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Review

Advances in understanding ferroptosis mechanisms and their impact on immune cell regulation and tumour immunotherapy

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Abstract
Ferroptosis is a novel mode of iron-dependent non-apoptotic cell death that occurs mainly due to excessive accumulation of lipid peroxides. Numerous studies in recent years have shown that ferroptosis plays a vital role in the organism and has important interactions with immune cells. Ferroptosis has been shown to have great potential in tumour therapy through studying its mechanism of action. In addition, ferroptosis plays a major role in many types of tumour cells that can potently suppress the tumourigenesis and metastasis, provide a basis for the treatment of many malignant tumour diseases and become a novel therapeutic modality of antitumour immunity in the clinic. Current tumour immunotherapy for ferroptosis in combination with other conventional oncological modalities is not well elaborated. In this paper, we mainly discuss the connection of ferroptosis with immune cells and their mediated tumour immunotherapy in order to provide a better theoretical basis and new thinking about ferroptosis mediated antitumour immunity.

Keywords Ferroptosis · Mechanism · Immune cell · Tumour immunotherapy

1 Introduction

Ferroptosis is a new type of iron-dependent cell death that differs from necrosis, apoptosis and autophagy. The concept of ferroptosis was initially introduced in 2012 by Dixon et al. [1]. Ferroptosis occurs mainly due to reduce glutathione peroxidase activity, couple with excessive accumulation of lipid peroxidation and reactive oxygen species (ROS). Ferroptosis is morphologically discernible from necrosis, apoptosis and autophagy and is characterized mainly by mitochondrial atrophy, reduction or disappearance of mitochondrial cristae, rupture of the outer mitochondrial membrane and a normal nucleus [2]. Ferroptosis exhibits a dual role in promoting and suppressing tumourigenesis. The tumour immune microenvironment (TME) is comprised mainly of tumour cells and immune cells, including T cells, B cells, macrophages, and dendritic cells etc. [3, 4]. Due to the complexity of TME, various cells demonstrate varying sensitivities to ferroptosis. Recent research has indicated that the significance of ferroptosis in the immune microenvironment and immunotherapy. In this review, we discuss the relationship between ferroptosis and immune cells and tumour therapy.

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2 Mechanisms for the development and regulation of ferroptosis

2.1 Iron homeostatic imbalance

Iron homeostasis is primarily regulated by a network of iron-regulatory related proteins. Iron ions gain entry into cells via the transferrin/transferrin receptor-1 (TF/TFR-1) transport system and are exported out of the cell via the ferroportin and ferritin export proteins, which transport iron ions and ferritin respectively through diverse pathways. Iron homeostasis mechanisms ensure a dynamic balance in the cellular uptake, utilization and release of iron. However, the iron homeostatic balance is affected by electron transfer [5]. Extracellular Fe^{3+} binds to transferrin to form a complex, which enters the cell membrane through the transferrin receptor (TFRC) and is reduced to Fe^{2+} by the six transmembrane epithelial antigens of prostate 3 (STEAP3) to be stored in the iron pool or in other forms. Conversely, when intracellular Fe^{2+} levels surpass normal limits, they combine with H_2O_2 via the Fenton reaction to generate hydroxyl radicals, which generate lipid peroxides and lead to the development of ferroptosis. Furthermore, iron-dependent lipoxygenase can also act on polyunsaturated fatty acids (PUFAs) to further catalyse the production of lipid peroxides, inducing ferroptosis [6]. Studies have shown that heat shock proteinβ-1 (HSPB1) is a negative regulator of ferroptosis, inhibiting ferroptosis by suppressing TFR-1 and simultaneously blocking the inducing effect of Erastin [7]. Ferroportin, as the sole iron exporter, enhances Erastin induced ferroptosis in neuroblastoma cells when it knocked out [8]. Furthermore, disturbances in iron homeostasis can also lead to the occurrence of diseases such as atherosclerosis, aortic dissection and cardiomyopathy [9–11].

2.2 Excessive lipid peroxidation

PUFAs exist within cells, which are commonly classified into omega-3 and omega-6 PUFAs. Studies have shown that most tumours invade and grow in acidic environments [12]. Omega-3 and omega-6 PUFAs tend to accumulate in acid-adapted cancer cells, selectively inducing ferroptosis [13]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) can influence the ability of intracellular PUFAs to form phospholipids [14]. After enzymatic or nonenzymatic oxidation reactions, lipid peroxidation by ROS on membrane phospholipids occurs. ACSL3 can convert fatty acids into fattyAcyl-CoA esters, which bind to membrane phospholipids and inhibit ferroptosis [15]. When mechanisms governing intracellular ferroptosis are inhibited, such as the glutamate-cystine antiporter system (System Xc^-),glutathione peroxidase 4 (GPX4) and the ferroptosis suppressor protein 1 (FSP1) etc., excessive accumulation of lipid peroxides can occur. This accumulation can disrupt cellular membranes and trigger the initiation of ferroptosis [16].

2.3 Regulation of the system Xc^-, GPX4 and FSP1

System Xc^- is an amino acid antiporter comprising two subunits, SLC7A11 and SLC3A2, located within the phospholipid bilayers. This system functions to transport intracellular glutamate outward and extracellular cystine inward. Cystine transported to the intracellular area is reduced to cysteine to participate in the formation of glutathione (GSH). GSH can reduce the binding of H_2O_2 to Fe^{2+} and prevent the generation of ROS and Fe^{3+} by reacting with H_2O_2 to stop ferroptosis [17]. GPX4 is a special antioxidant enzyme. The characteristics and functions of GPX4 are reflected mainly in changing toxic lipid hydroperoxides to nontoxic lipid alcohols, effectively scavenging lipid peroxides and preventing their excessive accumulation [18]. Furthermore, GPX4 has a substantial effect on the reaction between GSH and H_2O_2, which can reduce H_2O_2 to water, prevent the Fenton reaction and promote ferroptosis. Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important antioxidant transcription factor [19]. Current studies have shown that GPX4 and SLC7A11 in System Xc^- are target genes of Nrf2. When Nrf2 is overexpressed, the expression of SLC7A11 is coordinately upregulated, promoting the GSH in vivo, enhancing the antioxidant effect of astrocytes and reducing the incidence of gliomas [20]. In non-small cell lung cancer, Nrf2 regulates ferroptosis in lung cancer cells by targeting GPX4 and binding to its promoter region [21]. FSP1 is a novel antioxidant protein that primarily inhibits lipid peroxidation and ferroptosis by reducing CoQ to CoQH2 [22]. When GPX4 is absent, it can serve as a compensatory mechanism (Fig. 1).

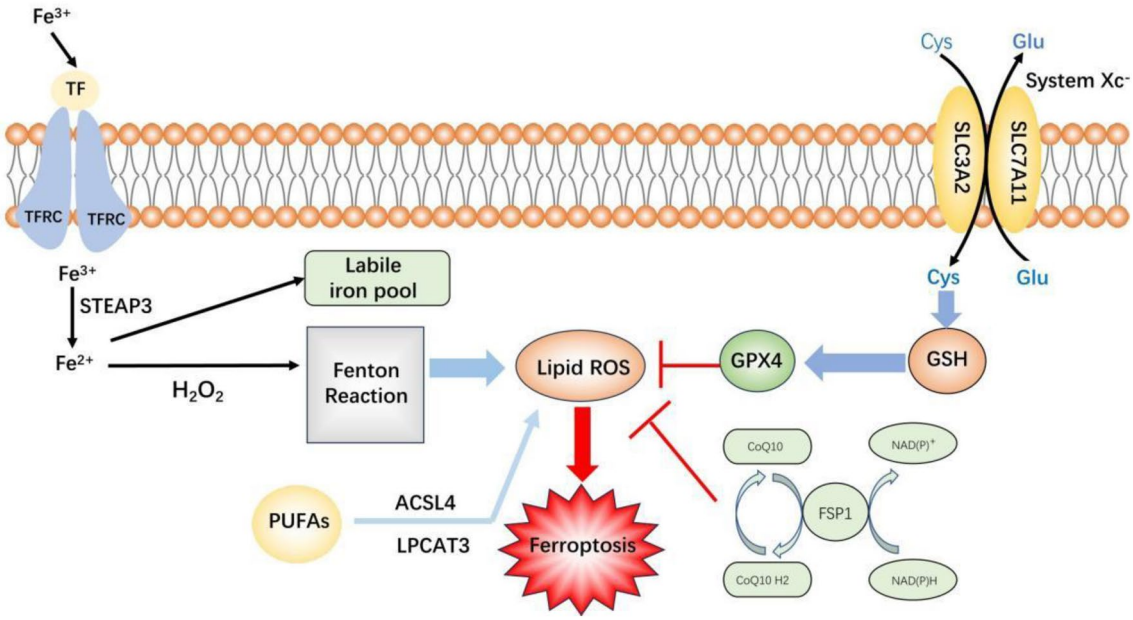

Fig. 1 Occurrence and regulation of Ferroptosis. *TF* transferrin, *TFRC* transferrin receptor, *STEAPE3* six transmembrane epithelial antigens of prostate 3, *PUFAs* polyunsaturated fatty acids, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *Lipid ROS* lipid reactive oxygen species, *LPCAT3* lysophosphatidylcholine acyltransferase 3, *GPX4* glutathione peroxidase 4, *GSH* glutathione, *FSP1* ferroptosis suppressor protein 1

3 Ferroptosis and the regulation of immune cells

3.1 Association of T lymphocytes with ferroptosis

T cells can undergo ferroptosis themselves and also induce ferroptosis in others. T lymphocytes are divided into $CD4^+$T and $CD8^+$T. Regulatory T cells (Tregs) differentiated from $CD4^+$T cells have powerful immunosuppressive functions that can inhibit the antitumour immune effects of effector T cells, natural killer cells and dendritic cells (DCs) and promote tumour progression through various mechanisms. Tregs are the key inhibitory cells in maintaining immune tolerance and escaping tumour cells [23]. Studies have shown that Tregs are closely associated with the key gene GPX4 involved in ferroptosis. By inhibiting GPX4, ferroptosis of Tregs can be induced, leading to the release of proinflammatory cytokines, such as IL-1B. This promotes the activation of DCs and $CD8^+$T cells and enhances antitumour immune responses [24]. $CD8^+$T cells secrete IFN-γ to downregulate the SLC7A11 and SLC3A2 subunits of System Xc^-, which reduces the exchange of cystine and glutamate, hinders the synthesis of GSH, promotes lipid peroxidation in tumour cells and leads to ferroptosis to inhibit tumour growth [25]. In addition, some PUFAs, such as arachidonic acid, can interact with IFN-γ secreted by $CD8^+$T cells, stimulate ACSL4 through the JAK-ASTAT1 pathway and alter the lipid status of tumour cells to induce ferroptosis [25]. GPX4 plays a crucial role in inhibiting ferroptosis by possessing unique abilities to scavenge membrane lipid peroxidation products and prevent oxidative stress [26]. When $CD4^+$T cells and $CD8^+$T cells specific deletion in GPX4 are prone to ferroptosis, which deprives T lymphocytes immune function and prevents them from exerting antitumour functions.

3.2 Association of B lymphocytes with ferroptosis

The subtypes of B cells can be categorized into B1 cells, follicular (FO) B cells and marginal zone (MZ) B cells [27]. The three subtypes differ in their susceptibility to ferroptosis. B1 and MZ B cells express relatively high levels of CD36, which enhances fatty acid uptake. Therefore, ferroptosis is more likely to occur [28]. In addition, sensitivity to ferroptosis is also influenced by GPX4, which plays a crucial role in regulating ferroptosis with the assistance of GSH. Experimental findings indicate that the absence of GPX4 does not significantly impact the susceptibility of FO B cells to ferroptosis. Although GPX4 is less closely linked to FO B cells in areas such as cell growth and development, GPX4 is essential for FO B cells.

Conversely, B1 and MZ B cells demonstrate a much higher sensitivity to ferroptosis in the absence of GPX4, which can accumulate continuous lipids, causing cytotoxic effects that lead to the development of ferroptosis [28].

3.3 Association of macrophages with ferroptosis

Macrophages are divided into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. These two fractions have different sensitivities to the ferroptosis inducer ras-selective lethal small molecule 3 (RSL3) [29]. Because M1 macrophages express higher levels of the enzyme inducible nitric oxide synthase and produce more NO, they are less sensitive to ferroptosis than M2 macrophages. When ferroptosis occurs in tumour cells, some damage-associated molecular patterns (DAMPs), such as $Kras^{G12D}$, can cause the conversion of macrophages to the M2 phenotype, promote tumour cell survival, proliferation and metastasis and inhibit the function of other immune cells [30]. However, studies have shown that inhibiting APOC1 in liver cancer cells can convert M2 macrophages into M1 macrophages through the ferroptosis pathway, thereby enhancing antitumour immunity [31]. Phagocytosis of senescent red blood cells (RBCs) by macrophages is one of the sources of iron in the body. Moreover, macrophages phagocytose RBCs to undergo erythrophagocytosis. As erythrophagocytosis increases, iron accumulates in macrophages such that J774 macrophages exhibit increased levels of ROS and lipid peroxidation. When a certain level is reached, the cell undergoes ferroptosis [32]. However, hepatic leukaemia factor (HLF) in triple-negative breast cancer is affected by transforming growth factor β1, which is secreted by tumour-associated macrophages and can stimulate gamma-glutamyltransferase 1 and enhance the function of GPX4. Therefore, the resistance of tumour cells to ferroptosis is further enhanced [33].

3.4 Association of dendritic cells with ferroptosis

Dendritic cells recognize tumour cells through lipid peroxides produced by ferroptosis, which can promote antigen presentation and stimulate T cells to perform immune functions [34]. Bone marrow-derived dendritic cells (BMDCs) coincubated with ML162, LRS-3 and Erastin-mediated ferroptotic tumour cells can increase exposure to CD86, CD40 and MHC II^{high}, indicating enhanced DCs maturation [35]. In contrast, when LOX12/15 expression levels are elevated, lipid peroxidation increases, which inhibits DCs maturation [36]. In addition, Efimova et al. compared the effects of RSL3-treated MCA205 cells for 1 h and 24 h on the maturation of mouse BMDCs and demonstrated that early-stage ferroptosis tumour cells promote the maturation of BMDCs, whereas late-stage ferroptosis tumour cells are phagocytosed by BMDCs [37].

3.5 Association of neutrophils with ferroptosis

Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), important constituent cells of the immunosuppressive microenvironment, have strong inhibitory effects on lymphocyte cytotoxicity and a role in promoting tumour growth. Studies have shown that by downregulating GPX4, ferroptosis can be induced in PMN-MDSCs. However, after PMN-MDSCs undergo ferroptosis, their immunosuppressive effects are enhanced. The application of ferroptosis inhibitors can effectively inhibit tumour growth [38]. In glioblastoma, tumour cells undergo injury, releasing DAMPs that induce the recruitment of neutrophils. Neutrophils transfer myeloperoxidase-containing granules to tumour cells, inducing the accumulation of lipid peroxides within tumour cells and causing ferroptosis in damaged tumour cells [39]. Patients with spontaneous intracerebral haemorrhagic stroke are commonly associated with hypertension and diabetes. In a mouse model of cerebral haemorrhage, hypertension and diabetes result in massive infiltration of neutrophils and disrupt the peroxisome proliferator activated receptorγof neutrophils, which affects the transcription and secretion of lactoferrin, ultimately leading to ferroptosis of neuronal cells [40]. In the presence of aconitate decarboxylase 1, tumour-infiltrating neutrophils can reduce the accumulation of intracellular lipid peroxides and prevent them from undergoing ferroptosis [41].

3.6 Association of others in the tumour microenvironment with ferroptosis

3.6.1 The connection between ferroptosis and mechanotransduction

Mechanotransduction is the process by which cells convert mechanical cues into biochemical signals, activate cellular pathways and influence their functions. The extracellular matrix (ECM) stiffening can induce the polarization of macrophages towards the M2 phenotype, resulting in immune tolerance in tumour cells [42]. Additionally, the Rho-associated

coiled-coil-containing protein kinase (ROCK)-myosin IIA-filamentous actin (F-actin) mechanosignaling pathway induced by stiffened ECM restricts the excretion of cyclic GMP-AMP (cGAMP), ultimately affecting the maturation of DCs and the activation of effector T cells in the tumour microenvironment [43]. Studies have shown that GPX4 promotes ferroptosis through the Yes-associated protein and transcriptional enhanced associate domain (YAP-TEAD) pathway under mechanical stress [44].

3.6.2 The connection between ferroptosis and autophagy

Autophagy is a cellular degradation pathway that primarily degrades intracellular proteins, organelles and other components needing degradation through the lysosomal pathway, thereby maintaining intracellular homeostasis [45]. Numerous studies have indicated that autophagy influences the immune response of immune cells [46]. Autophagy plays a crucial role in the proliferation and protection of T lymphocytes [47]. T lymphocytes with deficient autophagy function exhibit decreased secretory factor capabilities and compromised survival. Furthermore, some studies have reported that the induction of autophagy using mTOR inhibitors can activate the antitumour immune function of T lymphocytes [48]. Autophagy also affects the antigen-presenting function of dendritic cells. The autophagy protein ATG5 influences CD36 expression in dendritic cells and impacts the MHC II presentation pathway [49]. The occurrence of ferroptosis can be regulated by various autophagy pathways. Ferritinophagy is a selective autophagy process that regulates intracellular iron levels, primarily mediated by nuclear receptor coactivator 4 (NCOA4) [50]. NCOA4 binds to ferritin heavy chain and transports it to lysosomes for degradation, resulting in an increase in intracellular iron ion levels, which triggers the Fenton reaction and induces ferroptosis [51]. Lipophagy refers to the process of degrading intracellular lipid droplets [52]. It induces ferroptosis by reducing lipid storage and increasing lipid degradation [53]. However, studies have shown that overexpression of the oncogene tumour protein D52 which can inhibit ferroptosis by suppressing the occurrence of lipophagy [54]. Clockophagy is a newly discovered type of autophagy. ARNTL is a core clockophagy protein. Research has found that ARNTL blocks ferroptosis in cancer cells by controlling the EGLN2-HIF1A pathway [55].

3.6.3 The connection between ferroptosis and fibrosis

Fibrosis refers to the process in which there is an increase in fibrous connective tissue within an organ and tissue, accompanied by a decrease in parenchymal cells, ultimately leading to organ and tissue failure. When fibrosis occurs in the liver, it triggers dendritic cells to secrete TNF-α, which causes hepatic stellate cells to proliferate and activate, exacerbating liver fibrosis [56]. In the late stages of renal fibrosis, a large number of neutrophils are found, which activate fibroblasts by secreting IL-1β and other cytokines, thereby promoting renal fibrosis [57]. Recent studies have found a close connection between ferroptosis and fibrotic diseases. In tissues undergoing fibrosis, there is an increase in the level of transforming growth factor β, which induces oxidative stress in fibroblasts, triggering ferroptosis in cells [58]. When renal cells undergo ferroptosis, there is a significant increase in Fe^{2+} in the tissue, further promoting renal fibrosis [59].

3.6.4 The connection between ferroptosis and cancer associated fibroblasts as well as endothelial cells

The tumour microenvironment also includes cancer associated fibroblasts (CAFs) and endothelial cells [60]. CAFs are the primary component in the extracellular matrix of tumours and play a crucial role in the initiation, progression, and metastasis of tumours. Research has found that when CAFs are co-cultured with macrophages, they promote the transformation of macrophages into M2 type by secreting IL-6 and SDF-1, leading to tumourigenesis and immune escape [61]. Additionally, IL-6 secreted by CAFs can also activate STAT3 to promote the production of indoleamine 2,3-dioxygenase by dendritic cells, causing immunosuppression. [62]. Studies have shown that arachidonate 15-lipoxygenase (ALOX15) is associated with ferroptosis in gastric cancer. CAFs secrete exosomal miR-522, which targets ALOX15 to reduce the production of ROS and block the occurrence of ferroptosis in gastric cancer [63]. Furthermore, there is a close relationship between ferroptosis and pulmonary fibrosis. Under the induction of bleomycin, iron accumulates abundantly in lung tissue, triggering ferroptosis in lung tissue and promoting the development of pulmonary fibrosis [64]. Under the action of Erastin, ferroptosis in lung fibroblasts can be induced through the MAPK pathway. Endothelial cells form the inner lining of blood vessels and serve as the interface between the blood in the lumen and other parts of the vessel wall. Ferroptosis is involved in the process of inflammatory damage to vascular endothelial cells. Studies have shown that vascular endothelial growth factor can induce the expression of miR-17–92 in endothelial cells by activating the ERK/ELK1 pathway. miR-17–92 protects endothelial cells from Erastin-induced ferroptosis by targeting the A20-ACSL4 axis [65].

4 Ferroptosis mediated tumour immunotherapy

4.1 The dual role of ferroptosis in tumour treatment

Ferroptosis is a double-edged sword in tumour treatment. On the one hand, AKR1C2 inhibits ferroptosis by degrading lipid peroxides [66]. Meng et al. found through research that BET inhibitors inhibit AKR1C2 expression through BRD4, thereby inducing ferroptosis in melanoma [67]. Artesunate induces ferroptosis in pancreatic ductal adenocarcinoma by promoting ROS production, thereby hindering tumour growth [68]. On the other hand, when GPX4 is absent within cells, it can cause lipid peroxidation in tumour cells, triggering ferroptosis. However, this can also promote immune escape mediated by immunosuppressive mediators, thereby promoting tumourigenesis [69]. Furthermore, when ferroptosis occurs in certain tumour cells, it can adversely affect the antigen-presenting function of DCs, impeding antitumour immunity and promoting the development of certain tumour cells [35].

4.2 Overview of ferroptosis mediated tumour immunotherapy

In recent years, most tumours have an innate resistance to apoptosis. Research has revealed that ferroptosis induced by immune checkpoint inhibitors (ICIs) play crucial roles in antitumour immune tolerance [25]. ICIs include PD-1, CTLA-4, TIM3, and others. Different immune cells have distinct mechanisms of action on ICIs. $CD4^+$T cells primarily assist $CD8^+$T cells secreting cytokines, which can alter the TME and influence the outcomes of ICIs therapy. However, Tregs induced by oxidative stress can release a large amount of adenosine, which can undermine the therapeutic effects of ICIs [25, 70]. B lymphocytes present antigens to T lymphocytes, thereby forming antigen-specific immune responses within the TME and influencing the outcomes of ICIs therapy [71]. Macrophages primarily influence the outcomes of ICIs therapy by modulating inflammatory responses [72]. DCs influence the outcomes of ICIs therapy by integrating information from the TME and transmitting it to other immune cells, especially T cells [73]. Genetic and pharmacological approaches can inhibit the immunosuppressive activity of pathologically activated neutrophils, and they can produce synergistic effects with ICIs to suppress tumour activity [38, 74]. Currently, T lymphocytes are most widely combined with ICIs. Under the stimulation of ICIs, $CD8^+$T cells are activated to exert their immune function and facilitate the induction of ferroptosis in tumour cells [25]. However, when CD36 affects $CD8^+$T cells, it leads to constant uptake of fatty acids and accumulation of lipid peroxides, causing ferroptosis in $CD8^+$T cells and promoting tumourigenesis [75]. When tumour cells are damaged, they release DAMPs and exhibit immunogenicity, such as high mobility group Box 1(HMGB1), which can bind to pattern recognition receptors to activate the immune system. This activation enables immune cells to localize accurately to tumour cells and perform antitumour functions [69]. However, the knockout of HMGB1 in the HL-60 leukaemia cell line expressing $NRAS^{Q61L}$ (HL-60/$NRAS^{Q61L}$) can upregulate cyclooxygenase 2 and transferrin expression through the RAS-JNK/p38 pathway, which can reduce Erastin induced ferroptosis and inhibit Erastin anticancer activity [76]. In addition, programmed death 1 (PD-1) is commonly expressed on activated T cells, B cells, macrophages and other immune cells. $CD8^+$T cells release IFN-γ, which can induce high expression of programmed death 1 ligand (PD-L1) on the surface of hepatocellular cells that combines with PD-1 to promote the apoptosis of $CD8^+$T cells, thereby affecting antitumour immunity [77]. To address this situation, combination therapy with anti-PD-1/PD-L1 antibodies has been used to induce $CD8^+$T cells to secrete IFN-γ and activate STAT1 signaling, which significantly downregulates the expression of SLC3A2 and SLC7A11, increases lipid peroxidation in tumour cells and induces tumour cell death [78]. However, too much or too little GPX4 in T cells or B cells can affect the immune function of immune cells and impede the onset of ferroptosis in target cells [79]. Therefore, it is crucial to regulate the GPX4 content in immune cells appropriately to ensure the effectiveness of immunotherapy [80]. Moreover, when the antigen presentation system is abnormal, some types of tumour cells can become resistant to ICIs, which is one of the urgent problems to be solved currently. The issue of drug resistance can be overcome by researching new ICIs and implementing personalized treatment based on patients' biomarkers. Table 1 summarizes the connection among immune cells, ferroptosis, and ICIs (Fig. 2).

4.3 Immunotherapy combined with targeted therapy mediated by ferroptosis in cancer treatment

For targeted therapy mediated by ferroptosis, a classic approach involves the use of ferroptosis inducers and related ferroptosis-targeting drugs. Different types of cancer exhibit varying sensitivities to ferroptosis. RSL3 and Erastin are

Table 1 The connection among immune cells, ferroptosis, and immune checkpoints

Immune cells	The connection with ferroptosis	The impact on immune checkpoint therapy
T lymphocytes	The Treg cells differentiated from $CD4^+$ T cells maintain their homeostatic state and prevent the occurrence of ferroptosis primarily through GPX4. $CD8^+$ T cells induce ferroptosis in tumour cells by secreting IFN-γ and downregulating the System Xc^-. When the level of cystine decreases in $CD8^+$ T cells, it triggers CD36 uptake, leading to ferroptosis in the $CD8^+$ T cells [24, 25, 75]	$CD4^+$T cells primarily assist $CD8^+$T cells secreting cytokines, which can alter the tumour microenvironment, and influence the outcomes of ICIs therapy. However, Tregs induced by oxidative stress can release a large amount of adenosine, which can undermine the therapeutic effects of ICIs [25, 70]
B lymphocytes	Compared to follicular B (Fo B) cells, B1 and marginal zone (MZ) B cells express higher levels of CD36, which facilitates their high uptake of fatty acids, making them susceptible to ferroptosis [28]	B lymphocytes present antigens to T lymphocytes, thereby forming antigen-specific immune responses within the TME and influencing the outcomes of ICIs therapy [71]
Macrophages	M1 macrophages have higher levels of iNOS, which inhibits lipid peroxidation and reduces the occurrence of ferroptosis. In contrast, M2 macrophages, due to the lack of iNOS, are more prone to ferroptosis [29]	Macrophages primarily influence the outcomes of ICIs therapy by modulating inflammatory responses. [72]
Dendritic cells	Dendritic cells primarily exert immune function by presenting antigens to T cells and activating them [34]	Dendritic cells influence the outcomes of ICIs therapy by integrating information from the TME and transmitting it to other immune cells, especially T cells [73]
Neutrophils	Pathologically activated neutrophils induce ferroptosis in tumour cells by promoting lipid peroxidation. When the neutrophils themselves undergo ferroptosis, they contribute to tumour growth by limiting antitumour immunity [38, 39]	Genetic and pharmacological approaches can inhibit the immunosuppressive activity of pathologically activated neutrophils, and they can produce synergistic effects with ICIs to suppress tumour activity [38, 74]

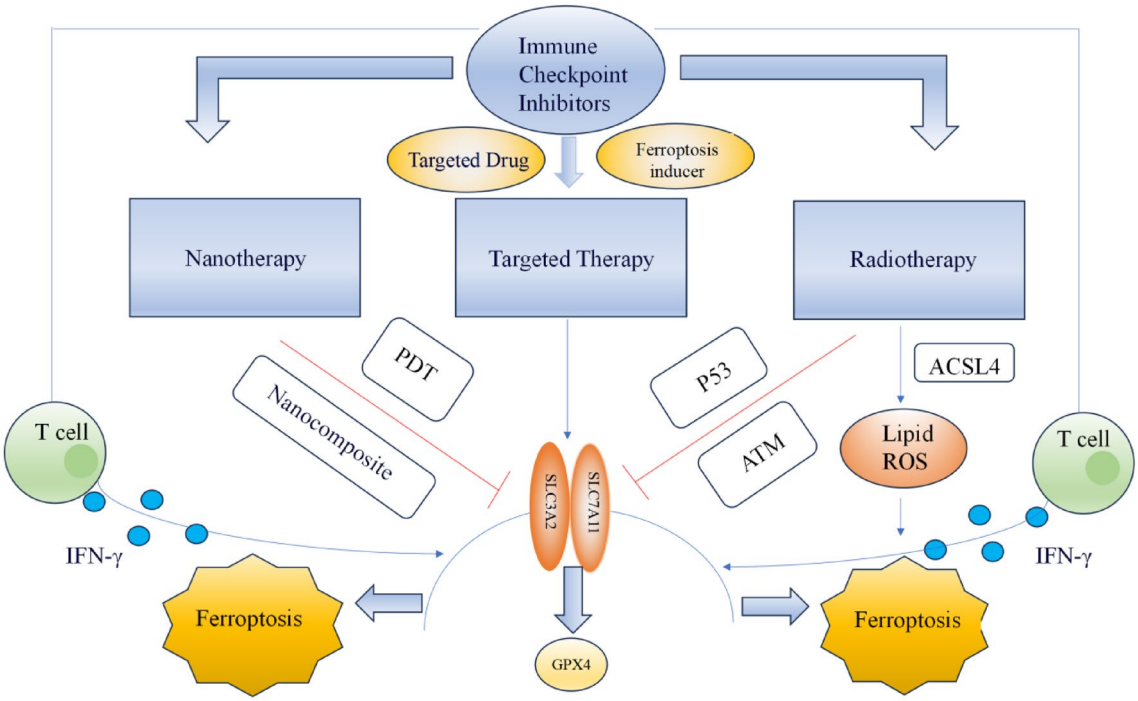

Fig. 2 Combination of immune checkpoint inhibitors with other cancer treatment modalities in ferroptosis. *PDT* photodynamic therapy, *IFN-γ* interferon-γ, *GPX4* glutathione peroxidase 4, *P53* tumour protein p53, *ATM* mutated in Ataxia-Telangiectasia, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *Lipid ROS* lipid reactive oxygen species

classic ferroptosis inducers that trigger ferroptosis in tumour cells by acting on different targets, without interfering with the expression of IFN-γ in T cells [25]. RSL3 functions by directly interacting with GPX4 to inhibit its activity, which leads to the accumulation of ROS in tumour cells and promotes the occurrence of cellular ferroptosis [81]. Erastin induces the onset of cellular ferroptosis by inhibiting the function of System Xc^-, preventing the exchange of amino acids across the cell membrane, reducing GSH synthesis and affecting the action of GPX4 [82]. Studies have shown that imidazone ketone Erastin (IKE), a derivative of Erastin, exerts an antitumour effect in xenograft models of diffuse large B cell lymphoma by inhibiting System Xc^- [83]. Furthermore, Erastin induced generation of ROS can also activate P53, which triggers cellular ferroptosis by inhibiting the SLC7A11 subunit of System Xc^- and interfering with cystine uptake [84]. However, the use of inducers can also cause problems such as bone marrow injury. Sorafenib mainly enhances the sensitivity of liver cancer cells to ferroptosis by reducing the HIF-1α/SLC7A11 signaling [85]. Sulfasalazine (SAS) induces ferroptosis in glioma cells by inhibiting SLC7A11 and the higher the concentration of SAS, the more pronounced the induction effect [86]. Statins induce ferroptosis by blocking the mevalonate pathway and inhibiting GPX4 and coenzyme Q10 [87]. Tanshinone IIA induces ferroptosis in gastric cancer by upregulating p53 and downregulating SLC7A11 [88]. However, further in-depth exploration and research are still required regarding drug resistance, dosage, and side effects associated with the drug. Currently, there have been no detailed reports on the combination of ferroptosis inducers or targeted drugs with immunotherapy, and a single treatment approach is predominantly adopted in clinical practice. However, studies have shown that inhibiting phosphoglycerate mutase 1 can downregulate lipid carriers, activate $CD8^+$T cells, and synergize with anti-PD-1 immunotherapy to induce ferroptosis in liver cancer [89]. TYRO3, which is expressed on the surface of tumour cells, can induce the polarization of M1 macrophages into M2 macrophages and promote the immune escape of tumour cells. In addition, TYRO3 can upregulate SLC3A2, resist treatment with anti-PD-1/PD-L1 antibodies and impede the occurrence of cellular ferroptosis. The combined application of relevant TYRO3 inhibitors can increase the sensitivity of tumour cells to anti-PD-1/PD-L1 antibodies, improve resistance to anti-PD-L1 therapy and induce the onset of ferroptosis [90]. In summary, combination therapy holds great research promise and significance, but we must also constantly pay attention to and prioritize the negative effects it may bring. Combination therapy may lead to reduced efficacy and the emergence of toxic side effects due to unknown drug interactions in terms of toxicity. To address this, we can explore novel drug administration modes and utilize advanced diagnostic tools and technologies to closely monitor patients' treatment responses. Additionally, investigating the mechanistic pathways through which combination therapy acts on

different types of cancers is a current challenge. To this end, basic scientific research should be strengthened to provide support for clinical treatment.

4.4 Immunotherapy combined with radiotherapy mediated by ferroptosis in cancer treatment

Ionizing radiation therapy mainly leverages the differences in cellular sensitivity to damage the DNA of tumour cells, thereby inhibiting their growth. Mutated in Ataxia-Telangiectasia (ATM) is an important gene that expresses a serine-threonine protein kinase. When DNA damage occurs, ATM is activated, leading to the downregulation of SLC7A11 and inducing ferroptosis [91]. Ionizing radiation can induce ferroptosis in tumour cells by resulting in the generation of ROS and the upregulation of ACSL4. ACSL4 is a lipid metabolism enzyme that promotes the onset of lipid peroxidation [92]. The authors found that radiotherapy led to elevated levels of lipid peroxidation in HT1080, B16F10 and ID8 cells. These results may indicate that radiotherapy can lead to the development of ferroptosis. Current studies have demonstrated that radiotherapy combined with PD-1/PD-L inhibitors can improve the abscopal effect [93], promote IFN-γ secretion from $CD8^+$T cells, synergistically inhibit SLC7A11 via radiotherapy, affect System Xc^- and promote ferroptosis in tumour [91]. P53, a major effector in radiotherapy, affects the exchange of glutamate and cystine by suppressing the expression of the SLC7A11 subunit, which reduces glutathione production and promotes radiotherapy induced ferroptosis, However, when P53 is deficient, it inhibits radiation induced ferroptosis and enhances the radioresistance of tumour cells. Ferroptosis also mediates the radiosensitizing effect of p53 [94]. At present, the combined treatment of the two modalities is still in its early stages. Many problems, including applicable groups and types of disease, still need to be explored in the clinic to achieve ideal treatment results. Combination therapy may cause certain damage to surrounding normal tissues and adversely affect the digestive tract and hematological system. To address these challenges, measures such as precise localization and planning, as well as improving the accuracy of dose distribution.

4.5 Immunotherapy combined with nanotherapy mediated by ferroptosis in cancer treatment

In recent years, nanotherapy has gradually been applied in tumour treatment. Compared to traditional tumour treatment methods, nanomaterials improve drug stability, enhance targeting, reduce transmembrane difficulty and decrease the occurrence of adverse reactions [95]. It has been discovered that Fe_3O_4-SAS@PLTs have the ability to escape the immune system and target tumour metastasis. This platform consists of sulfasalazine (SAS)-loaded mesoporous magnetic nanoparticles (Fe_3O_4) and a platelet (PLT) membrane that can induce the onset of ferroptosis and elicit an effective immune response by inhibiting Systemic Xc^- and decreasing the uptake of cystine. In addition, Fe_3O_4-SAS@PLTs can be combined with immunotherapy to exert antitumour immune effects by polarizing M2 macrophages to M1 macrophages, activating other immune cells and promoting the onset of ferroptosis in tumour cells [96]. HGF nanoparticles are formed by combining HACA-Fe nanoparticles (NPs) with the exosome inhibitor GW4869 in combination with PD-L1 blockers, which can effectively inhibit the secretion of exosomal PD-L1 of tumour cell origin, restore the function of T lymphocytes and induce ferroptosis of tumour cells [97]. Photodynamic therapy (PDT) is a minimally invasive treatment that combines a photosensitizer, visible light, and oxygen to initiate a photochemical reaction, thereby damaging the structure of tumour cells. Studies have demonstrated the role of PDT in inducing ferroptosis in tumour cells [98]. Haemoglobin is connected to the photosensitizer chlorin e6 to construct a 2-in-1 nanoplatform, SRF@Hb-Ce6, loaded with sorafenib. The oxygen-carrying capacity of Hb can significantly enhance photodynamic therapy and the intracellular iron content, induce the secretion of IFN-γ by immune cells and enhance the onset of ferroptosis in tumour cells [99]. Fe-HCOF-PEG^{2000} is a primary combination for both Type I/II PDT and ferroptosis, capable of promoting the generation of ROS under hypoxic conditions to induce the occurrence of ferroptosis [100]. A nanocomplex (PAF) of PEGylated polygalacturonic acid, 5,10,15,20-tetrakis (4-aminophenyl) porphyrin (TAPP), and Fe^{3+} induces ferroptosis in B16 melanoma cells by elevating intracellular ROS levels and triggering lipid peroxidation [101]. A nanosystem laoded with the poly (lactic-co-glycolic acid) (PLGA) containing ferrous Fe_3O_4 and Ce6. The Fe_3O_4-PLGA-Ce6 nanosystem can induce ferroptosis in cells by releasing iron ions that trigger the Fenton reaction [102]. Furthermore, ferroptosis can also enhance the sensitivity of PDT. Ce6-erastin, formed by the combination of the photosensitizer Ce6 and Erastin, under the induction of erastin, accumulates intracellular ROS and increases the concentration of O_2 through the Fenton reaction, alleviating the hypoxia issue in PDT and significantly enhancing the therapeutic efficacy of PDT. On the one hand, nanotherapy optimizes the deficiencies of traditional treatment methods; on the other hand, its combination with ferroptosis inducers and ICIs in the treatment of different types of cancers is still in its infancy, and the issues exposed require further efforts to overcome [103]. Currently, to prevent harm to normal cells, the biocompatibility of immune responses induced by nanoparticles can be assessed. Additionally, the

Table 2 The challenges of nanoparticles in cancer immunotherapy

The challenges encountered in nanoparticles
1.Cytotoxicity issue: Nanoparticles may have potential toxicity to cells, which may limit their safe range of use
2.Non-specific distribution and clearance: Nanoparticles may be recognized and rapidly cleared by the mononuclear phagocyte system in the body, thereby reducing the efficiency of drug delivery
3.Biocompatibility and immune response: The biocompatibility of nanoparticles and whether they can cause unnecessary immune responses must be considered
4.Durability and targeting accuracy: Currently, the duration of action of nanoparticles is relatively short, and they may cause damage to normal tissues

combination of immunomodulators with chemotherapeutic drugs should be evaluated to determine their synergistic effects on cancer treatment [104]. Regarding the safety of nanomaterials, the selection of material components should be based on the FDA's approved list. Table 2 the challenges of nanoparticles in cancer immunotherapy [105].

5 Conclusions and outlook

In summary, ferroptosis is more closely related to the interaction with immune cells. Ferroptosis, as an emerging mode of cell death, has been clinically used in tumour therapy protocols. Although there are great advances in antitumour immunity, ferroptosis also promotes tumourigenesis in the presence of some mechanisms. The article mainly discusses three parts. First, the occurrence and regulatory mechanisms of ferroptosis. Further research and exploration are needed into the emerging regulatory mechanisms of ferroptosis in order to discover more optimized modes of tumour treatment. Second, the connection between ferroptosis and immune cells. Due to the tumour microenvironment is vast and complex, we only discuss a few classic immune cells and tumour associated cells with ferroptosis in this paper. The association of ferroptosis with unmentioned immune cells and tumour associated cells and how to better regulate the effects of ferroptosis on tumours are the focus of our future research. Third, ferroptosis mediated immunotherapy combined with other tumour treatment methods. Ferroptosis inducers or inhibitors do not have cell specificity and may affect other non-tumour cells. Combination therapy is not yet widely used and requires further research and exploration in terms of the types of tumours targeted, suitable patient populations, dosage, off-target effects, and other aspects. In the future, ferroptosis holds great promise for research in tumour treatment. Our research focus will be on how to better induce or inhibit ferroptosis, with the aim of developing more innovative tumour treatment strategies.

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Declarations

Consent to participate Not applicable.

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