Asian Journal of Pharmaceutical Sciences 19 (2024) 100939

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Review Article

Recent progress of ferroptosis in cancers and drug discovery

Xiang Wang[a,1], *Xinxin Ren*[b,c,d,1], *Xu Lin*[e,1], *Qi Li*[a], *Yingqiong Zhang*[a], *Jun Deng*[a], *Binxin Chen*[a], *Guoqing Ru*[b,*], *Ying Luo*[a,*], *Nengming Lin*[a,f,g,*]

[a] *Department of Pharmacy, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou 310006, China*

[b] *Department of Pathology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, China*

[c] *Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, China*

[d] *Clinical Research Center for Cancer of Zhejiang Province, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, China*

[e] *Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*

[f] *Cancer Center, Zhejiang University, Hangzhou 310058, China*

[g] *Westlake Laboratory of Life Sciences and Biomedicine of Zhejiang Province, Hangzhou 310024, China*

ARTICLE INFO

Article history:
Received 17 May 2023
Revised 8 March 2024
Accepted 30 April 2024
Available online 26 June 2024

Keywords:
Ferroptosis
Cancer
Drug
Treatment

ABSTRACT

Ferroptosis is a nonapoptotic form of cell death characterized by iron dependence and lipid peroxidation. Ferroptosis is involved in a range of pathological processes, such as cancer. Many studies have confirmed that ferroptosis plays an essential role in inhibiting cancer cell proliferation. In addition, a series of small-molecule compounds have been developed, including erastin, RSL3, and FIN56, which can be used as ferroptosis inducers. The combination of ferroptosis inducers with anticancer drugs can produce a significant synergistic effect in cancer treatment, and patients treated with these combinations exhibit a better prognosis than patients receiving traditional therapy. Therefore, a thorough understanding of the roles of ferroptosis in cancer is of great significance for the treatment of cancer. This review mainly elaborates the molecular biological characteristics and mechanism of ferroptosis, summarizes the function of ferroptosis in cancer development and treatment,illustrates the application of ferroptosis in patient's prognosis prediction and drug discovery, and discusses the prospects of targeting ferroptosis.

* Corresponding authors.
E-mail addresses: 15868197173@163.com (G. Ru), haoluoying@163.com (Y. Luo), lnm1013@zju.edu.cn (N. Lin).

[1] These authors contributed equally to this work.

Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2024.100939

1. Introduction

Ferroptosis is a new programmed cell death (PCD) driven by iron and reactive oxygen species (ROS) accumulation and differs from other forms of regulatory cell death [1]. The occurrence of ferroptosis is always accompanied by some particular phenomena in terms of cell morphology, including reduced cell volume, loss of cell membrane integrity, and chromatin condensation [2]. In addition, ferroptosis istypically accompanied by the disintegration and aggregation of cells. At the ultrastructural level,ferroptotic cells are characterized by the destruction of mitochondrial crista and membrane [1]. These abnormalities are mainly caused by oxidative stress and lipid peroxidation.Iron overload and lipid peroxidation are two main aspects of ferroptosis induction. Increased iron uptake or decreased iron storage leads to free iron overload, which promotes the Fenton reaction that elevates ROS content, thereby increasing oxidative damage and activating downstream signaling pathways, ultimately inducing ferroptosis [2]. In addition, lipid peroxidation is a key feature of ferroptosis. Excessive iron enhances the activity of arachidonate lipoxygenase (ALOX) and its prolyl hydroxylase domain (PHD), which promotes lipid peroxidation [3]. In this process, several pathways such as cystine/glutathione/GPX4, FSP1/CoQ and GTPCH/BH4/DHFR are involved [4].

Ferroptosis is closely related to several biological processes, such as iron, amino acid, and polyunsaturated fatty acid (PUFA) metabolism and glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH) biosynthesis [3]. In addition, ferroptosis is involvedin a series of pathological processes, such as cerebral haemorrhage, osteoporosis and renal degeneration [5]. Recently, an increasing number of studies have shown that ferroptosis plays a part in cancer. This review summarizes the regulatory mechanisms underlying ferroptosis. The progress of ferroptosis in cancer treatment and drug development has also been discussed. Finally,problems associated with the therapeutic targeting of ferroptosis are discussed.

2. Overview of the regulatory mechanisms of ferroptosis

The excessive accumulation of lipid peroxides and ROS is often associated with ferroptosis. As ferroptosis is caused by the dysfunction of PUFA, iron and ROS metabolism, this review introduces the regulatory mechanisms of ferroptosis from three perspectives: lipid, iron, and antioxidant metabolism (Fig. 1).

2.1. *Lipid metabolism*

Lipid peroxidation is essential for ferroptosis. Specifically, ferroptosis is induced by peroxidation of membrane phospholipids, which causes the accumulation of phospholipid hydroperoxides (PLOOH), 4-hydroxynonenal, and malondialdehyde (MDA) [6]. These products trigger membrane instability and permeabilization, ultimately leading to cell death. Lipid peroxidation involves both enzymatic and nonenzymatic pathways. In one of enzymatic pathways, lipoxygenases (LOX) and cytochrome P450 oxidoreductase (POR) are the two main regulators mediating lipid peroxidation [6]. LOXs constitute a group of redox enzymes that catalyze the production of PLOOH from free and esterified PUFAs. Severalstudies have demonstrated that high levels of LOX-5are essential for inducing cellular ferroptosis [3]. In addition, POR transfers electrons from NADPH/NADH to downstream proteins to mediate redox reactions. In this process, POR transfers electrons to oxygen, generating hydrogen peroxide, which eventually activates lipid peroxidation. In the nonenzymatic pathway, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are key mediators of lipid peroxidation [1]. The two molecules primarily participate in the biosynthesis PUFAs and are associated with PUFA transmembrane activity. The downregulation of ACSL4 and LPCAT3 expression suppresses ferroptosis by decreasing lipid peroxides aggregation [6].

2.2. *Iron metabolism*

Ferroptosis is an iron-dependent type of cell death. Thus, iron metabolism plays a central role in ferroptosis. Iron metabolism involves iron uptake, storage, transfer and efflux. Iron absorption is regulated by the plasma membrane protein transferrin receptor 1 (TFR1), a marker of ferroptosis [1]. Studies have demonstrated that silencing TRF1 suppresses erastin-induced ferroptosis [6]. When iron enters thecell, $Fe^{3+}$is reduced by six-transmembrane epithelial antigen of prostate 3 (STEAP3) to Fe^{2+} and stored in the labile iron pool (LIP). An increase in LIP promotes lipid peroxidation and generates PLOOH [7]. Moreover, ferritin is degraded by nuclear receptor coactivator 4 (NCOA4) to increase the content of free iron. In addition, excess $Fe^{2+}$is converted to Fe^{3+}via ferroportin (FPN)-mediated oxidation and is then exported from the cell. Expect for iron metabolism, some regulators also participate in ferroptosis. For example, heat shock proteins (HSPs) suppress ferroptosis by blocking TRF1 expression [3]. Reducing the level of iron response element binding protein 2 (IREB2) can inhibit ferroptosis by upregulating FTH1 expression [3]. Moreover, heme oxygenase-1 (HMOX1) degrades heme, increasing the intracellular level of $Fe^{2+}$and promoting erastin-induced ferroptosis.

2.3. *Antioxidant metabolism*

The antioxidant system, especially the cysteine/glutamate transporter receptor (Xc-) system and GSH peroxidase 4 (GPX4), participates in ferroptosis. System Xc- exchanges cystine (Cys_2)for glutamate (Glu), and thus participates in the synthesis of cysteine (Cys) and GSH [3]. In addition, GPX4 is the core regulator of ferroptosis. At the physiological level, GPX4 converts GSH to oxidized GSH (GSSG), which then converts PLOOH into alcohol [8]. Moreover, a reduction inCys levels in cells caused by system Xc- suppression indirectly results in GPX4 inhibition. Therefore, system Xc- and GSH play synergistic roles in enhancing cellular antioxidant capacity, decreasing ROS accumulation, attenuating oxidative stress and ultimately inhibiting ferroptosis. For example,

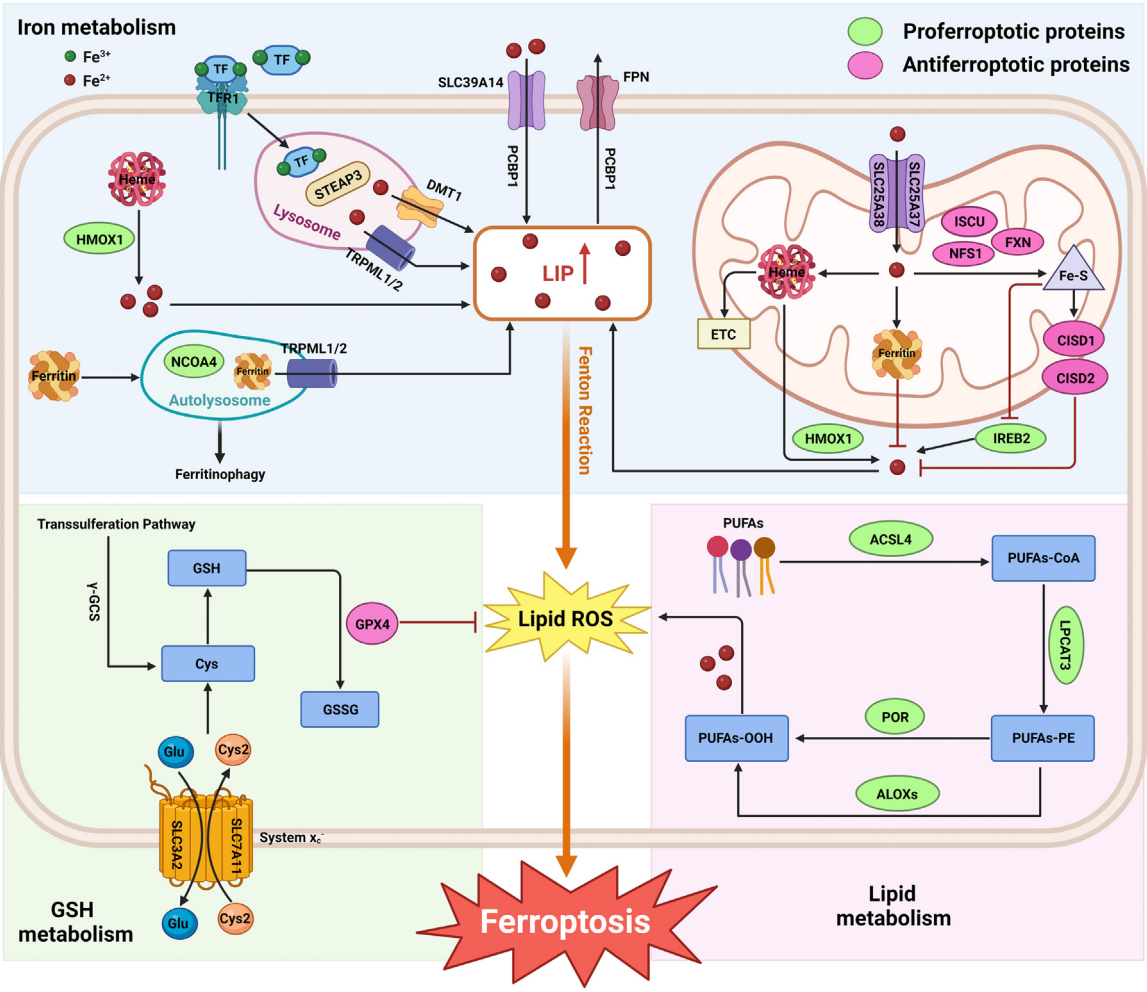

Fig. 1 – Schematic description of the ferroptosis signaling pathway. Cell death through ferroptosis is executed by lipid peroxidation, a process relying on iron metabolism, lipid metabolism and GSH metabolism. In general, excess iron is converted into ferritin and free iron can form the LIP. Ferritin is transferred to the autolysosome by binding to NCOA4 and then releases free iron. Heme is degraded by HMOX1 and increases the content of free iron. In mitochondria, the level of free iron is reduced through forming ferritin and transferring it to the outside by CISD1 and CISD2. Free iron takes part in the generation of lipid ROS by Fenton reaction. ACSL4 and LPCAT3 are essential to generate PUFAs-PE in ferroptosis. The activation of POR and ALOXs induces lipid peroxidation and then triggers ferroptosis. Lipid peroxidation can be removed by system x_c^- and GSH-GPX4 axis. Colouring: Proferroptotic proteins are shown in green; antiferroptotic proteins are shown in pink. (TF, transferrin; DMT1, divalent metal transporter1; TRPML1/2, Mucolipin TRP channel 1/2; ISCU, iron-sulfur cluster assembly enzyme; NFS1, cysteine desulfurase;FXN, frataxin; CISD1/2, CDGSH iron sulfur domain 1/2; IREB2, iron-responsive element binding protein 2; ETC, electron transport chain; ALOXs, arachidonate lipoxygenases; GCS, glutamylcysteine synthetase).

P53 downregulates SLC7A11 expression, which affects the synthesis of GSH andactivity of GPX4, thereby, inducing ferroptosis [6].

3. The role played by ferroptosis in cancer

Studies have demonstrated that ferroptosis plays an essential role in cancer. However, different cancer cells vary in their sensitivity to ferroptosis. These differences may be caused by differences in the pathological environment and metabolic status of cancer cells. Here, we discuss the role of ferroptosis in various cancers (Tables 1 and 2).

3.1. *Ovarian cancer*

There is a strong association between ferroptosis and ovarian cancer. Report found that upregulation of transferrin receptor (TFRC) or downregulation of FPN caused iron overload, inducing ferroptosis in ovarian cancer [9]. In addition, ROS levels increased in a variety of ovarian cancer cells, providing clear evidence that these cells were prone to ferroptosis. Ferroptosis also affects the progression and prognosis of ovarian cancer. You et al. constructed a model based onferroptosis-related genes and showed that ferroptosis might influence ovarian cancer development through affecting tumor metastasis and the

Table 1 – The application of models based on ferroptosis-related genes to various cancers.

Cancer	Models based on	Ferroptosis-related genes/mRNAs	Target	Prediction	Survival	Drugs	Ref
Ovarian cancer	13 ferroptosis-related genes	TGM2, ASAH1, STK3, RIN2, HERC3, FTH1, FMO2, EHD2, COL8A2, C5AR1, AXL, ADORA3, ADAM9	Tumor metastasis and immune landscape	Progression and prognosis	OS	NA	[10]
	8 ferroptosis-related genes	NFS1, ATG7, G6PD, VDAC2, SLC3A2, MAP1LC3C, ACSL3, PTGS2	Immune microenvironment	Prognosis	OS	Platinum	[11]
	6 ferroptosis-related genes	DNAJB6, RB1, VIMP/ SELENOS, STEAP3, BACH1, and ALOX12	Immune-related pathways	Prognosis	OS	DMOG	[12]
	15 ferroptosis-related mRNAs	CDKN1B, FAS, FOS, FOXO1, GABARAPL1, HDAC1, NFKB1, PEX3, PPP1R15A, SIRT2, CXCR4, IFNG, IL24, MTMR14, RB1	Immune score, function, and checkpoints	Prognosis	OS, DFS	A.443654, AZD.0530, AZD6482, AZD7762, AZD8055, BAY.61.3606, Bicalutamide, CGP.60474	[16]
HCC	3 ferroptosis-related genes	G6PD, SAT1 and SLC1A5	Immune-associated pathways and functions	Prognosis	OS	NA	[25]
	4 ferroptosis-related genes	ABCB6, FLVCR1, SLC48A1, SLC7A11	Immune cell infiltration and gene expression	Diagnosis and prognosis	OS	Erastin	[26]
	7 ferroptosis-related genes	G6PD, WDR76, CA9, and AHCYL1 were FRGs, HMOX1, FLT3	Immunotherapy and targeted therapy	Prognosis	OS	NA	[27]
Lung cancer	5 ferroptosis-related genes	NEDD4, ACSL3, ITGA6, SLC11A2, VDAC1	Immune cell infiltration	Prognosis	OS	NA	[42]
	14 ferroptosis-related genes	ALOX15, ATG7, CBS, CYBB, GCLC, GLS2, GPX4, MAP1LC3C, MT1G, NFS1, PTGS2, SLC3A2, SLC7A11, VDAC2	Immune cell infiltration and immunotherapy	Prognosis	OS	NA	[43]
Gastric cancer	17-ferroptosis-related-lncRNA	SCAT8, MACORIS, FP700111.1, AP000695.1, AL391152.1, AC131391.1, AC007391.1, AC104758.1, AC104260.2, AP000438.1, SPATA13-AS1, AL021154.1, AC021106.3, AL022316.1, AL355001.1, AP001107.6, RSF1-IT2	Stromal activation, EMT activation, immune escape, DNA replication, immune-flamed state, and genomic instability	Prognosis and treatment response	OS, RFS	Bleomycin, FGFR_0939, Temsirolimus	[94]

immune landscape [10]. Li et al. used a Gene Expression Omnibus (GEO) dataset to construct a model based on eight ferroptosis-related genes, which predicted the prognosis of ovarian cancer patients [11]. Yu et al. created another model (including six genes) based on the LASSO regression algorithm to predict the prognosis in such patients [12]. A high level of cytochrome B reductase 1 (CYBRD1) is closely associated with the poor prognosis of patients with ovarian cancer because it regulates ferroptosis-related pathways [13].

Furthermore, ferroptosis is used for exploring therapeutic targets and drug combinations for the treatment of ovarian cancer. ACSL1 increased N-myristoylation of FSP1 to inhibit ferroptosis in ovarian cancer cells [14]. LncRNA CACNA1G-AS1 suppressed ferroptosis and promoted ovarian cancer progression by upregulating FTH1 expression [15]. Based on the expression profiles of ferroptosis-related mRNA, Zhang et al. found that 15 ferroptosis-related mRNAs could be used as potential targets for ovarian cancer treatment [16]. Moreover, many small-molecule compounds can be beneficial in cancer therapy by inducing ferroptosis. Lidocaine promotes ferroptosis and inhibits cancer cells proliferation by upregulating miR-382–5p and downregulating SLC7A11 [17]. The mixed leukemia antagonist MI–463 combined with the antiproliferative drug auranofin synergistically induces ferroptosis in cancer cells [18]. Superparamagnetic iron oxide nanoparticles (SPIONs) inhibit cancer cell proliferation and invasion by inducing ferroptosis [19]. Artemisinin induced ferroptosis of cancer cells by promoting ROS accumulation [3]. The MAP30 protein in balsam pear and erastin cooperate with CDDP to induce ferroptosis and suppress the proliferation of

Table 2 – The function of small molecules and pathways to various cancers by targeting ferroptosis.

Cancer	Small molecules/ Pathways	Target	Function	Effect on ferroptosis	Cell type	Ref
Ovarian cancer	ACSL1	FSP1	Inhibition	Inhibit	OVCA429	[14]
	LncRNA CACNA1G-AS1	FTH1	Upregulation	Inhibit	SKOV3, A2780	[15]
	Lidocaine	miR-382–5p /SLC7A11 Axis	Activation	Induce	SKOV-3	[17]
	MI–463	SCD1	Inhibition	Induce	OVCAR-8	[18]
	SPIONs	ferroptosis-related genes	Activation/ Inhibition	Induce	Stem cells	[19]
	Artemisinin	mTOR signaling	Inhibition	Induce	SKOV-3, HEY1, HEY2, OVCAR8, IGROV-1, OVCAR3, TOV-21 G, OV-90, TOV-112D	[3]
	MAP30	AMPK signaling	Activation	Induce	OVCA433, SKOV-3	[20]
	Shikonin	HMOX1	Inhibition	Induce	A2780, SKOV3, OVCAR4	[21]
	PML	PGC-1α	Activation	Induce	SKOV3, OV90, CAOV3, OV7, COV504,OV56, IGROV1, OVCAR8, OC314, KURAMOCHI, OVSAHO, OVCAR4, FUOV1, COV318	[22]
	NRF2/CBS	Transsulfuration pathway	Activation	Inhibit	SKOV3, OVCA429	[23]
	SCD1	CoQ10	Upregulation	Inhibit	MDAH2774, SW626, SKOV3, TOV-112D	[24]
HCC	Donafenib	HMOX1	Upregulation	Induce	HepG2, Hep3B, HCCLM3, Huh7	[28]
	DHA	PEBP1/15-LO	Activation	Induce	Huh-7, HepG2	[29]
	Atractylodin	GPX4 and FTL ACSL4 and TFR1	Downregulation/ upregulation	Induce	Huh7, Hccm	[30]
	Docosahexaenoic acid nanoparticles	GPX4	Inhibition	Induce	PLC/PRF/5, HepG2	[31]
	p62-Keap1-NRF2	HMOX1, FTH1	Upregulation	Inhibit	HepG2, Hep3B, Hepa1–6, SNU-182	[32]
	LCN2	NF-κB signaling	Inhibition	Induce	Hep3B, HepG2, Mahlavu, PLC/PRF/5, HA59T, Tong, Huh-7	[33]
	ABCC5	SLC7A11	Upregulation	Inhibit	HuH7, HepG2, Sk-Hep-1	[34]
	YAP/TAZ	SLC7A11	Upregulation	Inhibit	Huh7, HLE, Hep3B	[35]
	Tiliroside	TBK1	Inhibition	Induce	HepG2	[36]
	SOCS2	SLC7A11	Inhibition	Induce	SK-Hep-1, HepG2	[37]
	PGAM1	LCN2	Downregulation	Induce	Hepa1-6	[38]
	TSPO	NRF2	Upregulation	Inhibit	HCCLM3, MHCC97H	[39]
	HCAR1/MCT1	AMPK signaling	Inhibition	Inhibit	Huh7, Hep3B	[40]
	FTH	Fe^{2+}	Downregulation	Inhibit	HCCLM3, MHCC97H	[41]
Lung cancer	β-Elemene	lncRNA H19	Upregulation	Induce	H1975, H1650, H1819	[44]
	Manoalide	NRF2/SLC7A11 axis	Inhibition	Induce	A549, H157, HCC827, PC9	[45]
	Bufotalin	GPX4	Downregulation	Induce	A549	[46]
	Zinc	circFOXP1	Downregulation	Induce	A549	[47]
	Celastrol+erastin	ATG5/ATG7 and PINK1/Parkin signaling, HSF1	Activation/ Upregulation	Induce	HCC827, A540, H1299	[48]
	eNVs-FAP	IFN-γ	Upregulation	Induce	LLC Lewis	[49]
	SOX2	SLC7A11	Upregulation	Inhibit	H5889, L78, H1299 SW620	[50]
	MiR-27a-3p	SLC7A11	Downregulation	Induce	A549	[51]
	RBMS1	SLC7A11	Upregulation	Inhibit	A549, NCI-H1299	[52]
	Glu	YAP	Inhibition	Induce	H1975, HCC827	[53]
	YTHDC2	SLC3A2	Downregulation	Induce	A549, NCI–H1299, PC-9, NCI–H1975, NCI–H441, NCI–H1650,HCC827, NCI–H292 Calu-1	[54]
	MIB1	NRF2	Downregulation	Induce	A549, MDA-MB-231	[55]
	USP11	NRF2	Upregulation	Inhibit	H1299, A549	[56]
	Acetaminophen	NRF2/HMOX1 signaling	Inhibition	Induce	H1299, A549	[57]
	ZVI-NP	NRF2	Downregulation	Induce	H1299, H460, A549	[58]
	USP35	FPN	Upregulation	Inhibit	A549, H358, H460, H1299, H1650	[59]
	AKR1C1	NA	NA	Inhibit	A549, PC-9, H1975	[60]

(*continued on next page*)

Table 2 (*continued*)

Cancer	Small molecules/ Pathways	Target	Function	Effect on ferroptosis	Cell type	Ref
Prostate cancer	RSL3	GPX4	Inhibition	Induce	PC3, PC3M, DU145, LNCaP	[61]
	Iron	Oxidative stress	Activation	Induce	VCaP, LNCaP, TRAMP-C2, DU-145 PC-3	[62]
	Erastin	Androgen receptor	Downregulation	Induce	LNCaP, PC3, 22Rv1, C4–2, C4–2B, Du145	[65]
	Flubendazole	P53	Upregulation	Induce	PC3, DU145	[66]
	Qiling decoction	FSP1	Inhibition	Induce	PC3, DU145, RWPE-1	[67]
	Luteolin	TFEB	Upregulation	Induce	DU145, PC-3	[68]
	SGK2	GPX4	Upregulation	Inhibit	PC3, DU145	[69]
	LncRNA OIP5-AS1	miR-128–3p/SLC7A11 signaling	Activation	Inhibit	PC3, DU145	[71]
	DECR1	PUFA oxidation	Inhibition	Inhibit	LNCaP, VCaP, 22RV1	[72]
	VCP	GSH	Upregulation	Inhibit	PC3	[74]
Breast cancer	HMPB/ML210@TA-BLM-Fe^{3+}nanocomplex	GPX4	Inhibition	Induce	NA	[76]
	Azo-CA4-loaded nanocarriers	Fe^{2+}	Upregulation	Induce	MDA-MB-231	[76]
	NLC/H($D + F + S$) NPs	ROS	Upregulation	Induce	4T1	[77]
	Metformin	SLC7A11	Downregulation	Induce	MCF-7, T47D, HCC1937, Bcap37, NHFB, HBL-100	[78]
	Simvastatin	HMGCR	Downregulation	Induce	MCF-7 MDA-MB-231	[78]
	Isoliquiritin	NF-κB	Inhibition	Induce	MDA-MB-231, MCF-7	[79]
	Curcumin	HMOX1	Upregulation	Induce	MCF-7 MDA-MB-231	[80]
	DMOCPTL	GPX4	Inhibition	Induce	MDA-MB-231, SUM159, BT574, 4T1	[80]
	Glycyrrhetinic acid	NADPH oxidases and iNOS	Activation	Induce	MDA-MB-231	[80]
	TYRO3	PD-1/PD-L1	Inhibition	Induce	BT549	[81]
	DDR2	Hippo pathway	Activation	Induce	SUM52, ZR751, BT474, MCF7 T47D, BT20, MDA-MB-231, Hs 578T, BT549 cells, MDA-MB-157	[82]
	HLF	GGT1	Activation	Inhibit	MDA-MB-231, HCC1937	[83]
Colorectal cancer	Osthole	AMPK/Akt	Inhibition	Induce	HCT116, SW480	[84]
	Talaroconvolutin A	SLC7A11/ALOXE3	Downregulation/ Upregulation	Induce	HCT116, SW480, SW620	[85]
	IMCA	SLC7A11	Downregulation	Induce	DLD-1, HCT-116	[85]
	DHA	Immunogenicity	Increasing	Induce	CT26, MC38	[86]
	Elesclomol	ATP7A	Downregulation	Induce	DLD-1, SW480	[87]
	FeOOH NSs	H_2S	Downregulation	Induce	CT26	[88]
	VZnO	H_2S	Downregulation	Induce	CT26, HCT116	[88]
	Cetuximab	NRF2/HMOX1 signaling	Inhibition	Induce	HCT116, DLD-1	[89]
	β-elemene+ cetuximab	Fe^{2+} and ROS	Increasing	Induce	HCT116, Lovo, $CaCO_2$	[90]
	CYP1B1	ACSL4	Downregulation	Inhibit	RKO, HCT116, HT29, MC38	[91]
	HIF-2α	Fe^{2+}	Increasing	Induce	HCT116, SW480, DLD1, RKO, HT29, MC38, CT26	[92]
	Lipocalin 2	xCT and GPX4	Upregulation	Inhibit	HCT116	[93]
Gastric cancer	Polyphyllin I	NRF2/FTH1	Inhibition	Induce	AGS, MKN-45	[95]
	Levobupivacaine	miR-489–3p/SLC7A11 signaling	Activation	Induce	HGC27, SGC7901	[96]
	Apatinib	SREBP-1a/GPX4	Inhibition	Induce	MGC803, MKN45, BGC823, SGC7901, AGS	[97]
	Tanshinone IIA	Stemness	Inhibition	Induce	BGC-823, NCI-H87	[97]
	A2	GPX4	Inhibition	Induce	HGC-27, MGC-803, BGC-823, AGS	[98]
	SIRT6	KEAP1/NRF2 signaling	Activation	Inhibit	NCIeN87, HGC-27	[99]
	ATF3	NRF2/KEAP1/xCT signaling	Inhibition	Induce	MNK45, SGC7901, BGC823	[100]
	miR-522	ALOX15	Inhibition	Inhibit	SGC7901, MGC803 MKN45	[101]
	CTS1	GPX4	Upregulation	Inhibit	AGS, HGC-27, MKN45, SNU-1	[102]
	miR-375	SLC7A11	Inhibition	Induce	SGC-7901, BGC-823	[103]
	Perilipin2	ACSL3, ALOX15, LC3A, PRDM11/ IPO7	Downregulation/ Upregulation	Inhibit	SGC7901, MGC803	[104]
	CPEB1	Twist1	Inhibition	Induce	AGS, SNU-1, Hs-746 T, HGC-27	[105]
	CDO1	GPX4	Inhibition	Induce	AGS, BGC823, MKN45, SGC7901, MGC803	[106]

(*continued on next page*)

Table 2 (*continued*)

Cancer	Small molecules/ Pathways	Target	Function	Effect on ferroptosis	Cell type	Ref
Pancreatic cancer	SLC38A5	GPX4	Inhibition	Induce	PANC-1, Capan-1	[110]
	GOT1	Fe^{2+}	Downregulation	Inhibit	PL45, Capan-1, BxPC-3, MIA PaCa-2, Panc10.05, Panc03.27, PANC-1, Capan-2, HPNE, IMR-90	[111]
	TRIM11	UBE2N/TAX1BP1 signaling	Activation	Inhibit	PANC-1, BXPC-3, SW1990, Capan-2	[112]
	Tomatidine	ATF4	Inhibition	Induce	MiaPaca-2, Panc-1	[113]
	Wogonin	NRF2/GPX4 axis	Inhibition	Induce	PANC-1, AsPC-1	[113]
	Dithiocarbazate-copper complexes	HMOX1 and ACSL4	Upregulation	Induce	ASPC-1	[114]
	DHA	Fe^{2+}	Upregulation	Induce	PANC1, SW1990	[29]
Renal cancer	PDIA4	ATF4/SLC7A11 axis	Activation	Inhibit	786-O, 769P, ACHN, CAKi-1	[115]
	bcc-USINPs	NA	NA	Induce	NA	[116]
	KDM5C	Pentose phosphate pathway	Inhibition	Induce	RCC4, ACHN, 786-O, 769-P, Caki-1, A498	[117]
	SUV39H1	DPP4	Downregulation	Inhibit	786-O, Caki-1, A498, 769-P and ACHN	[117]
	KLF2	GPX4	Downregulation	Induce	HK-2, 786-O, 769-P, ACHN, Caki-1, A498	[118]
	TAZ	EMP1-NOX4	Activation	Induce	RCC4 and 786O	[118]
	FH	GPX4	Downregulation	Inhibit	UOK262	[119]
Hematologic cancer	TXNRD1	NA	NA	Inhibit	K562	[120]
	DMF	IKK complex and Janus kinases	Inhibition	Induce	SU-DHL-6, HBL-1, VFN-D1, DOHH2, U2932, OCI-Ly3, OCI-Ly10	[120]
	Aldh3a2	ROS	Downregulation	Inhibit	HL60, MOLM-14, MONOMAC-6, NB4, NOMO-1, THP1	[121]
	LINC00618	SLC7A11	Downregulation	Induce	HL60, K562, MV4–11, CCRF-CEM	[122]
Glioma	Neutrophil	Lipid peroxides	Increasing	Induce	LN229, U87 MG, and LN18	[123]
Neuroblastoma	MYCN	Fe^{2+}	Increasing	Induce	RPE.1, IMR5, SIMA, SMS-SAN, LAN5, NB12, SK-N-BE(2), SK-N-SH, SK-N-DZ, SK-N-AS, KELLY	[124]

cancer cells [20]. Additionally, the combination of shikonin and cisplatin improved cisplatin resistance in ovarian cancer by promoting ferroptosis [21]. Erastin reversed docetaxel resistance in cancer cells. Promyelocytic leukemia protein (PML) promotes the sensitivity of cancer cells to chemotherapy by inducing ferroptosis [22].

In addition, certain pathways and metabolic enzymes affect ferroptosis in ovarian cancer cells. Liu et al. showed that activation of the NRF2/CBS pathway enhanced transsulfuration activity, which in turn led to the resistance of cancer cells to ferroptosis that had been induced by erastin [23]. Carbone et al. showed that knockout of SCD1 inhibited tumor growth in mice by inducing ferroptosis [24].

3.2. *Hepatocellular carcinoma (HCC)*

A model based on ferroptosis-related genes contributes to predict the immune microenvironment and immunotherapy effectiveness in HCC and identify markers for the prognosis of patients with HCC based on the proportion of immune cell types [25]. Tang et al. constructed a model that contributed to HCC immunotherapy by predicting the proportion of macrophages, neutrophils and memory B cells [26]. Liu et al. found that a high level of ferroptosis-related inhibitors, an increased percentage of immunosuppressive cells (including cancer-associated fibroblast cells), and bone marrow inhibition were associated with poor prognosis in patients with HCC [27]. In conclusion, the model based on ferroptosis-related genes not only helped to predict the prognosis of patients with HCC but was also used to identify patients who were suitable suitability for receiving immunotherapy and targeted therapy.

Additionally, ferroptosis has contributed to the identification of new drugs and targets for the treatment of HCC. Kinase inhibitor donafenib and GSK-J4 synergistically induced ferroptosis of HCC by upregulating HMOX1 expression andinhibitedthegrowthof HCC [28]. Dihydroartemisinin (DHA) promoted the formation of the PEBP1-ALOX 15 complex and induced lipid peroxidation to trigger ferroptosis in HCC cells [29]. Atractylodin upregulated ACSL4 and TFRC expressions and downregulated FTL1 and GPX4 expressions, thereby increasing intracellular ROS levels and promoting ferroptosis in HCC cells [30]. Low-density lipoprotein docosahexaenoic acid nanoparticles induced ferroptosis in HCC cells by increasing lipid hydrogen peroxide levels in tissues and inhibiting GPX4 expression [31]. Therefore, these drugs are expected to provide additional clinical alternatives for HCC therapies. Additionally, ferroptosis is involved in sorafenib resistance of HCC cells. HCC cells were susceptible to ferroptosis induced by erastin and sorafenib by suppression p62/NRF2 pathway, and enhanced the activity of sorafenib [32]. Yao et al. found that decreased LCN2 expression induced ferroptosis in cancer cells and reinforced the antitumor effects of sorafenib [33].

ABCC5 suppressed sorafenib-induced ferroptosis in HCC cells by enhancing the stability of SLC7A11 and increasing the level of GSH in cells [34]. YAP/TAZ could drive the expression of SLC7A11, inhibit ferroptosis and cause resistance of HCC cells to sorafenib [35]. Tiliroside induced ferroptosis by suppressing the activity of TBK1 and sensitized HCC cells to sorafenib [36]. Moreover, SOCS2 promoted ferroptosis by increasing the ubiquitination of SLC7A11 and enhancing the sensitivity of HCC to radiotherapy [37]. Suppression of PGAM1 induced ferroptosis in HCC and improved immunotherapy effect [38]. The mitochondrial protein TSPO accelerated HCC progression by strengthening the NRF2-dependent antioxidant defense system to inhibit ferroptosis [39]. HCAR1/MCT1 inhibited the uptake of lactate and activated adenylate-activated protein kinase to downregulate the expression of SCD1, and promoted ferroptosis in HCC cells, indicating that lactate is a potential target for cancer treatment [40]. By maintaining iron homeostasis, a recombinant FTH protein reduced the levels of ROS in the mitochondria, decreased the accumulation of peroxide, and restored mitochondrial homeostasis, thereby inhibiting ferroptosis in HCC cells [41]. In summary, these molecules deserve further verify their application.

3.3. *Lung cancer*

First, ferroptosis affects the efficacy of immunotherapy in patients with lung cancer. Teng et al. constructed a model based on ferroptosis and immunity-related genes to evaluate the prognosis and treatment of such patients [42]. Zhang et al. showed that the ferroptosis score was associated with the tumor microenvironment (TME) and cancer subtypes [43]. Their study demonstrated that a high ferroptosis score was positively correlated with immunosuppression in patients and that a low ferroptosis score, predicted immune activation. Moreover, patients with low ferroptosis scores responded better to anti-PD1/L1 therapy.

Additionally, small-molecule compounds exert antitumor effects by affecting ferroptosis. Anticancer drug β-elemene had ferroptosis-inducing effect by upregulating lncRNA H19 and improved erlotinib sensitivity of lung cancer [44]. The natural product, manoalide, promoted ferroptosis by inhibiting the NRF2-SLC7A11 axis and improved lung cancer therapy [45]. Bufotalin degraded GPX4 via ubiquitination and induced ferroptosis, thereby inhibiting the proliferation of lung cancer cells [46]. Trace element zinc inhibited the expression of circFOXP1 and increased the levels of iron, MDA and ROS, thus promoting ferroptosis in lung cancer cells [47]. Moreover, the combination of erastin and celastrol suppressed the proliferation of lung cancer cells by promoting mitochondrial lysis and autophagy, increasing ROS generation and inducing ferroptosis [48]. Exosome nanocapsules promoted ferroptosis in lung cancer cells by facilitating the release of interferonγ (IFNγ) from toxic T lymphocytes and activating the immune response [49].

Some molecules can function on system Xc- pathway. SOX2 bound to the SLC7A11 promoter and activated its expression of SLC7A11, inhibiting ferroptosis of lung cancer cells [50]. miR-27a-3p bound the 3′-UTR of SLC7A11 to block SLC7A11 activity and promote ferroptosis [51]. RBMS1 bound to the 3′ and 5′-UTRs of SLC7A11 to regulate the translation of SLC7A11 and inhibited ferroptosis [52]. Furthermore, exogenous Glu supplementation made lung cancer cells vulnerable to ferroptosis by suppressing YAP expression in an ADCY10-dependent manner when the system Xc- pathway was blocked [53]. In addition, the exogenous m6A recognition protein YTHDC2 induced ferroptosis when SLC3A2 activity was inhibited [54].

Moreover, NRF2, FPN, and AKR1C1 influence the ferroptosis of cancer cells. The E3 ubiquitin ligase, MIB1, degraded NRF2 through the lysosomal pathway to induce ferroptosis [55]. USP11 inhibited the degradation of NRF2 through deubiquitination and blocked ferroptosis [56]. Acetaminophen suppressed the transcription of NRF2 to reduce the expression of HMOX1 and enhanced the sensitivity of lung cancer cells to erastin-induced ferroptosis [57]. In addition, GSK3β-TrCP downregulated the expression of NRF2 by activating the AMPK/mTOR pathway to induce ferroptosis [58]. USP35 attenuated ferroptosis by inhibiting FPN degradation in lung cancer [59]. AKR1C1 inhibition induced ferroptosis and inhibited lung cancer cells progression [60].

3.4. *Prostate cancer*

Erastin and RSL3 can significantly reduce the proliferation and metastasis of prostate cancer cells. For example, RSL3 exerted an antitumor effect by interfering with glycolysis, promoting intracellular ROS accumulation and enhancing cell cycle arrest mediated by CDDP [61]. Moreover, iron enhanced the efficacy of antiandrogen therapy in prostate cancer by promoting lipid oxidation and inducing ferroptosis [62].

Ferroptosis is also associated with drug resistance in prostate cancer. A multimodal nanoplatform with ROS amplification has been used to overcome the multidrug resistance in prostate cancer [63]. Ingram et al. established noncancerous cell models to show that ferroptosis correlated with docetaxel resistance in prostate cancer [64]. Erastin can be used as a sensitizer for docetaxel because it inhibits the transcriptional activity of androgen receptors and their truncated mutants in prostate cancer cells [65]. Furthermore, the anthelmintic flubendazole activated ferroptosis in castration-resistant prostate cancer cells by upregulating the expression of p53, inhibiting the transcription of SLC7A11 and reducing the expression of GPX4 [66]. Some traditional Chinese medicines have also been shown to induce ferroptosis induction. Qiling decoction, a Chinese medicinal formula, induced ferroptosis by suppressing FSP1 in castration-resistant prostate cancer [67]. Luteolin promoted ferritinophagy by accelerating TFEB nuclear translocation of TFEB in prostate cancer cells [68].

Small molecules can interfere with ferroptosis in prostate cancer cells. SGK2 promoted prostate cancer metastasis by increasing GPX4 levels to suppress ferroptosis [69]. Testosterone levels higher than the normal concentration induced ferroptosis in prostate cancer cells through ferritinophagy. The interfering peptide, B8R, elevated the expression of p53, enhanced the phosphorylation of p38, promoted the aggregation of iron and ROS, and induced ferroptosis in prostate cancer cells [70]. LncRNA OIP5-AS1 promoted ferroptosis resistance in prostate cancer cells by regulating the miR-128–3p/SLC7A11 signaling

pathway [71]. 2,4-Dienoyl-CoA reductase (DECR) triggered ferroptosis by inducing mitochondrial oxidative stress and lipid peroxidation [72]. Moreover, DECR is a biomarker of castration-resistant prostate cancer [73]. The soluble ATPase VCP inhibited ferroptosis in prostate cancer cells by suppressing mitochondrial activity and reducing GSH consumption [74].

3.5. *Breast cancer*

Ferroptosis is a novel strategy for breast cancer treatment. The oxygen self-generating nanoreactor activated ferroptosis via GPX4 consumption and enhanced immunotherapy in breast cancer [75]. Metal-polyphenol-network coated Prussian blue nanoparticles and azobenzene combretastatin A4 nanospheres inhibited tumor growth by inducing ferroptosis [76]. A novel nanoparticle drug delivery system driven by heparanase blocked the metastasis of breast cancer cells by increasing intracellular ROS generation [77].

Ferroptosis can also be used to develop new applications of currently used drugs. Metformin and simvastatin downregulated the levels of SLC7A11 and GPX4, respectively, and induced ferroptosis to inhibit tumor growth [78]. Natural compounds exert antitumor effects by inducing ferroptosis. Isoliquiritin suppressed NF-κB signal pathway to regulate ferroptosis and alleviated doxorubicin resistance in breast cancer [79]. Curcumin, DMOCPTL and glycyrrhetinic acid triggered ferroptosis by upregulating redox-related genes, binding to GPX4, and activating NADPH oxidase and INOS [80].

Some kinases affect breast cancer development and treatment by interfering with ferroptosis. The tyrosine kinase protein TYRO3 led to resistance in breast cancer cells to immunotherapy by suppressing ferroptosis and reducing the ratio of M1/M2 macrophages [81]. DDR2 upregulation increased the sensitivity of breast cancer cells to ferroptosis by activating the Hippo signaling pathway [82]. HLF caused ferroptosis resistance through the transcriptional activation of GGT1 [83].

3.6. *Colorectal cancer*

Ferroptosis provides an additional treatment avenue in the treatment of colorectal cancer. Osthole induced ferroptosis by inhibiting the AMPK/Akt signaling pathway in cancer [84]. Talaroconvolutin A and 2-imino-6–methoxy-2H-chromene-3-carbothioamide downregulated SLC7A11 levels to induce ferroptosis in colorectal cancer cells [85]. Xia et al. showed that talaroconvolutin A was a novel ferroptosis inducer that exerted greater effects than erastin. The combination of DHA and pyropheophorbide iron induced ferroptosis and increased the sensitivity of colorectal cancer to anti-PD-L1 immunotherapy [86]. Elesclomol induced copper-dependent ferroptosis in colorectal cancer cells by degrading the copper transporter ATP7A [87]. Ironoxide hydroxide nanospheres and zinc oxide nanospheres suppressed the proliferation of cancer cells by triggering ferroptosis [88]. Furthermore, cetuximab enhanced RSL3-induced ferroptosis by inhibiting the p38/NRF2/HMOX1 signaling pathway [89]. Both β-elemene and vitamin C also elevated the sensitivity of cancer cells to cetuximab by inducing ferroptosis [90].

Additionally, CYP1B1 promoted the resistance of PD-1 inhibitor in colorectal cancer by degrading ACSL4, thereby suppressing ferroptosis [91]. OTUD1 and HIF-2α increased intracellular ROS production, promoting ferroptosis [92]. Lipocalin 2 promoted tumor progression by activating GPX4 and reducing intracellular iron [93].

3.7. *Gastric cancer*

Ferroptosis is important for the treatment of gastric cancer. A model based on ferroptosis-related lncRNAs reflects the biological process, immune microenvironment, genomic stability, and drug response involved in ferroptosis, and has been used with drugs, including methotrexate, paclitaxel, and gemcitabine, and immunotherapeutics in patients with gastric cancer [94]. Certain drugs and compounds mediate effects via the ferroptosis of gastric cancer cells. Polyphyllin I suppressed gastric cancer cell growth by downregulation of NRF2 and FTH1 to induce ferroptosis [95]. Levobupivacaine induced ferroptosis by upregulating miR-489–3p level and inhibiting that of SLC7A11 [96]. Apatinib and tanshinone IIA triggered ferroptosis by decreasing the level of GSH and suppressing lipid peroxidation [97]. Moreover, oridonin A2 and an *Andrographis paniculata* extract induced ferroptosis and exerted antitumor effects [98].

Ferroptosis also contributes to the development of drug resistance in gastric cancer. The inhibition of sirtuin 6 activity induced ferroptosis, attenuating sorafenib effects on gastric cancer by downregulating GPX4 activity and blocking KEAP1/NRF2 pathway [99]. ATF3 induced ferroptosis and attenuated CDDP resistance by inhibiting the NRF2/KEAP1/xCT signaling pathway in cancer [100]. miR-522, secreted by tumor-associated fibroblasts, activated the RNPA1/USP7 signaling pathway, inhibited ALOX15 expression, reduced ROS accumulation, and induced resistance to chemotherapy in gastric cancer cells [101].

In addition, several molecules can also disrupt ferroptosis. CTS1 improved the stability of GPX4 by suppressing ferroptosis and promoted gastric cancer metastasis [102]. Ni et al. showed that miR-375 bound directly to SLC7A11 and inhibited SLC7A11 activity, which led to ferroptosis in gastric cancer cells [103]. Perilipin2 and exosomal lncFERO suppressed ferroptosis by downregulating ACSL3, ALOX15 and PRDM11 and upregulating SCD1 [104]. CPEB1 downregulated TWIST1 and activated the ATF4/CHAC1 pathway to trigger ferroptosis in cancer [105]. Furthermore, inhibition of CDO1 expression blocked cancer cells to induce ferroptosis [106].

3.8. *Pancreatic cancer*

A study showed that GPX4 deletion promoted the occurrence of pancreatic cancer in mice, and this action was driven by $KRAS^{G12D}$ and reversed by liproxstatin-1 [107]. Dai et al. demonstrated that ferroptotic cells secreted the $KRAS^{G12D}$ protein and facilitated macrophage differentiation into the M2 subtype [107]. This study suggested that ferroptosis contributed to cancer cell development by inhibiting immune cell responses. These results indicated that ferroptosis contributed to the progression of pancreatic cancer. However,

the absence of SLC7A11 or Cys suppressed the development of pancreatic cancer, implying that ferroptosis negatively affects cancer cells [108]. Moreover, Bhutia et al. showed that mutant TP53 might be a checkpoint for ferroptosis-mediated tumor formation and suppression [109]. Therefore, elucidating the function of TP53 in ferroptosis is essential for pancreatic cancer treatment.

In addition, SLC38A5 could be used as a sensitizing target in pancreatic cancer by the regulation of ferroptosis [110]. GOT1 and NUPR1 knockdown contributed to ferroptosis in pancreatic cancer cells [111]. Shang et al. found that TRIM11 promoted the resistance of pancreatic cancer cells to gemcitabine by regulating the UBE2N/TAX1BP1 signaling pathway and inhibiting ferritinophagy [112].

Some compounds exert their antitumor effects by affecting ferroptosis in pancreatic cancer cells. Tomatidine and Wogonin exert anticancer effects by inducing ferroptosis in pancreatic cancer [113]. Dithiocarbazate–copper complexes induced ferroptosis in pancreatic cancer [114]. DHA increased the sensitivity of pancreatic cancer cells to CDDP by increasing free iron levels and triggering ferroptosis [29].

3.9. *Renal cancer*

PDIA4 confers resistance to ferroptosis through activating ATF4/SLC7A11 in renal cancer cells [115]. Renal clearable ultrasmall single-crystal Fe nanoparticles constitute a new delivery system for immunotherapy in renal cancer by inducing ferroptosis [116]. Loss of the protein demethylase KDM5C increased the levels of G6PD, NADPH, and GSH and inhibited ferroptosis, while deletion of the histone methylase SUV39H1 led to ferroptosis [117]. Ferroptosis induced by the transcription factors KLF2 and Hippo receptor TAZ inhibited the expression of GPX4 and upregulated NOX4, respectively [118]. In addition, fumarate hydratase promoted C93 modification of GPX4 and suppressed the activity of GPX4, which induced ferroptosis in renal cancer cells [119].

3.10. *Hematologic cancer*

TXNRD1 and dimethyl fumarate induced ferroptosis in chronic myelogenous leukemia and diffuse large B-cell lymphoma cells, respectively [120]. Aldehyde dehydrogenase 3A2 oxidized aliphatic aldehydes to inhibit oxidative damage and blocked ferroptosis in acute myeloid leukemia cells [121]. LINC00618 decreased LSH, attenuated the transcription of SLC7A11, and inhibited ferroptosis in leukemia cells [122].

3.11. *Others*

Neutrophils transferred myeloperoxidase into tumor cells, which led to the accumulation of iron-dependent lipid peroxides, promoting ferroptosis of glioma cells [123]. The *MYCN* oncogene increased the sensitivity of neuroblastoma cells to iron and inhibited the GSHaxis, and then inducing ferroptosis [124].

In addition, erastin inhibited melanoma and cervical cancer cells proliferation by blocking the system Xc- pathway. The erastin homologs imidazole ketone erastin and piperazine erastin inhibited the proliferation of diffuse large B-cell lymphoma and fibrosarcoma cells, respectively [125].

4. The role of ferroptosis on cancer characteristics

Ferroptosis is involved in cancer progression by influencing the epithelial-mesenchymal transition (EMT), invasion and migration. Ferroptosis has been identified as a regulator of EMT. Ferroptosis inhibits EMT and cancer development. Studies have shown that ROS accumulation and ferritinophagy prevent EMT in cancer cells by upregulating p53 expression and downregulating AKT/mTOR pathway, whereas the ferroptosis inhibitor, ferrostatin-1, reverses this phenomenon [126]. In gastric cancer cells, activation of the Keap1/Nrf2/HO-1 pathway and the occurrence of ferritinophagy contributed to EMT suppression by inducing ferroptosis [127]. In addition, the EMT increases the sensitivity of cancer cells to ferroptosis. TGF-β1 can induce EMT and promote cancer cells more vulnerable to ferroptosis by decreasing SLC7A11 level and GSH accumulation, and increasing MDA and ROS content. At the beginning of EMT, discoidin domain receptor tyrosine kinase 2 upregulation can activate YAP/TAZ signaling pathway, and resulting in the vulnerability to ferroptosis in breast cancer [82]. These results indicate an interaction between ferroptosis and EMT, which could influence each other.

Additionally, ferroptosis can suppress cancer cell invasion and migration by affecting EMT. Moreover, changes in lipid metabolism during ferroptosis may affect these two cancer characteristics. Higher GPX4 expression is positively associated with renal cancer cell invasion and migration through increasing GSH content and reducing ROS accumulation [118]. GPX4 deletion decreased the migration capability of cancer cells. SLC7A11 suppresses ferroptosis by promoting GPX4 expression and enhancing ROS content and then promotes colorectal cancer cell invasion and migration. However, ferroptosis can enhance cancer cell invasion. ACSL4 is a key molecule involved in the induction of ferroptosis and promotes the invasive phenotype of cancer cells. In certain cancer cells, the production of lipid peroxides such as PUFA-CoA and PUFA-phospholipids during ferroptosis enhances cell invasion and migration. This evidence indicates that ferroptosis has dual effects on cancer invasion and migration, which might depend on the cancer type and require further exploration.

5. Relationship between ferroptosis and cancer treatment

Recent studies have shown that different therapeutic approaches, including immunotherapy, chemotherapy and radiotherapy, can induce ferroptosis. As mentioned above, activated CD8+ *T* cells not only induce ferroptosis on their own but can also release IFNγ to increase the sensitivity of cancer cells to ferroptosis. Immunotherapy can activate $CD8^+$ *T* cells and induce ferroptosis in cancer cells, potentiating the antitumor effects. Moreover, a study has shown that

immunotherapy can stimulate CD8$^+$ *T* cells to release IFNγ and induce ferroptosis [128]. Therefore, the combination of ferroptosis induction and immunotherapy could generate a synergistic anticancer effect.

Many studies have shown that the induction of ferroptosis can overcome chemotherapy resistance in cancer cells. Recent studies have shown that certain chemotherapeutic drugs can induce ferroptosis. Cisplatin can induce ferroptosis via GSH consumption and GPX4 inactivation in several types of cancers. Moreover, the combination of ferroptosis inducers such as erastin, with cisplatin can overcome the resistance of cancer cells to cisplatin and improve its efficacy. In addition, a low dose of paclitaxel induces ferroptosis by regulating glutaminolysis and suppressing cancer cell growth.

Radiotherapy can induce ferroptosis directly. The combination of radiotherapy with a ferroptosis inducer causes a synergistic anticancer effect that can be observed in terms of ferroptosis-related gene expression, cancer cell death, lipid peroxidation and lipidomic changes. For example, radiation upregulated the expression of ACSL4 to increase lipid synthesis and oxidative damage, thereby inducing ferroptosis in cancer cells. In addition, radiotherapy decreased SLC7A11 levels by activating ATM and inducing ferroptosis. Mechanistically, cytoplasmic rather than nuclear radiation synergizes with ferroptosis. This phenomenon illustrates that radiotherapy mainly participates in the process of lipid peroxidation and GSH depletion in ferroptosis rather than its DNA-damaging function.

Furthermore, the ferroptosis-inducing effects of different treatments can generate synergistic effects. A previous study revealed that immunotherapy and radiotherapy could work together to promote ferroptosis through SLC7A11 downregulation and ATM activation, respectively [129]. The combination of immunotherapy and radiotherapy synergistically inhibits the expression of SLC7A11 and blocks the system Xc- pathway. This effect leads to the reducing of Cys_2 uptake, and then suppresses the growth of tumor by enhancing lipid peroxidation. As a DNA destroyer, cisplatin combined with radiotherapy can display a synergistic effect through DNA damage. A study has demonstrated that cisplatin can rapidly enhance the level of PD-L1 in a dose-dependent manner by activating PI3K/AKT pathway in non-small cell lung cancer cells, and the combination of cisplatin and anti-PD-L1 antibodies can obviously decrease tumor growth [130]. In addition, cisplatin promotes the consumption of GSH and results in toxic lipid peroxidation accumulation. Thus, expect for DNA damage and PD-L1 upregulation, lipid peroxidation is another potential mechanism for the combination of chemotherapy and radiotherapy or immunotherapy in cancer. These findings provide a solid theoretical basis for combining different therapies. In summary, this study demonstrates that ferroptosis-based therapies can combined with other treatments to achieve better clinical outcomes.

6. Effects of ferroptosis in TME

TME is a complex and diverse multicellular environment that plays an essential role in the growth, progression and treatment of cancer cells. Cancer cells release signal molecules during ferroptosis that can influence the TME. However, the exact functions of ferroptosis in TME are unclear. Further understanding of the relationship between ferroptosis and the TME will contribute to cancer therapy.

As we all known, ferroptotic cancer cells have enhanced immunogenicity. Early ferroptotic cancer cells can stimulate phenotypic maturation of dendritic cells (DCs) and have an effect similar to that of a vaccine. These cells release a series of immunostimulatory signals and mediators, such as damage-associated molecular pattern signals, which allow the immune cells to identify them accurately. For example, 1-steaoryl-2–15- hydroperoxyeicosaetetranoicacid-sn–glycero-3-phosphatidylethanolamine is a critical mediator of phagocytosis by macrophages [131]. Moreover, enhanced immunogenicity contributes to ferroptosis of cancer cells, causing tumor-specific immune responses and improving the therapeutic effect of immunotherapy.

Ferroptotic cancer cells also release immunosuppressive signals although they have immunostimulatory effects. Based on the lipid peroxidation features of ferroptosis, ferroptotic cancer cells release many oxidized phospholipids, oxidized eicosanoids, oxidatively truncated species and their derivatives. These signals block antigen cross-presentation and DC maturation. Moreover, ferroptotic cancer cells release 15-hydroperoxyeicosaetetranoic acid into the TME and high levels of 15-hydroperoxyeicosaetetranoic acid can induce ferroptosis in immune cells.

In addition to these signals, ferroptotic cancer cells inhibit antitumor immune responses by regulating other mechanisms. Ferroptosis inducer causes cancer cells to release 8–hydroxy-2′-deoxyguanosine and actives the DNA sensor pathway of tumor-associated macrophages (TAMs) [107]. This phenomenon can lead to the infiltration and M2 polarization of TAMs and accelerate the occurrence of pancreatic cancer [107]. Furthermore, TAMs convert to the M2 phenotype by absorbing the KRAS protein, thus facilitating the development of pancreatic cancer cells [108]. In addition, ferroptotic cancer cells are related to the release of prostaglandin E2, which leads to the inhibition of the functions of cytotoxic T cells, natural killer cells and DCs.

In addition, immune cells regulate ferroptosis in cancer cells. For example, macrophages can release the TGF-β that suppresses the transcription of system Xc- through SMAD signaling followed by ferroptosis. In addition, activated CD8$^+$ *T* cells contribute to ferroptosis induction by promoting lipid peroxidation, thus enhancing their antitumor functions. Moreover, activated CD8$^+$ *T* cells could release IFNγ that suppressed system Xc- expression through activating the JAK/STAT1 pathway and enhanced the sensitivity of cancer cells to ferroptosis [131]. These results suggest that CD8$^+$ *T* cell-mediated ferroptosis may be useful for strengthening cancer immunotherapy. However, in the context of IFNγ stimulating, cancer cells could release immunosuppressive signals to inhibit T cells survival and present a feedback-protective function. Thus, these findings indicated that the relationship between ferroptosis and TME was complicated and it should be careful for inducing ferroptosis by IFNγ.

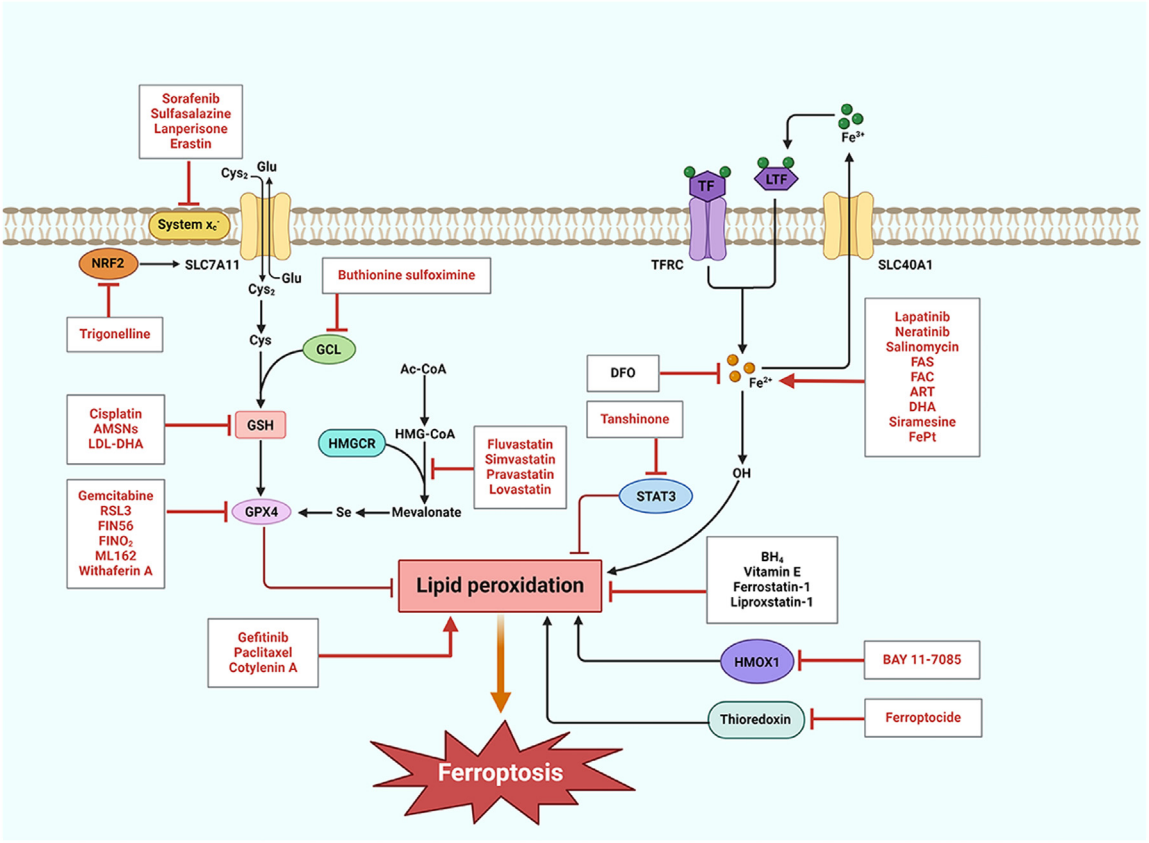

Fig. 2 – Description of ferroptosis inducers and inhibitors. Colouring: Agonists are shown in red; inhibitors are shown in black. (HMGCR, 3–hydroxy-3-methylglutaryl-CoA reductase; LTF, lactotransferrine; STAT3, signal transducer and activator of transcription 3; BH_4, tetrahydrobiopterin).

7. The role played by ferroptosis in drug discovery

Recently, several small molecule compounds targeting ferroptosis have become important in drug research and development. The targets of these compounds included GSH, system Xc-, GPX4, iron and lipid peroxidation (Fig. 2 and Table 3).

7.1. *GSH*

GSH plays a vital role in the antioxidant system. GSH removes peroxides and ROS from cells and prevents ferroptosis. Several compounds affect ferroptosis by targeting GSH. The antitumor drug cisplatin induces ferroptosis by promoting GSH depletion in lung and colorectal cancers [132]. Some nanoparticles, including arginine-rich manganese silicate nanobubbles (AMSNs), FaPEG-MnMSN, LDL-DHA and MnO_2@HMCu2-xS, triggered ferroptosis by their effect on the metabolism of GSH in liver and breast cancers [133].

7.2. *System Xc-*

System Xc- is the main pathway for GSH synthesis. SLC7A11 is highly expressed in various cancer cells. Therefore, the system Xc- pathway is a good target for cancer therapy. The ferroptosis inducers erastin and sorafenib, act on system Xc- to exert antitumor effects. For example, erastin inhibited the proliferation of melanoma cells and cervical cancer cells [125]. The erastin homologs imidazole ketone erastin and piperazine erastin suppress the proliferation of diffuse large B-cell lymphoma and fibrosarcoma cells, respectively [125]. In addition, in lung and pancreatic cancers, sorafenib inhibits cell proliferation by inhibiting the system Xc- pathway [32]. Furthermore, Dixon et al. showed that sulfasalazine induced ferroptosis in Calu-1 lung cancer cells and U251 glioma cells by inhibiting the system Xc- pathway, thereby inhibiting tumor growth [134]. Lanperisone inhibited the growth of KRAS-mutant tumors through triggering ferroptosis [135]. Some novel nanomedicines, including SRF@Fe^{III}TA nanoparticles and DS@MA-LS, exerted antitumor effects by targeting system Xc-[133].

7.3. *GPX4*

GPX4 converts GSH to oxidized GSH disulfide ether, leading to the reduction of lipid peroxide. Therefore, the inhibition of GPX4 activity contributes to ferroptosis. The ferroptosis inducers, RSL3, altretamine, FIN56, $FINO_2$ and ML162, inhibit GPX4 and induce ferroptosis in cancer cells [125]. In addition, withaferin A exerted antitumor effects by inhibiting the

Table 3 – The roles of ferroptosis-related agents in cancer.

Target	Agents	Effect on ferroptosis	Impact on cancer	Function	Cancer	Cell type	Ref
GSH	Cisplatin	Induce	Death	Induce	Lung cancer, colorectal cancer	A549, HCT116	[132]
	AMSNs	Induce	Growth	Inhibit	Liver cancer	Huh7	[133]
	FaPEG-MnMSN	Induce	Growth	Inhibit	Liver cancer	HepG2	[133]
	LDL-DHA	Induce	Growth	Inhibit	Liver cancer	PLC/PRF/5, HepG2	[133]
	MnO_2@$HMCu_2$-xS	Induce	Growth	Inhibit	Breast cancer	MCF-7	[133]
System Xc-	Erastin	Induce	Proliferation	Inhibit	Melanoma, cervical cancer, fibrosarcoma, lung cancer, rhabdomyosarcoma, osteosarcoma, prostate cancer	A375, Hela, HT1080, Calu-1, A-673, U2OS, DU-145	[125]
	Imidazole ketone erastin	Induce	Proliferation	Inhibit	Diffuse large B-cell lymphoma	SUDHL-5, SUDHL-6, SUDHL-16	[125]
	Piperazine erastin	Induce	Proliferation	Inhibit	Fibrosarcoma	HT1080	[125]
	Sorafenib	Induce	Proliferation	Inhibit	Fibrosarcoma,lung cancer,prostate cancer, liver cancer, pancreatic cancer	HT1080, Calu-1, DU-145, Huh7	[32]
	Sulfasalazine	Induce	Growth	Inhibit	Fibrosarcoma, lung cancer, glioblastoma, prostate cancer	HT1080, Calu-1, U251, DU-145	[134]
	Lanperisone	Induce	Growth	Inhibit	Kras-mutant tumor	NA	[135]
	SRF@Fe^{III}TA nanoparticles	Induce	Proliferation	Inhibit	Fibrosarcoma, breast cancer	HT-1080, 4T1	[133]
	DS@MA-LS	Induce	Growth	Inhibit	Breast cancer	4T1	[133]
GPX4	RSL3	Induce	Death	Induce	Fibrosarcoma,lung cancer, colon cancer, pancreatic cancer, CML	HT1080, A549, Calu-1, HCT116, MIA PaCa-2, KBM7	[125]
	FIN56	Induce	Death	Induce	Bladder cancer	J82, 253 J, T24, RT-112	[125]
	$FINO_2$	Induce	Death	Induce	Fibrosarcoma	HT1080	[125]
	ML162	Induce	Death	Induce	CML	KBM7	[125]
	Withaferin A	Induce	Growth, relapse rateproliferation, invasion, vasculogenic mimicry formation	Inhibit	Neuroblastoma, liver cancer	IMR-32, SK-N-SH, HepG2, SNU449	[3]
	Statins (fluvastatin, simvastatin, pravastatin, lovastatin)	Induce	Proliferation, growth, differentiation	Inhibit	Liver cancer, fibrosarcoma, breast cancer, AML, myeloma	HCC4006, HT-1080, MCF-7	[78]
	Gemcitabine	Induce	Death	Induce	Pancreatic cancer	PANC1, CFPAC1	[136]
	RSL3@COF-Fc	Induce	Death	Induce	Fibrosarcoma	HT-1080	[137]
	RSL3@mPEG-PLys-AA	Induce	Growth	Inhibit	Ovarian cancer	NCI/ADR-RES	[137]
	SRF@Hb-Ce6	Induce	Growth	Inhibit	Breast cancer, liver cancer, lung cancer	4T1, HepG2, A549	[137]
	BNP@R	Induce	Metastasis	Inhibit	Breast cancer	4T1	[137]
	Erastin@FA-exo	Induce	Proliferation, migration	Inhibit	Breast cancer	MDA-MB-231	[137]
	Ascorbate plus nanocarrier loading Fe^{3+} and RSL3	Induce	Growth	Inhibit	Breast cancer	4T1	[137]

(*continued on next page*)

activity of GPX4 and inducing ferroptosis in neuroblastoma cells [3]. Furthermore, Yao et al. suggested that statins inhibited the proliferation of HCC4006 (HCCcells) and HT-1080 (fibrosarcoma cells)by reducing the production of isopentenyl pyrophosphate in the mevalonic acid pathway, inhibiting the synthesis of GPX4 and coenzyme Q10, and inducing ferroptosis [78]. In addition, statins increased the therapeutic effect of idarubicin and cytarabine in patients with acute myeloid leukemia patients [3]. The targeted drug, gemcitabine, inactivates GPX4 and triggers ferroptosis in pancreatic cancer [136]. In addition, some novel drug including RSL3@COF-Fc, RSL3@mPEG-PLys-AA, SRF@Hb-Ce6, BNP@R, Erastin@FA-exo,

Table 3 (*continued*)

Target	Agents	Effect on ferroptosis	Impact on cancer	Function	Cancer	Cell type	Ref
Iron	FAS	Induce	Growth	Inhibit	Fibrosarcoma, neuroblastoma	HT-1080, IMR-32	[138]
	FAC	Induce	Death	Induce	Fibrosarcoma	HT-1080	[138]
	ART	Induce	Death	Induce	Pancreatic cancer, liver cancer	Panc-1, HepG2	[139]
	DHA	Induce	Death	Induce	Lung cancer, glioblastoma, colorectal cancer, breast cancer	NCI-H292, HCT116, HT29, SW480, MDA-MB-453, MCF7	[139]
	Salinomycin	Induce	Progression	Inhibit	Breast cancer	MCF-7	[140]
	Siramesine + lapatinib	Induce	Death	Induce	Breast cancer	MDA-MB-231, SKBR3, MCF-7, ZR-75–1	[141]
	Neratinib	Induce	Proliferation	Inhibit	AML	HL-60	[141]
	Low-temperature plasma	Induce	Proliferation	Inhibit	Mesothelioma	SM2, EM2	[142]
	Zero-valent iron nanoparticles	Induce	Death	Induce	OSCC	OC2, KOSC-3, OEC-M1	[137]
	FPEF nanoparticles	Induce	Progression	Inhibit	Breast cancer	MCF-7	[137]
	FeGd HN@Pt@LF/RGD2 nanoparticles	Induce	Growth	Inhibit	Glioblastoma	U251	[137]
	Pa-M/Ti-NC nanoparticles	Induce	Growth	Inhibit	Melanoma	B16F10	[129]
	Ferumoxytol	Induce	Growth	Inhibit	Breast cancer, fibrosarcoma	MDA-MB-468, HT1080	[137]
	FePt@MnO@DSPE	Induce	Growth	Inhibit	Cervical cancer, liver cancer	HeLa, HepG2	[137]
	UPDA-PEG@Fe2+/3+	Induce	Growth	Inhibit	Breast cancer	4T1	[137]
	TA-Fe/ART@ZIF	Induce	Growth	Inhibit	Breast cancer	MDA-MB-231, L929	[137]
	UCNP@LP(Azo-CA4)	Induce	Growth	Inhibit	Breast cancer	MDA-MB-231	[137]
	FePt	Induce	Growth	Inhibit	Breast cancer	4T1	[129]
	DFO	Inhibit	Death	Inhibit	Fibrosarcoma	HT-1080	[125]
Lipid peroxidation	Ferrostatin-1	Inhibit	Death	Inhibit	Fibrosarcoma, liver cancer	HT-1080, Huh7	[125]
	Liproxstatin-1	Inhibit	Death	Inhibit	Osteosarcoma	MG63, HOS	[125]
	Vitamin E	Inhibit	Death	Inhibit	Osteosarcoma Fibrosarcoma	MG63, HOS, HT-1080	[125]
	BH_4	Inhibit	Death	Inhibit	Colorectal cancer	HCT116	[125]
	Gefitinib	Induce	Death	Induce	Lung cancer	A549, H1299	[143]
	Paclitaxel	Induce	Growth	Inhibit	Colorectal cancer	HCT116	[143]
	Cotylenin A	Induce	Death	Induce	Pancreatic cancer	MIAPaCa-2, PANC-1, CFPAC-1	[144]
GCL	Buthionine sulfoximine	Induce	Death	Induce	Melanoma, neuroblastoma	SK-MEL 28, SK-N-BE-2C	[3]
STAT3	Tanshinone	Inhibit	Death	Inhibit	Pancreatic cancer	PANC1, CFPAC1	[145]
NRF2	Trigonelline	Induce	Death	Induce	HNC	AMC–HN2–11	[125]
HMOX1	BAY 11–7085	Induce	Proliferation	Inhibit	Breast cancer	MDA-MB-231	[125]
Thioredoxin	Ferroptocide	Induce	Proliferation	Inhibit	Ovarian cancer, lung cancer	ES-2, A549	[125]

Abbreviations: CML, chronic myeloid leukemia; AML, acute myeloid leukaemia.

and ascorbate plus nanocarrier loading Fe^{3+} and RSL3 induced ferroptosis by targeting GPX4, and thus exert an antitumor effect [137].

7.4. *Iron*

Ferrous ammonium sulfate (FAS) and ferric ammonium citrate (FAC) inhibit the proliferation of HT-1080 fibrosarcoma and IMR-32 neuroblastoma cells by increasing iron levels [138]. Moreover, some drugs indirectly increase ferrous iron content. The natural compounds artesunate(ART) and DHA induce lysosomal degradation of ferritin to increase cellular free iron [139]. Salinomycin inhibits the proliferation of MCF-7 cells by blocking iron transfer and degrading ferritin [140]. The combination of siramesine, lapatinib, and neratinib increases the level of ferrous ions and induces ferroptosis in breast cancer by upregulating the expression of TRFC and downregulating the expression of FPN [141]. In addition, low-temperature plasma reduced Fe^{3+} to Fe^{2+}, which promoted lipid peroxidation and inhibited mesothelial cell tumor growth [142]. In addition, numbers of nanoparticles including zero-valent iron nanoparticles, FPEF

nanoparticles, FeGd HN@Pt@LF/RGD2 nanoparticles, Pa-M/Ti-NC nanoparticles, ferumoxytol, FePt@MnO@DSPE, UPDA-PEG@$Fe^{2+/3+}$, TA-Fe/ART@ZIF, UCNP@LP(Azo-CA4) and FePt could inhibit the growth of tumor by inducing ferroptosis [129,137]. Furthermore, the iron chelator, deferoxamine (DFO), suppresses ferrous ion content in cancer cells and maintains the survival of cells [125].

7.5. *Lipid peroxidation*

Lipid peroxidation is a key process in ferroptosis. Compounds that target lipid peroxidation have attracted considerable attention in recent years. Ferrostatin-1 and liproxstatin-1 suppress lipid peroxidation and have been identified as ferroptosis inhibitors. In cancer cells, ferrostatin-1 and liproxstatin-1 block ferroptosis-induced cell death [125]. Natural antioxidants, vitamins E and BH_4, can facilitate the survival of cancer cells by inhibiting ferroptosis [125]. However, antitumor drugs gefitinib and paclitaxel promote lipid peroxidation to induce ferroptosis [143]. Moreover, the synthetic chemical substance cotylenin A exerts antitumor effects by inducing lipid peroxidation to trigger ferroptosis [144].

7.6. *Others*

Buthionine sulfoximine inhibits GSH levels and induces lipid peroxidation by suppressing GluCys ligase (GCL), triggering ferroptosis [3]. The natural compound cryptotanshinone inhibits ferroptosis in pancreatic cancer by suppressing STAT3[145]. Trigonelline enhances the sensitivity ofhead and neck cancer (HNC) cells to ferroptosis by inhibiting NRF2 activity [125]. BAY 11–7085, an inhibitor of $I\kappa B\alpha$, can upregulate the expression of HMOX1 and iron accumulation, which suppresses breast cancer cell proliferation [125]. Ferroptocides inhibit the proliferation of ES-2 ovarian and A549 lung cancer cells by disrupting the antioxidant activity of thioredoxin and positively modulating the immune system [125].

As discussed above, many drugs (salinomycin, ART, sorafenib), compounds (ferrostatin-1, liproxstatin-1, cryptotanshinone) and nanoparticles (Pa-M/Ti-NC, UPDA-PEG@$Fe^{2+/3+}$, TA-Fe/ART@ZIF) are discovered to present proferroptotic or antiferroptotic activity in preclinical studies. Although ferroptosis plays an important role in drug exploration, some challenges are waiting to be solved. At present, a lot of chemical reagents acting on ferroptosis have been discovered and confirmed in preclinical models and clinical tissues, however, the underlying specific mechanisms are unclear. Different species and tissues have different sensitivity to ferroptosis inducers. In addition, some old drugs, such as statins, have been clinically used for many years and are now have beendemonstrated to have proferroptotic properties in preclinical models. However, whether these drugs can be used for cancer treatment remains unknown.Moreover, studies have shown that some ferroptosis inducers can lead to serious side effects such as bone marrow suppression [3]. Decreasing the toxicity of components is a clinical challenge. To address the above problems, we propose some prospective solutions. Firstly, using multiple high technologies and omics analyses to clarify the specific mechanisms of drugs is essential. Searching for biomarkers to reflect the sensitivity of patients to ferroptosis inducers isbeneficial for clinical treatment. And these biological indicators can also be used for patient selection and patient prognosis prediction. Furthermore, the clinical safety and efficacy of drugs should be evaluated in randomized controlled trials involving large patient populations. In addition, structure reconstruction is needed to achieve the purpose of increasing efficiency and decreasing toxicity of compounds and then improving the side effects and off-target effects of drugs.

8. The prospect of targeting ferroptosis

In vitro and *in vivo* experiments have shown that targeting ferroptosis can contribute to cancer treatment. Cancer cells resistant to conventional therapies are prone to ferroptosis. Sorafenib and altretamine can also be used as inducers of ferroptosis, which raises the expectations of ferroptosis as a potential target for cancer treatment. However, before ferroptosis can be targeted to cancer cells, several problems must be solved (Fig. 3).

PCD induction depends on effector molecules in addition to obvious initial and intermediate signals. For example, the effector molecules of apoptosis and pyroptosis are caspase- and pyroptosis-related proteins (such as GSDMA), respectively. Ferroptosis is a complex process involving the metabolism of iron, lipids, amino acids and redox [1]. At present, many genes have been discovered to be the potential effector molecules of ferroptosis and are called ferroptosis-related genes. LIP is a key factor for ferroptosis induction. The expression of TFRC can influence LIP by controlling iron transport and then TFRC can act as an indicator of ferroptosis occurrence. Ferroptosis-related gene NCOA4-mediated ferritinophagy can regulate the content of iron. New technology of fluorescence resonance energy transfer iron probe 1 can also be used to detect the variation of LIP in cells through ratiometric fluorescence imaging. In addition, lipid peroxidation is the key step in ferroptosis.Inhibiting GPX4 and SLC7A11 can destroy the antioxidant system. Upregulation of ACSL4 and LPCAT3 expression contributes to the production of lipid peroxides. These molecules can be used as the effectors of lipid peroxidation. Moreover, using modern technologies such as fluorescent dyes, LC-MS/MS and antibody 1F83 can detect lipid peroxidation directly [1]. However, whether cytotoxicity is mediated by the products generated or by downstream signaling molecules activated during lipid peroxidation requires further clarification. Furthermore, an increase in the content of intracellular free iron is a characteristic of ferroptosis. Under physiological conditions, the maintenance of iron levels within a certain threshold range is essential for cell proliferation and signal transduction. When the iron levels exceed this threshold, oxidative damage and ferroptosis are triggered. However, the iron concentration threshold required to induce ferroptosis remains unclear. In addition, whether specific checkpoints regulatethe iron threshold during ferroptosis remains to be investigated.

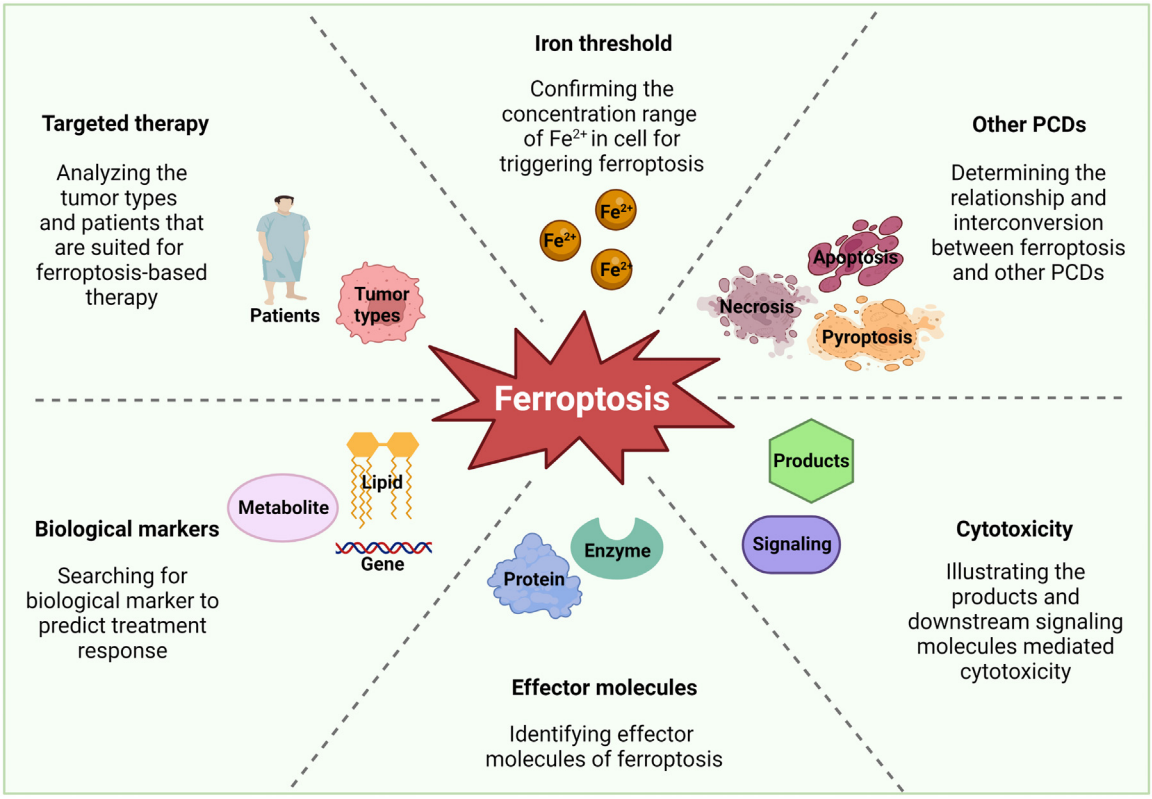

Fig. 3 – Prospect of targeting ferroptosis. Many unsolved mysteries like iron threshold triggering ferroptosis, the relationship between ferroptosis and other PCDs, and the production of cytotoxicity and effector molecules of ferroptosis. In the process of ferroptosis-based therapy, we need to identify the tumor types and patients that are suitable for the treatment. Moreover, finding the biomarkers for predicting treatment response is also a problem that needs to be solved in the future.

Studies have shown that each type of PCD, including ferroptosis, exhibits unique characteristics. However, certain features of ferroptosis are not unique. For example, knocking down GPX4 in mice induces an oxidative stress-triggered signaling cascade that promotes cell death but does not induce ferroptosis. A study shown that knockout of GPX4 can activate caspase11 expression and promote GSDMD cleavage, which indicates that GPX4 is a negative regulator for pyroptosis [146]. In addition, ROS can contribute to RIPK1 autophosphorylation and RIPK3 recruitment and then result in the occurrence of necroptosis. Upregulation of GPX4 can reduce ROS content, thus inhibiting ferroptosis and necroptosis. Furthermore, knockdown of ACSL4 can induce necroptosis, but suppress ferroptosis through *in vivo* and *in vitro* experiments [6]. These studies indicate that there is an interconnectivity among ferroptosis, pyroptosis and necroptosis. SLC7A11 deficiency does not induce ferroptosis in mice under normal conditions. These results suggest that GPX4, ACSL4 and SLC7A11 regulate oxidative stress in different ways. The death of keratinocytes lacking GSH is caused by apoptosis. These studies suggest that different types of PCD share the same molecules and signal pathways. Interference with apoptosis or necrosis pathways may lead to ferroptosis. Moreover, by inhibiting ferroptosis, the cells may undergo other types of cell death. However, determining the exact mode of cell deathis challenging. Different PCD modalities might be triggered by the same stimuli and modulated by the same regulatory molecules. In melanoma cells, iron accelerates the accumulation of ROS and regulates crosstalk between necroptosis and ferroptosis [147]. In myocardial fibrosis mice, mixed lineage kinase 3 can induce ferroptosis and pyroptosis simultaneously through JNK/p53 and NF-κB/NLRP3 signaling pathway, respectively [148]. The release of the damage associated molecular patterns during ferroptosis has been supposed to activate necroptosis and pyroptosis. Study has revealed that non-coding RNAs can also mediate the crosstalk between ferroptosis, necroptosis and pyroptosis. However, each PCD exhibits a unique regulatory program, which is the key to distinguishing the PCD type. Therefore, methods for determining the relationship and interconversion between ferroptosis and other PCD modalities remain to be elucidated.

Ferroptosis plays a variety of roles in cancer treatment, but to identify a method to select the tumor types or patients suitable for ferroptosis-targeted therapy, further research is needed. Considering the factors inducing ferroptosis and the related molecular mechanisms, patients can be evaluated from three perspectives: gene expression, iron level, and gene mutation [1]. First, different ferroptosis-related genes are expressed at different levels in different cancers. In ovarian cancer and liver cancer, the expression of FTH1 is significantly increased, and the induction of ferroptosis based on iron

autophagy may be more beneficial for cancer treatment [149]. In addition, using an SLC7A11 inhibitor may exert a better therapeutic effect in glioblastoma and esophageal cancer, in which SLC7A11 is significantly upregulated [150]. Moreover, the level of iron varies in different cancers. Ovarian, pancreatic and breast cancer cells, in which the iron level is abnormally elevated, may be more sensitive to drugs that induce ferroptosis. Furthermore, cancer genomics can be used to identify genes that undergo mutation during tumorigenesis and tumor progression, which will help to determine whether drugs that induce ferroptosis exert therapeutic effects. Therefore, a comprehensive evaluation of gene expression is beneficial to evaluate the sensitivity of cancer cells to ferroptosis. In addition, based on cancer susceptibility, many ferroptosis inducers can also be used for cancer treatment by targeting ferroptosis pathways. Therefore, a comprehensive understanding of the mechanisms underlying ferroptosis and the adaptation of cancer cells can maximize the effectiveness of ferroptosis-based therapies.

Finding biological markers to evaluate the response of cancer patients to ferroptosis-based treatment is another challenge. The currently used clinical biomarkers are measured via the analysis of biological samples, such as urine, blood, tumor tissue, and feces. In ferroptosis, lipids, iron, and metabolites in the blood might be potential biomarkers. In addition, substances that react to 2-thiobarbituric acid in combination with nonthermal plasma may be used to measure lipid peroxidation product levels. Some proteins, such as ACSL4, GPX4 and TFRC, also show the potential to be biomarkers of ferroptosis. However, these potential markers are still in basic or preclinical research and are not close to clinical application.

9. Conclusion

Recent studies have provided deep insights into the molecular mechanisms of ferroptosis, especially its relationship with cancer. Ferroptosis plays an important role in the invasion, metastasis, therapeutic resistance and immunity of cancer. Targeting ferroptosis offers potential therapeutic strategies for cancer. Specific biomarkers that can be used to evaluate a patient's background and novel treatments based on ferroptosis should be developed and applied clinically in the future.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

The study was supported bythe National Natural Science Foundation of China (82302918), Natural Science Foundation of Zhejiang Province (LQ24H160044, LQ24H160024), Medical and Health Research project of Zhejiang province (2024KY758, 2024KY1405), Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province (2020E10021), Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents (ZWB-2020–18, Nengming Lin), Zhejiang Medical Key Discipline Foundation (ZWB-2018–02–03), Hangzhou Medical Key Discipline Foundation (HWF-2021–21–16) and the grants from Seed Foundation of Zhejiang Provincial People's Hospital (ZRY2022J007).

References

[1] Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nature Rev Mol Cell Biol 2021;22(4):266–82.
[2] Zhang S, Xin W, Anderson GJ, Li R, Gao L, Chen S, et al. Double-edge sword roles of iron in driving energy production *versus* instigating ferroptosis. Cell Death Dis 2022;13(1):40.
[3] Chen X, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. Nat Rev Clin Oncol 2021;18(5):280–96.
[4] Nie Q, Hu Y, Yu X, Li X, Fang X. Induction and application of ferroptosis in cancer therapy. Cancer Cell Int 2022;22(1):12.
[5] Gleitze S, Paula-Lima A, Nunez MT, Hidalgo C. The calcium-iron connection in ferroptosis-mediated neuronal death. Free Radic Biol Med 2021;175:28–41.
[6] Pope LE, Dixon SJ. Regulation of ferroptosis by lipid metabolism. Trends Cell Biol 2023;33(12):1077–87.
[7] Lei G, Zhuang L, Gan B. Targeting ferroptosis as a vulnerability in cancer. Nature reviews Cancer 2022;22(7):381–96.
[8] Dixon SJ, Olzmann JA. The cell biology of ferroptosis. Nature Rev Mol Cell Biol 2024;25(6):424–42.
[9] Huang Y, Huang J, Huang Y, Gan L, Long L, Pu A, et al. TFRC promotes epithelial ovarian cancer cell proliferation and metastasis via up-regulation of AXIN2 expression. Am J Cancer Res 2020;10(1):131–47.
[10] You Y, Fan Q, Huang J, Wu Y, Lin H, Zhang Q. Ferroptosis-related gene signature promotes ovarian cancer by influencing immune infiltration and invasion. J Oncol 2021;2021:9915312.
[11] Li Y, Gong X, Hu T, Chen Y. Two novel prognostic models for ovarian cancer respectively based on ferroptosis and necroptosis. BMC Cancer 2022;22(1):74.
[12] Yu Z, He H, Chen Y, Ji Q, Sun M. A novel ferroptosis related gene signature is associated with prognosis in patients with ovarian serous cystadenocarcinoma. Sci Rep 2021;11(1):11486.
[13] Chen R, Cao J, Jiang W, Wang S, Cheng J. Upregulated expression of CYBRD1 predicts poor prognosis of patients with ovarian cancer. J Oncol 2021;2021:7548406.
[14] Zhang Q, Li N, Deng L, Jiang X, Zhang Y, Lee LTO, et al. ACSL1-induced ferroptosis and platinum resistance in ovarian cancer by increasing FSP1 N-myristylation and stability. Cell Death Discov 2023;9(1):83.
[15] Jin Y, Qiu J, Lu X, Ma Y, Li G. LncRNA CACNA1G-AS1 up-regulates FTH1 to inhibit ferroptosis and promote malignant phenotypes in ovarian cancer cells. Oncol Res 2023;31(2):169–79.
[16] Zhang J, Xi J, Huang P, Zeng S. Comprehensive analysis identifies potential ferroptosis-associated mRNA therapeutic targets in ovarian cancer. Front Med (Lausanne) 2021;8:644053.
[17] Sun D, Li YC, Zhang XY. Lidocaine promoted ferroptosis by targeting miR-382-5p /SLC7A11 axis in ovarian and breast cancer. Front Pharmacol 2021;12:681223.

[18] Kato I, Kasukabe T, Kumakura S. Menin–MLL inhibitors induce ferroptosis and enhance the anti–proliferative activity of auranofin in several types of cancer cells. Int J Oncol 2020;57(4):1057–71.
[19] Huang Y, Lin J, Xiong Y, Chen J, Du X, Liu Q, et al. Superparamagnetic iron oxide nanoparticles induce ferroptosis of human ovarian cancer stem cells by weakening cellular autophagy. J Biomed Nanotechnol 2020;16(11):1612–22.
[20] Chan DW, Yung MM, Chan YS, Xuan Y, Yang H, Xu D, et al. MAP30 protein from Momordica charantia is therapeutic and has synergic activity with cisplatin against ovarian cancer *in vivo* by altering metabolism and inducing ferroptosis. Pharmacol Res 2020;161:105157.
[21] Ni M, Zhou J, Zhu Z, Xu Q, Yin Z, Wang Y, et al. Shikonin and cisplatin synergistically overcome cisplatin resistance of ovarian cancer by inducing ferroptosis via upregulation of HMOX1 to promote Fe(2+) accumulation. Phytomedicine 2023;112:154701.
[22] Gentric G, Kieffer Y, Mieulet V, Goundiam O, Bonneau C, Nemati F, et al. PML-regulated mitochondrial metabolism enhances chemosensitivity in human ovarian cancers. Cell Metab 2019;29(1):156–73 e10.
[23] Liu N, Lin X, Huang C. Activation of the reverse transsulfuration pathway through NRF2/CBS confers erastin-induced ferroptosis resistance. Br J Cancer 2020;122(2):279–92.
[24] Carbone M, Melino G. Stearoyl coA desaturase regulates ferroptosis in ovarian cancer offering new therapeutic perspectives. Cancer Res 2019;79(20):5149–50.
[25] Wang J, Han K, Zhang C, Chen X, Li Y, Zhu L, et al. Identification and validation of ferroptosis-associated gene-based on immune score as prognosis markers for hepatocellular carcinoma patients. J Gastrointest Oncol 2021;12(5):2345–60.
[26] Tang B, Zhu J, Li J, Fan K, Gao Y, Cheng S, et al. The ferroptosis and iron-metabolism signature robustly predicts clinical diagnosis, prognosis and immune microenvironment for hepatocellular carcinoma. Cell Commun. Signal 2020;18(1):174.
[27] Liu Y, Zhang X, Zhang J, Tan J, Li J, Song Z. Development and validation of a combined ferroptosis and immune prognostic classifier for hepatocellular carcinoma. Front Cell Dev Biol 2020;8:596679.
[28] Zheng C, Zhang B, Li Y, Liu K, Wei W, Liang S, et al. Donafenib and GSK-J4 synergistically induce ferroptosis in liver cancer by upregulating HMOX1 expression. Adv Sci 2023;10(22):e2206798.
[29] Su Y, Zhao D, Jin C, Li Z, Sun S, Xia S, et al. Dihydroartemisinin induces ferroptosis in HCC by promoting the formation of PEBP1/15-LO. Oxid Med Cell Longev 2021;2021:3456725.
[30] He Y, Fang D, Liang T, Pang H, Nong Y, Tang L, et al. Atractylodin may induce ferroptosis of human hepatocellular carcinoma cells. Ann Transl Med 2021;9(20):1535.
[31] Ou W, Mulik RS, Anwar A, McDonald JG, He X, Corbin IR. Low-density lipoprotein docosahexaenoic acid nanoparticles induce ferroptotic cell death in hepatocellular carcinoma. Free Radic Biol Med 2017;112:597–607.
[32] Sun J, Zhou C, Zhao Y, Zhang X, Chen W, Zhou Q, et al. Quiescin sulfhydryl oxidase 1 promotes sorafenib-induced ferroptosis in hepatocellular carcinoma by driving EGFR endosomal trafficking and inhibiting NRF2 activation. Redox Biol 2021;41:101942.
[33] Yao F, Deng Y, Zhao Y, Mei Y, Zhang Y, Liu X, et al. A targetable LIFR-NF-kappaB-LCN2 axis controls liver tumorigenesis and vulnerability to ferroptosis. Nat Commun 2021;12(1):7333.
[34] Huang W, Chen K, Lu Y, Zhang D, Cheng Y, Li L, et al. ABCC5 facilitates the acquired resistance of sorafenib through the inhibition of SLC7A11-induced ferroptosis in hepatocellular carcinoma. Neoplasia 2021;23(12):1227–39.
[35] Gao R, Kalathur RKR, Coto-Llerena M, Ercan C, Buechel D, Shuang S, et al. YAP/TAZ and ATF4 drive resistance to sorafenib in hepatocellular carcinoma by preventing ferroptosis. EMBO Mol Med 2021;13(12):e14351.
[36] Yang C, Lu T, Liu M, Yuan X, Li D, Zhang J, et al. Tiliroside targets TBK1 to induce ferroptosis and sensitize hepatocellular carcinoma to sorafenib. Phytomedicine 2023;111:154668.
[37] Chen Q, Zheng W, Guan J, Liu H, Dan Y, Zhu L, et al. SOCS2-enhanced ubiquitination of SLC7A11 promotes ferroptosis and radiosensitization in hepatocellular carcinoma. Cell Death Differ. 2023;30(1):137–51.
[38] Zheng Y, Wang Y, Lu Z, Wan J, Jiang L, Song D, et al. PGAM1 inhibition promotes HCC ferroptosis and synergizes with anti-PD-1 immunotherapy. Advanced science 2023;10(29):e2301928.
[39] Zhang D, Man D, Lu J, Jiang Y, Ding B, Su R, et al. Mitochondrial TSPO promotes hepatocellular carcinoma progression through ferroptosis inhibition and immune evasion. Advanced science 2023;10(15):e2206669.
[40] Zhao Y, Li M, Yao X, Fei Y, Lin Z, Li Z, et al. HCAR1/MCT1 regulates tumor ferroptosis through the lactate-mediated AMPK-SCD1 activity and its therapeutic implications. Cell Rep 2020;33(10):108487.
[41] Hu W, Zhou C, Jing Q, Li Y, Yang J, Yang C, et al. FTH promotes the proliferation and renders the HCC cells specifically resist to ferroptosis by maintaining iron homeostasis. Cancer Cell Int 2021;21(1):709.
[42] Teng Y, Wang B, Shang D, Yang N. Identification and validation of an immune and ferroptosis-combined index for non-small cell lung cancer. Front Genet 2021;12:764869.
[43] Zhang W, Yao S, Huang H, Zhou H, Zhou H, Wei Q, et al. Molecular subtypes based on ferroptosis-related genes and tumor microenvironment infiltration characterization in lung adenocarcinoma. Oncoimmunology 2021;10(1):1959977.
[44] Xu C, Jiang ZB, Shao L, Zhao ZM, Fan XX, Sui X, et al. beta-Elemene enhances erlotinib sensitivity through induction of ferroptosis by upregulating lncRNA H19 in EGFR-mutant non-small cell lung cancer. Pharmacol Res 2023;191:106739.
[45] Ni Y, Liu J, Zeng L, Yang Y, Liu L, Yao M, et al. Natural product manoalide promotes EGFR-TKI sensitivity of lung cancer cells by KRAS-ERK pathway and mitochondrial Ca(2+) overload-induced ferroptosis. Front Pharmacol 2022;13:1109822.
[46] Zhang W, Jiang B, Liu Y, Xu L, Wan M. Bufotalin induces ferroptosis in non-small cell lung cancer cells by facilitating the ubiquitination and degradation of GPX4. Free Radic Biol Med 2022;180:75–84.
[47] Li H, Liu L. Zinc moderates circular RNA circFOXP1 expression in order to regulate ferroptosis during lung adenocarcinoma. Chem Biol Interact 2022;352:109760.
[48] Liu M, Fan Y, Li D, Han B, Meng Y, Chen F, et al. Ferroptosis inducer erastin sensitizes NSCLC cells to celastrol through activation of the ROS-mitochondrial fission-mitophagy axis. Mol Oncol 2021;15(8):2084–105.
[49] Hu S, Ma J, Su C, Chen Y, Shu Y, Qi Z, et al. Engineered exosome-like nanovesicles suppress tumor growth by reprogramming tumor microenvironment and promoting tumor ferroptosis. Acta Biomater 2021;135:567–81.
[50] Wang X, Chen Y, Wang X, Tian H, Wang Y, Jin J, et al. Stem cell factor SOX2 confers ferroptosis resistance in lung cancer via upregulation of SLC7A11. Cancer Res 2021;81(20):5217–29.

[51] Lu X, Kang N, Ling X, Pan M, Du W, Gao S. MiR-27a-3p promotes non-small cell lung cancer through SLC7A11-mediated-ferroptosis. Front Oncol 2021;11:759346.
[52] Zhang W, Sun Y, Bai L, Zhi L, Yang Y, Zhao Q, et al. RBMS1 regulates lung cancer ferroptosis through translational control of SLC7A11. J Clin Invest 2021;131(22):e152067.
[53] Zhang X, Yu K, Ma L, Qian Z, Tian X, Miao Y. Endogenous glutamate determines ferroptosis sensitivity via ADCY10-dependent YAP suppression in lung adenocarcinoma. Theranostics 2021;11(12):5650–74.
[54] Ma L, Zhang X, Yu K, Xu X, Chen T, Shi Y, et al. Targeting SLC3A2 subunit of system X(C)(-) is essential for m(6)A reader YTHDC2 to be an endogenous ferroptosis inducer in lung adenocarcinoma. Free Radic Biol Med 2021;168:25–43.
[55] Wang H, Huang Q, Xia J, Cheng S, Pei D, Zhang X, et al. The E3 ligase MIB1 promotes proteasomal degradation of NRF2 and sensitizes lung cancer cells to ferroptosis. Mol Cancer Res 2022;20(2):253–64.
[56] Meng C, Zhan J, Chen D, Shao G, Zhang H, Gu W, et al. The deubiquitinase USP11 regulates cell proliferation and ferroptotic cell death via stabilization of NRF2 USP11 deubiquitinates and stabilizes NRF2. Oncogene 2021;40(9):1706–20.
[57] Gai C, Yu M, Li Z, Wang Y, Ding D, Zheng J, et al. Acetaminophen sensitizing erastin-induced ferroptosis via modulation of Nrf2/heme oxygenase-1 signaling pathway in non-small-cell lung cancer. J. Cell. Physiol. 2020;235(4):3329–39.
[58] Hsieh CH, Hsieh HC, Shih FS, Wang PW, Yang LX, Shieh DB, et al. An innovative NRF2 nano-modulator induces lung cancer ferroptosis and elicits an immunostimulatory tumor microenvironment. Theranostics 2021;11(14):7072–91.
[59] Tang Z, Jiang W, Mao M, Zhao J, Chen J, Cheng N. Deubiquitinase USP35 modulates ferroptosis in lung cancer via targeting ferroportin. Clin Transl Med 2021;11(4):e390.
[60] Huang F, Zheng Y, Li X, Luo H, Luo L. Ferroptosis-related gene AKR1C1 predicts the prognosis of non-small cell lung cancer. Cancer Cell Int 2021;21(1):567.
[61] Li M, Chen X, Wang X, Wei X, Wang D, Liu X, et al. RSL3 enhances the antitumor effect of cisplatin on prostate cancer cells via causing glycolysis dysfunction. Biochem Pharmacol 2021;192:114741.
[62] Bordini J, Morisi F, Elia AR, Santambrogio P, Pagani A, Cucchiara V, et al. Iron induces cell death and strengthens the efficacy of antiandrogen therapy in prostate cancer models. Clin Cancer Res 2020;26(23):6387–98.
[63] Guan Y, Lei H, Xing C, Yan B, Lin B, Yang X, et al. Multimodal nanoplatform with ROS amplification to overcome multidrug resistance in prostate cancer via targeting P-Glycoprotein and ferroptosis. Adv Healthc Mater 2023;13(3):e2301345.
[64] Ingram LM, Finnerty MC, Mansoura M, Chou CW, Cummings BS. Identification of lipidomic profiles associated with drug-resistant prostate cancer cells. Lipids Health Dis 2021;20(1):15.
[65] Yang Y, Liu T, Hu C, Xia H, Liu W, Chen J, et al. Ferroptosis inducer erastin downregulates androgen receptor and its splice variants in castration–resistant prostate cancer. Oncol Rep 2021;45(4):25.
[66] Zhou X, Zou L, Chen W, Yang T, Luo J, Wu K, et al. Flubendazole, FDA-approved anthelmintic, elicits valid antitumor effects by targeting P53 and promoting ferroptosis in castration-resistant prostate cancer. Pharmacol Res 2021;164:105305.
[67] Cao H, Wu X, Gao R, Chen L, Feng Y, Wang D. QiLing Decoction promotes ferroptosis of castration-resistant prostate cancer cells by inhibiting FSP1 *in vitro* and *in vivo*. J Cancer 2023;14(12):2236–45.
[68] Fu W, Xu L, Chen Y, Zhang Z, Chen S, Li Q, et al. Luteolin induces ferroptosis in prostate cancer cells by promoting TFEB nuclear translocation and increasing ferritinophagy. Prostate 2023;84(3):223–36.
[69] Cheng L, He Q, Liu B, Chen L, Lv F, Li X, et al. SGK2 promotes prostate cancer metastasis by inhibiting ferroptosis via upregulating GPX4. Cell Death Dis 2023;14(1):74.
[70] Zhou J, Gao S, Hsieh CL, Malla M, Shemshedini L. Peptide B targets soluble guanylyl cyclase alpha1 and kills prostate cancer cells. PLoS One 2017;12(8):e0184088.
[71] Zhang Y, Guo S, Wang S, Li X, Hou D, Li H, et al. LncRNA OIP5-AS1 inhibits ferroptosis in prostate cancer with long-term cadmium exposure through miR-128-3p/SLC7A11 signaling. Ecotoxicol Environ Saf 2021;220:112376.
[72] Nassar ZD, Mah CY, Dehairs J, Burvenich IJ, Irani S, Centenera MM, et al. Human DECR1 is an androgen-repressed survival factor that regulates PUFA oxidation to protect prostate tumor cells from ferroptosis. Elife 2020;9:e54166.
[73] Blomme A, Ford CA, Mui E, Patel R, Ntala C, Jamieson LE. 2,4-dienoyl-CoA reductase regulates lipid homeostasis in treatment-resistant prostate cancer. Nat Commun 2020;11(1):2508.
[74] Ogor P, Yoshida T, Koike M, Kakizuka A. VCP relocalization limits mitochondrial activity, GSH depletion and ferroptosis during starvation in PC3 prostate cancer cells. Genes Cells 2021;26(8):570–82.
[75] Li K, Xu K, He Y, Yang Y, Tan M, Mao Y, et al. Oxygen self-generating nanoreactor mediated ferroptosis activation and immunotherapy in triple-negative breast cancer. ACS Nano 2023;17(5):4667–87.
[76] Zhou L, Chen J, Li R, Wei L, Xiong H, Wang C, et al. Metal-polyphenol-network coated prussian blue nanoparticles for synergistic ferroptosis and apoptosis via triggered GPX4 inhibition and concurrent *in situ* bleomycin toxification. Small 2021;17(47):e2103919.
[77] Zhang J, Yang J, Zuo T, Ma S, Xokrat N, Hu Z, et al. Heparanase-driven sequential released nanoparticles for ferroptosis and tumor microenvironment modulations synergism in breast cancer therapy. Biomaterials 2021;266:120429.
[78] Yao X, Xie R, Cao Y, Tang J, Men Y, Peng H, et al. Simvastatin induced ferroptosis for triple-negative breast cancer therapy. J Nanobiotechnology 2021;19(1):311.
[79] Wang J, Li Y, Zhang J, Luo C. Isoliquiritin modulates ferroptosis via NF-kappaB signaling inhibition and alleviates doxorubicin resistance in breast cancer. Immunopharmacol Immunotoxicol 2023;45(4):443–54.
[80] Wen Y, Chen H, Zhang L, Wu M, Zhang F, Yang D, et al. Glycyrrhetinic acid induces oxidative/nitrative stress and drives ferroptosis through activating NADPH oxidases and iNOS, and depriving glutathione in triple-negative breast cancer cells. Free Radic Biol Med 2021;173:41–51.
[81] Jiang Z, Lim SO, Yan M, Hsu JL, Yao J, Wei Y, et al. TYRO3 induces anti-PD-1/PD-L1 therapy resistance by limiting innate immunity and tumoral ferroptosis. J Clin Invest 2021;131(8):e139434.
[82] Lin CC, Yang WH, Lin YT, Tang X, Chen PH, Ding CC, et al. DDR2 upregulation confers ferroptosis susceptibility of recurrent breast tumors through the Hippo pathway. Oncogene 2021;40(11):2018–34.
[83] Li H, Yang P, Wang J, Zhang J, Ma Q, Jiang Y, et al. HLF regulates ferroptosis, development and chemoresistance of triple-negative breast cancer by activating tumor cell-macrophage crosstalk. J Hematol Oncol 2022;15(1):2.

[84] Zhou X, Kang J, Zhang L, Cheng Y. Osthole inhibits malignant phenotypes and induces ferroptosis in KRAS-mutant colorectal cancer cells via suppressing AMPK/Akt signaling. Cancer Chemother Pharmacol 2023;92(2):119–34.
[85] Xia Y, Liu S, Li C, Ai Z, Shen W, Ren W, et al. Discovery of a novel ferroptosis inducer-talaroconvolutin A-killing colorectal cancer cells *in vitro* and *in vivo*. Cell Death Dis 2020;11(11):988.
[86] Han W, Duan X, Ni K, Li Y, Chan C, Lin W. Co-delivery of dihydroartemisinin and pyropheophorbide-iron elicits ferroptosis to potentiate cancer immunotherapy. Biomaterials 2022;280:121315.
[87] Gao W, Huang Z, Duan J, Nice EC, Lin J, Huang C. Elesclomol induces copper-dependent ferroptosis in colorectal cancer cells via degradation of ATP7A. Mol Oncol 2021;15(12):3527–44.
[88] Pan X, Qi Y, Du Z, He J, Yao S, Lu W, et al. Zinc oxide nanosphere for hydrogen sulfide scavenging and ferroptosis of colorectal cancer. J Nanobiotechnology 2021;19(1):392.
[89] Yang J, Mo J, Dai J, Ye C, Cen W, Zheng X, et al. Cetuximab promotes RSL3-induced ferroptosis by suppressing the Nrf2/HO-1 signalling pathway in KRAS mutant colorectal cancer. Cell Death Dis 2021;12(11):1079.
[90] Chen P, Li X, Zhang R, Liu S, Xiang Y, Zhang M, et al. Combinative treatment of beta-elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation. Theranostics 2020;10(11):5107–19.
[91] Chen C, Yang Y, Guo Y, He J, Chen Z, Qiu S, et al. CYP1B1 inhibits ferroptosis and induces anti-PD-1 resistance by degrading ACSL4 in colorectal cancer. Cell Death Dis 2023;14(4):271.
[92] Singhal R, Mitta SR, Das NK, Kerk SA, Sajjakulnukit P, Solanki S, et al. HIF-2alpha activation potentiates oxidative cell death in colorectal cancers by increasing cellular iron. J Clin Invest 2021;131(12):e143691.
[93] Chaudhary N, Choudhary BS, Shah SG, Khapare N, Dwivedi N, Gaikwad A, et al. Lipocalin 2 expression promotes tumor progression and therapy resistance by inhibiting ferroptosis in colorectal cancer. Int J Cancer 2021;149(7):1495–511.
[94] Ma J, Hu X, Yao Y, Wu L, Sheng C, Chen K, et al. Characterization of two ferroptosis subtypes with distinct immune infiltration and gender difference in gastric cancer. Front Nutr 2021;8:756193.
[95] Zheng F, Wang Y, Zhang Q, Chen Q, Liang CL, Liu H, et al. Polyphyllin I suppresses the gastric cancer growth by promoting cancer cell ferroptosis. Front Pharmacol 2023;14:1145407.
[96] Mao SH, Zhu CH, Nie Y, Yu J, Wang L. Levobupivacaine induces ferroptosis by miR-489-3p/SLC7A11 signaling in gastric cancer. Front Pharmacol 2021;12:681338.
[97] Ni H, Ruan G, Sun C, Yang X, Miao Z, Li J, et al. Tanshinone IIA inhibits gastric cancer cell stemness through inducing ferroptosis. Environ Toxicol 2022;37(2):192–200.
[98] Liu Y, Song Z, Liu Y, Ma X, Wang W, Ke Y, et al. Identification of ferroptosis as a novel mechanism for antitumor activity of natural product derivative a2 in gastric cancer. Acta Pharm Sin B 2021;11(6):1513–25.
[99] Cai S, Fu S, Zhang W, Yuan X, Cheng Y, Fang J. SIRT6 silencing overcomes resistance to sorafenib by promoting ferroptosis in gastric cancer. Biochem Biophys Res Commun 2021;577:158–64.
[100] Fu D, Wang C, Yu L, Yu R. Induction of ferroptosis by ATF3 elevation alleviates cisplatin resistance in gastric cancer by restraining Nrf2/Keap1/xCT signaling. Cellular Molecul Biol Lett 2021;26(1):26.
[101] Zhang H, Deng T, Liu R, Ning T, Yang H, Liu D, et al. CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. Mol Cancer 2020;19(1):43.
[102] Li D, Wang Y, Dong C, Chen T, Dong A, Ren J, et al. CST1 inhibits ferroptosis and promotes gastric cancer metastasis by regulating GPX4 protein stability via OTUB1. Oncogene 2023;42(2):83–98.
[103] Ni H, Qin H, Sun C, Liu Y, Ruan G, Guo Q, et al. MiR-375 reduces the stemness of gastric cancer cells through triggering ferroptosis. Stem Cell Res Ther 2021;12(1):325.
[104] Sun X, Yang S, Feng X, Zheng Y, Zhou J, Wang H, et al. The modification of ferroptosis and abnormal lipometabolism through overexpression and knockdown of potential prognostic biomarker perilipin2 in gastric carcinoma. Gastric Cancer 2020;23(2):241–59.
[105] Wang J, Wang T, Zhang Y, Liu J, Song J, Han Y, et al. CPEB1 enhances erastin-induced ferroptosis in gastric cancer cells by suppressing twist1 expression. IUBMB Life 2021;73(9):1180–90.
[106] Chen M, Zhu JY, Mu WJ, Guo L. Cysteine dioxygenase type 1 (CDO1): its functional role in physiological and pathophysiological processes. Genes Dis 2023;10(3):877–90.
[107] Dai E, Han L, Liu J, Xie Y, Zeh HJ, Kang R, et al. Ferroptotic damage promotes pancreatic tumorigenesis through a TMEM173/STING-dependent DNA sensor pathway. Nat Commun 2020;11(1):6339.
[108] Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy 2020;16(11):2069–83.
[109] Bhutia YD, Ogura J, Grippo PJ, Torres C, Sato T, Wachtel M, et al. Chronic exposure to excess iron promotes EMT and cancer via p53 loss in pancreatic cancer. Asian J Pharm Sci 2020;15(2):237–51.
[110] Kim MJ, Kim HS, Kang HW, Lee DE, Hong WC, Kim JH, et al. SLC38A5 modulates ferroptosis to overcome gemcitabine resistance in pancreatic cancer. Cells 2023;12(20):2509.
[111] Kremer DM, Nelson BS, Lin L, Yarosz EL, Halbrook CJ, Kerk SA, et al. GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis. Nat Commun 2021;12(1):4860.
[112] Shang M, Weng L, Xu G, Wu S, Liu B, Yin X, et al. TRIM11 suppresses ferritinophagy and gemcitabine sensitivity through UBE2N/TAX1BP1 signaling in pancreatic ductal adenocarcinoma. J. Cell. Physiol. 2021;236(10):6868–83.
[113] Mukherjee D, Chakraborty S, Bercz L, D'Alesio L, Wedig J, Torok MA, et al. Tomatidine targets ATF4-dependent signaling and induces ferroptosis to limit pancreatic cancer progression. iScience 2023;26(8):107408.
[114] Gou Y, Chen M, Li S, Deng J, Li J, Fang G, et al. Dithiocarbazate-copper complexes for bioimaging and treatment of pancreatic cancer. J Med Chem 2021;64(9):5485–99.
[115] Chang K, Chen Y, Zhang X, Zhang W, Xu N, Zeng B, et al. DPP9 stabilizes NRF2 to suppress ferroptosis and induce sorafenib resistance in clear cell renal cell carcinoma. Cancer Res 2023;83(23):3940–55.
[116] Liang H, Wu X, Zhao G, Feng K, Ni K, Sun X. Renal clearable ultrasmall single-crystal Fe nanoparticles for highly selective and effective ferroptosis therapy and immunotherapy. J Am Chem Soc 2021;143(38):15812–23.
[117] Wang J, Yin X, He W, Xue W, Zhang J, Huang Y. SUV39H1 deficiency suppresses clear cell renal cell carcinoma growth by inducing ferroptosis. Acta Pharm Sin B 2021;11(2):406–19.
[118] Lu Y, Qin H, Jiang B, Lu W, Hao J, Cao W, et al. KLF2 inhibits cancer cell migration and invasion by regulating ferroptosis through GPX4 in clear cell renal cell carcinoma. Cancer Lett 2021;522:1–13.

[119] Kerins MJ, Milligan J, Wohlschlegel JA, Ooi A. Fumarate hydratase inactivation in hereditary leiomyomatosis and renal cell cancer is synthetic lethal with ferroptosis induction. Cancer Sci 2018;109(9):2757–66.
[120] Schmitt A, Xu W, Bucher P, Grimm M, Konantz M, Horn H, et al. Dimethyl fumarate induces ferroptosis and impairs NF-kappaB/STAT3 signaling in DLBCL. Blood 2021;138(10):871–84.
[121] Yusuf RZ, Saez B, Sharda A, van Gastel N, Yu VWC, Baryawno N, et al. Aldehyde dehydrogenase 3a2 protects AML cells from oxidative death and the synthetic lethality of ferroptosis inducers. Blood 2020;136(11):1303–16.
[122] Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, et al. A nuclear long non-coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis. Molecular therapy : the journal of the American Society of. Gene Ther 2021;29(1):263–74.
[123] Yee PP, Wei Y, Kim SY, Lu T, Chih SY, Lawson C, et al. Neutrophil-induced ferroptosis promotes tumor necrosis in glioblastoma progression. Nat Commun 2020;11(1):5424.
[124] Floros KV, Cai J, Jacob S, Kurupi R, Fairchild CK, Shende M, et al. MYCN-amplified neuroblastoma is addicted to iron and vulnerable to inhibition of the system Xc-/glutathione axis. Cancer Res 2021;81(7):1896–908.
[125] Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Res 2021;31(2):107–25.
[126] Xu Z, Feng J, Li Y, Guan D, Chen H, Zhai X, et al. The vicious cycle between ferritinophagy and ROS production triggered EMT inhibition of gastric cancer cells was through p53/AKT/mTor pathway. Chem Biol Interact 2020;328:109196.
[127] Guan D, Zhou W, Wei H, Wang T, Zheng K, Yang C, et al. Ferritinophagy-mediated ferroptosis and activation of Keap1/Nrf2/HO-1 pathway were conducive to EMT inhibition of gastric cancer cells in action of 2,2′-Di-pyridineketone hydrazone dithiocarbamate butyric acid ester. Oxid Med Cell Longev 2022;2022:3920664.
[128] Wang W, Green M, Choi JE, Gijon M, Kennedy PD, Johnson JK, et al. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. Nature 2019;569(7755):270–4.
[129] Zhao L, Zhou X, Xie F, Zhang L, Yan H, Huang J, et al. Ferroptosis in cancer and cancer immunotherapy. Cancer Commun 2022;42(2):88–116.
[130] Fournel L, Wu Z, Stadler N, Damotte D, Lococo F, Boulle G, et al. Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer. Cancer Lett 2019;464:5–14.
[131] Xu H, Ye D, Ren M, Zhang H, Bi F. Ferroptosis in the tumor microenvironment: perspectives for immunotherapy. Trends Mol Med 2021;27(9):856–67.
[132] Mou Y, Wang J, Wu J, He D, Zhang C, Duan C, et al. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol 2019;12(1):34.
[133] Liang C, Zhang X, Yang M, Dong X. Recent progress in ferroptosis inducers for cancer therapy. Adv Mater 2019;31(51):e1904197.
[134] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012;149(5):1060–72.
[135] Ensoy M, Bumin ZS, Jama HA, Cansaran-Duman D. The regulation role of ferroptosis mechanism of anti-cancer drugs and noncoding RNAs. Curr Med Chem 2023;30(14):1638–56.
[136] Yang J, Xu J, Zhang B, Tan Z, Meng Q, Hua J, et al. Ferroptosis: at the crossroad of gemcitabine resistance and tumorigenesis in pancreatic cancer. Int J Mol Sci 2021;22(20):10944.
[137] Sun S, Shen J, Jiang J, Wang F, Min J. Targeting ferroptosis opens new avenues for the development of novel therapeutics. Signal Transduct Target Ther 2023;8(1):372.
[138] Hassannia B, Wiernicki B, Ingold I, Qu F, Van Herck S, Tyurina YY, et al. Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma. J Clin Invest 2018;128(8):3341–55.
[139] Chen GQ, Benthani FA, Wu J, Liang D, Bian ZX, Jiang X. Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis. Cell Death Differ. 2020;27(1):242–54.
[140] Dewangan J, Srivastava S, Mishra S, Divakar A, Kumar S, Rath SK. Salinomycin inhibits breast cancer progression via targeting HIF-1alpha/VEGF mediated tumor angiogenesis *in vitro* and *in vivo*. Biochem Pharmacol 2019;164:326–35.
[141] Ma H, Liu Y, Miao Z, Cheng S, Zhu Y, Wu Y, et al. Neratinib inhibits proliferation and promotes apoptosis of acute myeloid leukemia cells by activating autophagy-dependent ferroptosis. Drug Dev Res 2022;83(7):1641–53.
[142] Motooka Y, Toyokuni S. Ferroptosis as ultimate target of cancer therapy. Antioxid Redox Signal. 2023;39(1–3):206–23.
[143] Zhang Y, Dong P, Liu N, Yang JY, Wang HM, Geng Q. TRIM6 reduces ferroptosis and chemosensitivity by targeting SLC1A5 in lung cancer. Oxid Med Cell Longev 2023;2023:9808100.
[144] Yamaguchi Y, Kasukabe T, Kumakura S. Piperlongumine rapidly induces the death of human pancreatic cancer cells mainly through the induction of ferroptosis. Int J Oncol 2018;52(3):1011–22.
[145] Gao H, Bai Y, Jia Y, Zhao Y, Kang R, Tang D, et al. Ferroptosis is a lysosomal cell death process. Biochem Biophys Res Commun 2018;503(3):1550–6.
[146] Kang R, Zeng L, Zhu S, Xie Y, Liu J, Wen Q, et al. Lipid peroxidation drives gasdermin D-mediated pyroptosis in lethal polymicrobial sepsis. Cell Host Microbe 2018;24(1):97–108 e4.
[147] Zhou B, Zhang JY, Liu XS, Chen HZ, Ai YL, Cheng K, et al. Tom20 senses iron-activated ROS signaling to promote melanoma cell pyroptosis. Cell Res 2018;28(12):1171–85.
[148] Wang J, Deng B, Liu Q, Huang Y, Chen W, Li J, et al. Pyroptosis and ferroptosis induced by mixed lineage kinase 3 (MLK3) signaling in cardiomyocytes are essential for myocardial fibrosis in response to pressure overload. Cell Death Dis 2020;11(7):574.
[149] Lin PL, Tang HH, Wu SY, Shaw NS, Su CL. Saponin formosanin C-induced ferritinophagy and ferroptosis in human hepatocellular carcinoma cells. Antioxidants 2020;9(8):682.
[150] Hu N, Hu WH, Zhou SL, Yang Z, Liang WL, Yang RY, et al. SLC7A11 negatively associates with mismatch repair gene expression and endows glioblastoma cells sensitive to radiation under low glucose conditions. Neoplasma 2021;68(6):1147–56.