein expression	HepG2 cells	[121]
Polyphyllin B		Natural product	Promotes ferric ion transport and ferritin autophagy; binds GPX4	Orthotopic gastric cancer mouse model	[122]
Ochratoxin		Mycotoxin	Up-regulation of TFR1 and FTH expression; down-regulation of FPN expression	HEK-293 cells	[123]
BPDE		In vivo metabolites of BP	Upregulates iron metabolism; promotes GPX4 catabolism	Swan 71 cells; HTR-8/Svneo cells	[124]
Juglone		Natural quinone	Increased iron accumulation; GSH depletion	A549 cells	[125]
Withaferin A		Natural steroidal lactone	Increased iron accumulation; inhibition of GPX4; inhibition of Nrf2	Pancreatic cancer metastasis model; Hepatocellular carcinoma xenograft tumor model	[126]
10p		Urea derivative	Add ROS	HT-29 cells	[127]

(Continued)

Table I (Continued).

Inducers	Structure	Types	Mechanism of Action	Experimental Models	Ref.
JB3		Sorafenib derivative	Suppression system Xc ⁻	Lung cancer xenograft model	[128]
GIC-20		MLI62 derivative	Covalent inhibition of GPX4	HT1080 xenograft model	[129]

Targeting Antioxidant Pathways

Targeting System Xc⁻

The synthesis of glutathione (GSH) heavily relies on the cystine imported into the cell through system Xc⁻.¹³⁰ Hence, system Xc⁻ significantly influences the progression of ferroptosis. Conversely, the inhibitory function of system Xc⁻ hinders cystine uptake, leading to decreased GSH production, cellular stress, and ultimately triggering ferroptosis.¹³¹

Erastin, a well-known inducer of ferroptosis, was first discovered in 2003 by Dolma et al.¹³² This quinazolinone derivative inhibits system Xc⁻ by targeting SLC7A11.¹³³ Moreover, erastin promotes oxidation and disruption of the mitochondrial permeability transition pore (mPTP) and acts through the Voltage-Dependent Anion Channel (VDAC), demonstrating anti-tumour effects.¹³⁴ Erastin effectively triggers ferroptosis in various cell types, including human promyelocytic leukemia cells (HL60),¹³⁵ endometriotic ectopic cyst cells (EESC),¹³⁶ and renal tubular cells.¹³⁷ Not only does erastin induce ferroptosis in cancer cells, but it also enhances the efficacy of traditional anticancer drugs like adriamycin,¹³⁸ cisplatin,¹³⁹ temozolomide,¹⁴⁰ and cytarabine¹⁴¹ on specific cancer cell lines. However, Erastin's limitations in stability, water solubility, and pharmacokinetic properties render it unsuitable for in vivo applications.¹⁴²

The quinazolinone present in erastin's structure is crucial for its cell-inhibitory effects. By modifying the structure of erastin, researchers have developed several drugs that outperform erastin. Wan Seok Yang et al incorporated a Piperazine Fragment into erastin's aniline to create Piperazine erastin (PE).⁵⁹ PE exhibits higher water solubility and metabolic stability compared to erastin (water solubility: 0.086×10^{-3} M for erastin, 1.4×10^{-3} M for PE). Imidazole ketone erastin (IKE) is an erastin analogue containing a carbonyl group, designed by Marie-Helene Larraufie et al.¹⁴³ IKE induces ferroptosis and demonstrates anti-tumour effects in a diffuse large B cell lymphoma (DLBCL) xenograft model.¹⁴⁴ IKE shows a superior inhibition rate and metabolic stability when compared to erastin, making it more suitable for in vivo assessments and offering promising application prospects.¹⁴⁴

Yuying Fang et al utilized phenotypic screening to discover a novel ferroptosis inducer known as 2-(trifluoromethyl) benzimidazole derivatives FA-S.⁶¹ They further developed 30 derivatives based on this scaffold, with FA16, containing the 4-SO₂NMe₂ group, demonstrating the highest lethality. By inhibiting the Xc⁻ transporter, FA16 effectively triggers ferroptosis in various human cancer cell lines.⁶¹ The IC₅₀ value of FA16 in HT1080 cells was measured at 1.26 μM. Moreover, in the HepG2 xenograft model, FA16 displayed significant inhibition of tumor growth. Both in vivo and in vitro studies have confirmed the favorable safety profile of FA16.⁶¹

Lepadins, natural alkaloids derived from the marine didemnum family, exhibit diverse biological activities including anti-cancer and anti-malarial properties.¹⁴⁵ Wenjun Wang et al introduced a novel synthetic approach to get seven compounds within the Lepadins series. Notably, lepadins E and H demonstrated notable cytotoxicity in cellular assays, enhancing p53 expression, elevating ROS and lipid peroxidation levels, reducing SLC7A11 and GPX4 expression, up-regulating ACSL4, and triggering ferroptosis through the classical p53-SLC7A11-GPX4 pathway.⁶² In animal studies, Lepadine H effectively suppressed melanoma growth. Nevertheless, Lepadins E and H exhibited only modest selectivity towards cancer cells over normal cells, necessitating further investigation into their safety profile.⁶²

Solasonine (SS) is a natural alkaloid-like compound extracted from potato tubers with anti-cancer and anti-arthritis effects.¹⁴⁶ Research has demonstrated that SS exhibits toxicity towards various cancer cell lines, including hepatocellular carcinoma,¹⁴⁷ lung cancer,¹⁴⁸ and gastric cancer cells.¹⁴⁹ The induction of ferroptosis in lung adenocarcinoma by SS is linked to redox imbalance and mitochondrial dysfunction.¹⁵⁰ In pancreatic cancer cells, SS triggers ferroptosis through the TFAP2A/OTUB1 SLC7A11 axis,⁷¹ while in liver cancer cells, it disrupts the GSH-GPX4 redox system to induce ferroptosis.¹⁵¹

Curcumin, a polyphenolic compound derived from turmeric rhizomes, possesses chologogic, antimicrobial, and anti-cancer properties.¹⁵² Studies have shown that curcumin induces ferroptosis in various tumors such as non-small cell lung cancer,⁷³ breast cancer,⁷⁴ and glioblastoma,¹⁵³ each with distinct mechanisms. For instance, curcumin inhibits breast cancer by up-regulating SLC1A5 expression, a crucial glutamine transporter.⁷⁴ In follicular thyroid carcinoma, curcumin induces ferroptosis by increasing Heme Oxygenase-1 (HO-1) expression.¹⁵⁴ The induction of ferroptosis in non-small cell lung cancer and hepatic stellate cells involves the activation of autophagy.¹⁵⁵

Sulfasalazine (SAS) is an anti-inflammatory agent commonly used to treat chronic inflammatory diseases.¹⁵⁶ It is a potent inhibitor of system Xc⁻ that characteristically inhibits cystine transport mediated by SLC7A11.⁵⁴ SAS can effectively induce ferroptosis in tumor cells such as Multiple myeloma (MM) cells,¹⁵⁷ Esophageal cancer (EC) cells⁶³ and TNBC cells.¹⁵⁸ Sorafenib is a protein kinase inhibitor approved for the treatment of hepatocellular carcinoma and advanced renal cell carcinoma.¹⁵⁹ It attenuates hepatic fibrosis and liver injury by inhibiting systemic Xc⁻ induced ferroptosis in hepatic stellate cells.¹⁶⁰ Sorafenib treatment was accompanied by a significant increase in Cyclooxygenase-2 (COX2) expression and a decrease in SLC7A11 and GPX4 proteins. Yun-Jeong Kim et al designed and synthesized JB3, a derivative compound of sorafenib, which showed significant tumor growth inhibition in both in vivo and in vitro experiments.¹²⁸ However, it has also been suggested that sorafenib fails to trigger ferroptosis in a wide range of cancer cell lines.¹⁶¹ Its cytotoxic effects in various cell lines, including HT1080, HEK293T and B16F10 cells, could not be prevented by ferroptosis inhibitors. The ability and mechanism of action of sorafenib as an ferroptosis inducer remains controversial. Marketed drugs such as the PARP inhibitor olaparib,¹⁶² the anti-malarial medicine flubendazole,⁶⁷ and the anti-leukemic drug 6-Thioguanine (6-TG),⁶⁸ which act on a variety of diseases, have also been found to Anti-tumour effect by inhibiting system Xc⁻-induced ferroptosis in cells. The classic Antidiabetic Drug metformin has also been found to inhibit breast cancer by inducing ferroptosis through down-regulation of SLC7A11 expression.⁶⁹

Targeting GSH-GPX4

GPX4 is a central regulator of ferroptosis, and inhibition of GPX4 is an important mechanism of action for ferroptosis inducers.

RAS-selective lethal 3 (RSL3) is a Tetrahydro- β -carboline (THBC) identified by Wan Seok Yang et al in 2008.¹⁶³ As a well-known inducer of ferroptosis, RSL3 effectively hinders the growth and proliferation of various cancer cells, such as those found in lung, breast, and liver cancers. By directly binding to selenocysteine residues in the GPX4 catalytic site, RSL3 deactivates them, leading to an increase in ROS and cellular LIP levels. This results in the accumulation of intracellular lipid peroxides and triggers ferroptosis.¹⁶⁴ It has been observed that while RSL3 alone does not induce ferroptosis in glioblastoma, its combination with NF- κ B pathway activation does.⁷⁵ However, the clinical use of RSL3 is hindered by side effects and drug resistance, necessitating further research and improvement for its application.¹⁶⁵

Congjun Xu et al synthesized a series of novel and efficient GPX4 inhibitors using RSL3 as lead-compound and scaffold hopping strategy.⁷⁷ By determining the compounds' IC₅₀ values and GPX4 inhibition in various cells, compound 26a containing Oxazole Fragment was identified as the most superior GPX4 inhibitor. Compound 26a inhibited GPX4 by

71.7% at 1.0 μM with an IC_{50} value of 0.15 μM in HT1080 cells.⁷⁷ It significantly inhibited tumor growth in a 4T1 xenograft model without significant toxicity. 26a ameliorates the selectivity and cytotoxicity problems of conventional chloroacetamide-based GPX4 inhibitors.⁷⁷

In addition, John T. Randolph et al designed and synthesized ferroptosis inducer using RSL3 as a lead compound 24.⁷⁸ Compound 24 has similar cell-killing activity ($\text{IC}_{50} = 0.117 \mu\text{M}$) and higher plasma stability ($t_{1/2} > 5 \text{ h}$) in mouse plasma compared to RSL3, but it has limited efficacy as a single-agent tumor-targeting therapy.⁷⁸

Michel Weïwer et al identified two novel molecular probes ML162 and ML210 by high throughput screening.⁷⁹ Both ML162 and ML210 are covalent inhibitors of GPX4, inactivating GPX4 selenocysteine residues by covalently binding them. ML162 is similar to RSL3 and also has the chloroacetamido group. However, it is now proposed that RSL3 and ML162 are not direct inhibitors of GPX4 but Thioredoxin reductase 1 (TXNRD1).¹⁶⁶ TXNRD1 is another cytoplasmic selenoprotein that regulates intracellular redox and is a newly proposed key regulator and drug target for ferroptosis.¹⁶⁷ ML210 is a compound containing nitroisoxazoles. ML210 has an intact cell-dependent inability to interact with purified GPX4 protein. It must be activated in intact cells to produce the critical metabolite JKE-1674 and undergo additional cellular activation and dehydration to generate an electrophile JKE-1777 that binds to GPX4.¹⁶⁸ GPX4 inhibitors acting via nitrile oxide exhibited significant selectivity for GPX4 and reduced off-target effect compared to chloroacetamide-based GPX4 inhibitors.¹⁶⁸

Conventional chloroacetamide GPX4 inhibitors suffer from off-target effect, poor stability and selectivity, limiting their use in in vivo therapy.¹⁶⁹ In order to optimize these inhibitors, Tingting Chen et al performed structural optimization of RSL3 and ML162 based on a molecular docking model that retained the chloroacetone fragment and introduced N-benzylaniline and diphenylamine skeleton and successfully synthesized a series of novel GPX4 covalent inhibitors.⁸⁰ Among them, compound C18 covalently binds to Sec46 of GPX4 and inhibits the function of GPX4, leading to ferroptosis in TNBC cells. Compound C18 showed a higher inhibition rate, better GPX4 inhibitory activity and in vivo antitumor pharmacokinetic properties compared to RSL3 and ML162. At a concentration of 1 μM , C18 almost completely inhibited the activity of TNBC cell lines and showed high selective inhibition of these cell lines without significant organ toxicity.⁸⁰

Furong Ma et al used pharmacophore hybridization and bioisosterism strategies to construct a series of ML162-quinone conjugates.¹²⁹ Among them, GIC-20 was identified as the most active compound. The IC_{50} of GIC-20 in HT-1080 cells is 1.6 μM . GIC-20 not only induces ferroptosis through proteasome-mediated GPX4 degradation but also induces apoptosis by up-regulating the level of the apoptotic protein Bax and down-regulating the level of the antiapoptotic protein Bcl -2.¹²⁹ Meanwhile, GIC-20 showed no significant toxicity compared with ML162.

Ferroptosis inducers targeting GPX4, also identified by screening, include FIN56,⁸¹ N6F11¹⁷⁰ and Metamizole sodium.⁸³ FIN56 not only promotes GPX4 degradation via Acetyl-CoA carboxylases (ACCs), but also degrades GPX4 by binding to and activating squalene synthase, an enzyme involved in cholesterol synthesis, thereby inducing ferroptosis.¹⁷¹ FIN56 can effectively exert anti-tumour effects. N6F11 binds to a specific structural domain of the ubiquitin E3 ligase TRIM25, predominantly expressed in tumor cells, triggering ubiquitination and degradation of GPX4.⁸² Thus, in contrast to conventional GPX4 inhibitors, N6F11 can selectively induce GPX4 protein degradation in tumor cells without causing damage to immune cells.

Unlike traditional GPX4 inhibitors targeting the active site selenocysteine, Hengrui Liu et al identified an unexpected variant site C66 on GPX4. They screened the lead compound LOC1886, which covalently binds this allosteric site to inhibit GPX4.⁸⁴ However, LOC1886 showed lower efficacy than RSL3 and ML162 in inducing cellular ferroptosis.

CH004 is a biologically active inhibitor of cystathionine β -synthase (CBS) with in vitro and in vivo effects designed and synthesized by Li Wang et al.⁸⁵ CH004 dose-dependently inhibits CBS activity in cells or in vivo, inhibiting cysteine and hydrogen sulfide production. CH004 can effectively inhibit tumor growth in vivo and in vitro with an IC_{50} value of 1 μM .⁸⁵ A compound that also indirectly inhibits GPX4 is Buthionine sulfoximine (BSO). BSO is a fast-acting and irreversible inhibitor of glutamate cysteine ligase (GCL), which inhibits glutathione synthesis, indirectly inactivates GPX4, induces lipid peroxidation, and thus inhibits cell viability, and has been shown to have an inhibitory effect on breast cancer, melanoma, and Others.¹⁷² However, its therapeutic effect as an ferroptosis inducer is only seen in tumors

with low levels of GSH expression. Simvastatin inhibits hepatic stellate cell (HSC) activation and induces ferroptosis in HSC by inhibiting the MVA pathway to downregulate GPX4 expression.⁸⁷

Orlistat is an anti-obesity drug approved by the US Food and Drug Administration (FDA), and fatty acid synthase (FASN) is the main lipomatose it inhibits.⁸⁸ Studies have shown that Orlistat induces ferroptosis-like cell death of lung cancer cells.⁸⁹ Orlistat reduces GPX4 expression, upregulates phosphorylated MAPK/ERK, and induces lipid peroxidation in lung cancer cells. Orlistat also promotes lipid peroxidation and ferroptosis in pancreatic neuroendocrine tumors (pNETs) cells by inhibiting the expression of xCT and GPX4 and increasing the expression of CD71.¹⁷³

Tubastatin A, an inhibitor of Histone deacetylase-6 (HDAC6), significantly induces ferroptosis in ferroptosis-sensitive cell lines, and this process was not dependent on its inhibition of HDAC6.¹⁷⁴ Radiotherapy not only induces ferroptosis by promoting ROS generation and ACSL4 expression in cancer cells, but also increases ferroptosis-resistance and radio-resistance of cancer cells by activating Nrf2-mediated GPX4 transcription and inhibiting lysosome-mediated GPX4 degradation.⁹⁰ Tubastatin A can overcome ferroptosis-resistance and radio-resistance in cancer cells by directly binding to GPX4 and inhibiting GPX4 enzyme activity.¹⁷⁴ In the xenograft model, it significantly promotes radiotherapy-induced lipid peroxidation and effectively improves tumor suppression. However, Tubastatin A is a hydroxamic acid and may cause some side effects in subsequent clinical trials.¹⁷⁴ Therefore, optimization of the structure of Tubastatin A is essential.

Gliotoxin⁹¹ and Timosaponin AIII⁹² are two natural products that induce ferroptosis by targeting GPX4. In addition to targeting GPX4, Gliotoxin was found to act on the protein SLC7A11 in H1975 cells.⁹¹ Timosaponin AIII promotes ferroptosis in NSCLC by targeting and promoting heat shock protein 90 (HSP90)-mediated GPX4 ubiquitination and degradation.⁹² Compound 31 is an indirubin derivative synthesized by Jiang-Min Zhu et al by combining the core of the natural product indirubin with the active fragment of a GPX4 covalent inhibitor via a linker.⁹³ The IC₅₀ of compound 31 in HCT-116 cells was 0.49 μ M. It significantly reduced GPX4 levels in HCT-116 cells by promoting GPX4 ubiquitination.

Sulforaphane (SFN) is a naturally occurring isothiocyanate found in various vegetables that has anti-cancer and anti-inflammatory properties.¹⁷⁵ Recently, Giulia Greco et al showed that in leukemia cells SFN triggers different patterns of cell death in a dose-dependent manner.⁹⁴ At 25 μ M, SFN induced caspase-dependent apoptosis, and at 50 μ M, ferroptosis was induced through GSH depletion, decreased GPX4 expression and lipid peroxidation. The anti-leukemic activity of SFN can be mediated by inducing both ferroptosis and apoptosis.⁹⁴

Targeting FSP1

The FSP1-CoQ10-NAD(P)H pathway and the xCT-GSH-GPX4 pathway are two parallel lipid antioxidant pathways.¹⁷⁶ The two pathways act synergistically to inhibit lipid peroxidation and ferroptosis. Inhibition of FSP1 would effectively inhibit the antioxidant effects of the FSP1-CoQ10-NAD(P)H pathway, thereby inducing the onset of ferroptosis.¹⁷⁷

Sebastian Doll et al conducted a screening of around 10,000 compounds, resulting in the discovery of a potent FSP1 inhibitor named iFSP1, which is the first targeted FSP1 inhibitor described in the literature.¹⁷⁸ iFSP1 induces ferroptosis to inhibit cancer cell growth in vitro by inhibiting GPX4. The IC₅₀ value of iFSP1 is 103nM. iFSP1 is specific for hFSP1, and residue F360 within hFSP1 is closely related to the binding of iFSP1 and its target. iFSP1 can inhibit the growth of hepatocellular carcinoma (HCC) by inducing ferroptosis and potential immunomodulatory effects.⁹⁵ Up-regulated chemokines after iFSP1 treatment promote infiltration of antigen-presenting cells, macrophages and cytotoxic T cells into the tumor.

Toshitaka Nakamura et al predicted the physicochemical properties and drug similarities of about 10,000 small molecule drugs and finally identified 3-phenylquinazolinones as a class of potent inhibitors of FSP1.⁹⁶ Of these, icFSP1 is the most representative. icFSP1 is a specific inhibitor of hFSP1, which triggers the Phase separation of FSP1 by inducing the formation of FSP1 condensate in tumor cells to induce ferroptosis in cancer cells.⁹⁶ In contrast to iFSP1, icFSP1 did not show off-target effects even at higher concentrations.

Joseph M. Hendricks et al identified several structurally distinct FSP1 inhibitors through chemical screens. Among them, FSEN1, a non-competitive inhibitor of FSP1, showed the highest potency in inducing cell death in NCI-H460 GPX4^{KO} cells (EC₅₀ = 69.363 nM).⁹⁷ However, in most cells, FSEN1 could not induce ferroptosis by inhibiting FSP1

alone. In vitro experiments showed that FSEN1 synergizes with dihydroartemisinin, an endoperoxide-containing ferroptosis inducer, to induce ferroptosis in tumor cells.⁹⁷

iFSP1, icFSP1, and FSEN1 specifically target hFSP1 and fail to be tested in vivo in tumor transplantation models. Whether they inhibit FSP1 in vivo and whether they have an effect on tumor growth remains to be investigated. Toshitaka Nakamura et al identified the first non-species-dependent FSP1 inhibitor, versatile inhibitor of FSP1 (viFSP1), which targets the NAD(P)H binding pocket.⁹⁸ Treatment with viFSP1 in Pfa1 cells expressing mouse FSP1 or hFSP1 led to significant lipid peroxidation and ferroptosis.

Compound NPD4928, screened from a chemical library by Hiromasa Yoshioka et al, also targets binding to FSP1 and inhibits its activity.⁹⁹ The combination of NPD4928 and GPX4 inhibitors induced ferroptosis; however, using FSP1 alone did not induce ferroptosis and was not sensitive in some cells. In addition to these drugs, curcumin¹⁷⁹ and sorafenib¹⁸⁰ have been found to induce ferroptosis in cells via the FSP1 pathway.

The study reveals that most FSP1 inhibitors alone are unable to induce ferroptosis in cells, or can only do so in cells with low GPX4 expression.¹⁸¹ Instead, these inhibitors primarily act as enhancers of ferroptosis and are often combined with other ferroptosis inducers to enhance their effects.¹⁸²

Targeting Nrf2

Nrf2 is involved in the regulation of oxidative homeostasis in vivo by acting on downstream target genes.¹⁸³ Inhibition of Nrf2, and thus its antioxidant effects, is also an important pathway of action for ferroptosis inducers.¹⁸⁴

S-3'-hydroxy-7', 2', 4'-trimethoxyisoxane (ShtIX) is a novel isoflavone compound derived from the heartwood of *Dalbergia latifolia*.¹⁰⁰ ShtIX has demonstrated broad-spectrum anticancer activity, with particularly high cytotoxicity against NSCLC cells. Research has shown that ShtIX induces ferroptosis in NSCLC cells by targeting the Nrf2/HO-1 signaling pathway, with an IC₅₀ of 7.9 μM in A549 cells. Importantly, ShtIX selectively eliminates non-small cell lung cancer cells.¹⁰⁰

Trigonelline, the primary alkaloidal component of the legume herbaceous *Trigonella foenum-graecum*, exhibits anti-HSV-1, antibacterial, and antifungal activities.¹⁸⁵ Acting as an Nrf2 inhibitor, trigonelline reduces cellular resistance to ferroptosis and shows potential for combination therapy with other ferroptosis inducers.¹⁰¹ In xenograft models, trigonelline enhances the anticancer effects of erastin, sorafenib, and RSL3, and increases the chemosensitivity of Etoposide in pancreatic cancer.¹⁸⁶

Baicalin, a flavonoid extracted from the dried root of Lamiaceae family plants *Scutellaria baicalensis* Georgi, possesses antibacterial, antiallergic, antitumor, and other pharmacological properties.¹⁸⁷ Research indicates that baicalin can induce ferroptosis in bladder cancer cells by activating Ferritin Heavy Chain 1 (FTH1).¹⁰⁴ In osteosarcoma cells, baicalin interacts with Nrf2, affecting their stability by promoting ubiquitination and degradation, leading to the inhibition of GPX4 and xCT expression, ultimately inducing ferroptosis in osteosarcoma cells.¹⁸⁸

Matrine, an alkaloid derived from the roots of *Sophora flavescens* Radix (Kushen), exhibits notable antitumor properties.¹⁰⁵ Research has demonstrated that matrine can trigger ferroptosis in various types of tumor cells, including cervical cancer cells,¹⁸⁹ rectal cancer cells,¹⁹⁰ and hepatocytes.¹⁹¹ The specific mechanisms through which matrine induces ferroptosis in different cell types vary. For instance, in cervical cancer, matrine hinders cervical cancer progression by activating the Piezo1-Ca²⁺ signaling pathway to induce ferroptosis.¹⁸⁹ Additionally, matrine induces ferroptosis in hepatocytes by suppressing the Nrf2/GPX4 antioxidant system.¹⁹¹

Acetaminophen (APAP) is a commonly used antipyretic and analgesic medication that can lead to liver damage in a dose-dependent manner when taken in excess, potentially causing acute liver failure in severe cases.¹⁹² Research indicates that the primary mechanism underlying APAP-induced liver damage is ferroptosis, although the exact process by which it triggers ferroptosis in liver cells remains unclear.¹⁹³ Studies have revealed that NSCLC cell lines exhibit reduced sensitivity to erastin-induced ferroptosis, but APAP can enhance this sensitivity by modulating the Nrf2/HO-1 signaling pathway.¹⁰² Similarly, Sunitinib (SUN), a multi-targeted tyrosine kinase inhibitor known for its anti-angiogenic and anti-tumor properties, is associated with cardiotoxic effects that limit its clinical utility.¹⁰³ It has been found that Nrf2-dependent ferroptosis plays a critical role in SUN-induced cardiotoxicity.¹⁹⁴

Targeting Lipid Metabolism

Lipid peroxidation is central to the development of ferroptosis, and regulation of lipid metabolism is also a critical action pathway for ferroptosis inducers.

Shuai Hua et al developed a series of quinazolinediones (QD)-based ROS inducers and screened the optimal compound, QD325, after testing it in pancreatic cancer preclinical models.¹¹⁴ They synthesized a set of QD derivatives by making structural modifications to QD325. QD394 was the optimal compound. The transcriptome profile of QD394 closely resembles that of napabucasin, a cancer stem cell inhibitor. Both small molecules inhibited STAT3 phosphorylation, increased cellular ROS, and decreased the GSH/GSSG ratio.¹¹⁴ The IC_{50} value of QD394 in PANC-1 cells was 0.34 μ M. It was optimized to give the derivative QD394-Me, which showed better plasma stability and reduced toxicity in mice compared to QD394. The IC_{50} value of QD394-Me in PANC-1 cells was 0.38 μ M. QD394-Me, as ROS-inducing drugs, exhibited potent antitumor effects on human pancreatic cancer cells.¹¹⁴

Imetelstat, a telomerase inhibitor, competitively inhibits telomerase activity by targeting the telomerase RNA template and is primarily used in the clinical treatment of myelofibrosis and myelodysplastic syndromes.¹¹⁵ Claudia Bruedigam et al discovered that imetelstat, a potent inducer of ferroptosis, effectively reduced the burden of acute myeloid leukemia (AML) and delayed relapse after oxidative stress-induced therapy.¹⁹⁵ Imetelstat increases the synthesis and subsequent oxidation of PUFA phospholipids, and its induced lipophagy triggers ferroptosis in AML. Imetelstat causes cell death by involving two regulators of fatty acid metabolism (FADS2 and ACSL4), leading to excessive lipid reactive oxygen species formation and ferroptosis.¹⁹⁶

Tingting Liang et al designed and synthesized a series of novel urea derivatives, among which the compound 10p exhibited the most effective antiproliferative activity against HT-29 cells.¹²⁷ 10p could induce both ferroptosis and autophagy in cells. It was shown that 10p-induced cell cycle arrest, ferroptosis, and autophagy may be related to the accumulation of ROS. 10p is a promising lead compound that can be used for further optimization.

Disulfiram (DSF), a specific inhibitor of aldehyde dehydrogenase type I (ALDH1), is commonly used in the treatment of alcoholism due to its acute sensitization to alcohol.¹⁹⁷ DSF has been found to possess antitumor properties in various tumor types, with induction of ferroptosis being one of its mechanisms.¹⁹⁷ DSF triggers lysosomal membrane permeabilization in a ROS-dependent manner, a key mechanism for inducing cell death.¹¹⁶ Additionally, DSF enhances cell sensitivity to chemotherapy and radiotherapy.¹⁹⁸ Furthermore, DSF exhibits copper-dependent anticancer activity, and when combined with copper, its ability to induce tumor cell death is significantly enhanced. Studies have shown that DSF/Cu effectively induces ferroptosis in TNBC cells.¹⁹⁹

Quercetin is a flavonoid that has shown anticancer activity in various cancers, including lung, ovarian, and prostate cancers.²⁰⁰ Induction of ferroptosis is one of its pathways of action against cancer. Quercetin increases ROS and transferrin receptor production, decreases mitochondrial membrane potential, GPX4 and SLC7A11 levels, and inhibits NF- κ B and Nrf2.¹¹⁷

Darapladib is an orally active, selective and reversible inhibitor of phospholipase A2s (PLA2s).²⁰¹ Lp-PLA2 is located in the cell membrane and cytoplasm, controls intracellular phospholipid metabolism and contributes to ferroptosis resistance.¹¹⁸ In the xenograft model, darapladib, combined with the GPX4 inhibitor PACMA31, sensitized cells to ferroptosis and showed antitumor activity that inhibited tumor growth.¹¹⁸

Auranofin (AUR), a therapeutic agent for rheumatoid arthritis, is a novel modulator of hepcidin expression.¹¹⁹ AUR can reduce iron overload by upregulating hepcidin expression through activation of the NF- κ B/IL-6/JAK-STAT signaling pathway, suggesting that AUR is a potential new drug for the treatment of hereditary hemochromatosis and iron overload-associated diseases triggered by hepcidin deficiency. However, when given at high doses (25 mg/kg bw), AUR triggered hepatic ferroptosis and 100% mortality by inhibiting TXNRD activity and increasing lipid peroxidation.¹¹⁹

Targeting Iron Metabolism

Abnormal iron metabolism plays a significant role in ferroptosis, with iron metabolic pathways being a key target for regulation of this process.

Hinokitiol, a natural compound derived from tropolone, acts as an iron chelator with various beneficial properties such as anti-inflammatory, antioxidant, antibacterial, and antifungal effects.²⁰² Research by Hongting Zhao et al revealed that the Hinokitiol-iron complex $\text{Fe}(\text{hino})_3$, formed by combining hinokitiol and iron in a 3:1 ratio, serves as an inducer of ferroptosis.¹²⁰ This redox-active complex triggers lipid peroxidation and decreases GSH-GPX4 production through the generation of $\cdot\text{OH}$ via the Fenton reaction upon cellular entry, ultimately leading to ferroptosis induction in TNBC. Notably, serum biochemical indices of $\text{Fe}(\text{hino})_3$ -treated tumor-bearing mice remained within normal ranges, suggesting a favorable safety profile of $\text{Fe}(\text{hino})_3$ in vivo.¹²⁰

Steroidal saponin SSPH I, extracted from plantain herb, has been identified as an anti-hepatocellular carcinoma compound.²⁰³ Research has demonstrated that SSPH I exhibits significant antiproliferative and antimigratory effects on HepG2 cells. In these cells, SSPH I upregulates the expression of SLC7A5, a negative regulator of ferroptosis, while also increasing the expression of TFR and FPN proteins, which are positive feedback factors of ferroptosis. This leads to the accumulation of Fe^{2+} and subsequent iron overload, ultimately inducing ferroptosis.¹²¹ Additionally, SSPH I induces a notable G2/M blockade in HepG2 cells.¹²¹

Polyphyllin B (PB) is a dioscin isolated from *Paris formosana* with antitumor activity and immunomodulatory effects.¹²² Can Hu et al found that PB could effectively inhibit the proliferation of GC cells by inducing ferroptosis and apoptosis, and could prevent the migration, invasion and cell cycle of tumor cells in vitro. PB can regulate iron metabolism by promoting iron ion transport and ferritin autophagy, directly binding to GPX4 and reducing GPX4 expression to ultimately induce ferroptosis.¹²² Its anti-GC function may also be related to its regulation of the MAPK signaling pathway, PI3K-AKT signaling pathway, and TNF signaling pathway.

Ochratoxin A (OTA) is one of the fungal toxins, a toxic metabolite produced by toxin-producing strains of *Aspergillus ochraceus* and *penicillium*, which is severely nephrotoxic.²⁰⁴ It has been shown that ferroptosis is a potential mechanism by which OTA causes renal injury. OTA disrupts renal cell iron homeostasis and induces ferroptosis by up-regulating the expression levels of the iron input genes TFR1 and FTH, down-regulating the expression level of FPN, and significantly increasing its negative regulator hepcidin.¹²³

Juglone is a natural product discovered from *Juglans regia* that has a variety of pharmacological properties, including antibacterial, antitumor, antiviral, and anti-inflammatory properties.²⁰⁵ Studies have shown that induction of ferroptosis is one of the mechanisms by which juglone is anti-tumor. The IC_{50} values of juglone in A549 cells and endometrial cancer cells were 18.5 μM and 20.81 μM . The mechanism of juglone-induced ferroptosis in A549 cells mainly involves an increase in iron accumulation and a decrease in GSH and MDA.¹²⁵ In endometrial cancer, juglone activates HMOX1, which induces ferroptosis. Similar to juglone, strigolactones Bufotalin (BT) isolated from *Venenum Bufonis* induced ferroptosis in A549 non-small cell lung cancer cells by accelerating the degradation of GPX4 and increasing the intracellular Fe^{2+} level.²⁰⁶ The IC_{50} value for BT in A549 cells was 4.21 μM .

Withaferin A (WA) is a natural product isolated from *withania* that targets vimentin and has anti-inflammatory and anti-tumor properties.²⁰⁷ By inducing ferroptosis, WA inhibited cell viability, invasive ability, vasculogenic mimicry (VM) formation, and VE-cadherin promoter levels in HepG2 and SNU449 cells, thereby attenuating hepatocellular carcinoma metastatic potential and sorafenib resistance.¹²⁶ WA has now been found to have multiple pathways for inducing ferroptosis. On the one hand, WA reduces the protein level and activity of GPX4. On the other hand, WA induces a novel atypical ferroptosis pathway by directly targeting Kelch-like ECH-Associated Protein 1 (Keap1), which increases unstable Fe^{2+} upon HMOX1 overactivation.¹²⁶ WA also elevates Keap1 expression, attenuating Nrf2 signaling activation-mediated Epithelial-Mesenchymal Transition (EMT) and xCT expression.

The environmental pollutant benzo-a-pyrene (BaP) is a carcinogenic Polycyclic aromatic hydrocarbon, and BPDE (benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide) is the end product of the breakdown of BAP in the human body.¹²⁴ BPDE is electrophilic and can covalently bind to the exocyclic amine terminus of guanine (G), a nucleophilic site of DNA, to form a BPDE-DNA complex. This complex causes DNA base mutations, thereby activating oncogenes and leading to malignant transformation of cells, ultimately resulting in tumorigenesis.¹²⁴ Studies have demonstrated that BPDE induces ferroptosis in human trophoblast cells by upregulating iron metabolism, promoting GPX4 proteasome degradation, and increasing intracellular free Fe^{2+} and excess ROS, leading to lipid peroxidation.¹²⁴

Dihydroartemisinin (DHA) in combination with cisplatin synergistically induces ferroptosis in pancreatic ductal adenocarcinoma cells by modulating iron metabolism.²⁰⁸ The combination of DHA and DDP significantly increased the expression of TFR and the accumulation of unstable free iron in pancreatic ductal carcinoma cells, impairing mitochondrial homeostasis. Co-treatment of DHA with DDP also synergistically reduced GPX4 expression. Additionally, the combined treatment of lapatinib (LAP) and doxorubicin (Dox) resulted in increased Fe²⁺ content, suppression of GPX4 expression, and elevation of ASCL4 levels in cardiomyocytes.²⁰⁹ These synergistic effects of LAP lead to pro-apoptotic, pro-mitochondrial dysfunction, pro-oxidative, and ferroptosis effects, resulting in cytotoxicity. Finally, the combination of lapatinib and the lysosomal pro-solubility drug siramesine induces ferroptosis by decreasing ferritin expression and increasing transferrin expression, ultimately leading to increased iron and ROS levels.¹¹¹

Others

While research on ferroptosis and related drugs is progressing, there are still some ferroptosis inducers with unclear mechanisms of induction. For instance, the natural product ginkgolic acid (GA) inhibits SUMO1-activating enzyme subunit 1 (SAE1), a potential anti-fibrotic target protein.²¹⁰ In both in vivo and in vitro experiments, GA was found to induce hepatic stellate cell ferroptosis by targeting SAE1, leading to an anti-hepatic fibrosis effect in a rat model of hepatic fibrosis.²¹⁰ However, the relationship between SAE1 and ferroptosis remains unclear.²¹⁰ On the other hand, small molecules EC330 and EC359 target the Transmembrane Receptor (LIFR) of the Leukemia inhibitory factor (LIF).²¹¹ By binding to LIFR at specific sites within the ligand-receptor complex, EC330/EC359 inhibit LIFR-induced activation of the STAT3 and AKT pathways, ultimately leading to cell death. Treatment with EC330/EC359 results in GPX4 inactivation and GSH depletion, potentially preventing cells from eliminating toxic lipid peroxides and triggering ferroptosis.²¹² However, the specific targets of EC330/EC359-induced ferroptosis require further investigation.

Statins are widely used, but atropostatin (Atv) administration leads to oxidative stress and cellular damage.²¹³ Indicators of ferroptosis, such as iron overload, ROS accumulation, and lipid peroxidation, were observed in Atv-treated muscle cells, especially in the mitochondria of the cells.²¹⁴ One study reported that simvastatin causes ferroptosis in cancer cells by inhibiting HMGCR expression.²¹⁵ However, it has been shown that Atv can attenuate myocardial dysfunction and remodeling after isoproterenol stimulation through inhibition of ferroptosis, as well as attenuate de-ironing-dependent myocardial injury and inflammation after coronary microembolization through the Hif1a/Ptgs2 pathway.²¹⁶ The specific role and mechanisms of Atv in ferroptosis continue to be studied.

JQ1, a small molecule inhibitor targeting the BET family protein BRD4, has been shown to inhibit the proliferation of cancer cells.²¹⁷ Studies have shown that ferroptosis is one of the mechanisms by which JQ1 exerts its anticancer effects in vivo. JQ1 enhances ferroptosis by increasing ferritin autophagy or suppressing BRD4 regulation of ferroptosis-related genes.²¹⁸ Expression of GPX4, SLC7A11, and SLC3A2 was downregulated under JQ1 treatment and BRD4 knockdown. However, the specific mechanism by which BRD4 regulates the expression of GPX4, SLC7A11 and SLC3A2 is unknown. JQ1 can induce ferroptosis in senescent cells by decreasing the expression of anti-ferroptosis genes in senescent cells,²¹⁹ thereby selectively eliminating senescent cells. However, JQ1-induced ferroptosis occurred in both cancer and normal cells, and therefore, its safety for therapeutic application as an ferroptosis inducer requires further consideration.

Artesunate is a water-soluble hemisuccinate derivative of artemisinin used to treat malaria, improve inflammation, protect nerves, and treat tumors.²²⁰ In 2015, Edna Ooko et al noted that artemisinin and its derivatives induce ferroptosis in tumor cells.²²¹ Co-action of artesunate and sorafenib induces ferroptosis in hepatocellular carcinoma cells; the former increases lysosomal activity and lipid peroxidation, and synergistically with the latter induces histone B/L activation and ferritin degradation.¹¹³ In addition, artesunate reduced GSH levels in head and neck cancer cells and ovarian cancer cells.²²² However, it has also been shown that artesunate may activate the NRF2 antioxidant response element pathway, leading to resistance to ferroptosis.²²³

Proteolysis-Targeting Chimeras

Proteolysis-targeting chimeras (PROTACs) is a drug development technology that leverages the Ubiquitin-Proteasome System (UPS) to degrade target proteins.²²⁴ A typical PROTACs consists of three key components: E3 ubiquitin ligase

ligands, target protein-ligand, and a specially designed “linker” structure that connects the two bioactive ligands.²²⁵ The application of PROTACs technology in modifying traditional ferroptosis drugs to enhance their targeting and antitumor properties represents a promising avenue for developing ferroptosis inducers (Figure 3).

Han Wang et al synthesized a series of GPX4 PROTACs utilizing ML210 as the binding ligand for GPX4, CRBN as the E3 ligase-binding ligand, and various lengths of piperazine rings as linkers.²²⁶ Among these, DC-2 exhibited the most potent degradation activity in HT1080 cells, with a DC₅₀ value of 0.03 μM and a significant inhibitory effect on HT1080 cells, with an IC₅₀ value of 0.1 μM. DC-2 not only triggers GPX4 degradation through the ubiquitin-proteasome pathway and the autophagy-lysosomal pathway but also induces the formation of GPX4 mitochondrial isoforms.²²⁶ DC-2 outperformed ML210 by degrading GPX4 22-fold more and demonstrated equivalent or superior antiproliferative activity against HT1080, Calu-1, and A375 cells compared to ML210. Additionally, DC-2 exhibited better tumor cell selectivity and safety. Compound 5i, a PROTAC synthesized using ML210 as the GPX4 ligand and VHL as the E3 ligase ligand, degraded GPX4 through the ubiquitin-proteasome and autophagy-lysosome pathways. Additionally, 5i was found to induce ROS accumulation in HT1080 cells.²²⁷

Tianli Luo et al designed a PROTAC dGPX4 targeting GPX4 by covalently coupling the GPX4 inhibitor ML162 with pomalidomide.²²⁸ This compound effectively reduces tumor cell GPX4 levels through proteasome degradation, leading to ferroptosis. Compared to ML162, dGPX4 was 5 times more efficient in inducing ferroptosis in HT1080 cells, with an IC₅₀ of 300 nM and a DC₅₀ of 200 nM. The nanoparticle formulation, dGPX4@401-TK-12, enhanced biocompatibility and cell selectivity, effectively inhibiting tumor growth without observable side effects.²²⁸ Maohua Cai et al also designed GPX4 PROTACs based upon ML162 and its derivatives, with CRBN-based PROTAC GDC-11 demonstrating balanced GPX4 degradation (33% at 10 μM), cytotoxicity (IC₅₀ = 11.69 μM), and lipid peroxide accumulation. This compound exhibited typical ferroptosis characteristics.²²⁹ Also based on ML162 are the PROTACs compounds PD-4 and PD-P2. They use pomalidomide as an E3 ligase ligand to promote efficient degradation of GPX4 via the ubiquitin-proteasome pathway.²³⁰

Chao Wang et al synthesized six MSL3-based PROTACs, identifying compound 8e as a potent GPX4 degrader.²³¹ Compound 8e significantly inhibited proliferation in HT1080 (IC₅₀ = 58 nM) and Calu-1 (IC₅₀ = 25 nM) cells through GPX4 degradation via the ubiquitin-proteasome system and autophagy lysosomal pathway, with a preference for tumor cells carrying oncogenic Ras genes for ferroptosis induction.

Haoze Song et al designed 36 PROTACs by covalently coupling RSL3 to four different ubiquitin ligase ligands. Among them, compound 18a, based on cIAP-E3 ligase ligands, showed the most potent inhibitory effect on GPX4 levels (DC₅₀, 48 h=1.68 μM) and HT1080 cell proliferation (IC₅₀ = 2.37 μM).²³² Compound 18a induces cell ferroptosis by forming a ternary complex with cIAP and GPX4 to induce GPX4 degradation. The antiproliferative effect on HT1080 cells was enhanced when compound 18a was combined with FeCl₂.²³²

PROTACs also constructed based on RSL3 are compound R17 and compound NC-R17. R17 is composed of carbon chain linker and lenalidomide E3 ligand. Compound NC-R17 is a non-covalent GPX4 degrader constructed by optimizing the POI ligand of R17 and replacing propionamide with chloroacetylamine. Both compounds showed the ability to degrade GPX4 in tumour cells.²³³

Compared with traditional small molecule ferroptosis inducers, PROTACs class of ferroptosis inducers have better targeting and anti-tumour effects with lower side effects. Therefore, PROTACs technology is a very promising development direction for ferroptosis inducers.

Nanomaterials

Nanomaterials are increasingly being investigated for their role in inducing ferroptosis due to their biocompatibility, nano effect, and permeability²³⁴ (Table 2).

Delivery of exogenous iron ions into the body via nanomaterials is a crucial approach for inducing ferroptosis.²⁷⁶

Mingqi Chen et al developed a ferroptosis inducer, D@FMN-M, to trigger ferroptosis in tumor cells and M2-type macrophages, enhancing tumor immunotherapy.²³⁵ They incorporated DHA into iron-ion doped hollow mesoporous silica nanoparticles (Fe-HMSNs) and further modified them with Outer Membrane Vesicles (OMVs) to create D@FMN-M. These nanoparticles accumulate at the tumor site and release Fe³⁺ ions and DHA in response to the slightly acidic

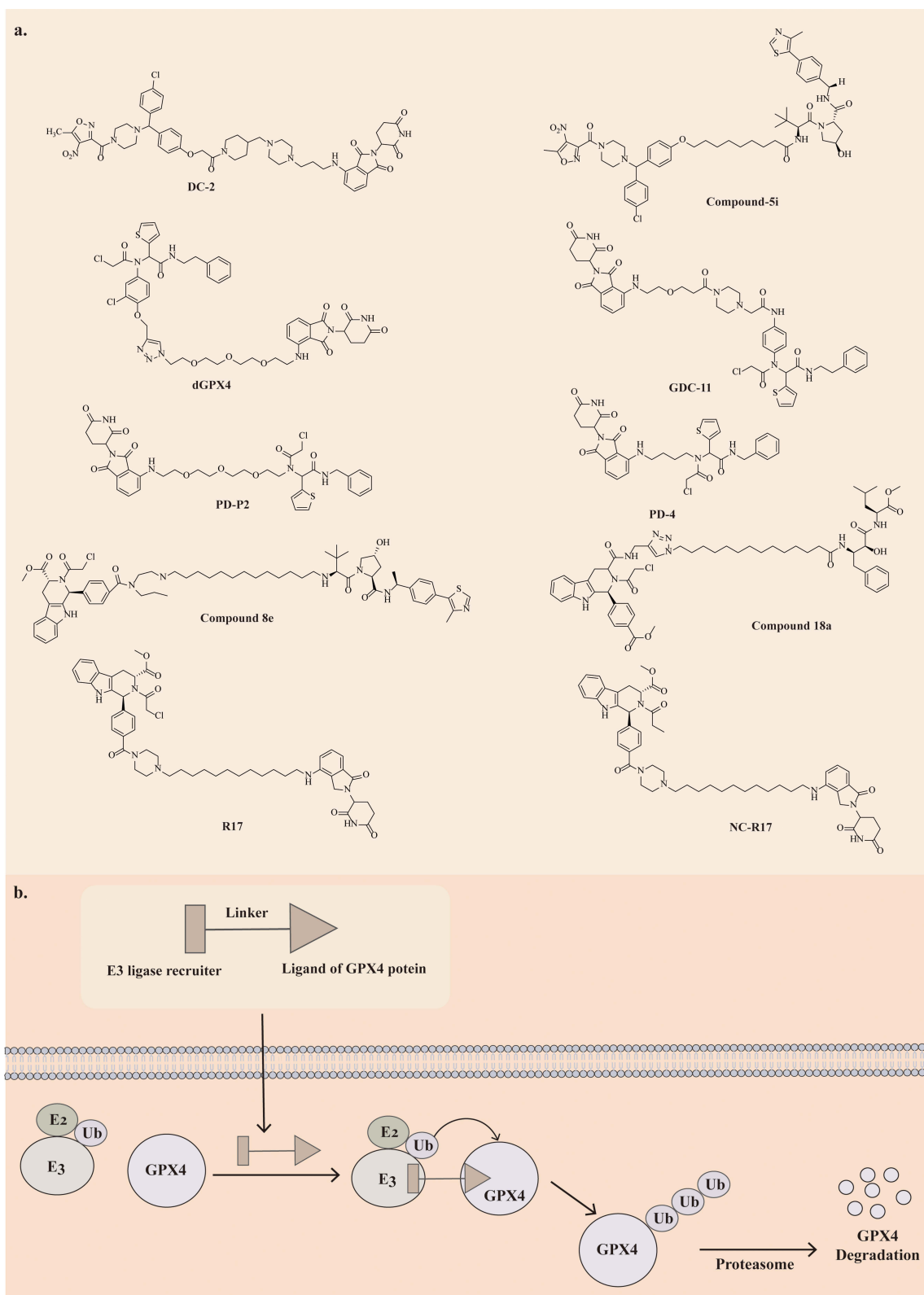


Figure 3 (a) Chemical structural formula of PROTAC-like ferroptosis inducers. (b) The process of PROTAC-mediated ubiquitination and proteasomal degradation of GPX4.

Table 2 Nanomaterials for Inducing Ferroptosis

Compound	Mechanism	In vivo	Reference
D@FMN-M	Release Fe ³⁺ and DHA	√	[235]
DOX/Fe ³⁺ /EGCG (DF) NPs	Release DOX and Fe ³⁺	√	[236]
Fe ₃ O ₄ -PLGA-Ce6	Release Fe ³⁺ and Ce6	√	[237]
BSO/ZIF-8@Au@MPN@HA(BZAMH)	Inhibit GSH synthesis	√	[238]
MTX-LDH@MnO ₂	Promoting ROS generation	√	[239]
GDY-FIN56-RAP (GFR)	Inhibit GPX4	√	[240]
Gel@WA-cRGD	Release WA	√	[241]
Fe ₃ O ₄ @PCBMA	Inhibit MVA pathway and GPX4	√	[242]
DMSN/Fe ₃ O ₄ -Mn@CB-839	Inhibit GSH	√	[243]
AuFCSP MOFs	Inhibit GSH and GPX4	√	[244]
SRF@Hb-Ce6	Inhibit GSH and GPX4	√	[245]
UCNP	Increase Fe ²⁺ and Fe ³⁺	√	[246]
CSO-SS-Cy7-Hex/SPION/Srfrn	Increase Fe ²⁺ and Fe ³⁺	√	[247]
NMIL-100@GOx@C	Increase Fe ²⁺ and H ₂ O ₂	√	[248]
ChA CQDs	Inhibit GPX4	√	[249]
RSL3@COF-Fc (2b)	Increase Fe ²⁺ and inhibit GPX4	√	[250]
AMSNs	Inhibit GPX4	√	[251]
ACC@DOX.Fe ²⁺ -CaSi-PAMAMFA/mPEG	Inhibit GSH	√	[252]
FGLC	Inhibit GSH	√	[253]
Fe ₃ O ₄ @PGL NPs	Increase Fe ³⁺ and ROS	√	[254]
DOX-TAF@FN	Increase Fe ²⁺ and Fe ³⁺	√	[255]
GNPIPP12MA	Inhibit GSH	√	[256]
Pa-M/Ti-NCs	Increase Fe ²⁺ and H ₂ O ₂	√	[257]
IONPs	Increase Fe ²⁺ and ROS	√	[258]
AFN@CM	Release Fe ³⁺ and inhibit GPX4	√	[259]
PPA/TF	Increase Fe ²⁺ and ROS	√	[260]
IONP-HA	Increase Fe ²⁺	√	[261]
mIONP-PL-Pt(IV)	Increase Fe ²⁺ and Pt	√	[262]
ovs-MnO ₂	Induces the release of intracellular free iron (Fe ²⁺)	√	[263]
ApoE-UPGs-DHA	Increase Fe ²⁺ and release DHA	√	[264]
FeO-PEI@TDN-DOX	Increase Fe ²⁺ and release DOX	√	[265]
Cu ₂ O@Au	Promote the Fenton reaction and deplete GSH	√	[266]
MP-FA@R-F NPs	Increase Fe ²⁺ and Rhein	√	[267]

(Continued)

Table 2 (Continued).

Compound	Mechanism	In vivo	Reference
I@P-ss-FRT	Increase Fe ²⁺	√	[268]
USPBNPs@MCSNs (UPM)	Inhibit Xc ⁻ -GSH-GPX4	√	[269]
FeE@PEG NPs	Increase Fe ²⁺ and release EGCG	√	[270]
HNK@Ir-HMONs- LOD(HIHL)	Release HNK and Ir	√	[271]
sora@Fe-MIL	Increase Fe ²⁺ and release sorafenib	√	[272]
Oxa@Mil-100(Fe)	Induce apoptosis and release Fe ³⁺	√	[273]
AsIr@PDA	Release IrFN	√	[274]
MitCuOHA	Inhibit GSH	√	[275]

tumor microenvironment. The released Fe³⁺ is then converted to Fe²⁺ by depleting intratumoral GSH, leading to the production of free radicals through the Fenton reaction and Fe²⁺-DHA reaction. This accumulation of lipid peroxides ultimately induces ferroptosis in tumor cells.²³⁵

Min Mu et al designed and synthesized a nanomaterial DF-NP consisting of epigallocatechin gallate (EGCG) and Fe³⁺ to deliver both doxorubicin hydrochloride (Dox) and iron ions to the tumor site.²³⁶ DOX/Fe³⁺/EGCG (DF) NPs have strong solubility and long-term storage stability and can efficiently release DOX and Fe³⁺ by cell internalization under high GSH levels and tumor acidic environment. On the one hand, DOX enters the cell nucleus and binds to DNA, inducing apoptosis in tumor cells. On the other hand, due to its high reducing capacity, EGCG can chemically reduce Fe³⁺ to Fe²⁺, which reacts with H₂O₂ and continuously induces ROS production through the Fenton reaction, thus inducing ferroptosis.²³⁶

Iron oxide nanoparticles (IONPs) are a class of nanomaterials composed of iron oxide (Fe₃O₄ or Fe₂O₃).²⁷⁷ Intracellular iron is the basis for the occurrence of ferroptosis. With the development of nanotechnology, IONPs have shown excellent therapeutic advantages due to their ability to deliver exogenous iron to activate tumor ferroptosis. IONPs are also one of the most classical nanoenzymes with intrinsic enzyme-like activity. IONPs have a peroxidase-like activity based on the Fenton reaction, which enables lipid peroxidation of unsaturated fatty acids and induces lipid peroxidation and ROS production.²⁷⁸

Xiangrong Tian et al synthesized iron oxide nanoparticles of different sizes (2–100 nm) to study their antitumor effects and toxicity mechanisms.²⁵⁸ Their study found that ultrasmall nanoparticles (<~5 nm) release Fe²⁺ faster and have greater cytotoxicity. However, Fe₃O₄-10 nm NPs showed the best antitumor efficiency due to the balanced abilities in tumor accumulation, intratumoral penetration, and cellular internalization. It showed an optimal antitumor effect in vivo, and its therapeutic effect was correlated with tumor accumulation and intratumor distribution of nanoparticles.²⁵⁸

Qifang Chen et al designed and synthesized a poly(lactic-co-glycolic acid) (PLGA) nanosystem Fe₃O₄-PLGA-Ce6 encapsulating Fe₃O₄ and Ce6.²³⁷ The Fe₃O₄-PLGA-Ce6 nanosystem can dissociate in an acidic tumor microenvironment, releasing iron ions and Ce6, followed by the generation of hydroxyl radicals via the Fenton reaction, which induces ferroptosis in tumor cells. At the same time, under laser irradiation, the released Ce6 increases the generation and accumulation of ROS, providing photodynamic therapy.²³⁷ The loading of iron ions and Ce6 allowed the nanoparticles to be fluorescence imaging and MRI-guided, respectively. The nanoparticles were injected intravenously into the body with high biocompatibility, permeability, and retention.²³⁷

Hanren Chen et al designed and synthesized an iron oxide (Fe₃O₄) nanoparticle AFN@CM coated with Arsenic trioxide (ATO) encapsulated by HCC cell membrane.²⁵⁹ For the first time, they demonstrated in their study that ATO can effectively induce lipid peroxidation and ferroptosis in HCC. Moreover, the iron oxide nanoparticles AFN@CM synthesized from ATO can target-induce ferroptosis in tumor cells, with excellent anti-cancer effects and almost no side effects. In addition to the synergistic effect of ATO and Fe, the stronger antitumor effect of AFN@CM may also be

attributed to the HCC cell membrane wrapping design feature. This feature endows AFN@CM with better biocompatibility and tumor targeting ability.²⁵⁹

Meanwhile, IONPs can also be used in therapeutic approaches such as chemotherapy, phototherapy, gene therapy and immunotherapy.²⁷⁹

Xiaolong Liang et al designed and synthesized a theranostic nanoplatform based on a relatively smaller (<20 nm) iron oxide loaded porphyrin-grafted lipid nanoparticles (Fe_3O_4 @PGL NPs).²⁵⁴ Fe_3O_4 @PGL NPs could generate ROS in the absence of light via the Fenton reaction at relatively high Fe^{2+} concentrations. At the same time, the presence of PDT further accelerated the Fenton reaction and oxidative stress on macrophages to generate synergistic ROS. Both in vivo and in vitro experiments showed that Fe_3O_4 @PGL NPs could almost completely inhibit tumor growth by combined PDT under fluorescence and magnetic resonance (MR) imaging guidance. Compared with other nanomaterials, Fe_3O_4 @PGL NPs have relatively small size, high PS loading efficiency, negligible dark toxicity and excellent biocompatibility.²⁵⁴

Amir Jalali et al synthesized Fe_3O_4 @Glu-menthol magnetic nanoparticles (MNPs) by encapsulating iron oxide (Fe_3O_4) nanoparticles with glucose and affixing them with menthol.²⁸⁰ Studies have shown that Fe_3O_4 @Glu-menthol MNPs can induce apoptosis in gastric cancer cells. Moreover, cells treated with Fe_3O_4 @Glu-menthol MNPs showed 1.6-fold higher expression of the oncogene Caspase 8 gene than untreated cells.²⁸⁰

In addition to Fe_3O_4 @PGL NPs and Fe_3O_4 @Glu-menthol MNPs, many other IONPs are associated with conventional tumor treatments such as chemotherapy, radiotherapy and immunotherapy. Zhuangzhuang Zhang et al designed and synthesized an acid-responsive, iron-coordinated polymer nanoparticle (PPA/TF) encapsulating the mitochondria-targeting drug alpha-tocopheryl succinate (α -TOS).²⁶⁰ In tumors' weakly acidic intracellular environment, PPA/TF promotes pH-responsive drug release, ROS generation, and GSH depletion. PPA/TF effectively inhibits tumor growth by combining ferroptosis induction with Chemodynamic therapy (CDT).²⁶⁰ Hyaluronan (HA)-encapsulated IONP (IONP-HA) can be combined with photothermal therapy to effectively induce ferroptosis in recurrent bladder cancers that have acquired chemoresistance after chemotherapy.²⁶¹ Phospholipid-modified Pt(IV) prodrug-loaded iron oxide nanoparticle (IONP)-filled micelles (mIONP-PL-Pt(IV)), which can be used in combination with chemotherapy for antimelanoma treatment.²⁶² Qingxin Mu et al designed and synthesized a multifunctional nanoparticle containing an iron oxide core. This NP can deliver chemotherapeutic and immunotherapeutic agents to breast cancer and dendritic cells simultaneously, thus enabling simultaneous chemo-immunotherapy and effective inhibition of TNBC growth and metastasis.²⁸¹

Another class of ferroptosis inducer nanomaterial combines traditional ferroptosis inducers with nanomaterials to address issues like low solubility, poor biocompatibility, and adverse reactions.²⁸²

BSO was encapsulated in a ZIF-8 matrix, followed by the growth of radiation-sensitive gold nanoparticles (NPs) on the surface to create BSO/ZIF-8@Au.²³⁸ This material served as a template for the formation of a Metal-phenolic network (MPN), which was further modified with hyaluronic acid (HA) to produce the BSO/ZIF-8@Au@MPN@HA (BZAMH) nanohybrid. Upon exposure to tumor microenvironmental stimuli, the nanohybrids disassembled, with BSO inhibiting γ -GCS to block GSH biosynthesis, Fe^{2+} triggering a favorable Fenton reaction, and Au NPs enhancing the deposition of X-ray radiation doses within the tumor.²³⁸ The inactivation of GPX4 and the local generation of hydroxyl radicals collectively induced potent ferroptosis, enabling intense radiotherapy and effective treatment of TNBC while suppressing TNBC lung metastasis. Furthermore, the inclusion of Fe and Au elements in the nanomedicine provides diagnostic capabilities for MRI and CT imaging, allowing for the tracking of nanomedicine distribution and movement while monitoring the therapeutic efficacy of cancer treatment.²³⁸

MTX-LDH@MnO₂ was developed by Liu et al through the incorporation of methotrexate (MTX) within layered double hydroxides (LDHs) interlayers and the electrostatic absorption of biomineralization ovalbumin (OVA)-MnO₂ onto the LDH surface, resulting in a multifunctional and dual-responsive nanosheet [250]. Within the tumor microenvironment, MTX-LDH@MnO₂ exhibited rapid dual-response release of MTX and Mn²⁺. This nanosheet effectively induced ferroptosis in tumor cells by synergistically enhancing ROS generation and modulating the GPX4/GSH and GCH1/BH4 pathways to facilitate LPO accumulation. Moreover, MTX-LDH@MnO₂ triggered the release of damage-associated molecular patterns (DAMPs), promoting immunogenic cell death (ICD) within tumors. This led to dendritic cell (DC) maturation and infiltration of CD⁴⁺/CD⁸⁺ T-cells, resulting in robust anti-tumor immune responses [250].

Ling-Xiao Zhao et al designed a GFR nanoplatfrom, GDY-FIN56-RAP (GFR), with the potential for photothermal therapy (PTT) for the treatment of GBM by encapsulating a RAP-polymer and an ferroptosis inducer, FIN56, on graphdiyne (GDY).²⁴⁰ GFR combined with 808 nm near-infrared radiation significantly triggered GPX4 down-regulation-mediated ferroptosis of GBM cells, which inhibited GBM growth and prolonged the lifespan of the GBM in situ xenograft mouse model. Near-infrared radiation facilitated the release of FIN56 from the GFR and directly induced GBM cell death through temperature elevation—directly induced GBM cell death. The GFR nanoplatfroms can penetrate the blood-brain barrier and induce an acidic environment-induced in situ release of FIN56.²⁴⁰

Cheng et al successfully developed an injectable hydrogel, Gel@WA-cRGD, that combines the induction of ferroptosis and immunomodulation effects. The hydrogel was created through Ca^{2+} -mediated cross-linking of natural sodium alginate, incorporating crgd-modified redox-responsive Withaferin prodrugs (WA-cRGD) and programmed cell death ligand 1 antibody (aPD-L1) for targeted tumor treatment. Following injection into postoperative trauma cavities, the hydrogels degrade in a microenvironment-responsive manner, releasing β -cyclodextrin (β -CD) and aPD-L1 to the trauma margins. These components are selectively taken up by tumor cells and activated by excess GSH in the cytoplasm, leading to WA-induced ferroptosis and the release of tumor-derived immune substances for recognition and activation of surrounding antigen-presenting cells (APCs). Additionally, aPD-L1 inhibits the PD-1/PD-L1 interaction between tumor and immune cells, reversing the immunosuppressive tumor microenvironment (TME). Gel@WA-cRGD shows promise for postoperative treatment of resected solid tumors to prevent primary tumor recurrence and suppress distal tumors.²⁴¹

There are many similar drugs that use nanomaterials to encapsulate ferroptosis inducers to enhance their efficacy. The toxicity of IKE was significantly reduced by using biodegradable nanoparticles for its delivery.¹⁴⁴ The nanomedicine Fe_3O_4 @PCBMA formed by loading SIM into magnetic nanoparticle-coated zwitterionic polymers induced ferroptosis and improved the therapeutic efficacy of TNBC.²⁴²

In addition to the above nanomaterials, there are many other nanomaterials with ferroptosis-inducing effects.

Lei et al developed biocompatible manganese molybdate nanoparticles (MnMoOx NPs) through a high-temperature liquid-phase method and DSPE-PEG5k modification [254]. MnMoOx NPs demonstrate antitumor effects by inducing ferroptosis and enhancing immunogenicity. These nanoparticles deplete GSH in tumors and inhibit GPX4 expression, triggering ferroptosis in tumor cells. Moreover, MnMoOx NPs induce immunogenic cell death in tumor cells, releasing DAMPs, promoting DC maturation, enhancing T cell infiltration, activating anti-tumor immune responses, and reversing the immunosuppressive tumor microenvironment. When combined with immune checkpoint inhibitors (ICIs) like α -PD-L1, MnMoOx NPs further enhance antitumor effects and suppress tumor metastasis.

Despite their many advantages, such as high drug loading capacity, increased water solubility, and improved selectivity, nanomedicines still have many problems at this stage. Excessive use of exogenous metals may cause potentially adverse effects on human health, including acute and chronic damage.²⁸³ The enhanced permeability and retention (EPR) effect is influenced by factors such as the nature of the nanomedicine itself, tumor growth, and patient heterogeneity. These factors make drug targeting inefficient and make it difficult to achieve complete drug enrichment in the tumor.²⁸⁴ This leads to an increased likelihood of damage to normal cells. Although a large number of tumor-targeted nanomedicines have been developed at this stage, factors such as tumor complexity and heterogeneity have led to off-target effects, and the expected targeting effect cannot be achieved. Studies have shown that the pharmacokinetics of different nanomedicines vary between species.²⁸⁵ However, at this stage, most of the studies on the behavior of nanoparticles in vivo are derived from animal experimental data, and few of them are relevant enough to predict their safety and efficiency in humans based on the results of animal experiments. There are no detailed findings on the immunogenic responses generated based on nanomedicine carriers and their impact on pharmacokinetic characterization, therapeutic efficacy and potential toxicity. After applying very small IONPs (ESIONPs) to a zebrafish model, Zhaojie Lyu et al found that ESIONPs may be neurotoxic and induce ferroptosis.²⁸³ The abnormal accumulation of iron ions may increase the risk of early degenerative neurological diseases. Therefore, the biosafety and selectivity of nanomedicines for therapeutic use remain highly questionable. In addition, due to the difficulty of synthesizing the same nanoparticles quickly, precisely, and reproducibly, large-scale and reproducible synthesis of nanoparticles is even more complicated

when it involves multi-step or complex techniques.²⁸⁶ All these make the clinical translation of nanomedicines a great challenge.

Ferroptosis-Inducing Therapy in PDT and SDT

Photodynamic Therapy

Photodynamic Therapy (PDT) is a new approach to treating tumors and pre-cancerous lesions with photosensitizing drugs and laser-activated treatment.²⁸⁷ Irradiating the lesion site with a specific wavelength activates photosensitizing drugs that selectively accumulate in the lesion tissue, causing the tumor to take up molecular oxygen to produce ROS, which leads to tumor destruction. Synthesizing photodegradation-targeting chimeras (PDTACs) by coupling photosensitizers with ferroptosis-inducing drugs is a new idea in the development of ferroptosis inducer (Figure 4). Protein targeting and photoactivation coupling makes PDTAC highly controllable compared to conventional therapies, enabling precise

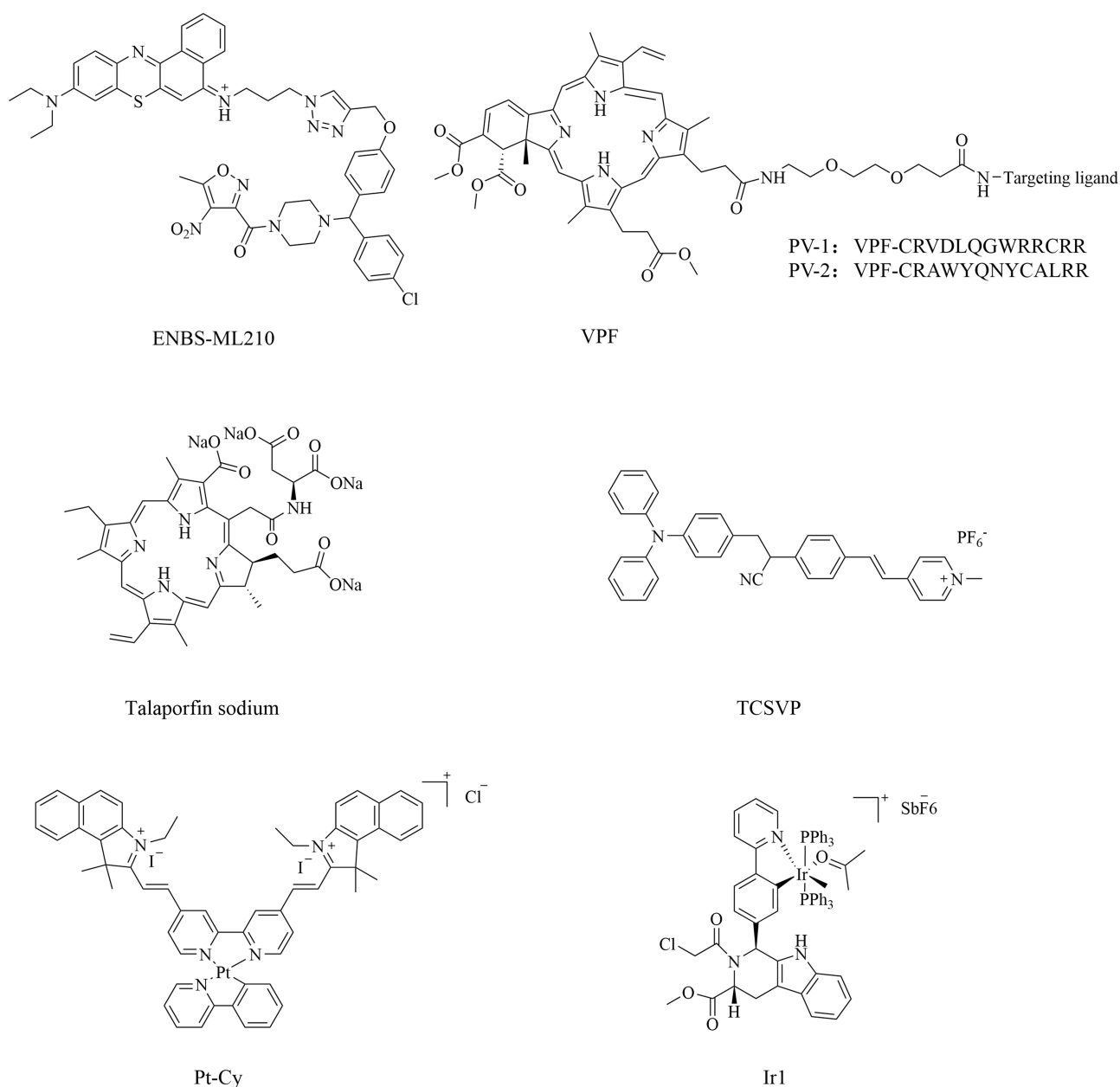


Figure 4 Chemical structural formula of PDTAC-like and SDTAC-like ferroptosis inducers.

and effective treatment.²⁸⁸ This therapy has few side effects, is safer, minimally invasive and better tolerated by the elderly, and has broad clinical applications in combination therapy.²⁸⁹

Qiao Hu et al synthesized the photosensitizer ENBS-ML210 by covalently linking the photosensitizer ENBS with the GPX4 inhibitor ML210.²⁹⁰ The hypoxic microenvironment of NSCLC severely inhibits ferroptosis, leading to the severely limited therapeutic efficacy of some ferroptosis inducers.²⁹¹ However, *in vitro* experiments showed that ENBS-ML210 effectively induced ferroptosis in H1299 cells under 21% and 2% O₂ conditions. ENBS-ML210 could directly target GPX4 in H1299 cells to produce superoxide anion radical (O₂⁻) under 660 nm light irradiation. Both *in vitro* and *in vivo* experiments confirmed its sound anti-tumor effects.²⁹⁰

Sijin Liu et al synthesized two PDTACs, PV1 and PV2, by coupling the photosensitizer verteporfin (VPF) to GPX4-targeting peptides.²⁹² PV1 and PV2 have neither inhibitory nor degradative activity, but they can selectively degrade intracellular GPX4 and generate ROS under red light irradiation, leading to ferroptosis of tumor cells. Dead cells induced by PDTACs exhibit robust immunogenicity *in vitro* and efficiently trigger anti-tumor immunity *in vivo*.²⁹² The coupling of protein degradation and photoactivation makes PDTAC highly controllable, which will greatly help further drug development and clinical application studies.

The second-generation photosensitizer talaporfin sodium (TS) is rapidly cleared from the body, requiring a shorter shading period (2 weeks) than the first-generation photosensitizer porfimer sodium (4 weeks), and the antitumor effect penetrates deeper into the submucosa and extends to the muscle layer.²⁹³ PDTAC synthesized by TS-PDT induces ferroptosis in tumor cells by generating ROS and inhibiting system Xc⁻. *In vivo*, TS-PDT combined with ferroptosis inducers (IKE or sorafenib) reduced tumor volume.²⁹³

TCSVP, a mitochondria-targeted porfimer sodium with aggregation-induced emission (AIE) properties, was developed by Shan Wang et al AIE-PS, in comparison to traditional porfimer sodium, maximizes energy conservation from heat dissipation, leading to enhanced reactive oxygen species (ROS) generation and fluorescence emission capabilities.²⁹⁴ Due to the more negative mitochondrial potential of cancer cells relative to normal cells, the positively charged AIEgen can effectively differentiate between cancerous and normal cells. TCSVP specifically targets cancer cell mitochondria, efficiently producing ROS in the presence of light, thereby sensitizing tumor cells to ferroptosis induction by RSL3.²⁹⁴

Xinyang Zhao et al synthesized the Iridium(III) complex Ir1, derived from hydrated Iridium, with adjustable photophysical and chemical properties. By incorporating triphenylphosphine as a mitochondria-targeting ligand and Py-RSL as a ferroptosis-inducing ligand, the complex not only triggers ferroptosis by inhibiting GPX4 and FSP1 but also suppresses the ErbB signaling pathway to enhance tumor suppression.²⁹⁵ The metal coordination in Ir1 confers fluorescent properties, enabling intracellular localization monitoring under visible light excitation (488 nm) for real-time cell tracking, while effectively reducing off-target toxicity of the Py-RSL ligand.²⁹⁵ With a dual inhibitory mechanism, Ir1 exhibits superior anticancer and ferroptosis-inducing capabilities with reduced toxicity and fewer side effects.

Sonodynamic Therapy

Sonodynamic therapy (SDT) is an innovative non-invasive treatment method that uses ultrasound (US) to activate a sensitizer and produce reactive oxygen species (ROS) to destroy cancer cells²⁹⁶ (Figure 5). Unlike light-based therapies, US has the advantage of deeper tissue penetration, making SDT particularly effective for treating tumors located deep within the body.

Yidan Lai et al designed and synthesized a platinum(II)-cyanine complex, Pt-Cy, which was shown to generate ROS under both ultrasound (US) and light irradiation in *in vitro* experiments. Pt-Cy exhibited US-induced cytotoxicity with an IC₅₀ of 6.94 mM under US irradiation, while showing minimal dark-cytotoxicity to 4T1 cells. Pt-Cy also reduced GSH content in cells under US irradiation, leading to the accumulation of lipid peroxides and triggering ferroptosis. In terms of *in vivo* tumor therapy, Pt-Cy demonstrated superior acoustic kinetic therapeutic effects compared to PDT.²⁹⁷

Liqiang Zhou et al designed a liposomal nanosystem called Lipo-PpIX@Ferumoxytol, which combines the nanosensitizer PpIX and the iron supplement ferumoxytol. Ferumoxytol was used to deliver excess iron to tumor cells, leading to ferroptosis and increased susceptibility to SDT-induced apoptosis. Additionally, SDT was found to enhance the

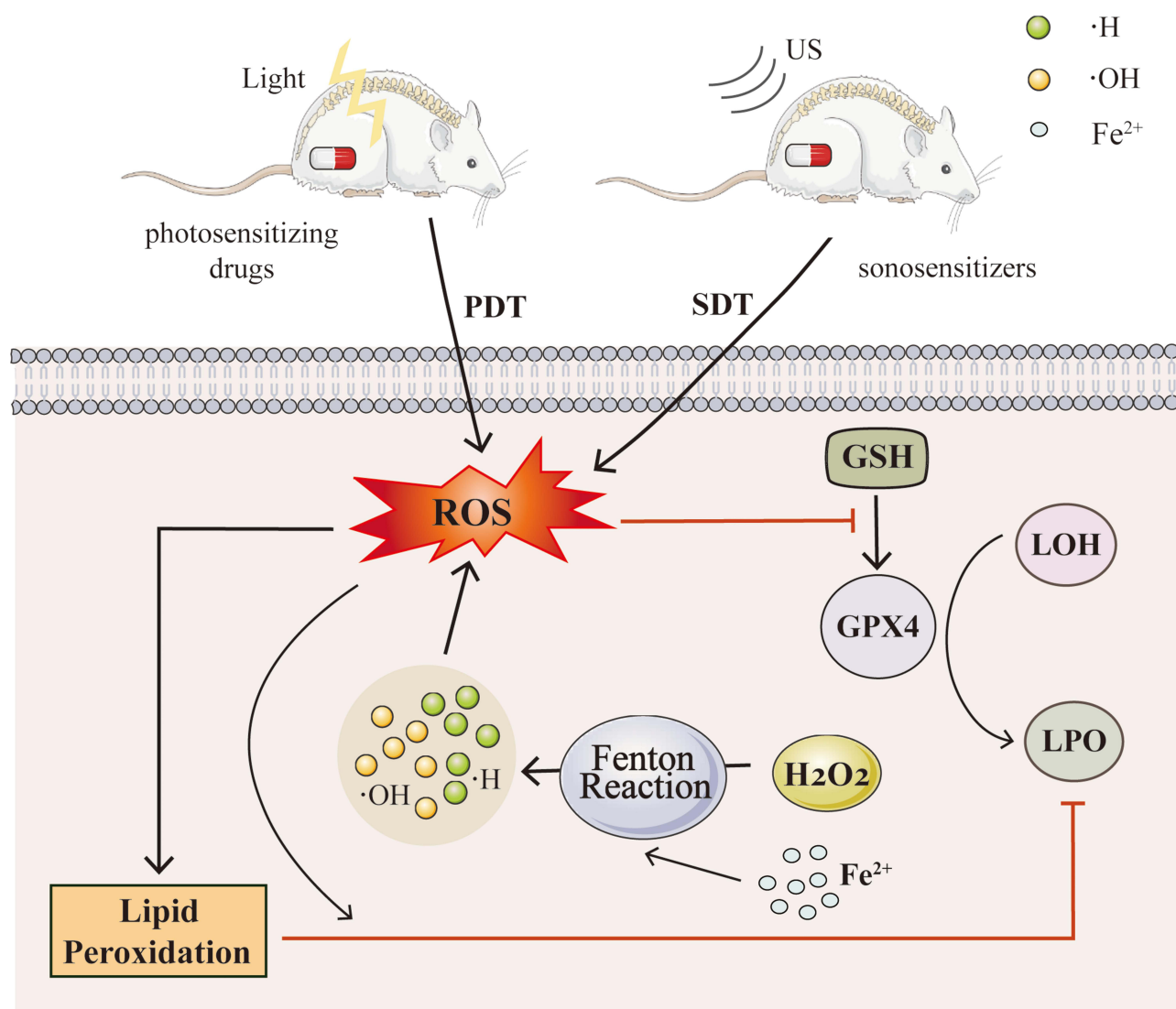


Figure 5 Ferroptosis-inducing therapy in PDT and SDT.

sensitivity to ferroptosis by modulating the ferritinophagy process. The dual ferroptosis/apoptosis pathway was triggered by Lipo-PpIX@Ferumoxytol, resulting in the inhibition of tumor growth.²⁹⁸

Jing Yu et al developed ultra-small iron-doped zinc oxide nanoparticles, FZO-NP, and surface-modified FZO nanoparticles to create FZO-ASP, which exhibited good water stability. FZO-ASP was capable of initiating the Fenton reaction and inducing ferroptosis in tumor cells. When combined with ultrasonic energy, FZO-ASP showed enhanced inhibition of cancer cell proliferation and mouse mammary tumor growth, with no significant toxicity observed in treated mice.²³⁴

Challenges and Opportunities in the Development of Ferroptosis Inducers

With in-depth research on the mechanisms and targets of ferroptosis, various ferroptosis inducers have been discovered and developed. Although many ferroptosis inducers have been reported, multiple types of ferroptosis inducers have different advantages and disadvantages (Table 3). Meanwhile, the clinical application of ferroptosis inducers is still in slow progress. Therefore, the research, development, and clinical translation of ferroptosis inducers still need to be continuously advanced. Improving the drawbacks of the existing inducers and developing ferroptosis inducers that can be better applied to the clinic is the focus of the current research and development of ferroptosis inducers.

Table 3 Comparing the Advantages and Disadvantages of Different Ferroptosis Inducers Methods

	Traditional Small Molecular Compounds	PROTACs	Nanomaterials	PDT and SDT
Advantages	Small molecular weight; Can penetrate the cell membrane; Can cross blood-brain barrier; Most do not involve immunogenicity; Good stability; Can be taken orally; Easily absorbed; Mature synthesis technology	Catalytic properties; Great target; Longer half-life; Low toxicity; Overcome drug resistance; Wide range of targets	Great target; Good stability; Longer half-life; Overcome drug resistance; High effectiveness; High oral bioavailability	High controllability; High selectivity; Low toxicity
Disadvantages	Poor solubility; Short half-life; Low specificity; drug resistance; Limited effectiveness	High molecular weight; Poor solubility; Low oral bioavailability; Poor drugability; Difficult to synthesize	Low biosecurity; Having some toxic effects; Off-target effect; Difficult to repeat synthesis	High dependence on tissue oxygen concentration; Weak penetration into deep tissues; Limited therapeutic effect
Ref.	[299,300]	[301,302]	[303–305]	[306–308]

Discovery of New Targets for Ferroptosis Inducers

Most of the existing ferroptosis-inducing agents act on classical ferroptosis-regulating targets such as system Xc⁻, GPX4, FSP1 and Nrf2, which have limited induction and tend to make cells resistant to drugs.³⁰⁹ Therefore, new targets for ferroptosis inducer action still need to be explored.

Xuejun Jiang et al found that membrane-bound O-Acyltransferase Domain Containing 2 (MBOAT2) could re-regulate the lipid composition of cell membranes through phospholipid metabolism by replacing monounsaturated fatty acid (MUFA)-rich phospholipids with polyunsaturated fatty acid (PUFA), thereby inhibiting ferroptosis. (MUFA)-rich phospholipids replace polyunsaturated fatty acid (PUFA), which is easily oxidized and thus inhibits ferroptosis.³¹⁰ MBOAT2 is a new regulator independent of GPX4 and FSP1. Meanwhile, MBOAT2 is regulated by the androgen receptor (AR), suggesting that AR becomes a new regulatory target for ferroptosis.

Ping Wang et al recently found that 7-Dehydrocholesterol (7-DHC) directly inhibits phospholipid peroxidation by relying on its unsaturated key structural property.³¹¹ The enzymes involved in distal cholesterol biosynthesis can affect the ferroptosis sensitivity of cells by regulating the level of 7-DHC.³¹¹ The enzymes involved in distal cholesterol biosynthesis can affect the ferroptosis sensitivity of cells by regulating differences in the levels of 7-DHC. Targeted regulation of 7-DHC levels is expected to be a therapeutic strategy for cancer. Zhigang Hu et al found that Apurinic/aprimidinic endonuclease 1 (APE1) regulates ferroptosis in hepatocellular carcinoma cells by modulating the AKT/GSK3 β /NRF2 axis.³¹² This suggests that APE1 is a novel ferroptosis regulator.

mTOR is a critical factor that regulates cellular protein synthesis, nutrient metabolism, and growth and proliferation.³¹³ Disheveled Egl-10 and pleckstrin domain-containing protein 5 (DEPDC5) is a newly discovered negative regulator upstream of the mTOR pathway in recent years.³¹⁴ Song li et al found that DEPDC5-deficient CD⁸⁺ T cells produced high levels of xanthine oxidase and lipid ROS due to high mTORC1-induced ATF4 expression, leading to spontaneous ferroptosis.³¹⁵ This suggests that DEPDC5 protects CD⁸⁺ T cells from ferroptosis by limiting mTORC1-mediated purine catabolism. Thus, DEPDC5 is also a target for ferroptosis regulation.

Furthermore, many studies have shown that epigenetic modifications and protein post-translational modifications (PTMs) play important roles in developing diseases involving ferroptosis.³¹⁶ Epigenetic mechanisms such as DNA methylation, histone acetylation and miRNAs may regulate cellular sensitivity to ferroptosis. DNA methylation can affect the expression of iron metabolism genes such as FPN, TFR2, HAMP, HJV, and bone morphogenetic protein 6 (BMP6) by regulating the promoter region of the methylation level.³¹⁷ Several miRNAs can target genes such as DMT1, FPN, TFR1, TFR2, and Ferritin H and affect the process of iron absorption, transport, storage, and utilization by inhibiting the expression of these key genes of iron metabolism.³¹⁸ Epigenetic regulation is also a very promising mechanism of action

for ferroptosis inducers. The discovery of these new mechanisms and targets provides new ideas and directions for developing ferroptosis inducers.

Drug Potency Enhancement

The limited potency of the action of ferroptosis inducers is an important reason that prevents their use in clinical practice.³¹⁹ How to make it more effective in killing tumor cells and thus inhibiting tumor growth is an important issue faced during the development of ferroptosis inducers.

Usually, drugs have a single target, but the pathophysiologic processes of most diseases are so complex that therapeutic modalities directed at a single target have limited effect.³²⁰ Thus, drugs targeting multiple cell death modes are better suited for clinical use. Existing ferroptosis inducers, such as matrine,³²¹ PB¹²² and LAP,³²² have the dual effect of inducing ferroptosis and apoptosis in cells. Meanwhile, drugs that act on multiple ferroptosis regulatory targets can better induce ferroptosis in tumor cells than on a single ferroptosis regulatory target.

In addition to developing drugs that can act on multiple targets, combining ferroptosis inducers with different mechanisms of action is a very important therapeutic strategy. For example, FSEN1 synergizes with DHA to induce ferroptosis in tumor cells.⁹⁷ Ferroptosis inducers can also be used in combination with conventional tumor therapies. Ferroptosis inducers such as Tubastatin A,¹⁷⁴ BZAMH²³⁸ and DSF¹⁹⁸ are effective in enhancing the therapeutic effect of radiotherapy on tumors when combined with radiotherapy.³²³

With the increasing research on ferroptosis, more and more natural products have been found to have ferroptosis-inducing effects.³²⁴ Although these natural products themselves have limited effects in inducing ferroptosis in tumor cells, their discovery has provided lead compounds for the development of ferroptosis inducers. For example, compound 31, synthesized by combining the core of the natural product indirubin with the active fragment of a GPX4 covalent inhibitor via a linker, effectively inhibited human colon cancer cells.⁹³

The continuous development of new technologies such as PROTACs, PDTACs and nanomaterials in ferroptosis inducers also contributes to drug potency. PROTAC DC-2 with ML210 as ligand degraded GPX4 22-fold more than ML210 and inhibited it better than ML210 in a wide range of cells.²²⁶ PROTAC dGPX4 with ML162 as ligand-induced ferroptosis 5-fold more efficiently than ML162.²²⁸ Developing these new technological fields is a significant direction for the future development of ferroptosis inducers.

Reduction of Toxic Side Effects of Drugs

As tumors are chronic wasting diseases, tumor patients are usually in poor general condition and their body energy is in negative balance.³²⁵ The side effects of the drug will cause serious physical burden to tumor patients. This is also a serious obstacle to the clinical application of ferroptosis inducers. Tumor cells are derived from normal tissues and are very similar to normal tissues in terms of internal and external cellular structure and survival conditions (eg, relationship to the immune system).³²⁶ For example, ferroptosis induced by Lepadins E, Lepadins H and JQ1 occurs in cancer cells and normal cells. How to selectively kill tumor cells without harming normal cells in therapy is an important issue in the development of ferroptosis inducers.²⁴

In selecting drug targets, the selection of tumor-specific targets can selectively induce ferroptosis in tumor cells.³²⁷ For example, N6F11 can bind to a specific structural domain of the E3 ubiquitin ligase TRIM25, predominantly expressed in tumor cells, thereby selectively causing GPX4 protein degradation in tumor cells. Studies have shown that the toxic effects of compounds are related to the structure of the compound.³²⁸ For example, nitro is the leading toxic group separating nitroaromatics and can covalently bind to hemoglobin.³²⁹ Therefore, in the design stage of compounds, the drug's toxicity can be reduced from the starting point of the structure-activity relationship.

Technologies such as PROTACs, PDTACs, and nanomaterials have been shown to improve the targeting of ferroptosis inducers.³³⁰ PROTAC-based ferroptosis inducers such as DC-2, dGPX4, and compound 8e have been shown to enhance the rate of inhibition while effectively improving the ability of the drugs to target the tumor cells and reducing the toxicity of the drugs. In photodynamic therapy, irradiating the lesion area with specific wavelengths activates the drugs that selectively accumulate in the lesion tissue. This treatment has better precision and controllability.³³¹ Nanomedicines, on the other hand, are more biocompatible and soluble and cause fewer toxic side effects than conventional ferroptosis inducers.³³²

Summary

Ferroptosis is an iron-dependent mode of programmed cell death. Ferroptosis has become a hot research topic since it was proposed in 2012. With in-depth research on the mechanism of ferroptosis and its targets, various ferroptosis inducers have been discovered and developed. At the same time, research on its application in cancer prevention and treatment has also deepened. Under the predicament that tumors are resistant to traditional therapies such as chemotherapy and radiotherapy and have poor therapeutic effects, the proposal and development of ferroptosis-inducing therapies have provided new ideas and prospects for tumor treatment.

In this article, we introduce the mechanism of ferroptosis, the various types of ferroptosis inducers, and the application of ferroptosis-inducing therapies in the field of PDT and SDT. The comprehensive and systematic summary of small molecule drug classes of ferroptosis inducers provides ideas for designing and optimizing a new generation of small molecule drugs. The summary of the research progress of ferroptosis inducers in PROTACs, nanomaterials, PDT, and SDT provides a reference for the development and clinical translation of ferroptosis inducers in new fields. We also compare the advantages and disadvantages of various ferroptosis inducers. More importantly, we present the challenges and opportunities for developing ferroptosis inducers. We not only show the problems encountered in developing ferroptosis inducers but also propose solutions to solve the problems. In conclusion, we hope that the comprehensive summary and in-depth discussion of ferroptosis inducers will provide a direction for further research and development and clinical translation of ferroptosis inducers, thus bringing more effective treatment for tumor patients.

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YiLin Luo, XinYue Bai and Lei Zhang share first authorship.

Author Contributions

YL.L, XY.B, L.Z is responsible for conceptualizing, designing, and writing the content of the article. QQ.H, N.Z, JZ.C, MZ.H is responsible for literature research, interpretation, and data collection. X.L.L is responsible for conceptualizing, funding, and guiding this article. All authors have critically reviewed the knowledge content of the final version of the article and approved the submitted version.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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