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Review

Current advances on the role of ferroptosis in tumor immune evasion

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Abstract
Ferroptosis is a non-apoptotic form of regulated cell death characterized by iron accumulation and uncontrolled lipid peroxidation, leading to plasma membrane rupture and intracellular content release. Cancer immunotherapy, especially immune checkpoint inhibitors (ICIs) targeting PD-1 and PD-L1, has been considered a breakthrough in cancer treatment, achieving encouraging clinical anti-tumor effects in a variety of cancers. However, tumor immune evasion is indispensable to immunotherapy failure. The mechanisms of tumor immune evasion are quite complex, and its occurrence is inseparable from the ferroptosis in tumor microenvironment (TME). Thus, a comprehensive understanding of the role of ferroptosis in tumor immune evasion is crucial to enhance the efficacy of immunotherapy. In this review, we provide an overview of the recent advancements in understanding ferroptosis in cancer, covering molecular mechanisms and interactions with the TME. We also summarize the potential applications of ferroptosis induction in immunotherapy, as well as ferroptosis inhibition for cancer treatment in various conditions. We finally discuss ferroptosis as a double-edged sword, including the current challenges and future directions regarding its potential for cancer treatment.

Keywords Ferroptosis · Tumor immune evasion · Tumor microenvironment · Cancer immunotherapy

1 Introduction

Recently, the understanding of regulated cell death (RCD) and its association with diseases has significantly expanded due to numerous accumulating studies. As a form of RCD, ferroptosis is closely correlated with several diseases, including cancer, neurodegeneration, tissue damage, inflammation, and infection [1]. Despite significant progress in oncological therapy, cancer remains a major threat to human health nowadays [2]. Many studies have confirmed that the mechanisms of ferroptosis are intricately linked to the genesis and progression of malignant tumors. Furthermore, ferroptosis is recognized as a potential anticancer target. Cancer immunotherapy, as an emerging and promising treatment, has attracted significant attention in recent years, with tumor immune evasion being one of the primary characteristics of cancer and a significant obstacle to cancer immunotherapy. In this context, the interaction between ferroptosis and tumor immune evasion has become a focal issue in the field of cancer therapy. Herein, we systematically review ferroptosis and its underlying mechanisms, the dual role of ferroptosis in tumor immune evasion, and explore the potential of ferroptosis in cancer immunotherapy, to provide new insights and strategies for targeting ferroptosis in cancer immunotherapy.

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1.1 Ferroptosis and its underlying mechanisms

Ferroptosis was first detected and defined by Brent R. Stockwell in 2012 [3]. Since then, an increasing number of researchers have dedicated themselves to studying this new concept, yielding fruitful results. Unlike other forms of RCD, ferroptosis is characterized by the accumulation of iron-dependent lipid peroxidation. Cells undergoing ferroptosis mainly exhibit morphological aberrations in mitochondria, such as shrunken mitochondria, reduced mitochondrial cristae, and rupture of the outer mitochondrial membrane, while the morphological changes in the nucleus are minimal [4]. More specifically, ferroptosis, as a complex physiological process, is dynamically regulated through the production and removal of lipid peroxides (LPO). Briefly, ferroptotic cell death occurs when the accumulation of reactive oxygen species (ROS) produced by iron-catalyzed oxidation of polyunsaturated fatty acids (PUFAs) overwhelms the antioxidant capacities of glutathione (GSH) and glutathione peroxidase 4 (GPX4) [5]. In fact, ferroptosis is driven and modulated by diverse molecular mechanisms, primarily involving amino acid metabolism, lipid metabolism, iron metabolism, and mitochondrial metabolism (Fig. 1).

1.2 Amino acid metabolism

Amino acid metabolism plays a pivotal role in the process of ferroptosis, especially cystine. Intracellular cystine is the raw material necessary for GSH synthesis, which is supplied by the cystine/glutamate transporter (also known as System Xc-), a heterodimer formed by glycosylated solute carrier family 3 member 2 (SLC3A2) and non-glycosylated solute carrier family 7 member 11 (SLC7A11), linked by disulfide bonds [6]. This transporter exchanges extracellular cystine for intracellular glutamate in a 1:1 ratio, providing raw material for intracellular GSH synthesis. GSH is an important intracellular antioxidant, which not only reduces H_2O_2 to H_2O to maintain the balance of free radicals in cells but also acts as a substrate for GPX4 in intracellular antioxidant reactions. GPX4 is a selenoprotein belonging to the glutathione peroxidase family (GPX 1–8) [7]. In the presence of GSH, GPX4 can protect cells undergoing ferroptosis

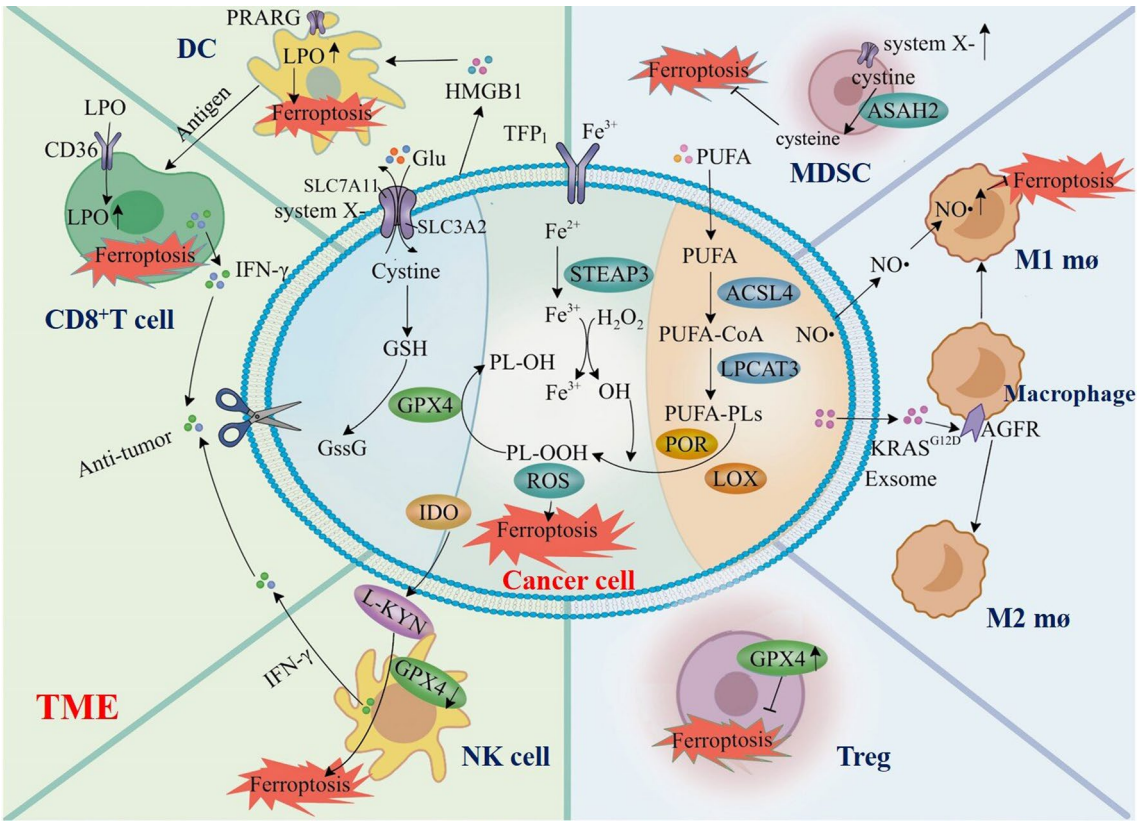

Fig. 1 Ferroptosis and tumor immune evasion. Ferroptosis and its major underlying mechanisms in cancer cells. The pro-tumor and anti-tumor impact of ferroptotic cancer cells interacting with major immune cells in the TME

by reducing lipid peroxides to nontoxic lipid alcohols or converting H_2O_2 to H_2O [8]. According to the description above, we can infer that GPX4, GSH, SLC7A11, and SLC7A5 are direct targets of ferroptosis induction in cells. Drugs such as Erastin [9], p53-activator [10, 11], BAP1 [12], sorafenib [13], the SLC7A11 inhibitors, can block cystine uptake and trigger ferroptosis. The antitumor efficacy of SLC7A11 inhibitors has been certified by substantial studies [14–17] in diverse cancer cell lines. On the contrary, cancer cells can acquire resistance to ferroptosis due to the overexpression of SLC7A11, which enhances GSH biosynthesis [18]. In line with SLC7A11 inhibitors, silencing of GPX4 and inhibitors of GPX4, such as RSL3 [19] or hexamethylmelamine [20], to trigger ferroptosis is also an effective strategy in tumor treatment. RSL3 [19, 21, 22] demonstrates a promising antitumor effect across various malignant tumors by covalently binding to GPX4, leading to GPX4 inactivation and subsequent lipid ROS accumulation in cancer cells [22]. Taken together, the cysteine-GSH-GPX4 axis and System Xc- are crucial components of ferroptosis regulation.

1.3 Lipid metabolism

The accumulation of lipid peroxides on the cell membrane is a distinct sign and a pivotal step of ferroptosis, wherein the generation of 4-hydroxynonenal and malondialdehyde from lipid peroxides causes membrane instability and permeabilization, ultimately leading to ferroptosis [23, 24]. Thus, lipid metabolism is a key process of ferroptosis. In brief, the final stage of ferroptosis involves excessive ROS expanding cellular oxidative stress, damaging DNA and proteins, and eventually leading to cell death [25, 26]. The formation of phospholipid hydroperoxides (PLOOH), a type of lipid ROS [27], depends on both enzymatic and non-enzymatic mechanisms. First, PUFAs in cells interact with Coenzyme A (CoA) to produce polyunsaturated fatty acid Coenzyme A (PUFA-CoA), catalyzed by acyl-CoA synthetase long-chain family member 4 (ACSL4). Second, PUFA-CoA is subsequently re-esterified to polyunsaturated fatty acid-phospholipids (PUFA-PLs) in the presence of lysophosphatidylcholine acyltransferase 3 (LPCAT3) [4]. Then, the enzymatic step involves lipoxygenases (LOXs), a family of iron-containing enzymes [28], which catalyze PUFA-PLs to PLOOH. Cytochrome P450 oxidoreductase (POR) [29], an NADPH-dependent oxidoreductase, also performs a similar role as LOXs. As we can see, ACSL4, LPCAT3, LOX and POR are the key executors through the whole lipid peroxidation. Put another way, targeting these aforementioned would be utilized as a knockdown weapon for ferroptosis-inducing and subsequently antitumor treatment. Based on accumulating evidence, lipophilic antioxidants, such as vitamin E, ferrostatin-1, and liproxstatin-1, can neutralize lipid ROS, thereby reversing ferroptosis in cells [27, 30, 31]. Moreover, Shah et al. [32]found that overexpression of LOX-5, LOX-12, and LOX-15 sensitizes cells to ferroptosis, while LOX inhibitors have also been shown to be potent antioxidants, protecting cells from lipid peroxidation.

1.4 Iron metabolism

Iron is an essential element for human body, and iron from food is absorbed through duodenal epithelial cells. Under physiological conditions, iron in the body exists in the form of iron ion (Fe^{3+}), which binds to transferrin (TF) and is taken up by cells through transferrin receptors (TFR1). After entering the cell, Fe^{3+} is converted to ferrous ions (Fe^{2+}) by the iron reductase STEAP3. Intracellular iron is stored in ferritin, referred to as the iron pool (IP), and is non-toxic to the cell [33]. As a form of iron-dependent cell death, ferroptosis is also characterized by the increase in intracellular free Fe^{2+}, referred to as the labile iron pool (LIP). The process of ferritin degradation to release free Fe^{2+} is positively correlated with nuclear receptor coactivator 4 (NCOA4) [34]. High levels of NCOA4 can increase intracellular free Fe^{2+} levels and promote ferroptosis; in contrast, knocking down the expression of NCOA4 can inhibit the degradation of ferritin, making cells less susceptible to oxidative damage [35, 36]. Elevated free Fe^{2+} can react with H_2O_2, oxidizing Fe^{2+} to Fe^{3+} and producing the highly active hydroxyl radical (OH·). Intracellular OH· participates in the peroxidation of PUFA-PLs through the Fenton reaction to produce deleterious lipid ROS. The large amount of lipid ROS promotes the destruction of the cell membrane and ultimately leads to ferroptosis [37]. It has been shown that cancer cells need more iron for survival than normal cells [38]. In rapidly proliferating cancer cells, intracellular iron levels are increased due to increased iron absorption, which demonstrates the potential of targeting ferroptosis as a novel approach for cancer therapy.

1.5 Mitochondria metabolism

Alterations in mitochondrial morphology are key manifestations of ferroptosis that distinguish it from other types of regulated cell death. Based on this characteristic, mitochondrial metabolism also modulates ferroptosis to some extent. On the one hand, studies have demonstrated that mitochondrial glutamine metabolism is closely linked to ferroptosis; specifically, glutamine hydrolysis promotes serum-dependent oxidative cell damage and ferroptosis in the absence of amino acids or cysteine [39, 40]. Furthermore, the mitochondrial TCA cycle and the electron transport chain (ETC) lead to potential hyperpolarization of the mitochondrial membrane, lipid peroxidation, and ferroptosis. On the other hand, mitochondrial dihydroorotate dehydrogenase (DHODH), a membrane-localized enzyme, has been shown to modulate the sensitivity to ferroptosis, where deletion or inhibition of DHODH could sensitize cancer cells to ferroptosis [41, 42]. Numerous studies have shown that cancer cells with low expression of GPX4 are a key factor in defense against ferroptosis [11, 22, 43], while in the mitochondrial inner membrane, DHODH synergizes in parallel to GPX4 on ferroptosis defense. Mao et al. investigated that the combination of the DHODH inhibitor brequinar and sulfasalazine can increase mitochondrial lipid peroxidation and ultimately induce ferroptosis in cancer [41]. All in all, further investigations will be required to shed more light on the connections between mitochondrial metabolism and ferroptosis.

1.6 Other pathways

p53 is a classical cancer suppressor gene, which is frequently mutated in multiple types of tumors [44]. Here, p53 can inhibit the expression of the cystine/glutamate antiporter (SLC7A11) by binding directly to the SLC7A11 promoter or by interacting with ubiquitin-specific processing protease 7 (USP7) to decrease histone H2B monoubiquitination levels on the SLC7A11 promoter, thereby playing a crucial role in regulating ferroptosis [10, 45–47]. Hence, we can notably see that p53 activators can induce ferroptosis through specific mechanisms. It is worth mentioning that N-acylsphingosine amidohydrolase 2 (ASAH2) can decrease the expression of p53 by inhibiting the p53–haeme oxygenase 1 (HMOX1) axis in myeloid-derived suppressor cells (MDSCs). In the newest research [48], targeting ASAH2 in MDSCs enhances the activation of tumor-infiltrating $CD8^+$T cells and promotes tumor suppression. Consequently, it will be a promising therapeutic strategy in cancer immunotherapy.

As a principal supervisor of antioxidant homeostasis, nuclear factor erythroid 2-related factor 2 (NrF2) modulates the cellular antioxidant mechanisms [49], as well as other roles in cell proliferation, and promotes the transcription of genes involved in ferroptosis suppression, such as SLC7A11 [49, 50]. Due to its antioxidant character and upregulation of the SLC7A11 gene, NRF2 normally promotes defense against ferroptosis [51]. Under physiological conditions, the level of Nrf2 is kept comparatively low due to the activity of Kelch-like ECH-associated protein 1 (KEAP1) [52, 53]. Therefore, activating KEAP1 to inhibit NrF2 may be a mechanism of ferroptosis induction in tumor.

In fact, the molecular mechanism of ferroptosis is extremely complex. In addition to the above mechanisms, ferroptosis is also regulated directly or in parallel by a variety of pathways and metabolites, such as hypoxia inducible factors (HIFs), heat shock proteins (HSPs), and so on [54]. At present, there are still many molecular mechanisms related to ferroptosis remain unclear, and its underlying mechanisms require further exploration by researchers in the future.

2 Ferroptosis and tumor immune evasion

The host immune system is a dynamic and intricate network, and its immune surveillance function is responsible for discovering and eradicating "non-self" components, such as tumor cells. Immune editing theory is one of the key reasons tumors evade immune surveillance, leading to cancer development. Tumor cells with immune evasion not only exhibit malignant biological behaviors, such as proliferation, invasion, migration, and metastasis, but also exhibit a poor response to immunotherapy. Hence, tumor immune evasion is a critical factor in immunotherapy failure. However, the mechanisms of tumor immune evasion are quite complex, and their occurrence is inseparable from the tumor microenvironment (TME). TME refers to the environment in which tumors or cancer stem cells survive, which is composed of tumor cells, immune cells, blood vessels, extracellular matrix, lymphocytes, and so on [55, 56]. Until now, there are several mechanisms of tumor immune evasion in the TME, including crippled antigen presentation, poor immunogenicity of cancer cells, and the poor function or insufficient infiltration of $CD8^+$T cells [57]. In addition, immunosuppressive cells in

TME, such as M2-type tumor-associated macrophage (M2-TAM), T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) also play a vital role in tumor immune evasion. Therefore, fully understanding the role of ferroptosis in tumor immune evasion is of great significance for cancer immunotherapy.

2.1 Ferroptosis and immunogenicity of tumor

During immunotherapy, if the tumor immunogenicity is weak, it cannot effectively recruit and activate antigen-presenting cells and anti-tumor immune cells, resulting in insufficient infiltration of anti-tumor immune cells into tumor tissues, which eventually leads to the failure of immunotherapy. Damage-associated molecular patterns (DAMPs) [58] are endogenous molecules released or exposed by dying cells in response to tissue damage. Released DAMPs acquire immunostimulatory hallmark and bind to pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and purinergic receptors (P2×7), to stimulate inflammation and activate the innate immune system [58]. Notably, cancer cells undergoing ferroptosis can release DAMPs signals, such as high-mobility group box 1(HMGB1), calreticulin, and ATP. These signals belong to immune stimulatory mediators which can activate innate immune cells including antigen-presenting cells, macrophages and dendritic cells (DCs), and continued to activate adaptive immune responses of $CD4^+$T and $CD8^+$T cells [59]. In addition, DAMPs can also be used as adjuvants in Immunogenic cell death (ICD) to enhance the effect of cancer immunotherapy. Wen's research [60] elucidated the enhancing effect of HMGB1 on immunogenicity and showed that ferroptosis inducers such as sorafenib, Erastin, and RSL3 can promote the release of HMGB1. In a recent study, Chen used the ferroptosis inducer RSL3 to induce ferroptosis in 4T1 cells [61]. After co-culture with various immune cells, the content of calreticulin and the status of immune cells were measured and the results showed that RSL3 strengthened the immunogenicity of tumor tissues and enhanced the efficacy of cancer combination therapy. But frustratingly, the immunogenicity induced by late ferroptotic cells is slightly weak, which is in sharp contrast to necrosis [62]. All in all, the strong immunogenicity of early ferroptotic cancer cells broadens the current concept of ICD and reveal the new possibilities for cancer treatment.

2.2 Ferroptosis and CD8+T cells

$CD8^+$T cells are one of anti-tumor immune cells in the TME, which play a crucial role in anti-tumor immune. Normally, cancer immunotherapy aims to restore or enhance the effector function of $CD8^+$T cells infiltrated in tumor tissues. Activated $CD8^+$T cells primarily eliminate tumors by inducing cell death through the perforin-granzyme and Fas/FasL pathways [63]. Previous studies have shown that activation of $CD8^+$T cells in immunotherapy enhances ferroptosis-specific lipid peroxidation in cancer cells, thus contributing to the efficacy of immunotherapy [64]. Mechanistically, activated $CD8^+$T cells release the effector cytokine interferon gamma (IFN γ), which binds to cancer cells and triggers the down-regulation of SLC7A11 expression, thereby affecting the cystine uptake of cells, leading to lipid peroxidation and ferroptosis of cancer cells. However, when ferroptosis inducers are used to induce ferroptosis in cancer cells, immune cells, as a member of TME, cannot be spared. Extensive macroscopic studies have showed that ferroptosis in $CD8^+$T cells was mainly associated with CD36 on the cell membrane [65]. In tumor tissues, infiltrating $CD8^+$T cells take up extracellular fatty acids through CD36, resulting in intracellular lipid accumulation, and as a consequence, $CD8^+$T cells suffer lipid peroxidation and ferroptosis, which leads to a bad outcome of immunotherapy. Hence, inhibiting the activity of CD36 is one of the effective measures to protect $CD8^+$T cells from ferroptosis. In addition, it has been shown that overexpression of GPX4 protects $CD8^+$T cells from ferroptosis induced by GPX4 inhibitors or lipid peroxidation [66]. Adoptive ferrostatin-1 treatment of $CD8^+$T cells enhanced the anti-tumor effect and increased the survival rate of tumor-bearing mice, while adoptive GPX4 inhibitor treatment of $CD8^+$T cells attenuated the anti-tumor effect. Furthermore, research showed that overexpression of GPX4 can increase the number of infiltrating $CD8^+$T cells in tumors, thereby enhancing antitumor capacity to a certain extent [65]. As set forth, we can assume that reducing the use of GPX4 inhibitor and combined with CD36 inhibitor can protect $CD8^+$T cells from ferroptosis, thereby enhancing the effect of immunotherapy. Whether this assumption is solid or not, of course, further studies are needed to confirm it.

2.3 Ferroptosis and NK cells

NK cells are important to tumor immunotherapy due to their powerful anti-tumor activity and pro-inflammatory effect although they cannot specifically kill cancer cells. NK cells kill cancer cells by releasing perforin, granzyme, TNF-α and expressing FasL. Similar to $CD8^+$T cells, NK cells can induce ferroptosis in cancer cells by releasing IFN γ [67]. This

phenomenon was confirmed in HCC cells. Mechanistically, IFN γ can induce ferroptosis of cancer cells by increasing GSH consumption and activating JAK/STAT pathway to inhibit System Xc-. There is a study proving that dihydroartemisinin (DHA) successfully induced ferroptosis and enhanced antitumor immunity in pancreatic cancer cells [68]. It was found that DHA induced ferroptosis while increasing the number of immune cells including NK cells in tumor tissues of animal models. Similarly, previous studies have reported that carbon quantum dots (CQDs) targeting GPX4 can induce ferroptosis in cancer cells and improve anti-tumor immunity [69]. In tumor-bearing mouse models, CQDs nanomaterials recruit a large number of immune cells, including T cells, NK cells and macrophages, thereby transforming "cold" tumors into "hot" tumors and activating systemic anti-tumor immune responses. Nevertheless, it has also been shown that NK cell dysfunction is associated with ferroptosis, which may be attributable to lipid peroxidation in NK cells [70]. Moreover, L-kynurenine (L-KYN), a tryptophan metabolite in TME of gastric cancer, has been discovered to trigger lipid peroxidation and ferroptosis in NK cells, thereby facilitating tumor growth in vivo [71].

2.4 Ferroptosis and DCs

DCs is the most potent antigen-presenting cell in the TME. During the cancer immunotherapy, they are responsible for presenting cancer cells to $CD8^+$T cells, and then $CD8^+$T cells exert their anti-tumor efficacy. Ferroptosis's feature on DCs is a double-edged sword. On the one hand, HMGB1 released at the early stage of ferroptosis contributes to maturation of DCs [70]. On the other hand, the increased level of 4-hydroxynonenal protein, a by-product of lipid peroxidation in the late stage of ferroptosis, can cause DCs dysfunction [72]. Particularly, bone marrow-derived DCs are highly sensitive to ferroptosis due to the high level of LOX12/15 during maturation, which produces abundant phospholipid oxidation products [73]. In addition, PPARG, a nuclear receptor involved in the regulation of lipid metabolism, facilitated ferroptosis in DCs limits antitumor immunity [74]. The association between ferroptosis and DCs is still elusive and needs to be further studied.

2.5 Ferroptosis and TAM

Macrophages (Mφ) are important not only in iron metabolism and circulation, but also in the TME. In terms of iron metabolism, macrophages, mainly spleen red pulp macrophages (RPMs) and liver macrophages (Kupffer cells), are involved in the removal of aging necrotic erythrocytes in the body and the recovery of iron for recycling [75]. While in TME, macrophages are often referred to as tumor-associated macrophages (TAM). In brief, TAM has two different polarization states, one is the anti-tumor M1 type (M1-TAM), and the other is the pro-tumor M2 type (M2-TAM). Therefore, eliminating the immunosuppressive effect of M2-TAM while preserving the immunostimulatory effect of M1-TAM is an elegant strategy for cancer immunotherapy.

Intriguingly, the sensitivity of M1-TAM to ferroptosis is different from that of M2-TAM. Accumulating evidence indicate that M1-TAM is resistant to ferroptosis, while M2-TAM is sensitive to ferroptosis [76, 77]. At the cellular level, high expression of inducible nitric oxide synthase (iNOS) and high production of NO radical (NO•) were observed in M1-TAM, while iNOS expression and NO• production were inhibited in M2-TAM. NO• can chemically react with lipid radicals and intermediates of lipid peroxidation to reduce the level of LPO in cells, thus making M1-TAM highly resistant to ferroptosis. At the same time, eliminating the immunosuppressive effects of M2-TAM or polarizing the M2-TAM to M1-TAM have been widely used in the field of cancer immunity. Evidence suggests that targeting TAM with ferroptosis inducers is a promising therapeutic strategy of cancer. Hsieh and colleagues found that zero-valent iron nanoparticles (ZVI-NP) could act like ferroptosis inducers [78]. Specifically, ZVI-NP can be rapidly converted to Fe^{3+} in the lysosomes of tumor cells, generating a large amount of ROS, which triggers ferroptosis. ZVI-NP also effectively transformed M2-TAM into M1-TAM in the tumor co-culture system. In contrast, ferroptosis promoted the autophagy-dependent release of $KRAS^{G12D}$ protein from exosomes of pancreatic cancer cells in the pancreatic cancer model [79]. Extracellular $KRAS^{G12D}$ binds to AGER/RAGE receptors on macrophages, resulting in macrophage polarization toward the M2 type. However, similar results have not been seen in other cancers. Whether this phenomenon is related to the heterogeneity of pancreatic cancer cells itself, further connotation should be explored in subsequent studies.

2.6 Ferroptosis and tregs

Tregs are a special subset of $CD4^+$T cells, which play a negative immunomodulatory role in the host immune response and have immunosuppressive effects in the TME. Tregs undergo less LPO compared to $CD8^+$T cells, indicating that Tregs

rarely undergo ferroptosis in the TME [80, 81]. This is due to the elevated expression of GPX4 in Treg cells under TCR/CD28 co-stimulation, thereby protecting Treg cells from ferroptosis. Meanwhile, GPX4-deficient Tregs can trigger ferroptosis and contribute to anti-tumor immunity. Therefore, inducing ferroptosis in Tregs by targeting GPX4 may be an effective strategy to enhance the effect of cancer immunotherapy.

2.7 Ferroptosis and MDSCs

Myeloid-derived suppressor cells (MDSCs) are also a kind of immunosuppressive cells, which reduce T lymphocytes activity and promote tumor immune evasion in the TME. MDSCs have certain resistance to ferroptosis in the TME. It has been shown that these tumor-infiltrated MDSCs are protected from ferroptosis by high expression of System Xc- and ASAH2 [48]. Specifically, MDSCs uptake abundant cystine but do not transport cysteine to the TME because of the absence of the ASC transporter [4]. As a consequence, MDSCs would deprive cystine from other immune cells including anti-tumor cells in the TME. As mentioned above [48], ASAH2 can decrease the expression of p53, and targeting ASAH2 in MDSCs enhances the activation of tumor-infiltrating $CD8^+$T cells and promotes tumor suppression. From this point of view, targeting ASAH2 to induce ferroptosis in MDSCs is a promising candidate for anti-tumor immune. Furthermore, ferroptosis induced by GPX4 deletion results in the release of high levels of HMGB1, which promotes the recruitment of immunosuppressive MDSCs in a hepatocellular tumor model. GPX4-deficient liver tumors also have increased expression of PD-L1. Thus, MDSCs infiltration and concomitant PD-L1 upregulation counteracted the cytotoxic $CD8^+$T cell response induced by ferroptotic liver tumor cells, ultimately resulting in a lack of significant tumor suppression [82].

2.8 Others

The association between ferroptosis and tumor immune evasion is not only reflected in its effect on tumor immunogenicity and various immune cells in the TME, but also the metabolites of ferroptotic cancer cells can modulate tumor immune evasion. It has been reported that increased release of prostaglandin E2 (PGE2) from cancer cells is associated with ferroptosis, and PGE2 is a major immunosuppressive factor that represses the antitumor function of NK cells, DCs, and cytotoxic T cells [83]. Moreover, ferroptotic cancer cells can also secrete 8-hydroxy-2′-deoxyguanosine (8-OHdG), a major product of oxidative DNA damage, which recruits the infiltration of M2-TAM and promotes pancreatic tumorigenesis subsequently [84].

Taken together, we can conclude that the role of ferroptosis in tumor immune evasion is a double-edged sword, and the complex molecular mechanisms between them need further exploration. Appropriate use of the dual aspects of ferroptosis in tumor immune evasion to achieve more accurate diagnosis and treatment is a key focus for future research (Fig. 1).

3 Ferroptosis and cancer immunotherapy

Although many molecular mechanisms of ferroptosis and tumor immune evasion have not been fully elucidated, researchers have made many active preclinical explorations for immunotherapy targeting ferroptosis [85].

3.1 Small-molecule ferroptosis inducers and inhibitors

There are many achievements in terms of common ferroptosis inducers for cancer immunotherapy. Dr. Zhao and his team used RSL3 to induce ferroptosis in head and neck cancer cells and explored the diversity of the TME, experimentally finding that the ferroptosis significantly reduced the number of MDSCs and M2-TAMs in the TME [86]. In the meantime, it was found that calreticulin and HMGB1 secretion was increased in the TME, as was the number of tumor-infiltrating $CD4^+$T and $CD8^+$T cells. In another study [68], DHA successfully induced ferroptosis and enhanced antitumor immunity in pancreatic cancer cells. It was found that DHA could upregulate the expression of GPX4 and SLC7A11, which not only significantly reduced the number of M2-TAM and MDSCs in tumor tissues of tumor-bearing mice, but also increased the number of immune cells in $CD8^+$T cells, NK cells and NKT cells. In addition, Sorafenib, an FDA-approved anticancer drug for the treatment of HCC, renal cell carcinoma, and thyroid cancer, as the system Xc- inhibitor, triggers ferroptosis by depleting the antioxidant GSH causing to the GPX4 system inactive sequentially [87, 88]. Similarly, octreotide, as a FDA-approved drug for ovarian cancer treatment, can directly target and inhibit GPX4 to induce ferroptosis [20]. Thus, we find that some

antineoplastic drugs not only induce ferroptosis but also regulate the tumor immune microenvironment. Therefore, this suggests that ferroptosis-related biomarkers have the potential to be used as new targets for cancer immunotherapy.

3.2 Nanoparticles

In recent years, many nanomedicines have been devoted to cancer immunotherapy. Nanomedicines have got good grades in cancer treatment due to their special physical and chemical properties, such as strong targeting and few side effects. In a model of liver cancer, carbon quantum dots recruited a large number of immune cells, including T cells, NK cells and macrophages, to activate the systemic anti-tumor immune response [69]. Besides, eNVs-FAP vaccine inhibits tumor growth by inducing cytotoxic T lymphocyte (CTL) to produce a strong and specific immune response to tumor cells and reprogramming immunosuppressive TME to induce ferroptosis [89]. It is worth mentioning that Liu and colleagues proposed a metal-phenolic networks (MPNs) nanoplatform, which consists of PD-L1 inhibiting DNAzyme, tannic acid (TA) and metal-ion complex of $Fe3^{+}/Mn2^{+}$ (DZ@TFM for short) [90]. In their study, the function of each component has been elaborated, wherein, Fe^{2+} is in situ generated from Fe^{3+} by TA reduction to trigger ferroptosis, while DZ is activated by Mn^{2+} to effectively silence PD-L1. Meanwhile, photothermal therapy is used to synergize with ferroptosis for enhance anti-tumor immunes. At the same time, Xie et al. [91] established a nexus of antiexosomal PD-L1 and ferroptosis under the background of MPNs. As a result, this novel synergy of antiexosomal PD-L1 with ferroptosis evoke potent anti-tumor immunity in B16F10 tumors and immunological memory against metastatic tumors in lymph nodes. In fact, these studies not only reveal the potential of ferroptosis combined with immunotherapy, but also serve as a model for the combination of multi-therapeutic modalities.

3.3 Targeting ferroptosis in combination with ICIs

Immune checkpoint inhibitors (ICIs), especially those targeting PD-1 and PD-L1, have been considered a breakthrough in cancer treatment, achieving encouraging clinical anti-tumor effects in a variety of cancers. However, low response rate and therapeutic resistance have largely limited its efficacy in this field. Wherein, one of the main factors contributing to primary resistance to ICIs is the lack of tumor-infiltrating T cells, such as $CD8^{+}$T cells. Instead, various immunosuppressive cells are infiltrated in this type of the TME. Therefore, as one of the RCD, ferroptosis can reshape the immunosuppressive TME via increasing the amount of $CD8^{+}$T cells. Hence, we hypothesize that there may be strong potential for the combination of ICIs with ferroptosis inducers in cancer immunotherapy. For example, combination therapy with GPX4 inhibitors and anti-PD-1 antibody significantly inhibited tumor growth and induced significant immune activity, with a significant increase in the proportion of activated $CD8^{+}$T cells [92]. IL-1β maintains the maintenance of Fe-S cluster, thereby inhibiting iron accumulation and ferroptosis. The combination of IL-1β blocker and anti-PD-1 antibody showed stronger tumor inhibition than monotherapy, but this effect could be reversed by liprostatin-1, indicating that IL-1β blocker indeed exerted synergistic anti-tumor effects through ferroptosis [93]. Fan and his team developed BEBT-908, a dual-targeted PI3K and HDAC inhibitor, which can upregulate MHC-I molecules through STAT1 signaling and activate endogenous IFN γ signaling in cancer cells, effectively inhibit tumor cell growth and enhance the effect of anti-PD-1 therapy by inducing immunogenic ferroptosis in cancer cells [94]. Besides, another study has found that tumors with high expression of TYRO3 are resistant to anti-PD-1 or anti-PD-L1 treatment, and the drug resistance induced by these proteins is partly due to ferroptosis defense [95]. TYRO3 inhibitors can be used to induce ferroptosis and combine anti-PD-1 or anti-PD-L1 treatment to reverse drug resistance and increase the therapeutic effect of ICI. Professor Li and his team found that USP8 antagonized ferroptosis by stabilizing GPX4 in tumor cells and indicated that targeting USP8 may serve as a potential therapeutic strategy to promote ferroptosis to enhance cancer immunotherapy [96]. Overall, IFN-γ-JAK1-STAT1 pathway, TYRO3 and USP8 are expected to be the common targets of ferroptosis inducers combined with PD-1/PD-L1 monoclonal antibodies [97]. Furthermore, the transcriptome analyses before and during nivolumab therapy was completed by professor Wang and his team [64]. The results reveal that the clinical benefits of nivolumab therapy are correlated with reduced expression of SLC3A2 and increased levels of IFN γ and $CD8^{+}$T cells. Additionally, bromodomain 4 (BRD4) expression has been reported to be upregulated in ICIs-resistant melanoma patients, and inhibition of the BRD4/AKR1C2 axis with small-molecule inhibitors has been shown to enhance the sensitivity of melanoma to ferroptosis and immunotherapy [98]. Thus, targeting tumor ferroptosis pathway in combination with ICIs will be a considerable aspect in cancer immunotherapy.

3.4 Individual therapy

Although preclinical studies have shown the potential of ferroptosis as a novel target for cancer immunotherapy, research on ferroptosis inducer monotherapy and combination therapy with ICIs is still in its infancy. Due to the significant heterogeneity of tumors, therapies related to ferroptosis require individualization. In this context, tumors possess distinct immune microenvironments and exhibit variability in iron, lipid, and amino acid metabolism, resulting in diverse or opposing responses to ferroptosis-related therapies. Thus, there are several recommendations for individualized therapy:

(I) According to the distribution of infiltrating immune cells, TME can be classified into three immunophenotypes: inflamed type, immune-altered type, and immune-desert type [99, 100]. Since different immune cells have diverse sensitivities to ferroptosis, different immunophenotypes must be differentiated when using ferroptosis-related therapies.

(i) TME of inflamed tumors owning high immunogenicity, abundant antigen presenting cells and infiltration of $CD8^+$T cells [101]. In this TIME, the application of ferroptosis inducers not only significantly kills $CD8^+$T cells, but also impairs the maturation and function of DCs, thereby affecting the presentation of tumor antigens and the killing effect of $CD8^+$T cells, and reducing the efficacy of ICI immunotherapy. However, due to low expression of the $CD8^+$T cell system Xc-, the targeting system Xc- does not affect the viability of T cells [64]. In some cases, ferroptosis inhibitors protect T cells from ferroptosis and suppress immunosuppressive signals released by ferroptotic tumor cells.

(ii) In immune-altered tumors, tumor cells undergo immune evasion due to the presence of immunosuppressive cells. From the perspective of ferroptosis, TAMs are sensitive to ferroptosis and can be polarized into M1-TAMs by certain cytokines released by ferroptosis tumor cells. Therefore, ferroptosis inducers may help to reverse the immunosuppressive microenvironment and overcome primary resistance to ICIs in immune-altered tumors with abundant TAM infiltration. In addition, GPX4 inhibitors can induce ferroptosis of Tregs and reduce their survival while promoting Th17 cell responses, which may enhance antitumor immunity and improve immunotherapy outcomes in tumors with high Treg infiltration [81]. However, tumors with a high degree of MDSCs infiltration may not be sensitive to ferroptosis inducers, as MDSCs have been shown to resist ferroptosis [102]. MDSCs express high levels of systemic Xc and compete with $CD8^+$T cells and NK cells for cystine uptake without returning cystine to the TME [102]. Thus, targeting system Xc- could alleviate MDSC-mediated cystine clearance in TME, thereby promoting the survival of $CD8^+$T cells and NK cells.

(iii) Immune-desert tumors, which are characterized by low immunogenicity, rapid growth, and a lack of immune cell infiltration, typically respond poorly to immunotherapy. Chemotherapy, radiotherapy, and targeted therapy can stimulate the generation of tumor neoantigens, potentially improving the efficacy of combined immunotherapy approaches [101]. Notably, some chemotherapy agents, targeted therapies, and radiotherapy also act as ferroptosis inducers [103–105]. These treatments may enhance ICI immunotherapy effectiveness by boosting tumor immunogenicity and converting "cold tumors" to "hot tumors". In clinical practice, combinations of immunotherapy with chemotherapy, radiotherapy, or targeted therapy have been successfully applied to various tumors [106, 107]. It remains critical to explore whether chemoradiotherapy or targeted drugs with ferroptosis-inducing properties can further improve the efficacy of ICI immunotherapy.

(II) Tumor heterogeneity determines the types of ferroptosis inducers. For example, tumors that are rich in iron (such as liver [108] and breast cancers [109]) or that are rich in reactive oxygen species (such as lung cancers [110]) are particularly sensitive to ferroptosis inducers.

(III) The selection of targeted drugs largely depends on the degree of expression of the drug target in cancer cells. Different ferroptosis regulatory genes have different expression levels in different tumors. For example, SLC7A11 is overexpressed in lung cancer [110]; therefore, ferroptosis inducers targeting SLC7A11 may be effective against it.

(IV) In addition to cancers, ferroptosis also plays pivotal roles in neurodegeneration, tissue damage, inflammation, and infection [1]. Therefore, the side effects of ferroptosis inducers in other body systems should also be taken into consideration during the process of treatment.

In summary, ferroptosis-related drugs are still in the preclinical development stage in the field of cancer immunotherapy, and there is still a long way to go before they can be truly applied in clinical practice.

4 Conclusions and perspectives

In summary, ferroptosis is a novel and unique type of metabolically regulated cell death discovered and defined in 2012, which is mainly characterized by the increase in intracellular free iron and the accumulation of lipid peroxides. Ferroptosis is related to amino acid metabolism, lipid metabolism, iron metabolism, mitochondrial metabolism, among others, and its underlying mechanisms and potential applications are rapidly advancing.

Tumor immune evasion is one of the main characteristics of cancer and is an obstacle to effective cancer immunotherapy. Ferroptosis is closely related to tumor immune evasion by affecting the immunogenicity of tumors and the composition and function of immune cell subsets in the tumor microenvironment. The exploration of ferroptosis in tumor immune evasion has opened new avenues in cancer immunotherapy. Furthermore, an emerging view is that targeting ferroptosis in tumors profoundly affects immune cells infiltrating the TME and the response to immunotherapy, including ICIs.

Until now, targeting ferroptosis seems to be an increasingly promising strategy to improve the efficacy of immunotherapy in the field of cancer therapy. However, before clinical application, many problems still need to be solved. It is greatly necessary to clarify the difference of ferroptosis in a variety of cancers both of its TME, to clarify the application of ferroptosis inducers or even inhibitors in different immunophenotypes, to identify other potential systemic side effects of ferroptosis-related drugs. Further clarification of the above problems will be of great benefit to achieve precise and individualized treatment in cancer immunotherapy.

Finally, it is expected that further in-depth basic and clinical research in the future, which will provide new ideas for the treatment candidate with ferroptosis as the therapeutic target in cancer immunotherapy.

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Declarations

Competing interests The authors declare no competing interests.

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