Inhibition of FSP1: A new strategy for the treatment of tumors (Review)

QIANGFANG DAI[1*], XIAOLI WEI[1*], JUMEI ZHAO[1*], DIE ZHANG[1], YIDAN LUO[1], YUE YANG[1], YANG XIANG[1,2] and XIAOLONG LIU[1]

[1]School of Medicine, Yan'an University, Yan'an, Shaanxi 716000, P.R. China;
[2]College of Physical Education, Yan'an University, Yan'an, Shaanxi 716000, P.R. China

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Abstract. Ferroptosis, a regulated form of cell death, is intricately linked to iron-dependent lipid peroxidation. Recent evidence strongly supports the induction of ferroptosis as a promising strategy for treating cancers resistant to conventional therapies. A key player in ferroptosis regulation is ferroptosis suppressor protein 1 (FSP1), which promotes cancer cell resistance by promoting the production of the antioxidant form of coenzyme Q10. Of note, FSP1 confers resistance to ferroptosis independently of the glutathione (GSH) and glutathione peroxidase-4 pathway. Therefore, targeting FSP1 to weaken its inhibition of ferroptosis may be a viable strategy for treating refractory cancer. This review aims to clarify the molecular mechanisms underlying ferroptosis, the specific pathway by which FSP1 suppresses ferroptosis and the effect of FSP1 inhibitors on cancer cells.

Contents

Correspondence to: Dr Xiaolong Liu, School of Medicine, Yan'an University, 580 Shengdi Road, Baota, Yan'an, Shaanxi 716000, P.R. China
E-mail: lxl3281@163.com

*Contributed equally

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1. Introduction

Cancer remains a public health threat worldwide, with the International Agency for Research on Cancer reporting a staggering 19.3 million new cases and nearly 10 million deaths in 2020 (1). Despite significant advances in its treatment, the battle against cancer is hampered by the significant side effects of traditional therapies and the inevitable emergence of resistance associated with such treatments. Therefore, the identification of more effective and better-tolerated anticancer therapies is critical to meet clinical requirements. As first described by Dixon *et al* (2) in 2012, ferroptosis is a distinct form of cell death characterized by the accumulation of LPOs (3,4). Recently, ferroptosis has garnered attention owing to its involvement in numerous diseases, ranging from neurodegeneration to lethal malignancies, such as liver, breast, and lung cancers (5-8). Over the past two decades, comprehensive studies have investigated the intricacies of ferroptosis in diverse cancer types, elucidating its pivotal role in governing cancer progression via diverse signaling cascades. Cancer cells that exhibit resistance to conventional therapies or possess a high propensity for metastasis are more susceptible to ferroptosis (9-11). Therefore, the regulation of ferroptosis and its target proteins represents a novel and promising strategy for cancer treatment (12,13). The various signaling pathways involved in ferroptosis have been extensively summarized those studies. Ferroptosis primarily occurs through the L-cystine/glutamate antiporter (system Xc-)/glutathione (GSH)/GSH peroxidase 4 (GPX4) pathway, the GTP cyclohydroxylase-1 (GCH1)/tetrahydrobiopterin (BH4) pathway, the dihydroorotate dehydrogenase (DHODH) pathway, the O-acyltransferase 1/2 (MBOAT1/2)-monounsaturated fatty acid (MUFA) pathway, the nuclear factor-erythroid 2-related factor 2 (Nrf2) pathways, the mevalonate pathway and the apoptosis-inducing factor mitochondria-associated 2 (AIFM2, also known as FSP1 and referred to as FSP1 throughout) pathway-mainly the FSP1-coenzyme Q10 (CoQ10)-NAD(P)H, FSP1-vitamin K (VK)-NAD(P)H and FSP1-endosomal sorting complex, required for transport (ESCRT)-III pathways (Fig. 1). Among these systems, the Xc-/GSH/GPX4 pathway has garnered significant attention as a crucial regulatory mechanism of ferroptosis, sparking extensive research on its ability to induce ferroptosis in tumor cells. However, the

clinical application of inhibitors targeting this system has been hindered by their poor selectivity, toxicity and the presence of FSP1, which runs parallel to GSH-GPX4. Furthermore, certain cancer cells exhibit resistance to ferroptosis induction (14-16).

FSP1, a crucial modulator of ferroptosis, has emerged as a key player in ferroptosis resistance, operating independently of the GSH-GPX4 pathway. This protein primarily blocks ferroptosis in tumor cells by regulating the oxidation of NADPH, thereby hampering the efficacy of cancer treatment strategies (17). Furthermore, FSP1 is highly expressed in various cancer cells and its expression has been linked to poor prognosis (18,19). Therefore, targeting FSP1 to inhibit its activity, thus promoting ferroptosis, may be a promising approach for cancer therapy, particularly in the case of difficult-to-treat tumors. This article provides a comprehensive review of the ferroptosis pathway, the mechanism by which FSP1 modulates ferroptosis and the potential of FSP1-related molecular inhibitors in cancer treatment.

2. Molecular mechanism and pathway of ferroptosis

Ferroptosis is a non-apoptotic form of iron-dependent cell death. Key hallmarks of ferroptosis include elevated iron levels, lipid peroxidation and disruption of the mitochondrial architecture (20-22). Ferroptosis has been associated with various factors, including iron metabolism level, GPX4, GCH1/BH4, DHODH, FSP1 and MBOAT1/2 (Fig. 1). There is a significant association between intracellular iron metabolism and ferroptosis. Excessive iron loading can lead to ferroptosis. Transferrin receptor 1, a marker of ferroptosis, has a pivotal role in facilitating the transport of Fe^{3+} into cells (23). Within the cellular milieu, divalent metal transporter 1 converts Fe^{3+} into Fe^{2+}, which is subsequently stored in ferritin. However, when intracellular levels of labile Fe^{2+} become excessively high, it reacts with hydroxyl radicals via the Fenton reaction, triggering a surge in reactive oxygen species (ROS) production and the accumulation of lipid peroxidation. These processes ultimately induce ferroptosis (24). Furthermore, a phospholipase present in the cytoplasm, namely platelet-activating factor (PAF)-acetylhydrolase (II), specifically inhibits short-chain fatty acid oxidation, interfering with the cell's redox capacity and blocking the aggregation of oxidized phospholipids such as PAF; this leads to membrane rupture, inhibiting cell ferroptosis (25). Acetyl-coenzyme A (CoA) of the mevalonate pathway inhibits ferroptosis by triggering the NADPH-FSP1-CoQ10 pathway via the regulation of CoQ10 synthesis. Furthermore, various types of fatty acids have different degrees of regulatory roles in ferroptosis. Among these, polyunsaturated fatty acids (PUFAs) are particularly prone to peroxidation during ferroptosis. This process involves the esterification of membrane-forming phospholipids with the assistance of acyl-CoA synthetase long-chain family member 4, which is a fatty acid-activating enzyme found in the endoplasmic reticulum and outer mitochondrial membrane. In addition, lysophosphatidylcholine acyltransferase (LPLAT) contributes to the destruction of the lipid bilayer structure, leading to enhanced membrane permeability and ultimately triggering ferroptosis (26,27). Conversely, the inhibition of lipid peroxidation has a pivotal role in preventing ferroptosis by suppressing the formation of LPOs and free radicals. This involves crucial pathways discussed in the following paragraphs.

System Xc-/GSH/GPX4 pathway. The system Xc-, GPX4 and GSH (system Xc-/GSH/GPX4) pathways have been identified as crucial players in ferroptosis (28,29) (Fig. 1). Among these pathways, GPX4 stands out as a principal regulator of ferroptosis (30,31). Inhibition GPX4 activity results in elevated intracellular lipid peroxide (LPO) levels, which leads to ferroptosis (32-34). GSH is a primary antioxidant that suppresses ferroptosis and acts as a crucial cofactor for GPX4 (35). It reduces the iron concentration by converting the peroxidised lipids accumulated during ferroptosis into non-toxic isoalcohols (36,37). In addition, GPX4 has a critical role in the repair of lipid peroxides. In the presence of GSH, GPX4 reduces the accumulation of lipid peroxidation. However, upon inactivation of GPX4 or depletion of GSH, lipid peroxidation in the cell induces ferroptosis (38,39).

GCH1/BH4 pathway. GCH1 and BH4 have a vital role in the process of ferroptosis (40) (Fig. 1). BH4, which is derived from its precursor GTP via three enzymatic reactions catalyzed by GCH1, 6-pyruboyl tetrahydrobiopterin synthase and sepiapterin reductase, exhibits robust antioxidant activity both *in vivo* and *in vitro*, directly protecting cells from lipid peroxidation. Among these enzymes, GCH1 serves as the rate-limiting step, thus determining the cellular resistance to ferroptosis to a certain extent. Inhibition of GCH1 leads to a dysfunctional state of BH4 biosynthesis, resulting in ROS accumulation and ferroptosis (41). Conversely, overexpression of GCH1 has been shown to selectively enhance BH4 biosynthesis, decrease ROS production and thereby inhibit ferroptosis (42).

Furthermore, BH4 pairs with dihydrobiopterin (BH2) to establish a redox cycle that reduces endogenous oxygen radicals and suppresses ferroptosis (43). Dihydrofolate reductase (DHFR) controls the regeneration of BH2 to BH4, in which NAD(P)H is the principal cofactor that supplements BH4 but not BH2. Increased BH4 levels trigger cellular lipid remodeling (42), which effectively halts the utilization of phospholipids containing two polyunsaturated fat acyl tails, thereby stalling ferroptosis (44). In addition, BH4 enhances the biosynthesis of CoQ10 by influencing the synthesis of its precursor, 4-OH-benzoate. This connection bridges the GCH1-BH4-DHFR pathway and the FSP1-CoQ10 axis, whose collaboration impedes the progression of ferroptosis.

DHODH pathway. The DHODH is another pathway involved in cellular resistance to ferroptosis (45) (Fig. 1). DHODH is a flavin-dependent protein, present in the inner mitochondrial membrane, that converts DHO to orotate, reducing ubiquitin to pantothenol and producing lipophilic antioxidants, which inhibits LPO accumulation and ferroptosis (46). DHODH also exhibits a remarkable synergistic interaction with mitochondrial GPX4, working in concert to mitigate lipid peroxidation and forestall ferroptosis within the mitochondrial inner membrane (47,48). DHODH holds a pivotal position in the biosynthetic pathway of pyrimidine nucleotides, playing a crucial role in the production of DNA and RNA (49), Inhibition of DHODH disrupts this pathway, leading to abnormalities in, or cessation of, pyrimidine nucleotide synthesis. This, in turn, results in a decrease in pyrimidine nucleotide availability, halting the purine-pyrimidine pairing process and ultimately impeding RNA synthesis (50). Given RNA is a cofactor of

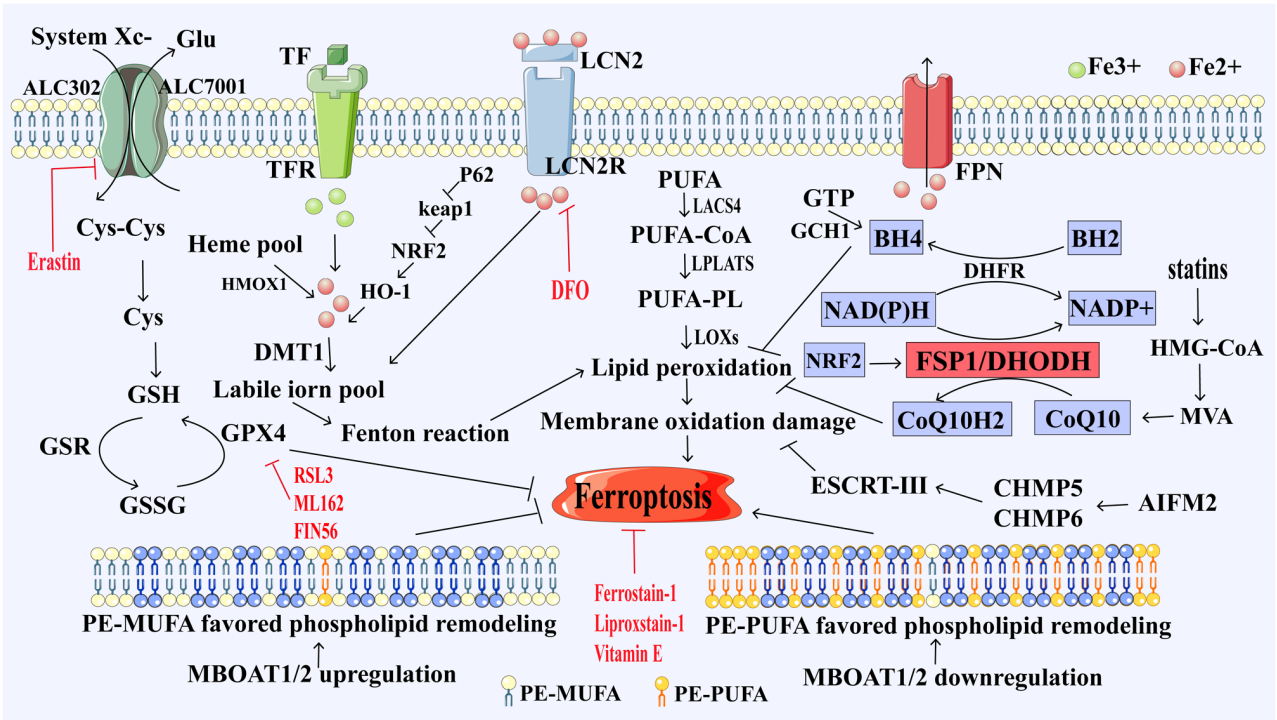


Figure 1. Ferroptosis pathway. System Xc uptake of cystine from extracellular sources, conversion of cystine to cysteine for GSH biosynthesis, GPX4 catalyzes the conversion of GSH to GSSG while reducing peroxidative unsaturated fat, protecting lipid bilayer cells from oxidative damage and inhibiting ferroptosis; long-chain LACS4 reduces arachidonic acid and adrenaline. PUFA is activated as CoA, oxidizes to perform lipid peroxidation and induces ferroptosis, while TFR1 transports Fe^{3+} into cells and, under the action of DMT1, converts Fe^{3+} to Fe^{2+}, ferroptosis is induced by the Fenton reaction. FSP1 inhibits ferroptosis by reducing ubiquitin to pantothenol through the NAD(P)H pathway. DHODH reduces ubiquitin to pantothenol, a process that produces lipophilic antioxidants; blocking the accumulation of lipid peroxidation inhibits ferroptosis. GCH1 promotes the synthesis of BH4, which exerts its antioxidant capacity to protect cells from lipid peroxidation and induce ferroptosis. MBOAT1 and MBOAT2 inhibit ferroptosis by reprogramming membrane phospholipids. GSH, glutathione; GSSG, GSH oxide; GPX4, GSH peroxidase 4; GSR, GSH reductase; FSP1, ferroptosis inhibitory protein 1; CoQ10, ubiquinone; CoQ10H2, ubiquinol; DHODH, dihydroorotate dehydrogenase; GTP, phosphohydrolases; GCH1, cyclohydrolase-1; BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; LACS4, long-chain acyl-CoA synthetase family member 4; LOX, lipoxygenase; LPCATs, lyso-phosphatidylcholine acyltransferase; PUFA, polyunsaturated fatty acids; CoA, coenzyme A; PUFA-PL, polyunsaturated fatty acids-polyunsaturated; HMG-CoA, 3-hydroxyl-3-methylglutaryl CoA; DHFR, dihydrofolate reductase; HO-1, heme oxygenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; p62, tumour suppressor gene Tp62; TFR, transferrin receptor; DMT1, divalent metal transporter 1; Keap1, Kelch-like ECH associated protein 1; LOX, lipoxygenase; MBOAT1/2, o-acyltransferase 1/2; AIFM2, apoptosis-inducing factor mitochondria-associated 2; ESCRT, endosomal sorting complex, required for transport; CHAM5/6, charged multivesicular proteins 5 and 6; MVA, mevalonate; HMOX1, heme oxygenase 1; Glu, glutamic acid; PE-PUFA, unsaturated fat phospholipids; LCN2R, lipocalin-2 receptors; FPN, ferroportin.

GSH, a decrease in RNA causes an increase in GSH levels. GPX4 restores LPO levels and the reduction of LPO accumulation inhibits ferroptosis (51,52).

MBOAT1/2-MUFA pathway. Liang *et al* (53) discovered that membrane-bound MBOAT1 and MBOAT2 are novel inhibitors of sex hormone-dependent ferroptosis. As LPLATs, they selectively introduce MUFAs to lyso-phosphatidylethanolamine (lyso-PE), elevating the PE-MUFA content and concurrently decreasing the levels of PE-PUFAs. PE-PUFAs, being the preferred substrate for LPO, exert inhibitory effects on cell ferroptosis through unsaturated fatty acid membrane phospholipids (53,54). MBOAT1 and MBOAT2 are regulated by estrogen receptor and androgen receptor, respectively. This cellular defense mechanism against ferroptosis operates independently of GPX4 and FSP1 (Fig. 1).

FSP1 mediated pathway. FSP1 possesses a myristylation sequence at its N-terminal region and mutations within this sequence are implicated in the induction of ferroptosis. CoQ10, alternatively known as ubiquinone, is an essential component of lipid membranes. It contributes to the production of ATP in the mitochondria and exists in its reduced form. FSP1 inhibits ferroptosis by mediating the NAD(P)H pathway and reducing NAD(P)H-dependent ubiquinone (oxidized form of CoQ10) to ubiquinol (reduced form of CoQ10) (Fig. 1). FSP1 acts as a GSH-independent ferroptosis suppressor and is compatible with GPX4 to inhibit lipid peroxidation (55).

All of the abovementioned antioxidant pathways inhibit the occurrence of ferroptosis to varying degrees (56,57). FSP1 holds a prominent position, exhibiting profound ferroptosis suppression. The mechanism by which FSP1 inhibits ferroptosis is described in detail in the next chapter.

3. FSP1 and ferroptosis

AIF, a group of flavoproteins, possess the ability to initiate caspase-independent apoptosis. The following isozymes of AIF have been reported in humans: AIFM1, AIFM2 and AIFM3. Among them, AIFM1-the most abundant isozyme-is initially translated and then transported to the mitochondrial membrane (58). It folds on the mitochondrial membrane and attains its functional conformation through the assistance of flavin adenine dinucleotide (FAD). AIFM2 (also known as

FSP1) lacks a mitochondrial targeting sequence, preventing its entry into mitochondria. Instead, it adheres to the outer mitochondrial membrane and possesses an N-terminal myristylation motif. FSP1 is a member of the nicotinamide adenine dinucleotide II-H (NADH): The quinone oxidoreductase (NDH-2) family (59), named after NDH-1, which is complex I of the respiratory chain. In fact, NDH-2 is thought to be a branch of the traditional mitochondrial respiratory system, whose structure includes an N-terminal hydrophobic membrane domain (aa 1-27), NADH oxidoreductase domain (AA 81-285) and FAD domain (aa 286-308) (60) (Fig. 2). FSP1 is an important cellular anti-ferroptotic factor that has a role in regulating iron metabolism and protecting cells from iron-dependent death. The antioxidant pathway mediated by FSP1 is parallel to the GSH-GPX4 pathway.

FSP1 exhibits oxidoreductase activity linked to ferroptosis, encompassing NADP/NADPH-dependent CoQ10 oxidoreductase and VK reductase activities (61). The reductase activity is influenced by its cofactors and substrates [such as NAD(P)H, FAD, CoQ10 and VK]. These cofactors and substrates can reduce CoQ10 or VK to their respective forms, including pantothenol and VK hydroquinone (VKH2). In addition, FSP1 mediates the production of compounds that function as antioxidants, trapping free radicals and suppressing LPO accumulation in the cell membrane, thus inhibiting ferroptosis in tumor cells (62). FSP1 inhibitors therefore have potential therapeutic value in cancer treatment, either as monotherapeutic agents or in combination with other ferroptosis inducers, for refractory tumor management (19,63). Therefore, FSP1 may represent a promising target for cancer therapy (64).

FSP1 mediates FSP1-CoQ10-NAD(P)H and FSP1-VK-NAD(P)H to inhibit ferroptosis. Zhang *et al* (65) demonstrated that FSP1 does not bind NADH to reduce LPO levels. Instead, it specifically binds NADPH to inhibit ferroptosis. Lv *et al* (66) proposed that when FSP1 binds FAD in the presence of NAD(P)H and substrate (CoQ10 or oxygen), it first accepts two electrons from NAD(P)H to form $FADH_2$ and then transfers two electrons to CoQ10 to form reduced CoQ10 or transfers electrons to oxygen to form H_2O_2. These two pathways cooperate to promote the oxidation of NAD(P)H. Furthermore, under the condition that the NAD(P)H redox cycle is widespread, the FAD bound by FSP1 in the presence of produced hydrogen peroxide undergoes hydroxylation to form 6-hydroxy-FAD. This reaction is catalyzed by Glu155 (Glu156 in human FSP1) within a specific FAD hydroxylation pocket. Finally, 6-hydroxy-FAD serves as a cofactor and potent antioxidant for FSP1, further enhancing its catalytic activity. These pathways work together to mediate the inhibition of ferroptosis by FSP1 (Fig. 3). These results indicate that FSP1 is an NADPH-selective enzyme. Of note, the anti-ferroptotic activity of FSP1 is strictly dependent on its affinity for NADPH. Its ferroptosis monitoring system uses NADPH as an electron transport system to inhibit ferroptosis through the oxidation of NADPH.

Guo *et al* (67) observed that FSP1 inhibits ferroptosis by generating an antioxidant form of CoQ10, thereby enhancing tumor cell resistance to ferroptosis; as a result, tumor cells contain a lower concentration of the oxidized form of CoQ10 (68,69). However, the addition of exogenous CoQ10 was not found to alleviate ferroptosis in FSP1-deficient cells,

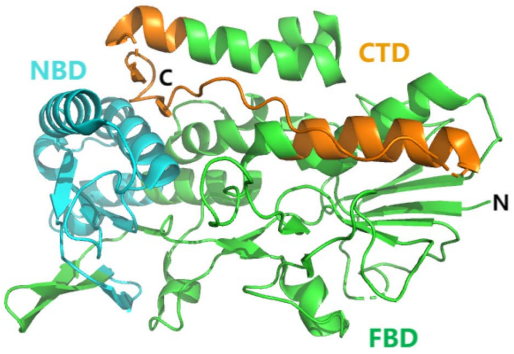


Figure 2. Tertiary structure of c ferroptosis inhibitory protein $1^{\Delta N}$, which adopts a glutathione reductase and is also composed of three domains, one containing the flavin adenine dinucleotide-FBD (residues 12-141 and 241-318), one NBD (residues 142-240) and one CTD (residues 319-373). FBD, flavin binding domain; NBD, NAD(P)H-binding domain; CTD, C-terminal domain.

indicating that exogenous CoQ10 does not directly affect ferroptosis but rather regulates it indirectly through endogenous CoQ10. In summary, FSP1 offsets the loss of GPX4 by mediating the conversion of NAD(P)H-dependent ubiquinone to ubiquinol; in turn, pantothenol acts as a lipophilic antioxidant to prevent the accumulation of lipid peroxidation (70), which inhibits ferroptosis in tumor cells (Fig. 4).

VK comprises a group of lipophilic molecules characterized by their 2-methyl-1,4-naphthoquinone structure and polyisoprene side chains, which exhibit variable lengths and hydrophobicity. VK exists in two forms in nature: The first, called phylloquinone (also known as VK1), is found in photosynthetic organisms, such as green plants, cyanobacteria and algae; the other, namely menadione (also known as VK2), is found in animals and bacteria. VK is a redox-active naphthoquinone (71,72), which can be converted into its corresponding hydroquinone VKH2 and is found mainly in the mature VK cycle (61,73). Recently, Mishima *et al* (74) found that FSP1 reduces VK in the manner of ubiquitin ketone. VKH2 exhibits remarkable antioxidant properties, effectively trapping free radicals and inhibiting lipid peroxidation, particularly that of phosphorus lipids (74). When recombinant human FSP1, NAD(P)H and VK were cultured *in vitro*, a notable consumption of NAD(P)H coincided with the generation of VK-hydroquinone. These findings suggest that FSP1 serves as a reductase for VK, consuming NAD(P)H and generating VKH2. This process not only blocks lipid peroxidation but also inhibits ferroptosis (17,75). In summary, FSP1-mediated VK reduction protects cells from harmful lipid peroxidation and ferroptosis during the atypical VK cycle (Fig. 4).

ESCRT-III-dependent membrane repair. ESCRT-III-dependent membrane repair is another mechanism underlying FSP1-mediated ferroptosis resistance. A crucial aspect of cell death involves damage to the plasma membrane. ESCRT-III, a membrane repair-dependent endosomal sorting complex critical for transportation, has a pivotal role in membrane deformation and fission, exerting a regulatory function that inhibits cancer cell ferroptosis (76). Studies have demonstrated that FSP1 can potentiate cell membrane repair and inhibit ferroptosis through the ESCRT-III-dependent membrane

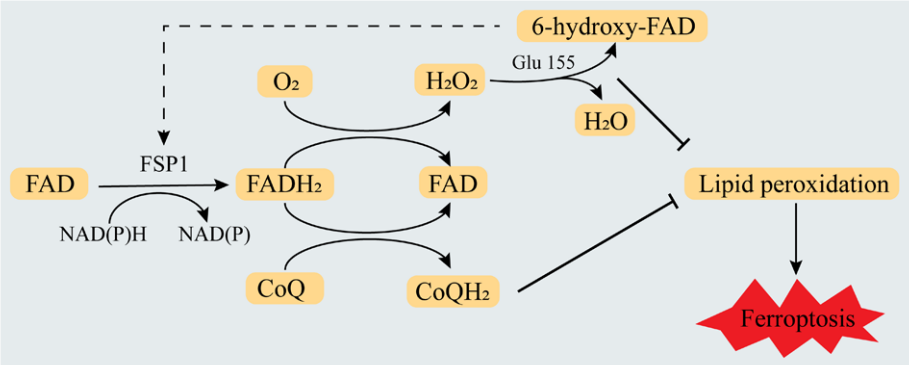


Figure 3. FSP1 anti-ferroptosis mechanism. FAD receives two electrons from NAD(P)H to form FADH2, transfers two electrons to CoQ10 to form pantothenol or transfers them to oxygen to form H_2O_2. H_2O_2 reacts with FAD to 6-hydroxy-FAD via the Glu155 (Glu156 in HFSP1) hydroxylation pocket. 6-hydroxy-FAD further promotes the activity of FSP1 and jointly carries out the inhibition of ferroptosis by FSP1. H_2O_2, hydrogen peroxide; FSP1, ferroptosis inhibitory protein 1; FAD, flavin adenine dinucleotide; CoQ, ubiquinone; CoQH2, ubiquinol; O_2, oxygen.

repair pathway, independently of CoQ10 (77). The presence of FSP1 has been shown to inhibit the occurrence of ferroptosis in tumor cells after the induction of ferroptosis using a ferroptosis inducer. Of note, *FSP1* knockdown in cells resulted in blockage of the RAS-selective lethal 3 (RSL3)-induced expression of charged multivesicular protein (CHMP)5 and CHMP6 at the plasma membrane. However, overexpression of CHMP5, a crucial subunit of the ESCRT-III-dependent membrane repair pathway, was shown to reverse ferroptosis induced by ferroptosis inducers and exert protective effects against cell death in *FSP1* knockdown cells (78). These results suggest that FSP1 mediates ferroptosis through the FSP1-ESCRT-III dependent membrane repair pathway (Fig. 4).

Regulators control FSP1 levels to induce ferroptosis. Nrf2 serves as a crucial regulator of cellular antioxidant responses and the Nrf2 signaling pathway plays a pivotal role in defending cells against lipid peroxidation and ferroptosis. Nrf2 needs to be activated to function as an antioxidant (79). The deficiency or mutation of Kelch-like ECH-associated protein 1 (KEAP1), mediated by p62, leads to the activation and upregulation of Nrf2. In KEAP1-deficient lung cancer cells, the upregulated Nrf2 translocates to the nucleus and binds to antioxidant response elements, activating genes critical for redox homeostasis. Inhibition of the p62-KEAP1-Nrf2 antioxidant signaling pathway can trigger ferroptosis, emphasizing the importance of this pathway in ferroptosis regulation (80,81). Nrf2 further plays a role in regulating the regeneration of the redox electron donor NADPH. By blocking the NADPH redox cycle, Nrf2 mitigates the inhibitory effect of FSP1, thus limiting its ability to induce ferroptosis (82). In addition to Nrf2, p53 is another transcription factor for FSP1 that regulates the level of FSP1 by binding to its promoter to exert its role in suppressing ferroptosis (83).

Acetyltransferase 10 (NAT10) regulates the stability and protein expression of FSP1 via modulation of the mRNA of the N4-acetylcysteine site, which in turn affects the stability and translation efficiency of the mRNA. Aberrant expression of NAT10 has been associated with tumorigenesis and progression. Of note, NAT10 knockdown has been found to promote ferroptosis and inhibit tumor proliferation and metastasis, indicating its significance in tumor biology (84,85). These findings indicate that NAT10 regulates the stability of *FSP1* mRNA to suppress ferroptosis, with potential for the treatment of tumors.

Non-coding RNA (ncRNA) has a pivotal role in regulating the expression and activity of FSP1 in cancer cells. Various types of ncRNAs, including small, long and circular RNAs, have been identified as targeting key genes and signaling pathways that govern ferroptosis (86). MicroRNA, a type of small ncRNA that regulates gene expression at the post-transcriptional level, has been shown to repress the expression of methyltransferase-like 3 in non-small-cell lung carcinoma (NSCLC). This repression leads to the methylation of N6-methyladenosine (m6A) and ultimately upregulation of FSP1 expression and inducing ferroptosis (87,88). Ferroptosis-associated long ncRNA can bind directly to FSP1, abrogating FSP1 ubiquitination degradation. This interaction lowers the vulnerability of liver cancer cells to ferroptosis and reduces the induction of ferroptosis (64,89,90).

Furthermore, the nuclear reader YTH N6-methyladenosine RNA binding protein C1 (YTHDC1), which possesses the YTH domain, has a role in nuclear m6A-tagged mRNAs and is crucial for normal physiological development processes (91). Recently, Yuan *et al* (92) demonstrated that YTHDC1 levels are inversely associated with the development and progression of lung cancer, with this association being mediated by FSP1-induced ferroptosis. When YTHDC1 was knocked down in A549 and H1299 cells, they exhibited resistance to RSL3-induced ferroptosis but remained sensitive to the FSP1 inhibitor iFSP1. This suggests that knockdown of the *YTHDC1* gene did not result in the upregulation of both *GPX4* and *FSP1* mRNA expression in A549 and H1299 cells. Instead, it significantly increased the protein levels of FSP1. However, in YTHDC1-knockdown cells, *FSP1* mRNA levels displayed a slight elevation, indicating that the regulation of FSP1 protein levels by YTHDC1 occurs beyond the transcriptional stage. Given that YTHDC1 functions as an m6A reader, analysis of *FSP1* mRNA levels revealed that most m6A sites reside in the 3'-untranslated region (UTR) of *FSP1* mRNA. In both A549 and H1299 cells, *FSP1* mRNA expression is modulated by m6A, which is recognized by YTHDC1. This interaction

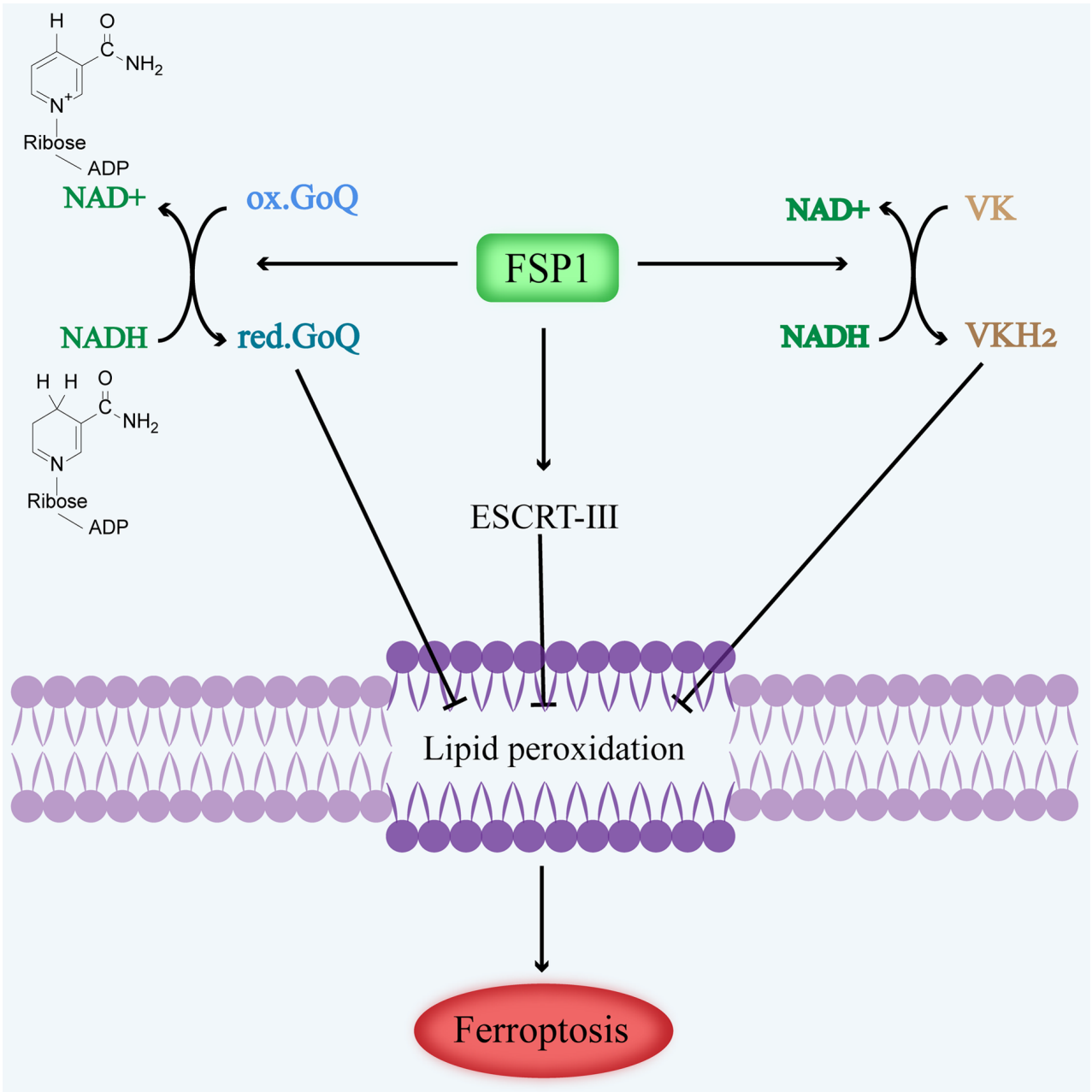


Figure 4. FSP1 mediates ferroptosis by reducing ubiquinone to ubiquinol and VK to VK-H2, inhibiting lipid peroxidation-induced ferroptosis, and through the ESCRT-III-dependent membrane repair pathway to enhance cell membrane repair inhibition of ferroptosis. NADPH, nicotinamide adenine dinucleotide phosphate; ESCRT, endosomal sorting complex, required for transport; VK, vitamin K; VKH_2, hydroquinone.

results in the formation of an unstable *FSP1* mRNA subtype with a truncated 3'-UTR. Consequently, when YTHDC1 is downregulated, the *FSP1* mRNA subtype with a longer 3'-UTR predominates, leading to elevated FSP1 protein levels. This mechanism highlights the role of YTHDC1 in suppressing FSP1 at the post-transcriptional level through m6A-dependent modulation, thereby attenuating resistance to ferroptosis and facilitating therapeutic intervention in lung cancer (92).

FSP1 expression poses a significant impediment to tumor treatment, as evidenced by the finding that its deletion in cells results in slower tumor growth and proliferation. These results suggest that the loss of FSP1 activity is sufficient to trigger ferroptosis under specific *in vivo* conditions, indicating its potential as a target for effective tumor cell treatment (18,93,94).

4. Relationship between FSP1 inhibitors, ferroptosis and tumor growth

Multiple studies have shown that inhibition of FSP1 enhances the antitumor efficacy of GPX4 inhibitors (95-97). For instance, FSP1-mediated ferroptosis can be effectively targeted for the treatment of challenging cancers, including triple-negative breast cancer (TNBC), hepatocellular carcinoma (HCC), colon cancer, acute lymphocyte leukemia and NSCLC. Laboratory studies have further demonstrated that FSP1 inhibitors can increase cancer cells' susceptibility to ferroptosis. Thus, FSP1 holds significant potential as a target for tumor therapy, offering hope for more effective treatment options.

Table I. FSP1-related inhibitors-structural formulas and mechanisms.

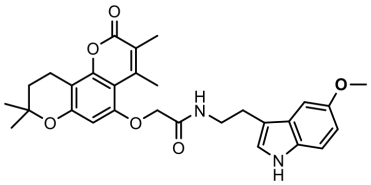
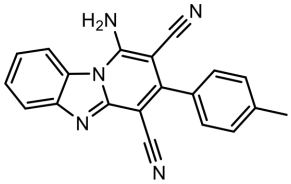
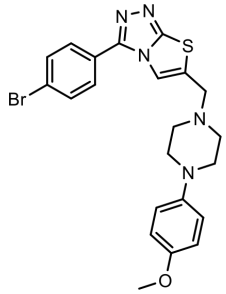
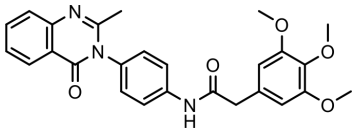
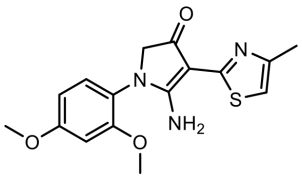
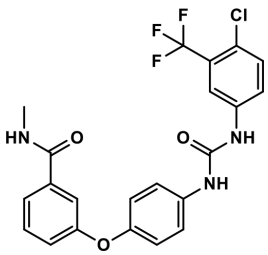
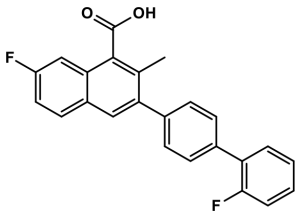
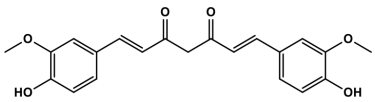
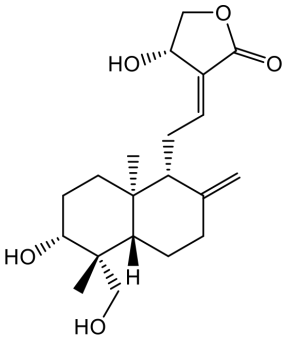
Name	Chemical structure	Mechanism	(Refs.)
NPD4928		Inhibition of FSP1 activity triggers ferroptosis in cancer therapy	(98)
iFSP1		Inhibition of FSP1 activity induces ferroptosis in the treatment of HCC	(99,100)
FSEN1		Inhibition of FSP1 activity triggers ferroptosis in cancer therapy	(101,102)
icFSP1		Induction of FSP1 phase separation triggers ferroptosis in tumor therapy	(103)
viFSP1		Inhibition of FSP1-induced ferroptosis in tumor therapy	(104)
Sorafenib		Promotes the ubiquitination of FSP1 to induce ferroptosis in the treatment of HCC	(105)
Brequinar		Inhibition of FSP1 activity triggers ferroptosis in cancer therapy	(107)
Curcumin		Inhibition of GPX4 and FSP1 induces ferroptosis in the treatment of lung cancer	(109)

Table I. Conrinued.

Name	Chemical structure	Mechanism	(Refs.)
Andrographis		Inhibition of GPX4 and FSP1 induces ferroptosis in the treatment of colorectal cancer	(110)

HCC, hepatocellular carcinoma; GPX4, glutathione peroxidase 4; FSP1, ferroptosis inhibitory protein 1.

FSP1 inhibitors are associated with ferroptosis and cancer

NPD4928 targets FSP1 to trigger ferroptosis in cancer cells. Yoshioka *et al* (98) discovered that the combination of NPD4928 and RSL3 enhances GPX4 inhibitor-induced ferroptosis, similar to that observed with FSP1 knockdown (Table I). Of note, NPD4928 stabilizes endogenous FSP1 in a dose-dependent manner by consuming NADH *in vitro*. Thus, NPD4928 stabilizes endogenous FSP1 in a dose-dependent manner, indicating that NPD4928-dependent ferroptosis is primarily mediated through the inhibition of FSP1 activity. In addition, NPD4928 does not show any cytotoxicity against the HCT116 cell line. However, it enhances ferroptosis in cancer cell lines when used to treat colon cancer, indicating its efficacy towards cancer cells. These findings underscore the potential of the FSP1 inhibitor NPD4928 to overcome resistance to ferroptosis in various types of cancer cell, thus emerging as a promising candidate for the treatment of multiple drug-resistant cancers.

iFSP1 targeting FSP1 triggers ferroptosis in HCC cells. Lee *et al* (99) proposed a strong connection between FSP1 overexpression and HCC, indicating that elevated FSP1 levels are associated with shorter overall survival among patients. iFSP1, a specific inhibitor of FSP1, effectively triggers ferroptosis in hepatoma cells by attracting immune cells. This approach has been shown to reduce HCC cell counts and enhance immune infiltration of dendritic cells, macrophages and T cells (Table I). When tested on MHCC97L cells at various concentrations, iFSP1 was shown to effectively suppress tumor-cell proliferation without causing significant changes in body weight. Treatment with iFSP1 also resulted in modifications to the immune landscape of HCC tumor cells. Therefore, iFSP1, as an FSP1 inhibitor, holds immense potential as a superior therapeutic agent for the treatment of HCC (99,100).

Ferroptosis sensitizer 1 (FSEN1) triggers ferroptosis in cancer cells by mediating FSP1. Hendricks *et al* (101) discovered that FSEN1 is an inhibitor of FSP1 and exerts synergistic effects with multiple ferroptosis inducers (Table I). Their findings demonstrated that FSEN1 acts specifically through FSP1. To induce ferroptosis in $H460^{C}$ Cas9 cells, an optimal dosage of FSEN1 at 0.55 mM and RSL3 at 0.55 mM was identified. This dosage achieved EC_{50} values of 69.363 nM in $H460^{C}$ GPX4 knockdown cells. Pharmacokinetics analysis conducted in mice revealed a plasma half-life of 8 h and an intrinsic clearance rate of 11.54 ml/min/mg in mouse liver microsomes. These findings suggest improved metabolic stability of FSEN1 *in vivo* (102). Evaluation of the impact of FSEN1 on cell ferroptosis triggered by GPX4 inhibitors across diverse cancer cell lines, including lung, liver and breast cancer cells, revealed that FSEN1 enhances the sensitivity of cancer cells, to varying degrees, towards RSL3-induced ferroptosis. Furthermore, preclinical studies have demonstrated synergistic effects when FSEN1 was used alongside endoperoxide-derived ferroptosis inducers, such as dihydroartemisinic acid (101). These findings provide further evidence supporting the potential of FSEN1 as an FSP1 inhibitor in cancer therapy.

icFSP1 targets phase separation of FSP1 to trigger ferroptosis in cancer cells. Nakamura *et al* (103) found that icFSP1 exhibits specificity towards ferroptosis and does not stimulate the myristylation of FSP1 *in vitro* (Table I). Their findings suggest that icFSP1 may regulate FSP1-membrane interactions, inducing the production of condensates that lead to reduced membrane-binding affinity of FSP1. Furthermore, the induction of FSP1 condensate formation within tumor cells triggers the phase separation of FSP1, ultimately inducing ferroptosis in cancer cells. the EC_{50} value of icFSP1, measured in Pfa1 cells, was found to be 0.21 μM. Treatment with the FSP1 inhibitor icFSP1 impaired tumor-cell growth and significantly reduced tumor weight. However, at higher concentrations, there was no significant impact on tumor weight, indicating no off-target effects. Furthermore, icFSP1 significantly improved microsomal stability and maximum tolerated dose in mouse plasma compared with iFSP1. The stronger pharmacokinetic and metabolic stability of icFSP1 renders it suitable for use *in vivo* (103), making it a promising candidate for targeting FSP1-dependent phase separation in anticancer therapy. These findings provide the basis for targeting FSP1-dependent phase separation as an effective anticancer therapy.

viFSP1 targets FSP1 to treat tumor. Nakamura *et al* (104) proposed that the treatment of Pfa1 cells expressing mouse

FSP1 or human FSP1 with viFSP1, a multifunctional inhibitor of FSP1, leads to ferroptosis, which can be reversed by administration of the ferroptosis inhibitor liproxstatin-1 (Table I), confirming that the dependence of viFSP1 on FSP1 causes ferroptosis. Specifically, viFSP1 targets the NADH binding pocket around residues A328, F294, M327 and T1 in FSP1. In addition, both human and mouse FSP1 cells exhibited similar sensitivity to viFSP1 with no significant difference in the calculated IC_{50} values. Thus, viFSP1 emerges as a species-independent direct inhibitor of FSP1, with an EC_{50} value of 170 nM in Pfa1 cells. In multiple human and mouse cancer cell lines, as well as in rat fibroblasts and Pfa1 cells overexpressing FSP1, the concurrent use of viFSP1 and the GPX4 inhibitor RSL3 synergistically enhanced ferroptosis induction, suggesting its potential therapeutic utility in tumor treatment (104).

Sorafenib mediates the ubiquitination and degradation of FSP1 to induce ferroptosis in the treatment of HCC. Ubiquitination, a form of posttranslational modification, has a crucial role in regulating cellular processes. Sorafenib, a multi-target kinase inhibitor, inhibits cell proliferation by interfering with serine-threonine kinase-related signaling pathways and hinders tumor angiogenesis by targeting specific tyrosine kinases (Table I). In HCC cells, sorafenib has been demonstrated to induce ferroptosis (105). Lai *et al* (106) revealed that sorafenib regulates the interaction between tripartite motif containing 54 and FSP1 through the MAPK/ERK kinase pathway, promoting the ubiquitination of FSP1. Elevated FSP1 expression partially reverses sorafenib-induced ferroptosis, whereas FSP1 inhibition enhances HCC cell sensitivity to sorafenib-induced ferroptosis (106). Thus, high levels of FSP1 inhibit sorafenib-induced ferroptosis in HCC cells (95). This suggests that downregulation of FSP1 in HCC cells may promote sorafenib-induced ferroptosis to facilitate therapeutic effects against HCC.

Brequinar, a DHODH inhibitor, inhibits FSP1-induced ferroptosis to treat tumors. Mishima *et al* (107), proposed that the DHODH inhibitor brequinar suppresses FSP1 activity at elevated dosages, thereby mitigating resistance to ferroptosis (Table I). Even in the absence of DHODH, high concentrations of brequinar were shown to effectively induce ferroptosis in Pfa1 cells derived from GPX4-deficient mouse fibroblasts. However, in FSP1-knockdown cells, ferroptosis was not induced, which was in contrast to the effects observed with BAY-2402234, another DHODH inhibitor that lacks inhibitory activity against FSP1 (108). These findings suggest that the ferroptosis-inducing effect of brequinar is mediated by the inhibition of FSP1 rather than DHODH.

Curcumin inhibits apoptosis of lung cancer cells induced by GPX4 and FSP1. Zhou *et al* (109) demonstrated that curcumin has the capacity to induce ferroptosis in highly tumorigenic A549 CD133+ cells via the GSH-GPX4 and FSP1-COQ10-NADH signaling pathways (Table I). Treatment with curcumin resulted in a dose-dependent decrease in the activity of $CD133^+$ cells and the expression levels of GPX4 and FSP1 protein. The levels of ROS, GSH, CoQ10 and NAD+/NADH in the curcumin-treated group were significantly lower than in the control group; this effect was attenuated by ferroptosis inhibitor Fer-1. Furthermore, the IC_{50} value of curcumin was determined to be 36 μM, indicating its high potency. In addition, curcumin demonstrated robust stability *in vivo*. Upon curcumin treatment, tumor growth was effectively suppressed, tumor pathology improved and the expression of Ki-67, a marker of tumor proliferation, was notably downregulated. Furthermore, the inhibitory effect of curcumin was higher than that of RSL3 and iFSP1. However, Fer-1 significantly inhibited the antitumor effects of curcumin (109). Thus, curcumin can inhibit GPX4 and FSP1 and promote ferroptosis to treat tumors.

Andrographis inhibits GPX4 and FSP1 to induce ferroptosis in colorectal cancer cells. Miyazaki *et al* (110) demonstrated that Andrographis exhibited comparable pharmacological effects to curcumin, effectively suppressing the activities of GPX4 and FSP1, thereby inducing ferroptosis in colorectal cancer cells (Table I). Treatment of SW480 and HCT116 cells with Andrographis significantly reduced cell viability as well as GPX4 and FSP1 expression; these effects were comparable to those elicited by RSL3 or iFSP1. In addition, the IC_{50} of Andrographis in both cell lines was 40 μg/ml, indicating its stability and reliability *in vivo*. Treatment with Andrographis was shown to inhibit the growth of cancer cells, with a reduction in invasiveness. Furthermore, the drug had no adverse effect on body weight. Fer-1 was found to mitigate the inhibitory action of Andrographis on colorectal cancer. The combination of Andrographis and curcumin exhibited a superior inhibitory effect against GPX4 and FSP1 to either drug alone.

Material complexes acting on FSP1-related pathways to treat tumors

Metabolic intervention nanoparticles Cu-silk fibroin (SF)-Rosuvastatin (RSV) nanoparticles (NPs) for treating TNBC through FSP1. Yang *et al* (111) effectively utilized SF to form a complex in coordination with Cu^{2+} ions. Rosuvastatin (RSV) was then encapsulated within this complex, yielding Cu-SF-RSV NPs, which were used to treat TNBC by overcoming FSP1-mediated ferroptosis. RSV was shown to hinder valproic acid metabolism, resulting in reduced CoQH2 levels and disruption of the redox balance. This, in turn, attenuated FSP1's inhibitory effect on ferroptosis. In addition, Cu^{2+} triggered the Fenton reaction to generate ROS, and SF consumed GSH in cells, thus promoting redox stress and amplifying the effect of Cu^{2+}. The accumulation and retention of Cu-SF-RSV NPs in tumor tissues markedly suppressed TNBC growth and metastasis. In addition, the plasma half-life of Cu-SF-RSV NPs *in vivo* was prolonged (7.03±1.18 h) compared with that of free RSV (0.42±0.02 h), indicating an extended blood circulation time for these nanomaterials. These results suggest that Cu-SF-RSV NPs may effectively eradicate TNBC tumors and inhibit tumor metastasis. Of note, compared to RSV, they do not induce histological damage or morphological alterations in various organs, with less systemic toxicity (111). Therefore, metabolic intervention with Cu-SF-RSV NPs may be a promising treatment for TNBC.

Multienzyme-like reactivity cooperatively impairs GPX4 and FSP1 pathways to induce ferroptosis in TNBC. Li *et al* (112) employed [Fe (III)] Cu-tetra (4-carboxyphenyl) porphyrin chloride [Cu-TCPP (Fe)] metal organic framework (MOF) nanosheets as substrates for the deposition of Au NPs through *in situ* nucleation. Subsequently, they successfully

deposited the ferroptosis inducer RSL3 onto the surface of these NPs via π-π stacking interactions to obtain NPs capable of targeting ferroptosis for TNBC therapy. Furthermore, they enhanced the system by integrating a long-circulating polyvinyl sugar segment and a tumor-targeting iRGD ligand (112). Liu *et al* (113) demonstrated that Au NPs possess similar activity to glucose oxidase, which oxidized glucose into gluconic acid, effectively depleting glucose levels, disrupting the pentose phosphate pathway and inhibiting GSH biosynthesis. This prevents the conversion of CoQ10 to CoQ10H2, leading to an elevation in the NADP+/NADPH ratio and effectively suppressing the FSP1-CoQ10H2 pathway. At the same time, increased $NADP^+$/NADPH ratios further inhibit the conversion of cystine to cysteine, reducing GSH and GPX4 biosynthesis. Furthermore, Yuan *et al* (114) showed that Cu^{2+} immobilized within the TCPP MOF nanoplates exhibited the ability to oxidize GSH into GSH oxide, depleting the cofactor essential for GPX4 activity. This process attenuated GPX4's inhibitory function against ferroptosis, effectively blocking the GPX4/GSH pathway. In addition, this nanosystem possessed the ability to release Cu^{2+}, further enhancing its inhibitory effect against the GPX4/GSH pathway. Studies have shown that Au/Cu-TCPP-Fe-polyethylene glycol (PEG) exhibits a prolonged blood circulation time and an enhanced tumor-targeting effect *in vivo*. Mice treated with Au/Cu-TCPP (Fe)@RSL3-PEG-iRGD had the longest survival with a median survival time of 60 days, and only a small number of tumor cells retaining proliferative activity. In addition, these nano-tablets demonstrate excellent tolerability *in vivo*, even at very high dosages. Thus, multienzyme-like reactions of NPs can simultaneously inhibit GPX4 and the FSP1-CoQ10H2 pathway in TNBC cells to promote ferroptosis, providing a promising avenue for the clinical treatment of drug-resistant tumors.

Photo-enhanced synergistic induction of ferroptosis used in anti-tumor immunotherapy. Yang *et al* (115) utilized photodynamic therapy to target FSP1-mediated ferroptosis. They employed a photoresponsive nanocomposite composed of boron-dipyrromethene (BODIPY)-modified polyamide (amidoamine) (BMP), which was used to encapsulate iFSP1 and chlorin e6 (Ce6); this was facilitated by π-π stacking and hydrophobic interactions between Ce6 and BODIPY. Thus, BMP and ferroptosis inducers were integrated into NPs. Under light irradiation, these NPs effectively triggered ferroptosis both *in vitro* and *in vivo*, leading to a significant slowing of tumor growth. Ferroptosis directly promotes immunogenic cell death, a process in which cells release ATP and high mobility group box 1 proteins, while exposing calreticulin on their surface. During this process damage-associated molecular patterns mediate the recruitment and activation of dendritic cells, thereby facilitating T-cell infiltration and cytotoxicity. It was suggested that IFN-γ secreted by T cells can trigger LPO of tumor cells; however, in the absence of NPs, cell death is not elicited, particularly when GPX4 and FSP1 are inhibited. In addition, pharmacokinetics studies have shown that the half-life of Ce6 is prolonged when it is encapsulated within NPs, and furthermore, during treatment, the drug did not accumulate in normal organs, with stable body weights maintained across groups. Of note, no significant histological damage or morphological alterations were observed in any of the organs. Therefore, light-responsive nanocomposites have the potential to synergistically induce ferroptosis in cancer immunotherapy.

5. Discussion and outlook

The exploitation of ferroptosis, a type of programmed cell death, holds great promise for various cancer therapies. Ferroptosis inducers heighten tumor cell sensitivity towards chemotherapeutic agents and facilitate the elimination of tumor cells that are refractory to other programmed cell death modalities. Consequently, the induction of ferroptosis has emerged as a promising approach for treating refractory tumors. Although numerous ferroptosis inducers have been identified, the primary focus has been limited to targeting the system xc-/GSH/GPX4 pathway. This limited perspective has somewhat hindered the exploration of the ferroptosis regulatory system as a target for cancer therapy.

FSP1, a linchpin anti-ferroptosis factor, enhances cancer-cell resistance to ferroptosis, making it an attractive target for cancer therapy. The current review reported on FSP1 inhibitors that boost cancer-cell sensitivity to ferroptosis. These inhibitors exhibit pharmacokinetic and metabolic stability, suitable for *in vivo* studies, and have been shown to effectively block the FSP1-mediated cellular defense mechanism against ferroptosis. Among them, the FSP1 inhibitors mentioned above have demonstrated remarkable potency in overcoming ferroptosis resistance in several cancer cell lines, potentially enabling the development of more effective cancer therapies.

Although FSP1 inhibitors may potentially have a significant role in cancer treatment, several challenges remain to be tackled. First, the specific mechanism by which FSP1 regulates ferroptosis remains unclear, necessitating further research. Although FSP1 is highly expressed in a variety of tumors, it is also expressed in normal tissues, making target selection a challenge. Furthermore, the association between FSP1 expression levels and tumor malignancy as well as poor prognosis further complicates treatment strategies. Third, research pertaining to FSP1 inhibitors is currently in its early stages. Although preliminary experimental studies have yielded encouraging outcomes, extensive further exploration is imperative to establish their clinical utility. Fourth, the number of reported FSP1 inhibitors is limited and it is crucial to develop more drug molecular structures through natural drug screening and AI technology. The goal is to develop inhibitors that are highly selective, exhibit low toxicity and possess desirable pharmaceutical characteristics. In addition, further research is required to investigate the potential clinical application of combinations of FSP1 inhibitors with other antineoplastic agents and immune checkpoint inhibitors. Moreover, nanomaterials hold immense promise in this domain, offering novel avenues for research.

In conclusion, although FSP1 inhibitors demonstrated tremendous potential in tumor therapy, further research is necessary to address existing challenges and optimize the application of these compounds in clinical practice.

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Authors' contributions

QD and XL were responsible for writing and revising the manuscript. YL was responsible for the preparation of figures and revisions of this article. XW, JZ and YY were responsible for the revisions of this article. DZ was responsible for data collection. YX was responsible for revising the article. XL was responsible for the conceptualization of the study, obtained funding and provided guidance in the preparation of the article. All authors contributed to the article and have read and approved the submitted version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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