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REVIEW

The Dual Roles of STAT3 in Ferroptosis: Mechanism, Regulation and Therapeutic Potential

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Abstract: Ferroptosis, an iron-dependent programmed mechanism of cell death that is driven by lipid peroxidation, is an important pathogenic factor in oncological and non-oncological disorders. Dysregulation of iron and lipid metabolism profoundly influences disease progression through ferroptosis modulation. Signal transducer and activator of transcription 3 (STAT3), a transcriptional regulator, regulates ferroptosis by binding to promoters of key molecules such as solute carrier family 7 member 11 (SLC7A11), glutathione peroxidase 4 (GPX4), and ferritin heavy chain 1 (FTH1). In this review, we described the role of STAT3 in supporting tumors survival by suppressing ferroptosis in malignancies, and bidirectionally regulating ferroptosis in non-tumors to regulate the development of the disease. We also reported emerging therapeutic strategies that target STAT3-mediated ferroptosis, including natural phytochemicals, inhibitors, and nanotechnology-enabled drug delivery systems. These advancements deepen the mechanistic understanding of ferroptosis regulation, and provide new theoretical bases and strategies to treat ferroptosis-related diseases.

Keywords: STAT3, dual roles, ferroptosis, cancer, vector therapy

Introduction

The physiological processes and pathological characteristics of ferroptosis differ from those of apoptosis and necrosis. Since ferroptosis was first identified in 2012 its involvement in pathological processes such as neurodegenerative diseases, cancers, and ischemia-reperfusion injury has been widely demonstrated.[1–3] For example, the classic tumor suppressor gene p53 inhibits activity of the cystine transporter SLC7A11 and reduces glutathione (GSH) synthesis, thereby enhancing the sensitivity of cancer cells to ferroptosis.[4] In doing so, ferroptosis be of potential value in the treatment of tumors. However, the biological effects of ferroptosis in diseases are cell- and environment-specific. In tumor cells, ferroptosis generally promotes cancer cell clearance and reduces cancer, but in some normal tissues, the activation of ferroptosis may lead to tissue damage and aggravate disease progression. Therefore, an understanding of how ferroptosis is regulated, and its cell-specific mechanisms is needed for precision treatment.

Signal transducers and activators of transcription (STATs) are the earliest discovered regulatory factors of signaling. The main function of STATs is to transmit extracellular stimulation signals into the nucleus by binding to the promoters of target genes, thereby completing the process of intracellular signal transmission.[5] The STATs family has seven main members, including STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. These STATs family members have similar structures and functions, but each family member is responsible for transmitting different stimuli and regulating different biological processes. For example, interferons mainly mediate STAT2 to play a defensive role against viral infection in organisms.[6] STAT6 is mediated by IL-4 and IL-13 and is involved mainly in pathological processes such as inflammatory and allergic reactions in the body.[7]

STAT3, as a core member of the STAT family, has attracted much attention due to its extensive regulatory functions. STAT3 is widely present in various mammals and is involved in a variety of physiological and pathological processes such as cell proliferation, angiogenesis and inflammation. Under physiological conditions, STAT3 mainly exists in the

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cytoplasm as a monomer or unphosphorylated dimer. Recent studies have revealed that STAT3, as an important transcription factor in redox reactions, can control the occurrence of ferroptosis by regulating intracellular ROS and the ferroptosis antioxidant core cystine/glutamate antiporter (xCT).[8] Another study also confirmed that STAT3 can bind to the promoter regions of key ferroptosis molecules including GPX4, SLC7A11 and FTH1 to regulate ferroptosis.[9] STAT3 has a unique and dual role in regulating ferroptosis in diseases. In tumor diseases, STAT3 activation promotes tumor cell survival and drug resistance by inhibiting ferroptosis, while in some non-tumor diseases, STAT3 activation exacerbates the disease's pathological damage by promoting ferroptosis. This cell-type-dependent regulatory difference may be related to the unique metabolic environment of different cells, the post-translational modification of STAT3, and its interaction with other signaling networks. However, how STAT3 regulates ferroptosis, and its targeting value in tumor treatment remain imperfectly known.

This review aims to analyze the dual regulatory mechanism of targeting STAT3 in ferroptosis, focusing on its targeted value in tumor treatment. By integrating the dual regulatory effects of targeting STAT3 on ferroptosis in tumors and non-tumor diseases, we propose that STAT3 can be used as a "molecular switch" for ferroptosis to treat diseases. In addition, this article explores for the first time the potential advantages of STAT3-targeted drug delivery strategies based on nanotechnology, providing a theoretical basis for the development of clinical research on targeted ferroptosis treatment of diseases.

Structure and Function of STAT3

The gene encoding human STAT3 is located on chromosome 17q21. STAT3 consists of 770 amino acids and is divided into three subtypes: STAT3α, STAT3β and STAT3γ. It mainly exerts biological functions through STAT3α. STAT3 is structurally homologous to the other six STAT family members and shares the same sequence.[10] STAT3 has six conserved domains: an N-terminal domain (NTD), a coiled-coil domain (CC), a DNA-binding domain (DBD), a linker domain (LD), a Src homology 2 domain (SH2), and a transactivation domain (TAD).[11] The SH2 domain is the core of STAT3's function because it recognizes and binds to the phosphotyrosine motif, allowing extracellular signals to bind to receptors on the cell membrane surface, thereby transmitting signals into the cell.[12] The phosphorylation and activation of STAT3 are catalyzed by tyrosine kinases. These tyrosine kinases are involved in two main processes. One is the cytokine receptor-related tyrosine kinase, the most important of which is the JAK tyrosine protein kinase.[12] Another kind of kinase is a cytoplasmic kinase, such as Src protein tyrosine kinase.[13] These tyrosine-related kinases activate STAT3, leading to its phosphorylation and nuclear translocation, allowing it to enter the nucleus and bind to DNA to stimulate the expression of related downstream genes.

As a messenger that transmits signals inside and outside cells and is directly involved in transcriptional regulation, activated STAT3 has been proven to regulate biological activities such as cell proliferation, activation, and migration. Early studies revealed the importance of STAT3 in the early embryonic development of mice.[14] When the STAT3 gene is lacking in vivo, mouse embryonic lethality results, possibly due to the loss of two or more of these STAT3-mediated signaling pathways. Many studies have confirmed the key role of STAT3 in tumors. A study on rectal cancer showed that STAT3 activated by IL-6 can regulate the expression of miR-34a, thereby promoting the invasion and metastasis of cancer cells.[15] Other studies have shown that janus kinase 2 (JAK2) and IL-6 can activate STAT3 and promote the proliferation of tumor cells and drug resistance in tumors.[16–18] Since various inflammatory factors can activate STAT3, STAT3 can also regulate the occurrence of inflammatory responses. The cascade reaction activated by the transcription factor NF-κB p65 can activate STAT3, promote the occurrence of the inflammatory factors TNF-α and IL-1β, and then induce inflammation in acute liver injury caused by sepsis.[19] STAT3 is also a redox regulatory protein that can play a regulatory role in oxidative stress. Research by Han confirmed that AMP-activated protein kinase (AMPK) can negatively regulate the NF-κB/STAT3 axis to inhibit premature aging induced by oxidative stress.[20]

Ferroptosis

As a new type of cell death, the role of ferroptosis in the field of disease has been increasingly valued by researchers. Typical ferroptosis regulatory mechanisms involve three main aspects: iron metabolism, lipid peroxidation and the antioxidant system.[21] Iron-dependent lipid peroxidation is central to ferroptosis. Intracellular iron can promote the

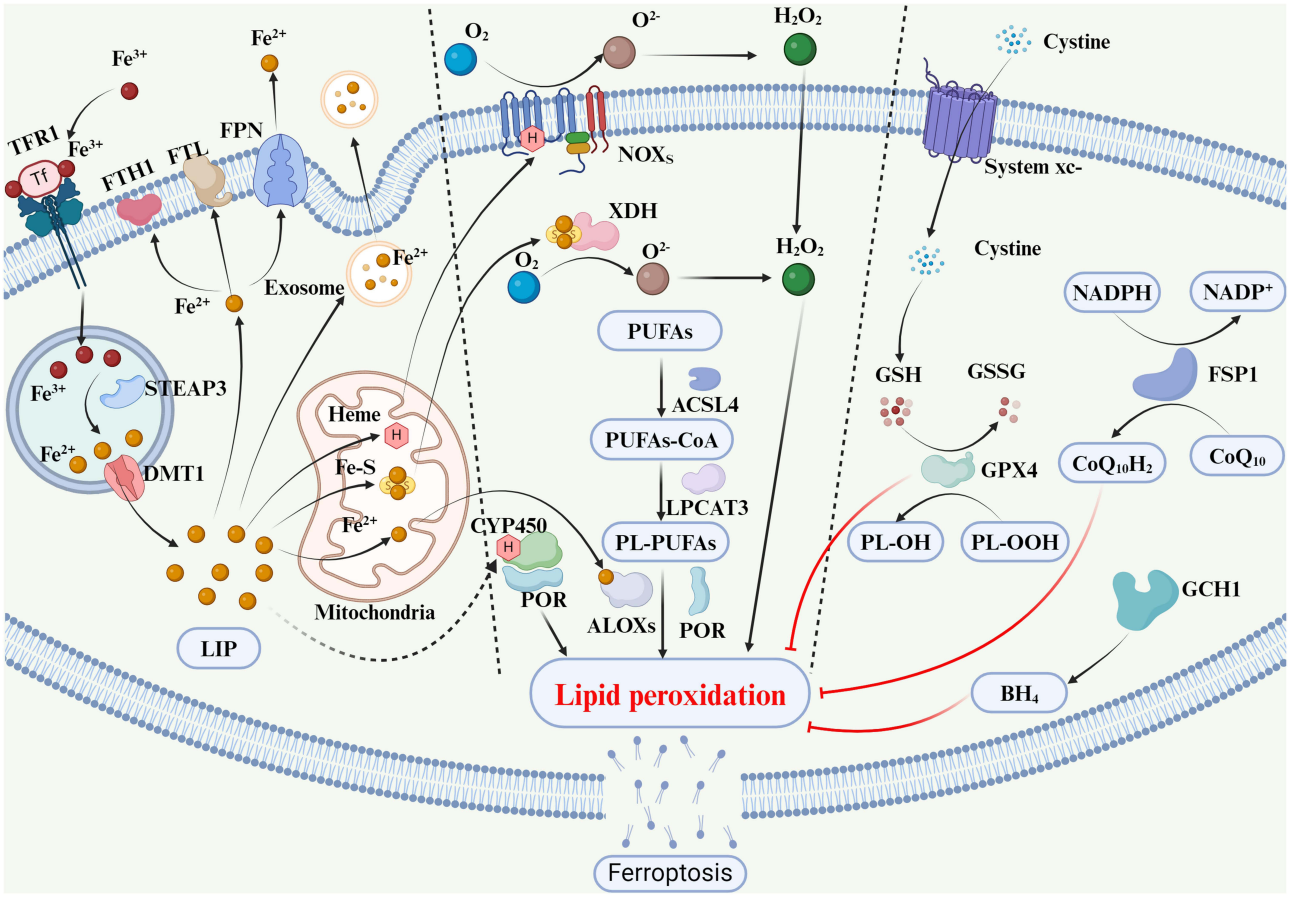

Figure 1 Pathogenesis of ferroptosis and mechanisms of resistance to ferroptosis. Ferroptosis mainly involves iron metabolism and lipid peroxidation. The anti-ferroptosis mechanism mainly involves the Xc(-)-glutathione-GPX4 axis, FSP1/CoQ10/NAD(P)H axis and GCH1-BH4 axis.

generation of the lipid peroxidation product reactive oxygen species (ROS) through the Fenton reaction, thereby leading to ferroptosis.[22] Unlike other forms of cell death, ferroptosis involves unique biological changes in microstructure, including changes in mitochondrial morphology. As the main site for ROS production in organisms, mitochondria undergo morphological changes such as increased membrane density, reduced or missing cristae, and outer membrane rupture when ferroptosis occurs.[23] With increasing research, the regulatory mechanism of ferroptosis has gradually improved. We summarize the relevant mechanisms of ferroptosis in Figure 1.

Iron Metabolism and Ferroptosis

Iron is an essential trace element necessary to maintain human activities. It participates in cell respiration and proliferation activities. There are two main forms of iron in cells: toxic soluble ferrous iron ions and insoluble oxidized ferric iron ions.[24] Iron in the human body is stored mainly in ferritin, which is involved in energy metabolism and oxygen transport in the human body and is also a regulator and antioxidant of iron homeostasis.[25] A very small amount of free ferrous iron gathers together to form an unstable iron pool (LIP). This iron pool has strong redox activity and can mediate the Fenton reaction to generate ROS and promote ferroptosis.

Under physiological conditions, extracellular ferric iron enters the cell through endocytosis via the combination of the plasma membrane proteins transferrin receptor 1 (TFR1) and transferrin.[26] The excretion of intracellular iron is regulated mainly by ferroportin 1 (FPN1), or it can be excreted from the cell in the form of ferritin through ferritin-containing multivesicular bodies and exosomes.[27] Owing to the acidic environment of the endosome, ferric iron is reduced to ferrous iron when it enters the cell through endocytosis. These ferrous ions are involved mainly in the formation of cytoplasmic LIPs, and a small number of them are involved in the formation of ferritin heavy chain 1 (FTH1) and ferritin light chain

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(FTL).[28] Most of the iron in LIP is used by mitochondria to synthesize heme or iron–sulfur (Fe–S) clusters. These hemes, Fe-S and iron can be incorporated into ROS-producing enzymes such as arachidonic acid lipoxygenase (ALOX) and NADPH oxidase (NOX) and then participate in the lipid peroxidation process.[29]

Therefore, iron can promote ferroptosis by directly participating in the Fenton reaction or by synthesizing heme or incorporating Fe-S into enzymes that catalyze ROS to mediate the lipid peroxidation process.

Lipid Peroxidation and Ferroptosis

Ferroptosis is accompanied by the production of large amounts of ROS, of which lipid peroxidation is a characteristic. Lipids are important components of cell membranes and are used to maintain the morphological structure and normal functions of cells. Lipid peroxidation is the process in which oxidants attack lipids such as polyunsaturated fatty acids (PUFAs). Once the PUFAs in the cell membrane are attacked by oxidants and ultimately broken, the cell membrane breaks, leading to cell death. ROS generally refer to a class of molecules with oxidative properties, including hydrogen peroxide (H_2O_2), hydroxyl radical ($HO\cdot$) and superoxide (O_2^-).[30] H_2O_2 and ferrous iron ions produce ferric iron ions and $HO\cdot$ under the action of the Fenton reaction, which continuously attacks PUFAs, causing cell membrane rupture and inducing ferroptosis.

Intracellular ROS are produced mainly in mitochondria. Many enzymes, such as those in the ALOX family and the NOX family, can catalyze the production of ROS and thereby induce ferroptosis. These oxidases promote the occurrence of ferroptosis. Experimental studies have shown that ALOX15-mediated lipid peroxidation enhances erastin and RSL3 induced ferroptosis.[31] Similarly, NOX4 has been confirmed to mediate lipid peroxidation through ROS generated by oxidative stress, thereby inducing ferroptosis in Alzheimer's disease.[32] In addition to the ALOX family and NOX family, cytochrome P450 oxidoreductase (POR) can also catalyze the occurrence of lipid peroxidation, thereby inducing ferroptosis.[33]

Ferroptosis Antioxidant Axis

Xc(-)-Glutathione-GPX4 Axis

As the earliest studied antioxidant axis of ferroptosis, its inhibition leads to the occurrence of ferroptosis. The Xc(-) system is a transmembrane protein complex containing SLC7A11 and SLC3A2 subunits that can regulate the intracellular transport of cystine and glutamate.[34] GSH is an important intracellular small-molecule antioxidant and is a tripeptide composed of the amino acids glutamic acid, glycine and cysteine.[35] As a peptide with powerful antioxidant function, GSH can serve as a substrate for GPX4, directly reducing toxic lipid peroxides into nontoxic fatty alcohols. This prevents the occurrence of ferroptosis.[36] GPX4 is considered the gatekeeper of ferroptosis and the core of resistance to ferroptosis. The commonly used ferroptosis inducer erastin can directly act on GPX4 to reduce its activity, thereby inducing ferroptosis.[37]

FSP1/CoQ10/NAD(P)H Axis

The FSP1/CoQ10/NAD(P)H axis is an independent antioxidant axis that is not dependent on GSH/GPX4 and can be used as an alternative axis to GPX4 to exert anti-ferroptotic effects. Apoptosis-inducing factor mitochondrial-associated 2 (AIFM2, also known as FSP1) is a member of the type II NADH: quinone oxidoreductase (NDH-2) family. Its main role is to reduce coenzyme Q10 to antioxidants.[38] In addition, some studies have shown that FSP1 can also directly block the occurrence of ferroptosis by activating endosomal sorting complex ESCRT-III-dependent membrane repair.[39] This blocking mode is not related to lipid peroxidation and is another independent way for FSP1 to inhibit ferroptosis. FSP1 is the only inhibitor of FSP1 and can promote ferroptosis by inhibiting the expression of FSP1.

GCH1-BH4 Axis

The GCH1-BH4-phospholipid pathway is also a GSH/GPX4-independent antioxidant axis. GCH1 is the rate-limiting enzyme in BH4 biosynthesis. In GCH1-expressing cells, BH4 can cause lipid remodeling and inhibit ferroptosis by preventing phospholipid consumption.[40] In addition, BH4 can also inhibit the occurrence of lipid peroxidation by converting tyrosine into 4-OH-benzoate, the precursor of coenzyme Q10, thereby inhibiting ferroptosis.[41]

Regulatory Role of STAT3 on Ferroptosis

STAT3, as a core member of the STATs family, has been shown to be an important regulator of ferroptosis. ChIP-seq and ChIP-qPCR experiments confirmed STAT3 can regulate the expression of key molecules such as SLC7A11, GPX4 and FTH1 in the antioxidant system by binding to their promoters, thus becoming a core regulator of ferroptosis.[9,42] At the same time, by regulating intracellular iron metabolism, STAT3 can also regulate the occurrence of ferroptosis. The regulation of ferroptosis by STAT3 is related to cell type and disease type. In tumors, STAT3 promotes cancer cell survival and drug resistance by inhibiting ferroptosis; in non-tumor diseases, STAT3 can promote ferroptosis to aggravate tissue damage, and can also inhibit ferroptosis to maintain cell homeostasis. We focus on upstream molecules that can target and regulate STAT3, and explore its bidirectional regulatory mechanism of ferroptosis by targeting STAT3 in tumors and non-tumor diseases. Recent research of targeting STAT3 to regulate ferroptosis is summarized in Table 1.

Table 1 Overview of Experiments in Which STAT3 Was Targeted to Regulate Ferroptosis

Disease Type	Upstream Molecule	Regulation of Ferroptosis by STAT3	Related Mechanism	Reference
Acute kidney injury	JAK2	Promote	IL-6 reduces GSH in renal tubular cells by activating the JAK2/STAT3 axis.	[43]
Chronic stress-induced duodenal injury	JAK2	Promote	IL-6 promotes hepcidin by activating the JAK2/STAT3 axis, inhibiting FPN1 and disrupting iron homeostasis in the duodenum.	[44]
Male reproductive injury	IL-6	Promote	TNF inhibits GPX4 expression in TM-3 by activating the IL-6/STAT3 axis.	[45]
Obesity cardiomyopathy.	JAK2	Promote	IL-6 promotes NCOA4 expression and FTH1 degradation in cardiomyocytes by activating the JAK2/STAT3 axis.	[46]
Crohn's disease	NF-κB	Promote	FGL1 inhibits the expression of GPX4 and SCL7A11 by activating the NF-κB/STAT3 axis.	[47]
Hepatitis B virus associated-glomerulonephritis	HDAC2	Promote	miR-223-3p targets HDAC2 to downregulate STAT3 phosphorylation in renal podocytes, thereby promoting the expression of GPX4 and SLC7A11.	[48]
Osteoporosis	IRF9	Inhibit	IRF9 inhibits the expression of STAT3, thereby inhibiting the expression of GPX4 and FTH1.	[49]
Doxorubicin-induced cardiotoxicity	H1R	Inhibit	Histamine-activated H1R-STAT3-SLC7A11 axis can activate SCL7A11 expression in cardiomyocytes.	[50]
Spinal cord injury	Syvn1	Inhibit	Syvn1 activates the STAT3/GPX4 axis in neuronal cells.	[51]
Preeclampsia	Nox2	Inhibit	Nox2 inhibits the STAT3/GPX4 axis in trophoblasts.	[52]
Triple-negative breast cancer	JAK2	Inhibit	HLF promote GSH in triple-negative breast cancer cells by activating the IL-6/JAK2/STAT3 axis.	[53]
Head and neck squamous cell carcinoma	JAK2	Inhibit	IL-6 activates xCT in head and neck squamous cell carcinoma by activating the JAK2/STAT3 signaling pathway.	[54]
Renal Cancer	JAK2	Inhibit	AMPK promotes P53 expression by inhibiting the JAK2/STAT3 axis, thereby suppressing GPX4 in renal cell carcinoma cells.	[55]
Osteosarcoma	JAK2	Inhibit	FANCD2 promotes GPX4 and FTH1 in human osteosarcoma cells by activating the JAK2/STAT3 axis.	[56]
Hepatocellular carcinoma	LINC00654	Inhibit	LINC00654 activates SLC7A11 in hepatocellular carcinoma cells by promoting the recruitment of STAT3 to the SLC7A11 promoter region.	[57]
Bladder cancer	LUCAT1	Inhibit	LUCAT1 binds to IGF2BP1 and increases STAT3 stability, promoting GPX4 and SLC7A11 expression in bladder cancer.	[58]

(*Continued*)

Table 1 (Continued).

Disease Type	Upstream Molecule	Regulation of Ferroptosis by STAT3	Related Mechanism	Reference
Breast cancer	miR-106a-5p	Inhibit	CircRHOT1 inhibits STAT3 expression by recruiting miR-106a-5p, thereby suppressing GPX4 and SLC7A11 in breast cancer cells.	[59]
Gastric cancer	miR-125b-5p	Inhibit	miR-125b-5p suppresses GPX4 and SLC7A11 in gastric cancer cells by inhibiting STAT3.	[60]
Osteosarcoma	LncRNA-PVT1	Inhibit	LncRNA-PVT1 promotes GPX4 expression in osteosarcoma cells by activating STAT3.	[61]
Diffuse large B-cell lymphoma	NF-κB	Inhibit	FASN promotes GPX4 expression in diffuse large B-cell lymphoma by activating the NF-κB/STAT3 signaling pathway.	[62]
Hepatocellular carcinoma	ATF4	Inhibit	ATF4 promotes GPX4 expression in hepatocellular carcinoma cells by activating STAT3.	[63]
Glioma	NEDD4L	Inhibit	NEDD4L binds to STAT3 and induces its ubiquitination, inhibiting its expression and activity, thereby inhibiting the expression of GPX4 in glioma cells.	[64]
Hepatocellular carcinoma	SHP-1	Inhibit	SHP-1 inhibits SLC7A11 by suppressing STAT3 activity, inhibiting MCL1 and subsequently increasing BECN1 binding to SLC7A11 in hepatocellular carcinoma cells.	[65]
Colorectal cancer	AKT	Inhibit	ENO1 promotes GPX4 and FTH1 in colorectal cancer cells by activating the AKT/STAT3 axis.	[66]
Osteosarcoma	MAT2A	Inhibit	miR-26b-5p inhibits the expression of SCL7A11 by suppressing the MAT2A/STAT3 axis.	[67]

Regulatory Effects of STAT3 in Non-Tumor Ferroptosis

STAT3 Promotes Ferroptosis in Non-Tumors

In non-tumor, STAT3 has a dual regulatory effect on ferroptosis. This contradictory regulation may be closely related to factors such as the complex signaling network and metabolic state in the disease and cells. In pathological processes including kidney disease and duodenal injury, STAT3 promotes ferroptosis by inhibiting the antioxidant axis and promoting iron metabolism imbalance. For example, Dong revealed that the IL-6/JAK2/STAT3 axis promoted the induction of ferroptosis in renal tubular cells to mediate the occurrence of cisplatin-induced nephrotoxicity.[43] In addition, Zhao revealed that the IL-6-mediated JAK2/STAT3 axis inhibited FPN1 expression in rats with duodenal injury, thereby increasing the production of hepcidin, disrupting the intracellular iron homeostasis and promoting ferroptosis.[44] Another study showed that bioinformatics technology identified that the TNF-mediated IL6/STAT3 axis can promote ferroptosis of TM3 cells, thereby promoting the male infertility.[45] Similarly, Zhu confirmed that IL6 can activate STAT3 in obesity-induced cardiac injury, thereby disrupting the intracellular iron homeostasis and promoting ferroptosis through the STAT3/NCOA4/FTH1 axis.[46] Another study showed that fibrinogen-like protein 1 (FGL1) can promote the NF-κB/STAT3 axis, thereby inhibiting the expression of SLC7A11 and GPX4 to promote ferroptosis of intestinal epithelial cells in Crohn's disease.[47] Chen's study showed that exosomal miR-223-3p can target HDAC2 and then downregulate STAT3 phosphorylation. This mechanism subsequently promoting the expression of GPX4 and SLC7A11, ultimately alleviating ferroptosis in Kidney podocytes and improving HBV-related glomerulonephritis.[48]

STAT3 Inhibits Ferroptosis in Non-Tumors

In other non-tumor, STAT3 can inhibit ferroptosis and maintain cell homeostasis by activating the antioxidant axis. For example, interferon regulatory factor 9 (IRF 9) can inhibit the activation of STAT3, leading to downregulation of GPX4 and FTH1, which promotes ferroptosis and attenuates osteoclast differentiation.[49] Zhu et al demonstrated that in azithromycin-induced cardiac injury, blockade of histamine/H1R signaling can reduce STAT3 phosphorylation and

downregulate SLC7A11 expression in cardiomyocytes, thereby exacerbating ferroptosis and cardiac damage.[50] In addition, overexpression of Syvn1 and inhibition of NOX2 can enhance the STAT3/GPX4 axis activity, inhibiting ferroptosis and ameliorating spinal cord injury and preeclampsia.[51,52]

STAT3 Inhibits Ferroptosis in Tumors

STAT3 plays a role in suppressing ferroptosis in tumor cells to maintain the malignant phenotype. The core way that STAT3 regulates ferroptosis in tumors is to promote the expression of key genes such as SLC7A11, GPX4 and FTH1, maintain GSH synthesis, and thus inhibit ferroptosis caused by lipid peroxidation. Recent studies have shown that the JAK2/STAT3 axis plays an important role in regulating ferroptosis of tumor cells. The JAK2/STAT3 axis is a classic stress–inflammatory signaling pathway. JAK2 can regulate the phosphorylation and nuclear translocation of STAT3 by binding to the SH2 domain of STAT3, allowing it to perform signal transduction and directly participate in transcriptional regulation. Previous studies have shown that IL-6/JAK2/STAT3 plays a crucial role in the HLF-mediated signaling pathway. Upon activation by IL-6, STAT3 phosphorylation and GSH in cancer cells increased, which in turn inhibited ferroptosis and promoted tumor resistance in triple-negative breast cancer.[53] Other studies have confirmed the important role of the JAK2/STAT3 axis in cancer cell ferroptosis. The JAK2/STAT3 axis mediated by IL6 inhibits the occurrence of ferroptosis by activating the anti-ferroptosis axis SLC7A11/xCT, conferred drug resistance to head and neck squamous cell carcinoma, and promotes tumor progression.[54] Research on renal cancer by Li revealed that energy stress-mediated AMPK can inhibit the JAK2/STAT3 axis to promote P53 and inhibit GPX4 expression, thereby increasing ferroptosis in renal cancer cells.[55] Similarly, some studies have confirmed the regulatory effect of the JAK2/STAT3 axis on ferroptosis in osteosarcoma. FANconi Anemia Complementation Group D2 (FANCD2) is highly expressed in osteosarcoma cells, and promotes the expression of FTH1 and GPX4 by activating the JAK2/STAT3 axis, inhibiting ferroptosis and promoting the proliferation and migration of osteosarcoma cells.[56]

ncRNA has also been shown to affect ferroptosis in tumor cells by regulating STAT3. Peng's research revealed that LINC00654 is highly expressed in patients with hepatocellular carcinoma.[57] LINC00654 can increase the recruitment of STAT3 to the SLC7A11 promoter region, thereby activating the expression of SLC7A11, inhibiting ferroptosis and enhancing the drug resistance of hepatocellular carcinoma. Another study on lncRNA regulating ferroptosis revealed that LUCAT1 can inhibit ferroptosis in bladder cancer by regulating STAT3.[58] The binding of LUCAT1 to insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) affects the mRNA stability of STAT3, promoting the expression of SLC7A11 and GPX4, thereby inhibiting ferroptosis. In addition, Zhang confirmed the regulatory effect of circRHOT1 on ferroptosis in breast cancer.[59] In this study, circRHOT1 acts as a "sponge" for miR-106a-5p, downregulating the expression of miR-106a-5p in breast cancer cells, thereby promoting the expression of STAT3, GPX4 and SLC7A11 to inhibit ferroptosis and promote the malignant progression of breast cancer. Liu showed that miR-125b-5p can inhibit the expression of STAT3, SLC7A11 and GPX4, thereby inducing ferroptosis and inhibiting the proliferation of gastric cancer cells.[60] Li's study also confirmed that lncRNA-PVT1 can inhibit ferroptosis in osteosarcoma by activating the STAT3/GPX4 axis, thereby promoting the progression of osteosarcoma.[61] These findings suggest that targeting the ncRNA-STAT3-ferroptosis pathway could offer a new direction for future cancer therapies.

In addition, some other transcription factors and enzymes have also been shown to regulate ferroptosis in tumor cells by targeting STAT3. For example, Zhong's study showed that FASN can inhibit the ferroptosis in diffuse large B-cell lymphoma by activating the NF-κB/STAT3 signaling pathway, and activated STAT3 can promote GPX4 expression by directly binding to the GPX4 promoter.[62] Hu's study found that ATF4 can promote STAT3 phosphorylation nuclear translocation and promote the expression of ferroptosis biomarker GPX4, thereby inhibiting ferroptosis in hepatocellular carcinoma.[63] Another study confirmed that, the E3-ubiquitin protein ligase NEDD4L negatively regulates the expression of STAT3 by mediating STAT3 ubiquitination, promoting ferroptosis in glial cell by the STAT3/GPX4 axis, and thus inhibiting tumor growth.[64] Other studies have shown that in hepatocellular carcinoma, SHP-1 (Src homology 2 domain phosphatase-1) can dephosphorylate STAT3, inhibiting its nuclear translocation and signal transduction function.[65] This in turn reduces the expression of its downstream MCL1, promotes the binding of BECN1 and SLC7A11, and promotes ferroptosis. Another study on colorectal cancer cells showed that inhibiting the expression of ENO1 can reduce the expression of GPX4 and FTH1, promote ferroptosis, and thus reduce glycolysis by activating AKT/STAT3 signal

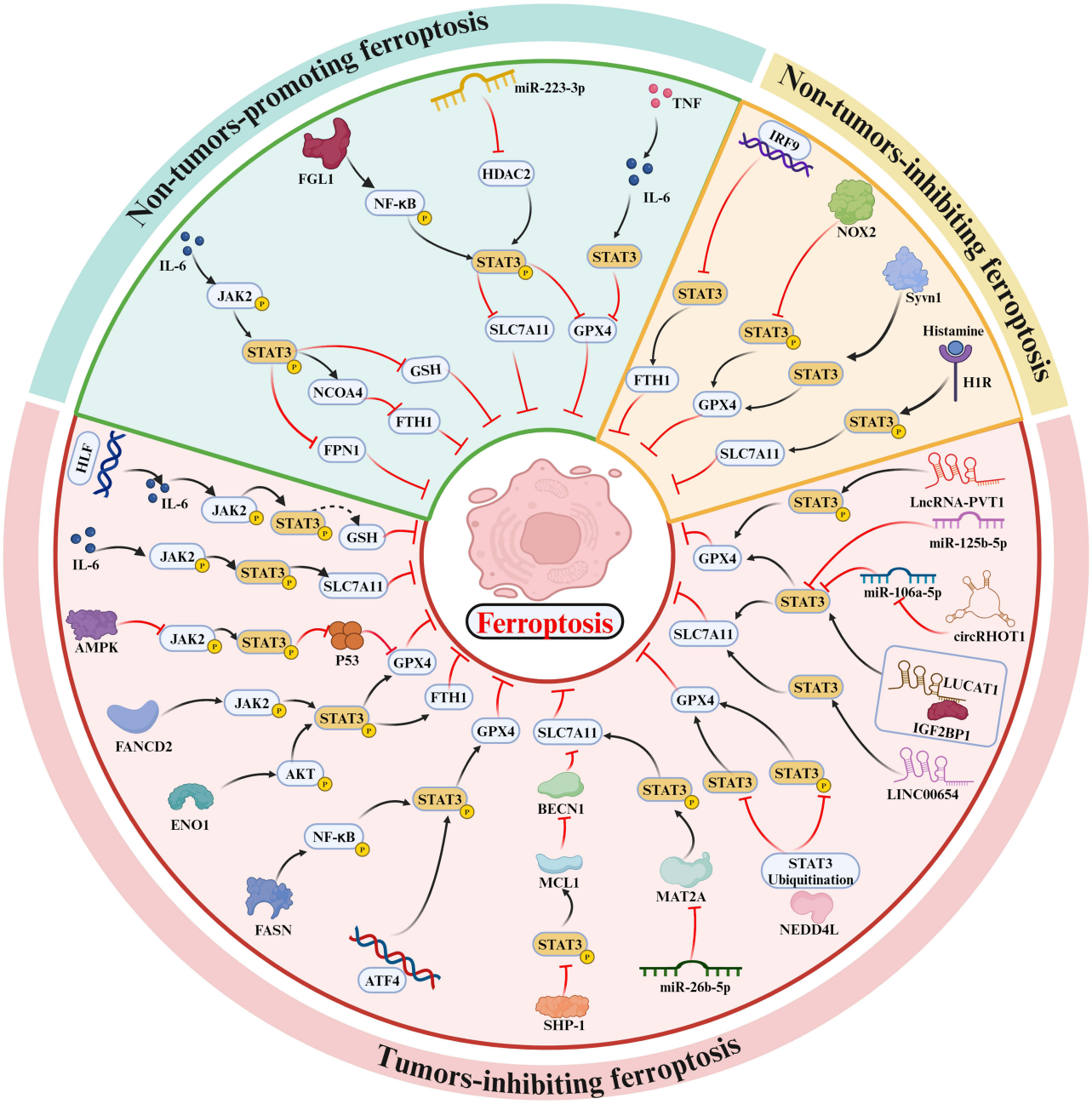

Figure 2 Diagram of the molecular mechanism of targeting STAT3 to regulate ferroptosis in non-tumor and tumors. In some non-tumors, STAT3 promotes ferroptosis by inhibiting the expression of FPN1, FTH1, GSH, SLC7A11, and GPX4. In other non-tumors, STAT3 inhibits ferroptosis by promoting the expression of FTH1, SLC7A11, and GPX4. In tumors, STAT3 inhibits ferroptosis by promoting the expression of GSH, FTH1, SLC7A11, and GPX4.

transduction.[66] In addition, Xia's study found that a methionine adenosyltransferase II α (MAT2A) inhibited by miR-26b-5p can inhibit the ferroptosis of osteosarcoma cell by promoting the expression of p-STAT3 and SLC7A11.[67] Finally, we summarized the diagram of the molecular mechanism of targeting STAT3 to regulate ferroptosis in Figure 2.

Drugs Targeting STAT3

Natural Compounds Targeting STAT3

The monomeric chemical components extracted from natural plants are multitargeted, have low toxicity and are very suitable for targeting STAT3 to treat diseases. Currently, many natural compounds, such as flavonoids and terpenoids,

have been found to inhibit STAT3 and its related pathways. For example, Li used the traditional Chinese medicine extract n-butanol (JFNE) and its active isolate JFNE-C to treat LPS-induced cell models and reported that LPS inhibited the phosphorylation of STAT3, thereby inhibiting the expression of P53 and then inhibiting the SLC7A11/GPX4 antioxidant axis to promote ferroptosis.[68] Another study showed that the active ingredient of traditional Chinese medicine, ginsenoside Rh3, can inhibit the phosphorylation of STAT3 and promote the expression of the anticancer factor p53, thereby preventing the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) from the cytoplasm to the nucleus and preventing the antioxidant function of NRF2, promoting the occurrence of ferroptosis in cancer cells to treat rectal cancer.[69] Similarly, Luo and Huang reported that bavachin, a flavonoid compound extracted from traditional Chinese medicine, and polyphyllin VI, an active saponin, could inhibit the antioxidant axis by targeting the STAT3/P53/SLC7A11 axis and the STAT3/GPX4 axis, respectively, thereby promoting ferroptosis in osteosarcoma cells and hepatocellular carcinoma cells and inhibiting tumor proliferation.[70,71] Cucurbitacin B, which is extracted from plants of the Cucurbitaceae family, can regulate the STAT3/SLC7A11 axis to induce ferroptosis in non-small cell lung cancer (NSCLC) cells, thereby mitigating the progression of lung cancer.[72] Additionally, ascorbic acid, which is abundant in fruits, induces ferroptosis in oropharyngeal cancer by inhibiting the STAT3/GPX4 axis.[73] These studies indicate that the therapeutic effects of natural compounds on cancer primarily involve the inhibition of STAT3, which in turn suppresses the antioxidant axis of ferroptosis, thereby inducing ferroptosis in cancer cells.

Inhibitors Targeting STAT3

In addition, several small molecule inhibitors have been shown to regulate the expression of STAT3 to regulate the occurrence of ferroptosis in cancer cells. Zhan's research on the treatment of pancreatic cancer with thiostrepton, a protein translation inhibitor, revealed that thiostrepton induced intracellular iron overload, ROS accumulation and GSH consumption by inhibiting the expression of the STAT3 protein and its downstream protein GPX4, ultimately inducing ferroptosis in pancreatic cancer cells.[74] In addition, Cang reported that the ferroptosis inhibitor erastin can promote the phosphorylation of STAT3, causing macrophages to polarize toward M2 macrophages, secrete IL-8 to regulate the EMT program of cancer cells, and increase metastatic potential of ferroptosis-resistant ovarian cancer.[75] In previous studies, Ouyang and colleagues identified a series of effective and selective STAT3 inhibitors based on the dominant structure of 2-phenylimidazo [1,2-a] pyridine, and selected W1131 for further analysis.[9] Docking studies of W1131 and STAT3 showed that W1131 can bind to the pY705 binding site of STAT3. Subsequent studies showed that W1131 can inhibit STAT3 by inhibiting STAT3 tyrosine phosphorylation and dimerization, nuclear pY705-STAT3 accumulation, and transcriptional activity. Then, inhibiting the expression of GPX4, SLC7A11 and FTH1.[9] He's study screened 2726 drugs and identified TAK875, a selective G-protein-coupled receptor 40 agonist, as an inhibitor of STAT3. He found that TAK875 occupied the SH2 domain of STAT3 and inhibited STAT3 phosphorylation at Tyr705.[76]

Drug Development Based on Different Carriers

Simply taking the drug or intramuscular injection reduces the absorption and utilization effect of the drug and has certain side effects. The construction of different carriers to deliver drugs accurately to target organs can protect the drug throughout the administration time, reduce the loss of active substances and limit drug side effects.[77] At this stage, the use of nanotechnology to construct drug carriers loaded with small-molecule inhibitors of STAT3 to treat diseases has been widely verified in animal studies. The targeted delivery of drugs by nanocarriers has become an important direction for future research in the biomedical industry. In the future, it can be used to target STAT3-mediated ferroptosis to treat diseases.

Lipid Carriers

Since nanocarriers composed of lipids have a chemical composition similar to that of cell membranes, they have the advantage of being easily absorbed by cells.[78] Hydrophobic and hydrophilic drugs are placed inside and outside the lipid nanocarrier, respectively, which allows the drug to be quickly absorbed by cells and play a role. A study showed that nanostructured lipid carriers (NLCs) loaded with STAT3 inhibitors enhance the cytotoxicity of doxorubicin against melanoma cancer cells by inhibiting STAT3 signaling and antiapoptotic Bcl-2 family genes.[79] Lipid nanocarriers increase

the bioavailability of STAT3 inhibitors and the sustained release of this formulation in the tumor microenvironment. Cationic liposomes have been used to encapsulate curcumin and complex it with STAT3 siRNA to form a lipid nanobody to target STAT3 for the treatment of skin cancer.[80] This lipid nanocomplex improves the cellular uptake and utilization of curcumin and reduces the risk of siRNA being broken down. Similarly, Pindiprolu used solid lipid nanoparticles (SLNs) to carry the STAT3 inhibitor niclosamide (Niclo) and successfully delivered it to triple-negative breast cancer (TNBC) cells, improving the anticancer efficacy of Niclo.[81]

Colloidal Carriers

Colloidal nanocarriers are biodegradable and have excellent biocompatibility, which has important research significance in some medical research fields. Using colloidal nanocarriers to carry medicine targeted STAT3 can effectively improve its absorption and utilization and reduce its side effects. Zheng and Kim used hydrogels to carry baricitinib and STAT3-small hairpin RNA, respectively, to target and inhibit STAT3 to treat acute SCI-related inflammation and inhibit tumor development.[82,83] Similarly, Bu used gelatin carriers to load gelatinase-sensitive nanoparticles with STAT3 inhibitors. After these gelatin nanoparticles reach the target area in the body, the drug delivery system is degraded by the MMP and releases the loaded drug, thereby achieving targeted drug delivery and functional immunotherapy for head and neck squamous cell carcinoma.[84]

Micellar Carriers

Micellar carriers are self-assembled nanocolloidal particles with a hydrophobic core and a hydrophilic shell. Polymer micelles are widely used in drug delivery systems because of their high stability and good biocompatibility and can dissolve a variety of poorly soluble drugs. Another study used micellar nanocarriers composed of poly (ethylene oxide)-block-poly (ε-caprolactone) (PEO-b-PCL) and STAT3 inhibitors to form dimer micelle polymers for cancer immunity treatment.[85] This micellar polymer takes advantage of enhanced permeability and retention effects to solve the problems of poor water solubility and low tumor selectivity of STAT3 inhibitors. In addition, Tavares prepared a colloidal polymer–drug conjugate based on the combination of N-(2-hydroxypropyl) methacrylamide (HPMA) and cucurbitacin-D. With lower toxicity, it enables targeted treatment of breast cancer.[86]

Chitosan-Based Nanocarriers

Chitosan is a biotechnological derivative produced by the hydrolysis of chitin under alkaline conditions. It has unique biocompatibility and biodegradability properties and is widely used in the biological and medical industries.[87] By processing chitosan to form nanoparticles to encapsulate and control drug release, premature clearance of drugs can be effectively avoided, resulting in high permeability and retention.[88] Fong and team members utilized chitosan-coated polylactic-glycolic acid (C-PLGA) nanocarriers loaded with the STAT3 inhibitor Stattic to inhibit tumor proliferation and migration.[89] This chitosan nanocarrier improved the efficacy of Stattic. Wang constructed an optimized chitosan/L-leucine-based swollen microparticle system to carry cryptotanshinone to target STAT3 for the treatment of pulmonary fibrosis and achieve deep lung delivery.[90] Another study constructed a hyaluronic acid-TAT trimethyl/thiolated chitosan carrier system to carry STAT3 siRNA for the treatment of mouse cancer.[91] Since many cancer cells express hyaluronic acid receptors, this nanocarrier, which is composed of hyaluronic acid, can easily enter cancer cells and play a role. Labala and colleagues constructed chitosan-coated gold nanoparticles that could be loaded with STAT3 siRNA and used an iontophoresis method to improve the skin permeability of the carrier system for the treatment of melanoma.[92] Similarly, Janardhanam used the continuous layering of chitosan and alginate to prepare LbL films to carry STAT3 siRNA for the treatment of colon cancer.[93] This functionalized LbL film can selectively adhere to colon cancer tissue and then release STAT3 siRNA.

Endogenous Extracellular Vesicles and Exosome Carriers

Extracellular vesicles (EVs) and exosomes are nanoscale biological particles that are secreted endogenously by different cells.[94] EVs and exosomes are natural nanocarriers and are now widely used in research on the targeted delivery of drugs to treat diseases. Extracellular vesicles from macrophages were applied to load oxaliplatin, retinoic acid, and Libidibia ferrea to increase the bioavailability of oxaliplatin and block STAT3-related pathways involved in tumor cell proliferation

and migration.[95] In addition, Zhuang et al used exosomes to encapsulate curcumin and STAT3 inhibitors and deliver them to the brain through intranasal administration for targeted induction of microglial apoptosis.[96] This research provides a safe and novel treatment for brain-related diseases.

Other Nanocarriers

Other materials, such as graphene and silicon materials, also play important roles in research in the biomedical field as nanocarriers for the targeted delivery of drugs. For example, Yin used functional graphene as a carrier system to construct a (GO-PEI-PEG) carrier carrying STAT3 siRNA.[97] This graphene carrier shows improved therapeutic effects and can improve the efficacy of STAT3 siRNA in treating malignant melanoma in mice. Another researcher constructed STAT3 siRNA-loaded nanoparticles based on polyethylenimine (PEI) and poly(lactide-co-glycolide) (PLGA).[98] This carrier can physically protect siRNA to avoid its inactivation and can be delivered to lung cancer cells through targeted delivery by virtue of its effective tissue penetration and cellular uptake capabilities. Kostka also used HPMA to construct a high-molecular-weight star polymer containing doxorubicin and protease inhibitor derivatives.[99] This star-shaped polymer increases the half-life of the drug in the blood circulation and enhances its accumulation in solid tumors.

Discussion

Unresolved Issues and Challenges

Although significant progress has been made in understanding the regulatory role of STAT3 in ferroptosis, many unresolved issues and potential challenges remain. First, significant differences exist in how STAT3 regulates ferroptosis in different cell types and diseases. STAT3 usually inhibits ferroptosis in tumor cells, but promotes ferroptosis in some non-tumor cells—a difference possibly related to cell-specific metabolic environments, post-translational modifications of STAT3, and cross-regulation with other signaling pathways. The molecular mechanisms behind these differences require further exploration, especially the specific roles in different disease models.

The translational application of targeting STAT3 to regulate ferroptosis faces many problems. Although STAT3 is a potential target for treating ferroptosis-related diseases, its involvement in many physiological and pathological processes may lead to off-target effects and adverse reactions. For example, excessive inhibition of STAT3 may disrupt immune homeostasis or affect the survival of normal cells.[14,100] Therefore, the development of highly specific and selective STAT3 inhibitors has been a recent research focus. Although various STAT3 inhibitors show promising anti-tumor effects in preclinical studies, these drugs still face challenges in clinical application such as drug selectivity, toxic side effects, and drug resistance.[101] For safety, the development of low-toxic natural drugs or the targeted delivery of drugs using technologies such as nanocarriers are potential areas for future research.

Future Research Avenues and Clinical Significance

New research should focus on analysis of the specific regulatory mechanism of STAT3 in ferroptosis, especially for differences in different disease contexts. By combining technologies such as single-cell sequencing, proteomics, and metabolomics, the complex regulatory network of STAT3 in ferroptosis can be more comprehensively revealed. Secondly, based on the unique molecular structure of STAT3 to develop more selective and less toxic STAT3 inhibitors, or enhance their anti-tumor effects through combination drug strategies. For example, the combination of STAT3 inhibitors and ferroptosis inducers may have a synergistic anti-tumor effect.[102]

Nanotechnology-based drug delivery systems represent new ways to target STAT3 to regulate ferroptosis. By designing targeted nanocarriers, STAT3 inhibitors can be precisely delivered to tumor tissues, reducing toxicity to normal tissues. For example, the use of tumor microenvironment-responsive nanocarriers (such as pH-sensitive or enzyme-sensitive nanoparticles) can achieve controlled release of drugs, improve therapeutic effects, and reduce side effects.[103,104]

For clinical significance, STAT3, as a key regulator of ferroptosis, is potentially valuable for tumor treatment, and it may play an important role in other ferroptosis-related diseases. For example, the regulatory role of STAT3 in Alzheimer's and Parkinson's diseases has been recently explored.[105,106] Future studies could explore how neuronal ferroptosis is inhibited by regulating STAT3, thereby delaying disease progression. Additionally, the role of STAT3 in

regulating ferroptosis may produce synergistic effects with other treatments. For example, in cancer treatment, the combination of STAT3 inhibitors and immune checkpoint inhibitors may enhance the anti-tumor effect.[107] The role of STAT3 in regulating ferroptosis may also provide a theoretical basis for the development of new combination treatments.

Conclusion and Prospects

As a key regulator of ferroptosis, STAT3 plays an important role in various diseases by regulating key molecules such as GPX4 and SLC7A11. Although many studies have reported the regulatory mechanism of STAT3 in ferroptosis, unresolved issues and challenges remain. New research could focus on analyzing the specific regulatory mechanism of STAT3 in different disease contexts, the development of more-selective and less-toxic STAT3 inhibitors, and in achieving precise drug delivery via technological advances in methods such as nanotechnology. These studies will help to improve understanding of the role of STAT3 in ferroptosis, and provide new strategies and targets for the treatment of related diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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