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*Review*

# Ferroptosis: New Strategies and Ideas for the Treatment of Pancreatic Ductal Adenocarcinoma

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**Abstract**

Pancreatic cancer is a malignancy that affects the digestive tract and has a low 5-year survival rate of lower than 15%. Owing to its genetic mutation and metabolic complexity, pancreatic cancer is difficult to treat with surgical resection, radiotherapy, and chemotherapy. The predominant modality of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), primarily attributed to mutations in *KRAS* gene. Ferroptosis, an iron-mediated reactive oxygen species (ROS)-elevated nonapoptotic cell death caused by lipid peroxidation, is distinct from any other known type of cell death. Ferroptosis is closely related to the occurrence and progression of different types of cancers, including PDAC. Previous research has demonstrated that ferroptosis not only triggers cell death in PDAC and hampers tumor growth but also enhances the effectiveness of antitumor medications. In our review, we mainly focus on the core mechanism of ferroptosis, reveal its interrelationship with PDAC, and illustrate the progress of ferroptosis in different treatment methods of PDAC.

**Keywords:** ferroptosis; pancreatic cancer; pancreatic ductal adenocarcinoma; PDAC; treatment; therapy

## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent form of pancreatic cancer, characterized by its highly malignant nature in the digestive tract. With a low 5-year survival rate of lower than 15%, it ranks as the fourth leading cause of cancer-related death in both genders. The incidence and mortality rates of PDAC have been steadily increasing over the years [1,2]. The primary mutant genes found in PDAC are *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, with *KRAS* gene mutations accounting for approximately 90% of PDAC cases [3]. Common risk factors associated with PDAC include age (being over 50 years old), smoking, drinking, obesity, and diabetes [4–8]. Despite significant advancements in cancer treatment methods such as surgical resection, chemotherapy, radiotherapy, and immunotherapy, PDAC remains relatively insensitive to these approaches [9]. Thus, it is pivotal to comprehend the molecular mechanisms involved in the formation and development of PDAC, and to identify more precise, safer, and effective therapeutic targets.

In recent years, programmed cell death (PCD) has seen significant advancements in cancer treatment, with breakthroughs in various forms including apoptosis, necroptosis, pyroptosis, and ferroptosis [10]. Among these, ferroptosis is a distinct nonapoptotic modality of programmed cell death which is characterized by iron accumulation, reactive oxygen species (ROS) production, and lipid peroxidation [11]. Extensive research has established a close link between ferroptosis and the occurrence and development in several diseases, including Alzheimer's disease [12], chronic obstructive pulmonary disease [13], liver disease [14], and various tumors including PDAC [15–17]. Moreover, ferroptosis has been found to influence the effectiveness of chemotherapy, radiotherapy, and immunotherapy [18–20], and is being explored as a potential strategy to reverse drug resistance [21]. Despite the incomplete understanding of the regulatory mechanism of ferroptosis, it holds promise as a new target for PDAC therapy due to its interrelationship with tumors. Our review aims to thoroughly examine the fundamental mechanism of ferroptosis and its correlation with PDAC. Additionally, we explore the promising prospects of utilizing ferroptosis as a potential therapeutic approach for the treatment of PDAC.

## 2. The Core Mechanism of Ferroptosis

Unlike other well-known modalities of cell death, such as apoptosis, necrosis, and pyroptosis, ferroptosis is distinct and can be identified by the accumulation of iron, the generation of ROS and lipid peroxidation. The induction of ferroptosis can be achieved by the compound erastin, which inhibits the cystine/glutamate antiporter (system $X_c^-$) and subsequently reduces cystine absorption.

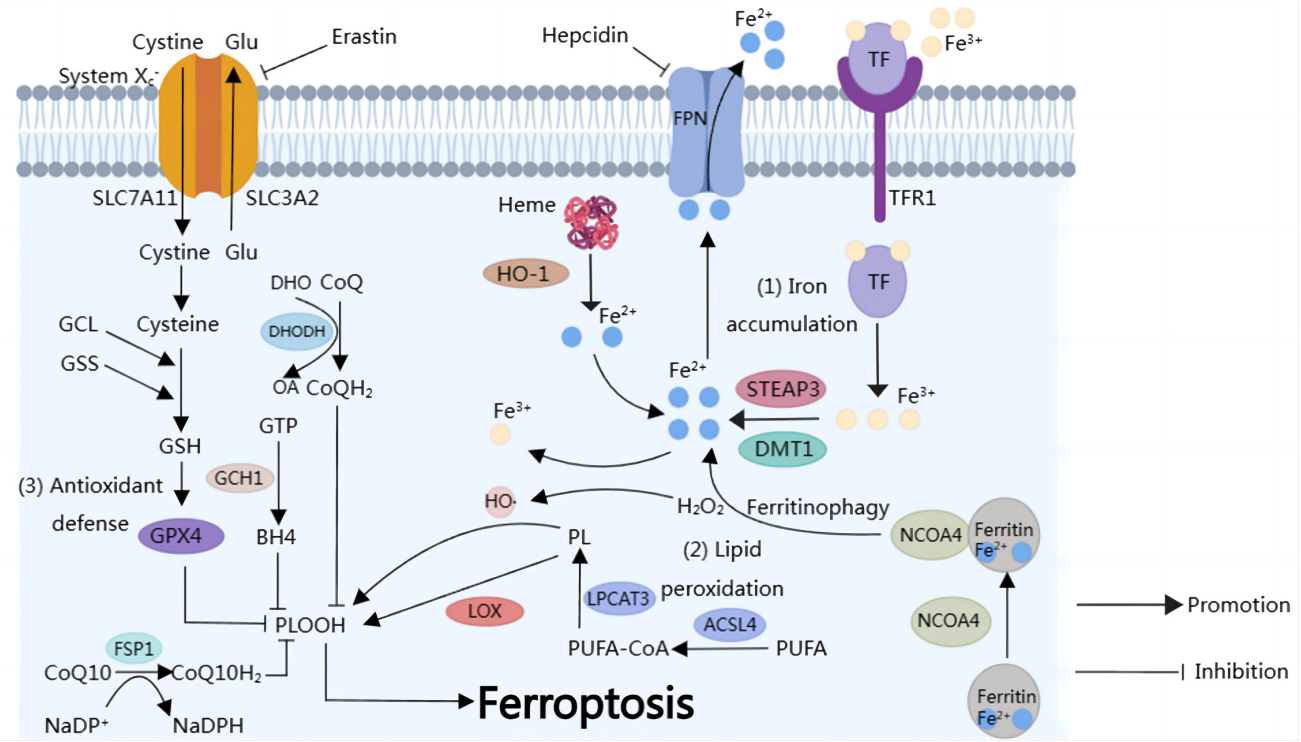


**Fig. 1. Overview of ferroptosis.** (1) Iron accumulation. $Fe^{3+}$ combines with TF and enters the cell, where it is catalyzed by STEAP3 and DMT1 to generate $Fe^{2+}$. Subsequently, Ferritin forms a complex with NCOA4, leading to an increase in ferritinophagy and $Fe^{2+}$ levels. Under the catalysis of HO-1, heme releases $Fe^{2+}$. $Fe^{2+}$ then undergoes a Fenton reaction with $H_2O_2$, resulting in the generation of HO·. (2) Lipid peroxidation. PUFA enters PL after undergoing treatment by ACSL4 and LPCAT3. PL can react with HO or be catalyzed by LOX to generate PLOOH, ultimately leading to ferroptosis. (3) Antioxidant defense. GPX4, FSP1, DHODH, and GCH1 inhibit lipid peroxidation, with the GPX4 pathway being the most important. Abbreviations: ACSL4, acyl-CoA synthetases long-chain family member 4; BH4, tetrahydrobiopterin; CoQ, Coenzyme Q; DHO, dihydroorotate; DHODH, Dehydrogenase; DMT1, divalent metal transporter 1; FPN, ferroportin; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase-1; GCL, glutamate-cysteine ligase; Glu, Glutamate; GSH, Glutathione; GPX4, glutathione peroxidase 4; GSS, glutathione synthetase; HO·, hydroxyl radical; HO-1, heme oxygenase-1; LOX, lipoxygenases; LPCAT3, lysophosphatidylcholine acyltransferase 3; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NCOA4, nuclear receptor coactivator 4; OA, orotate; PL, Phospholipid; PLOOH, PL hydroperoxide; PUFA, polyunsaturated fatty acid; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of the prostate 3; TF, transferrin; TFR1, transferrin receptor 1.

This inhibition ultimately leads to iron-dependent oxidative death, giving rise to the term "ferroptosis" [11] (Fig. 1).

### *2.1 Iron Accumulation*

Intracellular iron metabolism plays a direct role in modulating ferroptosis. The biological contributions of iron rely on the electron transfer that occurs when iron is transformed between its ferrous bivalent ($Fe^{2+}$) and ferric trivalent ($Fe^{3+}$) states through various biochemical reactions [22]. Adequate iron levels are essential for triggering ferroptosis. Several pathways have been identified for transporting iron into cells, with the most significant one being iron import facilitated by transferrin (TF) and its receptor, transferrin receptor 1 (TFR1). TF can bind to TFR1 on the cell membrane after capturing stable $Fe^{3+}$ from the blood, and then transport $Fe^{3+}$ into cells via endocytosis to form endosomes. Once $Fe^{3+}$ enters the endosomes, it is converted to $Fe^{2+}$ via the metal reductase six-transmembrane epithelial antigen of the prostate 3 (STEAP3). Subsequently, divalent metal transporter 1 (DMT1) aids in the transfer of $Fe^{2+}$ from the endosomes to the cytoplasm, thereby playing a role in the creation of the labile iron pool (LIP) [23–25]. Moreover, iron can be reserved in the form of ferritin, which forms a complex with nuclear receptor coactivator 4 (NCOA4) in autophagosomes. This complex promotes the degradation of ferritin and increases $Fe^{2+}$ levels, a process known as "ferritinophagy" [26]. Additionally, elevated heme oxygenase-1 (HO-1) in cardiomyocytes can catalyze the release of $Fe^{2+}$ into LIP [27,28]. While there are various mechanisms for iron uptake, the transport of $Fe^{2+}$ from cells to the blood primarily occurs through ferroportin (FPN). Hepcidin, a peptide hormone secreted by hepatocytes, binds to the FPN, resulting in its internalization and subsequent degradation in lysosomes. This ultimately

results in decreased intracellular iron export [29]. However, the limited ability of cells to excrete iron can result in the accumulation of iron, which subsequently contributes to the ROS generation and ferroptosis.

### *2.2 ROS Production and Lipid Peroxidation*

ROS, which includes superoxide ($O_2\cdot$), peroxide ($H_2O_2$/ROOH), and free radicals (HO·/RO·), plays a crucial role in initiating the peroxidation of polyunsaturated fatty acids (PUFAs) [30]. Superoxide is produced in the endoplasmic reticulum through the catalysis of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) by NADPH-cytochrome P450 reductase (POR) and NADH-cytochrome b5 reductase (CYBSR1). Subsequently, superoxide is converted into hydrogen peroxide ($H_2O_2$) by the action of superoxide dismutase (SOD) [31]. The decomposition of $H_2O_2$ by $Fe^{2+}$ leads to the generation of hydroxyl radicals (HO·) and $Fe^{3+}$, which is referred to as the Fenton reaction. Overall, this entire process of HO· generation serves as the foundation for lipid peroxidation [32].

Previous studies have indicated that PUFAs are highly susceptible to peroxidation during ferroptosis [33]. Phospholipids (PLs) play a crucial role in the composition of cell membranes, consisting primarily of glycerophospholipids and sphingomyelin. Glycerophospholipids contain PUFAs, particularly arachidonic acid (AA) and adrenaline acid (AdA), which are impressionable to peroxidation and can cause damage to the cell membrane [34,35]. Before entering PLs, PUFAs require modification by acyl-CoA synthetases long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3).

Under the catalysis of ACSL4, AA and AdA react with coenzyme A (CoA) to produce AA-CoA and AdA-CoA, respectively. These compounds then undergo esterification reaction catalyzed by LPCAT3, resulting in the formation of AA- phosphatidylethanolamine (PE) and AdA-PE. Finally, they enter PLs [36–38]. The HO· produced by the Fenton reaction reacts with PUFA in PL, generating PL radical species (PL·). These radicals react with intracellular $O_2$, leading to the production of PL peroxyl radical (PLOO·). Subsequently, PLOO· acquires a hydrogen atom from PUFA in another PL, leading to the production of PL hydroperoxide (PLOOH) [39]. This process is known as nonenzymatic lipid peroxidation. On the other hand, enzymatic lipid peroxidation occurs when PUFA in PL is oxidized to PLOOH under the catalysis of lipoxygenases (LOX) [40]. Ultimately, lipid peroxidation causes a decrease in the thickness of the cell membrane phospholipid bilayer, disorganization, and hole formation, ultimately resulting in bilayer rupture [41].

### *2.3 Antioxidant Defense*

Several antioxidant systems in cells can negatively regulate the progress of ferroptosis by suppressing lipid peroxidation. Among these systems, the antioxidant system mediated by glutathione peroxidase 4 (GPX4) is considered to be the most decisive.

System $X_c^-$, composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), transports cystine into the cells at a 1:1 ratio and transfers glutamic acid extracellularly [42]. Upon entering the cell, cystine undergoes oxidation to form cysteine, facilitated by the enzymes glutamate-cysteine ligase (GCL) and glutathione synthetase (GSS). This process ultimately contributes to the production of glutathione (GSH) [43]. GPX4, with GSH as a cofactor, reduces lipid peroxides (PLOOH) to lipid alcohols (PLOH), thereby inhibiting ferroptosis [44].

Coenzyme Q10 (CoQ10) is a crucial intracellular free radical scavenger that is present in all cell membranes [45]. Ferroptosis suppressor protein 1 (FSP1) is an independent suppressor of ferroptosis. FSP1 utilizes intracellular NADPH to reduce CoQ10 to reduced CoQ10 ($CoQ10H_2$), effectively inhibiting the formation of ROS [46].

Dehydrogenase (DHODH) is situated in the inner mitochondrial membrane and catalyzes the conversion of dihydroorotate into orotate. It provides 2 electrons to the electron transport chain (ETC). Coenzyme Q (CoQ) is reduced to reduced Coenzyme Q ($CoQH_2$) after accepting two electrons. This reduction prevents lipid peroxidation and inhibits ferroptosis [47,48].

GTP cyclohydrolase-1 (GCH1) serves as the enzyme that limits the rate of tetrahydrobiopterin (BH4) biosynthesis. Both BH4 and its oxidized form, dihydrobiopterin (BH2), can inhibit lipid peroxidation and ferroptosis. Additionally, BH4 indirectly promotes CoQ synthesis by converting phenylalanine to tyrosine. This process helps cells protect against ferroptotic death [49].

Therefore, the four parallel antioxidant pathways of GPX4, FSP1, DHODH, and GCH1 work together to resist lipid peroxidation and subsequently suppress ferroptosis.

## 3. Interrelationship between Ferroptosis and PDAC

### *3.1 Iron Metabolism and PDAC*

Ferritinophagy is a vital pathway that contributes to the buildup of intracellular iron. NCOA4, a cargo receptor responsible for ferritinophagy, is overexpressed, resulting in the autophagic breakdown of ferritin and an increase in $Fe^{2+}$ levels. This process is linked to the development of ferroptosis in pancreatic cancer. Autophagy-related genes (*Atg*) play a pivotal role in autophagy within pancreatic cancer cells. When *Atg5* and *Atg7* are knocked down, the levels of $Fe^{2+}$ and the production of lipid peroxidation end products like malondialdehyde decrease, indicating the involvement of *Atg5*- and *Atg*7-dependent autophagy in ferroptosis [50]. The antiviral drug zalcitabine induces the degradation of transcription factor A, mitochondrial (TFAM), resulting in the depletion of mitochondrial DNA (mtDNA)

and oxidative damage. This, in turn, activates the cyclic GMP-AMP synthase (CGAS)-stimulator of interferon response cyclic GMP-AMP interactor 1 (STING1) pathway, subsequently triggering autophagy-dependent ferroptosis in human pancreatic cancer cells [51]. Except autophagy, pancreatic cancer cells have the ability to modulate ferroptosis through the manipulation of iron accumulation. Treatment of pancreatic cancer cells with ruscogenin upregulates TF expression and decreases FPN expression, resulting in increased intracellular iron levels and ultimately inducing ferroptosis [52]. Lactotransferrin (LTF), a direct binding protein of neuronal precursor cell-expressed developmentally downregulated 4 (NEDD4)-like protein E3 ubiquitin ligase (NEDD4L), has the ability to trigger ferroptosis by enhancing iron accumulation and subsequent lipid peroxidation. In human PDAC cell lines, NEDD4L acts as a novel inhibitor of ferroptosis, exerting its effect through the degradation of LTF mediated by NEDD4L [53]. The activation of nuclear protein 1, transcriptional regulator (NUPR1) by activating transcription factor 4 (ATF4) promotes the expression of its effector gene lipocalin 2 (*LCN2*), which helps reduce $Fe^{2+}$ concentration and suppress oxidative damage-mediated ferroptosis in pancreatic cancer cells [54]. Therefore, understanding the relationship between iron metabolism and pancreatic cancer ferroptosis is crucial and can lead to the development of new treatments for PDAC.

### *3.2 Lipid Metabolism and PDAC*

Lipid metabolism plays a vital role in ferroptosis in various malignancies, including pancreatic cancer. The combination of PUFAs and PLs, catalyzed by ACSL4, leads to the formation of PUFA-PL. ADP Ribosylation Factor 6 (ARF6) negatively regulates ACSL4 levels, thereby regulating the sensitivity of PDAC cells to RAS-selective lethal 3 (RSL-3)-mediated lipid peroxidation and influencing the occurrence of ferroptosis [55]. Pirin (PIR) is a nuclear redox-sensitive regulator and a target gene of nuclear factor, erythroid 2-like 2 (*NFE2L2*). It plays a role in inhibiting ferroptosis in cancer cells, specifically in PDAC, by restricting the autophagy induced by high-mobility group box 1 (HMGB1) and subsequently negatively regulating ACSL4 levels [56]. The oxidation of PUFA, catalyzed by LOX, is a critical step in ferroptosis. Knockdown of arachidonate 15-lipoxygenase (ALOX15) significantly reduces erastin- or RSL3-mediated ferroptosis, while overexpression or using an ALOX15 activator can enhance ferroptosis in PDAC cells [57]. Luciferase reporter gene assays demonstrated that microsomal glutathione S-transferase 1 (*MGST1*) is the target gene of *NFE2L2*, a crucial cellular antioxidant regulator. Activation of *MGST1* by *NFE2L2* contributes to its binding with arachidonate 5-lipoxygenase (*ALOX5*), resulting in reduced lipid peroxidation and suppression of ferroptosis in cancer cells, specifically in PDAC [58]. In the context of elevated glucose levels, downregulation of pyruvate dehydrogenase kinase 4 (PDK4) mediated by SLC2A1 promotes ferroptosis in pancreatic cancer cells. This promotion occurs via enhanced pyruvate oxidation-mediated fatty acid synthesis and ALOX5-dependent lipid peroxidation [59]. These studies emphasize the role of different modulators in regulating lipid metabolism in PDAC, offering a novel perspective for the prevention and treatment of PDAC.

### *3.3 Antioxidative System and PDAC*

The antioxidant system, including the GSH/GPX4 axis, is a protective mechanism that counteracts lipid peroxidation and scavenges ROS. It acts a crucial function in the regulation of ferroptosis. Ferroptosis inducers such as erastin, sorafenib, and sulfasalazine can activate the AMP-activated protein kinase (AMPK)/sterol response element binding protein 1 (SREBP1) pathway through ferritinophagy. Branched-chain amino acid aminotransferase 2 (BCAT2), a pivotal enzyme participated in sulfur amino acid metabolism, is overexpressed to enhance glutamate synthesis, which in sequence increases the activity of system $X_c^-$ and promotes cystine ingestion, which ultimately inhibits ferroptosis in liver and pancreatic cancer cells [60]. BECN1, a critical modulator of macroautophagy, is essential for the induction of ferroptosis by system Xc inhibitors. AMPK-mediated phosphorylation of beclin 1 (BECN1) at Ser90/93/96 leads to the generation of a complex between BECN1 and SLC7A11. The BECN1-SLC7A11 complex blocks the vitality of system $X_c^-$ and facilitates GSH depletion, ultimately inducing ferroptosis in various tumor cells, including PDAC [61]. Heat shock 70 kDa protein 5 (HSPA5) is a molecular chaperone located in the endoplasmic reticulum that functions as a negative regulator of ferroptosis in human PDAC cells. It has been observed that overexpression of HSPA5, mediated by activating transcription factor 4 (ATF4), can protect against erastin-induced degradation of GPX4 and subsequent lipid peroxidation, thereby limiting ferroptotic cell death [62]. Apart from its antioxidant role in the GSH/GPX4 axis, cystine also contributes to the biosynthesis of CoA in PDAC cell lines. CoA is involved in various metabolic pathways, particularly lipid metabolism, and in conjunction with GSH, it regulates ferroptosis in pancreatic tumors [63]. Based on these findings, it is suggested that targeting GPX4 function and reducing cystine uptake could be potential strategies for regulating ferroptosis in PDAC. Regulators of ferroptosis in PDAC are listed in Table 1 (Ref. [23,24,26,29,44,50,51,53–63]). Interrelationship between ferroptosis and PDAC is shown in Fig. 2.

## 4 Ferroptosis in PDAC Treatment

### *4.1 Systemic Therapy*

Systemic therapy refers to the use of conventional cytotoxic and targeted agents to induce tumor cell death and exert anti-cancer effects. One important mechanism of tumor cell death is ferroptosis, which also inhibits tumor cell growth. Increasing evidence suggests that inducing ferrop-

**Table 1. The regulators of ferroptosis in PDAC.**

| Compound | Positive or Negative regulators | Mechanism | Refs |
|---|---|---|---|
| ALOX15 | Positive | Promote ROS production | [57] |
| AMPK | Positive | Inhibit BCAT2 transcription | [60] |
| ARF6 | Negative | Negatively regulate ACSL4 level | [55] |
| Atg5/7 | Positive | Promote the formation of the autophagosome and ferroptosis | [50] |
| BCAT2 | Negative | Increase synthesis of glutamate | [60] |
| BECN1 | Positive | Bind to SLC7A11 and block system $X_c^-$ activity | [61] |
| CoA | Negative | cooperate with GSH to downregulate ferroptosis | [63] |
| DMT1 | Positive | Promote iron uptake | [24] |
| FPN1 | Negative | Promote iron export | [29] |
| GPX4 | Negative | Inhibit lipid peroxidation | [44] |
| Hepcidin | Positive | Induce FPN1 internalization | [29] |
| HSPA5 | Negative | Protect against degradation of GPX4 | [62] |
| LCN2 | Negative | Decrease iron accumulation | [54] |
| LTF | Positive | Increase iron accumulation | [53] |
| MGST1 | Negative | Bind to ALOX5 and limit lipid peroxidation | [58] |
| NCOA4 | Positive | Induce ferritinophagy | [26,50] |
| NEDD4L | Negative | Promote LTF protein degradation | [53] |
| NFE2L2 | Negative | Mediate MGST1 upregulation during ferroptosis | [58] |
| NUPR1 | Negative | Promote LCN2 expression | [54] |
| PDK4 | Negative | Inhibit pyruvate oxidation and subsequent lipid peroxidation | [59] |
| PIR | Negative | Limit oxidative damage of DNA | [56] |
| SREBP1 | Positive | Inhibit BCAT2 transcription | [60] |
| TFAM | Negative | Inhibit autophagy-dependent ferroptosis | [51] |
| TFR1 | Positive | Increase iron level | [23] |

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; ALOX15, 15-lipoxygenase; AMPK, AMP-activated protein kinase; ARF6, ADP Ribosylation Factor 6; Atg5/7, autophagy-related genes 5/7; BCAT2, branched-chain amino acid aminotransferase 2; BECN1, beclin 1; CoA, coenzyme A; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; GPX4, glutathione peroxidase 4; HSPA5, heat shock 70 kDa protein 5; LCN2, lipocalin 2; LTF, lactotransferrin; MGST1, microsomal glutathione S-transferase 1; NCOA4, nuclear receptor coactivator 4; NEDD4L, neuronal precursor cell-expressed developmentally downregulated 4-like protein E3 ubiquitin ligase; NFE2L2, nuclear factor, erythroid 2-like 2; NUPR1, nuclear protein 1, transcriptional regulator; PDK4, pyruvate dehydrogenase kinase 4; PIR, pirin; SREBP1, sterol response element binding protein 1; TFAM, transcription factor A, mitochondrial; TFR1, transferrin receptor 1.

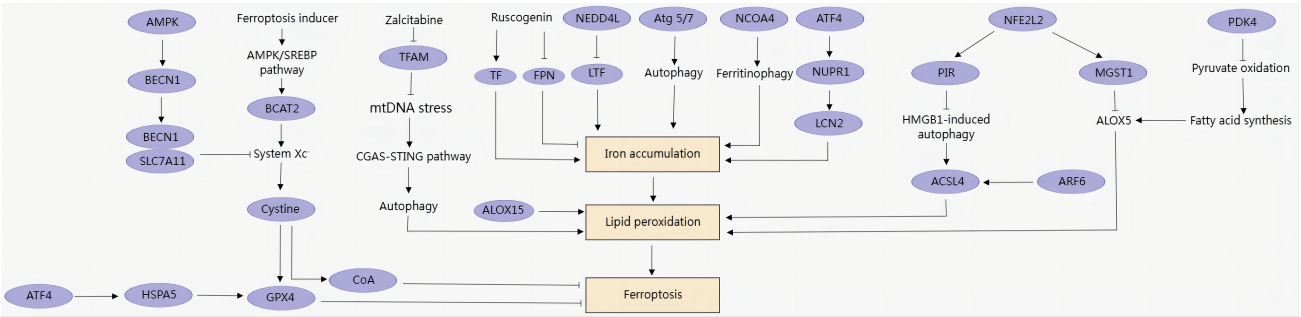


**Fig. 2. Interrelationship between ferroptosis and PDAC.**

tosis in tumor cells could be a promising new therapeutic strategy. Furthermore, ferroptosis inducers have the potential to synergize with traditional antitumor drugs in order to inhibit tumor progression.

Despite the challenges of drug resistance and poor efficacy, gemcitabine remains the first-line chemotherapy drug for PDAC patients. Latest studies have verified that ferroptosis plays a crucial role in overcoming gemcitabine resistance [64]. Mechanistically, the overexpression of HSPA5 protects GPX4 from degradation, which in turn inhibits lipid peroxidation in ferroptosis. In pancreatic cancer, inhibiting the HSPA5-GPX4 pathway in a ferroptosis-

mediated manner has been shown to reverse gemcitabine resistance [62]. Gene expression profiling revealed that F-box and WD repeat domain-containing 7 (FBW7) plays a crucial role in regulating ferroptosis in pancreatic cancer through its involvement in lipid peroxidation. Targeting FBW7 enhances the cytotoxicity of gemcitabine in PDAC by inducing both ferroptosis and apoptosis [65]. Therefore, inducing ferroptosis in pancreatic cancer cells could potentially reverse gemcitabine resistance and offer a new strategy for systemic therapy of pancreatic cancer.

Artemisinin, a Chinese-derived antimalarial drug, and its derivatives, such as artesunate (ART) and dihydroartemisinin (DHA), have shown multiple mechanisms of action, including ferroptosis, which exhibits potent anticancer activity [66,67]. ART promotes the generation of ROS through a lysosomal iron-dependent manner, inducing ferroptosis in PDAC while not affecting non-neoplastic human pancreatic ductal epithelial cells [68]. In KRAS-mutant pancreatic cancer, the 78-kDa Glucose-regulated protein 78 (GRP78), an active molecular chaperone in the endoplasmic reticulum, has a negative regulatory effect on ART-induced ferroptosis [69]. DHA induces ferroptotic cell death by upregulating the expression of arachidonate 12-lipoxygenase (ALOX12), thereby inhibiting the proliferation of pancreatic cancer cells [70]. Therefore, artemisinin derivatives either alone or in conjunction with other medications may offer fresh treatment options for PDAC patients. However, further research is needed to explore whether the least toxic artemisinin derivatives have the ability to induce ferroptotic activity.

In addition to gemcitabine and artemisinin derivatives, there have been recent reports of more drugs affecting ferroptosis in pancreatic cancer cells. Baicalein, an efficient ferroptosis inhibitor in pancreatic cancer cells, not only inhibits the production of malondialdehyde (MDA), the end product of lipid peroxidation, but also prevents iron accumulation, protects against GSH depletion and GPX4 degradation, consequently preventing ferroptotic cell death [71]. Irisin, a multi-functional myokine, has been found to increase iron accumulation and the production of the lipid peroxidation end product MDA. It also downregulates GSH and inhibits the expression of SLC7A11, ultimately leading to ferroptotic cell death in PDAC [72]. QD394, a novel redox modulator, destabilizes the GPX4 protein and lessens the GSH/oxidized glutathione (GSSG) ratio, resulting in iron- and ROS-mediated ferroptosis in pancreatic cancer cells [73]. Cotylenin A (CN-A) and phenethyl isothiocyanate (PEITC), a plant growth regulator and a dietary antitumor phytochemical compound, have been found to synergistically trigger ferroptosis in human PDAC cells in a ROS-dependent pattern. However, CN-A or PEITC alone do not have the same effect [74]. Sorafenib, the first approved anticancer drug capable of inducing ferroptosis in different tissues, including liver and kidney cancers, is found to be less effective against PDAC [75,76]. *SLC1A5*, a ferroptosis regulatory gene, has been positively associated with sorafenib sensitivity in pancreatic cancer cells [77]. Therefore, it appears that the induction of ferroptosis can help address the limitations of sorafenib in PDAC treatment. In conclusion, investigating novel ferroptosis inducers or combination therapies to enhance tumor sensitivity to ferroptosis could offer a fresh approach to PDAC treatment.

### *4.2 Immunotherapy*

Immunotherapy, which utilizes immune checkpoint inhibitors (ICIs), has markedly improved the prognosis for cancer patients. ICIs function by stimulating cytotoxic T cells and enhancing antitumor immunity through the targeting of specific proteins, including cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death protein 1 (PD-1), and its ligands programmed death-ligand 1 (PD-L1) [78]. Research studies have indicated that the release of interferon gamma (IFN$\gamma$) by immunotherapy-activated $CD8^+$ T cells can downregulate the level of SLC7A11 and SLC3A2, inhibiting system $X_c^-$ by activating the Janus kinase (JAK)-signal transducer and activator of transcription 1 (STAT1) signaling pathway. This, in turn, heightens the susceptibility of cancer cells to ferroptosis. Utilizing an engineered enzyme called cyst(e)inase, which degrades cystine and cystine, can synergistically promote lipid peroxidation with IFN$\gamma$, thereby inducing ferroptosis in tumor cells. Furthermore, the combination of cyst(e)inase and PD-L1 blockade can synergistically enhance lipid peroxidation, leading to the exertion of antitumor immunity in a ferroptotic manner [64,79]. Although there is a lack of experimental results specifically on PDAC, this approach broadens the potential of immunotherapy for PDAC. Immune evasion remains a significant challenge in cancer treatment today. In the context of PDAC, the autophagy cargo receptor NBR1-mediated autophagy pathway has been observed to result in decreased levels of the major histocompatibility complex class I (MHC-I), thereby promoting immune evasion [80]. BEBT-908, a dual phosphoinositide 3-kinase (PI3K)/histone deacetylase (HDAC) inhibitor, has been discovered to induce ferroptotic cell death. Moreover, it has the ability to enhance the expression of MHC-I in ferroptotic cells, thereby rendering tumor cells more susceptible to T cell-mediated killing [81]. While $CD8^+$ T cells are known for their killing effect, T regulatory (Treg) cells have a different function in sustaining immune tolerance and suppressing antitumor immunity. Studies have demonstrated that GPX4, a key enzyme involved in ferroptosis, plays a protective role in Treg cells by preventing lipid peroxidation and ferroptosis, thus maintaining immune homeostasis and suppressing anti-tumor immunity. However, depletion of GPX4 in Treg cells within tumors has been shown to induce ferroptosis, preventing tumor immune escape and ultimately enhancing antitumor immunity [82]. Despite the significant potential of ferroptosis in cancer therapy, tumors have developed mechanisms to re-

sist cell death. In the case of PDAC, autophagy-dependent ferroptosis induces the release of the $KRAS^{G12D}$ protein. This protein is then encapsulated into exosomes and internalized by macrophages through the advanced glycosylation end-product specific receptor (AGER)-dependent mechanism. Consequently, the macrophages undergo a transformation into the M2 phenotype, which promotes tumor growth. Therefore, inhibiting the transport of $KRAS^{G12D}$ from PDAC cells to macrophages could effectively prevent the progression of PDAC. Targeting the transport of $KRAS^{G12D}$ between tumors and macrophages presents potential novel strategies for PDAC therapy [83]. Toll-like receptor 2 (TLR2) on macrophages has the ability to detect 1-stearyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine (SAPE-OOH), an "eat-me" signal located on the surface of ferroptotic cells. This recognition ultimately enhances the phagocytosis of ferroptotic cells, indicating that ferroptosis promotes macrophage-mediated phagocytosis [84]. Taken together, the integration of traditional immunotherapy with ferroptosis has the potential to improve the prognosis of PDAC patients.

### *4.3 Radiotherapy*

The effect of radiation therapy in the treatment of locally advanced pancreatic cancer (LAPC) has been a subject of controversy. However, studies have shown that single-modality radiotherapy can provide potential benefits for LAPC patients [85]. With a deeper understanding of the mechanism of ferroptosis, radiotherapy may become more clinically significant in the therapy of PDAC. Research has demonstrated that radiotherapy not only induces ferroptosis in various cancer cells through promoting the ACSL4 expression and ROS production, but also elevates the adaptability of SLC7A11 or GPX4, leading to radioresistance. It has been observed that ferroptosis inducers can render tumor cells more sensitive to radiotherapy. Furthermore, the combination of ferroptosis inducers and radiation therapy synergistically promotes ferroptosis in various cancer cells such as lung cancer, breast adenocarcinoma and fibrosarcoma [86]. Additionally, IFN$\gamma$ released via immunotherapy-activated $CD8^+$ T cells, including anti-PD-L1 and anti-CTLA4, can inhibit the expression of SLC7A11 when combined with radiotherapy-activated Ataxia-Telangiectasia mutated gene (*ATM*), thereby inducing ferroptosis in tumor cells, including ovarian cancer and melanoma [87]. The release of irradiated tumor cell–released microparticles (RT-MPs) can enhance the phagocytosis of tumor cells such as lung cancer cells and melanoma cells by macrophages through ferroptosis-mediated immunogenic death [88]. Although the studies mentioned above do not specifically involve pancreatic cancer cell lines, it is important to consider the clinical significance of the ferroptosis mechanism in radiotherapy for lung cancer, ovarian cancer, and other malignant tumors. Conducting extensive research on the precise mechanism of radiotherapy-induced ferroptosis in PDAC and exploring the potential role of ferroptosis inducers in combination with radiotherapy can provide novel strategies to improve the survival rate of PDAC patients.

### *4.4 Nanotherapy*

Nanotherapy involves the encapsulation of drugs in nanoparticles, enabling them to effectively bypass biological barriers and deliver drugs directly to tumor cells. Nanoparticles not only accumulate in tumors through the enhanced permeability and retention effect (EPR), but also interact with tumor cells, thereby increasing selectivity and reducing adverse drug reactions [89]. The development of nanomedicine targeting ferroptosis is a promising approach to enhance the effectiveness of existing ferroptosis inducers and improve the prognosis of PDAC patients. In order to overcome the limitations of conventional chemotherapy drugs, researchers prepared biocompatible $MnFe_2O_4$-loaded carbonaceous (MFC) nanoparticles loaded with gemcitabine (MFC-Gem) as a therapeutic platform. In comparison to gemcitabine alone, MFC-Gem exhibited a synergistic effect in enhancing PDAC ferroptosis by promoting ROS generation and GSH depletion. Furthermore, MFC-Gem enhanced the chemotherapeutic efficacy of gemcitabine through ferroptosis. The high magnetic susceptibility of MFC-Gem also allows for simultaneous magnetic resonance imaging (MRI) monitoring of PDAC. Additionally, MFC-Gem demonstrated pH-responsive release, low toxicity, and good biocompatibility, making it a promising tool for precise treatment and monitoring of PDAC [90]. To address the issue of poor efficacy of anti-angiogenic therapy drugs on PDAC, researchers developed platelet vesicles (PVs)-encapsulated ferroptosis inducer RSL-3 (RSL-3@PVs). The experimental findings demonstrate that the combined use of RSL-3 and PVs not only maintains the effectiveness of each element, but also counteracts PDAC through tumor vascular embolism and ferroptosis. Furthermore, RSL-3@PVs have exhibited favorable biosafety, with no structural damage observed in other organs [91]. Another approach involves DHA-conjugated and RSL-3-loaded nanoparticles (PDBA@RSL-3 NPs), which trigger ferroptosis in PDAC by depleting GSH and inhibiting GPX4. Additionally, they stimulate antitumor immunity via inducing ferroptosis in tumor cells. Moreover, combining PDBA@RSL-3 NPs with PD-L1 blockade therapy synergistically inhibits PDAC cell growth [92]. While nanomedicine holds promise in improving the current state of drug resistance in PDAC and enhancing the effectiveness of conventional drugs, it is imperative to evaluate the toxicity and efficacy of nanomedicine on humans, considering the variations between animal models and humans. Thus, further research is necessary to facilitate the clinical implementation of nanotherapy in the treatment of PDAC. The ferroptosis inducers and inhibitors are listed in Table 2 (Ref. [11,51,52,68–74,79,90–93]).

**Table 2. The ferroptosis pharmacological inducers and inhibitors in PDAC.**

| Compound | Mechanism | Refs |
|---|---|---|
| ART | Promote ROS production in lysosomal iron-dependent manner | [68] |
| Baicalein | Limit iron accumulation and lipid peroxidation and suppresses GSH depletion and GPX4 degradation | [71] |
| CN-A and PEITC | Induce the generation of ROS | [74] |
| Cyst(e)inase | Synergistically promote lipid peroxidation with IFN$\gamma$ | [79] |
| DHA | Upregulate ALOX12 | [70] |
| Erastin | Inhibit system $X_c^-$ | [11] |
| GRP78 | Negatively regulate ART-induced ferroptosis | [69] |
| Irisin | Increase iron accumulation, ROS level and GSH depletion | [72] |
| MFC-Gem | Promote ROS generation and GSH depletion | [90] |
| PDBA@RSL-3 NPs | Induce GSH depletion and GPX4 inhibition and stimulate antitumor immunity | [92] |
| QD394 | Destabilize the GPX4 protein and decrease the GSH/GSSG ratio | [73] |
| Rapamycin | Induce autophagy-dependent ferroptosis | [93] |
| Ruscogenin | Increase intracellular iron | [52] |
| RSL-3@PVs | Induce ferroptosis and tumor vascular embolism | [91] |
| Zalcitabine | Trigger mitochondrial DNA stress and subsequent autophagy-dependent ferroptosis | [51] |

Abbreviations: ART, artesunate; CN-A, cotylenin A; DHA, dihydroartemisinin; GRP78, glucose-regulated protein 78; MFC-Gem, $MnFe_2O_4$-loaded carbonaceous nanoparticles loaded with gemcitabine; PDBA@RSL-3 NPs, DHA-conjugated and RSL-3-loaded nanoparticles; PEITC, phenethyl isothiocyanate; RSL-3@PVs, platelet vesicles-encapsulated ferroptosis inducer RSL-3.

## 5. Conclusions and Perspectives

Ferroptosis, a lately discovered modality of non-apoptotic cell death, is distinguished by iron accumulation, ROS generation, and lipid peroxidation. Inducing ferroptosis in PDAC cells not only inhibits tumor growth but also enhances the sensitivity of PDAC to systemic therapy, immunotherapy, radiotherapy, and nanotherapy when combined with other antitumor drugs. This article focuses on the regulatory mechanisms of ferroptosis, its connection to PDAC, and the research progress in PDAC treatment. Despite the potential of ferroptosis in PDAC treatment, there are several noteworthy challenges that need to be addressed. Firstly, the comprehension of the underlying mechanisms of ferroptosis is still in its nascent stages. Although diverse major regulators of ferroptosis in PDAC have been identified, further research is required to explore potential signaling pathways and key regulators. Secondly, the development of drugs targeting the ferroptosis pathway and the exploration of ferroptosis's role in immunotherapy and nanotherapy hold promise for advancing PDAC treatment strategies. However, although several drugs targeting the ferroptosis pathway have shown promising results in preclinical studies using cells and animal models, their effects on humans and the optimal dosages for inducing ferroptosis have not yet been determined. Furthermore, the efficacy and safety of combination therapy using ferroptosis inducers still require further investigation. Additionally, the development of resistance to ferroptosis inducers poses a challenge to their clinical application.

To address these issues, future research should focus on elucidating the underlying molecular regulation of ferroptosis and its specific targets for the treatment of PDAC. The induction of ferroptosis by anti-tumor drugs has shown potential in exerting anti-cancer activity. This discovery offers new possibilities and avenues for the clinical treatment of pancreatic cancer. Moreover, efforts should be made to minimize drug side effects and overcome drug resistance through the use of combination therapy and the development of nano-medicines. Overall, ferroptosis, as a recently discovered form of non-apoptotic cell death, demonstrates significant potential as an anticancer mechanism. We believe that targeting ferroptosis and its associated mechanisms will facilitate the discovery of new ferroptosis inducers and novel combination therapy strategies, ultimately enhancing the prognosis and quality of life for PDAC patients.

## Author Contributions

CY and QD collected the literatures and interpreted the data. CY and QD wrote the original manuscript. HB organized the tables. YG and ZX drew the figures. JL and XJ analyzed the contents from the reviewed literature. YX and XZ designed manuscript conception and critically revised manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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