Dai *et al. Cancer Cell International* (2025) 25:83
https://doi.org/10.1186/s12935-025-03681-6

Cancer Cell International

REVIEW Open Access

JAK/STAT signaling as a key regulator of ferroptosis: mechanisms and therapeutic potentials in cancer and diseases

Yimeng Dai[1†], Chunguo Cui[2†], Dan Jiao[3*] and Xuewei Zhu[4*]

Abstract

Ferroptosis is a distinct form of regulated cell death characterized by iron-dependent lipid peroxidation, playing a critical role in various diseases, including cancer, neurodegeneration, and tissue damage. This study reviews the intricate relationship between ferroptosis and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, highlighting its regulatory functions across multiple biological processes. Dysregulation of the JAK/STAT pathway is implicated in promoting or inhibiting ferroptosis, depending on the context. JAK2 promotes ferroptosis by activating STAT proteins, modulating the expression of key regulators like SLC7A11 and GPX4, and influencing iron homeostasis through pathways such as ferritinophagy and hepcidin regulation. STAT1 activation primarily enhances ferroptosis through the suppression of cystine-glutamate antiporter (System Xc^-), leading to glutathione depletion and lipid peroxidation, contributing to cell death in conditions like Sjogren's syndrome and age-related macular degeneration. In contrast, STAT3 plays a protective role by upregulating SLC7A11 and GPX4, which inhibits ferroptosis and promotes cell survival, particularly in cancers such as hepatocellular carcinoma, prostate cancer, and renal cell carcinoma. This study also discusses STAT6's involvement in ferroptosis suppression in diseases like asthma and lung injury by regulating antioxidant defenses. Furthermore, the review explores potential therapeutic strategies targeting the JAK/STAT pathway to manipulate ferroptosis for disease treatment. In cancer therapy, modulating this pathway can enhance the effectiveness of ferroptosis inducers, offering promising avenues to overcome drug resistance. Additionally, the interplay between ferroptosis and JAK/STAT signaling in immune responses, oxidative stress, and lipid metabolism underscores its significance in disease progression and therapeutic intervention. By exploring these mechanisms, this study provides insights into the development of novel treatments targeting ferroptosis through JAK/STAT modulation, with implications for cancer, inflammatory diseases, and neurodegenerative conditions.

Keywords Ferroptosis, JAK/STAT signaling, JAK2, STAT3, STAT1, STAT6, Therapy

[†]Yimeng Dai and Chunguo Cui made equal contributions to the manuscript. They are co first authors.

*Correspondence:
Dan Jiao
jiaodan@jlu.edu.cn
Xuewei Zhu
xwzhu@jlu.edu.cn

[1]Department of Radiology, China-Japan Union Hospital, Jilin University, Changchun, China
[2]Department of Breast Surgery, China-Japan Union Hospital, Jilin University, Changchun, China
[3]Department of Ultrasound, China-Japan Union Hospital, Jilin University, Changchun, China
[4]Department of Otolaryngology, China-Japan Union Hospital, Jilin University, Changchun, China

Introduction

Ferroptosis is a regulated cell death (RCD) caused by iron-dependent lipid peroxide accumulation, particularly in cell membranes. Unlike apoptosis, necroptosis, and pyroptosis, it involves oxidative damage to membrane lipids due to compromised antioxidant defenses [1]. Ferroptosis requires iron and polyunsaturated fatty acids in the membrane, which undergo peroxidation, leading to cell destruction. Ferroptosis has gained attention for its potential to target and eliminate cancer cells selectively, particularly those resistant to conventional therapies, making it a promising area in cancer research [2]. Ferroptosis is vital in health and disease, regulating cell death through iron and lipid peroxidation. It plays a key role in cancer, neurodegenerative diseases, and ischemia-reperfusion injuries. By controlling oxidative stress and lipid metabolism, ferroptosis influences both cell destruction and tissue repair. This mechanism offers therapeutic opportunities to either inhibit cell death to prevent tissue damage or trigger it to fight diseases like cancer [3]. The JAK/STAT pathway is a critical signal transduction mechanism that mediates cellular responses to extracellular signals such as cytokines and growth factors. It consists of Janus kinases (JAKs) and signal transducers and activators of transcription (STATs), which regulate essential processes like cell proliferation, differentiation, apoptosis, and immune function. Upon activation by cytokines or growth factors, JAKs phosphorylate STAT proteins, leading to their dimerization and translocation to the nucleus, which influences gene transcription. Dysregulation of this pathway is linked to a variety of diseases, including cancers (such as leukemia and breast cancer), autoimmune disorders (like rheumatoid arthritis), and inflammatory conditions. In normal health, it plays a key role in maintaining immune responses, tissue development, and cell survival. Therapeutically, JAK inhibitors are used to treat conditions like myelofibrosis, psoriasis, and rheumatoid arthritis, while targeting STATs holds potential in cancer therapies [4]. Recent reviews have highlighted the role of key cancer-related pathways such as AMPK, PI3K/Akt/mTOR, Wnt, Hippo, and cGAS-STING play crucial roles in regulating ferroptosis, either promoting or inhibiting it to influence tumor growth and survival. Different cells exploit these pathways to resist ferroptosis, while immune interactions in the tumor microenvironment (TME) can trigger or suppress ferroptosis [5, 6]. Although accumulating evidence exists regarding the involvement of the JAK/STAT signaling pathway in ferroptosis regulation, no comprehensive review has yet fully explored this relationship. Recent studies suggest that JAK/STAT signaling influences ferroptosis by modulating cellular antioxidant defenses, such as the regulation of glutathione peroxidase 4 (GPX4), which can suppress lipid peroxidation and protect against ferroptotic cell death [7]. Moreover, inflammatory cytokines, such as IL-6, which activate JAK/STAT signaling, may create a pro-ferroptotic microenvironment, depending on the context [8]. This role of JAK/STAT signaling in regulating ferroptosis represents a promising area of research with potential therapeutic implications, particularly in cancer.

In this review, we will discuss the interplay between ferroptosis and JAK/STAT signaling in human diseases. We will highlight the significance of this interaction not only in understanding disease mechanisms but also in developing targeted treatments. By exploring how ferroptosis and JAK/STAT signaling converge, we aim to uncover potential therapeutic avenues that could improve disease management and outcomes.

Overview of JAK/STAT signaling pathway

The JAK/STAT pathway plays a crucial role in transmitting signals from cytokines and growth factors to regulate gene expression and cellular functions like immune response, cell proliferation, and differentiation. Dysregulation of this pathway is implicated in various diseases, including cancers, autoimmune disorders, and inflammatory conditions. In oncology, the persistent activation of STAT3 drives tumor growth, immune evasion, and resistance to therapy, while in immune-related diseases, it contributes to chronic inflammation and impaired immune responses. JAK/STAT inhibitors, such as Ruxolitinib and Tofacitinib, are already used clinically to treat conditions like rheumatoid arthritis and myelofibrosis. Ongoing research is focused on further exploring the therapeutic potential of targeting JAK/STAT, either as monotherapy or in combination with other treatments, particularly for cancer, to improve outcomes and manage drug resistance. Additionally, mechanotransduction studies reveal that physical forces can influence the JAK/STAT pathway, affecting tissue development and healing [9]. The JAK/STAT signaling pathway is a crucial cellular communication system that mediates the effects of various cytokines and growth factors. This pathway involves JAKs, including JAK1, JAK2, JAK3, and TYK2, that associate noncovalently with cytokine receptors. Upon ligand binding, JAKs are activated, leading to the tyrosine phosphorylation of the receptors, which creates docking sites for STATs. Once recruited, STATs undergo phosphorylation by JAKs, allowing them to dimerize and translocate into the nucleus, where they bind to specific DNA sequences to regulate gene transcription. The STAT family consists of seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6, each with distinct roles in immune responses, cell growth, differentiation, and apoptosis. Negative regulatory mechanisms, such as the suppressor of cytokine signaling (SOCS) family, protein inhibitor of activated STAT (PIAS) proteins,

and protein tyrosine phosphatases (PTPs), modulate the pathway to maintain cellular homeostasis. Through these mechanisms, the JAK/STAT pathway orchestrates a wide range of biological functions essential for normal cellular operations and immune responses (activation of JAK/STAT pathway is depicted in Fig. 1 [10].

Overview of ferroptosis

Ferroptosis is initiated by a loss of the cell's antioxidant defenses, specifically through the inhibition of GPX4, an enzyme that normally detoxifies lipid peroxides. Ferroptosis is reliant on iron, which, through the Fenton reaction, generates reactive oxygen species (ROS) that cause severe oxidative stress and damage to cell membranes. The regulation of ferroptosis, either by promoting or preventing it, holds significant therapeutic potential for

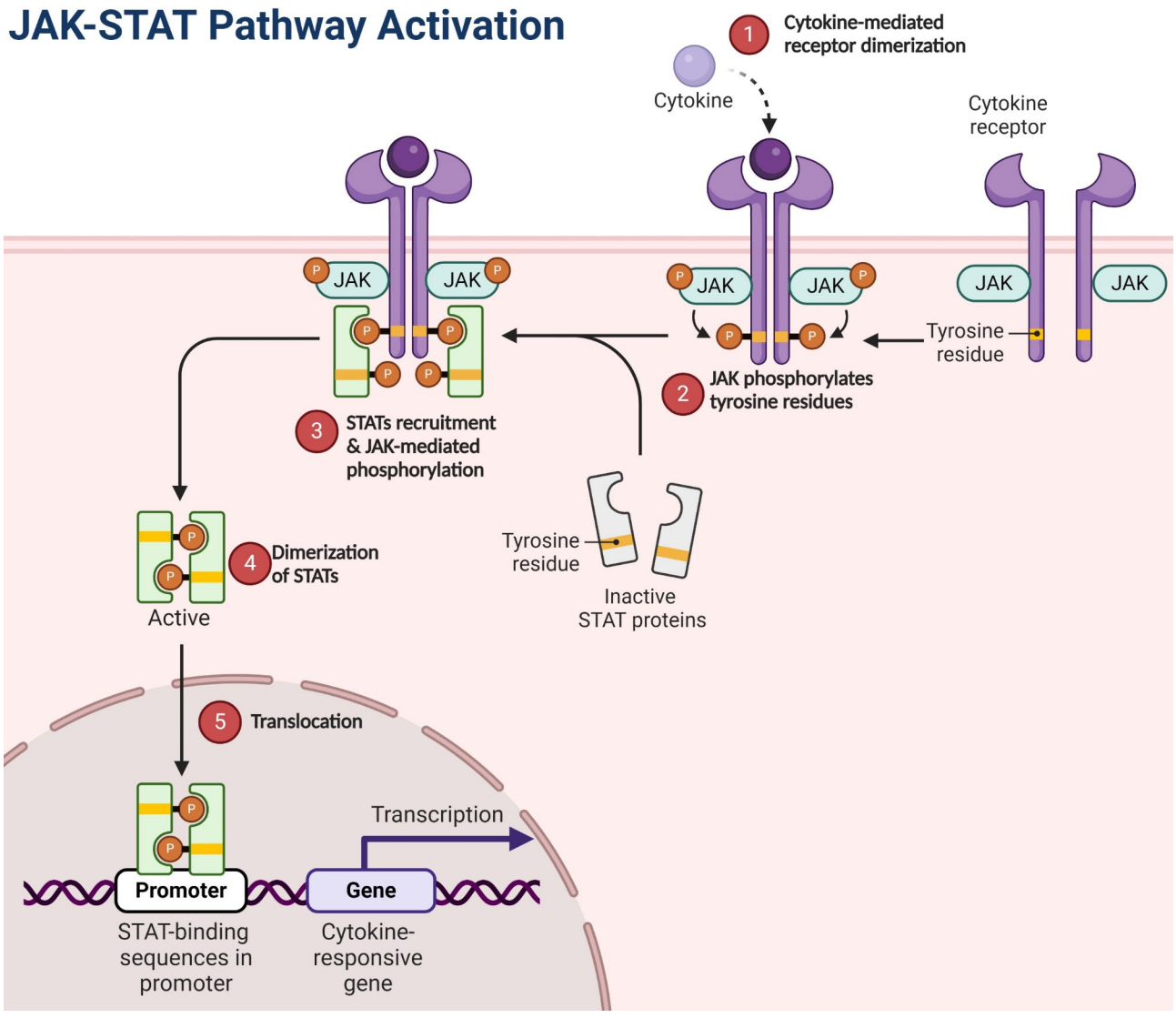

Fig. 1 The molecular steps involved in the activation of the JAK-STAT signaling pathway, a critical mechanism for transmitting signals from extracellular cytokines to the nucleus, influencing gene expression. The process begins with cytokine-mediated receptor dimerization (step 1), where a cytokine binds to its specific receptor on the cell surface, leading to the dimerization (pairing) of the receptor subunits. This brings the JAKs in proximity. Once the receptors dimerize, JAK phosphorylates tyrosine residues (step 2) on the intracellular domain of the receptor, activating the JAK proteins themselves. This phosphorylation creates docking sites for STAT proteins. In step 3, these phosphorylated tyrosine residues recruit inactive STAT proteins to the receptor complex, where JAK then phosphorylates the STATs on specific tyrosine residues. This phosphorylation triggers dimerization of STATs (step 4), where two phosphorylated STAT molecules pair up. This activated STAT dimer is now able to translocate into the nucleus. In step 5, the dimerized STATs move into the nucleus, where they bind to specific sequences in the promoter region of target genes, known as STAT-binding sequences. This binding initiates transcription of cytokine-responsive genes, ultimately leading to cellular responses such as immune modulation, growth, or differentiation. Each step in this pathway is tightly regulated and essential for proper cellular function in response to external signals like cytokines [11]

managing different diseases [12]. Ferroptosis is driven by disruptions in several key metabolic pathways, primarily involving amino acid, iron, and lipid metabolism. **Amino acid metabolism**, particularly the cystine-glutathione (GSH) axis, plays a critical role, as reduced cystine uptake or GSH depletion increases oxidative stress and leads to lipid peroxidation. **Iron metabolism** is another major contributor, where excessive iron accumulation promotes the Fenton reaction, generating ROS that damage cellular membranes through lipid peroxidation. Finally, **lipid metabolism**, particularly involving enzymes like acyl-CoA synthetase long-chain family member 4 (ACSL4), facilitates the incorporation of polyunsaturated fatty acids (PUFAs) into phospholipids, making them susceptible to peroxidation. Together, these metabolic disruptions create an environment conducive to ferroptosis, characterized by an overwhelming buildup of lipid peroxides and ROS [12]. In addition, the nuclear factor erythroid 2–related factor 2 (NRF2) pathway plays a pivotal role in regulating ferroptosis. NRF2, a key transcription factor activated in response to oxidative stress, controls the expression of various antioxidant and detoxifying enzymes that are critical in inhibiting ferroptosis. One of its major functions is upregulating the synthesis of GSH, a vital antioxidant that acts as a cofactor for GPX4, an enzyme that prevents lipid peroxidation by neutralizing lipid hydroperoxides. Additionally, NRF2 regulates iron metabolism by controlling the expression of genes involved in iron storage and export, such as ferritin and ferroportin, which helps maintain intracellular iron homeostasis and prevent excessive free iron, a catalyst for ferroptosis. By activating these protective mechanisms, the NRF2 pathway effectively mitigates the accumulation of ROS and lipid peroxides, thereby preventing the onset of ferroptosis and contributing to cellular resilience against oxidative damage [13]. In this section, we review the most important ferroptosis regulators that have intricate interplay with JAK/STAT signaling pathway:

Metabolism of amino acids in Ferroptosis and antioxidant system

The System Xc-GSH-GPX4 pathway is crucial for safeguarding cells against oxidative damage and preventing ferroptosis, a type of regulated cell death driven by lipid peroxidation. This pathway starts with System Xc-, a transporter on the cell membrane that consists of the subunits **SLC7A11** and **SLC3A2** [14]. It facilitates the exchange of intracellular glutamate for extracellular cystine, allowing the import of cystine into the cell. Once inside, cystine is reduced to cysteine, which is then used to synthesize GSH, a tripeptide made of cysteine, glutamate, and glycine, and a vital cellular antioxidant. GSH acts as a cofactor for the enzyme **GPX4**, which reduces harmful lipid hydroperoxides (PL-OOH) to non-toxic lipid alcohols (PL-OH) [15]. This reaction, driven by GSH, prevents lipid peroxidation and the accumulation of ROS that can damage cellular membranes and trigger ferroptosis. When System Xc^- is inhibited, the reduction in cystine uptake lowers intracellular GSH levels. This, in turn, deactivates GPX4, limiting its ability to neutralize lipid peroxides, leading to oxidative damage and cell death via ferroptosis. Therefore, the System Xc-GSH-GPX4 pathway is essential for regulating oxidative balance and protecting cells from oxidative stress-induced ferroptosis (Fig. 2) [16].

Metabolism of lipids in ferroptosis

Lipid metabolism regulation in ferroptosis is primarily governed by the balance between PUFAs and monounsaturated fatty acids (MUFAs), with specific enzymes modulating their incorporation into membrane phospholipids. Enzymes like ACSL4 promote ferroptosis by incorporating PUFAs into phospholipids, making them susceptible to lipid peroxidation, while ACSL3 promotes MUFA incorporation, which resists oxidation and thus protects against ferroptosis [17]. Key desaturase enzymes, such as FADS1 and ELOVL5, elongate and desaturate fatty acids to enhance PUFA content, increasing ferroptosis sensitivity [18]. Conversely, stearoyl-CoA desaturase (SCD1) synthesizes MUFAs, which protect against ferroptosis by reducing peroxidizable substrates in membranes [19]. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) plays a critical role in ferroptosis by promoting the incorporation of PUFAs into phospholipids, facilitating lipid peroxidation, and increasing ferroptosis sensitivity [20]. Additionally, arachidonate 15-lipoxygenase (ALOX15) catalyzes the direct oxidation of PUFAs, further driving lipid peroxidation and ferroptosis [21]. Alongside these enzymes, antioxidant systems like GPX4 and coenzyme Q10 (CoQ10) reduce lipid peroxides, preventing lethal lipid peroxidation [22]. Overall, the regulation of lipid metabolism, including the actions of LPCAT3 and ALOX15, determines susceptibility to ferroptosis by influencing the lipid composition of cellular membranes and their vulnerability to oxidative damage (Fig. 2) [23].

Iron-related pathways

Iron is essential for the induction of ferroptosis because it plays a central role in generating ROS, which drive the lipid peroxidation that is critical for this form of cell death. Specifically, iron, in its ferrous form (Fe^{2+}), participates in the Fenton reaction, where it reacts with hydrogen peroxide (H_2O_2) to produce hydroxyl radicals (OH), highly reactive species that can damage lipids. These ROS trigger the peroxidation of polyunsaturated fatty acids in cellular membranes, leading to membrane damage and eventually cell death. Iron's ability to catalyze

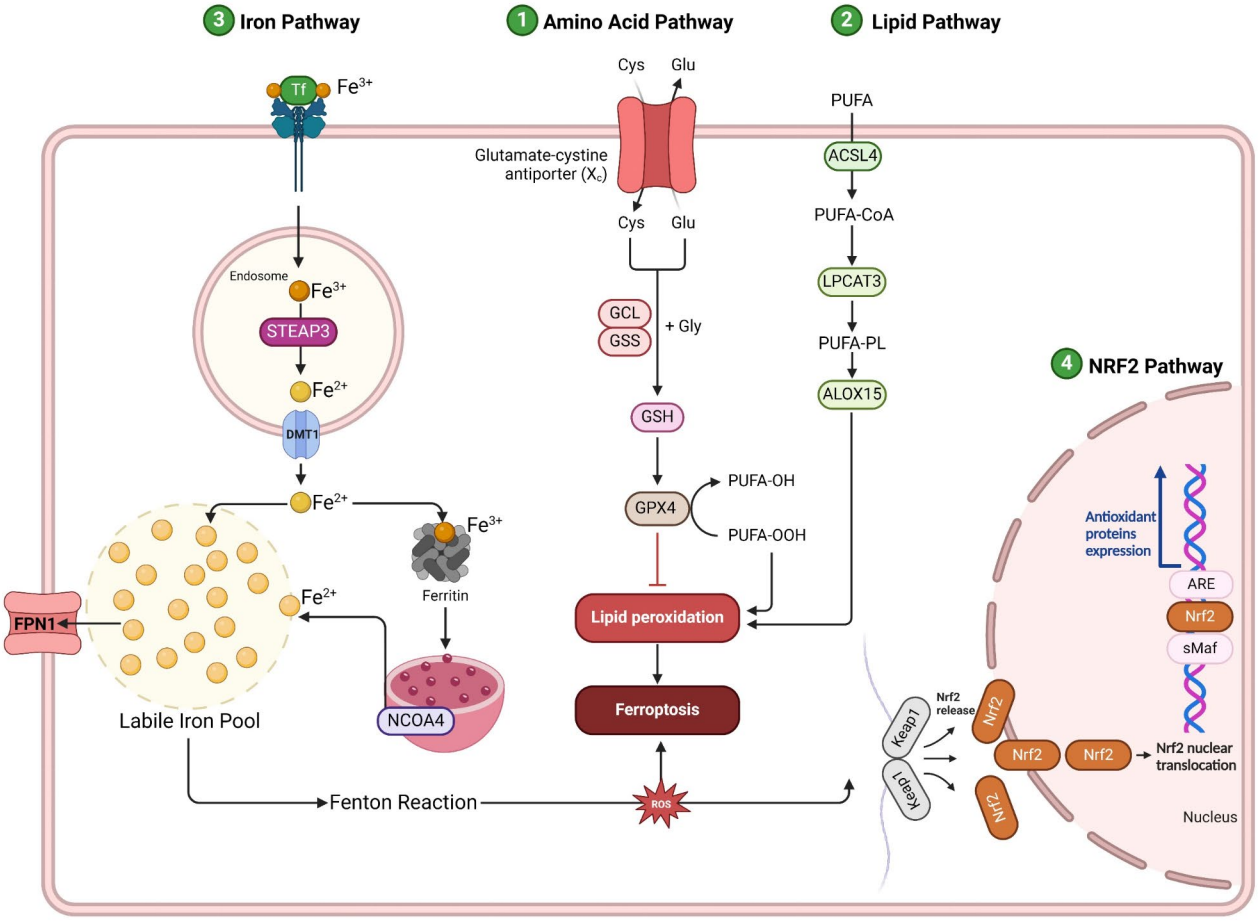

Fig. 2 This diagram illustrates the interconnected pathways involved in ferroptosis. First, the amino acid pathway is crucial for GSH production, a key antioxidant. Cystine enters the cell through the Xc- antiporter, is converted into cysteine, and combines with glutamate and glycine to form GSH. GPX4 then uses GSH to neutralize lipid peroxides, preventing ferroptosis. Second, the lipid pathway shows how PUFAs are processed by enzymes such as ACSL4, LPCAT3, and ALOX15, resulting in the formation of PUFA-OOH, which, if not neutralized by GPX4, triggers ferroptosis. Third, the iron pathway highlights how Fe^{2+} contributes to ferroptosis by generating ROS through the Fenton reaction. Iron enters cells via Tf, is reduced to Fe^{2+} by STEAP3, and either stored in ferritin or exported by FPN1. Excess Fe^{2+} leads to ROS production, enhancing lipid peroxidation and promoting ferroptosis. Lastly, the Nrf2 pathway serves as a protective mechanism against ferroptosis. Nrf2, typically inhibited by Keap1, is released during oxidative stress, translocates to the nucleus, and activates the expression of antioxidant genes like GPX4. This helps mitigate oxidative stress, regulate lipid peroxidation, and control iron metabolism, thereby preventing ferroptosis

this oxidative process is unique compared to other metals, making it a key factor in ferroptosis. Without sufficient iron, the lipid peroxidation cascade is not initiated, and ferroptosis cannot occur effectively. Therefore, iron's redox activity is fundamental in promoting the oxidative stress required to execute ferroptosis [24]. Transferrin is the primary iron-transport protein in the blood, responsible for delivering iron to cells by binding to transferrin receptors on cell membranes. During ferroptosis, the uptake of iron via transferrin and its receptor increases intracellular iron levels, which catalyze the formation of ROS through the Fenton reaction. When transferrin binds to its receptor (transferrin receptor 1, or TfR1) on the cell surface, the complex is internalized through receptor-mediated endocytosis, forming an endosome within the cell [25, 26]. Inside the acidic environment of the endosome, iron ($Fe^{3+,}$ ferric iron) is released from transferrin and is then reduced to Fe^{2+} (ferrous iron) by a membrane-bound enzyme called six-transmembrane epithelial antigen of prostate 3 (STEAP3) [27]. The Fe^{2+} is transported into the cytoplasm via the divalent metal transporter 1 (DMT1) [28]. This form of ferrous iron (Fe^{2+}) is highly reactive and can participate in the Fenton reaction, generating ROS. In conditions where iron homeostasis is disrupted or when iron overload occurs, this increased intracellular ferrous iron can induce lipid peroxidation, a key event in ferroptosis. Therefore, the iron imported via transferrin-TfR1 interaction can indeed be used to induce ferroptosis under appropriate cellular conditions [29]. Ferritin stores iron in the non-toxic form

of Fe^{3+} by converting Fe^{2+} into Fe^{3+} through a process of oxidation. This iron is sequestered inside the ferritin protein shell to prevent cellular damage caused by free Fe^{2+} and its involvement in oxidative reactions. Ferritinophagy, a selective autophagy process mediated by nuclear receptor coactivator 4 (NCOA4), degrades ferritin in autophagosomes, releasing Fe^{3+} into the lysosome. Inside the lysosome, Fe^{3+} is reduced back to $Fe^{2+,}$ which is then released into the cytosol. This free Fe^{2+} contributes to the labile iron pool (LIP) and can drive the Fenton reaction, generating ROS that promote lipid peroxidation and ferroptosis [30]. Ferroportin 1 (FPN1) is the only known cellular iron exporter, playing a crucial role in maintaining iron homeostasis and preventing ferroptosis by exporting excess iron from cells. FPN1 transports iron from the cytoplasm to the extracellular space, where it binds to transferrin, preventing the buildup of toxic intracellular iron levels. When iron accumulates inside cells, it leads to the formation of ROS through the Fenton reaction, triggering lipid peroxidation and ferroptosis. By exporting iron, FPN1 reduces the intracellular labile iron pool, thereby limiting oxidative stress and preventing the onset of ferroptosis, particularly in iron-sensitive tissues like the heart and liver (Fig. 2) [31].

NRF2 pathway

Nrf2 plays a pivotal role in regulating ferroptosis by enhancing the cell's defenses against oxidative damage. As a key transcription factor, Nrf2 activates the expression of antioxidant genes, including GPX4, which is vital for detoxifying lipid peroxides and preventing ferroptosis. It also regulates iron metabolism by controlling genes that manage iron storage and export, such as ferritin and heme oxygenase-1 (HO-1), thereby reducing the pool of free iron that fuels ferroptosis through oxidative reactions. In addition, Nrf2 boosts glutathione production, a crucial component for GPX4's function, further strengthening the cell's ability to combat lipid peroxidation. By maintaining oxidative balance, ensuring proper mitochondrial function, and managing iron levels, Nrf2 helps inhibit ferroptosis, making it an essential factor in preventing oxidative cell death, especially in the context of neurodegenerative diseases (Fig. 2) [32, 33].

Regulation of ferroptosis by JAK/STAT signaling

Regulation of SLC7A11 by JAK/STAT signaling

Regulation by STAT1/SLC7A11 Axis

The JAK/STAT1 pathway plays a pivotal role in regulating ferroptosis, particularly in the context of Sjogren's syndrome (SS). When interferon-γ (IFN-γ) is elevated, as seen in SS, it activates the JAK/STAT1 signaling cascade. This activation leads to phosphorylation of STAT1, which then inhibits the expression of key components of the cystine-glutamate antiporter, known as System Xc^-. As a result, lipid ROS accumulate, leading to oxidative damage and ferroptosis in salivary gland epithelial cells (SGEC). By suppressing the System Xc^-/GSH/GPX4 axis, the JAK/STAT1 pathway effectively promotes ferroptosis, contributing to cell death and tissue damage in SS. Inhibiting JAK or STAT1 can rescue SGECs from this IFN-γ-induced ferroptosis, underscoring the pathway's central role in mediating this cell death process [34]. JAK1-2/STAT1 pathway is identified as a crucial mechanism through which IFN-γ induces ferroptosis in retinal pigment epithelial (RPE) cells, contributing to the pathogenesis of age-related macular degeneration (AMD). IFN-γ activates the JAK1-2/STAT1 signaling cascade, which downregulates the expression of System Xc^- components SLC7A11 and SLC3A2. This leads to a reduction in intracellular cystine uptake, depletion of GSH, and suppression of GPx4, a key enzyme that protects against lipid peroxidation. The resulting GSH depletion and increased lipid peroxidation, along with elevated intracellular iron levels (due to IFN-γ-induced inhibition of the iron efflux protein SLC40A1), drive ferroptosis in RPE cells. Inhibiting the JAK1-2/STAT1 pathway using specific inhibitors (ruxolitinib and fludarabine) can rescue the downregulation of SLC7A11, SLC3A2, and GPX4, and prevent IFN-γ-induced cell death, suggesting that targeting this pathway could serve as a therapeutic strategy to mitigate RPE cell damage and slow AMD progression (Fig. 3) [35].

Regulation by of STAT3/SLC7A11 Axis

The JAK2/STAT3 signaling pathway plays a crucial role in regulating the expression of SLC7A11. When the JAK2/STAT3 pathway is activated, typically by cytokines or growth factors, JAK2 phosphorylates STAT3, which then translocates to the nucleus and binds to the promoter region of target genes, including SLC7A11. This upregulation of SLC7A11 enhances cystine uptake, boosting glutathione production, neutralizing ROS and inhibiting lipid peroxidation, a key driver of ferroptosis. Therapeutic interventions, such as iron chelators like deferasirox, can restore JAK2/STAT3 activity, enhancing SLC7A11 expression and mitigating ferroptosis, thus protecting against conditions such as insulin resistance and liver damage associated with iron overload [36]. IL-6 plays a crucial role in modulating ferroptosis, particularly in the context of renal cell carcinoma (RCC) resistance to tyrosine kinase inhibitors (TKIs). IL-6 is known to activate the JAK2-STAT3 signaling pathway, which leads to the upregulation of SLC7A11. By promoting SLC7A11 expression, IL-6 inhibits lipid peroxidation, a critical process in ferroptosis, thereby preventing ferroptotic cell death. This ferroptosis inhibition allows RCC cells to evade cell death despite therapeutic pressure, contributing to TKI resistance. Thus, IL-6 not only promotes tumor survival and proliferation through the IL-6-STAT3

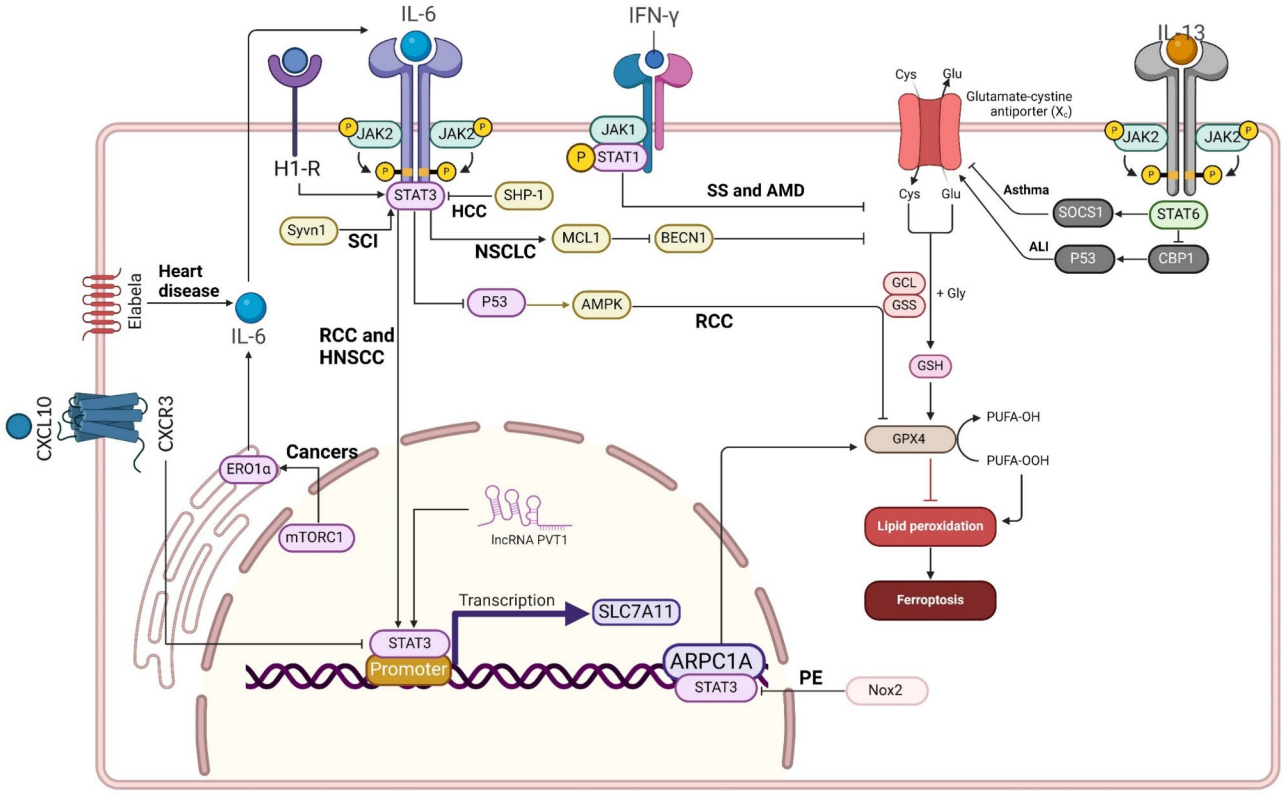

Fig. 3 The regulation of ferroptosis by JAK/STAT signaling pathways, focusing on the roles of different STAT proteins, including STAT1, STAT3, and STAT6, in modulating ferroptosis through pathways like SLC7A11 and GPX4 (Amino acid metabolism). *STAT1 and ferroptosis*: Upon activation by interferon-γ (IFN-γ), the JAK1/2-STAT1 pathway downregulates the cystine-glutamate antiporter (System Xc−), reducing cystine uptake and leading to GSH depletion. This suppression of the GSH/GPX4 axis results in increased lipid peroxidation and ferroptosis, contributing to cell death in diseases such as SS AMD. *STAT3 and ferroptosis*: The IL-6/JAK2/STAT3 pathway plays a crucial role in regulating ferroptos is resistance across various cancers, including RCC and HNSCC. IL-6 activates STAT3, promoting the transcription of SLC7A11, which enhances cystine uptake and GSH synthesis, thereby inhibiting ferroptosis. Additionally, the SHP-1/STAT3/SLC7A11 axis regulates the MCL1-BECN1 interaction, impacting ferroptosis in HCC and NSCLC. ARPC1A, transcriptionally regulated by STAT3, also inhibits ferroptosis in prostate cancer by reducing GPX4 and SLC7A11 expression, facilitating tumor progression. *STAT6 and ferroptosis*: In conditions such as asthma and ALI, IL-13 activates the JAK2/STAT6 pathway, which promotes the degradation of SLC7A11 via SOCS1, leading to increased ferroptosis in airway epithelial cells. Furthermore, STAT6 inhibits P53 acetylation, thereby enhancing SLC7A11 expression, which mitigates ferroptosis during lung injury

pathway but also actively suppresses ferroptosis, making it a significant factor in the development of drug resistance in RCC [37]. In the in vivo experiments conducted on head and neck squamous cell carcinoma (HNSCC), the role of IL-6 in ferroptosis resistance was explored using a xenograft model. CAL27 cells, either with xCT knockdown or treated with the ferroptosis inducer erastin, were injected into BALB/c-nu mice. Tumor growth was significantly reduced in the groups where xCT was knocked down, or erastin was administered, indicating the induction of ferroptosis. However, when IL-6 was co-administered, tumor growth inhibition was reversed, with a notable increase in tumor weight and volume. Immunohistochemistry (IHC) analysis of the xenografts revealed that IL-6 reduced the levels of 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation associated with ferroptosis, which were elevated by erastin treatment. These results indicate that IL-6 promotes ferroptosis resistance by upregulating xCT in vivo, allowing tumor cells to overcome oxidative stress and continue proliferating despite treatment aimed at inducing ferroptosis [38]. The IL-6/STAT3/SLC7A11 pathway plays a pivotal role in the mechanistic target of rapamycin complex 1 (mTORC1)-mediated ferroptosis resistance and tumor growth. Upon mTORC1 activation, the expression of endoplasmic reticulum oxidoreductase 1 alpha (ERO1α) is upregulated, which in turn stimulates the secretion of IL-6. IL-6 activates the STAT3 signaling pathway, promoting the transcription of SLC7A11. Elevated SLC7A11 levels enhance the cellular defense against ferroptosis by maintaining glutathione levels and reducing lipid peroxidation, thus conferring resistance to ferroptosis. Consequently, this pathway not only facilitates the survival of mTORC1-activated cells under ferroptotic stress but also promotes tumor growth through increased cell proliferation and angiogenesis. Inhibition

of the IL-6/STAT3/SLC7A11 axis, therefore, emerges as a potential therapeutic strategy to overcome ferroptosis resistance and impede tumor progression in mTORC1-driven cancers [39]. Sorafenib is a multi-kinase inhibitor used in cancer treatment that targets pathways involved in tumor cell proliferation and angiogenesis. It affects the STAT3/MCL1/BECN1/SLC7A11 axis by inhibiting STAT3 activation, leading to the downregulation of myeloid cell leukemia-1 (MCL1). MCL1 typically binds to and sequesters Beclin-1 (BECN1), preventing BECN1 from interacting with the cystine/glutamate antiporter subunit SLC7A11, which helps import cystine and protect against oxidative stress. When MCL1 is downregulated by sorafenib, BECN1 is freed to bind SLC7A11, inhibiting its activity. This disruption in cystine import leads to increased lipid peroxidation and triggers ferroptosis, a type of cell death, especially in MCL1-downregulated non-small cell lung cancer (NSCLC) cells [40]. In Hepatocellular carcinoma (HCC), sorafenib induces ferroptosis through the SHP-1/STAT3 signaling axis, which regulates the interaction between BECN1 and SLC7A11. Sorafenib activates SHP-1 (Src homology region 2 domain-containing phosphatase-1), which in turn inhibits STAT3 phosphorylation. This inhibition downregulates STAT3 activity, reducing the expression of anti-apoptotic and ferroptosis-resistant genes. As a result, MCL1, which binds to BECN1 to prevent its interaction with SLC7A11, is downregulated. This allows BECN1 to bind to and inhibit SLC7A11 for importing cystine to neutralize oxidative stress. By inhibiting SLC7A11, sorafenib increases lipid peroxidation and induces ferroptosis in HCC cells, enhancing its antitumor effects. Thus, the SHP-1/STAT3 signaling axis plays a crucial role in promoting ferroptosis by modulating the BECN1-SLC7A11 interaction in sorafenib-treated HCC [41]. Methionine adenosyltransferase 2 A (MAT2A) inhibits ferroptosis in osteosarcoma progression by modulating the STAT3/SLC7A11 signaling pathway. It was found that high expression of MAT2A correlates with poorer patient prognosis and promotes tumor malignancy. MAT2A suppression, through shRNA or the inhibitor FIDAS-5, significantly increased intracellular ferrous iron levels and reduced GSH synthesis, both critical for inducing ferroptosis. In vivo experiments using a mouse osteosarcoma xenograft model showed that MAT2A knockdown led to a marked reduction in tumor size and weight, demonstrating its potent anticancer effect. Mechanistically, MAT2A inhibition decreased the phosphorylation of STAT3 (p-STAT3), a key regulator that enhances SLC7A11 expression, which in turn blocks ferroptosis by promoting cystine uptake and GSH synthesis [42]. Similarly, ARPC1A (actin-related protein 2/3 complex subunit 1 A) is involved in prostate cancer (PCa) progression by inhibiting ferroptosis. ARPC1A is transcriptionally regulated by STAT3, which binds to its promoter region, leading to its overexpression. Knockdown of ARPC1A significantly reduces prostate cancer cell viability and invasion while promoting ferroptosis. The reduction of ARPC1A decreases the expression of key ferroptosis regulators GPX4 and SLC7A11, thereby facilitating ferroptosis. In vivo experiments using a mouse xenograft model confirmed that ARPC1A knockdown inhibited tumor growth and induced ferroptosis, providing evidence that ARPC1A acts as a negative regulator of ferroptosis through the STAT3 pathway, promoting prostate cancer progression. Thus, ARPC1A may serve as a potential therapeutic target and a prognostic marker in PCa [43]. Doxorubicin-induced cardiotoxicity (DIC) refers to the severe heart damage caused by the chemotherapeutic drug doxorubicin (DOX), widely used in cancer treatment. While highly effective against various cancers, DOX can lead to oxidative stress, mitochondrial dysfunction, and a distinct form of cell death known as ferroptosis in cardiomyocytes, the heart muscle cells. The histamine/H1 receptor (H1R) pathway plays a crucial protective role in this context. Histamine, a biogenic amine, signals through H1R to activate the STAT3-SLC7A11 pathway, which helps regulate oxidative stress and suppress ferroptosis. SLC7A11, a key transporter in the cystine/glutamate antiporter system, supports GSH synthesis, essential for combating lipid peroxidation. When histamine/H1R signaling is disrupted, through histamine deficiency or pharmacological inhibition, there is decreased activation of STAT3, leading to reduced SLC7A11 expression and heightened susceptibility to ferroptosis in cardiomyocytes. As a result, the heart becomes more vulnerable to DOX-induced oxidative damage, worsening cardiotoxicity [44]. Neuronal ferroptosis, driven by GPX4-GSH dysfunction, significantly contributes to the susceptibility of epilepsy. In epileptic mice, neuronal injury and increased ROS production were observed in the hippocampus, along with higher expression of ferroptosis markers such as DPP4, 4-HNE, and phosphorylated Erk, while GPX4 levels were downregulated. Inhibition of ferroptosis using Fer-1 or GSH reduced seizure severity, improved neuronal survival, and decreased ferroptosis-related protein expression. Neurotoxic A1 astrocytes were identified as key inducers of neuronal ferroptosis in epilepsy, with increased activation in epileptic brains, evidenced by higher expression of A1 markers such as C3 and S100a10. A1 astrocyte activation elevated ROS levels and ferroptosis markers, while inhibiting GPX4-GSH antioxidant signaling in neurons. In vitro, A1 astrocyte-conditioned medium induced neurotoxicity and ferroptosis in neuronal cells, which was mitigated by ferroptosis inhibitors. A1 astrocyte-secreted CXCL10 sensitized neurons to ferroptosis via the CXCR3 receptor, activating the STAT3/SLC7A11 pathway,

leading to lipid peroxidation and neuronal injury. Clinical relevance was confirmed as epileptic patients displayed elevated markers of A1 astrocytes, increased CXCL10 levels, and decreased expression of GPX4 and SLC7A11, linking A1 astrocyte-induced ferroptosis to epilepsy (Fig. 3) [45].

Regulation by STAT6/SLC7A11 Axis

STAT6 inhibits ferroptosis and alleviates acute lung injury (ALI) by modulating the P53/SLC7A11 pathway. During ALI, STAT6 was found to be upregulated and serves as a key regulator in reducing ferroptosis in lung epithelial cells. Mechanistically, STAT6 inhibits the acetylation of P53, a crucial regulator of ferroptosis, by competitively binding to the CREB-binding protein (CBP), an acetyltransferase that enhances P53 acetylation. This inhibition of P53 acetylation decreases P53's ability to suppress the expression of SLC7A11. By restoring SLC7A11 expression, STAT6 enhances the cells' capacity to combat oxidative stress and lipid peroxidation, thereby reducing ferroptosis and mitigating lung injury. This pathway highlights STAT6 as a potential therapeutic target for treating ALI [46]. IL-13 exacerbates asthma by driving ferroptosis in airway epithelial cells through a pathway mediated by SOCS1. Upon IL-13 stimulation, STAT6 becomes activated, promoting the transcription of SOCS1. As an E3 ubiquitin ligase, SOCS1 binds to SLC7A11. SOCS1 facilitates the ubiquitinated degradation of SLC7A11, thereby reducing cellular antioxidant defenses, which leads to an accumulation of lipid peroxidation and the depletion of glutathione. This shift in redox balance sensitizes cells to ferroptosis. The degradation of SLC7A11 weakens the cells' ability to manage oxidative stress, resulting in increased lipid ROS, mitochondrial damage, and cellular death. In the context of asthma, this IL-13/SOCS1/SLC7A11 axis promotes ferroptotic death of airway epithelial cells, contributing to airway inflammation, mucus hypersecretion, and airway hyperresponsiveness (AHR), thereby exacerbating the symptoms and progression of Th2-high asthma (Fig. 3) [47].

Regulation of GPX4 pathway by JAK/STAT signaling

Regulation by STAT3/GPX4 Axis

JAK2/STAT3 signaling plays a pivotal role in regulating ferroptosis in renal cancer under energy-stress conditions. Inactivation of the JAK2/STAT3 pathway leads to the upregulation of P53, which in turn promotes AMP-activated protein kinase (AMPK)-mediated ferroptosis by suppressing GPX4. Glucose deprivation, simulating energy stress, activated AMPK and significantly increased erastin-induced ferroptosis in renal cancer cells, as evidenced by mitochondrial shrinkage, GSH depletion, malondialdehyde (MDA) production, and increased cellular iron levels. AMPK activation not only suppressed GPX4 at the transcriptional level but also enhanced the ferroptotic response, which could be reversed by overexpressing GPX4. Further, P53 upregulation contributed to this process, as inhibition of P53 restored GPX4 expression and reduced ferroptosis. Importantly, AMPK activation was shown to inhibit the JAK2/STAT3 pathway, and overexpression of JAK2 counteracted the ferroptotic effects by reducing P53 expression and restoring GPX4 levels. These findings suggest that the JAK2/STAT3/P53 axis is crucial in mediating energy-stress-induced ferroptosis in renal cancer, and targeting this pathway may provide a therapeutic strategy for enhancing ferroptosis in cancer treatment [48]. JAK2/STAT3 plays a crucial role in growth differentiation factor 15 (GDF15)-mediated protection against sepsis-induced cardiomyopathy (SIC) by inhibiting cardiomyocyte ferroptosis through the SOCS1/GPX4 signaling pathway. GDF15, a member of the transforming growth factor beta (TGF-β) family, exerts its cardioprotective effects by activating the ALK5-SMAD2/3 pathway, which downregulates SOCS1 expression. This downregulation of SOCS1 relieves its inhibitory effect on the JAK2/STAT3 pathway, allowing STAT3 activation. Once activated, STAT3 translocates to the nucleus, where it promotes the transcription of GPX4, a key enzyme that prevents ferroptosis by reducing lipid peroxidation. By enhancing GPX4 expression, the JAK2/STAT3 pathway helps preserve cardiomyocyte function, reduces oxidative stress, and maintains mitochondrial integrity, all of which are critical for preventing ferroptotic cell death. In contrast, antagonizing GDF15 worsens myocardial damage in SIC, highlighting its role in restoring cardiac function [49]. Elabela is an endogenous peptide and a ligand for the apelin receptor (APJ), primarily expressed in cardiac microvascular endothelial cells (CMVECs). It plays a crucial role in cardiovascular homeostasis. In hypertensive mice, elabela alleviates ferroptosis, myocardial remodeling, fibrosis, and heart dysfunction by modulating the IL-6/STAT3/GPX4 signaling pathway. Angiotensin II (Ang II), a key mediator in hypertension, induces oxidative stress, inflammation, and ferroptosis in CMVECs, leading to adverse cardiac remodeling and dysfunction. Elabela counters these effects by inhibiting the IL-6/STAT3 signaling, which reduces inflammation and oxidative damage. Simultaneously, elabela activates the xCT/GPX4 axis, a critical defense against ferroptosis, by enhancing antioxidant activity and iron regulation. Through these mechanisms, elabela protects the heart from Ang II-induced injury, reducing fibrosis, hypertrophy, and improving overall cardiac function, offering a potential therapeutic target for hypertensive heart disease [50]. Blue light (BL), especially from LED devices, has been found to induce ferroptosis in conjunctival epithelial cells, both in vivo and in vitro, by affecting key regulatory pathways. BL exposure

inhibits the phosphorylation and activation of STAT3. This transcription factor normally promotes the expression of critical ferroptosis regulators such as GPX4, SLC7A11, and FTH1. This downregulation disrupts iron metabolism, leading to increased intracellular Fe^{2+}, ROS, and lipid peroxidation. These changes contribute to the initiation of ferroptosis in conjunctival epithelial cells, resulting in significant cell injury. Treatment with Ferrostatin-1 (Fer-1), a ferroptosis inhibitor, has been shown to alleviate these BL-induced injuries, reducing Fe^{2+} levels, LPO accumulation, and oxidative stress. This suggests that modulating the STAT3/GPX4/SLC7A11/FTH1 axis could be a promising therapeutic approach to mitigate BL-induced conjunctival damage and related dry eye syndromes [51]. In mice, the E3 ubiquitin ligase Syvn1 plays a crucial role in inhibiting neuronal ferroptosis and promoting recovery after spinal cord injury (SCI) by stabilizing the transcription factor Stat3 and activating the Stat3/Gpx4 signaling axis. After SCI, Syvn1 interacts with Stat3, enhancing its stability through K63-linked ubiquitination, preventing degradation. This stabilized Stat3 promotes the transcription of Gpx4. By enhancing Gpx4 expression, Syvn1 reduces oxidative damage, suppresses ferroptosis, and promotes neuronal survival. These actions collectively contribute to improved motor function and recovery in SCI models, highlighting Syvn1 as a potential therapeutic target for SCI treatment [52]. LncRNAs (long non-coding RNAs) are RNA molecules longer than 200 nucleotides that do not encode proteins but regulate gene expression and cellular processes [53]. The long non-coding RNA PVT1 was found to promote osteosarcoma progression by inhibiting ferroptosis through the activation of the STAT3/GPX4 signaling pathway. PVT1 was shown to increase the levels of phosphorylated STAT3, which in turn upregulated GPX4, an enzyme that protects cells from lipid peroxidation and ferroptosis. Knockdown of PVT1 in osteosarcoma cells led to increased ferroptosis markers such as ROS, MDA, and Fe^{2+}, along with reduced GPX4 expression, ultimately inhibiting cell proliferation, migration, and invasion. However, overexpression of STAT3 rescued these effects, restoring GPX4 levels and reducing ferroptosis. This suggests that PVT1 drives osteosarcoma metastasis by activating the STAT3/GPX4 axis to suppress ferroptosis, highlighting PVT1 as a potential therapeutic target for osteosarcoma treatment [54]. Researchers have investigated the role of NADPH oxidase 2 (Nox2) in regulating ferroptosis in trophoblast cells and its contribution to the pathogenesis of preeclampsia (PE). Nox2 was significantly upregulated in the placentas of PE patients, while STAT3 and GPX4, key regulators of ferroptosis, were downregulated. Nox2 was shown to promote ferroptosis in trophoblasts, characterized by increased ROS and lipid peroxidation, leading to impaired cell proliferation, invasion, and mitochondrial dysfunction. Knockdown of Nox2 inhibited ferroptosis by restoring STAT3 and GPX4 expression, improving mitochondrial respiration, reducing glycolysis, and promoting angiogenesis. Further results demonstrated that Nox2 interacts with STAT3, regulating the STAT3/GPX4 pathway to drive ferroptosis (Fig. 3) [55].

Regulation of NRF2/HO-1 pathway by JAK/STAT signaling

Regulation by STAT3/NRF2 Axis

NRF2 plays a critical role in suppressing ferroptosis and promoting osteogenic differentiation by interacting with phosphorylated STAT3 (p-STAT3) in the nucleus. It has been found that erastin-induced ferroptosis, which leads to oxidative stress and cell death in osteoblasts, aggravates alveolar bone loss, a condition worsened in periodontitis. However, IL-17 alleviated these effects by upregulating NRF2 expression, increasing the expression of ferroptosis-related molecules such as GPX4 and SLC7A11. IL-17 facilitated the nuclear translocation of NRF2, where it physically interacted with p-STAT3, forming a complex that promoted the transcription of key antioxidant and osteogenesis-related genes, including Runx2, Alp, Osx, and Ocn. This interaction between NRF2 and p-STAT3 enhanced osteoblast differentiation and mineralization, thus reversing the detrimental effects of ferroptosis on bone formation [56]. The induction of ferroptosis by impairing the STAT3/Nrf2/GPX4 signaling pathway enhances the sensitivity of osteosarcoma cells to cisplatin by counteracting the cells' defense mechanisms against oxidative stress and cell death. Osteosarcoma cells often develop resistance to cisplatin, a commonly used chemotherapy drug, by increasing their antioxidant capacity through the upregulation of the STAT3/Nrf2/GPX4 pathway. This pathway promotes cell survival by reducing oxidative damage and inhibiting ferroptosis. In cisplatin-resistant osteosarcoma cells (MG63/DDP and Saos-2/DDP), the proteins p-STAT3, Nrf2, and GPX4 are overexpressed, which enhances the cells' ability to neutralize ROS and lipid peroxides, effectively preventing ferroptosis and maintaining cell viability. By inhibiting STAT3 with specific inhibitors like BP-1-102, or by using ferroptosis inducers such as Erastin and RSL3, this protective signaling cascade is disrupted. This impairment leads to a reduction in Nrf2 and GPX4 levels, weakening the cells' antioxidant defenses. Consequently, the accumulation of ROS and lipid peroxides triggers ferroptosis, increasing cell death and making the cisplatin-resistant osteosarcoma cells more vulnerable to the cytotoxic effects of cisplatin. This suggests that targeting the STAT3/Nrf2/GPX4 pathway can sensitize resistant cancer cells to chemotherapy by promoting ferroptosis, offering a novel strategy to overcome drug resistance in osteosarcoma (Fig. 4) [57].

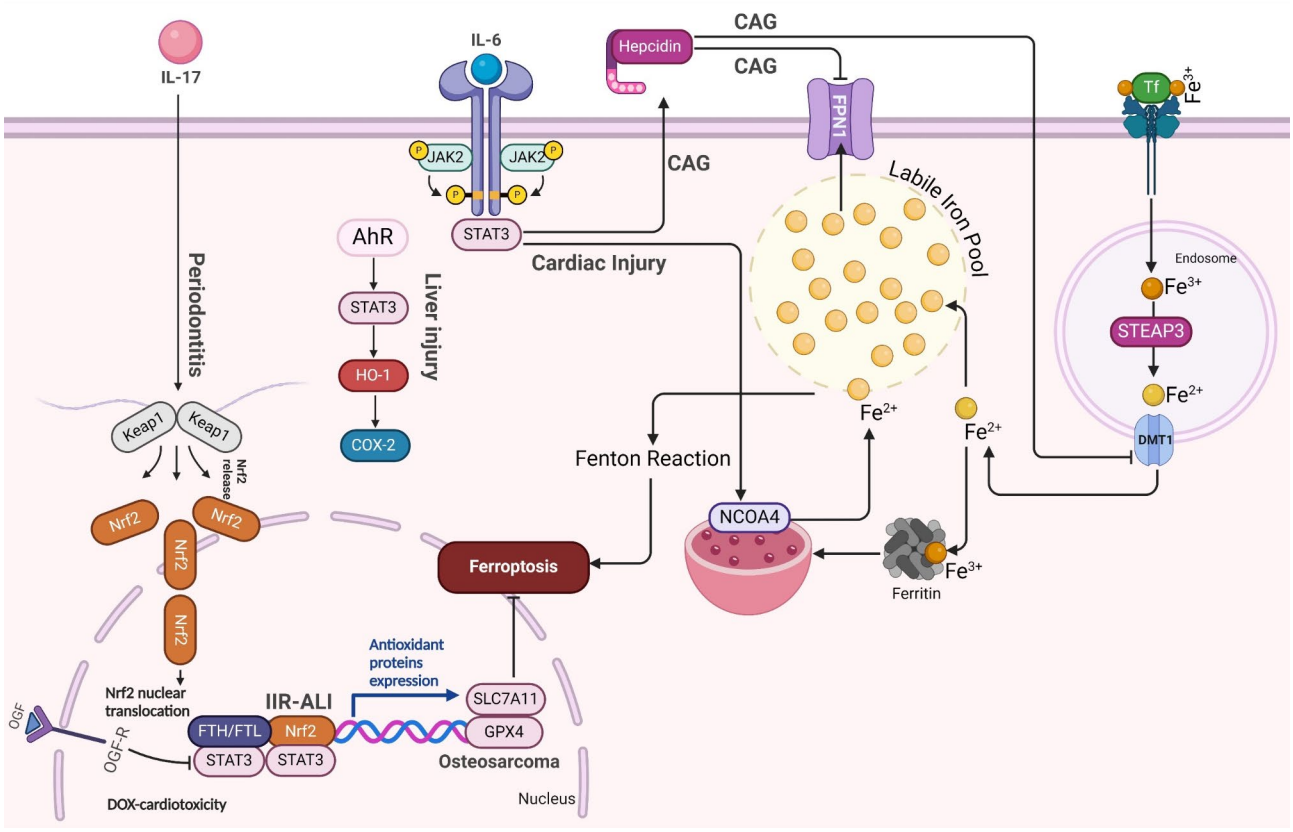

Fig. 4 The regulation of ferroptosis through the interaction of iron metabolism and the STAT3/NRF2 pathway. In conditions like osteosarcoma and periodontitis, STAT3 activates NRF2, promoting antioxidant defense and osteogenic differentiation by upregulating key genes such as GPX4 and SLC7A11, which protect against ferroptosis. IL-6/STAT3 signaling increases hepcidin expression, inhibiting ferroportin and leading to iron accumulation and ferroptosis through the Fenton reaction. Additionally, STAT3 drives ferritin degradation via NCOA4, releasing iron and exacerbating ferroptosis in cardiac injury. In chemotherapy-resistant osteosarcoma, the STAT3/NRF2/GPX4 axis enhances resistance to ferroptosis, while targeting this pathway could sensitize cancer cells to ferroptosis inducers. The STAT3/HO-1 pathway in liver injury also contributes to ferroptosis by promoting iron dysregulation and oxidative stress. This integration highlights STAT3's pivotal role in modulating ferroptosis through iron metabolism and antioxidant pathways across different diseases

Regulation by STAT3/HO-1

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that regulates the body's response to environmental toxins and influences various biological processes, including immune function, cell growth, and differentiation. AhR is primarily triggered by environmental pollutants like dioxins, as well as endogenous compounds, leading to its movement into the nucleus, where it modulates gene expression. It also plays a critical role in managing iron levels, oxidative stress, and inflammation, making it relevant to health and disease, including ferroptosis. In liver disease, the AhR–STAT3–HO-1/COX-2 signaling pathway helps control ferroptosis, which is driven by iron accumulation and lipid peroxidation. Inhibiting AhR reduces the activation of the STAT3 pathway, which normally promotes the production of HO-1 and cyclooxygenase-2 (COX-2). HO-1 breaks down heme to release free iron, contributing to ferroptosis by increasing the labile iron pool, while COX-2 triggers inflammation and lipid damage. By blocking AhR, these effects are mitigated, leading to reduced ferroptosis in the liver. This creates a more favorable environment for human mesenchymal stem cells (hMSCs), enhancing their survival, accumulation, and therapeutic effectiveness in treating liver injury (Fig. 4) [58].

Iron metabolism regulation pathway by JAK/STAT signaling

Regulation by STAT1/Ferritin Axis

STAT1, a key transcription factor known for promoting the expression of ferritin genes (FTH and FTL), was observed to be dissociated from the promoters of these genes by OGFR during doxorubicin-induced cardiotoxicity (DIC). OGFR, when activated by opioid growth factor (OGF), translocates to the nucleus and binds to the promoter regions of FTH and FTL, competitively inhibiting STAT1 from accessing these sites. This disruption of STAT1's ability to promote ferritin gene transcription results in downregulating ferritin production, a critical protein involved in iron storage. The reduced ferritin levels lead to iron dysregulation, exacerbating

cardiomyocyte ferroptosis, thus intensifying DIC-related cardiac damage. This mechanism highlights the pivotal role of OGFR in repressing ferritin gene expression and promoting ferroptosis during Dox-induced cardiotoxicity (Fig. 4) [59].

Regulation by STAT3/FPN-1 and DMT1 Axis

High hepcidin levels play a crucial role in promoting abnormal iron metabolism and ferroptosis in chronic atrophic gastritis (CAG). Hepcidin, primarily produced by gastric parietal cells, inhibits the iron-exporting protein FPN1, leading to iron accumulation in gastric tissues. This iron overload contributes to oxidative stress through the Fenton reaction, which generates ROS, triggering lipid peroxidation and ultimately causing ferroptosis, a form of cell death dependent on iron. In CAG, hepcidin levels are elevated due to the activation of the IL-6/STAT3 signaling pathway. IL-6, a pro-inflammatory cytokine, binds to its receptor (IL-6R), activating the JAK2/STAT3 pathway, which enhances the transcription of hepcidin. This cascade not only results in iron retention in gastric tissue, promoting ferroptosis, but also impairs iron absorption in the duodenum by downregulating the expression of FPN1 and DMT1. As a result, the IL-6/STAT3-induced upregulation of hepcidin exacerbates iron metabolism disorders in CAG, contributing to tissue damage and disease progression (Fig. 4) [60].

Regulation by STAT3/ NCOA4 Axis

The STAT3/NCOA4/FTH1 pathway plays a critical role in driving ferroptosis in high-fat diet (HFD)-induced cardiac injury by regulating the degradation of ferritin, a key iron-storage protein. In response to HFD, the activation of STAT3 signaling, often triggered by elevated IL-6 levels, leads to the upregulation of NCOA4, a cargo receptor that mediates ferritinophagy, an autophagic process that degrades ferritin. This degradation releases iron into the cytoplasm, causing iron overload, which fuels ROS production through Fenton reactions. The resulting oxidative stress and lipid peroxidation trigger ferroptosis, a form of regulated cell death. FTH1, a subunit of ferritin, normally helps store and sequester iron, but its levels are diminished due to increased ferritinophagy driven by NCOA4. Thus, the STAT3/NCOA4/FTH1 axis promotes iron dysregulation, ROS accumulation, and lipid peroxidation, culminating in ferroptosis and contributing to the progression of cardiac injury under HFD conditions (Fig. 4) [61].

Regulation of lipid metabolism by JAK/STAT signaling pathway

Regulation by STAT1/ACSL Axis

The STAT1-IRF1-ACSL4 pathway plays a pivotal role in triggering ferroptosis in intestinal epithelial cells (IECs) following radiation exposure by upregulating the expression of ACSL4, a key enzyme responsible for driving ferroptosis. Upon radiation exposure, STAT1 becomes activated through phosphorylation. This phosphorylated STAT1 translocates into the nucleus, where it enhances the expression of downstream transcription factors, notably IRF1 (interferon regulatory factor 1). IRF1, in turn, directly binds to the promoter region of the ACSL4 gene, inducing its transcription. ACSL4 is crucial for promoting ferroptosis as it facilitates the esterification of PUFAs, particularly arachidonic acid (AA), into phospholipids, which are subsequently oxidized to form lipid peroxides. These lipid peroxides are toxic and act as key executioners of ferroptosis. In this process, the accumulation of lipid peroxides leads to oxidative damage to the cell membranes of IECs, resulting in cell death. Thus, the radiation-induced activation of the STAT1-IRF1 axis directly upregulates ACSL4, amplifying lipid peroxidation and triggering ferroptosis in IECs, which contributes to the overall pathology of radiation-induced intestinal injury (RIII) [62]. STAT1 has a pivotal function in regulating ACSL1 and promoting ferroptosis, particularly in diabetic nephropathy (DN). STAT1 is activated by hyperglycemic conditions, leading to its translocation from the cytoplasm to the nucleus, where it binds to specific promoter regions of target genes, including ACSL1. A key STAT1 binding site within the ACSL1 promoter region has been identified and confirmed through chromatin immunoprecipitation (ChIP) assays and mutational analysis, which revealed that STAT1 directly enhances ACSL1 transcription. The upregulation of ACSL1 by STAT1 increases the expression of enzymes involved in PUFA metabolism, which are highly susceptible to lipid peroxidation, a hallmark of ferroptosis. By stimulating ACSL1 expression, STAT1 drives the production of phospholipid-PUFAs, amplifying lipid peroxidation and triggering ferroptosis in renal cells. Furthermore, PRMT6 modulates STAT1 activity by methylating STAT1, which reduces its phosphorylation and nuclear translocation, thus attenuating its ability to promote ACSL1 transcription. Therefore, the STAT1-mediated increase in ACSL1 expression significantly contributes to lipid peroxidation and ferroptosis, making STAT1 a critical regulator in the ferroptotic cell death pathway within hyperglycemic environments, such as those found in DN (Fig. 5) [63].

Regulation by STAT3/Lipid Axis

Lipid metabolism plays a crucial role in the pathophysiology of acute kidney injury (AKI), particularly in the regulation of tubular epithelial cells (TECs) during stress conditions. In the study on AKI, it was observed that STAT3 signaling drives the expression of ACSL4. However, in the context of ER-stress-induced AKI, the upregulation of ACSL4 by STAT3 leads to a remodeling

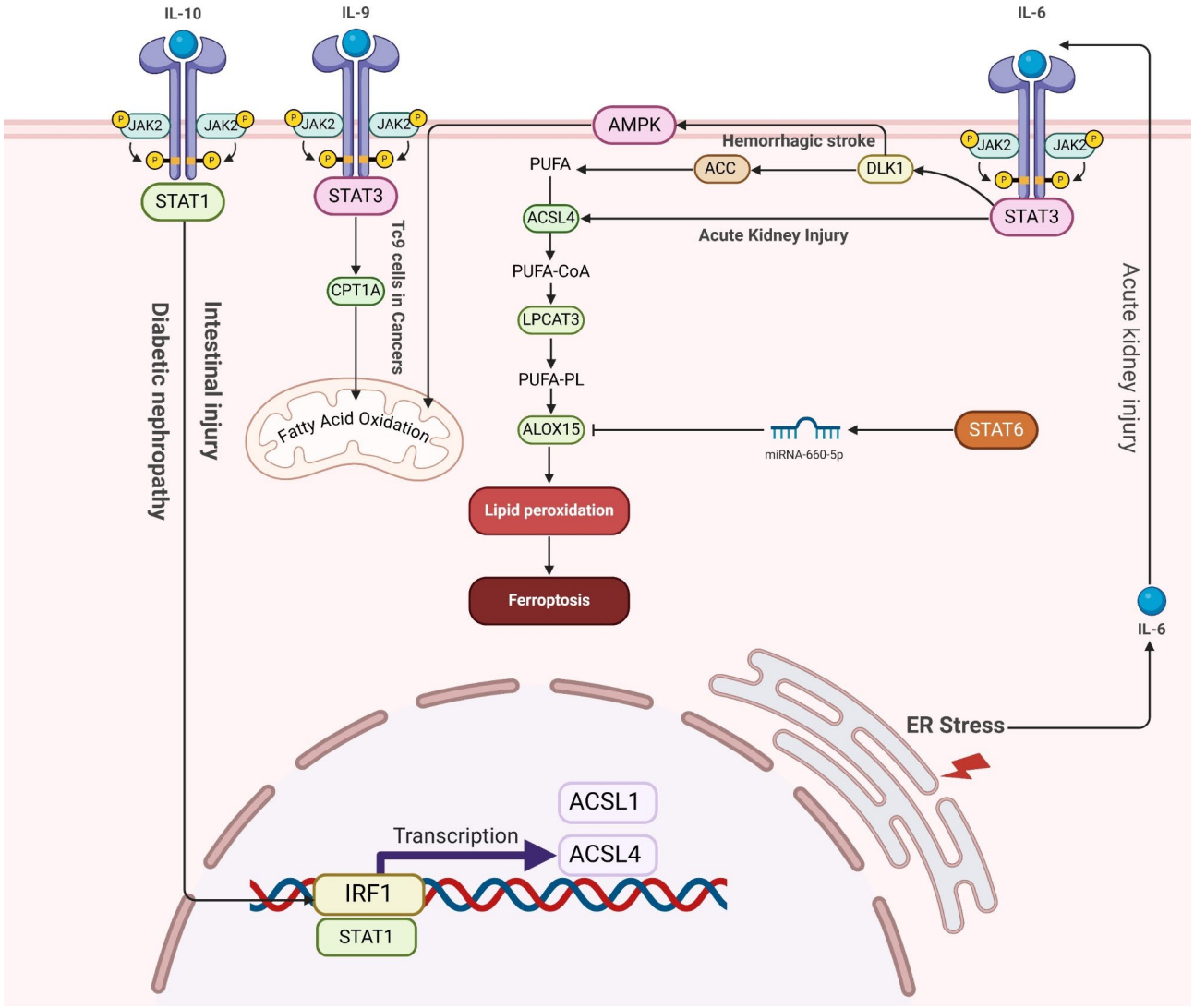

Fig. 5 The interaction of lipid metabolism pathways of ferroptosis with STAT proteins in human diseases. The figure illustrates how STAT proteins (STAT1, STAT3, and STAT6) regulate lipid metabolism and ferroptosis in various diseases. STAT1, activated by IL-10, promotes ferroptosis in diabetic nephropathy and intestinal injury by upregulating ACSL1/ACSL4 and enhancing lipid peroxidation. STAT3, induced by IL-9 and IL-6, modulates fatty acid oxidation and reduces ferroptosis in acute kidney injury and cancers by altering lipid metabolism. STAT6, activated by IL-4/IL-13, suppresses ferroptosis in cervical cancer via TAM-derived miRNA-660-5p, which downregulates ALOX15

of the TEC lipidome that directs PUFAs toward triglyceride (TAG) synthesis instead of phospholipids, reducing the vulnerability of TECs to ferroptosis. This process begins with endoplasmic reticulum (ER) stress, which induces the unfolded protein response (UPR) and drives the secretion of IL-6 family cytokines such as IL-6 and oncostatin M (OSM). These cytokines activate STAT3 signaling in TECs. In vivo, ER stress triggered by tunicamycin significantly increased the expression of ACSL4 in TECs at both the transcript and protein levels, a process largely dependent on STAT3 activation. IL-6 and OSM were shown to induce ACSL4 expression through STAT3, and inhibition of STAT3 signaling using the chemical inhibitor Stattic or STAT3-specific siRNA blunted this ACSL4 upregulation, confirming STAT3's central role in this pathway. Interestingly, despite the robust upregulation of ACSL4, the TECs did not exhibit increased susceptibility to ferroptosis. Lipidomic analysis revealed that ER stress decreased phosphatidylethanolamines (PEs) and phosphatidylcholines (PCs), key lipid species prone to peroxidation. Instead, PUFAs were preferentially stored in TAGs, which are less susceptible to oxidative damage. This shift in lipid metabolism, particularly the suppression of LPCAT3, the enzyme responsible for incorporating PUFAs into PEs, likely prevents ferroptosis. Moreover, mitochondrial functional analysis

indicated that ER-stressed TECs experienced impaired fatty acid oxidation (FAO) and reduced ATP production, contributing to an energetic depression, further supporting the protective shift away from ferroptosis-prone lipid species [64]. The IL-9/STAT3/fatty acid oxidation pathway is crucial in enhancing the longevity and antitumor activity of Tc9 cells, a specialized subset of $CD8^+$ T cells. These cells demonstrate lower levels of lipid peroxidation and greater resistance to ferroptosis compared to other cytotoxic T cells, such as Tc1 cells, which contributes to their enhanced persistence in the TME. This is due to the upregulation of fatty acid oxidation, driven by IL-9 signaling through the STAT3 pathway, which activates the key enzyme carnitine palmitoyltransferase I (CPT1A). By boosting mitochondrial fatty acid oxidation, Tc9 cells maintain lower levels of harmful lipid peroxides and protect themselves from the oxidative stress typically found in tumors. In human cancer, such as melanoma, circulating CD8 + T cells exhibit lower lipid peroxidation and higher IL-9 expression than tumor-infiltrating CD8 + T cells, suggesting that lipid peroxidation contributes to T cell dysfunction in tumors. Targeting this pathway by enhancing fatty acid oxidation or inhibiting ferroptosis could improve the efficacy of T cell-based cancer therapies, such as adoptive cell transfer (ACT). Conversely, blocking IL-9 or STAT3 signaling increases lipid peroxidation and ferroptosis, impairing Tc9 cell persistence and antitumor effects. These findings indicate that regulating lipid metabolism in T cells could be a promising strategy to enhance immunotherapy outcomes [65]. IL-10 alleviates hemin-induced lipid ROS accumulation and ferroptosis in oligodendrocyte progenitor cells (OPCs) by activating the IL-10/STAT3/DLK1/ACC axis, a pathway that regulates lipid metabolism and oxidative stress. Upon binding to its receptor (IL-10R) on OPCs, IL-10 initiates the phosphorylation and activation of STAT3, which then translocates to the nucleus. This activated STAT3 induces the transcription of DLK1 (Delta-like 1 homolog), a key regulator in this pathway. DLK1 plays a crucial role in inhibiting the activity of acetyl-CoA carboxylase (ACC), an enzyme involved in fatty acid synthesis. By inhibiting ACC, DLK1 reduces the synthesis of PUFAs that are prone to peroxidation, thus limiting lipid ROS production. Moreover, DLK1 indirectly activates AMPK (AMP-activated protein kinase), which further inhibits ACC through phosphorylation, reducing the availability of substrates for lipid peroxidation. This suppression of ACC activity prevents excessive lipid peroxidation and ferroptosis, which is primarily driven by the oxidation of PUFA-containing phospholipids. The result is a significant reduction in lipid ROS accumulation in OPCs exposed to hemin, a compound that mimics the toxic effects of hemorrhagic stroke. Through this mechanism, IL-10 effectively protects OPCs from ferroptotic cell death, preserving white matter integrity and promoting recovery after intracerebral hemorrhage (ICH) (Fig. 5) [66, 67].

Regulation by STAT6/ALOX15 Axis

The STAT6 pathway plays a key role in suppressing ferroptosis in cervical cancer by regulating tumor-associated macrophages (TAM)-derived exosomal delivery of miRNA-660-5p. Activation of STAT6 by IL-4 and IL-13 upregulates miRNA-660-5p in TAMs, which is then packaged into exosomes and transferred to cervical cancer cells. Once inside the cancer cells, miRNA-660-5p downregulates ALOX15, a crucial enzyme for ferroptosis, thereby reducing lipid ROS production and inhibiting cell death. This suppression of ferroptosis by TAMs was reversed when exosomes were removed or miRNA-660-5p was inhibited, restoring cancer cell sensitivity to ferroptosis inducers like erastin. In mouse models, combining erastin with miRNA-660-5p inhibitors enhanced antitumor effects. Clinically, high ALOX15 expression was linked to better prognosis and survival in cervical cancer patients, while low ALOX15 levels were associated with increased macrophage infiltration. These findings suggest that targeting the STAT6 pathway, TAMs, or miRNA-660-5p in combination with ferroptosis inducers could be an effective treatment strategy for cervical cancer, with ALOX15 serving as a potential prognostic marker (Fig. 5) [68].

STAT3/Other Ferroptosis regulators

Numerous studies have explored the involvement of STAT3 in regulating ferroptosis-related proteins and genes, though they frequently do not identify the precise genes targeted by STAT3. Therefore, this section offers a disease-specific overview to elucidate STAT3's role in ferroptosis regulation across pathological conditions, including those previously mentioned. Table 1 highlights the significant role of various STAT pathways, particularly STAT3 and STAT1, in regulating ferroptosis across multiple diseases, including cancers, autoimmune disorders, diabetes, cardiovascular, and neurological conditions. In many cancers, such as breast, head and neck, lung, and osteosarcoma, the STAT3 pathway promotes resistance to ferroptosis, thus aiding tumor progression, while inhibiting STAT3 can increase sensitivity to ferroptosis and enhance treatment efficacy. Similarly, in autoimmune diseases like Sjogren's syndrome and asthma, the JAK/STAT pathways regulate ferroptosis, contributing to disease pathology. In diabetic and cardiovascular conditions, STAT pathways modulate ferroptosis and related oxidative stress, offering potential therapeutic targets to alleviate complications. Across neurological diseases and infections, STAT signaling influences ferroptosis,

Table 1 The role of various STAT proteins, particularly STAT3 and STAT1, in regulating ferroptosis across multiple diseases

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Cancers						
Breast Cancer	MDA-MB-231, T47D	In vitro (erastin-induced ferroptosis), In vivo (nude mice)	GPX4, SLC7A11, ROS, Iron, Fe2+	miR-106a-5p/STAT3	- CircRHOT1 promotes proliferation, migration, invasion, and inhibits apoptosis and ferroptosis in breast cancer. - CircRHOT1 inhibits ferroptosis by sponging miR-106a-5p, which targets STAT3. - STAT3 overexpression and miR-106a-5p inhibition reverse circRHOT1 knockdown effects. - CircRHOT1 knockdown increases ROS, iron, and Fe2 + levels and reduces GPX4 and SLC7A11 expression. - CircRHOT1 promotes tumor growth in vivo in nude mice.	[69]
HNSCC	HN4, CAL27	In vivo (xenografts), In vitro (si-SLC7A11-transfected cells, erastin treatment)	SLC7A11 (xCT), 4-HNE, GSH/GSSG, ROS, Ferrous ion	IL-6/JAK2/STAT3 pathway	- IL-6 transcriptionally activates xCT expression via the JAK2/STAT3 pathway, inducing ferroptosis resistance and promoting tumor progression in HNSCC. - Knockdown of xCT or inhibition by ferroptosis inducer (erastin) promotes lipid peroxidation and ferroptosis, reducing tumor growth. - IL-6 reverses ferroptosis and tumor suppression induced by xCT knockdown. - IL-6/xCT axis is identified as a novel mechanism driving HNSCC progression, making it a potential therapeutic target for early intervention in HNSCC carcinogenesis.	[38]
Laryngeal squamous cell carcinoma (LSCC)	Tsc1−/−, Tsc2−/− MEFs, LIU-LSC-1, TU177	In vivo (xenografts, PDX, CAM) / In vitro	ERO1α, SLC7A11, GPX4	IL-6/STAT3	ERO1α promotes ferroptosis resistance and tumor growth via IL-6/STAT3/SLC7A11 pathway. ERO1α inhibition sensitizes tumors to ferroptosis inducers like IKE, showing synergistic effects.	[39]
NSCLC	H322, H1299, H520, H460	In vivo (xenografts) / In vitro	SLC7A11, MCL1, GPX4	STAT3/MCL1	Sorafenib induces ferroptosis in sensitive NSCLC cell lines by downregulating STAT3/MCL1, promoting BECN1/SLC7A11 binding. MCL1 knockdown sensitizes resistant cells to sorafenib-induced ferroptosis.	[40]
HCC	Huh7, Hep3B, HepG2	In vivo (xenografts) / In vitro	SLC7A11, MCL1, BECN1, GPX4	SHP-1/STAT3	Sorafenib induces ferroptosis via SHP-1/STAT3-mediated downregulation of MCL1, leading to BECN1 binding to SLC7A11, inhibiting system Xc−, reducing GSH, increasing lipid ROS, and triggering ferroptosis.	[41]
Osteosarcoma	MNNG/HOS, U2OS, hFOB1.19	In vivo (xenografts) / In vitro	SLC7A11, MAT2A, GSH	STAT3/SLC7A11	miR-26b-5p/MAT2A axis triggers ferroptosis by inhibiting STAT3 and SLC7A11, increasing intracellular Fe^{2+} levels, reducing GSH, and inhibiting osteosarcoma progression. MAT2A promotes osteosarcoma growth.	[42]
Osteosarcoma	MG63, Saos-2, MG63/DDP, Saos-2/DDP	In Vitro	GPx4, Nrf2, STAT3, ROS, MDA	STAT3/Nrf2/GPx4	Cisplatin-resistant osteosarcoma cells (MG63/DDP, Saos-2/DDP) showed lower levels of ROS, lipid peroxides, and MDA, and higher levels of GPx4. Inhibition of STAT3 with BP-1-102 or co-treatment with ferroptosis agonists (Erastin, RSL3) increased ferroptosis and sensitized resistant cells to cisplatin.	[57]
Osteosarcoma	MG-63, U2OS, hFOB1.19	In vivo (mice), In vitro (MG-63 and U2OS cells)	FTH1, GPX4, COX2, MDA, SOD, CAT	JAK2/STAT3	- FANCD2 is up-regulated in osteosarcoma cells and promotes cell viability, migration, invasion, and tumor growth. - Silencing FANCD2 induces ferroptosis and reduces osteosarcoma progression. - FANCD2 knockdown affects ferroptosis-related markers (iron levels, LIP, Fe2+, MDA, GPX4, FTH1). - FANCD2 regulates ferroptosis via the JAK2/STAT3 pathway, and activation of STAT3 (via colivelin) reverses FANCD2's effects on ferroptosis. - Colivelin reverses FANCD2 knockdown-induced ferroptosis, supporting the role of FANCD2 in osteosarcoma regulation through the JAK2/STAT3 pathway.	[70]

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Osteosarcoma	MG63 (OS cells)	In vitro	GPX4, GSH, MDA	STAT3, p-STAT3	PVT1 inhibits ferroptosis by activating the STAT3/GPX4 axis, promoting osteosarcoma cell proliferation, migration, and invasion.	[54]
Clear-cell Renal Cell Carcinoma (ccRCC)	786-O, 786-O-R, A498, HK-2	In vivo (xenografts), In vitro (Sunitinib-resistant 786-O-R cell lines)	SLC7A11, 4-HNE, Ferrous ion, MDA, GPX4	IL6/JAK2/STAT3 pathway	- IL6-induced ferroptosis inhibition via the JAK2/STAT3/SLC7A11 pathway contributes to resistance against TKI (Sunitinib) in ccRCC. - SLC7A11 knockdown promotes ferroptosis, increasing lipid peroxidation and reducing tumor growth. - IL6 reverses the ferroptosis and growth inhibition caused by SLC7A11 knockdown. - Ferroptosis inducer Erastin reverses IL6-mediated ferroptosis inhibition and improves response to TKI therapy. - Tumor-infiltrating macrophages, especially TAMs, play a role in IL6 signaling.	[37]
Renal cancer	786-O, A498	In vitro (cell culture)	GPX4, AMPK, P53, JAK2, STAT3	JAK2/STAT3, P53	Energy stress (glucose deprivation) promotes GPX4-dependent ferroptosis via AMPK activation and JAK2/STAT3 axis.	[48]
PCa	C4-2, DU-145, RWPE-1	In vivo (xenograft) / In vitro	GPX4, SLC7A11, ARPC1A	STAT3/ARPC1A	ARPC1A, regulated by STAT3, inhibits ferroptosis and promotes PCa progression. Knockdown of ARPC1A reduces cell viability, invasion, and induces ferroptosis by decreasing GPX4/SLC7A11.	[43]
Bladder Cancer (BC)	T24, UMUC3, 5637, J82, SV-HUC-1	In vivo (mouse model), In vitro (BC cell lines)	COX2, ACSL4, NOX1, SLC7A11, GPX4, GSH, MDA, 4-HNE, ROS	STAT3/IGF2BP1 (LUCAT1-IGF2BP1-STAT3 axis)	- LUCAT1 is highly expressed in BC and localized in the cytoplasm. - LUCAT1 promotes BC cell proliferation, migration, invasion, and inhibits ferroptosis. - LUCAT1 interacts with IGF2BP1 and stabilizes STAT3 mRNA. - Overexpression of LUCAT1 reduces ferroptosis-related markers and increases tumor growth. - Silencing STAT3 reverses LUCAT1's effects on ferroptosis suppression and tumor progression. - The LUCAT1-IGF2BP1-STAT3 axis regulates ferroptosis inhibition, making it a potential therapeutic target for BC.	[71]
Cervical Cancer	HeLa, SiHa, THP-1	In vivo (mouse xenograft) & In vitro	ALOX15, GPX4, FSP1, ACSL4	STAT6 (IL4/IL13-activated pathway)	Tumor-associated macrophages (TAMs) suppress ferroptosis in cervical cancer by exosomal delivery of miRNA-660-5p, which downregulates ALOX15 expression. STAT6 activation in TAMs induces miRNA-660-5p, and targeting TAMs may enhance ferroptosis therapy. ALOX15 is a prognostic marker.	[68]
Cervical Squamous Cell Carcinoma (CESC)	SiHa, C33A, Caski, SiHa-R	In vitro	ACSL4, GPX4, SLC7A11, FTL	JAK2/STAT3	CDKN2A inhibits cisplatin-induced ferroptosis by activating the JAK2/STAT3 pathway. Cisplatin treatment inhibited cell proliferation and induced ferroptosis in CESC. CDKN2A knockdown suppresses cell proliferation and induces ferroptosis in cisplatin-resistant cells. WP1066, a JAK2/STAT3 inhibitor, promotes ferroptosis in cisplatin-resistant cells. Erastin-induced ferroptosis is also inhibited by CDKN2A overexpression.	[72]

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Gastric Cancer	MGC803, AGS, HGC27	MGC803/5-FU resistant cells, xenografts, gastric cancer PDX, organoids model	GPX4, SLC7A11, FTH1, MDA, Lipid ROS, Fe2+, GSH	STAT3/IL6-JAK-STAT3 Pathway	- Inhibition of STAT3 triggers ferroptosis by reducing GPX4, SLC7A11, and FTH1 expression. - STAT3 acts as a key negative regulator of ferroptosis through multi-pronged mechanisms including lipid peroxidation and iron metabolism. - STAT3 inhibitor W1131 shows strong anti-tumor effects by inducing ferroptosis, downregulating GPX4, SLC7A11, and FTH1, and increasing lipid ROS and Fe2 + accumulation. - STAT3 inhibition re-sensitizes 5-FU resistant cells to chemotherapy by promoting ferroptosis. - Combination of W1131 and 5-FU significantly enhances ferroptosis and tumor growth suppression in chemotherapy-resistant models.	[73]
Colorectal Cancer (CRC)	HCT116, Caco2, LoVo, SW480 (CRC cell lines)	In vitro	GPX4, FTH1, ACSL4, GSH, ROS, MDA, Iron levels	AKT/STAT3 signaling	- ENO1 is highly expressed in CRC cells. - Knockdown of ENO1 decreases glycolysis by lowering glucose consumption, lactate production, and glycolysis-related proteins (GLUT1, HK2, PKM2). - ENO1 silencing potentiates ferroptosis by increasing iron levels, ROS, MDA, and ACSL4 while reducing GPX4, FTH1, and GSH. - ENO1 deficiency inhibits the AKT/STAT3 pathway, which mediates the observed effects on glycolysis, proliferation, and ferroptosis.	[74]
Autoimmune diseases						
Sjogren's syndrome (SS)	Salivary gland epithelial cells (SGEC)	In vivo (ICR, NOD mice), In vitro	GPX4, SLC3A2, AQP5, GSH, Fe^{2+}, MDA	JAK/STAT1	IFN-γ induces SGEC ferroptosis via JAK/STAT1-mediated inhibition of system Xc^-, downregulating GPX4 and SLC3A2. Ferroptosis inhibition alleviates SS symptoms, while induction worsens them.	[34]
Th2-high asthma	BEAS-2B, NCI-H292	In vitro (cell culture), in vivo (OVA-induced mice)	SOCS1, SLC7A11, GPX4, NRF2	STAT6	IL-13 induces ferroptosis in airway epithelial cells via SOCS1-mediated degradation of SLC7A11, involving STAT6. SOCS1 promotes ferroptosis through ubiquitination of SLC7A11, exacerbating airway hyperresponsiveness in asthma.	[47]
Ulcerative Colitis	IEC-6 (rat intestinal epithelial cells)	In vitro (H_2O_2-induced ferroptosis), In vivo (DSS-induced colitis in mice, S. Typhimurium colitis)	GPX4, SLC7A11, PTGS2, MDA, 4HNE	STAT3 / Phosphorylation	- Ferroptosis is increased in DSS-induced and S. Typhimurium-induced colitis. - STAT3 is identified as a hub gene and plays a key role in regulating ferroptosis in UC. - Inhibition of STAT3 phosphorylation increases ferroptosis in IEC-6 cells. - Ferroptosis-related markers (GPX4 and SLC7A11) are reduced in colitis, while lipid peroxidation markers (MDA, PTGS2) are increased. - STAT3 could serve as a biomarker for diagnosis and treatment of ulcerative colitis.	[75]
Diabetes						
Insulin Resistance (Hepatic)	HepG2	In vivo (Iron dextran mice), In vitro (FAC-treated HepG2 cells)	GPX4, SLC7A11, PTGS2, MDA, GSH, Ferritin	JAK2/STAT3/SLC7A11	Iron overload induces ferroptosis and insulin resistance by inhibiting JAK2/STAT3/SLC7A11 pathway. Deferasirox ameliorates insulin resistance and ferroptosis by up-regulating JAK2/STAT3/SLC7A11, increasing GPX4 and SLC7A11 levels, and reducing PTGS2 and MDA. Mitochondrial damage is alleviated.	[36]

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Diabetic nephropathy (DN)	HGECs (human glomerular endothelial cells), HK-2 (human kidney epithelial cells)	In Vivo (wild-type and PRMT6-knockout mice), In Vitro (HGECs, HK-2 cells)	ACSL1, MDA, C11-BODIPY	PRMT6/STAT1/ACSL1 axis	PRMT6 downregulation in DN promotes ferroptosis via the STAT1/ACSL1 axis. PRMT6 regulates STAT1 methylation and ACSL1 transcription. STAT1 inhibitor fludarabine reduced ferroptosis and DN progression.	[63]
Diabetic Retinopathy (DR)	ARPE-19 (Human Retinal Pigment Epithelial Cells)	In Vitro: High Glucose-induced ARPE-19 cells In Vivo: STZ-induced diabetic C57BL/6 mice	GPX4, FTH1, xCT, HO-1, MDA, Fe^{2+}	STAT3/STAT3 Phosphorylation	- Sestrin2 inhibits ferroptosis by enhancing autophagy and inhibiting ER stress and STAT3 phosphorylation. - Overexpression of Sestrin2 promotes cell viability, reduces apoptosis, ROS, MDA, and Fe^{2+} levels, and upregulates autophagy-related proteins. - In vivo, Sestrin2 reduced blood glucose, glycated hemoglobin, and retinal damage in diabetic mice. Treatment with the ferroptosis activator (erastin) or autophagy inhibitor (3-MA) reversed Sestrin2's protective effects.	[76]
Diabetic Cardiomyopathy (DCM)	HL1 Cardiomyocytes	High-Fat Diet (HFD)/ Streptozotocin (STZ)-Induced Diabetic Mice	GPX4, PTGS2, GSH, MDA, LPO	STAT3/STAT3-Pgc1a Pathway	STAT3 phosphorylation promotes ferroptosis, while its inhibition alleviates ferroptosis and mitochondrial dysfunction. STAT3 activation increases oxidative stress and ferroptosis, while inhibition reduces lipid peroxidation and mitochondrial damage. - STAT3 directly suppresses Pgc1a expression, which controls mitochondrial biogenesis and function.	[77]
Infectious diseases						
Sepsis-induced cardiomyopathy (SIC)	Primary cardiomyocytes	In vivo (mouse), in vitro (cell culture)	GPX4, SOCS1, SLC7A11, COX2, NRF2	JAK2/STAT3, ALK5-SMAD2/3	GDF15 protects against SIC by inhibiting SOCS1, activating JAK2/STAT3, promoting GPX4 transcription, and reducing ferroptosis through ALK5-SMAD2/3 pathway activation.	[49]
Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)	BEAS-2B (human bronchial epithelial cells), THP-1 (monocyte cells)	In vitro (LPS-induced model in BEAS-2B and THP-1 cells)	ACSL4, GPX4, SLC7A11, ROS, Iron, Lipid peroxides	STAT3 phosphorylation (p-STAT3) signaling	- STAT3 was identified as a key diagnostic marker for sepsis-induced ARDS using WGCNA and machine learning. - LPS treatment elevated p-STAT3 levels, promoting ferroptosis in BEAS-2B and THP-1 cells. - Stattic (STAT3 inhibitor) reduced LPS-induced ferroptosis by decreasing p-STAT3 and ACSL4 levels while restoring GPX4 and SLC7A11 expression. - STAT3 correlates with immune cell infiltration, particularly monocytes and neutrophils, in sepsis-induced ARDS.	[78]
HBV-associated Glomerulonephritis (HBV-GN)	Human renal podocyte cells (HPCs)	In vivo: HBx transgenic mice In vitro: HPCs	GPX4, SLC7A11, ACSL4, ROS, MDA, Fe2+	STAT3 phosphorylation (p-STAT3)/ HDAC2/STAT3 Pathway	- HBx induces ferroptosis in podocytes by increasing ROS, MDA, Fe2+, ACSL4 while decreasing GPX4 and SLC7A11. - HDAC2 promotes STAT3 phosphorylation, enhancing ferroptosis. - Inhibition of STAT3 phosphorylation reverses HBx-induced podocyte ferroptosis. - miR-223-3p in BMSC-Exo directly targets HDAC2, reducing STAT3 phosphorylation, which in turn attenuates ferroptosis and podocyte injury caused by HBx.	[79]
Cardiovascular diseases						

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Hypertension-mediated cardiac remodeling	CMVECs (Cardiac Microvascular Endothelial Cells)	In vivo (hypertensive mice), in vitro (CMVECs)	GPX4, xCT, Nrf2, IL-6	IL-6/STAT3	Elabela prevents cardiac ferroptosis, myocardial remodeling, fibrosis, and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 pathway, activating xCT/GPX4 signaling.	[50]
Hypoxic Pulmonary Hypertension (HPH)	Human pulmonary arterial smooth muscle cells (hPASMCs)	In vivo (rat model) / In vitro (hPASMCs)	PTGS2, LC3B-II, OPN, α-SMA, ROS, LPO	STAT3 Pathway / HIF-2α	- MIR210HG is highly expressed in HPH and promotes the transition of PASMCs from a contractile to synthetic phenotype via autophagy-dependent ferroptosis. - Knockdown of MIR210HG decreases autophagy markers (Beclin-1, LC3-II) and ferroptosis markers (PTGS2), increasing α-SMA levels and reducing synthetic marker OPN, ROS, and LPO levels. - Ferroptosis activator (Erastin) enhances the synthetic phenotype, while ferroptosis inhibitor (Ferrostain-1) reverses hypoxia-induced ferroptosis. - STAT3 regulates the transcription of MIR210HG, and its overexpression activates autophagy and ferroptosis. - MIR210HG promotes ferroptosis by binding to HIF-2α, increasing its stability and activating autophagy.	[80]
Heart Failure (HF)	H9c2 cells (rat cardiomyocytes)	In vitro (DOX-induced H9c2 cells), In vivo (DOX-induced HF model in Wistar rats)	PTGS2, MDA, SLC7A11, GPX4, FTH1	JAK2/STAT1	- PRDX6 alleviated heart failure by inhibiting ferroptosis. - DOX treatment increased ferroptosis markers (PTGS2, MDA) and decreased GPX4, SLC7A11, FTH1. - PRDX6 overexpression reversed these effects, inhibiting JAK2/STAT1 phosphorylation and suppressing ferroptosis. - RO8191 (JAK2 agonist) and erastin (ferroptosis inducer) reversed PRDX6 effects, proving the involvement of the JAK2/STAT1 pathway.	[81]
Eye diseases						
Blue light-induced conjunctival injury, Dry eye syndrome	Human Conjunctival Epithelial Cells (HCECs)	In vivo (C57BL/6 mice), In vitro (HCECs)	GPX4, SLC7A11, FTH1	STAT3 (Phosphorylated)	Blue light exposure reduced phosphorylation of STAT3, downregulating GPX4, SLC7A11, and FTH1, causing an accumulation of Fe2+, ROS, and lipid peroxidation, which ultimately triggered ferroptosis in conjunctival epithelial cells.	[51]
Age-related macular degeneration	ARPE-19 (Retinal Pigment Epithelial Cells)	In vivo (NaIO3-treated mice), In vitro	SLC7A11, GPX4, SLC40A1, GSH, Fe^{2+}, MDA, 4-HNE	JAK1/2, STAT1	IFN-γ induces ferroptosis via JAK1-2/STAT1/SLC7A11 pathway, increasing intracellular Fe^{2+} and depleting GSH. Ferroptosis inhibitors (Fer-1, DFO) reverse RPE cell death and protect against NaIO3-induced damage.	[35]
Neurological diseases						
SCI	VSC 4.1 neurons, BV2 microglia, HEK 293T cells, bEnd.3 cells, SD rats	In vivo (rats), In vitro	Syvn1, Gpx4	Stat3	Syvn1 inhibits neuronal ferroptosis via the Stat3/Gpx4 axis, leading to improved neuronal survival and functional recovery post-SCI by stabilizing Stat3 through K63-linked ubiquitination.	[52]
Epilepsy	N2a neuronal cells, BV2 microglial cells, C57BL/6 mice, Human specimens	In vivo (mice), In vitro, Human	GPX4, SLC7A11, DPP4	STAT3, CXCL10/CXCR3 axis	A1 astrocytes induce neuronal ferroptosis through the CXCL10/CXCR3 axis, activating STAT3 and suppressing SLC7A11, exacerbating ferroptosis in neurons and epilepsy.	[45]

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
ICH	Primary OPCs	In vivo (mouse), in vitro	DLK1, ACC, p-ACC, p-STAT3, AMPK	STAT3 (via IL-10R)	IL-10 protects OPCs from ferroptosis by reducing lipid ROS via the IL-10/STAT3/DLK1/ACC axis. IL-10 deficiency increases OPC death, white matter injury, and cognitive deficits post-ICH.	[66]
Hypoxic-Ischemic Brain Damage (HIBD)	HT22 (mouse hippocampal neuronal cells)	In vitro (glutamate-induced HIBD)	LCN2, ACSL4, 4-HNE, SLC7A11, GPX4, FTH1, Mitofusin2, VDAC, TOM20	STAT3 / NF-κB	- LCN2 identified as key ferroptosis-related gene. - LCN2 silencing inhibits ferroptosis in HT22 cells. - Glutamate stimulation causes mitochondrial dysfunction. - NF-κB/STAT3 pathway is activated during ferroptosis and LCN2 knockdown inhibits this activation. - LCN2 regulates ferroptosis via the NF-κB/STAT3 axis and induces mitochondrial damage in HIBD.	[82]
Organ injury						
Acute Lung Injury (ALI) due to Ischemia-Reperfusion (IIR-ALI)	MLE12 (mouse lung epithelial cells)	In vivo (C57BL/6 mice, Nrf2-/- mice), In vitro (oxygen-glucose deprivation and reoxygenation (OGD/R) model in MLE12 cells)	Nrf2, SLC7A11, GPX4, MDA, GSH	STAT3, pSTAT3	Nrf2 and STAT3 co-regulate ferroptosis via SLC7A11. Ferroptosis is confirmed in IIR-ALI and OGD/R-induced damage. Fer-1 inhibits ferroptosis and improves ALI. STAT3 activation alleviates ferroptosis, while its inhibition worsens it.	[83]
Acute Lung Injury (ALI)	BEAS2B (Human lung epithelial cells)	In vivo (mice) / In vitro (BEAS2B cells)	PTGS2 (positive marker), SLC7A11, GPX4, FTH (negative markers), MDA (lipid peroxidation), Total Iron	STAT3 / STAT3 Pathway	- LPS increases STING expression, activating ferroptosis in ALI. - STING knockout or inhibition reduces inflammation and ferroptosis markers in lung tissue and epithelial cells. - Ferroptosis inhibitor (ferrostatin-1) alleviates lung inflammation and injury. - STAT3 negatively regulates ferroptosis, and STING suppresses STAT3 activation. - STING knockout upregulates p-STAT3 levels, reducing ferroptosis. - STAT3 inhibitor exacerbates ferroptosis after STING knockout. - The ferroptosis inducer erastin reverses the protective effects of STING knockout on lung injury.	[84]
Liver injury	AML12 (murine hepatocytes), hMSC	In Vivo (mice with iron overload and hepatic I/R injury)	GPx4, HO-1, COX-2, MDA, ROS, Tfrc	STAT3 (AhR–STAT3–HO-1/COX-2)	Ferroptosis decreased the survival of hMSCs in mouse liver. AhR inhibition via CH223191 decreased ferroptosis by downregulating iron, MDA, ROS, and inflammatory markers, enhancing hMSC survival and efficacy in liver injury models. AhR inhibition was more effective than the ferroptosis inhibitor DFO. AhR–STAT3 pathway played a critical role.	[58]
Radiation-induced intestinal injury (RIII)	FHs74Int (human intestinal epithelial cells), mouse intestinal organoids	In Vivo (mice), In Vitro (IECs, organoids)	ACSL4, GPX4, MDA, 4-HNE	STAT1–IRF1–ACSL4 pathway	Ferroptosis was implicated in RIII. IR increased ACSL4 expression, promoting ferroptosis. STAT1–IRF1 axis regulated ACSL4 transcription. Ferrostatin-1 (ferroptosis inhibitor) alleviated RIII. AA enhanced ferroptosis in IECs. AMPK activation negatively regulated ferroptosis.	[62]

Table 1 (continued)

Type of Disease	Cell lines	Model (in vivo/ In vitro)	Ferroptosis-Related Proteins	Type of STAT Protein/Pathway	Highlights	Ref.
Acute kidney injury (AKI)	HK-2 (human kidney epithelial cells)	In Vivo (mouse model with ER stress-induced AKI), In Vitro (HK-2 cells)	ACSL4, TAG, LPCAT3, PE, PUFA	STAT3, IL-6/STAT3 signaling	ACSL4 is upregulated by STAT3 in AKI via IL-6 signaling. ACSL4 is involved in lipid remodeling but does not sensitize cells to ferroptosis in this context. STAT3 inhibition blocks ACSL4 upregulation.	[64]
Other diseases						
Osteoporosis	RAW264.7	In vivo (Ovariectomized mice), In vitro (RAW264.7 cells)	GPX4, FTH1, MDA, Bax	STAT3 Activation	- Knockdown of IRF9 in osteoclasts promoted differentiation and decreased ferroptosis. - IRF9 knockdown led to STAT3 activation, which inhibited ferroptosis. - STAT3 inhibition reduced osteoclast activity. - Ferroptosis agonist erastin suppressed osteoclast differentiation, while IRF9 knockdown mitigated this suppression.	[85]
Preeclampsia	HTR8/sVneo (trophoblast cells), placental tissue	In vitro, In vivo	Nox2, GPX4, ROS, lipid peroxides, MDA	STAT3, p-STAT3	Nox2 promotes trophoblast ferroptosis via the STAT3/GPX4 pathway, reducing proliferation, invasion, and angiogenesis. Nox2 knockdown mitigates these effects.	[55]
Periodontitis	Primary mouse mandibular osteoblasts, in vivo (C57BL/6 mice)	In vitro, In vivo	NRF2, GPX4, SLC7A11, ROS, MDA	p-STAT3	IL-17 alleviates erastin-induced ferroptosis, promotes osteogenic differentiation via NRF2/p-STAT3 interaction. NRF2-pSTAT3 complex suppresses ferroptosis.	[56]

impacting recovery and tissue damage, making it a critical mechanism for therapeutic intervention.

Ferroptosis also regulates the JAK/STAT signaling pathway

Ferroptosis regulates the STAT pathway through the activation of specific signaling cascades, particularly the p38 MAPK (mitogen-activated protein kinase) pathway, which is a crucial regulator of oxidative stress [86]. In a recent study, ferroptosis in endometrial stromal cells (ESCs) was found to activate p38 MAPK, which subsequently led to the phosphorylation and activation of STAT6. This activation was critical for upregulating the expression of pro-angiogenic and inflammatory cytokines such as VEGFA (vascular endothelial growth factor A) and IL8 (interleukin 8). The study identified STAT6 as a key mediator, where its direct binding to promoter regions of VEGFA and IL8 was demonstrated using luciferase reporter assays. Knockdown experiments using STAT6 siRNA further confirmed its role, as silencing STAT6 significantly reduced the ferroptosis-induced expression of these cytokines. This suggests that ferroptosis triggers the p38 MAPK/STAT6 pathway, which in turn drives the production of cytokines that promote angiogenesis and inflammation, playing a crucial role in the progression of endometriotic lesions [87]. The activation of STAT3 is intricately dependent on ferroptosis induced by SSPH I in HepG2 cells. SSPH I, a steroidal saponin, was identified as a potent ferroptosis inducer, driving iron overload and oxidative stress through ROS and lipid peroxidation. This ferroptosis, characterized by these cellular stressors, was found to trigger the phosphorylation (activation) of STAT3, a critical transcription factor involved in cell survival and proliferation. Notably, when ferroptosis was inhibited using Fer-1, a well-known ferroptosis inhibitor, the phosphorylation of STAT3 was significantly reduced, indicating that the activation of STAT3 was contingent upon the ongoing ferroptotic process. This finding suggests that STAT3 activation occurs downstream of ferroptosis and is likely a cellular response to the oxidative and metabolic disruptions caused by SSPH I. Further experiments support this by showing that blocking ferroptosis not only prevented STAT3 activation but also curtailed the subsequent downstream signaling events associated with STAT3, including its influence on other ferroptosis-related proteins such as SLC7A11. Thus, ferroptosis serves as a key regulator of STAT3 activation in this context, positioning STAT3 as part of a feedback mechanism that cancer cells might use to mitigate ferroptotic damage and survive, highlighting its potential as a target to enhance the therapeutic effects of ferroptosis inducers like SSPH I in HCC cells [88]. DNMT1 is known for its role in DNA methylation, which controls gene expression. In cancer cells, DNMT1 is often overexpressed, leading to aberrant methylation patterns that silence tumor suppressor genes and promote cancer progression. DNMT1 has been shown to regulate the expression of IGFBP2, a protein involved in tumor growth and survival, which also plays a critical role in activating the EGFR/STAT3 signaling pathway. By promoting the EGFR/STAT3 axis, IGFBP2 enhances the expression of PD-L1, allowing cancer cells to evade immune detection.Ferroptosis, through the oxidative stress it induces, can inhibit DNMT1 expression, thereby downregulating IGFBP2. This downregulation weakens the activation of the EGFR/STAT3 pathway and consequently reduces PD-L1 expression. As a result, cancer cells become less capable of suppressing T cell activity, enhancing the immune system's ability to target and destroy tumor cells. Therefore, ferroptosis not only disrupts STAT3 and PD-L1 directly through oxidative mechanisms but also indirectly by inhibiting DNMT1 and IGFBP2, both of which are key to sustaining STAT3/PD-L1 signaling in cancer cells. This multi-level regulation is critical for suppressing tumor growth and improving immune response in the TME [89].

Immunologic significance of STAT/Ferroptosis Axis

Regulation of tumor-associated macrophages

Erastin, a known ferroptosis-inducing agent, paradoxically enhances the metastatic potential of ferroptosis-resistant ovarian cancer (OC) cells by modulating the tumor microenvironment. The researchers discovered that erastin significantly promotes the polarization of tumor-associated macrophages (TAMs) towards the M2 phenotype, which is typically associated with tumor-promoting activities, including cancer cell invasion, migration, and metastasis. This M2 polarization is driven through the activation of the STAT3 signaling pathway. Once polarized, the erastin-stimulated macrophages secrete elevated levels of interleukin-8 (IL-8), a key cytokine that further enhances epithelial-mesenchymal transition (EMT) in OC cells, promoting their invasive and migratory capacities. The study showed both in-vitro and in-vivo evidence that conditioned media from erastin-treated macrophages increased metastasis in ferroptosis-resistant OC cell lines, such as SKOV3 and HO8910, without significantly affecting their proliferation. Importantly, the researchers found that blocking IL-8 with reparixin, an inhibitor of its receptors CXCR1/2, effectively reversed the metastatic enhancement induced by erastin-stimulated macrophages, suggesting that the STAT3/IL-8 axis plays a critical role in this process. In mouse models, erastin-treated OC cells exhibited significantly more metastatic spread within the peritoneal cavity, further reinforcing the pro-metastatic effects of erastin in the presence of macrophages. Overall, this study highlights a previously unrecognized side effect of

erastin in the context of ferroptosis-resistant OC cells, where it enhances their metastatic potential through M2 macrophage polarization and IL-8 secretion, implicating the STAT3/IL-8 pathway as a potential therapeutic target to counteract these effects and improve the efficacy of anti-cancer therapies [90].

Autophagy-dependent ferroptosis drives TAM polarization through the release and uptake of oncogenic KRASG12D protein, forming a unique intercellular communication pathway between pancreatic ductal adenocarcinoma (PDAC) cells and macrophages. In response to oxidative stress, PDAC cells undergo autophagy-dependent ferroptosis, a form of regulated cell death characterized by lipid peroxidation and iron accumulation. During this process, KRASG12D, a mutated and oncogenic form of the KRAS protein, is released from dying cancer cells and packaged into exosomes, small extracellular vesicles that mediate cell-cell communication. These exosomes, containing KRASG12D, are then taken up by macrophages in the TME through an AGER (advanced glycation end product-specific receptor)-dependent mechanism. Once inside the macrophages, KRASG12D triggers a metabolic shift towards fatty acid oxidation (FAO), facilitated by the activation of the STAT3 signaling pathway. This metabolic reprogramming drives the polarization of macrophages into the M2-like phenotype, which is pro-tumorigenic and supports tumor growth and immune evasion. Thus, autophagy-dependent ferroptosis in PDAC cells not only leads to the release of KRASG12D but also promotes TAM polarization through exosome-mediated protein transfer, enhancing the tumor's ability to thrive by recruiting and reprogramming the immune system to support cancer progression [91].

M2 macrophages in the arthritis synovium are particularly vulnerable to ferroptosis, which leads to a significant imbalance between pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. In arthritis synovium, the iron-rich environment and oxidative stress in the synovium promote ferroptosis in M2 macrophages, reducing their population. This reduction in M2 macrophages, which are crucial for resolving inflammation, tilts the balance towards M1 macrophages, which are responsible for producing pro-inflammatory cytokines like IL-1β and IL-6. The death of M2 macrophages through ferroptosis not only decreases their anti-inflammatory effects but also releases damage-associated molecular patterns (DAMPs), such as HMGB1, which further activate M1 macrophages via the TLR4/STAT3 signaling pathway. This activation exacerbates the inflammatory response, leading to joint inflammation and tissue destruction. Thus, ferroptosis of M2 macrophages disrupts the delicate M1/M2 balance, driving chronic inflammation in rheumatoid arthritis [92].

In TAMs, the expression of ceruloplasmin (CP) mRNA is upregulated under the control of hypoxia-inducible factor 2 (HIF-2) and STAT1. This CP mRNA is then packaged into extracellular vesicles (EVs) and transferred to nearby fibrosarcoma cells (HT1080 cells). Once inside the tumor cells, CP mRNA is translated into ceruloplasmin protein, which facilitates the export of iron by oxidizing Fe(II) to Fe(III), reducing the intracellular iron pool and thereby mitigating the Fenton reaction, which drives lipid peroxidation. This transfer of CP mRNA helps tumor cells lower their iron levels and protects them from ferroptosis triggered by agents such as RSL3. The reduction in iron availability also limits lipid peroxidation, further shielding tumor cells from ferroptotic cell death, thus promoting tumor survival in the challenging TME [93].

STAT/Ferroptosis axis in immunotherapy

The induction of ferroptosis through the IFN-γ-STAT1-IRF1-LPCAT3 pathway enhances the efficacy of anti-PD-1 immunotherapy by promoting lipid peroxidation and ROS accumulation in tumor cells, leading to their programmed cell death. IFN-γ, produced by activated T cells, initiates the STAT1-IRF1 signaling cascade, which upregulates the expression of LPCAT3, a key enzyme involved in lipid peroxidation. LPCAT3 enhances the incorporation of PUFAs into membrane phospholipids, which are subsequently oxidized, driving ferroptosis in tumor cells. This process not only directly kills cancer cells but also improves the immune microenvironment by promoting dendritic cell activation and phagocytosis of ferroptotic cells, which enhances the overall antitumor immune response. By increasing the susceptibility of tumor cells to ferroptosis, the pathway amplifies the effects of anti-PD-1 immunotherapy, as more tumor cells are killed, leading to a more robust and effective T-cell-mediated immune attack, ultimately overcoming resistance to immunotherapy in cancers like melanoma and lung cancer [94]. Researchers explored the mechanism by which chimeric antigen receptor T-cells (CAR T) engineered to secrete IFNκ enhance their antitumor efficacy by inducing tumor ferroptosis. IFNκ enhances the sensitivity of tumor cells to ferroptosis, especially when combined with arachidonic acid (AA), a polyunsaturated fatty acid. This combination promotes ferroptosis through the IFNAR/STAT1/ACSL4 signaling pathway. Mechanistically, IFNκ binds to the IFNAR1/IFNAR2 receptor complex, activating the JAK-STAT1 signaling pathway, which in turn upregulates ACSL4, an enzyme critical for converting AA into arachidonyl-CoA, a necessary step in lipid peroxidation. This chain of events leads to ferroptosis in tumor cells, as demonstrated in both in vitro and in vivo models using human lung cancer cell lines. Furthermore, CAR T cells engineered to express

IFNκ showed significantly enhanced antitumor efficacy in both antigen-positive and antigen-negative tumor models. Thus, engineering CAR T cells to secrete IFNκ represents a promising strategy to improve CAR T-cell therapy's effectiveness against solid tumors by inducing tumor ferroptosis [95]. APOL6 predicts the immunotherapy efficacy of bladder cancer (BLCA) by promoting ferroptosis. High levels of APOL6 expression are associated with "immunologically hot" tumors, which have greater immune cell infiltration and respond better to immune checkpoint inhibitors (ICIs). APOL6 interacts with ACSL4, an enzyme that contributes to ferroptosis by reducing the expression of GPX4, a key ferroptosis inhibitor. This mechanism enhances tumor sensitivity to immunotherapy. Additionally, APOL6 is regulated by the STAT1 transcription factor, and its elevated expression correlates with improved survival outcomes and response to ICIs in BLCA, positioning APOL6 as a promising biomarker for predicting immunotherapy success [96].

Therapeutic strategies in Targeting STAT/Ferroptosis pathway

STAT Proteins, particularly STAT3, play a crucial role in regulating the expression of antioxidant capacity biomarkers (ACBs) in cancer cells, particularly those sensitive to ferroptosis. In these sensitive cells, high activity levels of STAT3 contribute to the repression of ACBs, resulting in a decreased ability to buffer ROS and reactive nitrogen species (RNS). This repression leads to a diminished redox capacity, making the cells more vulnerable to oxidative stress induced by redox-targeting and ferroptosis-inducing drugs. Consequently, the inhibition of STAT3 not only enhances the expression of ACBs but also increases the sensitivity of resistant cells to these therapies, highlighting their significance as potential therapeutic targets for improving the efficacy of cancer treatments that exploit ferroptosis mechanisms [97]. Thus, targeting these factors in cancer therapy holds promise for increasing the sensitivity of cancer cells to ferroptosis (Fig. 6), while simultaneously ensuring that non-cancer cells remain resistant to ferroptosis under non-malignant conditions (Table 2).

Natural products

Herbs, their natural compounds, and traditional herbal formulas significantly contribute to the treatment of various diseases by influencing the intricate JAK/STAT signaling pathways. This pathway is essential for managing numerous biological functions, such as cell growth, inflammation, and immune responses, and its disruption is linked to multiple conditions, including cancer and autoimmune disorders. Traditional Chinese Medicine (TCM) employs a diverse range of herbs that contain active ingredients capable of modulating JAK/STAT signaling, presenting therapeutic opportunities for issues like rheumatoid arthritis, viral infections, and chronic inflammatory disorders. Research has revealed several herbal formulations that can either enhance or inhibit specific STAT signaling pathways, demonstrating their capacity to address the root causes of disease. This growing knowledge underscores the potential for merging TCM with contemporary pharmacology to create effective treatment approaches for a variety of health issues [98–102].

Cucurbitacin

Cucurbitacin B (CuB) is a triterpenoid compound found in plants of the Cucurbitaceae family, known for its diverse pharmacological properties, including anti-inflammatory, antiviral, and anticancer effects. In NSCLC, CuB has been shown to inhibit the growth of cancer cells effectively, particularly by inducing ferroptosis through activation of oxidative stress pathways, leading to increased levels of ROS, MDA, and ferrous ions, while simultaneously reducing GSH levels and mitochondrial membrane potential (MMP). Critical to its action, CuB targets the STAT3 signaling pathway. Network pharmacology analyses revealed STAT3 as a significant target, and experimental results demonstrated that CuB inhibits the phosphorylation of STAT3 (P-STAT3), which is necessary for its activation. Silencing STAT3 enhances CuB-induced accumulation of lipid ROS and iron ions, suggesting that the suppression of STAT3 is essential for CuB's ferroptotic effects [103].

Baicalein

Baicalein, a flavonoid extracted from Scutellaria baicalensis, has been shown to induce ferroptosis in colorectal cancer (CRC) cells, a group of tumoral cells that occur in the epithelium of the large intestine [104, 105], by inhibiting the JAK2/STAT3/GPX4 signaling axis. Baicalein was found to block the phosphorylation of JAK2 and STAT3, which are key signaling molecules in many cancer cell survival pathways. This blockage results in the downregulation of GPX4, a critical enzyme that protects cells from lipid peroxidation and ferroptosis. By inhibiting the JAK2/STAT3/GPX4 axis, baicalein increases the levels of ROS, reduces mitochondrial membrane potential, and promotes lipid peroxidation in CRC cells, ultimately leading to their death via ferroptosis [106]. In addition, it protects renal tubule cells against cisplatin-induced ferroptosis by restoring disrupted GSH metabolism and inhibiting the IL6/JAK/STAT3 signaling pathway. Cisplatin induces ferroptosis in renal cells by depleting GSH, which leads to increased ROS and lipid peroxidation, ultimately causing oxidative stress and cell death. Baicalein replenishes GSH levels, reducing oxidative stress and mitigating lipid peroxidation, thus preventing ferroptosis.

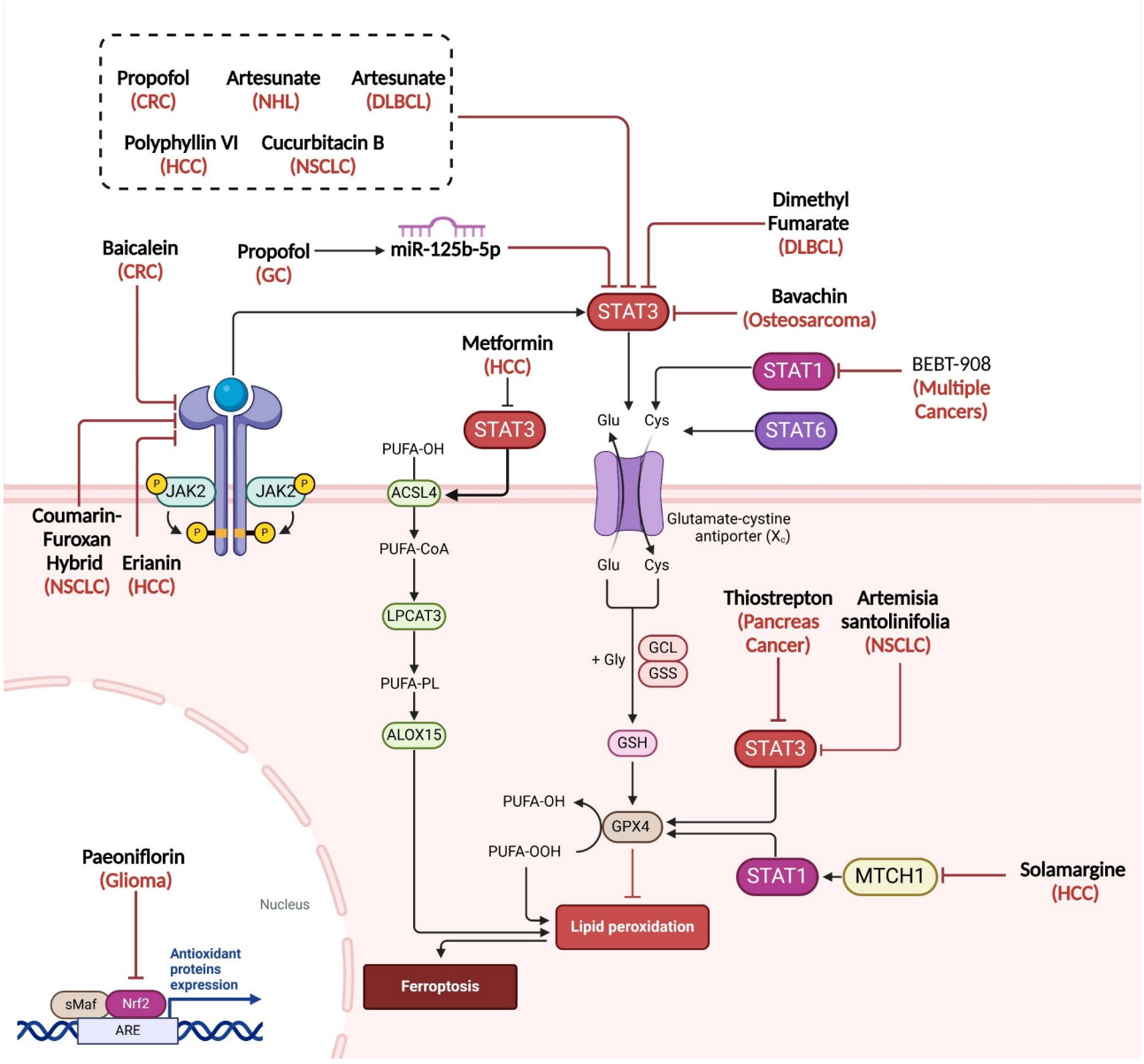

Fig. 6 Regulation of ferroptosis and STAT signaling pathways by various compounds in cancer models. The figure illustrates the role of key signaling molecules, such as JAK2, STAT3, STAT1, and STAT6, in mediating responses to natural and synthetic compounds targeting different cancer types. Inhibition or activation of these pathways leads to alterations in lipid peroxidation and ferroptosis

Additionally, baicalein inhibits the activation of the JAK/STAT3 pathway, which is involved in driving both apoptosis and ferroptosis in response to cisplatin [107].

Salidroside

Salidroside, derived from Rhodiola rosea, mitigates lung ischemia-reperfusion injury (LIRI) by targeting the JAK2/STAT3 pathway. This pathway is involved in inflammation and ferroptosis during LIRI. Salidroside inhibits JAK2/STAT3 activation, reducing STAT3-mediated expression of ferroptosis markers like ROS, MDA, and iron accumulation. This leads to decreased lipid peroxidation, restored GSH levels, and reduced pro-inflammatory cytokines. By modulating both ferroptosis and JAK2/STAT3, salidroside protects lung tissue and enhances lung function post-reperfusion [108].

Thiostrepton

Thiostrepton (TST), a thiopeptide antibiotic, induces ferroptosis in pancreatic cancer cells through the STAT3/GPX4 pathway. TST inhibits STAT3 activity, leading to downregulation of GPX4, which normally protects cells by neutralizing lipid peroxides. With reduced GPX4, lipid peroxides accumulate, triggering lipid peroxidation and

Table 2 Treatments targeting STAT/Ferroptosis axis in different diseases

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
Cucurbitacin B	Triterpenoid Compound	NSCLC	STAT3, GPX4, SLC7A11, COX2, ACSL4	H358, A549, H23, H1650, PC9	Inhibition of STAT3 Activation	In vitro	- CuB Inhibits the Growth of Several NSCLC Cells at Low Doses: CuB showed potent growth inhibition across various NSCLC cell lines with IC50 values ranging from 0.044 to 4.021 μM. - CuB-Mediated Cytotoxicity is Dependent on Ferroptosis: CuB induced cell death counteracted by ferroptosis inhibitors like DFO, Lip-1, and Fer-1. - CuB Triggered Ferroptosis in H358 Cells Based on Transcriptomic Analysis: Transcriptomic analysis confirmed CuB's role in inducing ferroptosis. - Network Pharmacology Analysis Uncovers Key Genes Implicated in CuB-Induced Ferroptosis in NSCLC: 170 potential targets identified, with STAT3 being a significant target. - CuB Inhibited STAT3 Activation in H358 Cells: CuB decreased levels of P-STAT3 in a dose-dependent manner, indicating effective targeting of the STAT3 pathway. - CuB Induced Ferroptosis in H358 Cells Through Targeting of STAT3: Silencing of STAT3 enhanced lipid ROS accumulation and ferroptosis-related proteins. Overexpression of STAT3 alleviated CuB's ferroptotic effects.	[103]
Baicalein	Flavonoid	Colorectal Cancer	GPX4, ROS, GSH, MDA, Fe2+	HCT116, DLD1, NCM460	JAK2/STAT3	In vivo (CRC xenograft mouse model), In vitro	Ferroptosis in CRC cells: Baicalein induces ferroptosis, characterized by increased ROS, lipid peroxidation, iron accumulation, and mitochondrial damage in CRC cells. Ferroptosis-dependent effect: Liproxstatin-1 (ferroptosis inhibitor) rescues CRC cells from baicalein-induced death. JAK2/STAT3/GPX4 Axis: Baicalein inhibits GPX4 expression by blocking JAK2/STAT3 signaling. Direct Targeting of JAK2: Molecular docking and assays confirm baicalein directly interacts with JAK2. In vivo Efficacy: Baicalein reduces tumor growth and induces ferroptosis in CRC xenograft models.	[106]

Table 2 (continued)

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
Salidroside	Natural compound (from *Rhodiola rosea*)	Lung ischemia-reperfusion injury (LIRI)	GPX4, FSP1, SLC1A5, GLS2, ROS, MDA, GSH, Iron	BEAS-2B (human lung epithelial cells)	JAK2/STAT3 signaling	In vivo (mice) & In vitro (BEAS-2B cells)	- Severe ferroptosis occurs in LIRI mice models and H/R-induced BEAS-2B cells. - Salidroside alleviated ferroptosis, inflammation, and lung injury in LIRI mice. - Reduced ROS and MDA levels, restored GSH levels, and downregulated pro-ferroptosis molecules (SLC1A5, GLS2). - Salidroside inhibited the JAK2/STAT3 signaling pathway activation in LIRI. - STAT3 knockdown enhanced salidroside's effect in reducing ferroptosis in vitro. - Salidroside decreased TNF-α and IL-6 levels, mitigating inflammatory responses. - Reduced lung edema and improved lung function (wet/dry ratio).	[108]
Thiostrepton	Thiopeptide antibiotic	Pancreatic cancer	STAT3, GPX4, ROS, MDA, GSH-PX	Panc-1, MIA PaCa-2, BxPC-3, hTERT-HPNE	STAT3/GPX4 signaling	Both (in vivo mouse model, in vitro pancreatic cancer cells)	TST reduces cell viability and clonogenesis, induces intracellular iron overload, increases ROS and MDA, depletes GSH-PX. TST inhibits STAT3, downregulates GPX4, promoting ferroptosis. In vivo, TST inhibits tumor growth without significant toxicity.	[109]
Paeoniflorin (PF)	Active compound from traditional Chinese medicine	Glioma	NEDD4L, GPX4, Nrf2, STAT3	U251, U87	STAT3/NEDD4L	In vivo (xenograft mouse model), In vitro	Paeoniflorin upregulates NEDD4L, leading to the degradation of STAT3 and the induction of ferroptosis. PF increases ROS levels and reduces cell viability by suppressing Nrf2 and GPX4. PF treatment, combined with RSL3, enhances ferroptosis and tumor suppression.	[110]
Artemisia santolinifolia (AS) + Docetaxel (DTX)	Natural extract + chemotherapeutic	NSCLC	GPX4, ROS	A549, H23	STAT3, Survivin	In vitro (A549, H23)	AS enhanced the cytotoxic effect of DTX via apoptosis in H23 cells (caspase-dependent) and ferroptosis in A549 cells (ROS and GPX4 suppression). STAT3/Survivin signaling was suppressed in both cell lines.	[111]
Bavachin	Flavonoid	Osteosarcoma (OS)	GPX4, ROS, MDA, GSH, SLC7A11, TFRC, DMT1, FTL, FTH	MG63, HOS	STAT3/P53/SLC7A11	In vitro	- Bavachin induces ferroptosis in osteosarcoma cells by increasing intracellular iron and ROS levels. - Downregulates GPX4, SLC7A11, and inhibits p-STAT3 while upregulating P53. - Ferroptosis reversed by ferroptosis inhibitors and P53 or STAT3 overexpression.	[112]

Table 2 (continued)

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
Ferulic Acid (FA)	Naturally occurring cinnamic acid derivative (Phenolic compound)	Gamma-radiation-induced liver injury	Upregulated: GPX4, SLC7A11, Nrf2 Downregulated: p-JAK1, p-STAT3	Not applicable (In Vivo Rat Model)	JAK1/STAT3	In Vivo (Rat model)	- Liver Protection: FA significantly inhibited liver damage and restored liver structure and function post-irradiation. - Enzyme Levels: Reduced serum SGPT and SGOT levels. - Oxidative Stress: Decreased MDA and ROS; increased GSH - Iron Metabolism: Lowered ferrous ion (Fe^{2+}) content and suppressed iron deposition in liver tissues. - Signaling Pathways: Inhibited the JAK/STAT pathway (decreased p-JAK1 and p-STAT3) and activated the Nrf2 pathway. - Ferroptosis Inhibition: Enhanced expression of GPX4 and SLC7A11, preventing ferroptotic cell death. - Histological Improvements: Reduced inflammatory infiltrates, edema, hepatocyte apoptosis, and iron deposits in liver tissues.	[113]
Jing-Fang n-butanol extract (JFNE) and JFNE-C	Traditional Chinese Medicine extract (n-butanol extract from *Nepeta cataria* L. and *Saposhnikovia divaricata* (Trucz.) Schischk.)	Lipopolysaccharide (LPS)-induced inflammation in RAW264.7 macrophages	Upregulated: STAT3, p-STAT3, SLC7A11, GPX4 Downregulated: p53, p-p53	RAW264.7 macrophages	STAT3/p53/SLC7A11	In Vitro (LPS-induced RAW264.7 cell model)	- Anti-Inflammatory: Reduced IL-6, IL-1β, TNF-α levels. - Antioxidant: Decreased ROS and MDA; increased GSH, GSH-Px, SOD. - Ferroptosis Inhibition: Lowered Fe^{2+} levels and protected mitochondria. - Molecular Mechanism: Modulated STAT3/p53/SLC7A11 pathway. - Active Components: Identified key compounds like Hesperidin and Luteolin in JFNE-C. - Enhanced Efficacy: JFNE-C showed stronger effects than JFNE.	[114]
Xue-Jie-San (XJS)	Traditional Chinese Herbal Medicine	Crohn's Disease (CD)	SLC7A11, GPX4, FGL1, NF-κB, STAT3, PTGS2 (COX2), FPN, FTH, FTL	Intestinal epithelial cells (IECs) from rat colitis model	NF-κB, STAT3 pathways	In vivo (TNBS-induced colitis in rat model)	XJS inhibited ferroptosis in IECs by reducing iron overload and lipid peroxidation. It enhanced the SLC7A11/GSH/GPX4 antioxidant system and suppressed the FGL1/NF-κB/STAT3 positive feedback loop, which reduced inflammation and prevented further damage. XJS also upregulated anti-inflammatory cytokines (IL-10) and downregulated pro-inflammatory cytokines (IL-6, IL-17, TNF-α). Histological assessments confirmed reduced inflammation and improved colon structure.	[115]

Table 2 (continued)

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
EGCG	Bioactive compound from green tea	Obesity-exacerbated lung cancer	SLC7A11	A549 (lung cancer), RAW264.7 (macrophages)	STAT1/SLC7A11	In vivo (mice), In vitro (A549)	EGCG inhibits leptin-induced cancer cell proliferation, migration, and invasion. It reverses M2 macrophage polarization and promotes ferroptosis by downregulating STAT1 and SLC7A11 expression. EGCG also modulates gut microbiota, reducing pro-inflammatory bacteria and increasing beneficial microbes, ultimately reducing tumor burden in mice fed a high-fat diet.	[117]
Solamargine (SM)	Glycoalkaloid	Hepatocellular carcinoma	MTCH1, Fe^{2+}, MDA, ROS, GSH	HepG2, Huh-7	STAT1/MTCH1	In vivo (mice xenograft), in vitro	SM induces apoptosis and ferroptosis by decreasing MTCH1 expression via the STAT1/MTCH1 axis. Overexpression of STAT1 or MTCH1 reverses the effects of SM in HCC cells and mouse models.	[118]
MaiJiTong (MJT) Granule	Traditional Chinese Medicine	Atherosclerosis	DMT1, SOCS1, p53, SLC7A11, GPX4, ACSL4, LPCAT3, FTH1	RAW264.7 macrophages	STAT6	LDLR−/− mice (in vivo), RAW264.7 cells (in vitro)	MJT attenuates atherosclerosis by inhibiting ferroptosis through STAT6 activation, reducing lipid peroxidation, and improving iron homeostasis by downregulating DMT1/SOCS1.	[119]
Erianin	Natural compound (derived from *Dendrobium*)	HCC	ROS, Fe^{2+}, MDA, GSH, SLC7A11, GPX4	Huh-7, HepG2, L02	JAK2/STAT3 (inactivation)	In vivo (mouse xenograft model) and in vitro (cell culture)	Erianin promotes ferroptosis by increasing ROS, Fe^{2+}, and MDA levels while decreasing GSH and ferroptosis-resistance proteins (SLC7A11, GPX4). It suppresses HCC cell proliferation and invasion, and inhibits tumor growth without significant toxicity in mice.	[120]
BEBT-908	Dual PI3K/HDAC Inhibitor	Multiple cancers (hematologic, solid)	p53, SLC7A11, GPX4, Nrf2	Daudi (Burkitt lymphoma), H2122 (NSCLC), HCT116 (colorectal), MC38 (colon adenocarcinoma)	STAT1	Both in vivo (mice) and in vitro	BEBT-908 induces ferroptosis by hyperacetylating p53 and downregulating SLC7A11/GPX4. It enhances MHC I expression and IFNγ signaling, promoting immune cell infiltration and boosting anti-PD1 therapy. Tumor regression and immune memory were observed in vivo models.	[121]
Fer-1	Ferroptosis Inhibitor	ICH	GPx4, ROS	Organotypic hippocampal slices (OHS), mouse ICH model	JAK1/STAT6	Both in vivo (mouse ICH model) and in vitro (OHS)	Fer-1 inhibits neuronal apoptosis by suppressing GPx4 dysfunction and ROS production. It polarizes microglial cells to the M2 phenotype, enhances phagocytic function, alleviates inflammation, improves neurological function, and promotes hematoma absorption after ICH.	[122]

Table 2 (continued)

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
Coumarin-Furoxan Hybrid (Compound 9)	Nitric Oxide (NO) Donor	NSCLC	SLC7A11, GPX4, GSH, MDA	A549, H1975, H1299, H2030	JAK2-STAT3 (Negative Regulation)	In vitro (NSCLC cell lines) and In vivo (H1975 xenograft model)	- Induces apoptosis and ferroptosis via NO release in mitochondria. - Promotes S-nitrosylation of STAT3, inhibiting its phosphorylation and DNA binding. - Suppresses JAK2-STAT3 pathway. - Significantly reduces tumor growth in vivo. - Decreases GSH, increases MDA, and downregulates ferroptosis-related proteins (SLC7A11, GPX4).	[123]
Polyphyllin VI (PPVI)	Traditional Chinese Medicine	Hepatocellular carcinoma (HCC)	GSH, MDA, Fe2+, GPX4	HCCLM3, Huh7	STAT3/GPX4 (Negative regulation)	In vitro (HCC cell lines) and In vivo (Huh7 xenograft model)	- PPVI induces ferroptosis in HCC cells by reducing GSH, increasing MDA, ROS, and Fe2+. - PPVI inhibits the invasion and migration of HCC cells through the STAT3/GPX4 axis. - PPVI blocks STAT3 phosphorylation and decreases GPX4 expression, promoting ferroptosis. - In vivo, PPVI effectively suppresses tumor growth without notable toxicity.	[125]
Artesunate (ART) + Sorafenib (SOR)	Small-molecule drugs	Non-Hodgkin Lymphoma (NHL)	GPX4, FTH1, GSH, ROS	U2932, SU-DHL4, SU-DHL6 (B-cell lymphoma), Jurkat (T-cell lymphoma), EL4	STAT3 inhibition (p-STAT3 downregulation)	In vitro and In vivo (xenograft mouse model)	ART and SOR synergistically induced ferroptosis and apoptosis via STAT3 inhibition, leading to downregulation of MCL-1 and GPX4, causing cell death, lipid peroxidation, and ROS accumulation. Tumor growth and angiogenesis were significantly suppressed in vivo, showing potential for combination therapy in NHL.	[127]
Propofol	Anesthetic, Antitumor Agent	Gastric Cancer	ROS, Iron, Fe2+, GPX4, SLC7A11, MDA, GSH	SGC7901, BGC823	STAT3 inhibition (via miR-125b-5p)	In vitro (cell lines) and In vivo (xenograft in nude mice)	Propofol induces ferroptosis and inhibits malignant phenotypes (proliferation, invasion, migration) of gastric cancer cells by upregulating miR-125b-5p, which targets STAT3. Increased ROS, iron, Fe2 + levels, and decreased GPX4, SLC7A11, and GSH were observed. Tumor growth was suppressed in vivo.	[128]
Propofol	Anesthetic	Colorectal Cancer (CRC)	STAT3, CHAC1, PTGS2, GPX4, ROS, Fe2+, GSH	SW480 (CRC), NCM460 (normal colonic cells)	Downregulates STAT3 expression	In vitro	Propofol induced ferroptosis in CRC cells by downregulating STAT3. It increased cellular iron, ROS, and Fe2 + levels, while promoting the expression of CHAC1 and PTGS2 and inhibiting GPX4. Overexpression of STAT3 reversed these effects.	[129]
Dimethyl Fumarate (DMF)	FDA-approved drug	DLBCL (Diffuse Large B-cell Lymphoma)	GPX4, GSH, 5-lipoxygenase (5-LOX), FSP1	GCB DLBCL, ABC DLBCL, SU-DHL-6, DOHH2, OCI-Ly10	NF-κB/STAT3 pathways	In vitro, In vivo (Zebrafish, Mouse models)	DMF induces ferroptosis in GCB DLBCL by depleting GSH and inhibiting GPX4, increasing lipid peroxidation. In ABC DLBCL, DMF impairs NF-κB and STAT3 signaling by succinating IKK2 and JAK1. Synergistic effects seen when combined with FSP1 and BCL-2 inhibitors. Significant tumor reduction observed in xenograft models.	[130]

Table 2 (continued)

Treatment name	Drug type	Disease	Ferroptosis regulator molecules	Cell Lines	STAT Pathways	Model (in vivo/in vitro)	Highlights	Ref.
Metformin + Sorafenib	Antidiabetic + Anticancer	HCC	GPX4 (downregulated), ACSL4 (upregulated), ROS, Fe^{2+}	Huh7, Hep3B (and sorafenib-resistant versions Huh7/SR, Hep3B/SR)	ATF4/STAT3, p-STAT3, p-STAT1	Both in vitro (cell lines) and in vivo (mouse model)	Metformin promotes ferroptosis by increasing ROS, lipid peroxidation, and Fe^{2+} accumulation. Downregulating ATF4 inhibits STAT3 activity, enhancing sensitivity to sorafenib. Reverses drug resistance.	[132]
Artesunate	Antimalarial/Anticancer	Diffuse Large B Cell Lymphoma (DLBCL)	GPX4 (downregulated), FTH1 (downregulated), ROS, MDA	U2932, SU-DHL2, SU-DHL4, SU-DHL6	STAT3, p-STAT3	Both in vitro (cell lines) and in vivo (xenograft mouse model)	ART induces apoptosis, autophagy, and ferroptosis in DLBCL cells. Inhibits STAT3 signaling, reducing proliferation. Knockdown of STAT3 enhances ART-induced autophagy, ferroptosis, and apoptosis. Validated in vivo using a xenograft model.	[133]
Auranofin (AUR)	FDA-approved anti-rheumatoid arthritis (anti-RA) drug	Hereditary hemochromatosis, hepcidin-deficiency related disorders	TXNRD (Thioredoxin Reductase), GPX4, SLC7A11, P53, STAT3, IL-6, NF-κB, ROS, MDA, GSH	Huh7 cells, C57BL/6J mice, $Hfe^{-/-}$ mice	NF-κB/IL-6/STAT3 and BMP/SMAD pathways	In vitro (Huh7 cells) and In vivo (C57BL/6J and $Hfe^{-/-}$ mice)	- Hepcidin Upregulation: Auranofin (AUR) upregulated hepcidin via NF-κB/IL-6/STAT3 signaling. - Iron Overload Reduction: In male $Hfe^{-/-}$ mice, AUR reduced systemic iron overload. - Ferroptosis Induction: High-dose AUR induced ferroptosis, characterized by lipid peroxidation and ROS accumulation. - Sex-Specific Effects: Estrogen reduced AUR effectiveness in female mice. - Toxicity: High-dose AUR caused 100% mortality through ferroptosis in mice, but this was mitigated by ferroptosis inhibitor (Fer-1).	

ferroptosis. Additionally, TST promotes iron overload, further enhancing oxidative stress. By targeting STAT3 and GPX4, TST selectively triggers ferroptosis in pancreatic cancer cells, positioning it as a potential cancer therapy [109].

Paeoniflorin

Paeoniflorin (PF) is an active compound derived from the traditional Chinese medicinal plant Paeonia lactiflora. It has shown significant potential as an antitumor agent, particularly in human glioma cells, by inducing ferroptosis. PF exerts its effects by upregulating NEDD4L, an E3 ubiquitin ligase that promotes the degradation of STAT3. This downregulation of STAT3 leads to increased intracellular ROS levels and the suppression of key ferroptosis inhibitors, such as Nrf2 and GPX4, ultimately triggering ferroptosis and inhibiting glioma cell growth. PF's ability to enhance ferroptosis suggests its potential as a therapeutic option, especially when combined with other ferroptosis-inducing agents like RSL3 [110].

Artemisia santolinifolia

Artemisia santolinifolia (AS) is a species of the Artemisia genus, known for its medicinal properties, including anticancer activity. In NSCLC, Artemisia santolinifoli has been shown to act as a chemosensitizer when combined with the chemotherapeutic drug docetaxel (DTX). This combination enhances cancer cell death by activating two distinct modes of cell death, ferroptosis in A549 cells and apoptosis in H23 cells. In A549 cells, the ethanol extract of AS increases ROS levels, depletes the antioxidant enzyme GPX4, and triggers ferroptosis. AS enhances chemosensitization by inhibiting the oncogenic STAT3 signaling pathway and downregulating survivin, a protein that promotes cell survival. By suppressing STAT3 phosphorylation and survivin expression, AS weakens the cancer cells' resistance to apoptosis, making them more responsive to chemotherapy [111].

Bavachin

Bavachin is a bioactive flavonoid extracted from Psoralea corylifolia, known for its diverse biological activities, including anticancer effects. In osteosarcoma (OS) cells, Bavachin induces ferroptosis. Mechanistically, Bavachin downregulates the antioxidant enzyme GPX4 and the cystine transporter SLC7A11, while also inhibiting the STAT3 signaling pathway and upregulating the tumor suppressor protein P53. This disruption of the STAT3/P53/SLC7A11 axis triggers ferroptosis, making Bavachin a promising potential therapeutic agent for treating osteosarcoma by overcoming resistance to conventional therapies [112].

Ferulic acid

Ferulic acid is a naturally occurring cinnamic acid derivative renowned for its potent antioxidant, anti-inflammatory, and hepatoprotective properties. Gamma-radiation exposure leads to the overactivation of the JAK/STAT pathway, which promotes inflammation and ferroptosis. Concurrently, radiation suppresses the Nrf2 pathway, reducing the liver's antioxidant defenses. Ferulic acid mitigates these detrimental effects by inhibiting the JAK/STAT signaling, thereby decreasing inflammatory responses, and activating the Nrf2 pathway, which enhances the expression of antioxidant enzymes like GPX4 and SLC7A11 [113].

Jing-Fang n-butanol extract

Jing-Fang n-butanol extract (JFNE) is derived from a traditional Chinese medicinal combination of Nepeta cataria L. (Jing Jie) and Saposhnikovia divaricata (Trucz.) Schischk. (Fang Feng), renowned for their anti-inflammatory and antioxidant properties. In studies using LPS-induced RAW264.7 macrophages, JFNE and its isolated component JFNE-C have demonstrated significant inhibition of both ferroptosis and inflammation. This protective effect is mediated through the modulation of the STAT3/p53/SLC7A11 signaling pathway. Specifically, JFNE-C upregulates the activation of STAT3 and its phosphorylated form p-STAT3, which in turn suppresses the tumor suppressor protein p53. This suppression leads to increased expression of SLC7A11 and GPX4, crucial regulators that prevent ferroptosis by enhancing glutathione synthesis and reducing lipid peroxidation [114].

Xue-Jie-San (XJS)

Xue-Jie-San (XJS) is a traditional Chinese herbal formula consisting of Dragon's blood (Resina draconis) and Myrrh (Myrrha), which has been shown to alleviate Crohn's disease (CD), a chronic inflammatory bowel disease. Gao et al. investigated how XJS alleviates CD symptoms by inhibiting ferroptosis. In a rat model of colitis, XJS reduced inflammation by downregulating pro-inflammatory cytokines and increasing IL-10. It prevented ferroptosis in intestinal epithelial cells by decreasing iron accumulation and lipid peroxidation. XJS enhanced the SLC7A11/GSH/GPX4 antioxidant axis to reduce ROS and lipid peroxides. Additionally, it suppressed the FGL1/NF-κB/STAT3 loop, reducing ferroptotic damage and aiding intestinal barrier repair. These findings suggest that XJS targets both ferroptosis and inflammation, offering a promising approach for CD treatment [115].

Ginsenoside Rh3

Ginsenoside Rh3 (GRh3) is a seminatural triterpene compound derived from ginseng, known for its potent anticancer properties. In CRC cells, GRh3 exerts its

tumor-suppressive effects by inducing two forms of regulated cell death: pyroptosis and ferroptosis, primarily through the Stat3/p53/NRF2 axis. GRh3 inhibits the phosphorylation of Stat3, leading to the upregulation of the tumor suppressor p53. Elevated p53 then prevents NRF2 from entering the nucleus, which blocks its antioxidant functions. GRh3 induces ferroptosis by suppressing the xCT/SLC7A11 system, depleting intracellular GSH, and increasing lipid ROS, iron, and MDA levels. This oxidative stress overwhelms the cells' antioxidant defenses, further inhibiting GPX4, a key enzyme in preventing lipid peroxidation, leading to ferroptosis [116].

EGCG

Epigallocatechin gallate (EGCG) is a bioactive compound found in green tea, known for its antioxidant, anti-inflammatory, and anti-cancer properties. In obesity-exacerbated lung cancer, EGCG alleviates tumor progression by targeting the STAT1/SLC7A11 pathway. Leptin, a hormone elevated in obesity, promotes lung cancer cell growth and immune escape by activating STAT1, which in turn upregulates SLC7A11, a gene that inhibits ferroptosis. EGCG reverses leptin's effects by downregulating STAT1 and SLC7A11, promoting ferroptosis and reducing cancer cell survival [117].

Solamargine

Solamargine (SM), a glycoalkaloid from Solanum nigru, has demonstrated significant anti-tumor properties in HCC by inducing both apoptosis and ferroptosis in cancer cells. SM suppresses HCC cell proliferation and enhanced apoptosis and ferroptosis by decreasing the expression of mitochondrial carrier 1 (MTCH1), a protein involved in cancer cell survival. MTCH1, which was overexpressed in HCC cells, promoted tumor growth, but its knockdown resulted in increased apoptosis and ferroptosis. STAT1 was found to enhance MTCH1 expression by binding to its promoter region, but SM treatment reduced STAT1 levels, thereby decreasing MTCH1 expression. In both in vitro and in vivo models, SM hindered HCC progression by modulating this pathway, confirming its potential as a therapeutic agent in targeting HCC [118].

MaiJiTong granule

MaiJiTong (MJT) granule is a Traditional Chinese Medicine composed of various herbs known for their cardiovascular benefits, including Astragalus membranaceus, Radix Salviae Miltiorrhizae, Poria Cocos, and Cinnamomi Ramulus. MJT attenuates atherosclerosis by reducing ferroptosis, which contributes to plaque formation and instability in arteries. The primary mechanism involves activating STAT6, a signal transducer that, when phosphorylated, translocates to the nucleus to suppress ferroptosis. STAT6 activation by MJT inhibits two critical pathways: DMT1 (a ferrous ion transporter responsible for iron uptake) and SOCS1/p53, which regulates lipid peroxidation and cell death. By downregulating DMT1 and SOCS1, MJT reduces iron overload, improves iron homeostasis, and enhances lipid peroxide scavenging through increased expression of SLC7A11 and GPX4, which are involved in reducing oxidative stress [119].

Erianin

Erianin is a bioactive compound derived from traditional Chinese medicinal plants like Dendrobiu species, known for its anti-cancer properties. In HCC, erianin inhibits tumor growth by inducing ferroptosis via increasing ROS and ferrous ion (Fe^{2+}) levels while reducing antioxidant defenses like GSH. Erianin achieves this by inactivating the JAK2/STAT3 signaling pathway, which downregulates key ferroptosis-resistance proteins SLC7A11 and GPX4, leading to increased cell death and reduced tumor invasion [120].

Synthetic drugs

BEBT-908

BEBT-908 is a novel dual inhibitor that targets both the PI3K (phosphoinositide 3-kinase) and HDAC (histone deacetylase) pathways, two key regulators often dysregulated in cancers. By simultaneously inhibiting these pathways, BEBT-908 potently induces ferroptosis, facilitated through hyperacetylation of p53, downregulation of SLC7A11 and GPX4 (key regulators of ferroptosis), and suppression of the Nrf2 pathway, which typically inhibits ferroptosis. Additionally, BEBT-908 increases the immunogenicity of cancer cells by upregulating MHC class I molecules and activating IFNγ signaling via the STAT1 pathway. This creates a proinflammatory tumor microenvironment, enhancing the infiltration and activity of immune cells such as cytotoxic T lymphocytes (CTLs) [121].

Ferrostatin-1

Ferrostatin-1 (Fer-1) is a ferroptosis inhibitor known for preventing cell death by blocking the accumulation of lipid peroxides, a key feature of ferroptosis. In the context of ICH, Fer-1 has been shown to alleviate inflammation and promote recovery by influencing the behavior of microglial cells, the brain's primary immune cells. Fer-1 activates the JAK1/STAT6 signaling pathway, further promoting M2 polarization and enhancing the phagocytic function of microglial cells, which aids in hematoma absorption and the resolution of inflammation. By modulating these immune responses, Fer-1 improves neurological function and reduces brain tissue damage in ICH models, presenting a potential therapeutic strategy for stroke recovery [122].

Nitric oxide donor

The coumarin-furoxan hybrid, specifically referred to as a compound, is a novel nitric oxide (NO) donor drug designed to target NSCLC. This hybrid compound combines the coumarin structure with furoxan, which is responsible for its ability to release large amounts of NO within cancer cells, particularly in mitochondria. This compound promotes S-nitrosylation of STAT3, a key oncogenic protein, which inhibits its phosphorylation and reduces its DNA-binding ability. By negatively regulating the JAK2-STAT3 signaling pathway, compound 9 suppresses tumor survival and proliferation. This action, inducing ferroptosis while inhibiting the JAK2-STAT3 axis, presents a potent therapeutic strategy for combating NSCLC [123].

Polyphyllin VI

Polyphyllin VI (PPVI) is a natural saponin compound extracted from Paris polyphylla, traditionally used in Chinese medicine, and has shown potent anticancer properties. Mechanistically, PPVI inhibits STAT3 phosphorylation, which downregulates the expression of GPX4. By targeting the STAT3/GPX4 axis, PPVI not only promotes ferroptosis but also suppresses EMT, which is associated with cancer cell invasion and migration [124]. Consequently, PPVI attenuates the ability of HCC cells to invade and migrate, thereby reducing tumor metastasis. This dual mechanism of inducing ferroptosis and inhibiting metastasis highlights PPVI's potential as a therapeutic agent for HCC [125].

Artesunate

Artesunate (ART) and sorafenib (SOR) are two anticancer agents that synergistically induce cell death in non-Hodgkin lymphoma (NHL) cells by promoting apoptosis and ferroptosis, primarily through inhibition of the STAT3 pathway. The mechanism involves suppressing the STAT3 signaling pathway, which downregulates key anti-apoptotic proteins, such as myeloid cell leukemia-1 (MCL-1), and ferroptosis regulators, like GPX4. The combination of ART and SOR induces lipid peroxidation, ROS accumulation, mitochondrial dysfunction, and reduced GSH levels, all hallmarks of ferroptosis. Additionally, the inhibition of the AKT and MEK/ERK pathways, which is crucial in chemoresistance [126], further enhances the anticancer effects of this combination [127].

Propofol

Propofol is a short-acting sedative-hypnotic agent commonly used in clinical settings as an anesthetic and sedative for the induction and maintenance of general anesthesia, procedural sedation, and intensive care unit sedation.Propofol induces ferroptosis and inhibits the malignant phenotypes of gastric cancer cells by regulating the miR-125b-5p/STAT3 axis. It upregulates miR-125b-5p, which directly targets and suppresses STAT3, a critical oncogene involved in gastric cancer progression. This suppression leads to the promotion of ferroptosis, characterized by increased levels of ROS, iron, and Fe2+, alongside the downregulation of key ferroptosis-inhibitory proteins like GPX4 and SLC7A11. Additionally, propofol reduces GSH levels and increases MDA, further amplifying oxidative stress and lipid peroxidation, hallmark processes of ferroptosis [128]. Similarly, In CRC cells, propofol increased the levels of ROS, iron, and $Fe^{2+}$and promoted lipid peroxidation. The inhibitory effects of propofol on CRC cell proliferation and colony formation were significantly reversed by STAT3 overexpression, suggesting that STAT3 plays a central role in regulating propofol-induced ferroptosis [129].

Fludarabine

Fludarabine, a STAT1 inhibitor, is commonly used in cancer therapy, particularly for B-cell lymphoma (BCL). It enhances the sensitivity of BCL to radiotherapy by promoting ferroptosis. Radiotherapy is a primary treatment for BCL, with STAT1 playing a significant role in regulating cell growth and survival, which influences the response to radiation. Combining fludarabine with radiation significantly reduces BCL cell viability, boosts apoptosis, and triggers ferroptosis, as shown in both lab-cultured BCL cells (Raji and Su-DHL-10) and animal models with Raji cell xenografts. Additionally, using a ferroptosis inhibitor reversed these effects, confirming ferroptosis as the underlying mechanism. Clinical data further indicated that higher co-expression of STAT1 and the ferroptosis regulator GPX4 is linked to poorer survival outcomes in diffuse large B-cell lymphoma (DLBCL) patients [131].

Metformin

Metformin is a widely used drug for treating type 2 diabetes, known for its pleiotropic effects, including its anticancer properties. In HCC, metformin has been shown to enhance the efficacy of sorafenib, a first-line drug for advanced liver cancer, by promoting ferroptosis. This effect is mediated through the ATF4/STAT3 signaling pathway. The ATF4 transcription factor, which plays a key role in cellular stress responses, interacts with STAT3, a protein involved in cell survival and drug resistance. By inhibiting ATF4, metformin reduces STAT3 activity, leading to increased ferroptosis and decreased resistance to sorafenib in HCC cells. This mechanism ultimately enhances the sensitivity of cancer cells to sorafenib [132].

Artesunate

Artesunate (ART) is a water-soluble derivative of artemisinin, primarily used as an antimalarial drug, but it has also shown significant anticancer effects. In diffuse large B cell lymphoma (DLBCL) cells, ART induces ferroptosis by impairing the STAT3 signaling pathway. ART downregulates the expression of STAT3 and its phosphorylated form (p-STAT3), which disrupts cellular processes that promote resistance to cell death. This inhibition leads to increased levels of ROS and MDA, as well as the downregulation of ferroptosis-regulating proteins such as GPX4 and FTH1. The combination of these effects triggers ferroptosis, enhancing ART's anticancer properties in DLBCL [133].

Auranofin

Auranofin (AUR), a drug approved for rheumatoid arthritis, has been found to have dual functions in iron metabolism and cell death mechanisms. It potently upregulates hepcidin expression, the hormone responsible for regulating iron homeostasis, by activating the NF-κB/IL-6/STAT3 pathway, reducing systemic iron levels, and mitigating iron overload in male mice, particularly in a hemochromatosis model. High doses of AUR induce ferroptosis, a form of iron-dependent cell death marked by lipid peroxidation, by inhibiting thioredoxin reductase (TXNRD) [134].

Conclusion

This review highlights the critical crosstalk between JAK/STAT signaling and ferroptosis, underscoring its significance in various diseases, particularly cancer, autoimmune disorders, and neurodegenerative conditions. STAT proteins, notably STAT1, STAT3, and STAT6, play pivotal roles in regulating ferroptosis across a broad spectrum of diseases. These include cancers (such as breast, prostate, renal, and lung cancers), neurodegenerative disorders (like Parkinson's disease), autoimmune diseases (including Sjögren's syndrome and asthma), and cardiovascular conditions. The activation of JAK/STAT signaling by binding cytokines, particularly interleukins such as IL-6, IL-13, and IL-4, commonly inhibits ferroptosis, facilitating disease progression by modulating key regulators of ferroptosis. JAK/STAT signaling significantly impacts amino acid metabolism, particularly through the regulation of GPX4 and the cystine-glutamate antiporter System Xc-. This control of glutathione synthesis and lipid peroxidation prevention is crucial for ferroptosis resistance. In addition, the JAK/STAT pathway modulates the NRF2/HO-1 signaling axis, primarily through STAT3, enhancing antioxidant responses and iron homeostasis to inhibit ferroptosis. Furthermore, iron metabolism plays a central role in the crosstalk between ferroptosis and JAK/STAT signaling, with key regulators such as ferritin, ferroportin (FPN), divalent metal transporter 1 (DMT1), and NCOA4. These molecules dictate cellular iron levels, driving or preventing ferroptosis depending on their regulation within the JAK/STAT pathway. Ferroptosis also feeds back into the JAK/STAT signaling pathway, influencing diseases such as cancer, neurodegenerative conditions, and cardiovascular disorders. In these cases, oxidative stress and lipid peroxidation products can further activate or inhibit JAK/STAT components, leading to a complex interplay that affects disease progression. This bidirectional regulation makes the JAK/STAT-ferroptosis axis a crucial therapeutic target.The immunological significance of this crosstalk is especially pronounced in cancer. JAK/STAT signaling, particularly through STAT3, is known to facilitate immune evasion by tumor cells, promote survival under oxidative stress, and enhance resistance to conventional therapies. By inhibiting ferroptosis, this pathway helps cancer cells escape immune detection and resist ferroptotic cell death. Importantly, inducing ferroptosis by inhibiting JAK/STAT signaling in cancers can overcome these resistance mechanisms, making it a promising therapeutic approach to halt tumor progression. Many natural products have been identified that target the STAT/ferroptosis axis, offering substantial therapeutic benefits. These natural compounds, such as erianin and curcumin, can inhibit STAT3 and enhance ferroptosis, contributing to cancer cell death while minimizing toxicity to normal tissues. Their anti-cancer properties are particularly beneficial in overcoming drug resistance and reducing the side effects associated with conventional therapies. In addition to natural compounds, several synthetic products have been developed to target the JAK/STAT-ferroptosis interaction. These innovative approaches allow for more precise targeting of the signaling pathways involved, enhancing therapeutic efficacy and potentially reducing off-target effects. The exploration of the JAK/STAT-ferroptosis axis presents exciting opportunities for advancing therapeutic strategies, particularly in cancer and other diseases where ferroptosis plays a key regulatory role.

Future research should focus on several key areas to further unravel the complex relationship between ferroptosis and the JAK/STAT signaling axis. While some studies have explored this interaction, much remains to be understood, particularly how ferroptosis regulates the JAK/STAT pathway, with only a few studies investigating this dynamic. Greater emphasis should be placed on understanding its role across different cancers, especially given the absence of studies on hematological malignancies. The immunological aspects of the JAK/STAT pathway also require more exploration, particularly in the context of developing novel immunotherapies, such as mRNA vaccines, CAR T-cell therapies, and engineered

immune cells [135, 136]. Investigating the efficacy of drugs targeting this pathway at the clinical level is critical for advancing treatment strategies. A deeper understanding of the molecular mechanisms governing the interaction between JAK/STAT signaling and ferroptosis is essential, especially in varying disease contexts. The development of more advanced models, such as patient-derived organoids and in vivo systems, will be crucial for testing the specificity and therapeutic efficacy of JAK/STAT and ferroptosis-targeting interventions. Special attention should be given to cytokines like IL-6, IL-13, and IL-4, which regulate JAK/STAT and influence ferroptosis, as targeting these interleukin-driven pathways may provide novel treatments for cancer, autoimmune diseases, and neurodegenerative conditions. Furthermore, exploring natural and synthetic products that target the STAT-ferroptosis axis could lead to promising combinational therapies, offering solutions for overcoming drug resistance, particularly in cancers. Nanotechnology, in particular, holds immense potential [137, 138]. Developing nanoparticles that specifically target the JAK/STAT pathway while inducing ferroptosis could offer a more precise, less toxic alternative to current treatments [139, 140]. By targeting ferroptosis inducers alongside JAK/STAT inhibitors, we could significantly improve therapeutic outcomes, particularly in cancers resistant to conventional therapies. The importance of cutting-edge CRISPR technology cannot be overstated in this context [141]. CRISPR-based gene editing holds enormous potential to directly manipulate genes involved in the JAK/STAT-ferroptosis axis, enabling precise functional studies and the development of more effective, personalized treatments. It could also facilitate the creation of novel models that mimic human disease more accurately, providing new insights into therapeutic vulnerabilities and enhancing drug discovery efforts. Integrating CRISPR with other technologies, such as RNA interference or gene therapy, could further accelerate progress in targeting these pathways with unprecedented precision.

However, several limitations must be acknowledged. While the potential of targeting the JAK/STAT-ferroptosis axis is clear, much remains unknown about the full spectrum of its effects across different cell types and tissues. There is also a need for more clinical data to validate preclinical findings, particularly with regard to the safety and efficacy of these treatments in humans. Another challenge is the inherent complexity of ferroptosis regulation, which involves multiple metabolic pathways, including amino acid and lipid metabolism, as well as iron homeostasis. Therapeutic interventions may carry risks of unintended side effects, such as excessive tissue damage in diseases where ferroptosis is beneficial, such as certain neurodegenerative diseases and tissue repair contexts. Furthermore, resistance to ferroptosis may evolve as a secondary complication in chronic diseases or prolonged treatments, necessitating more refined and adaptable approaches. The development of resistance mechanisms, particularly in cancer, is a significant concern and underscores the need for ongoing research into combination therapies that can sustainably target the JAK/STAT pathway while preventing disease adaptation. In summary, while there is enormous potential in targeting the JAK/STAT-ferroptosis axis, future studies must address these limitations through enhanced mechanistic understanding, better translational models, and comprehensive clinical trials to ensure both safety and efficacy in therapeutic applications.

Author contributions

YD: Writing– original draft; CC: Investigation, Methodology, Writing– original draft; DJ: Writing– original draft; XZ: Project administration, Supervision, Visualization, Writing– original draft, Writing– review & editing.

Funding

No fund was received for this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Informed consent to consent for publication

Not applicable.

Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT by OpenAI to improve paper readability. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

Competing interests

The authors declare no competing interests.

Received: 21 October 2024 / Accepted: 7 February 2025
Published online: 07 March 2025

References

1. Zhou Q, Meng Y, Li D, Yao L, Le J, Liu Y, et al. Ferroptosis in cancer: from molecular mechanisms to therapeutic strategies. Signal Transduct Target Ther. 2024;9:55. https://doi.org/10.1038/s41392-024-01769-5.
2. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72.
3. Berndt C, Alborzinia H, Amen VS, Ayton S, Barayeu U, Bartelt A, et al. Ferroptosis in health and disease. Redox Biol. 2024;75:103211. https://doi.org/10.1016/j.redox.2024.103211.
4. Luo Y, Alexander M, Gadina M, O'Shea JJ, Meylan F, Schwartz DM. JAK-STAT signaling in human disease: from genetic syndromes to clinical inhibition. J Allergy Clin Immunol. 2021;148:911–25.
5. Pang Q, Tang Z, Luo L. The crosstalk between oncogenic signaling and ferroptosis in cancer. Crit Rev Oncol Hematol. 2024;197:104349.
6. Su H, Peng C, Liu Y. Regulation of ferroptosis by PI3K/Akt signaling pathway: a promising therapeutic axis in cancer. Front Cell Dev Biol. 2024;12:1372330.

7. Wu D, Wang Z, Zhang Y, Yang Y, Yang Y, Zu G, et al. IL15RA-STAT3-GPX4/ACSL3 signaling leads to ferroptosis resistance in pancreatic cancer. Acta Biochim Biophys Sin (Shanghai); 2024.
8. Zhao Y, Zhao Y, Wang C, Yang T, Wang H, Zhao S, Sun N, Chen Y, Zhang H FHC acid alleviates chronic stress-induced duodenal ferroptosis via the inhibition of the I-6/JAK2/STAT3 signaling pathway in rats. JAFC (, Wang C, Yang T, Wang H, Zhao S, Sun N et al. Chlorogenic acid alleviates chronic stress-induced duodenal ferroptosis via the inhibition of the IL-6/JAK2/STAT3 signaling pathway in rats. J Agric Food Chem 2022;70:4353–61.
9. Hu Q, Bian Q, Rong D, Wang L, Song J, Huang H-S et al. JAK/STAT pathway: extracellular signals, diseases, immunity, and therapeutic regimens. Front Bioeng Biotechnol 2023;11.
10. Hu X, li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6:402. https://doi.org/10.1038/s41392-021-00791-1.
11. Copf T, Goguel V, Lampin-Saint-Amaux A, Scaplehorn N, Preat T. Cytokine signaling through the JAK/STAT pathway is required for long-term memory in Drosophila. Proc Natl Acad Sci. 2011;108:8059–64.
12. Wang Y, Sun Y, Wang F, Wang H, Hu J. Ferroptosis induction via targeting metabolic alterations in triple-negative breast cancer. Biomed Pharmacother. 2023;169:115866. https://doi.org/10.1016/j.biopha.2023.115866.
13. Song X, Long D. Nrf2 and ferroptosis: a new research direction for neurodegenerative diseases. Front Neurosci. 2020;14:267.
14. Tang X, Chen W, Liu H, Liu N, Chen D, Tian D, et al. Research progress on SLC7A11 in the regulation of cystine/cysteine metabolism in tumors. Volume 23. Spandidos; 2022.
15. Zheng X, Jin X, Ye F, Liu X, Yu B, Li Z, et al. Ferroptosis: a novel regulated cell death participating in cellular stress response, radiotherapy, and immunotherapy. Exp Hematol Oncol. 2023;12:65.
16. Liu M, Kong X-Y, Yao Y, Wang X-A, Yang W, Wu H et al. The critical role and molecular mechanisms of ferroptosis in antioxidant systems: a narrative review. Ann Transl Med 2022;10.
17. Magtanong L, Ko P-J, To M, Cao JY, Forcina GC, Tarangelo A, et al. Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. Cell Chem Biol. 2019;26:420–32.
18. Kim JW, Lee J-Y, Oh M, Lee E-W. An integrated view of lipid metabolism in ferroptosis revisited via lipidomic analysis. Exp Mol Med. 2023;55:1620–31.
19. Sen U, Coleman C, Sen T. Stearoyl coenzyme a desaturase-1: multitasker in cancer, metabolism, and ferroptosis. Trends in Cancer; 2023.
20. Shao G, Qian Y, Lu L, Liu Y, Wu T, Ji G, et al. Research progress in the role and mechanism of LPCAT3 in metabolic related diseases and cancer. J Cancer. 2022;13:2430.
21. Yang L, Cao L, Zhang X, Chu B. Targeting ferroptosis as a vulnerability in pulmonary diseases. Cell Death Dis. 2022;13:649.
22. da Nishida T, Friedmann Angeli JP, Ingold I. GPX4: old lessons, new features. Biochem Soc Trans. 2022;50:1205–13.
23. Pope LE, Dixon SJ. Regulation of ferroptosis by lipid metabolism. Trends Cell Biol. 2023;33.
24. Ou R, Aodeng G, Ai J. Advancements in the application of the Fenton reaction in the Cancer Microenvironment. Pharmaceutics. 2023;15:2337.
25. Motooka Y, Toyokuni S. Ferroptosis as ultimate target of cancer therapy. Antioxid Redox Signal. 2023;39:206–23.
26. Chen L, Ma Y, Ma X, Liu L, Jv X, Li A, et al. TFEB regulates cellular labile iron and prevents ferroptosis in a TfR1-dependent manner. Free Radic Biol Med. 2023;208:445–57.
27. Venkataramani V. Iron homeostasis and metabolism: two sides of a coin. Ferroptosis Mech Dis. 2021;1301:25–40.
28. Zhang X-D, Liu Z-Y, Wang M-S, Guo Y-X, Wang X-K, Luo K et al. Mechanisms and regulations of ferroptosis. Front Immunol 2023;14.
29. Zhao J, Wang Y, Tao L, Chen L. Iron transporters and ferroptosis in malignant brain tumors. Front Oncol. 2022;12:861834.
30. Li S, Huang P, Lai F, Zhang T, Guan J, Wan H, et al. Mechanisms of ferritinophagy and ferroptosis in diseases. Mol Neurobiol. 2024;61:1605–26.
31. Mancardi D, Mezzanotte M, Arrigo E, Barinotti A, Roetto A. Iron overload, oxidative stress, and ferroptosis in the failing heart and liver. Antioxidants. 2021;10. https://doi.org/10.3390/antiox10121864.
32. Lane DJR, Metselaar B, Greenough M, Bush AI, Ayton SJ. Ferroptosis and NRF2: an emerging battlefield in the neurodegeneration of Alzheimer's disease. Essays Biochem. 2021;65:925–40.
33. Yan R, Lin B, Jin W, Tang L, Hu S, Cai R. NRF2, a superstar of Ferroptosis. Antioxidants. 2023;12:1739.
34. Cao T, Zhou J, Liu Q, Mao T, Chen B, Wu Q, et al. Interferon-γ induces salivary gland epithelial cell ferroptosis in Sjogren's syndrome via JAK/STAT1-mediated inhibition of system Xc-. Free Radic Biol Med. 2023;205:116–28. https://doi.org/10.1016/j.freeradbiomed.2023.05.027.
35. Wei T-T, Zhang M-Y, Zheng X-H, Xie T-H, Wang W, Zou J, et al. Interferon-γ induces retinal pigment epithelial cell ferroptosis by a JAK1-2/STAT1/SLC7A11 signaling pathway in Age-related Macular Degeneration. FEBS J. 2022;289:1968–83. https://doi.org/10.1111/febs.16272.
36. Mo M, Pan L, Deng L, Liang M, Xia N, Liang Y. Iron Overload induces hepatic ferroptosis and insulin resistance by inhibiting the Jak2/stat3/slc7a11 signaling pathway. Cell Biochem Biophys. 2024. https://doi.org/10.1007/s12013-024-01315-8.
37. Chen W, Pan X, Song X, Liu Z, Xu D, Chen J, et al. Preoperative neoadjuvant targeted therapy remodels intra-tumoral heterogeneity of clear-cell renal cell carcinoma and ferroptosis inhibition induces resistance progression. Cancer Lett. 2024;593:216963. https://doi.org/10.1016/j.canlet.2024.216963.
38. Li M, Jin S, Zhang Z, Ma H, Yang X. Interleukin-6 facilitates tumor progression by inducing ferroptosis resistance in head and neck squamous cell carcinoma. Cancer Lett. 2022;527:28–40. https://doi.org/10.1016/j.canlet.2021.12.011.
39. Wang Z, Zong H, Liu W, Lin W, Sun A, Ding Z, et al. Augmented ERO1α upon mTORC1 activation induces ferroptosis resistance and tumor progression via upregulation of SLC7A11. J Exp Clin Cancer Res. 2024;43:112. https://doi.org/10.1186/s13046-024-03039-2.
40. Huang C-Y, Chen L-J, Chen C-S, Wang C-Y, Hong S-Y. MCL1 inhibition: a promising approach to augment the efficacy of sorafenib in NSCLC through ferroptosis induction. Cell Death Discov. 2024;10:137. https://doi.org/10.1038/s41420-024-01908-5.
41. Huang C-Y, Chen L-J, Chen G, Chao T-I, Wang C-Y. SHP-1/STAT3-Signaling-Axis-regulated coupling between BECN1 and SLC7A11 contributes to Sorafenib-Induced ferroptosis in Hepatocellular Carcinoma. Int J Mol Sci. 2022;23. https://doi.org/10.3390/ijms231911092.
42. Xia S, Liang Y, Shen Y, Zhong W, Ma Y. MAT2A inhibits the ferroptosis in osteosarcoma progression regulated by miR-26b-5p. J Bone Oncol. 2023;41:100490. https://doi.org/10.1016/j.jbo.2023.100490.
43. Ji J, Li H, Wang W, Yuan B, Shen T. ARPC1A is regulated by STAT3 to inhibit ferroptosis and promote prostate cancer progression. Hum Cell. 2022;35:1591–601. https://doi.org/10.1007/s13577-022-00754-w.
44. Zhu X, Wang X, Zhu B, Ding S, Shi H, Yang X. Disruption of histamine/H1R-STAT3-SLC7A11 axis exacerbates doxorubicin-induced cardiac ferroptosis. Free Radic Biol Med. 2022;192:98–114. https://doi.org/10.1016/j.freeradbiomed.2022.09.012.
45. Liang P, Zhang X, Zhang Y, Wu Y, Song Y, Wang X, et al. Neurotoxic A1 astrocytes promote neuronal ferroptosis via CXCL10/CXCR3 axis in epilepsy. Free Radic Biol Med. 2023;195:329–42. https://doi.org/10.1016/j.freeradbiomed.2023.01.002.
46. Yang Y, Ma Y, Li Q, Ling Y, Zhou Y, Chu K, et al. STAT6 inhibits ferroptosis and alleviates acute lung injury via regulating P53/SLC7A11 pathway. Cell Death Dis. 2022;13:530. https://doi.org/10.1038/s41419-022-04971-x.
47. Miao M, Pan M, Chen X, Shen J, Zhang L, Feng X, et al. IL-13 facilitates ferroptotic death in asthmatic epithelial cells via SOCS1-mediated ubiquitinated degradation of SLC7A11. Redox Biol. 2024;71:103100. https://doi.org/10.1016/j.redox.2024.103100.
48. Li Y, Zhang Y, Qiu Q, Wang L, Mao H, Hu J et al. Energy-stress-mediated AMPK activation promotes GPX4-Dependent ferroptosis through the JAK2/STAT3/P53 Axis in Renal Cancer. Oxid Med Cell Longev 2022;2022:2353115. https://doi.org/10.1155/2022/2353115
49. Li X, Sun H, Zhang L, Liang H, Zhang B, Yang J, et al. GDF15 attenuates sepsis-induced myocardial dysfunction by inhibiting cardiomyocytes ferroptosis via the SOCS1/GPX4 signaling pathway. Eur J Pharmacol. 2024;982:176894. https://doi.org/10.1016/j.ejphar.2024.176894.
50. Zhang Z, Tang J, Song J, Xie M, Liu Y, Dong Z, et al. Elabela alleviates ferroptosis, myocardial remodeling, fibrosis and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling. Free Radic Biol Med. 2022;181:130–42. https://doi.org/10.1016/j.freeradbiomed.2022.01.020.
51. Yang Q, Xia Y, Chen K, Wang Y, Song D, Zhu J, et al. Blue light induced ferroptosis via STAT3/GPX4/SLC7A11/FTH1 in conjunctiva epithelium in vivo and in vitro. J Photochem Photobiol B Biol. 2024;255:112908. https://doi.org/10.1016/j.jphotobiol.2024.112908.
52. Xiao S, Zhang Y, Wang S, Liu J, Dan F, Yang F et al. The Syvn1 inhibits neuronal cell ferroptosis by activating Stat3/Gpx4 axis in rat with spinal cord injury. Cell Prolif 2024;n/a:e13658. https://doi.org/10.1111/cpr.13658

53. Zhu Q, Sun J, An C, Li X, Xu S, He Y, et al. Mechanism of LncRNA Gm2044 in germ cell development. Front Cell Dev Biol. 2024;12:1410914.
54. Li G, Feng J, Huang S, Li Q. LncRNA-PVT1 Inhibits Ferroptosis through Activating STAT3/GPX4 Axis to Promote Osteosarcoma Progression. FBL. 2024;29:207-null.
55. Xu X, Zhu M, Zu Y, Wang G, Li X, Yan J. Nox2 inhibition reduces trophoblast ferroptosis in preeclampsia via the STAT3/GPX4 pathway. Life Sci. 2024;343:122555. https://doi.org/10.1016/j.lfs.2024.122555.
56. Bao J, Wang Z, Yang Y, Yu X, Yuan W, Sun W, et al. Interleukin-17 alleviates erastin-induced alveolar bone loss by suppressing ferroptosis via interaction between NRF2 and p-STAT3. J Clin Periodontol. 2024;51:233–50. https://doi.org/10.1111/jcpe.13898.
57. Liu Q, Wang K. The induction of ferroptosis by impairing STAT3/Nrf2/GPx4 signaling enhances the sensitivity of osteosarcoma cells to cisplatin. Cell Biol Int. 2019;43:1245–56. https://doi.org/10.1002/cbin.11121.
58. Han L, Ma C, Wu Z, Xu H, Li H, Pan G. AhR–STAT3–HO-1/COX-2 signalling pathway may restrict ferroptosis and improve hMSC accumulation and efficacy in mouse liver. Br J Pharmacol. 2024;181:125–41. https://doi.org/10.1111/bph.16208.
59. Chen X, Jian D, Xing J, Cheng X, Wang C, Wang C, et al. Targeting OGF/OGFR signal to mitigate doxorubicin-induced cardiotoxicity. Free Radic Biol Med. 2024;223:398–412. https://doi.org/10.1016/j.freeradbiomed.2024.08.005.
60. Zhao Y, Zhao J, Ma H, Han Y, Xu W, Wang J, et al. High hepcidin levels promote abnormal Iron metabolism and ferroptosis in Chronic Atrophic Gastritis. Biomedicines. 2023;11. https://doi.org/10.3390/biomedicines11092338.
61. Zhu M, Peng L, Huo S, Peng D, Gou J, Shi W, et al. STAT3 signaling promotes cardiac injury by upregulating NCOA4-mediated ferritinophagy and ferroptosis in high-fat-diet fed mice. Free Radic Biol Med. 2023;201:111–25. https://doi.org/10.1016/j.freeradbiomed.2023.03.003.
62. Kong P, Yang M, Wang Y, Yu KN, Wu L, Han W. Ferroptosis triggered by STAT1-IRF1-ACSL4 pathway was involved in radiation-induced intestinal injury. Redox Biol. 2023;66:102857. https://doi.org/10.1016/j.redox.2023.102857.
63. Hong J, Li X, Hao Y, Xu H, Yu L, Meng Z, et al. The PRMT6/STAT1/ACSL1 axis promotes ferroptosis in diabetic nephropathy. Cell Death Differ. 2024. https://doi.org/10.1038/s41418-024-01357-8.
64. Poindessous V, Lazareth H, Crambert G, Cheval L, Sampaio JL, Pallet N. STAT3 drives the expression of ACSL4 in acute kidney injury. IScience. 2024;27. https://doi.org/10.1016/j.isci.2024.109737.
65. Xiao L, Ma X, Ye L, Su P, Xiong W, Bi E et al. IL-9/STAT3/fatty acid oxidation–mediated lipid peroxidation contributes to Tc9 cell longevity and enhanced antitumor activity. J Clin Invest 2022;132.
66. Wu W, Luo Z, Shen D, Lan T, Xiao Z, Liu M, et al. IL-10 protects against OPC ferroptosis by regulating lipid reactive oxygen species levels post stroke. Redox Biol. 2024;69:102982. https://doi.org/10.1016/j.redox.2023.102982.
67. Liao J, Duan Y, Liu Y, Chen H, An Z, Chen Y, et al. Simvastatin alleviates glymphatic system damage via the VEGF-C/VEGFR3/PI3K-Akt pathway after experimental intracerebral hemorrhage. Brain Res Bull. 2024;216:111045.
68. Luo Y, Chen Y, Jin H, Hou B, Li H, Li X et al. The suppression of cervical cancer ferroptosis by macrophages: the attenuation of ALOX15 in cancer cells by macrophages-derived exosomes. Acta Pharm Sin B. 2023;13.
69. Zhang H, Ge Z, Wang Z, Gao Y, Wang Y, Qu X. Circular RNA RHOT1 promotes progression and inhibits ferroptosis via mir-106a-5p/STAT3 axis in breast cancer. Aging. 2021;13:8115.
70. Li X, Liu J. FANCD2 inhibits ferroptosis by regulating the JAK2/STAT3 pathway in osteosarcoma. BMC Cancer. 2023;23:179. https://doi.org/10.1186/s12885-023-10626-7.
71. Cao Y, Zou Z, Wu X, Li W, Lu Z, Hu J et al. LUCAT1 inhibits ferroptosis in bladder cancer by regulating the mRNA stability of STAT3. Gene. 2024;894:147974. https://doi.org/10.1016/j.gene.2023.147974
72. Yong X, Zhang Y, Tang H, Hu H, Song R, Wu Q. CDKN2A inhibited ferroptosis through activating JAK2/STAT3 pathway to modulate cisplatin resistance in cervical squamous cell carcinoma. Anticancer Drugs. 2024;35:10–1097.
73. Ouyang S, Li H, Lou L, Huang Q, Zhang Z, Mo J, et al. Inhibition of STAT3-ferroptosis negative regulatory axis suppresses tumor growth and alleviates chemoresistance in gastric cancer. Redox Biol. 2022;52:102317. https://doi.org/10.1016/j.redox.2022.102317.
74. Liu Y, Hou Y, Zhang F, Wang X. ENO1 deletion potentiates ferroptosis and decreases glycolysis in colorectal cancer cells via AKT/STAT3 signaling. Exp Ther Med. 2024;27:127. https://doi.org/10.3892/etm.2024.12415.
75. Huang F, Zhang S, Li X, Huang Y, He S, Luo L. STAT3-mediated ferroptosis is involved in ulcerative colitis. Free Radic Biol Med. 2022;188:375–85. https://doi.org/10.1016/j.freeradbiomed.2022.06.242.
76. Xi X, Chen Q, Ma J, Wang X, Zhang J, Li Y. Sestrin2 ameliorates diabetic retinopathy by regulating autophagy and ferroptosis. J Mol Histol. 2024;55:169–84. https://doi.org/10.1007/s10735-023-10180-3.
77. Zhao M, Shen Z, Zheng Z, Xu Y, Zhang J, Liu J, et al. Cardiomyocyte LGR6 alleviates ferroptosis in diabetic cardiomyopathy via regulating mitochondrial biogenesis. Metabolism. 2024;159:155979. https://doi.org/10.1016/j.metabol.2024.155979.
78. Lin S, Yan J, Wang W, Luo L. STAT3-Mediated ferroptosis is involved in Sepsis-Associated Acute Respiratory Distress Syndrome. Inflammation. 2024;47:1204–19. https://doi.org/10.1007/s10753-024-01970-2.
79. Chen Y, Yang X, Feng M, Yu Y, Hu Y, Jiang W. Exosomal mir-223-3p from bone marrow mesenchymal stem cells targets HDAC2 to downregulate STAT3 phosphorylation to alleviate HBx-induced ferroptosis in podocytes. Front Pharmacol 2024;15.
80. Wang E, Zhang B, Huang L, Li P, Han R, Zhou S, et al. LncRNA MIR210HG promotes phenotype switching of pulmonary arterial smooth muscle cells through autophagy-dependent ferroptosis pathway. Apoptosis. 2024;29:1648–62. https://doi.org/10.1007/s10495-024-01963-4.
81. Xiong J, Zhou R, Deng X. PRDX6 alleviated heart failure by inhibiting doxorubicin-induced ferroptosis through the JAK2/STAT1 pathway inactivation. Vitr Cell Dev Biol - Anim. 2024;60:354–64. https://doi.org/10.1007/s11626-024-00889-0.
82. Luo L, Deng L, Chen Y, Ding R, Li X. Identification of Lipocalin 2 as a ferroptosis-related Key Gene Associated with hypoxic-ischemic brain damage via STAT3/NF-κB signaling pathway. Antioxidants 2023;12. https://doi.org/10.3390/antiox12010186
83. Qiang Z, Dong H, Xia Y, Chai D, Hu R, Jiang H. Nrf2 and STAT3 alleviates ferroptosis-mediated IIR-ALI by regulating SLC7A11. Oxid Med Cell Longev. 2020;2020:5146982. https://doi.org/10.1155/2020/5146982.
84. Gu Y, Lv L, Jin J, Hua X, Xu Q, Wu R, et al. STING mediates LPS-induced acute lung injury by regulating ferroptosis. Exp Cell Res. 2024;438:114039. https://doi.org/10.1016/j.yexcr.2024.114039.
85. Lan C, Zhou X, Shen X, Lin Y, Chen X, Lin J, et al. Suppression of IRF9 promotes osteoclast differentiation by decreased ferroptosis via STAT3 activation. Inflammation. 2024;47:99–113. https://doi.org/10.1007/s10753-023-01896-1.
86. Lin Y, Li H, Zheng S, Han R, Wu K, Tang S, et al. Elucidating tobacco smoke-induced craniofacial deformities: Biomarker and MAPK signaling dysregulation unraveled by cross-species multi-omics analysis. Ecotoxicol Environ Saf. 2024;288:117343. https://doi.org/10.1016/j.ecoenv.2024.117343.
87. Li G, Lin Y, Zhang Y, Gu N, Yang B, Shan S, et al. Endometrial stromal cell ferroptosis promotes angiogenesis in endometriosis. Cell Death Discov. 2022;8:29. https://doi.org/10.1038/s41420-022-00821-z.
88. Sun Y, Huang D, Li J, Zhou Y, Zhou G, Chen Q. Inhibition of STAT3-NF-κB pathway facilitates SSPH I-induced ferroptosis in HepG2 cells. Med Oncol. 2024;41:184. https://doi.org/10.1007/s12032-024-02425-2.
89. Xu W, Li Y, Liu L, Xie J, Hu Z, Kuang S, et al. Icaritin-curcumol activates CD8 + T cells through regulation of gut microbiota and the DNMT1/IGFBP2 axis to suppress the development of prostate cancer. J Exp Clin Cancer Res. 2024;43:149. https://doi.org/10.1186/s13046-024-03063-2.
90. Cang W, Wu A, Gu L, Wang W, Tian Q, Zheng Z, et al. Erastin enhances metastatic potential of ferroptosis-resistant ovarian cancer cells by M2 polarization through STAT3/IL-8 axis. Int Immunopharmacol. 2022;113:109422. https://doi.org/10.1016/j.intimp.2022.109422.
91. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy. 2020;16:2069–83.
92. Feng Z, Meng F, Huo F, Zhu Y, Qin Y, Gui Y, et al. Inhibition of ferroptosis rescues M2 macrophages and alleviates arthritis by suppressing the HMGB1/TLR4/STAT3 axis in M1 macrophages. Redox Biol. 2024;75:103255. https://doi.org/10.1016/j.redox.2024.103255.
93. Schwantes A, Wickert A, Becker S, Baer PC, Weigert A, Brüne B, et al. Tumor associated macrophages transfer ceruloplasmin mRNA to fibrosarcoma cells and protect them from ferroptosis. Redox Biol. 2024;71:103093. https://doi.org/10.1016/j.redox.2024.103093.
94. Tao Q, Liu N, Wu J, Chen J, Chen X, Peng C. Mefloquine enhances the efficacy of anti-PD-1 immunotherapy via IFN-γ-STAT1-IRF1-LPCAT3-induced ferroptosis in tumors. J Immunother Cancer. 2024;12:e008554. https://doi.org/10.1136/jitc-2023-008554.
95. Gao Y, Liu S, Huang Y, Wang H, Zhao Y, Cui X, et al. CAR T cells Engineered to secrete IFNκ induce Tumor Ferroptosis via an IFNAR/STAT1/ACSL4 Axis. Cancer Immunol Res. 2024;OF1–12. https://doi.org/10.1158/2326-6066.CIR-24-0130.

96. Fan Z, Liu Y, Wang X, Xu Y, Huang R, Shi W, et al. APOL6 predicts immunotherapy efficacy of bladder cancer by ferroptosis. BMC Cancer. 2024;24:1046. https://doi.org/10.1186/s12885-024-12820-7.
97. Samarin J, Fabrowski P, Kurilov R, Nuskova H, Hummel-Eisenbeiss J, Pink H, et al. Low level of antioxidant capacity biomarkers but not target overexpression predicts vulnerability to ROS-inducing drugs. Redox Biol. 2023;62:102639. https://doi.org/10.1016/j.redox.2023.102639.
98. Chen J-Y, Tian X-Y, Wei S-S, Yang Y-J, Deng S, Jiao C-J et al. Perspectives of herbs and their natural compounds, and herb formulas on treating diverse diseases through regulating complicated JAK/STAT signaling. Front Pharmacol 2022;13.
99. He J, Feng X, Liu Y, Wang Y, Ge C, Liu S, et al. Graveoline attenuates D-GalN/LPS-induced acute liver injury via inhibition of JAK1/STAT3 signaling pathway. Biomed Pharmacother. 2024;177:117163.
100. Cheng X, Huang J, Li H, Zhao D, Liu Z, Zhu L, et al. Quercetin: a promising therapy for diabetic encephalopathy through inhibition of hippocampal ferroptosis. Phytomedicine. 2024;126:154887.
101. Sun D, Li X, Nie S, Liu J, Wang S. Disorders of cancer metabolism: the therapeutic potential of cannabinoids. Biomed Pharmacother. 2023;157:113993. https://doi.org/10.1016/j.biopha.2022.113993.
102. Lou J-S, Zhao L-P, Huang Z-H, Chen X-Y, Xu J-T, Tai WC-S, et al. Ginkgetin derived from Ginkgo biloba leaves enhances the therapeutic effect of cisplatin via ferroptosis-mediated disruption of the Nrf2/HO-1 axis in EGFR wild-type non-small-cell lung cancer. Phytomedicine. 2021;80:153370.
103. Zeng Z, Hu Y, Xiang J, Su J, Tan H, Lai T, et al. Cucurbitacin B targets STAT3 to induce ferroptosis in non-small cell lung cancer. Eur J Pharmacol. 2024;978:176805. https://doi.org/10.1016/j.ejphar.2024.176805.
104. Tong G, Peng T, Chen Y, Sha L, Dai H, Xiang Y, et al. Effects of GLP-1 receptor agonists on biological behavior of colorectal cancer cells by regulating PI3K/AKT/mTOR signaling pathway. Front Pharmacol. 2022;13:901559.
105. Su Y, Tian X, Gao R, Guo W, Chen C, Chen C, et al. Colon cancer diagnosis and staging classification based on machine learning and bioinformatics analysis. Comput Biol Med. 2022;145:105409. https://doi.org/10.1016/j.compbiomed.2022.105409.
106. Lai J, Zhao L, Hong C, Zou Q, Su J, Li S, et al. Baicalein triggers ferroptosis in colorectal cancer cells via blocking the JAK2/STAT3/GPX4 axis. Acta Pharmacol Sin. 2024;45:1715–26. https://doi.org/10.1038/s41401-024-01258-z.
107. Dong X-Q, Chu L-K, Cao X, Xiong Q-W, Mao Y-M, Chen C-H, et al. Glutathione metabolism rewiring protects renal tubule cells against cisplatin-induced apoptosis and ferroptosis. Redox Rep. 2023;28:2152607. https://doi.org/10.1080/13510002.2022.2152607.
108. Yu X, Xu B, Zhang M, Yao X, Xu K, Gao F. Salidroside inhibits the ferroptosis to alleviate lung ischemia reperfusion injury via the JAK2/STAT3 signalling pathway. Biochem Biophys Res Commun. 2024;722:150132. https://doi.org/10.1016/j.bbrc.2024.150132.
109. Zhang W, Gong M, Zhang W, Mo J, Zhang S, Zhu Z, et al. Thiostrepton induces ferroptosis in pancreatic cancer cells through STAT3/GPX4 signalling. Cell Death Dis. 2022;13:630. https://doi.org/10.1038/s41419-022-05082-3.
110. Nie X-H, Qiu S, Xing Y, Xu J, Lu B, Zhao S-F, et al. Paeoniflorin regulates NEDD4L/STAT3 pathway to induce ferroptosis in human glioma cells. J Oncol. 2022;2022:6093216. https://doi.org/10.1155/2022/6093216.
111. Batbold U, Liu J-J. Artemisia santolinifolia-mediated chemosensitization via activation of distinct cell death modes and suppression of STAT3/survivin-signaling pathways in NSCLC. Molecules. 2021;26:7200.
112. Luo Y, Gao X, Zou L, Lei M, Feng J, Hu Z. Bavachin induces ferroptosis through the STAT3/P53/SLC7A11 axis in osteosarcoma cells. Oxid Med Cell Longev. 2021;2021.
113. Gawish RA, Samy EM, Aziz MM. Ferulic acid protects against gamma-radiation induced liver injury via regulating JAK/STAT/Nrf2 pathways. Arch Biochem Biophys. 2024;753:109895. https://doi.org/10.1016/j.abb.2024.109895.
114. Li X, Qi H, Zhang X, Liang H, Zeng N. Jing-Fang n-butanol extract and its isolated JFNE-C inhibit ferroptosis and inflammation in LPS induced RAW264.7 macrophages via STAT3/p53/SLC7A11 signaling pathway. J Ethnopharmacol. 2023;316:116689. https://doi.org/10.1016/j.jep.2023.116689.
115. Gao Y, Zhang Z, Du J, Yang X, Wang X, Wen K, et al. Xue-Jie-San restricts ferroptosis in Crohn's disease via inhibiting FGL1/NF-κB/STAT3 positive feedback loop. Front Pharmacol. 2023;14:1148770.
116. Wu Y, Pi D, Zhou S, Yi Z, Dong Y, Wang W, et al. Ginsenoside Rh3 induces pyroptosis and ferroptosis through the Stat3/p53/NRF2 axis in colorectal cancer cells: Ginsenoside Rh3 has anti-colorectal cancer properties. Acta Biochim Biophys Sin (Shanghai). 2023;55:587.
117. Li F, Hao S, Gao J, Jiang P. EGCG alleviates obesity-exacerbated lung cancer progression by STAT1/SLC7A11 pathway and gut microbiota. J Nutr Biochem. 2023;120:109416.
118. Zhang L, Wang J, Deng W, Gui F, Peng F, Zhu Q. Solamargine induces Hepatocellular Carcinoma Cell apoptosis and ferroptosis via regulating STAT1/MTCH1 Axis. Biochem Genet. 2024. https://doi.org/10.1007/s10528-024-10749-x.
119. Shi J, Yang MM, Yang S, Fan F, Zheng G, Miao Y, et al. MaiJiTong granule attenuates atherosclerosis by reducing ferroptosis via activating STAT6-mediated inhibition of DMT1 and SOCS1/p53 pathways in LDLR–/– mice. Phytomedicine. 2024;128:155489. https://doi.org/10.1016/j.phymed.2024.155489.
120. Chen L, Sun R, Fang K. Erianin inhibits tumor growth by promoting ferroptosis and inhibiting invasion in hepatocellular carcinoma through the JAK2/STAT3/SLC7A11 pathway. Pathol Int. 2024;74:119–28. https://doi.org/10.1111/pin.13403.
121. Fan F, Liu P, Bao R, Chen J, Zhou M, Mo Z, et al. A dual PI3K/HDAC inhibitor induces immunogenic ferroptosis to potentiate cancer immune checkpoint therapy. Cancer Res. 2021;81:6233–45.
122. Huang L, Zhang Y, Zhao L, Chen Q, Li L. Ferrostatin-1 polarizes microglial cells toward M2 phenotype to alleviate inflammation after Intracerebral Hemorrhage. Neurocrit Care. 2022;36:942–54. https://doi.org/10.1007/s12028-021-01401-2.
123. Cao F, Li M, Wang W, Yi Y, Chen Y, Liu H. A coumarin-furoxan hybrid as novel nitric oxide donor induced cell apoptosis and ferroptosis in NSCLC by promoting S-nitrosylation of STAT3 and negative regulation of JAK2-STAT3 pathway. Biochem Pharmacol. 2024;222:116068. https://doi.org/10.1016/j.bcp.2024.116068.
124. Huang H, Huang F, Liang X, Fu Y, Cheng Z, Huang Y, et al. Afatinib reverses EMT via inhibiting CD44-Stat3 axis to promote radiosensitivity in nasopharyngeal carcinoma. Pharmaceuticals. 2022;16:37.
125. Huang Q, Li J, Ma M, Lv M, Hu R, Sun J, et al. High–throughput screening identification of a small–molecule compound that induces ferroptosis and attenuates the invasion and migration of hepatocellular carcinoma cells by targeting the STAT3/GPX4 axis. Int J Oncol. 2023;62:42. https://doi.org/10.3892/ijo.2023.5490.
126. Lin X, Liao Y, Chen X, Long D, Yu T, Shen F. Regulation of Oncoprotein 18/Stathmin Signaling by ERK Concerns the Resistance to Taxol in Nonsmall Cell Lung Cancer cells. Cancer Biother Radiopharm. 2016;31:37–43. https://doi.org/10.1089/cbr.2015.1921.
127. Chen Y, Tao H, Wang F, Wu P, Gao J, Zhang X, et al. Artesunate synergistically promotes sorafenib–induced apoptosis and ferroptosis in non–Hodgkin lymphoma cells through inhibition of the STAT3 pathway. Oncol Rep. 2023;50:147. https://doi.org/10.3892/or.2023.8584.
128. Liu Y-P, Qiu Z-Z, Li X-H, Li E-Y. Propofol induces ferroptosis and inhibits malignant phenotypes of gastric cancer cells by regulating miR-125b-5p/STAT3 axis. World J Gastrointest Oncol. 2021;13:2114.
129. Zhao X, Chen F. Propofol induces the ferroptosis of colorectal cancer cells by downregulating STAT3 expression. Oncol Lett. 2021;22:1–9.
130. Schmitt A, Xu W, Bucher P, Grimm M, Konantz M, Horn H, et al. Dimethyl fumarate induces ferroptosis and impairs NF-κB/STAT3 signaling in DLBCL. Blood. 2021;138:871–84. https://doi.org/10.1182/blood.2020009404.
131. Long Q, Tao H, Wang P, Wu B, Zhu Q, Chen H, et al. Fludarabine enhances radiosensitivity by promoting ferroptosis in B-Cell lymphoma. Radiat Res. 2024;201:224–39.
132. Hu Z, Zhao Y, Li L, Jiang J, Li W, Mang Y, et al. Metformin promotes ferroptosis and sensitivity to sorafenib in hepatocellular carcinoma cells via ATF4/STAT3. Mol Biol Rep. 2023;50:6399–413.
133. Chen Y, Wang F, Wu P, Gong S, Gao J, Tao H, et al. Artesunate induces apoptosis, autophagy and ferroptosis in diffuse large B cell lymphoma cells by impairing STAT3 signaling. Cell Signal. 2021;88:110167. https://doi.org/10.1016/j.cellsig.2021.110167.
134. Yang L, Wang H, Yang X, Wu Q, An P, Jin X, et al. Auranofin mitigates systemic iron overload and induces ferroptosis via distinct mechanisms. Signal Transduct Target Ther. 2020;5:138.
135. Du F, Ye Z, He A, Yuan J, Su M, Jia Q, et al. An engineered α1β1 integrin-mediated FcγRI signaling component to control enhanced CAR macrophage activation and phagocytosis. J Control Release. 2025;377:689–703. https://doi.org/10.1016/j.jconrel.2024.11.064.
136. Lin W, Shen C, Li M, Ma S, Liu C, Huang J, et al. Programmable macrophage vesicle based Bionic Self-Adjuvanting Vaccine for immunization against

Monkeypox Virus. Adv Sci. 2024;n/a:2408608. https://doi.org/10.1002/advs.202408608.
137. Dong Q, Jiang Z. Platinum–Iron nanoparticles for oxygen-enhanced Sonodynamic Tumor Cell suppression. Inorganics. 2024;12:331.
138. Zhang D, Song J, Jing Z, Qin H, Wu Y, Zhou J et al. Stimulus responsive nanocarrier for enhanced antitumor responses against Hepatocellular Carcinoma. Int J Nanomed. 2024;19:13339–55.
139. Yang R, Yan L, Xu T, Zhang K, Lu X, Xie C, et al. Injectable bioadhesive hydrogel as a local nanomedicine depot for targeted regulation of inflammation and ferroptosis in rheumatoid arthritis. Biomaterials. 2024;311:122706. https://doi.org/10.1016/j.biomaterials.2024.122706.
140. Zhang Z, Wang L, Guo Z, Sun Y, Yan J. A pH-sensitive imidazole grafted polymeric micelles nanoplatform based on ROS amplification for ferroptosis-enhanced chemodynamic therapy. Colloids Surf B Biointerfaces. 2024;237:113871.
141. Bayat M, Nahand JS. Let's make it personal: CRISPR tools in manipulating cell death pathways for cancer treatment. Cell Biol Toxicol. 2024;40:61.

Publisher's note