Journal of **Exploratory** Research in Pharmacology 2023 vol. 8(3) | 242–252
DOI: 10.14218/JERP.2023.00003

Review Article

Ferroptosis: Opportunities and Challenges in Cancer

Ying-Jie Jia[1], Yu Zhang[1], Xu-Bin Ma[1], Yang Wang[1], Ying-Qi Tian[1], Peng-Xing He[1,2*] and Yi-Chao Xu[1,2*]

[1]*Key Laboratory of Advanced Drug Preparation Technologies, Ministry of Education, Institute of Pharmaceutical Sciences, Institute of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China;* [2]*The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, China*

Received: January 11, 2023 | **Revised:** March 30, 2023 | **Accepted:** April 17, 2023 | **Published online:** May 23, 2023

Abstract

Ferroptosis is a programmed cell death mainly manifested as accumulation of ferrous ions and cell lipid peroxidation. Ferroptosis is well regulated by multiple signaling pathways, of which SLC7A11/GPX4 axis is the key pathway negatively regulating ferroptosis by eliminating lipid peroxidation. While disorder of iron homeostasis catalyzes the lipid peroxidation by supplying ferrous iron. Lipid metabolism participates in ferroptosis by offering lipid substrates. In addition, transsulfuration pathway and FSP1/CoQ10 also involve in ferroptosis. Evading ferroptosis is one strategy that cancer bypasses cell death and develops resistance to chemotherapy or radiotherapy, making ferroptosis inducers the potential treatment for cancer. The objective of this review is to summarize the ferroptosis signaling pathways and ferroptosis inducers, thus exploring the opportunities and challenges of inducing ferroptosis in cancer.

Introduction

In 2012, Dixony *et al*. proposed a type of unique programmed cell death type, ferroptosis, which is mainly characterized by high intracellular lipid peroxidation and iron disorders.[1] Morphologically, ferroptosis is mainly manifested by decreased mitochondrial volume or disappeared mitochondrial crest, increased mitochondrial membrane potential and membrane density.[2] In terms of biochemistry, it is mainly involved the increase of reactive oxygen species (ROS), decreased activity of glutathione peroxidase 4 (GPX4), iron disorder and accumulation of lipid peroxidation.[3] Ferroptosis is a newly discovered programmed cell death, many signaling pathways and proteins involved in ferroptosis are continuously discovered and reported (Fig. 1). It is well known that Solute Carrier Family 7 Member 11 (SLC7A11)/GPX4 inhibits ferroptosis by eliminating the ROS and lipid peroxidation. While iron metabolism and lipid metabolism participate in ferroptosis by supplying ferrous iron and unsaturated lipid.[4,5] In addition, ferroptosis can also be regulated by transsulfuration pathway and mevalonate pathway through regulating cysteine level and coenzyme Q10 (CoQ10) content, respectively.[6,7]

Ferroptosis is associated with various diseases, including (neuro)degenerative diseases, ischemia-reperfusion injury, acute kidney injury, and cancer.[8] Evading ferroptosis is one of manners that tumor cells bypass cell death, inhibiting different key molecules of ferroptosis can re-sensitive tumor cells to ferroptosis. In addition, the higher the level of ferroptosis in cancer patients receiving radiotherapy, the better the radiation response and the longer the survival of patient.[9] Evading ferroptosis plays key role in resistance of cancer to chemotherapy or radiotherapy, inducing ferroptosis might overcome chemotherapy or radiotherapy resistance.[10] Recently reported ferroptosis inducers can be divided into four categories according to their mechanisms. The first and second categories are the ferroptosis inducers that directly targeting SLC7A11 and GPX4, respectively.[11–13] The third type of ferroptosis inducers is ferroptosis inducing 56 (FIN56) inducers that consume CoQ10 by activating squalene synthase, promoting cellular lipid peroxidation, and ultimately inducing ferroptosis.[7,12] The fourth type is 1,2-dioxolane FINO2 inducers that indirectly inhibit GPX4 and directly oxidize iron to induce lipid peroxidation.[14]

Keywords: Ferroptosis; SLC7A11; Iron metabolism; Lipid metabolism; Ferroptosis inducer.

Abbreviations: AA, arachidonic acid; AACT, acetoacetyl-CoA thiolase; ACSL4, Acyl-CoA synthase long chain member 4; AdA, adrenal acid; AHCYL1, adenosine homocysteine 1; CARS, cysteinyl- tRNA synthetase; CBS, cystathionine-β-synthase; CTH, cystathionine c-lyase; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; FPP, farnesyl pyrophosphate; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GR, glutathione reductase; GSH, glutathione; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; HMGR, hydroxymethylglutaryl CoA reductase; HMGS, 3-hydroxy-3-methylglutaryl CoA synthase; IPP, isopentenyl pyrophosphate; LOXs, lipoxygenases; LPCAT3, lysophosphatidylcholine transferase 3; MAT1A/MAT2A, methionine adenosine transferase Iα/Iiα; MS, methionine synthetase; MTs, methyltransferase; MVA, mevalonic acid; NCOA4, nuclear receptor coactivator 4; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SAH, s-adenosine homocysteine; SAHH, S-adenosine homocysteine hydrolase; SAM, S-adenosine methionine; STEAP3, six-transmembrane epithelial antigen of prostate 3; Tf, transferrin; TfR1, transferrin receptor 1.

***Correspondence to:** Yi-Chao Xu and Peng-Xing He, Key Laboratory of Advanced Drug Preparation Technologies, Ministry of Education, Institute of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China. ORCID: https://orcid.org/0000-0002-4558-0518 (YCX) and https://orcid.org/0000-0003-2679-127X (PXH). Tel: +0086-0371-67781907 (YCX) and +0086-0371-67781907 (PXH), E-mail: xuyc2017@zzu.edu.cn (YCX) and hepengxing@zzu.edu.cn (PXH)

How to cite this article: Jia YJ, Zhang Y, Ma XB, Wang Y, Tian YQ, He PX, *et al*. Ferroptosis: Opportunities and Challenges in Cancer. *J Explor Res Pharmacol* 2023;8(3):242–252. doi: 10.14218/JERP.2023.00003.

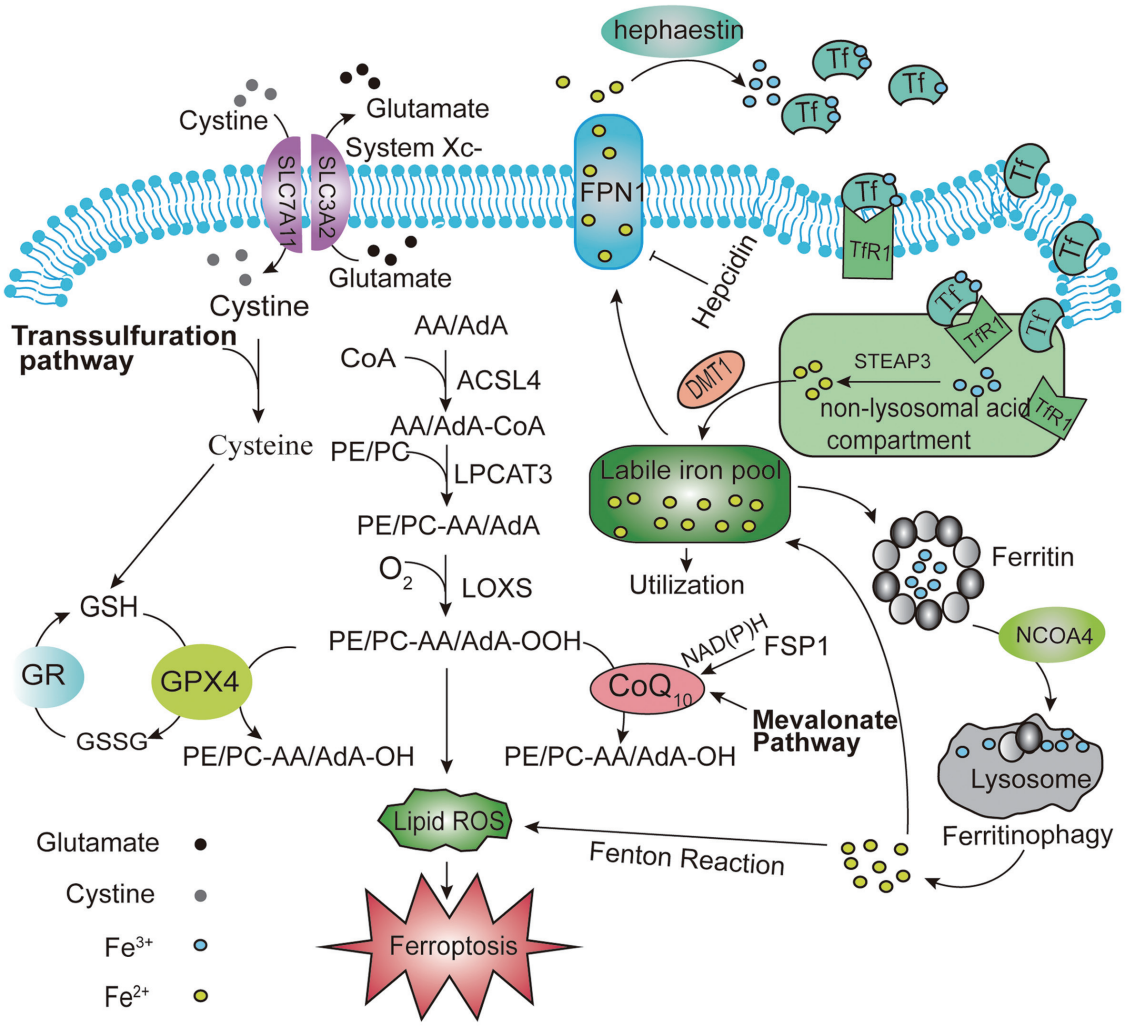

Fig. 1. Ferroptosis signaling pathways. AA, arachidonic acid; ACSL4, Acyl-CoA synthase long chain member 4; AdA, adrenal acid; CoA, coenzyme A; CoQ10, Coenzyme Q10; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GR, glutathione reductase; GSH, glutathione; GSSG, oxidized; LOXs, lipoxygenases; LPCAT3, lysophosphatidylcholine transferase 3; NADH, reduced form of nicotinamide adenine dinucleotide; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; NCOA4, nuclear receptor coactivator 4.; PC, phosphatidylcholine; PE, phosphatidylethanolamine; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7, member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; Tf, transferrin; TfR1, transferrin receptor 1.

Ferroptosis signaling pathways

SLC7A11/GPX4 axis

SLC7A11, also known as xCT, together with heavy chain subunit Solute Carrier Family 3 Member 2 (SLC3A2) form cystine-glutamate acid reverse transporter (System Xc^-), mediating the exchange of intracellular glutamate with extracellular cystine at 1:1. Once transported into the cell, cystine is rapidly converted into cysteine (L-cysteine), which is then utilized to synthesize glutathione (GSH).[15] In the heterodimer of System Xc-, SLC7A11 executes the function of transporting amino acids, while SLC3A2 is required for the stability and trafficking of SLC7A11 to the cell membrane.[16] mTORC2, as a growth factor integrating variety of signaling pathway, phosphorylates the 26th serine of SLC7A11 to reduce its activity, thereby inhibiting cystine intake and glutathione metabolism.[17] The regulation of SLC7A11 has been well reviewed by Boyi Gan group.[18] GPX4 plays a pivotal role in ferroptosis by reducing lipid hydroperoxides to lipid alcohols.[19] GPX4, as a selenase, requires the participation of GSH acts as a cofactor.[20,21] Inhibition of SLC7A11 or GPX4 activity can induce the production of lipid ROS, which in turn induces ferroptosis.[19,22]

Transsulfuration pathway

Transsulfuration pathway, as the backup supply of cysteine, plays important role in the growth of cancer cells. Transsulfuration pathway negatively regulates ferroptosis by de novo synthesizing cysteine (Fig. 2), which is a rate-limiting precursor for the synthesis of GSH.[23] Intracellular cysteine is indirectly supplied with cystine by System Xc^- or directly produced by the transsulfuration pathway.[15] Once intracellular cysteine is deficient, the cell will initiate transsulfuration pathway to synthesize cysteine from methionine.[6] In transsulfuration pathway, methionine reacts with ATP to form S-adenosine methionine (SAM) under the catalysis of methionine adenosine transferase Iα/IIα (MAT1A/MAT2A).[24,25] Then

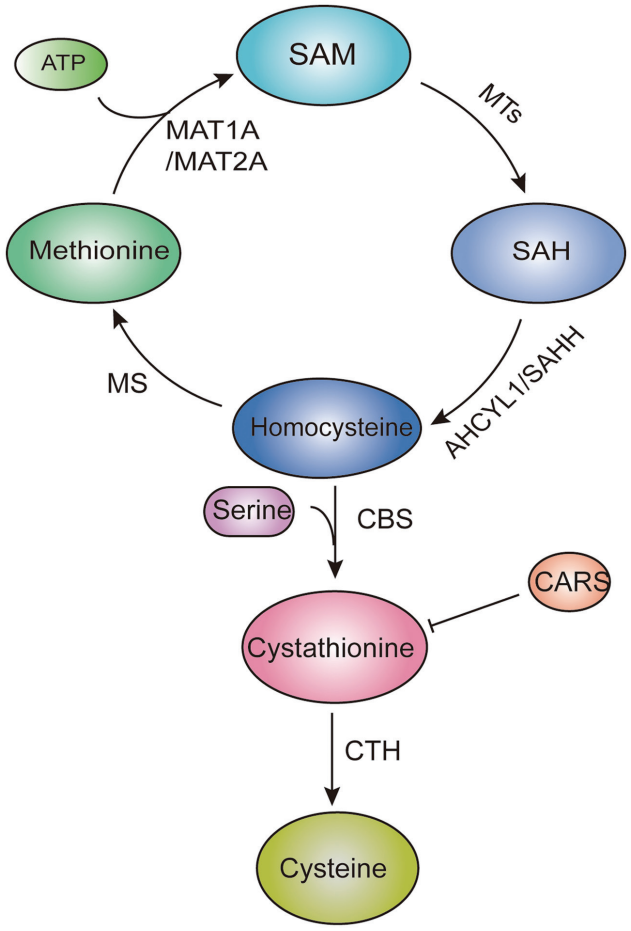

Fig. 2. Transsulfuration pathway. AHCYL1, adenosine homocysteine 1; ATP, adenosine triphosphate; CARS, cysteinyl- tRNA synthetase; CBS, cystathionine-β-synthase; CTH, cystathionine c-lyase; MAT1A/MAT2A, methionine adenosine transferase Iα/Iiα; MS, methionine synthetase; MTs, methyltransferase; SAH, s-adenosine homocysteine; SAHH, S-adenosine homocysteine hydrolase; SAM, S-adenosine methionine.

SAM is converted to s-adenosine homocysteine (SAH) by losing a methyl group in the presence of methyltransferase (MTs).[25] SAH is then hydrolyzed to form homocysteine in the presence of adenosine homocysteine 1 (AHCYL1) or S-adenosine homocysteine hydrolase (SAHH).[25,26] Finally, Under the action of the enzyme cystathionine-β-synthase (CBS), serine is coupled into homocysteine to form cystathionine, which can then be cleaved by cystathionine c-lyase (CTH) to release cysteine.[6,27]

Several investigations have reported that upregulation of transsulfuration pathway prevented ferroptosis induced by SLC7A11 inhibition. Knockdown of cysteinyl- tRNA synthetase (CARS) could upregulate the transsulfuration pathway by accumulation of cystathionine, thus suppressing erastin induced ferroptosis.[28] It has been reported that transformation of SAM to SAH determined the transsulfuration pathway activity, inducible of which contributed to cellular cysteine pool and promoted cancer cell growth upon cysteine restriction.[27] Depletion of parkinsonism-associated deglycase DJ-1, an oncogene located at 1P36.12-13 of human genome, reduced the activity of SAHH, thus leading to inhibition of transsulfuration pathway, enhancing the sensitivity of cancer cells to SLC7A11 inhibitor.[29,30]

Iron metabolism

Iron is an indispensable trace element in the human body and is widely involved in metabolism and biology process as a cofactor or component of the enzymes.[31] Excess irons will damage cells by catalyzing Fenton reaction, thus inducing ferroptosis.[32–35] Normally, absorbed irons in blood vessel are ferric irons (Fe^{3+}) bound by transferrin (Tf). Tf containing one or two ferric ions binds to transferrin receptor 1 (TfR1), forming a complex that enters the cell via receptor-mediated endocytosis and then enters the non-lysosomal acid compartment.[36] Ferric ions are then released from the transferrin complex by endosomal acidification and reduced to ferrous ions (Fe^{2+}) by six-transmembrane epithelial antigen of prostate 3 (STEAP3), Tf will separate from its receptor TfR1 and re-enter the bloodstream to capture ferric ions.[37,38] Meanwhile, divalent metal transporter protein 1 (DMT1) accounts for the transfer of ferrous ions to the labile iron pool, in which ferrous ions are easily transported to different cell machinery to participate in the synthesis of DNA synthase, heme and iron-sulfur cluster enzymes.[38,39] The excess ferrous ions are then stored in ferritin as the type of ferric irons.[39] Nuclear receptor coactivator 4 (NCOA4), as the selective cargo receptor of ferritin, participating in the autophagy of ferritin, thus releasing the stored ferrous irons.[40] Ferroportin 1 (FPN1) is a transmembrane protein responsible for iron output and iron balance in cells, degradation of which is regulated by hepcidin, a circulatory regulatory hormone peptide produced by liver cells.[41,42]

Accumulation of ferrous irons in tumor cells affected by various factors will induce ferroptosis by participating in the production of lipid ROS. Knock-down of NCOA4 could abolish degradation of ferritin and reduce the intracellular Fe^{2+} level, thus inhibiting ferroptosis induced by erastin.[43] New studies have shown that upregulated FPN1 can also inhibit ferroptosis, while silencing or downregulating FPN1 enhances the sensitivity of tumor cells to ferroptosis inducer.[44,45]

IRE (iron response element) /IRP (iron regulatory protein) axis plays critical role in maintaining iron homeostasis through post-transcriptional regulation of iron-related genes. IRP1 and IRP2 specifically recognize the IREs and regulate cell iron homeostasis by blocking or promoting the translation of target mRNAs bound by IRE, which contains conserved stem-loop.[46,47] Binding of IREs with IRPs is well regulated by iron concentration.[48] When intracellular irons are deficient, IRP1 binds to the IRE of TfR1 and ferritin, thus increasing the iron uptake and reducing iron storage.[49] On the contrary, high iron content in cells will reduce iron intake and increase iron storage by releasing of IRP1/2 from IRE of TfR1 and ferritin.[38,50] It has been found dihydroartemisinin made cells sensitive to ferroptosis by impinging IRP-IRE system and lysosomal mediated ferritin degradation, both of which increased the intracellular free iron content.[51]

Lipid metabolism pathway

Lipid peroxidation is an important manifestation of ferroptosis and unsaturated fatty acids are the substrates of lipid peroxidation, thus disorder of lipid metabolism is closely related with ferroptosis. Identifying the lipid substances and pivotal enzymes for lipid peroxidation will supply more information for ferroptosis. Among the various lipids, phospholipid-related polyunsaturated fatty acids (PUFAs) such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC) play key role in ferroptosis as the substrates for lipid peroxidation.[52] Genome-wide CRISPR-based genetic screen uncovers that Acyl-CoA synthase long chain member 4 (ACSL4) is essential for ferroptosis execution.[53] ACSL4 connects CoA to arachidonic acid (AA) and adrenal acid (AdA) to form fatty acyl-

coA esters.[53] Then, under the catalysis of lysophosphatidylcholine transferase 3 (LPCAT3), AA-CoA and AdA-CoA react with PC or PE to form PE-AA and PE-AdA.[54] Lipoxygenases (LOXs) are dioxygenases that catalyze the peroxidation of PUFAs to produce various lipid peroxides and bioactive lipids in the presence of molecular oxygen.[55,56] Genetic or pharmacological inhibition of ACSL4 inhibited ferroptosis by preventing the esterification of AA or AdA into PE, which was the only lipid oxidized in endoplasmic-reticulum-associated compartments during ferroptosis.[57] Arachidonate 12-Lipoxygenase (ALOX12) was indispensable for p53 induced ferroptosis and dispensable for erastin induced ferroptosis.[58] In addition, Genome-wide CRISPR/Cas9-mediated screen uncovered that cytochrome P450 oxidoreductase promoted ferroptosis across a wide range of lineages and cell-states by peroxidation of membrane polyunsaturated phospholipids.[59] The relationship between ferroptosis and lipid metabolism is complex, and its specific mechanism still needs to be further explored.

Mevalonate pathway

The mevalonate pathway occurs in the cytoplasm, where Acetoacetyl-CoA thiolase (AACT) produces acetoacetyl-CoA by condensation of two units of acetyl-coA, and then 3-hydroxy-3-methylglutaryl CoA synthase (HMGS) condensates acetoacetyl-CoA and acetyl-CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), which is then catalyzed by hydroxymethylglutaryl-CoA reductase (HMGR) to generate mevalonic acid (MVA).[60] MVA is then phosphorylated by MVA kinase and converted to isopentenyl pyrophosphate (IPP), which contributes to the synthesis of farnesyl pyrophosphate (FPP). FPP is converted to squalene, and finally squalene is converted to cholesterol.[61] In addition, FPP can also participate in the production of CoQ10.[62] Thus, the mevalonate pathway finally leads to the production of CoQ10, cholesterol, and IPP (Fig. 3).[7,52,63] CoQ10 is a fat-soluble antioxidant with the function of scavenging oxygen free radicals, protecting lipids in golgi and plasma membranes from oxidation.[7,64] Ferroptosis suppressor protein 1 (FSP1) with myristic acylation is recruited to the plasma membrane to reduce CoQ10 by using NAD(P)H, preventing the reproduction of lipid peroxides, thus inhibiting ferroptosis.[65–68] FSP1-CoQ10-NAD(P)H pathway is the stand-alone parallel system with GSH-GPX4 pathway to inhibit phospholipid peroxidation and ferroptosis.[69]

In addition, the mevalonate pathway participates in ferroptosis by supplying IPP for production of selenoproteins, including GPX4. As an intermediate product of the mevalonate pathway, IPP is required for isoprenylation of selenocysteine tRNA, which is indispensable for synthesizing selenoprotein GPX4.[70] HMGR inhibitor statins reduced GPX4 expression in cancer cells, leading to elevated lipid peroxides and making cancer cells sensitive to ferroptosis.[71]

p53

p53 is a well-known tumor suppressor that induces cell cycle arrest and cell apoptosis. Recently, it has been reported that p53 induces ferroptosis through pleiotropic effect.[72] Mutant $p53^{3KR}$, which is defective for the conventional p53 functions, still be able to repress SLC7A11 and induce ferroptosis upon ROS-induced stress.[73,74] In addition, p53 induced ferroptosis required enzymatic activity of ALOX12, which is inhibited by SLC7A11, but independent of GPX4.[58] Recently, scientists found that p53-driven ferroptosis under ROS stress can also suppressed by calcium-independent phospholipase iPLA2β, which mediated detoxification of peroxidized lipids.[75]

Moreover, p53 induced ferroptosis by directly activating its target gene spermidine/spermine N1-acetyltransferase 1 (SAT1), which induced lipid peroxidation.[76] p53 suppresses tumor through regulating its target gene, glutamine synthase 2 (GLS2), which exerts antioxidant defense function.[77] Another article reported that GLS2 knockdown inhibits ferroptosis in mouse embryonic fibroblasts.[78] Therefore, whether p53 induces ferroptosis by promoting GLS2 expression is worth further investigation.

However, wild-type p53 could delay induction of ferroptosis by regulating its transcriptional target CDKN1A (encoding p21).[79] p53 can also inhibit ferroptosis in a transcription-independent manner. For example, the deletion of p53 prevents the nuclear accumulation of dipeptidyl peptidase-4 (DPP4), thus facilitates plasma-membrane-associated DPP4-dependent lipid peroxidation, which finally results in ferroptosis.[80]

Targeting ferroptosis in cancer

In recent years, more and more researchers are committed to discovering the development process of cancer, and found that ferroptosis is closely related to the occurrence and development of cancers. The ferroptosis inducers are attracting increasing attention in cancer treatment. In addition, ferroptosis inducers can enhance the effect of chemotherapy by inducing ferroptosis and reducing chemotherapy resistance, thereby improving the treatment effect. In this part, we elucidate the rational of targeting ferroptosis and the reported ferroptosis inducers (Table 1)[1,7,13,22,81–115].

SLC7A11 inhibitors

SLC7A11 mediates uptake of extracellular cystine, which guarantees glutathione synthesis and maintains GPX4 enzyme activity to inhibit ferroptosis.[15,20] SLC7A11 overexpression has been observed in hepatocellular carcinoma and is associated with poor prognosis.[116,117] SLC7A11 is regulated by multiple enzymes and pathways. It has been reported that mutant p53 fail to induce cell cycle arrest and cell apoptosis, but still be able to repress SLC7A11 and induce ferroptosis upon ROS-induced stress.[73,74] Tumor suppressor BRCA1-associated protein 1 (BAP1) frequently mutated or deleted in sporadic human cancers, inactivation of BAP1 inhibited ferroptosis by releasing SLC7A11 inhibition, thus BAP1 mutated cancer cells were sensitive to SLC7A11 inhibitor erastin.[118] OTUB1 is overexpressed in a variety of human cancers, and it can inhibit ferroptosis by stabilizing SLC7A11.[119] In short, SLC7A11 is an important target for the treatment of cancer and more and more SLC7A11 inhibitors have been discovered and reported.

In 2012, researchers firstly proposed that erastin induced ferroptosis by inhibiting System Xc^- activity.[1] Later, more reports proved that erastin induce ferroptosis by inhibiting SLC7A11 activity in variety of cancer cells.[81,120] Given the fact that poor water solubility and unstability of erastin, a metabolically stable erastin analogue, imidazole ketone erastin (IKE), has been developed.[22,82] Sorafenib, as a multi-target kinase inhibitor, is clinically used for the treatment of unresectable hepatocellular carcinoma.[121] In 2014, it was firstly reported that sorafenib can induce ferroptosis by inhibiting System Xc^-.[122] However, it was recently reported that Sorafenib could not induce ferroptosis by inhibiting System Xc^-, thus it might not be a true ferroptosis inducer.[123] Sulfasalazine is clinically used for treating ulcerative colitis.[124] Recent study found that sulfasalazine is also a novel potent inhibitor of the System Xc^-.[83] However, all SLC7A11 inhibitors currently identified, including sulfasalazine and erastin, have off-target effects, which limits their clinical use as SLC7A11 specific inhibitors.[125]

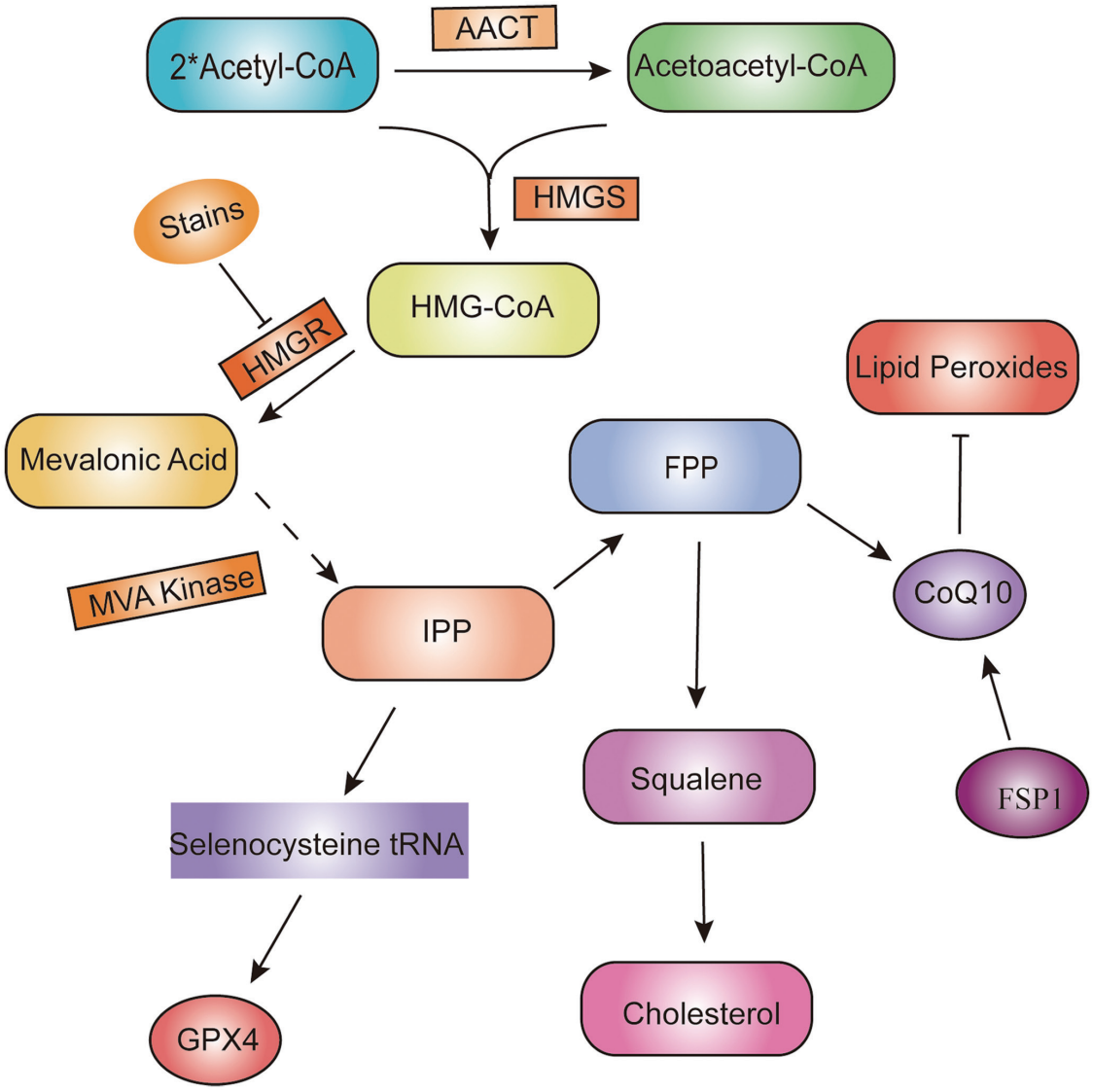

Fig. 3. Mevalonate pathway. AACT, acetoacetyl-CoA thiolase; HMGS, 3-hydroxy-3-methylglutaryl-CoA synthase; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; HMGR, hydroxymethylglutaryl CoA reductase; MVA, mevalonic acid; IPP, isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; CoQ10, Coenzyme Q10; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4.

In addition, a variety of compounds have been reported to be able to indirectly inhibit SLC7A11, such as the newly discovered small molecule compound 6-Thioguanine,[84] the drug Tirapazamine,[85] and T-2 Toxin.[86] The oral anti-diabetic drug metformin can also reduce the stability of SLC7A11 by inhibiting UFMylation of SLC7A11, and its combination with sulfasalazine can synergistically induce ferroptosis in breast cancer cells.[87] Some natural products, including Talaroconvolutin A,[88] Tanshinone IIA,[89] Actinidia chinensis Planch and Capsaicin,[90,91] can also induce ferroptosis by partially inhibiting SLC7A11.

GPX4 inhibitors

GPX4 is a selenase that utilizes GSH as a cofactor to reduce membrane phospholipid peroxide to maintain cellular redox homeostasis, thus negatively regulating ferroptosis.[20] Pharmacological inhibition or genetic absence of GPX4 induce ferroptosis in mouse tumor xenografts.[19] Analyzing the data from TCGA, scientists found that GPX4 expression in various cancer tissues is higher than that in normal tissues, and it is negatively correlated with the prognosis of cancer patients.[126] High expression of GPX4 promotes tumor recurrence in melanoma xenograft mice models.[71] In addition, GPX4 plays important role in the survival of drug resistant cancer cells.[127] Therefore, GPX4 serves as the potential target to treat cancer by inducing ferroptosis.

The first reported GPX4 inhibitor RSL3 covalently interacts with selenocysteine, the active site of GPX4, to inhibit enzymatic activity of GPX4, thus inducing ferroptosis.[13] Poor pharmacokinetic property of RSL3 restricted its application in vivo. Recent studies reported that small-molecule compound QD394 and compound 26a induce ferroptosis by directly targeting GPX4.[92,93] In addition, many small-molecule compounds induce ferroptosis mainly through GPX4 inhibition, including Jiyuan oridonin A

Table 1. Ferroptosis inducers

Ferroptosis inducers	Target	Basic mechanism	Tumor type	Reference
Erastin, IKE, Sorafenib, Sulfasalazine, 6-Thioguanine	SLC7A11	Inhibit System Xc^-	Fibrosarcoma, Colorectal cancer, Diffuse large B cell lymphoma, Astrocytoma, Lung carcinoma cancer, Lymphoma, Non-Hodgkin's lymphoma,Gastric cancer	1,86,22,82,83,84
Tirapazamine, T-2 Toxin,Tanshinone IIA, Talaroconvolutin A	SLC7A11	Inhibit the expression of SLC7A11	Osteosarcoma, Lung cancer,Gastric cancer,Colorectal cancer	85,86,88,89
Metformin	SLC7A11	Reduces the protein stability of SLC7A11	Breast cancer	87
Actinidia chinensis Planch, Capsaicin	SLC7A11	Inhibit the expression of SLC7A11 and GPX4	Gastric cancer, Non-small cell lung cancer	90,91
RSL3, QD394, Compound 26a, Honokiol, FINO2,	GPX4	Inhibit GPX4 enzymatic activity	Renal carcinoma, Colon cancer, B-lymphoblastic cell leukemia line, Pancreatic cancer, Breast cancer, Breast adenocarcinoma, Fibrosarcoma	13,92,93,103,110
Jiyuan oridonin A derivative a2 Compound 21, Tetrahydro citrate, Bufortaline, Dihydroisotanshinone I Solasonine, Cucurbitin B, Gambogenic acid, Thiostrepton, Red ginseng polysaccharide, Apatinib, Simvastatin, Atorvastatin	GPX4	Downregulate GPX4 expression	Gastric cancer, Hepatocellular carcinoma, Nasopharyngeal carcinoma, Melanoma, Human cardiomyocytes, Murine skeletal muscle cells, Breast cancer, Non-small cell lung cancer, Lung cancer, Gastric cancer, Triple-negative breast cancer, Pancreatic cancer	94–109,102,104–109
DMOCPTL, FIN56	GPX4	Promote degradation of GPX4,	Triple-negative breast cancer, Fibrosarcoma	7,101
Curcumin analogues EF24, Cadmium	HMOX1	Directly up-regulating HMOX1 expression	Osteosarcoma, Hepatic stellate cells	111,112
Artesunate, Saponin Formosanin C	Ferritin	Promote ferritin phagocytosis	Hepatic stellate cells, Hepatocellular carcinoma	113,114
Baicalin	Ferritin	Down-regulate ferritin	Bladder cancer	115

DMOCPTL, derivative of natural product parthenolide; EF24, 3,5-bis (2-fluorobenzylidine)-4-pyperidone; FIN56, ferroptosis inducing 56; FINO2, 1,2-dioxolane; HMOX1, heme-oxygenase 1; IKE, imidazole ketone erastin; QD394, quinazolinedione reactive oxygen species inducer; RSL3, RAS-selective lethal 3; SLC7A11, solute carrier family 7 member 11.

derivative a2,[94] compound 21,[95] tetrahydrocitrate,[96] and Bufortaline.[97] It has long been reported that many natural products inhibited cancer cells through multiple targets. Accompany with the report of ferroptosis, researchers found that many natural compounds, including dihydroisotanshinone I,[98,99] solasonine,[100] DMOCPTL,[101] cucurbitin B,[102] and honokiol[103] could induce ferroptosis by inhibiting GPX4 activity or reducing GPX4 protein level. Natural products gambogenic acid,[104] thiostrepton,[105] and red ginseng polysaccharide[106] could suppress GPX4 expression by regulating upstream transcriptional factors, thus inducing ferroptosis. In addition, small molecule compounds atorvastatin, apatinib, and simvastatin induce ferroptosis by indirectly downregulating GPX4.[107–109] The discovery of GPX4 inhibitors also supplies the information for the regulation of GPX4 in cancer cells.

FIN56

As a type 3 ferroptosis inducer, FIN56 induces ferroptosis by promoting GPX4 degradation.[7] Except degrading GPX4, FIN56 can also reduce intracellular antioxidants (like CoQ10) by activating squalene synthase, thus promoting cellular lipid peroxidation and ferroptosis.[7] In addition, FIN56-induced ferroptosis is related to autophagy, and inhibition of autophagy at different stages could weaken FIN56-induced lipid peroxidation and GPX4 degradation.[128]

FINO2

FINO2 triggers ferroptosis through mechanisms different from that of SLC7A11 inhibitors or GPX4 inhibitors.[14] FINO2, serves as an endoperoxide, induces ferroptosis by directly oxidizing iron and indirectly inhibiting GPX4, which effect can be reversed by iron chelating agents.[110]

Others ferroptosis inducers

In addition to above mentioned ferroptosis inducers, researchers have developed many ferroptosis inducers by targeting other key ferroptosis regulators, like heme oxygenase-1 (HMOX1), ferrous ions or ACSL4 etc. HMOX1 protects cell through its byproduct

bilirubin, and its overexpression reduces ROS levels and lipid peroxidation.[129] Combination of lapatinib and cilacine co-induces ferroptosis by reducing heme oxygenase-1 protein expression.[129] However, it has also been reported that HMOX1 can induce cell death by promoting intracellular ferrous accumulation.[130] Newly discovered ferroptosis inducers such as curcumin analogues EF24[111] and heavy metal cadmium[112] can induce ferroptosis by directly up-regulating HMOX1 expression.

Triggering ferritin phagocytosis, a lysosome-mediated autophagy process that degrading ferritin and inducing ferroptosis, is a new strategy to induce ferroptosis.[131] It had been reported that natural compounds Artesunate,[113] Saponin Formosanin C,[114] and Arsenite[132] can induce ferroptosis by promoting ferritin phagocytosis. The natural product Baicalin can also induce ferroptosis by down-regulating ferritin heavy chain 1.[115]

In addition, Yiqi Huayu Decoction, created by Professor Liu Shenlin, can cause ferroptosis through multiple targets, such as reducing the content of GSH in cells and up-regulating the expression of ACSL4.[133]

Future directions

Ferroptosis, as a newly discovered programmed cell death, plays important role in cancer. The biology functions of SLC7A11 and GPX4 in ferroptosis have been well investigated. Relationship of ferroptosis with iron and lipid metabolisms are complicated, and are gradually investigated. Ferroptosis also co-occur with autophagy and apoptosis, but the mechanism is still unclear. In addition, diversity of cancer makes ferroptosis executing differently in different cancer types. Thus, it is still a challenge to totally understand the ferroptosis in cancer. Like the other anti-tumor drugs or molecules, ferroptosis inducers also face the problems of selectivity, sensitivity and pharmacokinetics. There is an urgent need to develop high selective ferroptosis inducer to reduce toxicity.

Conclusions

Ferroptosis has been discovered for 10 years, we have known many knowledge of ferroptosis, but the mechanism of ferroptosis, especially the lipid metabolism in ferroptosis, is still unclear. Given the role of ferroptosis in cancer, many ferroptosis inducers have been discovered and reported, and the ferroptosis inducers also help the investigation of ferroptosis. This paper reviews the research progress of ferroptosis signaling pathways and ferroptosis inducers. Although great progress has been made in ferroptosis-related research in recent years, specific regulatory mechanisms and targets of ferroptosis inducers have yet to be explored.

Acknowledgments

None.

Funding

This work was supported by grants from Key Science Project of University in Henan (23A350007 for YCX), and National Natural Science Foundation of China (No. U2004101 for PXH).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization and supervision (YCX), drafting of the manuscript (YJJ), critical revision of the manuscript (PXH), review and editing (YZ, XBM, YW and YQT). All authors have made a significant contribution to this study and have approved the final manuscript.

References

[1] 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):1060–1072. doi:10.1016/j.cell.2012.03.042, PMID:22632970.

[2] Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, *et al*. Ferroptosis: process and function. Cell Death Differ 2016;23(3):369–379. doi:10.1038/cdd.2015.158, PMID:26794443.

[3] Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, *et al*. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell 2017;171(2):273–285. doi:10.1016/j.cell.2017.09.021, PMID:28985560.

[4] Bai Y, Meng L, Han L, Jia Y, Zhao Y, Gao H, *et al*. Lipid storage and lipophagy regulates ferroptosis. Biochem Biophys Res Commun 2019;508(4):997–1003. doi:10.1016/j.bbrc.2018.12.039, PMID:30545638.

[5] Nakamura T, Naguro I, Ichijo H. Iron homeostasis and iron-regulated ROS in cell death, senescence and human diseases. Biochim Biophys Acta Gen Subj 2019;1863(9):1398–1409. doi:10.1016/j.bbagen.2019.06.010, PMID:31229492.

[6] McBean GJ. The transsulfuration pathway: a source of cysteine for glutathione in astrocytes. Amino Acids 2012;42(1):199–205. doi:10.1007/s00726-011-0864-8, PMID:21369939.

[7] Shimada K, Skouta R, Kaplan A, Yang WS, Hayano M, Dixon SJ, *et al*. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat Chem Biol 2016;12(7):497–503. doi:10.1038/nchembio.2079, PMID:27159577.

[8] Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, *et al*. Ferroptosis: past, present and future. Cell Death Dis 2020;11(2):88. doi:10.1038/s41419-020-2298-2, PMID:32015325.

[9] Lei G, Zhang Y, Koppula P, Liu X, Zhang J, Lin SH, *et al*. The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression. Cell Res 2020;30(2):146–162. doi:10.1038/s41422-019-0263-3, PMID:31949285.

[10] Wang Y, Wu X, Ren Z, Li Y, Zou W, Chen J, *et al*. Overcoming cancer chemotherapy resistance by the induction of ferroptosis. Drug Resist Updat 2023;66:100916. doi:10.1016/j.drup.2022.100916, PMID:36610291.

[11] Yang WS, Stockwell BR. Ferroptosis: Death by Lipid Peroxidation. Trends Cell Biol 2016;26(3):165–176. doi:10.1016/j.tcb.2015.10.014, PMID:26653790.

[12] Feng H, Stockwell BR. Unsolved mysteries: How does lipid peroxidation cause ferroptosis? PLoS Biol 2018;16(5):e2006203. doi:10.1371/journal.pbio.2006203, PMID:29795546.

[13] Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proc Natl Acad Sci U S A 2016;113(34):E4966–E4975. doi:10.1073/pnas.1603244113, PMID:27506793.

[14] Gaschler MM, Andia AA, Liu H, Csuka JM, Hurlocker B, Vaiana CA, *et al*. $FINO_2$ initiates ferroptosis through GPX4 inactivation and iron oxidation. Nat Chem Biol 2018;14(5):507–515. doi:10.1038/s41589-018-0031-6, PMID:29610484.

[15] Ji X, Qian J, Rahman SMJ, Siska PJ, Zou Y, Harris BK, *et al*. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. Oncogene 2018;37(36):5007–5019. doi:10.1038/s41388-018-0307-z, PMID:29789716.

[16] Nakamura E, Sato M, Yang H, Miyagawa F, Harasaki M, Tomita K, *et al*. 4F2 (CD98) heavy chain is associated covalently with an amino acid transporter and controls intracellular trafficking and membrane topology of 4F2 heterodimer. J Biol Chem 1999;274(5):3009–3016. doi:10.1074/jbc.274.5.3009, PMID:9915839.

[17] Gu Y, Albuquerque CP, Braas D, Zhang W, Villa GR, Bi J, *et al*. mTORC2 Regulates Amino Acid Metabolism in Cancer by Phosphorylation of the Cystine-Glutamate Antiporter xCT. Mol Cell 2017;67(1):128–138. e7. doi:10.1016/j.molcel.2017.05.030, PMID:28648777.
[18] Koppula P, Zhuang L, Gan B. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. Protein Cell 2021;12(8):599–620. doi:10.1007/s13238-020-00789-5, PMID:33000412.
[19] Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, *et al*. Regulation of ferroptotic cancer cell death by GPX4. Cell 2014;156(1-2):317–331. doi:10.1016/j.cell.2013.12.010, PMID:24439385.
[20] Seiler A, Schneider M, Förster H, Roth S, Wirth EK, Culmsee C, *et al*. Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. Cell Metab 2008;8(3):237–248. doi:10.1016/j.cmet.2008.07.005, PMID: 18762024.
[21] Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Buday K, *et al*. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. Cell 2018;172(3):409–422.e21. doi:10.1016/j.cell.2017.11.048, PMID:29290465.
[22] Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu H, Brown LM, *et al*. Imidazole Ketone Erastin Induces Ferroptosis and Slows Tumor Growth in a Mouse Lymphoma Model. Cell Chem Biol 2019;26(5):623–633. e9. doi:10.1016/j.chembiol.2019.01.008, PMID:30799221.
[23] Armstrong JS, Steinauer KK, Hornung B, Irish JM, Lecane P, Birrell GW, *et al*. Role of glutathione depletion and reactive oxygen species generation in apoptotic signaling in a human B lymphoma cell line. Cell Death Differ 2002;9(3):252–263. doi:10.1038/sj.cdd.4400959, PMID:11859408.
[24] Yudkoff M. Chapter 42 - Disorders of Amino Acid Metabolism. In: Basic Neurochemistry. 8th ed. Elsevier; 2012:737–754. doi:10.1016/B978-0-12-374947-5.00042-0.
[25] Mota-Martorell N, Jové M, Borrás C, Berdún R, Obis È, Sol J, *et al*. Methionine transsulfuration pathway is upregulated in long-lived humans. Free Radic Biol Med 2021;162:38–52. doi:10.1016/j.freeradbiomed.2020.11.026, PMID:33271279.
[26] Liang Q, Ou M, Ren Y, Yao Z, Hu R, Li J, *et al*. Molecular cloning, characterization and expression analysis of S- adenosyl- L-homocysteine hydrolase (SAHH) during the pathogenic infection of Litopenaeus vannamei by Vibrio alginolyticus. Fish Shellfish Immunol 2019;88:284–292. doi:10.1016/j.fsi.2019.02.058, PMID:30849500.
[27] Zhu J, Berisa M, Schwörer S, Qin W, Cross JR, Thompson CB. Transsulfuration Activity Can Support Cell Growth upon Extracellular Cysteine Limitation. Cell Metab 2019;30(5):865–876.e5. doi:10.1016/j.cmet.2019.09.009, PMID:31607565.
[28] Hayano M, Yang WS, Corn CK, Pagano NC, Stockwell BR. Loss of cysteinyl-tRNA synthetase (CARS) induces the transsulfuration pathway and inhibits ferroptosis induced by cystine deprivation. Cell Death Differ 2016;23(2):270–278. doi:10.1038/cdd.2015.93, PMID:26184909.
[29] Takahashi-Niki K, Niki T, Iguchi-Ariga SMM, Ariga H. Transcriptional Regulation of DJ-1. Adv Exp Med Biol 2017;1037:89–95. doi:10.1007/978-981-10-6583-5_7, PMID:29147905.
[30] Cao J, Chen X, Jiang L, Lu B, Yuan M, Zhu D, *et al*. DJ-1 suppresses ferroptosis through preserving the activity of S-adenosyl homocysteine hydrolase. Nat Commun 2020;11(1):1251. doi:10.1038/s41467-020-15109-y, PMID:32144268.
[31] Gao G, Li J, Zhang Y, Chang YZ. Cellular Iron Metabolism and Regulation. Adv Exp Med Biol 2019;1173:21–32. doi:10.1007/978-981-13-9589-5_2, PMID:31456203.
[32] Galaris D, Pantopoulos K. Oxidative stress and iron homeostasis: mechanistic and health aspects. Crit Rev Clin Lab Sci 2008;45(1):1–23. doi:10.1080/10408360701713104, PMID:18293179.
[33] Puntarulo S. Iron, oxidative stress and human health. Mol Aspects Med 2005;26(4-5):299–312. doi:10.1016/j.mam.2005.07.001, PMID:16102805.
[34] Huang LL, Liao XH, Sun H, Jiang X, Liu Q, Zhang L. Augmenter of liver regeneration protects the kidney from ischaemia-reperfusion injury in ferroptosis. J Cell Mol Med 2019;23(6):4153–4164. doi:10.1111/jcmm.14302, PMID:30993878.
[35] Zhao Z. Iron and oxidizing species in oxidative stress and Alzheimer's disease. Aging Med (Milton) 2019;2(2):82–87. doi:10.1002/agm2.12074, PMID:31942516.
[36] van Renswoude J, Bridges KR, Harford JB, Klausner RD. Receptor-mediated endocytosis of transferrin and the uptake of fe in K562 cells: identification of a nonlysosomal acidic compartment. Proc Natl Acad Sci U S A 1982;79(20):6186–6190. doi:10.1073/pnas.79.20.6186, PMID:6292894.
[37] Dautry-Varsat A, Ciechanover A, Lodish HF. pH and the recycling of transferrin during receptor-mediated endocytosis. Proc Natl Acad Sci U S A 1983;80(8):2258–2262. doi:10.1073/pnas.80.8.2258, PMID: 6300903.
[38] Wang J, Pantopoulos K. Regulation of cellular iron metabolism. Biochem J 2011;434(3):365–381. doi:10.1042/BJ20101825, PMID:21348856.
[39] Torti SV, Torti FM. Iron and cancer: more ore to be mined. Nat Rev Cancer 2013;13(5):342–355. doi:10.1038/nrc3495, PMID:23594855.
[40] Mancias JD, Pontano Vaites L, Nissim S, Biancur DE, Kim AJ, Wang X, *et al*. Ferritinophagy via NCOA4 is required for erythropoiesis and is regulated by iron dependent HERC2-mediated proteolysis. Elife 2015;4:e10308. doi:10.7554/eLife.10308, PMID:26436293.
[41] Ramey G, Deschemin JC, Durel B, Canonne-Hergaux F, Nicolas G, Vaulont S. Hepcidin targets ferroportin for degradation in hepatocytes. Haematologica 2010;95(3):501–504. doi:10.3324/haematol.2009.014399, PMID:19773263.
[42] Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, *et al*. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 2004;306(5704):2090–2093. doi:10.1126/science.1104742, PMID:15514116.
[43] Gryzik M, Asperti M, Denardo A, Arosio P, Poli M. NCOA4-mediated ferritinophagy promotes ferroptosis induced by erastin, but not by RSL3 in HeLa cells. Biochim Biophys Acta Mol Cell Res 2021;1868(2):118913. doi:10.1016/j.bbamcr.2020.118913, PMID:33245979.
[44] Geng N, Shi BJ, Li SL, Zhong ZY, Li YC, Xua WL, *et al*. Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells. Eur Rev Med Pharmacol Sci 2018;22(12):3826–3836. doi:10.26355/eurrev_201806_15267, PMID:29949159.
[45] Ma S, Henson ES, Chen Y, Gibson SB. Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells. Cell Death Dis 2016;7(7):e2307. doi:10.1038/cddis.2016.208, PMID:27441659.
[46] Maio N, Zhang DL, Ghosh MC, Jain A, SantaMaria AM, Rouault TA. Mechanisms of cellular iron sensing, regulation of erythropoiesis and mitochondrial iron utilization. Semin Hematol 2021;58(3):161–174. doi:10.1053/j.seminhematol.2021.06.001, PMID:34389108.
[47] Volz K. Conservation in the Iron Responsive Element Family. Genes (Basel) 2021;12(9):1365. doi:10.3390/genes12091365, PMID:34573347.
[48] Zhou ZD, Tan EK. Iron regulatory protein (IRP)-iron responsive element (IRE) signaling pathway in human neurodegenerative diseases. Mol Neurodegener 2017;12(1):75. doi:10.1186/s13024-017-0218-4, PMID:29061112.
[49] Anderson GJ, Frazer DM. Current understanding of iron homeostasis. Am J Clin Nutr 2017;106(Suppl 6):1559S–1566S. doi:10.3945/ajcn.117.155804, PMID:29070551.
[50] Nemeth E, Ganz T. Hepcidin-Ferroportin Interaction Controls Systemic Iron Homeostasis. Int J Mol Sci 2021;22(12):6493. doi:10.3390/ijms22126493, PMID:34204327.
[51] 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):242–254. doi:10.1038/s41418-019-0352-3, PMID:31114026.
[52] Lee JY, Kim WK, Bae KH, Lee SC, Lee EW. Lipid Metabolism and Ferroptosis. Biology (Basel) 2021;10(3):184. doi:10.3390/biology10030184, PMID:33801564.
[53] Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, *et al*. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol 2017;13(1):91–98. doi:10.1038/nchembio.2239, PMID:27842070.
[54] Hishikawa D, Shindou H, Kobayashi S, Nakanishi H, Taguchi R, Shimizu T. Discovery of a lysophospholipid acyltransferase family essential for membrane asymmetry and diversity. Proc Natl Acad Sci U S A 2008;105(8):2830–2835. doi:10.1073/pnas.0712245105, PMID:18287005.
[55] Pidgeon GP, Lysaght J, Krishnamoorthy S, Reynolds JV, O'Byrne K, Nie

D, *et al*. Lipoxygenase metabolism: roles in tumor progression and survival. Cancer Metastasis Rev 2007;26(3-4):503–524. doi:10.1007/s10555-007-9098-3, PMID:17943411.
[56] Merchant N, Bhaskar LVKS, Momin S, Sujatha P, Reddy ABM, Nagaraju GP. 5-Lipoxygenase: Its involvement in gastrointestinal malignancies. Crit Rev Oncol Hematol 2018;127:50–55. doi:10.1016/j.critrevonc.2018.05.012, PMID:29891111.
[57] Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, *et al*. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol 2017;13(1):81–90. doi:10.1038/nchembio.2238, PMID:27842066.
[58] Chu B, Kon N, Chen D, Li T, Liu T, Jiang L, *et al*. ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. Nat Cell Biol 2019;21(5):579–591. doi:10.1038/s41556-019-0305-6, PMID:30962574.
[59] Zou Y, Li H, Graham ET, Deik AA, Eaton JK, Wang W, *et al*. Cytochrome P450 oxidoreductase contributes to phospholipid peroxidation in ferroptosis. Nat Chem Biol 2020;16(3):302–309. doi:10.1038/s41589-020-0472-6, PMID:32080622.
[60] Liao P, Hemmerlin A, Bach TJ, Chye ML. The potential of the mevalonate pathway for enhanced isoprenoid production. Biotechnol Adv 2016;34(5):697–713. doi:10.1016/j.biotechadv.2016.03.005, PMID:26995109.
[61] Guerra B, Recio C, Aranda-Tavío H, Guerra-Rodríguez M, García-Castellano JM, Fernández-Pérez L. The Mevalonate Pathway, a Metabolic Target in Cancer Therapy. Front Oncol 2021;11:626971. doi:10.3389/fonc.2021.626971, PMID:33718197.
[62] Zaleski AL, Taylor BA, Thompson PD. Coenzyme Q10 as Treatment for Statin-Associated Muscle Symptoms-A Good Idea, but…. Adv Nutr 2018;9(4):519S–523S. doi:10.1093/advances/nmy010, PMID:30032220.
[63] Zheng J, Conrad M. The Metabolic Underpinnings of Ferroptosis. Cell Metab 2020;32(6):920–937. doi:10.1016/j.cmet.2020.10.011, PMID:33217331.
[64] Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. Biochim Biophys Acta 2004;1660(1-2):171–199. doi:10.1016/j.bbamem.2003.11.012, PMID:14757233.
[65] Frei B, Kim MC, Ames BN. Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci U S A 1990;87(12):4879–4883. doi:10.1073/pnas.87.12.4879, PMID:2352956.
[66] Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, *et al*. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature 2019;575(7784):688–692. doi:10.1038/s41586-019-1705-2, PMID:31634900.
[67] Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, *et al*. FSP1 is a glutathione-independent ferroptosis suppressor. Nature 2019;575(7784):693–698. doi:10.1038/s41586-019-1707-0, PMID:31634899.
[68] Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Res 2021;31(2):107–125. doi:10.1038/s41422-020-00441-1, PMID:33268902.
[69] Hadian K. Ferroptosis Suppressor Protein 1 (FSP1) and Coenzyme Q(10) Cooperatively Suppress Ferroptosis. Biochemistry 2020;59(5):637–638. doi:10.1021/acs.biochem.0c00030, PMID:32003211.
[70] Warner GJ, Berry MJ, Moustafa ME, Carlson BA, Hatfield DL, Faust JR. Inhibition of selenoprotein synthesis by selenocysteine tRNA[Ser]Sec lacking isopentenyladenosine. J Biol Chem 2000;275(36):28110–28119. doi:10.1074/jbc.M001280200, PMID:10821829.
[71] Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, *et al*. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. Nature 2017;547(7664):453–457. doi:10.1038/nature23007, PMID:28678785.
[72] Jiang L, Hickman JH, Wang SJ, Gu W. Dynamic roles of p53-mediated metabolic activities in ROS-induced stress responses. Cell Cycle 2015;14(18):2881–2885. doi:10.1080/15384101.2015.1068479, PMID:26218928.
[73] Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, *et al*. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015;520(7545):57–62. doi:10.1038/nature14344, PMID:25799988.
[74] Kang R, Kroemer G, Tang D. The tumor suppressor protein p53 and the ferroptosis network. Free Radic Biol Med 2019;133:162–168. doi:10.1016/j.freeradbiomed.2018.05.074, PMID:29800655.
[75] Chen D, Chu B, Yang X, Liu Z, Jin Y, Kon N, *et al*. iPLA2β-mediated lipid detoxification controls p53-driven ferroptosis independent of GPX4. Nat Commun 2021;12(1):3644. doi:10.1038/s41467-021-23902-6, PMID:34131139.
[76] Ou Y, Wang SJ, Li D, Chu B, Gu W. Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. Proc Natl Acad Sci U S A 2016;113(44):E6806–E6812. doi:10.1073/pnas.1607152113, PMID:27698118.
[77] Hu W, Zhang C, Wu R, Sun Y, Levine A, Feng Z. Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. Proc Natl Acad Sci U S A 2010;107(16):7455–7460. doi:10.1073/pnas.1001006107, PMID:20378837.
[78] Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and Transferrin Regulate Ferroptosis. Mol Cell 2015;59(2):298–308. doi:10.1016/j.molcel.2015.06.011, PMID:26166707.
[79] Tarangelo A, Magtanong L, Bieging-Rolett KT, Li Y, Ye J, Attardi LD, *et al*. p53 Suppresses Metabolic Stress-Induced Ferroptosis in Cancer Cells. Cell Rep 2018;22(3):569–575. doi:10.1016/j.celrep.2017.12.077, PMID:29346757.
[80] Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, *et al*. The Tumor Suppressor p53 Limits Ferroptosis by Blocking DPP4 Activity. Cell Rep 2017;20(7):1692–1704. doi:10.1016/j.celrep.2017.07.055, PMID:28813679.
[81] Xu X, Zhang X, Wei C, Zheng D, Lu X, Yang Y, *et al*. Targeting SLC7A11 specifically suppresses the progression of colorectal cancer stem cells via inducing ferroptosis. Eur J Pharm Sci 2020;152:105450. doi:10.1016/j.ejps.2020.105450, PMID:32621966.
[82] Larraufie MH, Yang WS, Jiang E, Thomas AG, Slusher BS, Stockwell BR. Incorporation of metabolically stable ketones into a small molecule probe to increase potency and water solubility. Bioorg Med Chem Lett 2015;25(21):4787–4792. doi:10.1016/j.bmcl.2015.07.018, PMID:26231156.
[83] Gout PW, Buckley AR, Simms CR, Bruchovsky N. Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x(c)- cystine transporter: a new action for an old drug. Leukemia 2001;15(10):1633–1640. doi:10.1038/sj.leu.2402238, PMID:11587223.
[84] Zhang J, Gao M, Niu Y, Sun J. From DNMT1 degrader to ferroptosis promoter: Drug repositioning of 6-Thioguanine as a ferroptosis inducer in gastric cancer. Biochem Biophys Res Commun 2022;603:75–81. doi:10.1016/j.bbrc.2022.03.026, PMID:35278883.
[85] Shi Y, Gong M, Deng Z, Liu H, Chang Y, Yang Z, *et al*. Tirapazamine suppress osteosarcoma cells in part through SLC7A11 mediated ferroptosis. Biochem Biophys Res Commun 2021;567:118–124. doi:10.1016/j.bbrc.2021.06.036, PMID:34147710.
[86] Wang G, Qin S, Zheng Y, Xia C, Zhang P, Zhang L, *et al*. T-2 Toxin Induces Ferroptosis by Increasing Lipid Reactive Oxygen Species (ROS) and Downregulating Solute Carrier Family 7 Member 11 (SLC7A11). J Agric Food Chem 2021;69(51):15716–15727. doi:10.1021/acs.jafc.1c05393, PMID:34918923.
[87] Yang J, Zhou Y, Xie S, Wang J, Li Z, Chen L, *et al*. Metformin induces Ferroptosis by inhibiting UFMylation of SLC7A11 in breast cancer. J Exp Clin Cancer Res 2021;40(1):206. doi:10.1186/s13046-021-02012-7, PMID:34162423.
[88] 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. doi:10.1038/s41419-020-03194-2, PMID:33203867.
[89] Guan Z, Chen J, Li X, Dong N. Tanshinone IIA induces ferroptosis in gastric cancer cells through p53-mediated SLC7A11 down-regulation. Biosci Rep 2020;40(8):BSR20201807. doi:10.1042/bsr20201807, PMID:32776119.
[90] Gao Z, Deng G, Li Y, Huang H, Sun X, Shi H, *et al*. Actinidia chinensis Planch prevents proliferation and migration of gastric cancer associated with apoptosis, ferroptosis activation and mesenchymal phenotype suppression. Biomed Pharmacother 2020;126:110092. doi:10.1016/j.biopha.2020.110092, PMID:32203890.
[91] Liu XY, Wei DG, Li RS. Capsaicin induces ferroptosis of NSCLC by regulating SLC7A11/GPX4 signaling in vitro. Sci Rep 2022;12(1):11996. doi:10.1038/s41598-022-16372-3, PMID:35835852.
[92] Hu S, Sechi M, Singh PK, Dai L, McCann S, Sun D, *et al*. A Novel Redox Modulator Induces a GPX4-Mediated Cell Death That Is Dependent

on Iron and Reactive Oxygen Species. J Med Chem 2020;63(17):9838–9855. doi:10.1021/acs.jmedchem.0c01016, PMID:32809827.
[93] Xu C, Xiao Z, Wang J, Lai H, Zhang T, Guan Z, *et al*. Discovery of a Potent Glutathione Peroxidase 4 Inhibitor as a Selective Ferroptosis Inducer. J Med Chem 2021;64(18):13312–13326. doi:10.1021/acs.jmedchem.1c00569, PMID:34506134.
[94] 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):1513–1525. doi:10.1016/j.apsb.2021.05.006, PMID:34221865.
[95] Wang H, Wu D, Gao C, Teng H, Zhao Y, He Z, *et al*. Seco-Lupane Triterpene Derivatives Induce Ferroptosis through GPX4/ACSL4 Axis and Target Cyclin D1 to Block the Cell Cycle. J Med Chem 2022;65(14):10014–10044. doi:10.1021/acs.jmedchem.2c00664, PMID:35801495.
[96] Yin J, Lin Y, Fang W, Zhang X, Wei J, Hu G, *et al*. Tetrandrine Citrate Suppresses Breast Cancer via Depletion of Glutathione Peroxidase 4 and Activation of Nuclear Receptor Coactivator 4-Mediated Ferritinophagy. Front Pharmacol 2022;13:820593. doi:10.3389/fphar.2022.820593, PMID:35614944.
[97] 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. doi:10.1016/j.freeradbiomed.2022.01.009, PMID:35038550.
[98] Lin YS, Shen YC, Wu CY, Tsai YY, Yang YH, Lin YY, *et al*. Danshen Improves Survival of Patients With Breast Cancer and Dihydroisotanshinone I Induces Ferroptosis and Apoptosis of Breast Cancer Cells. Front Pharmacol 2019;10:1226. doi:10.3389/fphar.2019.01226, PMID:31736748.
[99] Wu CY, Yang YH, Lin YS, Chang GH, Tsai MS, Hsu CM, *et al*. Dihydroisotanshinone I induced ferroptosis and apoptosis of lung cancer cells. Biomed Pharmacother 2021;139:111585. doi:10.1016/j.biopha.2021.111585, PMID:33862493.
[100] Jin M, Shi C, Li T, Wu Y, Hu C, Huang G. Solasonine promotes ferroptosis of hepatoma carcinoma cells via glutathione peroxidase 4-induced destruction of the glutathione redox system. Biomed Pharmacother 2020;129:110282. doi:10.1016/j.biopha.2020.110282, PMID:32531676.
[101] Ding Y, Chen X, Liu C, Ge W, Wang Q, Hao X, *et al*. Identification of a small molecule as inducer of ferroptosis and apoptosis through ubiquitination of GPX4 in triple negative breast cancer cells. J Hematol Oncol 2021;14(1):19. doi:10.1186/s13045-020-01016-8, PMID:33472669.
[102] Huang S, Cao B, Zhang J, Feng Y, Wang L, Chen X, *et al*. Induction of ferroptosis in human nasopharyngeal cancer cells by cucurbitacin B: molecular mechanism and therapeutic potential. Cell Death Dis 2021;12(3):237. doi:10.1038/s41419-021-03516-y, PMID:33664249.
[103] Guo C, Liu P, Deng G, Han Y, Chen Y, Cai C, *et al*. Honokiol induces ferroptosis in colon cancer cells by regulating GPX4 activity. Am J Cancer Res 2021;11(6):3039–3054. PMID:34249443.
[104] Wang M, Li S, Wang Y, Cheng H, Su J, Li Q. Gambogenic acid induces ferroptosis in melanoma cells undergoing epithelial-to-mesenchymal transition. Toxicol Appl Pharmacol 2020;401:115110. doi:10.1016/j.taap.2020.115110, PMID:32533954.
[105] Zhang W, Gong M, Zhang W, Mo J, Zhang S, Zhu Z, *et al*. Thiostrepton induces ferroptosis in pancreatic cancer cells through STAT3/GPX4 signalling. Cell Death Dis 2022;13(7):630. doi:10.1038/s41419-022-05082-3, PMID:35859150.
[106] Zhai FG, Liang QC, Wu YY, Liu JQ, Liu JW. Red ginseng polysaccharide exhibits anticancer activity through GPX4 downregulation-induced ferroptosis. Pharm Biol 2022;60(1):909–914. doi:10.1080/13880209.2022.2066139, PMID:35575436.
[107] Zhao L, Peng Y, He S, Li R, Wang Z, Huang J, *et al*. Apatinib induced ferroptosis by lipid peroxidation in gastric cancer. Gastric Cancer 2021;24(3):642–654. doi:10.1007/s10120-021-01159-8, PMID:33544270.
[108] 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. doi:10.1186/s12951-021-01058-1, PMID:34627266.
[109] Zhang Q, Qu H, Chen Y, Luo X, Chen C, Xiao B, *et al*. Atorvastatin Induces Mitochondria-Dependent Ferroptosis via the Modulation of Nrf2-xCT/GPx4 Axis. Front Cell Dev Biol 2022;10:806081. doi:10.3389/fcell.2022.806081, PMID:35309902.
[110] Abrams RP, Carroll WL, Woerpel KA. Five-Membered Ring Peroxide Selectively Initiates Ferroptosis in Cancer Cells. ACS Chem Biol 2016;11(5):1305–1312. doi:10.1021/acschembio.5b00900, PMID:26797166.
[111] Lin H, Chen X, Zhang C, Yang T, Deng Z, Song Y, *et al*. EF24 induces ferroptosis in osteosarcoma cells through HMOX1. Biomed Pharmacother 2021;136:111202. doi:10.1016/j.biopha.2020.111202, PMID:33453607.
[112] Zeng L, Zhou J, Wang X, Zhang Y, Wang M, Su P. Cadmium attenuates testosterone synthesis by promoting ferroptosis and blocking autophagosome-lysosome fusion. Free Radic Biol Med 2021;176:176–188. doi:10.1016/j.freeradbiomed.2021.09.028, PMID:34610361.
[113] Kong Z, Liu R, Cheng Y. Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. Biomed Pharmacother 2019;109:2043–2053. doi:10.1016/j.biopha.2018.11.030, PMID:30551460.
[114] Lin PL, Tang HH, Wu SY, Shaw NS, Su CL. Saponin Formosanin C-induced Ferritinophagy and Ferroptosis in Human Hepatocellular Carcinoma Cells. Antioxidants (Basel) 2020;9(8):E682. doi:10.3390/antiox9080682, PMID:32751249.
[115] Kong N, Chen X, Feng J, Duan T, Liu S, Sun X, *et al*. Baicalin induces ferroptosis in bladder cancer cells by downregulating FTH1. Acta Pharm Sin B 2021;11(12):4045–4054. doi:10.1016/j.apsb.2021.03.036, PMID:35024325.
[116] Huang Y, Dai Z, Barbacioru C, Sadée W. Cystine-glutamate transporter SLC7A11 in cancer chemosensitivity and chemoresistance. Cancer Res 2005;65(16):7446–7454. doi:10.1158/0008-5472.CAN-04-4267, PMID:16103098.
[117] Guo W, Zhao Y, Zhang Z, Tan N, Zhao F, Ge C, *et al*. Disruption of xCT inhibits cell growth via the ROS/autophagy pathway in hepatocellular carcinoma. Cancer Lett 2011;312(1):55–61. doi:10.1016/j.canlet.2011.07.024, PMID:21906871.
[118] Zhang Y, Shi J, Liu X, Feng L, Gong Z, Koppula P, *et al*. BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nat Cell Biol 2018;20(10):1181–1192. doi:10.1038/s41556-018-0178-0, PMID:30202049.
[119] Liu T, Jiang L, Tavana O, Gu W. The Deubiquitylase OTUB1 Mediates Ferroptosis via Stabilization of SLC7A11. Cancer Res 2019;79(8):1913–1924. doi:10.1158/0008-5472.CAN-18-3037, PMID:30709928.
[120] Song X, Zhu S, Chen P, Hou W, Wen Q, Liu J, *et al*. AMPK-Mediated BECN1 Phosphorylation Promotes Ferroptosis by Directly Blocking System X(c)(-) Activity. Curr Biol 2018;28(15):2388–2399.e5. doi:10.1016/j.cub.2018.05.094, PMID:30057310.
[121] Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008;7(10):3129–3140. doi:10.1158/1535-7163.MCT-08-0013, PMID:18852116.
[122] Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, *et al*. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 2014;3:e02523. doi:10.7554/eLife.02523, PMID:24844246.
[123] Zheng J, Sato M, Mishima E, Sato H, Proneth B, Conrad M. Sorafenib fails to trigger ferroptosis across a wide range of cancer cell lines. Cell Death Dis 2021;12(7):698. doi:10.1038/s41419-021-03998-w, PMID:34257282.
[124] Northfield TC. Ulcerative colitis and Crohn's colitis: differential diagnosis and treatment. Drugs 1977;14(3):198–206. doi:10.2165/00003495-197714030-00003, PMID:332482.
[125] Koppula P, Zhang Y, Zhuang L, Gan B. Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer. Cancer Commun (Lond) 2018;38(1):12. doi:10.1186/s40880-018-0288-x, PMID:29764521.
[126] Zhang X, Sui S, Wang L, Li H, Zhang L, Xu S, *et al*. Inhibition of tumor propellant glutathione peroxidase 4 induces ferroptosis in cancer cells and enhances anticancer effect of cisplatin. J Cell Physiol 2020;235(4):3425–3437. doi:10.1002/jcp.29232, PMID:31556117.
[127] Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, *et al*. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. Nature 2017;551(7679):247–250. doi:10.1038/nature24297, PMID:29088702.

[128] Sun YD, Berleth N, Wu WX, Schlutermann D, Deitersen J, Stuhldreier F, *et al*. Fin56-induced ferroptosis is supported by autophagy-mediated GPX4 degradation and functions synergistically with mTOR inhibition to kill bladder cancer cells. Cell Death Dis 2021;12(11):1028. doi:10.1038/s41419-021-04306-2, PMID:34716292.
[129] Villalpando-Rodriguez GE, Blankstein AR, Konzelman C, Gibson SB. Lysosomal Destabilizing Drug Siramesine and the Dual Tyrosine Kinase Inhibitor Lapatinib Induce a Synergistic Ferroptosis through Reduced Heme Oxygenase-1 (HO-1) Levels. Oxid Med Cell Longev 2019;2019:9561281. doi:10.1155/2019/9561281, PMID:31636810.
[130] Chang LC, Chiang SK, Chen SE, Yu YL, Chou RH, Chang WC. Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis. Cancer Lett 2018;416:124–137. doi:10.1016/j.canlet.2017.12.025, PMID:29274359.
[131] Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos AT, Haupt S, *et al*. Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol 2018;14:100–115. doi:10.1016/j.redox.2017.08.015, PMID:28888202.
[132] Xiao J, Zhang S, Tu B, Jiang X, Cheng S, Tang Q, *et al*. Arsenite induces ferroptosis in the neuronal cells via activation of ferritinophagy. Food Chem Toxicol 2021;151:112114. doi:10.1016/j.fct.2021.112114, PMID:33722599.
[133] Song S, Wen F, Gu S, Gu P, Huang W, Ruan S, *et al*. Network Pharmacology Study and Experimental Validation of Yiqi Huayu Decoction Inducing Ferroptosis in Gastric Cancer. Front Oncol 2022;12:820059. doi:10.3389/fonc.2022.820059, PMID:35237519.