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Ferroptosis and cancer: interlinkages and potential applications

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Abstract

The buildup of lipid peroxides on the cell membrane is critical in the initiation of Ferroptosis, an iron-dependent form of controlled cell death. Ferroptosis is a type of cell death that varies from other types of cell death in both mechanics and morphology, and it holds significant promise for cancer therapy. As a result, there has been increasing interest in the cancer research community regarding the exploration and understanding of Ferroptosis in recent years. This review article aims to provide a solid theoretical foundation for the management of Ferroptosis in cancer. It accomplishes this by summarizing the processes that contribute to the development of Ferroptosis and outlining the underlying mechanisms of Ferroptosis in various types of tumors.

KEYWORDS

Ferroptosis; Mechanism; Cancer; Targeted therapy; Drug resistance

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Introduction

The concept of Ferroptosis, a novel form of cell death initially proposed in 2012, has captured significant attention from researchers in various fields. Ferroptosis has been linked not only to degenerative diseases, stroke, renal failure, and local ischemia-reperfusion injury in mammals but also to the development and regulation of cancer cells. Extensive research in modern medicine has established Ferroptosis as a crucial tumor suppressor mechanism, leading to substantial advancements in tumor biology and cancer therapy. In this review, we aim to consolidate the current understanding of the mechanisms underlying Ferroptosis and its role in different types of tumors by synthesizing a comprehensive body of literature. This collective knowledge may present new opportunities for clinical treatment strategies in the future, benefiting patients in the fight against cancer.

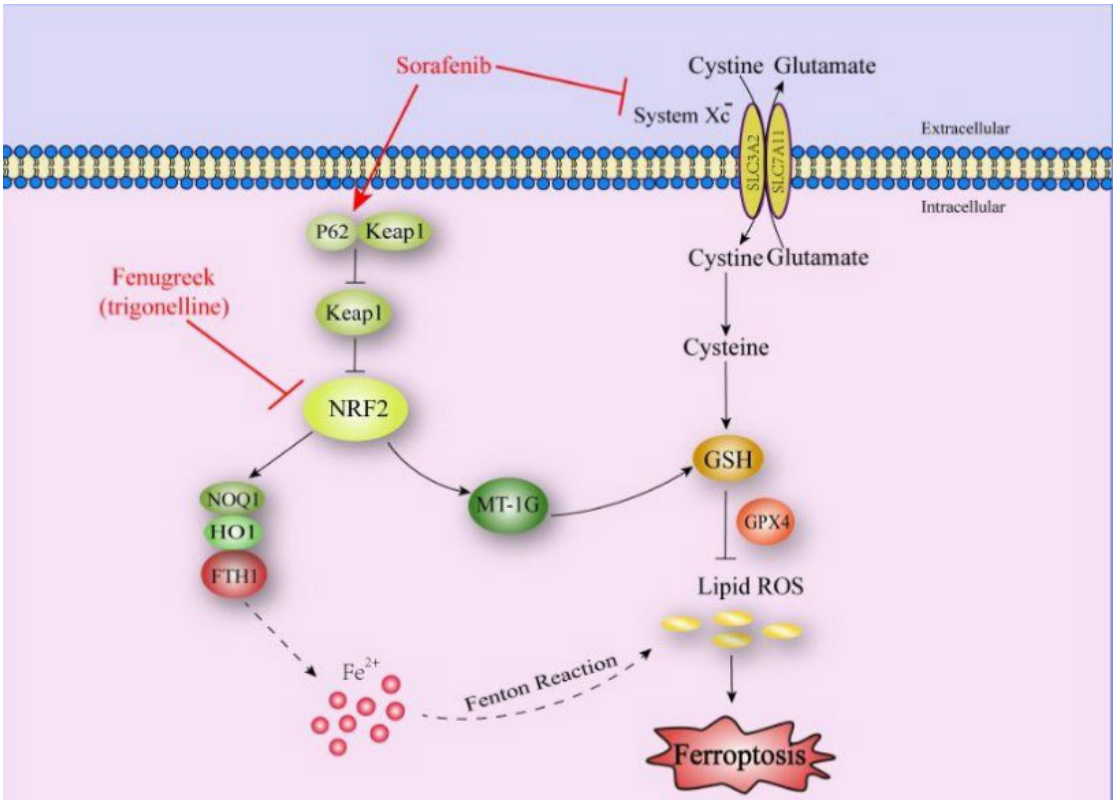

FIGURE 1

The mechanisms of Ferroptosis induction.

Sorafenib activates the p62-Keap1-NRF2 pathway, resulting in an increase in NRF2, which also leads to an increase in GSH and a reduction in ferroptosis. The p62-Keap1-NRF2 pathway plays an important role in the fight against Ferroptosis by regulating the NRF2-targeted genes HO1, NQO1, and FTH1. System XC-(SLC3A2 and SLC7A11) induces GSH deficiency and GPX4 inactivation via glutamate and cystine, increases lipid peroxide accumulation, thus contributing to Ferroptosis.

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1.Mechanism of Ferroptosis

Generally speaking, the development of cancer is associated with cellular changes, including cell growth, development, differentiation and death[1]. Among them, Ferroptosis in cell death is the focus of medical research in recent years. The imbalance between the formation and breakdown of lipid reactive oxygen species (ROS) in cells causes ferroptosis[2]. The essence is the depletion of glutathione, the decreased activity of peroxidase GPX4, the decreased antioxidant capacity, and the accumulation of ROS, which promotes the occurrence of Ferroptosis[3, 4]. This process is different from other cell death methods at the morphological, biological and genetic levels[5]. Specifically, the morphological features of the cells include the reduction of mitochondria, increased membrane density, cristoid decrease or absence, and mitochondrial outer membrane rupture[6]. In terms of cellular components, it manifests as increased lipid peroxidation, increased ROS, and alterations in a few key genes[7]. Herein, we enumerate some inducers of Ferroptosis to clarify the mechanism of Ferroptosis.

1.1 System XC- induces Ferroptosis

Systemic XC- is a heterodimer composed of SLC7A11 and SLC3A2, which is embedded on the cell membrane surface and plays a key role in the regulation of cellular ferritin deposition[8, 9]. Systemic XC-mediated cystine uptake has an important role in Ferroptosis[10]. Inhibition of systemic XC- activity inhibits cystine uptake and affects GSH synthesis, which in turn leads to reduced activity of the membrane lipid repair enzyme GPX4 and a decrease in cellular antioxidant capacity, inducing the development of Ferroptosis[11, 12], as shown in Figure 1.

1.2 Erastin induces Ferroptosis

Erastin is a widely used inducer of ferroptosis that triggers the development of ferroptosis by inhibiting System XC-activity. This inhibition prevents the entry of cystine into cells, leading to the inability to synthesize glutathione (GSH) and reducing antioxidant capacity (Figure 2)[13, 14](Figure 2). In a study on lung cancer, erastin was found to increase ROS levels, which subsequently activated p53 and further elevated intracellular ROS levels[15]. This process exacerbates the toxic and inhibitory effects of erastin on lung cancer cells, ultimately leading to Ferroptosis. Erastin-induced Ferroptosis in other types of cancer is also accompanied by an accumulation of intracellular ferric ions[16]. Furthermore, other studies have demonstrated that erastin enhances the sensitivity of many cancer cells to chemotherapeutic agents and radiation, highlighting its potential as a novel anti-cancer agent[17, 18].

1.3 GPX4 induces ferroptosis

GPX4, the fourth member of the selenium-containing GPX family, is a core regulator of Ferroptosis[19, 20]. Studies have shown that some inhibitors of GPX4, such as ML162, RSL3, DPI compounds and FIN56, induce Ferroptosis by inhibiting GPX4, resulting in a decrease in cellular antioxidant capacity and an increase in lipid reactive oxygen species[21, 22](Figure 2). RSL3, for example, causes Ferroptosis by inactivating GPX4, resulting in the accumulation of intracellular peroxides[23, 24]. Similarly, RSL3, ML162, and related compounds directly inhibit the function of GPX4 via covalent modifications, causing Ferroptosis without affecting intracellular glutathione levels[25, 26]. FIN56 causes ferroptosis not only by degrading GPX4, but also by binding to squalene synthase (SQS) and depleting CoQ10[22, 27]. Furthermore, another GPX4 inhibitor, FINO2, can cause Ferroptosis by inactivating GPX4[28, 29].

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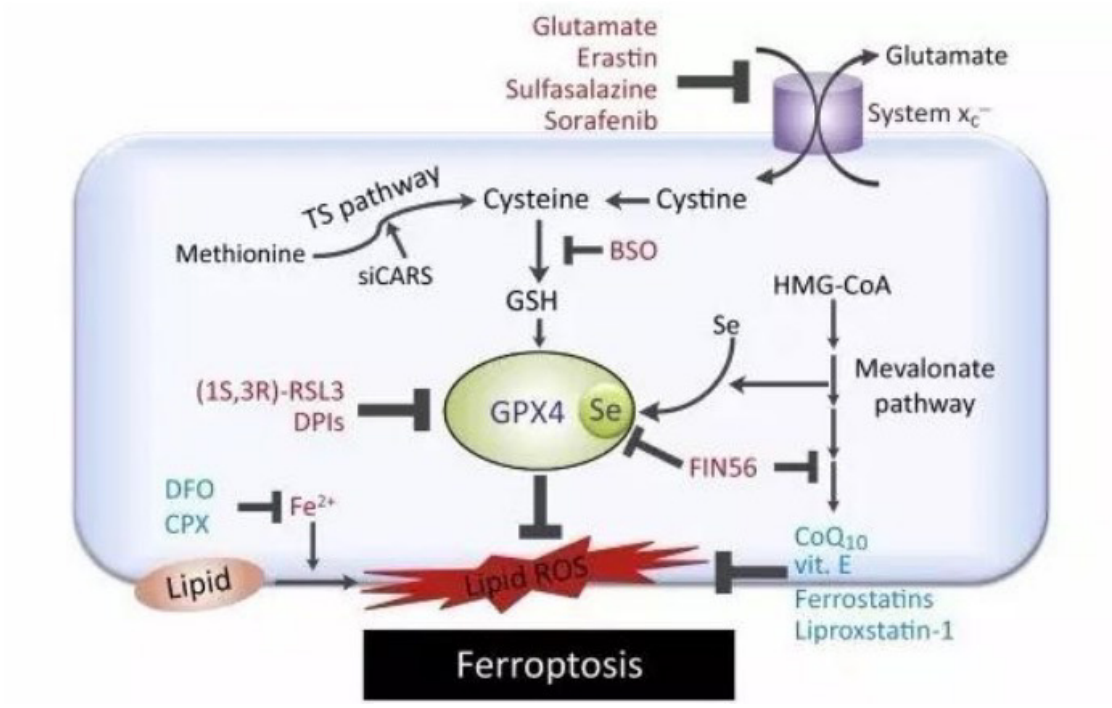

FIGURE 2

Small molecule and drug inducer for lipid metabolism.

Erastin inhibits the activity of System XC, which leads to the development of Ferroptosis. By deactivating GPX4, RSL3 and DPIs induce ferroptosis by buildup of intracellular peroxides. By attaching to squalene synthase (SQS) and depleting CoQ10, FIN56 contributes to Ferroptosis. Statins can induce cellular Ferroptosis by depleting CoQ10 through inhibition of HMG-CoA reductase. Iron ion chelators contain DFO and CPX, and Ferroptosis inhibitors include Ferrostatins and Liproxstain-1.

1.4 p53 induces Ferroptosis

p53 is an important regulator of Ferroptosis and plays a role in GPX4-centred Ferroptosis, acting as a tumor suppressor[30]. p53 is an important Ferroptosis regulator that plays a role in GPX4-centred Ferroptosis and acts as a tumor suppressor[31, 32]. Several studies have found that p53 prevents Ferroptosis under low ROS stress and promotes Ferroptosis under high oxidative stress[33, 34]. p53 enhances cellular sensitivity to Ferroptosis by transcriptionally repressing SLC7A11 and thereby inhibiting cystine uptake[35, 36](Figure 3). In some cellular environments, Ferroptosis can also be adversely regulated by p53. For example, stabilization and restoration of wild-type p53 activity by nutlin-3 protects fibrosarcoma, renal carcinoma and osteosarcoma cells from iron death by maintaining intracellular GSH levels through a p53-21-dependent pathway that inhibits system XC- function[37]. According to Jiang L et al., p53 decreases cystine absorption and makes cells more susceptible to ferroptosis by reducing the expression of SLC7A11[38]. Inactivation of ALOX12 ROS-induced p53-mediated iron sagging was diminished, and p53-dependent tumor growth inhibition was removed[39].

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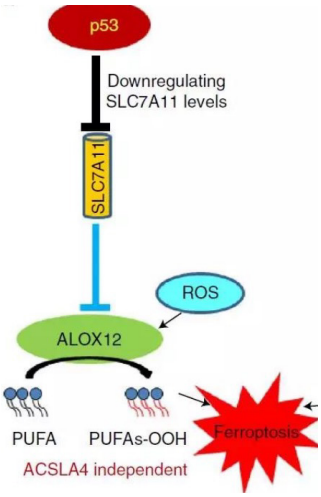

FIGURE 3

The induction pathway of p53.

p53 triggers Ferroptosis, which is regulated by the lipoxygenase ALOX12, indirectly by down-regulating SLC7A11 expression and reducing cystine uptake. p53-mediated ferroptosis of the ACSL4 non-dependent type.

PUFA: Polyunsaturated fatty acids; PUFA-OOH: The state of peroxidation of PUFA.

1.5 Lipid peroxidation induces Ferroptosis

The oxidative degradation of lipids in response to the loss of hydrogen atoms by the action of free radicals or lipid peroxidases, resulting in the oxidation, breakage, and shortening of lipid carbon chains and the production of cytotoxic substances that cause cellular damage, is an important marker of ferroptosis[40]. Zhang HL et al. mentioned the positive feedback axis of lipid peroxidation-PKCII-ACSL4 may represent a viable target for the therapy of ferroptosis-related disorders[41]. Ferroptosis in astrocytes can be accomplished by NOX4-mediated oxidative stress-induced lipid peroxidation impairing mitochondrial metabolism in Alzheimer's disease[42]. A study by Zhao L et al. found that in gastric cancer cells apatinib negatively regulated Ferroptosis through SREBP-1-mediated GPX4-induced lipid peroxidation[43].

1.6 NRF2 induces Ferroptosis

NRF2 is a transcription factor involved in antioxidant activities and has been shown to be closely associated with Ferroptosis in recent years[44, 45]. The NRF2-GPX4-mediated Ferroptosis pathway is involved in the neuroprotective effects of dexmedetomidine in rats with cerebral hemorrhage[46]. A review by Dodson M et al. discusses that increased upregulation of NRF2 expression prevents Ferroptosis, while downregulation of NRF2 expression effectively enhances the sensitivity of cancer cells to Ferroptosis prodrugs, suggesting that NRF2 levels correlate with Ferroptosis sensitivity[47]. NRF2 also inhibits Ferroptosis by increasing target genes associated with iron and ROS metabolism[48, 49]. In studies of chronic obstructive pulmonary disease, dihydroquercitrin intervention is shown to inhibit cigarette smoke exposure-induced Ferroptosis by modulating the NRF2 signaling pathway[50]. Additionally, NRF2 mediates the antioxidant, iron and intermediate metabolic states of cells and is involved in Ferroptosis through the regulation of xCT and GPX4[47].

1.7 Sorafenib induces Ferroptosis

Sorafenib is a new multi-targeted drug for cancer therapy, which has a significant anti-tumor effect as a Ferroptosis inducer in a variety of cancers[51, 52]. Sorafenib can promote Ferroptosis by blocking SLC7A11-mediated cystine import into cells[35, 53]. The study by Li ZJ et al. confirm that sorafenib and artesunate can play a combined role in the therapy of liver cancer, which can significantly aggravate lipid peroxidation and Ferroptosis in cancer cells[54]. In an animal study, Yuan S et al. explored the anti-fibrotic effects of sorafenib and found that sorafenib triggered hepatic stellate cell Ferroptosis via HIF-1α/SLC7A11 signaling and attenuated the extent of liver injury and fibrosis[55]. QSOX1 promoted the sensitivity of hepatocellular carcinoma cells to sorafenib therapy by suppressing NRF2 activation and

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induced Ferroptosis[56, 57]. Yu Y et al. reported sorafenib inhibited ARG2 expression in murine melanoma cells, but overexpressed ARG2 reduced lipid peroxidation through stimulating the Akt/GPX4 signaling pathway, which adversely controlled sorafenib-induced Ferroptosis in melanoma cells[58]. Other studies have also highlighted the significance of ATF3/Slc7a11-mediated ferroptosis as the underlying mechanism of sorafenib-induced cardiotoxicity[59]. Additionally, sorafenib has been demonstrated to enhance ferroptosis in thyroid cancer cells, thereby expediting the process of cancer cell death[60, 61].

1.8 Heat shock protein (HSPs) induced Ferroptosis

HSPs serve as tumor markers and are commonly utilized in tumor diagnosis and differentiation[62]. HSPs can be categorized into various types based on their size, including HSP110, HSP90, HSP70, HSP60, and small molecule HSPs, all of which have demonstrated the ability to induce ferroptosis[63-65]. Furthermore, different HSPs exert distinct effects on ferroptosis in various diseases. HSPB1 and NCOA4 play roles in regulating iron homeostasis and are capable of preventing ferroptosis induced by elevated intracellular iron levels[66]. Conversely, HSP90 may mitigate ferroptosis by inhibiting the degradation of GPX4 protein[33, 67]. Overexpression of HSPB1 inhibits erastin-induced iron uptake, while downregulation of HSPB1 expression has the opposite effect, thereby rendering cancer cells more susceptible to ferroptosis in cases where iron and HSPB1 levels are excessively high and the HSPB1 pathway is downregulated[68].

2 Ferroptosis in different cancers

Apoptosis, autophagy, necrosis, and other forms of cell death have been extensively investigated in clinical studies and shown to impact tumor development[69]. Ferroptosis is a specific process of regulated cell death led by iron-mediated oxidative damage and subsequent degradation of cell membranes[70, 71]. Increased iron buildup, free radical production, fatty acid availability, and lipid peroxidation are all important variables in the commencement of this process[72]. Ferroptosis promotes tumor development while also reducing tumor progression during tumorigenesis[73]. The vulnerability of various cancer cell types to ferroptosis varies greatly, and it significantly influences the effectiveness of chemotherapy, radiation, and immunotherapy. Combining therapies that induce ferroptosis can enhance the therapeutic outcomes of these treatments[12, 74, 75]. Further investigations have revealed that the combination of certain chemotherapeutic drugs with the ferroptosis-inducing agent erastin exhibits potent synergistic anti-tumor effects[76]. In this section, an overview of the potential processes of ferroptosis in different malignancies was provided and discussed the potential therapeutic implications of targeting iron dysregulation.

2.1 Breast cancer

Ferroptosis-related genes have been demonstrated to inhibit proliferation and distant metastasis of breast cancer cells through activation of the Ferroptosis pathway, which can be used not only as a novel adjuvant chemotherapy for breast cancer, but also as a prognostic target for breast cancer patients[77, 78]. Li R et al. reported in the literature that curcumin inhibited the growth of cancer cells by inducing Ferroptosis in breast cancer cells[79]. Li K et al. found through their study that multi-enzyme active nanases could inhibit the anti-Ferroptosis pathway, such as GPX4 and FSP1, inducing significant Ferroptosis damage and thus used for Ferroptosis treatment of triple negative breast cancer[80]. Another study found that Holo-Lactoferrin triggered Ferroptosis in triple-negative breast cancer cells and improved radiation sensitivity[81]. Yang J et al. demonstrated that metformin synergized with sulfasalazine and systemic xc-inhibitors to induce iron sagging, thereby achieving inhibition of breast cancer cell growth[82].

2.2 Hepatocellular carcinoma

Sorafenib is used to treat advanced hepatocellular carcinoma

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as a first-line therapy. Gao R et al. found that YAP/TAZ in combination with ATF4 was able to promote resistance to sorafenib by inhibiting Ferroptosis[53]. PSTK has an important role in ferroptosis resistance in hepatocellular carcinoma cells, according to Chen Y et al., and its depletion is associated with GPX4 inactivation and disruption of GSH metabolism, which also increases the induction of Ferroptosis during targeted chemotherapy in hepatocellular carcinoma[83]. In a study of drug resistance mechanisms in hepatocellular carcinoma, Lu Y et al. demonstrate that Ferroptosis is regulated by the ETS1/miR-23a-3p/ACSL4 axis[84]. Through experiments in mice, Grube J et al. found that Ferroptosis, which lacked the ACSL4-dependent process, significantly stalled the development of hepatocellular carcinoma[85]. Guan L et al. reported that miR-3200-5p regulated Ferroptosis by targeting ATF4, which directly affected the proliferation and metastasis of hepatocellular carcinoma cells[86].

2.3 Ovarian cancer

Ferroptosis is influenced by various inducers and inhibitors, and the induction of drug-induced Ferroptosis in ovarian cancer cells represents a promising avenue for clinical treatment[74]. PARP inhibitors have been shown to promote ferroptosis by inhibiting SLC7A11 and are used in combination with ferroptosis inducers (FINs) for the treatment of ovarian cancer[87]. The binding of p14ARF to the transcription factor NRF2 inhibits NRF2-mediated transcriptional activity of SLC7A11, leading to the induction of ferroptosis and exerting an inhibitory effect on tumorigenesis[88]. You Y et al. developed a scoring system based on Ferroptosis-related genes in ovarian cancer, which can predict the correlation between Ferroptosis and tumor progression, as well as distant metastasis[89]. Jing T et al. reported that a specific dose of CMP induces ferroptosis in ovarian cancer cells, thereby demonstrating its potential as an antitumor therapy approach[90].

2.4 Colorectal cancer

Tagitinin C, a new ferroptosis inducer, causes ferroptosis in colorectal cancer cells by activating the ER stress-mediated PERK-NRF2-HO-1 signaling pathway. When coupled with erastin, it has a synergistic anti-tumor effect[91, 92]. Cetuximab is a common targeted therapeutic agent for colorectal cancer[93]. In mouse studies, Yang J et al. discovered that cetuximab can suppress the Nrf2/HO-1 pathway and enhance RSL3-induced Ferroptosis in KRAS mutant CRC cells via activation of p38 MAPK, suggesting the potential for combination therapy[94]. Apatinib, an orally administered small molecule anti-angiogenic inhibitor, is a mainstay treatment for advanced colorectal cancer[95]. It has been found that apatinib increases iron and ROS levels in colorectal cancer cells by targeting ELOVL6/ACSL4, thereby promoting the mechanism of ferroptosis[96, 97].

2.5 Prostate cancer

Researchers have found that some Ferroptosis inducers, such as erastin and RSL3, when combined with conventional anticancer drugs, can induce ROS production in prostate cancer cells, which can significantly suppress the growth and development process of cancer cells and can achieve effective anti-tumor effects[24, 98]. Kim KS et al. reported that ferumoxytol-mediated Ferroptosis could enhance the anti-cancer effect of NK cells in prostate cancer with significant tumor volume regression[99]. According to Cheng L et al., overexpression of SGK2 hinders ferroptosis and facilitates metastasis in prostate cancer by acting on the Thr-24 and Ser-319 sites of FOXO1. This mechanism causes FOXO1 to be translocated from the nucleus to the cytoplasm, thereby alleviating the inhibitory effect of FOXO1 on GPX4. These findings suggest that targeting this pathway could serve as a novel therapeutic strategy for metastatic prostate cancer[100].

2.6 Gastric cancer

An increasing number of studies are focusing on the role of ferroptosis and its associated non-coding RNAs (ncRNAs) in the development, drug resistance, and prognosis of gastric cancer[101, 102]. For instance, long non-coding RNAs (lncRNAs) such as A2M-AS1 and C2orf27A have been found to target ferroptosis-related genes, modulate immune cells, and participate in the immunotherapy of gastric cancer[103, 104]. The miR-375/SLC7A11 axis has been shown to stimulate cellular ferroptosis and reduce the stem cell population in gastric cancer cells[105]. By modulating the miR-103a-3p/GLS2 axis, rhodopsin methyl ether 8-O--glucopyranoside causes ferroptosis in gastric cancer cells, increasing their susceptibility to chemotherapeutic

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drugs[106]. Cisplatin and paclitaxel promote the secretion of miR-522 by gastric cancer cells through activation of the USP7/hnRNPA1 axis. This, in turn, inhibits ALOX15 and reduces lipid-ROS accumulation, thereby inhibiting ferroptosis and resulting in decreased chemosensitivity[107].

2.7 Pancreatic cancer

Ductal adenocarcinoma of the pancreas is the primary type of pancreatic cancer, and its cells are susceptible to ferroptosis[108]. Sulfasalazine, which is associated with Ferroptosis, can be binned in combination with gemcitabine and sorafenib in the treatment of clinical pancreatic ductal adenocarcinoma[109]. MMRi62, an antitumor drug from the quinoline class, induces cell death in pancreatic ductal adenocarcinoma cells through ferroptosis, a process characterized by increased autophagy, elevated reactive oxygen species levels, and lysosomal degradation of NCOA4 and FTH1[110]. Yang J et al. discussed the association between pancreatic cancer and gemcitabine resistance and proposed the potential of combining NRF2 inhibitors with ferroptosis inducers to eliminate gemcitabine-resistant cells. Among them, HSPA5 controls ferroptosis in pancreatic cancer to prevent gemcitabine resistance, while FBXW7 enhances the cytotoxic effects of gemcitabine by FBXW7-NR4A1-SCD1 pathway, promoting Ferroptosis and apoptosis[111]. Furthermore, other studies have demonstrated that NUPR1-mediated LCN2 expression inhibits the development of ferroptosis by reducing iron accumulation and oxidative damage in ductal adenocarcinoma of the pancreas[112, 113].

2.8 Renal cell cancer

GPX4 plays a critical role as a key regulator in the ferroptosis signaling pathway in renal cell carcinoma (RCC) cells, and its knockdown leads to increased lipid peroxidation in these cells[114]. Both SLC7A11 and GPX4, two ferroptosis-associated proteins, are highly expressed in renal cancer and are closely associated with various clinical parameters such as tumor size, distant metastasis, prognosis, and clinical stage[115, 116]. Several studies have demonstrated that KDM5C mutations in renal cell carcinoma can modulate glycogen metabolism and counteract ferroptosis[117]. Additionally, the article by Lu Y et al. highlights the close relationship between KLF2 and GPX4, suggesting that KLF2 can regulate ferroptosis through GPX4, thereby inhibiting the growth of renal clear cell carcinoma cells[114].

2.9 Melanoma

The upregulation of miR-21-3p has been found to impact IFN-γ-induced ferroptosis in melanoma[118]. CAMKK2 protects against ferroptosis by activating the AMPK-NRF2 pathway, presenting a potential therapeutic approach for melanoma treatment[119]. Yang Y et al. reported that knockdown of NEDD4 increased the protein levels of VDAC2/3 and enhanced the sensitivity of melanoma cells to erastin. Moreover, FOXM1 suppresses ferroptosis in melanoma cells by modulating NEDD4 expression and VDAC2/3 degradation[120]. SREBP2, a transcription factor crucial in lipid metabolism, stimulates the transcription of the iron transporter transferrin, resulting in lower reactive oxygen species and lipid peroxidation and giving resistance to ferroptosis inducers[121-123]. Luo M et al. mentioned that miR-137 regulated erastin and RSL3-induced melanoma Ferroptosis, inhibiting lipid peroxidation and iron accumulation in Ferroptosis, a process that involves glutamine catabolism[124].

2.10 Cholangiocarcinoma

NDRG2 has been identified as a regulator of ferroptosis in cholangiocarcinoma cells, inhibiting tumor growth and increasing the sensitivity of radiotherapy[125-127]. Yao X et al. established a prognostic model for cholangiocarcinoma using public databases, which included four ferroptosis-related genes: ACSL4, IREB2, NFE2L2, and TP53[128]. The IDH1 mutation has been identified as a potential therapeutic target for cholangiocarcinoma[129, 130]. Su L et al. experimentally demonstrated that in cholangiocarcinoma, the IDH1 mutation sensitizes cells to erastin-induced ferroptosis as a mechanism to inhibit tumor progression[131]. Lei S et al. reported that LINC00976 regulates cholangiocarcinogenesis and metastasis and inhibits ferroptosis through the regulation of the miR-3202/GPX4 axis[132]. Zhu Z et al. explored that By boosting ferroptosis and proteasomal degradation of GPX4, the tumor suppressor FBXO31 increases the susceptibility of cholangiocarcinoma cells to cisplatin (CDDP)[133].

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2.11 Thyroid cancer

Sorafenib is a new multi-targeted oral medication for the treatment of malignancies that has been demonstrated to accelerate the Ferroptosis of thyroid cancer cells[134, 135]. Wang HH et al. reported Ferroptosis was reduced in thyroid cancer cells by Circ 0067934 via miR-545-3p/SLC7A11 signaling, a process that could serve as a potential direction for thyroid cancer[136]. In the study of Ferroptosis-related genes, Wang Y et al. found that AKR1C3 was associated with the prognosis of thyroid cancer and that knockdown of this gene significantly enhanced the growth of thyroid cancer cells[137]. Ji FH et al. demonstrated through cellular assays that in thyroid cancer, FTO suppressed cancer progression by downregulating SLC7A11 expression through Ferroptosis[138]. Besides, ALKBH5 combined with m6A-TIAM1-Nrf2/HO-1 axis induced Ferroptosis as a way to inhibit thyroid cancer progression[139].

2.12 Glioblastoma

Two Ferroptosis-related genes, GPX4 and SLC7A11, were found to be upregulated in glioblastoma, which might be associated with the development and progression of glioblastoma[140, 141]. The NRF2 pathway can inhibit glioblastoma iron death by enhancing the cystine/glutamate reverse transporter System-Xc[142]. The first-line therapeutic agent for glioblastoma (TMZ) also selectively induces glioma stem cell Ferroptosis[143, 144]. The NF-κb pathway was mentioned in the literature of Li S et al. to inhibit RSL3-induced Ferroptosis in glioblastoma cells, which could be a potential target for clinical chemoradiotherapy[145]. COPZ1 is a crucial regulator of iron metabolism, and its deletion causes NCOA4-mediated autophagy and Ferroptosis in glioblastoma cells, according to Zhang Y et al[146].

2.13 Cervical cancer

The HSPB1 pathway plays a role in inhibiting erastin-induced ferroptosis in cervical cancer cells by reducing the increase in iron and ROS levels[68]. Cisplatin treatment activates macrophages through inducing ferroptosis in cervical cancer, leading to effective tumor cell killing[147]. Propofol and paclitaxel exhibit synergistic anticancer effects and induce ferroptosis in cervical cancer cells[148]. CircLMO1 promotes ferroptosis by upregulating the expression of ACSL4 in cervical cancer, while overexpression of miR-4291/low expression of ACSL4 reverses this process[149]. Oleanolic acid-promoted ACSL4-dependent Ferroptosis could be a new approach for clinical therapy of cervical cancer[150].

Conclusion

Currently, we have gained a preliminary understanding of the characteristics and mechanisms of ferroptosis. Through numerous examples, we have illustrated the relationship between ferroptosis and cancer and explored treatment strategies involving ferroptosis in clinical cancers. However, researches are required to further delve deeper into the specific connections between ferroptosis and cancer cells.

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Conflict of interest statement

All authors declare that there are no conflicts of interest.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contribution

(1) Conception and design of the study, or acquisition of data, or analysis and interpretation of data: Xiaofeng Hu.

(2) Drafting the article or revising it critically for important intellectual content: Xiaofeng Hu and Jun Jiang.

(3) Final approval of the version to be submitted: Xiaofeng Hu and Jun Jiang.

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