

## REVIEW

# The crosstalk between ferroptosis and anti-tumor immunity in the tumor microenvironment: molecular mechanisms and therapeutic controversy

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## Abstract

The advent of immunotherapy has significantly reshaped the landscape of cancer treatment, greatly enhancing therapeutic outcomes for multiple types of cancer. However, only a small subset of individuals respond to it, underscoring the urgent need for new methods to improve its response rate. Ferroptosis, a recently discovered form of programmed cell death, has emerged as a promising approach for anti-tumor therapy, with targeting ferroptosis to kill tumors seen as a potentially effective strategy. Numerous studies suggest that inducing ferroptosis can synergistically enhance the effects of immunotherapy, paving the way for a promising combined treatment method in the future. Nevertheless, recent research has raised concerns about the potential negative impacts on anti-tumor immunity as a consequence of inducing ferroptosis, leading to conflicting views within the scientific community about the interplay between

**Abbreviations:** 8-OHG, 8-hydroxyguanosine; 15-HpETE-PE, 15-hydroperoxyeicosatetraenoic acid; AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family member 4; AGER, advanced glycosylation end-product specific receptor; APOC1, Apolipoprotein C1; ASAH2, neutral ceramidase N-acylsphingosine amidohydrolase; ATP, adenosine triphosphate; Chol-DHA, cholesterol derivative of DHA; COX-2, cyclooxygenase 2; CRTH2, chemoattractant receptor expressed on Th2 cells; CRT, calcium reticulum protein; DC, dendritic cell; DCN, proteoglycan decorin; DAMPs, damage-associated molecular patterns; DHA, dihydroartemisinin; DP, receptor for D-series prostaglandins; DNA, deoxyribonucleic acid; FSP1, ferroptosis suppressor protein 1; GCH1, guanosine triphosphate cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; HETE, hydroxyeicosatetraenoic acid; HMGB1, high mobility group protein 1; ICB, immune checkpoint inhibitor; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IFN, interferon; IL, interleukin; IL-12p40, interleukin-12 subunit p40; iNOS, inducible nitric oxide synthase; IRF, interferon regulatory factor; JAK, janus kinase; MHC, major histocompatibility complex; MDSCs, myeloid-derived suppressor cells; NK cell, nature killer cell; NO, nitric oxide; NKG2D, natural killer group 2D; NF- $\kappa$ B, nuclear factor- $\kappa$ B; ox-LDL, oxidized low-density lipoprotein; PMN-MDSCs, polymorphonuclear MDSCs; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PLT, platelet; PPARG, proliferator-activated receptor gamma; PUFA-PL, phospholipid containing polyunsaturated fatty acid chains; PYRO-Fe, pyrophosphorbiide-iron; ROS, reactive oxygen species; RT-MP, radiated tumor cell-released microparticles; SAS, sulfasalazine; SAPE-OOH, 1-stearoyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine; STAT, signal transducer and activator of transcription; system Xc-, cystine-glutamate antiporter comprising SLC7A11 and SLC3A2 subunits; TAMs, tumor-associated macrophages; TLR, toll-like receptor; TME, tumor microenvironment; TXA2, thromboxane A2; Tc, cytotoxic T lymphocyte subset; Th, T-helper; Treg, regulatory T cell; ULBP, UL16-binding protein; XBP1, X-box-binding protein-1; ZnP, Zn-pyrophosphate.

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ferroptosis and anti-tumor immunity, thereby underscoring the necessity of a comprehensive review of the existing literature on this relationship. Previous reviews on ferroptosis have touched on related content, many focusing primarily on the promoting role of ferroptosis on anti-tumor immunity while overlooking recent evidence on the inhibitory effects of ferroptosis on immunity. Others have concentrated solely on discussing related content either from the perspective of cancer cells and ferroptosis or from immune cells and ferroptosis. Given that both cancer cells and immune cells exist in the tumor microenvironment, a one-sided discussion cannot comprehensively summarize this topic. Therefore, from the perspectives of both tumor cells and tumor-infiltrating immune cells, we systematically summarize the current conflicting views on the interplay between ferroptosis and anti-tumor immunity, intending to provide potential explanations and identify the work needed to establish a translational basis for combined ferroptosis-targeted therapy and immunotherapy in treating tumors.

#### KEYWORDS

anti-tumor immunity, ferroptosis, ferroptosis-targeted therapy, immunogenic cell death, immunotherapy, tumor microenvironment

## 1 | BACKGROUND

Ferroptosis, a distinct form of programmed cell death [1], is characterized by iron-dependent reactive oxygen species (ROS) generation and consequent peroxidation of phospholipids containing polyunsaturated fatty acid chains (PUFA-PLs) [2], which lead to membrane rupture and increased permeability, culminating in cell death [3, 4]. Key regulators of this process include glutathione peroxidase 4 (GPX4) [5], system Xc-cystine/glutamate antiporter (a transmembrane protein complex containing subunits SLC7A11 and SLC3A2, referred to as system Xc- throughout the review article) [6], ferroptosis suppressor protein 1 (FSP1) [7, 8], guanosine triphosphate cyclohydrolase 1 (GCH1) [9], and acyl-CoA synthetase long-chain family member 4 (ACSL4) [10]. The molecular mechanisms of ferroptosis regulation have been comprehensively reviewed elsewhere [11, 12]; hence, we will not delve into them in detail in this article.

Ferroptosis was initially described in cancer research when erastin and RSL3 were discovered as potent killers of RAS mutant cancer cells [13, 14]. It has since been associated with a critical role in degenerative and neoplastic diseases [15]. Various cancer-related signaling pathways can regulate cancer cell ferroptosis [16, 17], and certain cells, due to their unique metabolism, high ROS levels, and specific mutations, are more susceptible to ferroptosis [18, 19]. Notably, ferroptosis has proven significant in overcoming resistance to traditional therapies [18, 20], with studies indicating that anti-oxidative mecha-

nisms crucially contribute to therapy resistance in tumors [21]. Recent findings also hint at ferroptosis's substantial role in inhibiting tumor metastasis [22, 23]. Given these insights, the therapeutic targeting ferroptosis has gained prominence in cancer treatment discussions.

The link between tumors and immunity was initially acknowledged with the introduction of the "cancer immunosurveillance" concept [24, 25], which later evolved into "cancer immunoediting". This principle underscores the immune system's dual role in battling tumors. On the one hand, the immune system can detect and eliminate early-stage tumors; on the other hand, it may inadvertently select tumor cells that evade immune recognition, thereby promoting tumor progression [26, 27]. Several immune cells within the tumor microenvironment (TME) significantly contribute to this process [25, 28]. For example, CD8<sup>+</sup> T cells and natural killer (NK) cells perform tumor-eliminating functions [29, 30], while dendritic cells (DCs) support this process by presenting antigens to T cells [31]. Certain immune cells, such as tumor-associated macrophages (TAMs), serve dual roles in anti-tumor immunity due to their ability to polarize into the anti-tumor M1 phenotype and the pro-tumor M2 phenotype, yet they primarily manifest pro-tumor effects within the TME [32, 33]. Immune inhibitory cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are critical in suppressing anti-tumor immunity and accelerating tumor progression [34, 35]. Tumor immunotherapy, including immune checkpoint inhibitors (ICIs), seeks to rejuvenate the immune system's ability

to eradicate tumors [36]. Despite the demonstrated efficacy of ICIs in various cancers [37], the response rate remains low in most solid tumors, aside from certain types such as melanoma, or tumors exhibiting favorable predictive factors for ICI treatment outcomes, like microsatellite instability-high (MSI-H) [38], thereby underscoring the need for improved therapeutic outcomes.

Immunogenic cell death (ICD) is a specific type of cell death capable of activating the immune system and synergizing with ICIs [39–41]. Characterized by the release of various damage-associated molecular patterns (DAMPs) such as high mobility group protein 1 (HMGB1), adenosine triphosphate (ATP), and calcium reticulum protein (CRT) [42, 43], ICD acts as an adjuvant to trigger immune responses [44, 45]. Current research indicates that ICD can enhance the therapeutic effects of conventional treatments and improve the response rate when combined with ICIs [39–41]. Recent studies have suggested the potential of integrating ferroptosis-targeted therapy with immunotherapy for tumor treatment [46, 47]. Several studies have indicated a cooperative effect between ferroptosis induction and ICIs [48–58], suggesting a promising future for this combined treatment approach. However, further investigation has shown that ferroptosis has a complex impact on anti-tumor immunity, affecting the feasibility of such a combination strategy. While some studies regard ferroptosis as a form of ICD [59–63], a recent study offers a contrary view [64], with additional research implying that ferroptosis may even exert immunosuppressive functions [65–67]. Moreover, inducing ferroptosis affects various immune cells in the TME, potentially suppressing anti-tumor immunity [67]. The relationship between ferroptosis and anti-tumor immunity is intricate and contradictory, necessitating further comprehensive and profound understanding to lay a robust translational foundation for the future of this combined therapy.

Since concerns have been raised regarding pro-ferroptotic compounds' potential detrimental effects on the immune system [67, 68], which could limit their clinical use, a better understanding of the interplay between ferroptosis and anti-tumor immunity is crucial for developing more effective strategies for ferroptosis-targeted therapy. Previous studies have primarily focused on the connection between ferroptosis and either tumor cells [69, 70] or immune cells in the TME [68, 71]. Given that the TME comprises both cancer and immune cells [72, 73], assessing the pros and cons of targeting ferroptosis as an anti-tumor treatment requires a comprehensive view. Therefore, a thorough literature review on the interplay between ferroptosis and anti-tumor immunity is vitally important. In this review, we initially explore this relationship from the perspective of cancer cells to understand whether ferroptosis activates the immune

system to enhance anti-cancer effects or instead inhibits the immune response. We then focus on TME immune cells to discuss the potential synergies of combining pro-ferroptotic agents with immunotherapy and the possible negative impacts of ferroptosis inducers on these cells. Finally, we propose perspectives and therapeutic considerations for combining ferroptosis-targeted therapy and immunotherapy in tumor treatment.

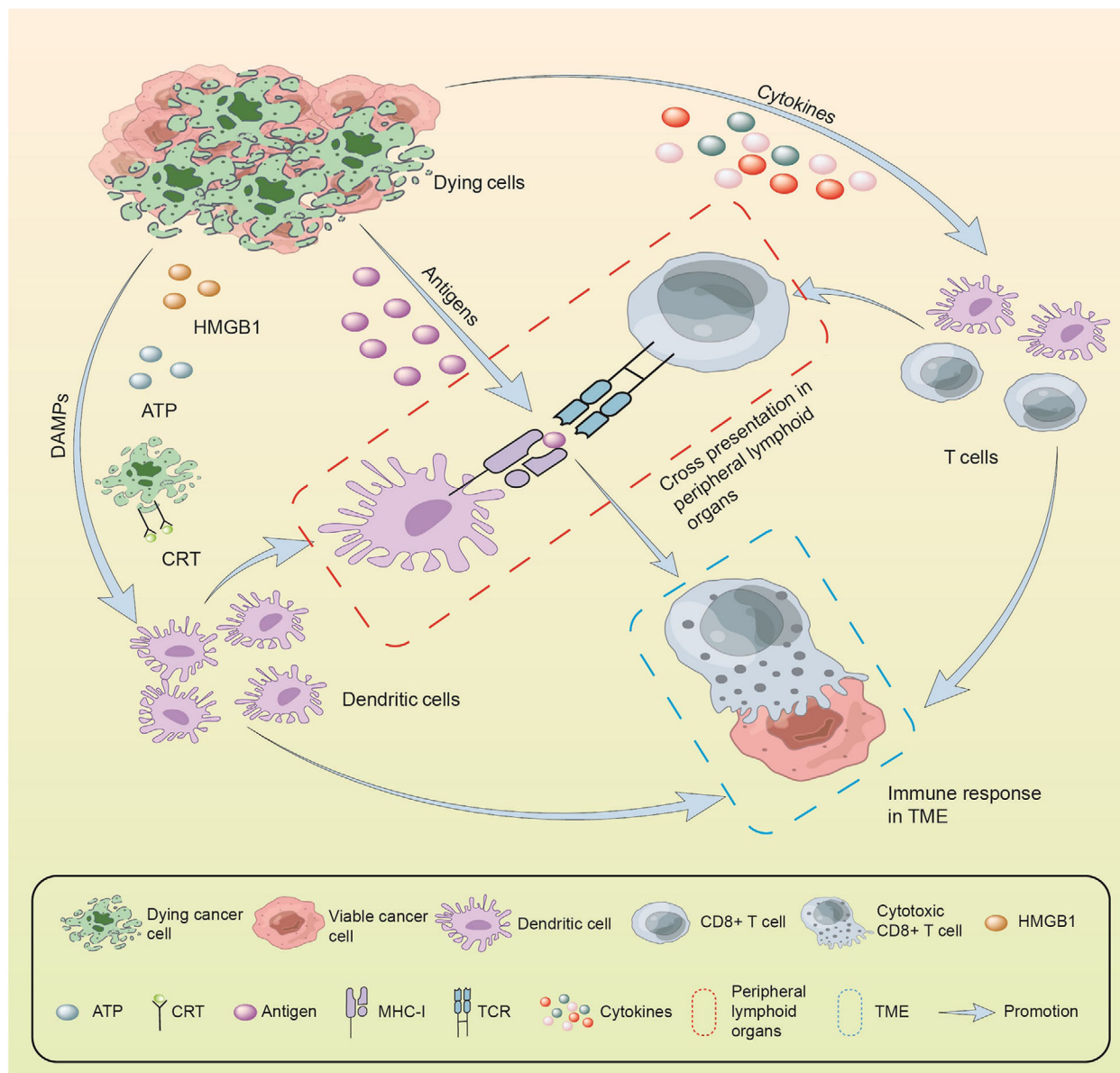
## 2 | THE CROSSTALK BETWEEN FERROPTOSIS AND ANTI-TUMOR IMMUNITY IN CANCER CELLS: WHETHER FERROPTOSIS IN CANCER ACTIVATES THE ANTI-TUMOR IMMUNITY OR CONVERSELY IMPEDES IMMUNE RESPONSES?

### 2.1 | Immunogenicity of ferroptotic cancer cells: is ferroptosis a kind of ICD?

#### 2.1.1 | Supporting evidence

As research on ferroptosis deepens, attention has turned to whether ferroptosis is a type of ICD. ICD is characterized by three hallmarks: DAMPs, cytokines, and antigenicity [40] (Figure 1). To determine if ferroptosis qualifies as ICD, we can initially assess whether it exhibits these three features.

In terms of DAMPs, studies have reported that treating cancer cells (HT1080 and PANC1 cell lines) with ferroptosis-inducing compounds led to the release of HMGB1, which depended on the autophagic pathway [74]. A subsequent research showed that HMGB1 released from ferroptotic cells relied on the advanced glycosylation end-product specific receptor (AGER) in macrophages for functionality but not on toll-like receptor (TLR) 4 [74]. Another study found that early ferroptotic cancer cells (MCA205 and GL261 cell lines treated with RSL3 for 1 h and 3 h, respectively) released the highest level of HMGB1, promoting the maturation of bone marrow-derived DCs [59]. Furthermore, ATP concentration also increased in early ferroptotic cells. Blocking the P2X7 purinergic channel in mice significantly weakened the immune protection provided by ferroptotic cancer cells [59]. RSL3 treatment significantly increased the expression of HMGB1 and CRT in head and neck squamous cell carcinoma xenografts [62]. Human head and neck squamous cell carcinoma specimens with low expression of GPX4 tend to express high CRT, which also suggests that ferroptosis may increase CRT exposure [62]. Dihydroartemisinin (DHA) can induce ferroptosis in CT26 cells [75]. Additionally, the Zn-pyrophosphate (ZnP)<sub>2</sub>@DHA/PYRO-Fe core-shell



**FIGURE 1** Three hallmarks of ICD: DAMPs, cytokines, and antigenicity. There are three hallmarks of ICD: DAMPs, cytokines, and antigenicity. HMGB1, ATP, and CRT are classical DAMPs, among which HMGB1 and ATP are released by dying cells, while CRT is expressed on the surface of dying cells. Antigens released by dying cells are cross-presented by DCs to CD8<sup>+</sup> T cells by MHC I molecules. DAMPs and cytokines provide adjuvants, while antigens provide antigenicity, which together promote the generation of anti-tumor immunity. The resulting cytotoxic CD8<sup>+</sup> T cells migrate to the tumor site, where they eliminate antigen-expressing cancer cells. Abbreviations: ATP: adenosine triphosphate; CRT: calcium reticulum; DAMPs: damage-associated molecular patterns; HMGB1: high mobility group protein 1; MHC-I: major histocompatibility complex class I; TCR: T-cell receptor; TME: tumor microenvironment.

nanoparticles, composed of a cholesterol derivative of DHA (Chol-DHA) and pyropheophorbide-iron (PYRO-Fe), enhanced the pro-ferroptotic effects of DHA and increased the exposure of CRT as well as the release of HMGB-1 in CT26 cells [75]. The radiated tumor cell-released microparticles (RT-MP) released by irradiated lung carcinoma cells can cause ferroptosis of tumor cells, and the release of extracellular CRT and ATP

in the medium increased after treatment with RT-MP [76]. Similarly, in recent studies investigating the use of nanomedicines to induce ferroptosis for cancer treatment, a few findings have highlighted the release of DAMPs by drug-induced ferroptotic cancer cells [52, 54, 60, 62, 77–85], and in several studies, the promotion of DC maturation has also been reported [54, 82–85]. In addition to the most well-known DAMPs, namely HMGB1, ATP and CRT,



Liu et al. [63] found that proteoglycan decorin (DCN) was also a DAMP released by ferroptotic cells (HT1080, HeLa, PANC1 and KPC cells). Its release depended on the autophagy pathway. After discharge, it acted on AGER in macrophages to promote inflammation and anti-tumor immunity, which can be enhanced by HMGB1. The release of DCN precedes other DAMPs [63].

Ferroptotic cancer cells have also been found to release cytokines. Wiernicki et al. [64] evaluated the role of ferroptosis in inducing ICD. They successfully detected the release of C-X-C motif chemokine ligand 1, tumor necrosis factor, and interferon (IFN)- $\beta$  in the supernatant of ferroptotic MCA205 cells, which demonstrated the ability of ferroptotic cancer cells to secrete cytokines. Nonetheless, their subsequent experiments did not support ferroptosis as ICD [64] (see section 1.1.2 Contradictory Evidence).

Compared with DAMPs and cytokines, our current understanding regarding the impact of ferroptosis on the antigenicity of cancer cells remains limited. Currently, there is no direct evidence supporting the involvement of ferroptosis in antigenicity regulation. Only a few studies have speculated on the existence of this effect based on observations of immune system activation in response to ferroptotic cancer cells. For instance, to improve the efficacy of cancer treatment, Zhang et al. [86] developed a biomimetic magnetosome composed of a ferroptosis inducer and immune modulators. This magnetosome substantially increased CD4<sup>+</sup> and CD8<sup>+</sup> T cells and M1 TAMs in the TME of B16F10 and 4T1 tumor models. Importantly, even in the absence of immune modulators, the ferroptosis inducer alone moderately increased the proportion of anti-tumor immune cells, potentially due to the release of immunogenic antigens from ferroptosis-induced cancer cells [86]. However, this is a speculative hypothesis and requires verification. Further research is needed to elucidate the role of ferroptosis in antigenicity.

While the assessment of the three hallmarks can provide an initial indication of whether ferroptosis qualifies as an ICD, the gold standard for determining the immunogenicity of a specific cell death modality is the prophylactic vaccination model [87, 88]. In this prophylactic vaccination model, mouse cancer cells are initially exposed to a potential inducer of ICD *in vitro*. Subsequently, the treated cancer cells are administered as a subcutaneous vaccine without any immunological adjuvant and by removing any exogenous chemical entities. Approximately 1-2 weeks later, mice were subcutaneously challenged with living cancer cells of the same type, using a minimal dose known to generate progressing lesions in naïve mice with 100% effectiveness. The mice were then monitored for tumor incidence and growth for 40-60 days. The results showed that if the cancer cells in the vaccine indeed underwent ICD, the vaccine could confer immune protection to the

mice, resulting in a lower tumor incidence or growth rate when rechallenged with the cancer cells [87, 88]. Efimova et al. [59] conducted both *in vitro* and *in vivo* studies using MCA205 cells to investigate the immunogenicity of ferroptosis. They found that early ferroptotic MCA205 cells (RSL3 treatment for a short time) not only released DAMPs and promoted bone marrow-derived DCs maturation *in vitro* but also conferred protection against tumors in a prophylactic vaccination model *in vivo*. These findings strongly suggest that ferroptosis qualifies as a form of ICD [59].

Despite a considerable body of evidence suggesting ferroptosis as a form of ICD, as referenced in this section, it is crucial to note that definitive evidence is presently absent. The existing evidence primarily focuses on the release of DAMPs by ferroptotic cancer cells, which has been demonstrated in various tumor types. Nevertheless, there is sparse research regarding the regulation of cytokines, antigenicity, and the application of the prophylactic vaccination model in the context of ferroptosis. Present research regarding cytokines and the prophylactic vaccination models have concentrated primarily on a single tumor cell line, and the conclusions derived from one tumor type may not be readily applicable to others due to inherent tumor heterogeneity [89, 90]. As such, the current evidence base is inadequate to definitively classify ferroptosis as ICD. Furthermore, there is a lack of direct evidence regarding the modulation of antigenicity by ferroptosis. A recent research using the prophylactic vaccination model has even denied the classification of ferroptosis as ICD [64]. Thus, further investigation is necessary to explore cytokine release, antigenicity modulation, and the prophylactic vaccination model to obtain more comprehensive evidence and strengthen the case for considering ferroptosis as a form of ICD.

### 2.1.2 | Contradictory evidence

A recent study by Wiernicki et al. [64] indicated that ferroptosis might not be a form of ICD despite the release of DAMPs and cytokines by ferroptotic cancer cells. The study found that ferroptotic cancer cells were not immunogenic in a prophylactic vaccination model, regardless of the stage of ferroptosis. Notably, when these ferroptotic cancer cells were added to a prophylactic vaccination composed of intrinsically immunogenic apoptotic cells, they significantly diminished the immunogenic potential of the apoptotic cells. The study also showed that early ferroptotic cancer cells not only failed to promote the maturation of DCs but also inhibited their activity, cytokine release and ability to present antigens. Furthermore, gene expression related to the adaptive immune response in DCs was

significantly suppressed after phagocytosis of ferroptotic cancer cells [64]. These results contradict the conclusions drawn by Efimova et al. [59]. One possible reason for this discrepancy could be the study by Efimova et al. [59], which considered MCA205 cells treated with RSL3 for a short period as early ferroptotic cancer cells. However, short-term treatment with ferroptosis inducers does not lead to complete cell death induction and still leaves many living cells (as confirmed by Efimova et al. [59]). The presence of living cells in the vaccine mixture can lead to tumor growth at the vaccination site, rendering the data meaningless and difficult to interpret. In contrast, the study by Wiernicki et al. [64] used an inducible model of ferroptosis via doxycycline-inducible knockdown of GPX4, which allowed for synchronous and complete cell death induction, eliminating the impact of this bias.

There are several potential reasons why ferroptotic cells release DAMPs and cytokines but are still not immunogenic. One possible explanation is that the immunogenic effects of DAMPs and cytokines may be counteracted by producing immunosuppressive substances during ferroptosis. For example, cyclooxygenase 2 (COX-2) expression increases during ferroptosis [5], leading to the synthesis of prostaglandin E2 (PGE2) [91, 92], which has an immunosuppressive effect [93–96]. PGE2 has been observed to suppress the expression of anti-tumor T-helper (Th) 1 cytokines while concurrently upregulating the expression of pro-tumor Th2 cytokines in immune cells [97, 98]. Furthermore, PGE2 enhances the functionality of immune suppressive cells such as Tregs and MDSCs [97]. In addition to these effects, PGE2 also increases the expression of programmed cell death protein 1 (PD-1) in TAMs and MDSCs, thereby exerting immunosuppressive effects [99]. COX-2 can also upregulate the synthesis of prostaglandin D2 (PGD2) [100]. PGD2 can potentially impair human NK cells' function by activating the receptor for D-series prostaglandins (DP) [101]. Moreover, the interaction between PGD2 and the chemoattractant receptor expressed on Th2 cells (CRTH2) has been associated with immune suppression and establishing a tumor-friendly microenvironment [102]. Additionally, Wiernicki et al. [64] found that ferroptotic cancer cells underwent lipid peroxidation before releasing DAMPs, resulting in the production of phospholipid peroxide [103, 104]. Oxidized phospholipids have been demonstrated to impede the activation of DCs and diminish their responsiveness to TLR activation ligands, as well as their ability to stimulate T cells [104]. Mechanistically, oxidized phospholipids impede the differentiation and maturation of DCs, resulting in reduced expression of the hallmark differentiation factor CD1a. Moreover, oxidized phospholipids can inhibit the phosphorylation of histone H3 and the recruitment of nuclear factor- $\kappa$ B (NF- $\kappa$ B) to the interleukin (IL)-12

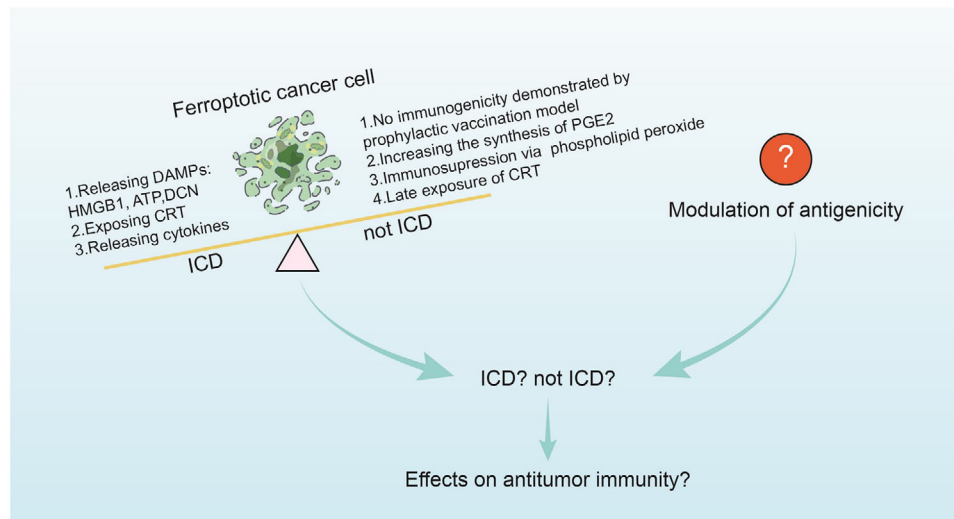
subunit p40 (IL-12p40) promoter, leading to decreased production of IL-12 by DCs and a weakened capacity to stimulate T cells [103]. Another potential explanation is that the CRTs of ferroptotic cells are exposed shortly before cell membrane rupture, which differs from other forms of cell death and may not promote their uptake by DCs, thereby reducing their immunogenicity [64]. Furthermore, Wiernicki et al. [64] observed that while bone marrow-derived DCs exposed to ferroptotic cancer cells showed signs of increased maturation [indicated by increased expression of CD86, CD40, major histocompatibility complex (MHC) II], their ability to induce proliferation of antigen-specific T cells was reduced. The authors hypothesized that the antigen processing and presentation process in DCs may be inhibited [64]. Our understanding of how ferroptosis affects the antigenicity of cancer cells and the resulting impact on the immunogenicity of ferroptotic cancer cells is still currently limited.

To sum up, the role of ferroptotic cancer cells in anti-tumor immunity will affect the application of ferroptosis-targeted therapy in cancer. It remains controversial whether ferroptotic cancer cells can serve as ICD inducers (Figure 2). Further studies are needed to clarify the immunogenicity of ferroptotic cancer cells. It is worth noting that Chen et al. [105] recently developed a novel high-performance photothermal nanoparticle, triphenylamine with methoxy group (TPA)-naphthalene diimide-fused 2-(1,3-dithiol-2-ylidene) acetonitrile (NDTA) nanoparticle, which, when combined with the ferroptosis inducer RSL3, was found to effectively enhance the immunogenicity of ferroptosis. The authors confirmed the synergistic effect of this approach in animal experiments [105]. Therefore, exploring methods that can enhance the immunogenicity of ferroptosis is also one of the future directions to improve the efficacy of ferroptosis-targeted therapy in cancer.

## 2.2 | The impact of ferroptotic cancer cells on anti-tumor immunity: facilitation or inhibition?

### 2.2.1 | Facilitating effects

In addition to DAMPs and cytokines released by ferroptotic cancer cells, previous studies have shown that oxidized phosphatidylserine on the outer layer of the cell membrane in apoptotic cells can promote phagocytosis by macrophages [106, 107]. Is there a similar effect in ferroptotic cancer cells? While the eversion of phosphatidylserine in the cell membrane does not occur in ferroptotic cells, a recent research has identified the oxidation products of phosphatidylethanolamine,



**FIGURE 2** Whether ferroptosis qualifies as ICD remains debatable. Ferroptotic cancer cells can release DAMPs and cytokines, such as HMGB1, ATP, and DCN, and they can also express CRT on the cell surface, which conforms to two of the three hallmarks of ICD. However, the prophylactic vaccination model has shown that ferroptotic cancer cells are non-immunogenic. They can also synthesize immunosuppressive substances, such as PGE2 and phospholipid peroxides. Furthermore, the late expression of CRT on the surface of ferroptotic cancer cells may reduce its immune-promoting effect. Additionally, the regulation of ferroptosis on antigenicity, one of the hallmarks of ICD, remains unclear. Therefore, whether ferroptosis belongs to ICD is still a controversial topic. Abbreviations: ATP: adenosine triphosphate; CRT: calcium reticulum protein; DAMPs: damage-associated molecular patterns; DCN: proteoglycan decorin; HMGB1: high mobility group protein 1; ICD: immunogenic cell death; PGE2: prostaglandin E2.

particularly 1-stearoyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine (SAPE-OOH), as an “eat-me” signal delivered by ferroptotic cancer cells (HL60 and 4T1 cells) to macrophages [108]. Macrophages can recognize this signal through TLR2, mediating the phagocytosis of ferroptotic cancer cells. Besides, there may be unidentified compensatory mechanisms that mediate the recognition of SAPE-OOH when TLR2 is unavailable [108]. The authors of the study suggested that macrophages can recognize the “eat-me” signal of ferroptotic cancer cells and mediate their phagocytosis. However, further research is necessary to determine whether other immune cells, such as DCs, can recognize ferroptotic cancer cells through a similar mechanism and exert anti-tumor immunity.

Furthermore, a study has shown that ferroptotic cancer cells may activate anti-tumor NK cells [109]. Specifically, the study found that the NK cell + Ferumoxytol (ferroptosis inducer) treatment group exhibited significant upregulation of IFN- $\gamma$ , an indicator of NK cell activity. Additionally, the expression of CD107a, a marker of NK cell degranulation, was also significantly increased. In addition, the study also observed an increase in the expression of UL16-binding protein (ULBP) family members (ULBP1, ULBP2, and ULBP3) on the surface of cancer cells (PC-3 cells) after ferumoxytol-induced ferroptosis. ULBP is a stress-inducible molecule that can be recognized by natural killer group 2D (NKG2D) expressed on the membrane of NK cells, leading to NK cells’ activation and anti-tumor effects.

Moreover, several studies have indirectly suggested that ferroptotic cancer cells might promote anti-tumor immunity. For instance, Zhang et al. [110] found that DHA can induce ferroptosis in cancer cells (Panc02 and Panc1 cells). They also observed that DHA reduced the frequency of M2-type TAMs and MDSCs in tumors while increasing the frequencies of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, NK cells, and natural killer T cells. In contrast, it did not affect immune cells in lymph nodes [110]. However, this study did not explore the mechanism underlying the phenomenon, nor did it rule out the influence of the drug itself on immune cells through further experiments. The study only examined the effect of DHA on the frequency of immune cells, without exploring whether it affected their function. Another study on DHA demonstrated that Zn-pyrophosphate (ZnP)@DHA/pyropheophorbide-iron (PYRO-Fe) core-shell nanoparticles could induce ferroptosis and the release of DAMPs in CT26 cells, thereby promoting the maturation of co-cultured bone marrow DCs [75]. Its combination with programmed cell death ligand 1 (PD-L1) blockade significantly delayed tumor growth in mice bearing CT26 and MC38 tumors. However, this effect was substantially reduced in immunodeficient mice, affirming the role of ferroptosis in activating anti-tumor immunity [75]. Nonetheless, the researchers also noted that ZnP@DHA/Pyro-Fe enhanced tumor cells’ apoptosis. Therefore, the activation of anti-tumor immunity in their study cannot be solely attributed to ferroptosis. In

fact, DHA has been reported to induce various forms of cell death, including apoptosis [111–114], pyroptosis [115, 116], and autophagy [111, 117]. Consequently, the impact of DHA on cell death and the subsequent anti-tumor immunity cannot be exclusively explained by ferroptosis alone, and further research is required to elucidate its precise mechanisms. Despite that, a recent study has reported that increased immunogenicity in lung cancer cells treated with DHA can be negated by ferroptosis inhibitors, supporting the theory that DHA fosters anti-tumor immunity via ferroptosis [79].

Furthermore, recent studies, particularly those focused on nanoparticle-based approaches, have provided ample evidence for the immunomodulatory effects of inducing ferroptosis in cancer cells. For example, many studies have demonstrated that ferroptotic cancer cells promote immune cell infiltration or activation, thereby improving the immunosuppressive TME [48–58, 62, 79, 84, 85, 118–122]. Several studies have also shown that inducing ferroptosis in cancer cells significantly enhances the efficacy of immunotherapy [48–58]. Certain studies have even reported that inducing ferroptosis in cancer cells can lead to durable immune memory *in vivo*, directly eliminating rechallenged cancer cells and preventing tumor formation [56, 121]. Collectively, these studies provide substantial evidence for the ability of ferroptotic cancer cells to promote anti-tumor immunity.

Similar to the evidence presented in the section exploring whether ferroptosis is a form of ICD, numerous studies have provided substantial proof for the immunomodulatory effects of ferroptotic cancer cells in fostering anti-tumor immunity. Nonetheless, there are certain vital aspects to consider. Certain drugs that trigger ferroptosis also have multiple anti-tumor mechanisms of action, meaning the activation of the immune system they instigate cannot be exclusively attributed to ferroptosis. For instance, DHA can provoke various forms of cell death [111–117, 123, 124]. Several studies involving nanoparticle-based methodologies have discovered that certain particles can trigger apoptosis in cancer cells [55, 57] in addition to ferroptosis, and apoptosis is recognized as a form of ICD [125]. Moreover, many studies have not meticulously ruled out the direct effects of the employed drugs on anti-tumor immunity. Some drugs may harbor immunostimulatory elements that can independently influence the tumor immune response [54, 78]. Therefore, it is challenging to ascertain whether the observed alterations in anti-tumor immunity are solely induced by ferroptotic cancer cells or influenced by additional factors like the drugs employed. Also, numerous studies mainly concentrate on gauging the drug efficacy instead of probing the molecular mechanisms by which ferroptotic cancer cells manipulate anti-tumor immunity. They may note the immune

system activation as an observed event without probing deeper into the underlying molecular pathways. Despite these considerations, this body of evidence still supports the notion that ferroptotic cancer cells activate anti-tumor immunity.

### 2.2.2 | Inhibitory effects

Some studies have also suggested that ferroptotic cancer cells have an inhibitory effect on anti-tumor immunity. For example, inducing ferroptosis in mice resulted in the release of 8-hydroxyguanosine (8-OHG) [65]. Elevated 8-OHG activated a transmembrane protein 173 (TMEM173, also known as STING)-dependent DNA sensor pathway, leading to macrophage infiltration and polarization towards the M2 phenotype. This promoted Kras-driven pancreatic tumorigenesis in mice [65]. Additionally, Dai et al. [66] found that pancreatic cancer cells carrying KrasG12D mutations released KrasG12D protein during ferroptosis. Macrophages can uptake KrasG12D through AGER, leading to their polarization towards an M2-like pro-tumor phenotype via fatty acid oxidation mediated by the AGER-signal transducer and activator of transcription (STAT) 3 pathway. Further studies showed that KrasG12D-ingested macrophages promoted pancreatic tumor growth, and blocking KrasG12D release and uptake could inhibit this effect [66]. However, this conclusion was drawn from KRAS-mutated pancreatic ductal adenocarcinoma, and it is still unclear whether a similar effect exists in other tumors.

Moreover, considering the extensive roles of arachidonic acid (AA) metabolites in inflammation and immune regulation [126], these metabolites may also participate in the modulation of anti-tumor immunity by ferroptotic cancer cells. AA metabolites are primarily produced through three enzymatic pathways: the COX pathway, the lipoxygenase pathway, and the cytochrome P450 pathway. COX predominantly generates prostaglandins and thromboxanes, lipoxygenase chiefly produces leukotrienes and lipoxins, and cytochrome P450 yields hydroxyeicosatetraenoic acid (HETE) [91, 126]. As previously mentioned, ferroptotic cancer cells upregulate the expression of COX-2 [5], which may increase the synthesis of PGE2 downstream of COX-2 and exert an immunosuppressive effect. Another metabolite of AA through the COX-2 pathway, PGD2 [100], may also be synthesized in increased quantities due to enhanced COX-2 expression [5]. PGD2 has been found to potentially inhibit human NK cell function by signaling through the receptor for DP [101]. Additionally, the PGD2-CRTH2 axis has been implicated in immune suppression and the establishment of a tumor-supportive microenvironment [102]. Thromboxane A2



(TXA2), another metabolite of AA through the COX pathway [91, 126], can exert immunosuppressive effects, thereby facilitating tumor growth as well [127]. Inhibitory effects of TXA2 on CD8<sup>+</sup> T cells and DCs have also been noted in studies using melanoma and breast cancer allografts [128]. Aside from the derivatives of the COX pathway, metabolites of the lipoxygenase and cytochrome P450 pathways can also foster tumor growth [50, 129–131]. Both lipoxygenase and cytochrome P450 are important regulators in the process of ferroptosis [11]. Leukotriene B4, produced via the lipoxygenase pathway, can stimulate tumor growth by recruiting neutrophils and driving pro-tumor inflammation [131]. Additionally, cells undergoing ferroptosis in response to inducible GPX4 depletion can release other AA derivatives, such as HETE [132]. Among these, 20-HETE may promote pro-tumor inflammation by facilitating the release of various inflammatory factors [130]. Recent discoveries have also revealed that 20-HETE can facilitate the ubiquitination and degradation of ACSL4, resulting in cancer cells' resistance to ferroptosis and immunotherapy [50]. Furthermore, 20-HETE stimulated the immune checkpoint PD-L1 expression in cancer-associated fibroblasts through the STAT pathway and promoted the secretion of angiogenic factors like IL-6 and transforming growth factor  $\beta$  [129]. This action fostered resistance to immunotherapy in non-small cell lung cancer [129]. On the other hand, 12-HETE and 15-HETE do not significantly affect DC maturation [133]. Besides, the associated 15-hydroperoxyeicosatetraenoic acid (15-HpETE-PE) can induce ferroptosis in immune cells [134]. However, it is crucial to note that the modulatory effects of these aforementioned substances (e.g., PGD2, TXA2, etc.) on anti-tumor immunity have not yet been directly demonstrated in ferroptotic cancer cells. The association between other AA metabolites and immune suppression in cancer remains unclear.

Ferroptotic cancer cells can produce phospholipid peroxide, which has a potent immunosuppressive effect on DCs [103, 104]. These phospholipids obstructed the differentiation and maturation of DCs by lowering the expression of the hallmark differentiation factor, CD1a. Additionally, they inhibited the phosphorylation of histone H3 and limited the recruitment of NF- $\kappa$ B to the IL-12p40 promoter, which resulted in decreased IL-12 production by DCs and a subsequent reduction in T cell stimulation [103]. Additionally, ferroptotic MCA205 cancer cells led to the accumulation of lipid droplets in DCs [64], which can inhibit the function of DCs. The possible mechanism underlying the inhibitory effect of lipid droplets on DCs' function is that the oxidative products in lipid droplets interacted with HSP70, thereby preventing the presentation of peptide-MHC-I complexes on the surface of DCs [135, 136]. Furthermore, Liu et al.

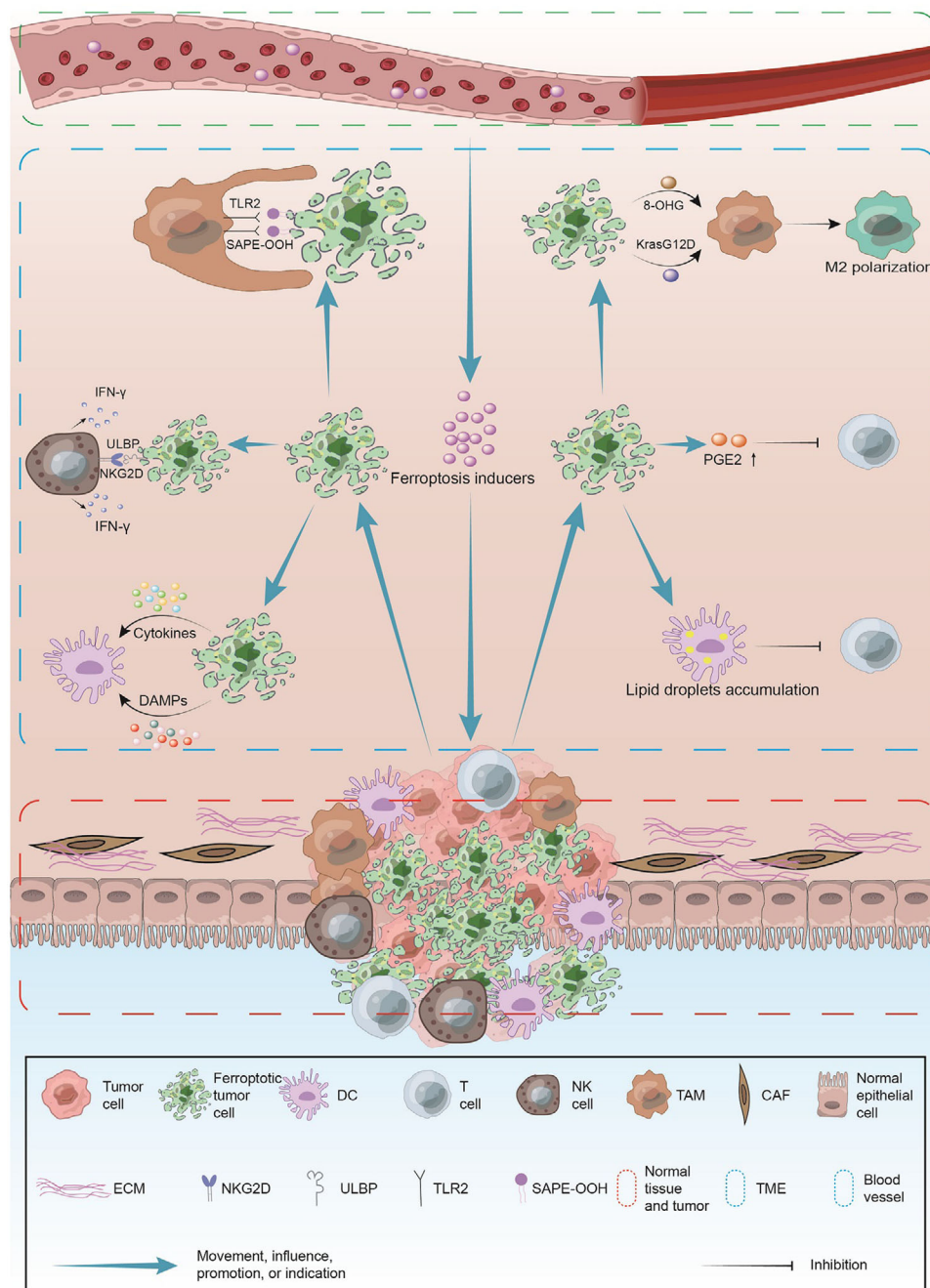
[137] found that although immune cells were more abundant in glioblastoma patients with high ferroptosis scores, most of these cells were immunoregulatory cells, leading to an immunosuppressive microenvironment in glioblastoma. Ferroptosis in glioblastoma promoted not only TAM infiltration but also their M2 polarization. Inhibition of ferroptosis increased T cells' activity and tended to decrease the proportion of MDSCs [137]. However, the study did not investigate the mechanism underlying this phenomenon. Moreover, although HMGB1 released by ferroptotic cancer cells can act as a DAMP to improve its immunogenicity, it can also accelerate the generation of tumor-promoting inflammation through NF- $\kappa$ B and inflammasome pathways [138]. The release of HMGB1 from ferroptotic hepatocellular carcinoma (HCC) cells has been shown to promote MDSC infiltration, thereby suppressing anti-tumor immunity, although this effect has not been observed in colorectal cancer [49].

In summary, the role of ferroptotic cancer cells in anti-tumor immunity is multifaceted (Figure 3). While there is substantial evidence bolstering their immunostimulatory effects, there is comparatively less evidence directly illustrating their inhibitory influence on anti-tumor immunity. The primary support for this inhibition mostly comes from localized and mechanistic studies, with sparse comprehensive evidence demonstrating direct suppression of anti-tumor immunity by ferroptotic cancer cells. It appears that the overall influence of ferroptotic cancer cells on anti-tumor immunity might be contingent on the specific tumor type and its surrounding microenvironment. Further research is essential to more thoroughly understand the complex relationship between ferroptosis and anti-tumor immunity and discern the specific conditions under which ferroptotic cancer cells either promote or inhibit anti-tumor immunity. Gaining this knowledge will be instrumental in leveraging the positive impacts and mitigating the negative repercussions of ferroptosis within the context of future anti-tumor immune responses.

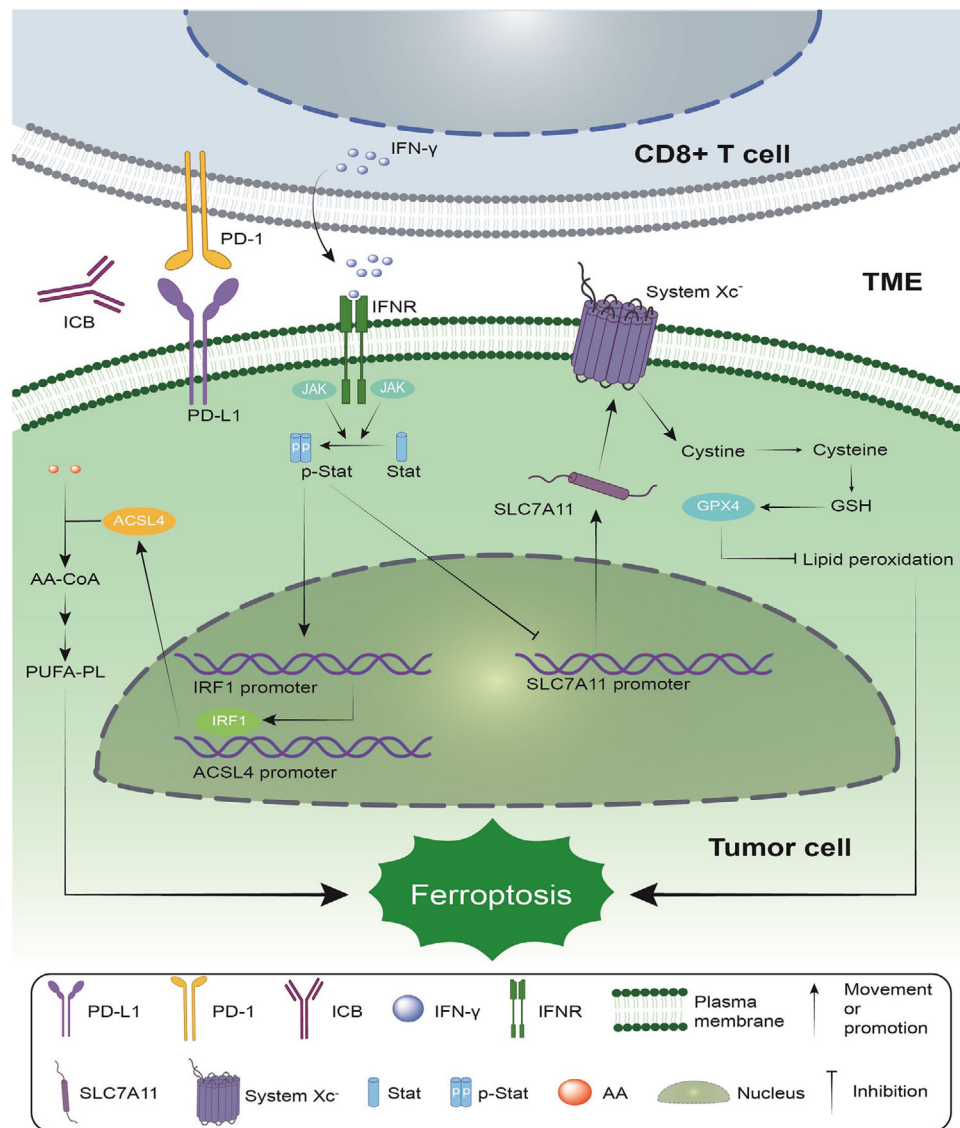
### 3 | THE CROSSTALK BETWEEN FERROPTOSIS AND ANTI-TUMOR IMMUNITY IN IMMUNE CELLS

#### 3.1 | Immune cells activate anti-tumor immunity by promoting the ferroptosis of cancer cells: the possible synergistic effects of pro-ferroptotic agents in combination with immunotherapy

Previous studies have suggested that CD8<sup>+</sup> T cells primarily eliminate tumor cells through the perforin-granzyme and Fas (also known as CD95)-Fas ligand pathways



**FIGURE 3** Ferroptotic cancer cells exhibit both promoting and suppressing effects on anti-tumor immunity. Ferroptotic cancer cells have both promoting and inhibiting effects on anti-tumor immunity. Ferroptotic cancer cells express SAPE-OOH on the surface, which can be recognized by TLR2 of macrophages as an “eat-me” signal, promoting the phagocytosis and clearance of ferroptotic cancer cells by macrophages. In addition, the expression of ULBP on the surface of ferroptotic cancer cells is increased, which can be recognized by NKG2D in NK cells, promoting the release of IFN-γ and the expression of CD107a (a marker of NK cell degranulation) by NK cells. Furthermore, ferroptotic cancer cells can release DAMPs and cytokines to promote the maturation of DCs. However, ferroptotic cancer cells can also release immunosuppressive substances, such as 8-OHG and KrasG12D, to differentiate macrophages towards the tumor-promoting M2 type. Additionally, they can increase the synthesis of PGE2 to inhibit anti-tumor immunity. Moreover, they can increase lipid droplet accumulation in DCs and inhibit their function. Therefore, the role of ferroptosis in cancer cells in anti-tumor immunity is complex. Abbreviations: 8-OHG: 8-hydroxyguanosine; CAF: cancer-associated fibroblasts; DAMPs: damage-associated molecular patterns; DC: dendritic cell; ECM: extracellular matrix; IFN: interferon; NKG2D: natural killer group 2D; NK cell: Nature killer cell; PGE2: prostaglandin E2; SAPE-OOH: 1-stearoyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine; TAM: tumor-associated macrophage; TLR2: toll-like receptor; TME: tumor microenvironment; ULBP: UL16-binding protein.



**FIGURE 4** CD8<sup>+</sup> T cells kill cancer cells through ferroptosis. CD8<sup>+</sup> T cells activated by immunotherapy can release IFN- $\gamma$ , sensitizing cancer cells to ferroptosis. After IFN- $\gamma$  binds to IFNR on the surface of cancer cells, it reduces the expression of SLC7A11 through the JAK-STAT pathway, inhibiting the function of system Xc<sup>-</sup>, reducing the uptake of cystine, and ultimately affecting the function of GPX4, promoting cancer cells' ferroptosis. Moreover, IFN- $\gamma$  can increase the expression of ACSL4 through the IFN- $\gamma$ /STAT1/IRF1 pathway, thus increasing the synthesis of PUFA-PL with AA as a substrate, and ultimately promoting cancer cells' ferroptosis. Abbreviations: AA: arachidonic acid; ACSL4: acyl-CoA synthetase long-chain family member 4; GPX4: glutathione peroxidase 4; GSH: glutathione; ICB: immune checkpoint inhibitor; IFN: interferon; IFNR: interferon receptor; IRF: interferon regulatory factor; JAK: Janus kinase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; p-STAT: phosphorylated Signal Transducer and Activator of Transcription; PUFA-PL: phospholipid containing polyunsaturated fatty acid chains; STAT: signal transducer and activator of transcription; System Xc<sup>-</sup>: cystine-glutamate antiporter comprising SLC7A11 and SLC3A2 subunits; TME: tumor microenvironment.

[139–142]. However, recent studies indicated that CD8<sup>+</sup> T cells can kill tumor cells by inducing ferroptosis (Figure 4). Wang et al. [46] demonstrated that CD8<sup>+</sup> T cells activated by immunotherapy could sensitize tumor cells (ID8, B16, HT1080 cells) to ferroptosis by secreting IFN- $\gamma$ , thereby exerting an anti-tumor effect. Mechanistically, IFN- $\gamma$  can activate the Janus kinase (JAK)-STAT1 pathway in tumor cells, enhancing the binding of STAT1 to the transcrip-

tion initiation site of SLC7A11, thereby down-regulating the expression of system Xc<sup>-</sup> and sensitizing cancer cells to ferroptosis induction or cystine deprivation [46]. The study reveals ferroptosis of tumor cells as a previously unrecognized CD8<sup>+</sup> T cell-mediated anti-tumor mechanism in vivo. Cystine limitation may be a potential endogenous factor in the TME that triggers ferroptosis in tumor cells. Similarly, Liao et al. [47] found that IFN- $\gamma$  can cooperate with

AA to promote ferroptosis in melanoma cells. This effect depends on the expression of ACSL4 in tumor cells rather than the system Xc-. Mechanistically, IFN- $\gamma$  promotes ACSL4 expression through the IFN $\gamma$ /STAT1/interferon regulatory factor 1 (IRF1) signaling axis, and then phospholipids associated with AA reprogramming sensitize cells to ferroptosis. The loss of ACSL4 in tumors can weaken the anti-tumor T-cell response. Combining AA and an ICI can synergistically inhibit tumor (Lewis lung carcinoma, MC38 and Yumm5.2 tumors) growth through IFN- $\gamma$  [47]. The study reveals another mechanism by which immune cells play an anti-tumor role by promoting the ferroptosis of tumor cells. However, aside from promoting tumor cells' ferroptosis through the above two mechanisms, IFN- $\gamma$  can also up-regulate the expression of PD-L1 on the surface of tumor cells, thereby exerting an immunosuppressive effect and promoting tumor growth [143, 144]. In addition, Kim et al. [109] found that NK cell-treated prostate cancer cells exhibited similar levels of ferroptosis as in ferumoxyl treatment, suggesting that NK cells may also induce ferroptosis in cancer cells.

Considering these aspects alone, ferroptosis-targeted therapy can enhance the anti-tumor immunity of immune cells. The combination of ferroptosis-inducing therapy and immunotherapy may exhibit synergistic effects and represent a potential treatment strategy.

### 3.2 | The sensitivity of immune cells in TME to ferroptosis: the latent effects of ferroptosis inducers on the immune cell population

When using ferroptosis-targeted therapy to treat tumors as it may be effective against drug resistance [20, 145], the effect of ferroptosis inducers on immune cells in TME cannot be ignored. It is crucial to consider the potential adverse effects of ferroptosis inducers on immune cell populations. This impact on anti-tumor immunity may directly influence the therapeutic effect of ferroptosis-targeted therapy on tumors and its potential combination with immunotherapy. Additionally, the TME itself has factors that promote ferroptosis, and its impact on immune cells also needs to be considered. Therefore, exploring the sensitivity of immune cells in the TME to ferroptosis is crucial (Figure 5).

#### 3.2.1 | T cells

CD8<sup>+</sup> T cells and conventional CD4<sup>+</sup> T cells are more sensitive to GPX4 inhibitors than B16 and MC38 cancer cells. FSP1 or GPX4 overexpression lessened CD8<sup>+</sup> T cells' fer-

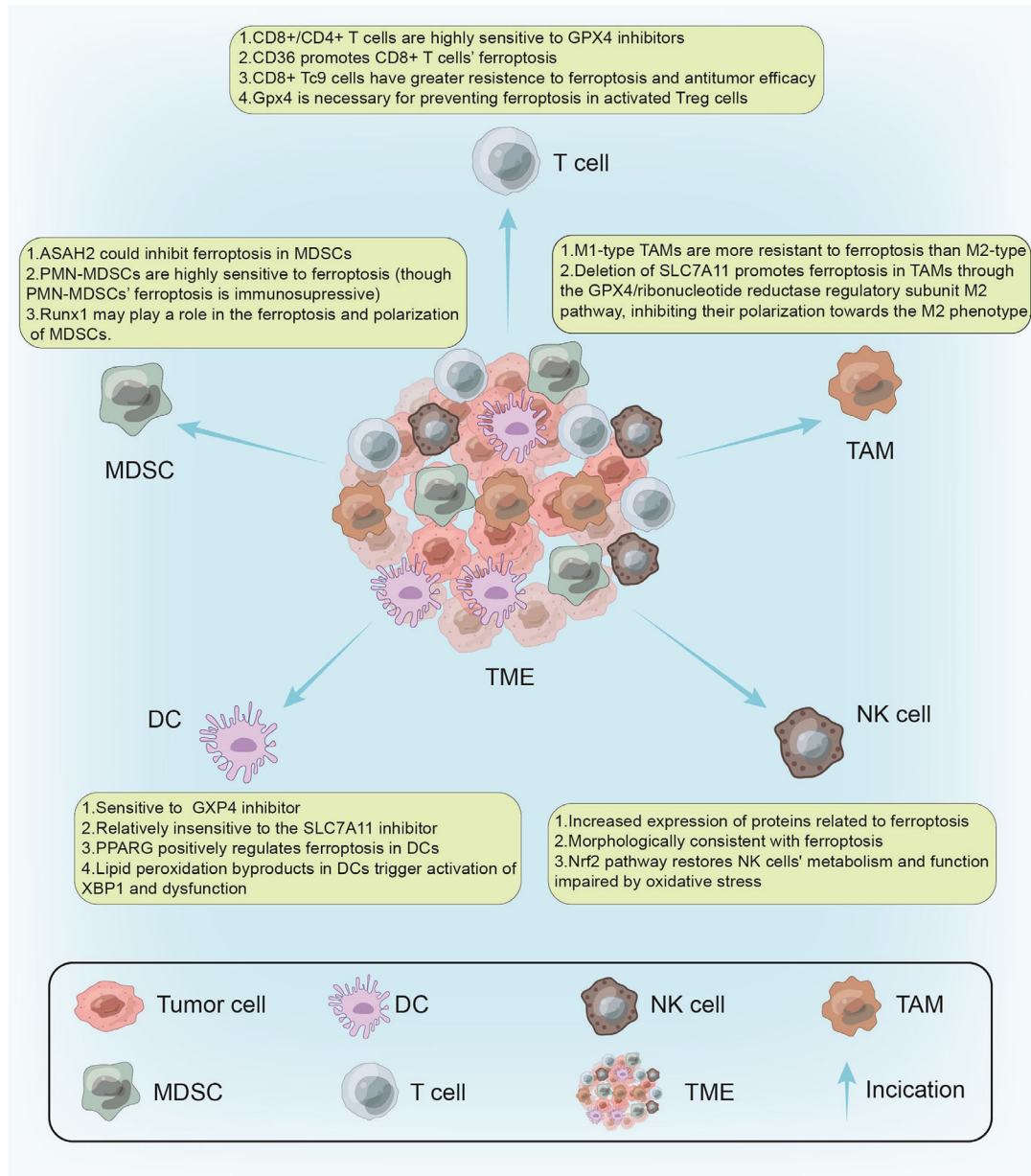
roptosis sensitivity without affecting anti-tumor function, whereas ACSL4 inhibition reduced ferroptosis sensitivity and impairs their function. [68]. Moreover, inhibition of system Xc- or deprivation of cysteine in vivo did not affect T cells in MC38 tumor-bearing mice [146]. Therefore, inducing ferroptosis with adoptive reinfusion of T cells after ferroptosis inhibition treatment or using system Xc- inhibitors to induce ferroptosis in tumor cells may be a desirable way for tumor therapy.

Furthermore, CD36 also plays a crucial role in promoting the ferroptosis of T cells in the TME. CD36 is a scavenger receptor that acts as a transporter of free fatty acids and oxidized lipids [147–149]. It has been implicated in various processes such as angiogenesis, inflammatory responses, atherosclerotic thrombotic disease, and metabolic disorders [150]. Ma et al. [151] discovered that CD36 on CD8<sup>+</sup> T cells in melanoma and multiple myeloma can uptake AA to promote lipid peroxidation and ferroptosis in the lipid-rich TME, thus impairing their anti-tumor function. Additionally, Xu et al. [152] found that in B16 and MC38 tumors, CD36 on CD8<sup>+</sup> T lymphocytes can uptake oxidized low-density lipoprotein (ox-LDL), enhancing the lipid peroxidation level and the phosphorylation of p38, leading to their dysfunction. Overexpression of GPX4 can restore their anti-tumor function [152]. Incidentally, it is worth mentioning that CD36 expression of Treg cells in TME promotes their survival and immunosuppressive function [153]. These studies suggested that targeting CD36 may be a feasible strategy to improve anti-tumor immunity.

CD8<sup>+</sup> T cells can be classified into Tc1 (cytotoxic T lymphocyte subset 1), Tc2, Tc9, Tc17 and Tc22 subsets [154]. A previous study demonstrated that IL-9-secreting CD8<sup>+</sup> Tc9 cells, which were differentiated ex vivo and then reintroduced into the body, exhibited better persistence and anti-tumor efficacy than Tc1 cells when used for adoptive cell therapy [155]. Tc9 cells have greater resistance to ROS-rich tumor tissue-induced ferroptosis due to their secretion of IL-9, which can activate the STAT3 signaling pathway, upregulating fatty acid oxidation so that Tc9 cells have lower fatty acid content [156]. The study suggested that targeting fatty acid oxidation in T cells may be one strategy to improve their resistance to ferroptosis and enhance their anti-tumor ability.

Treg cells are a subset of CD4<sup>+</sup> T cells that can suppress anti-tumor immunity [35, 157, 158]. Tumor-derived Treg cells showed fewer lipid peroxides than tumor-infiltrating CD8<sup>+</sup> T cells [68]. Gpx4 is necessary for preventing excessive lipid peroxidation and ferroptosis in activated Treg cells. However, ACSL4 is not essential for inducing ferroptosis in Gpx4-deficient Treg cells, and system Xc- inhibitors rarely impair the viability of Treg cells [159]. This study suggested that targeting GPX4 to induce ferroptosis in Treg cells may be a strategy to enhance anti-tumor immunity.





**FIGURE 5** The sensitivity of immune cells in TME to ferroptosis is different. When using ferroptosis inducers to kill tumor cells, it inevitably affects immune cells in the TME. The TME contains many different types of immune cells that perform different functions in anti-tumor immunity. The sensitivity of these immune cells to ferroptosis varies, as detailed in the figure. Abbreviations: ASA2: neutral ceramidase N-acylsphingosine amidohydrolase; DC: dendritic cell; GPX4: glutathione peroxidase 4; MDSC: MDSCs: myeloid-derived suppressor cell; NK cell: Nature killer cell; Nrf2: Nuclear factor erythroid 2-related factor 2; PMN-MDSC: polymorphonuclear MDSC; PPARG: proliferator-activated receptor gamma; RUNX1: runt-related transcription factor 1; Tc9 cell: cytotoxic T lymphocyte subset9; TAM: tumor-associated macrophages; TME: tumor microenvironment; XBP1: X-box-binding protein-1.

However, since anti-tumor CD8<sup>+</sup> T cells are also highly sensitive to GPX4 inhibitors, the pros and cons of this approach need to be weighed. Additionally, reducing the impact of GPX4 inhibitors on CD8<sup>+</sup> T cells before applying this strategy (such as CD8<sup>+</sup> T cells overexpressing FSP1 in vitro, adoptive reinfusion in vivo, and then combined with GPX4 inhibitory treatment) may yield better results.

To sum up, CD8<sup>+</sup> T cells generally exhibit a higher sensitivity to ferroptosis than B16 and MC38 tumor cells, as well as Treg cells. As a result, ferroptosis-inducing therapies aimed at eradicating tumors might inadvertently impact CD8<sup>+</sup> T cells' survival and functionality, potentially encouraging tumor growth. The sensitivity of CD8<sup>+</sup> T cells varies with different ferroptosis inducers: they

demonstrate high susceptibility to GPX4 inhibitors but tolerance towards system Xc<sup>-</sup> inhibition or cysteine deprivation. Enhancing GPX4 or FSP1 expressions could increase CD8<sup>+</sup> T cells' ferroptosis resistance, thereby restoring their anti-tumor capacities. The surface marker CD36 amplifies CD8<sup>+</sup> T cells' ferroptosis sensitivity via AA and ox-LDL uptake. However, the Tc9 subset, via the IL-9-STAT3 pathway, shows greater ferroptosis tolerance and superior anti-tumor properties. Treg cells, like CD8<sup>+</sup> T cells, are highly sensitive to GPX4 inhibition but tolerate Xc<sup>-</sup> system inhibition. This selective susceptibility provides a foundation for specifically inducing tumor cell ferroptosis while minimizing effects on CD8<sup>+</sup> T cells.

### 3.2.2 | TAMs

TAMs can be divided into anti-tumor M1 and tumor-promoting immunosuppressive M2 phenotypes [160, 161]. In general, TAMs in the TME are predominantly of the M2 phenotype [33, 162]. Previous studies have demonstrated that iron overload induced the polarization of macrophages toward the M1 phenotype [163, 164]. Considering the substantial promoting effect of iron in the occurrence of ferroptosis [11], it is plausible to suggest that ferroptosis is involved in this phenotypic transition. Kapralov et al. [134] found that M1-type TAMs were more resistant to ferroptosis than M2-type TAMs in Lewis lung carcinoma, primarily owing to their higher levels of inducible nitric oxide synthase (iNOS) and nitric oxide (NO)-free radical, which plays a role in anti-ferroptosis. The recent development of the nano-drug D/L-Arginine@Ruthenium provides further support to the study by facilitating the polarization of TAMs towards the M1 phenotype in Lewis lung carcinoma. This effect is achieved through the enhanced production of NO and ROS [165]. Similarly, Hao et al. [166] found that Apolipoprotein C1 (APOC1) is overexpressed in TAMs of HCC. In vitro, APOC1 suppression reversed TAMs from the M2 phenotype to the M1 phenotype via the ferroptosis pathway. In vivo, APOC1<sup>-/-</sup> mice demonstrated notably smaller tumors and increased proportions of M1 macrophages [166]. Additionally, there is evidence to suggest that ferroptosis-promoting nanoparticles, such as iron oxide nanoparticles and Fe<sub>3</sub>O<sub>4</sub>-SAS@PLT nanoparticles (constructed using sulfasalazine [SAS]-loaded mesoporous magnetic nanoparticles [Fe<sub>3</sub>O<sub>4</sub>] and platelet [PLT] membrane camouflage), zero-valent-iron nanoparticle and cancer cell membrane-camouflaged gold nanocage loading doxorubicin and l-buthionine sulfoximine, can facilitate the polarization of M2-type TAMs into the M1 phenotype [119, 167–169]. Moreover, the deletion of SLC7A11 has been found to promote ferroptosis in TAMs via the GPX4/ribonucleotide reductase regulatory

subunit M2 pathway, which prevents polarization towards the M2 phenotype. As a result, the efficacy of PD-L1 inhibition in HCC was enhanced [170]. Consequently, M2-type TAMs exhibit a higher sensitivity to ferroptosis than their M1 counterparts. Thus, promoting ferroptosis could drive TAM polarization towards the M1 phenotype, thereby amplifying anti-tumor capabilities. Leveraging ferroptosis inducers to raise the M1/M2 ratio presents a potential strategy for bolstering anti-tumor immunity.

### 3.2.3 | MDSCs

MDSCs are an important immunosuppressive cell population in the TME [34, 171]. Tumor-infiltrating MDSCs exhibit resistance to ferroptosis-induced cell death, primarily due to the elevated expression of system Xc<sup>-</sup> and the neutral ceramidase N-acylsphingosine amidohydrolase (ASAH2). Inhibition of ASAH2 can reverse this resistance and suppress tumor growth in 4T1, CT26 and ABL tumors [71]. Recent research has highlighted Runx1 (runt-related transcription factor 1)'s part in managing MDSC ferroptosis. Restraining Runx1 may boost polarized cells' death and MDSCs' numbers by triggering the ferroptosis pathway [172]. Additionally, Kim et al. [67] recently discovered that polymorphonuclear MDSCs (PMN-MDSCs) in the TME are highly sensitive to ferroptosis and spontaneously undergo ferroptosis. However, this does not enhance anti-tumor immunity by reducing the number of PMN-MDSCs. Instead, it confers immunosuppressive activity on PMN-MDSCs [67] (see section 2.3. Ferroptotic immune cells suppress anti-tumor immunity).

In summary, MDSCs typically demonstrate resistance to ferroptosis, a phenomenon associated with the upregulation of the system Xc<sup>-</sup> and ASAH2 expression. The Runx1 gene might contribute to the ferroptosis and polarization of MDSCs. Intriguingly, despite MDSCs' generally defensive response to ferroptosis, PMN-MDSCs display sensitivity to this process, which paradoxically enhances their immunosuppressive function.

### 3.2.4 | DCs

DCs are professional antigen-presenting cells that play a critical role in the activation of naïve T cells and sustaining T cell-dependent immunity [61, 173]. Han et al. [174] demonstrated that DCs were sensitive to ferroptosis induced by the GPX4 inhibitor RSL3 but relatively insensitive to the SLC7A11 inhibitor erastin. Peroxisome proliferator-activated receptor gamma (PPARG) is a positive regulator of ferroptosis in DCs and a critical factor in preventing the maturation and activation of DCs

during ferroptosis [174]. Therefore, combining the ferroptosis inducer and the PPARG inhibitor may be a potential therapeutic strategy. Alternatively, the use of SLC7A11 inhibitors can kill tumors while having less impact on DCs, which is also a potentially feasible method [174]. Furthermore, evidence suggests that lipid peroxidation byproducts in tumor-associated DCs can trigger the activation of the structural X-box-binding protein-1 (XBP1) [175]. The resulting dysfunction in DCs can drive ovarian cancer progression [175]. It also potentially suggested that ferroptosis-targeted therapy may adversely affect DCs.

In a nutshell, DCs display sensitivity to GPX4 inhibitors while demonstrating resistance to system Xc- inhibitors. The generation of lipid peroxides during ferroptosis can activate XBP1, subsequently impairing DCs functionality. PPARG has a notable role in stimulating DCs ferroptosis and concurrently inhibiting DCs maturation and activation.

### 3.2.5 | NK cells

NK cells play a crucial role in the body's defense against tumors [30]. Any malfunction of these cells can elevate the risk of tumorigenesis and tumor growth [176]. In an ovarian cancer model, Poznanski et al. [177] found that oxidative stress in the TME inhibited glucose metabolism in NK cells, negatively affecting their function. Interestingly, while peripheral blood NK cells underwent oxidative damage and exhibited ferroptosis markers in the TME, NK cells expanded using IL-21-expressing feeder cells exhibited metabolic resilience. These cells utilized the IL-21-STAT3 pathway to achieve a metabolic profile akin to tumor cells, prioritizing serine and glutamine for glutathione (GSH) production, offering protection against oxidative damage [177]. Furthermore, a recent study found that gastric cancer cells can induce ferroptosis in NK cells and impair their function via L-kynurenine production [178]. Yet, elevated GPX4 expression reestablished the anti-tumor prowess of NK cells [178]. These findings suggest that ferroptosis might play a crucial role in the dysfunction of NK cells within the TME.

## 3.3 | Ferroptotic immune cells suppress anti-tumor immunity

### 3.3.1 | Ferroptosis kills immune cells that are important for anti-cancer immunity

As previously mentioned, pro-ferroptosis therapy may lead to the death of immune cells within the TME. The most direct adverse impact of ferroptosis on anti-tumor immu-

nity includes the killing of anti-tumor immune cells and subsequent loss of their functionality. Specifically, lipid peroxidation and ferroptosis in tumor-infiltrating CD8<sup>+</sup> T cells can impair their proliferation and secretion of anti-tumor cytokines, leading to their dysfunction [151, 152]. Tc1 cells are more sensitive to ferroptosis compared to Tc9 cells, resulting in weaker anti-tumor activity in B16 melanoma [156]. Similarly, inhibiting the anti-ferroptotic capacity of Tc9 cells can shorten their lifespan and weaken their anti-tumor capabilities [156].

### 3.3.2 | Ferroptotic immune cells lose their activity

Generally, cell death has a direct impact on immune cells, leading to a decrease in both their quantity and functionality. Nevertheless, sometimes, the effects of cell death on immune cell function can vary depending on the specific circumstances. For example, Collins et al. [179] found that the necroptosis of DCs abnormally enhanced their ability to activate  $\gamma\delta$ T cells. Conversely, inhibiting necroptosis of DCs can decrease their ability to activate  $\gamma\delta$ T cells. Regarding ferroptosis, no such abnormal phenomenon has been observed in anti-tumor immune cells. Ferroptosis impairs DCs' ability to secrete cytokines, express MHC-II, and activate CD8<sup>+</sup> T cells. Ferroptotic DCs lost their anti-tumor activity against KPC cells, as verified in a prophylactic vaccination model [174]. Moreover, apart from the functional loss resulting from direct cellular killing, byproducts associated with ferroptosis may also impact cellular functionality. For instance, the byproducts of lipid peroxidation in DCs triggered the activation of the XBP1, leading to DC dysfunction [175].

### 3.3.3 | Ferroptotic immune cells gain immunosuppressive activity

Kim et al. [67] found that ferroptotic PMN-MDSCs have strong immunosuppressive activity in several cancer types. Mechanistically, this can be attributed to two factors. The first factor is the notable upregulation of the PGE2 gene synthesis observed within ferroptotic PMN-MDSCs. Inhibition of ferroptosis led to a significant reduction of PGE2 released by PMN-MDSCs while inhibiting PGE2 synthesis also partially suppressed their immunosuppressive activity. Secondly, oxidized phospholipids produced during ferroptosis of PMN-MDSCs can directly inhibit T cells. For instance, oxidized phosphatidylethanolamine and phosphatidylcholine can cause a significant decrease in T cells' proliferation in mice [67]. Furthermore, oxidized phosphatidylethanolamine can also lead to a significant decline

in human T cells' proliferation [67]. However, it remains unclear whether other types of immune cells undergoing ferroptosis would acquire similar immunosuppressive capabilities.

Overall, the relationship between immune cells and ferroptosis in anti-tumor immunity is complex. While immune cells can promote anti-tumor immunity by inducing ferroptosis of cancer cells, different immune cells in the TME have varying sensitivities to ferroptosis. Furthermore, several immune cells may actually inhibit anti-tumor immunity through different mechanisms after ferroptosis. Therefore, ferroptosis-targeted therapy can be a double-edged sword. While it can kill tumor cells and certain immunosuppressive cells (such as M2-TAMs and Tregs), it may also compromise the activity of anti-tumor immune cells (such as CD8<sup>+</sup> T cells, NK cells, and DCs) and further promote the immunosuppressive effects of some ferroptotic immune cells. It is crucial to carefully consider the benefits and drawbacks of ferroptosis-targeted therapy in terms of its anti-tumor efficacy and make targeted decisions based on the sensitivity of different cells to different ferroptosis inducers.

#### 4 | CLINICAL TRIALS OF DRUGS ABLE TO INDUCE FERROPTOSIS

Currently, there are no intervention trials specifically targeting ferroptosis in humans [15]. Despite conducting thorough searches on databases such as PubMed, Embase, and ClinicalTrials, we did not find any clinical trials directly focused on using ferroptosis as a therapeutic approach for cancer. However, certain commonly used drugs in clinical practice, including cisplatin [180], sorafenib [6, 181], SAS [6], DHA [123] and statins [182], have demonstrated the ability to induce ferroptosis in cancer cells. Clinical trials associated with these drugs may provide a few insights. For example, combination therapy of cisplatin with ICIs has shown greater effectiveness than cisplatin monotherapy in various tumor types [183–187]. This suggests a possible synergy between ferroptosis induction and anti-tumor immunity. It seems that systematic reviews and meta-analyses should be considered to obtain more robust evidence comparing the efficacy of cisplatin combined with immunotherapy to cisplatin alone or ICIs alone. However, it is important to note that these drugs are not specifically designed as ferroptosis inducers, and their ability to induce ferroptosis may be relatively modest [6]. Moreover, their anti-tumor mechanisms are multifaceted, and ferroptosis induction is just one aspect of their overall effects. Therefore, the interaction between these drugs and anti-tumor immunity cannot be solely attributed to ferroptosis. As a result, the clinical data from these

non-specialized ferroptosis inducers have limited value in providing comprehensive evidence for our review. Further clinical trials directly targeting ferroptosis as a therapeutic approach for cancer are necessary to generate more valuable clinical evidence.

### 5 | THE INTERPLAY BETWEEN FERROPTOSIS AND ANTI-TUMOR IMMUNITY IN DIFFERENT TYPES OF CANCER

Tumor heterogeneity is a prevalent characteristic across different types of tumors and even within different regions of the same tumor [89, 90]. This heterogeneity can result in diverse responses to therapeutic approaches, including ferroptosis induction. Consequently, the interaction between ferroptosis and anti-tumor immunity may vary among different tumor types. Generalizing and categorizing all tumor types based on the relationship between ferroptosis and anti-tumor immunity may not be accurate. Therefore, it is crucial to assess and evaluate potential differences among different tumor types. Based on the details described in the preceding text, we now present a summary of the relationship between ferroptosis and anti-tumor immunity across different tumor types.

#### 5.1 | Melanoma

Two studies involving nanomedicines have observed that ferroptotic melanoma cells released DAMPs [78, 84]. This release promoted the phagocytosis and maturation of bone marrow-derived DCs [84]. Furthermore, a synergistic effect has been observed between ferroptotic melanoma cells and ICIs, leading to an enhanced anti-tumor immune response [78]. Ferroptotic melanoma cells have also been found to modulate the immune phenotype of the TME, possibly facilitating the exposure of tumor antigens [86]. These findings support ferroptosis as ICD and its ability to enhance anti-tumor immunity in melanoma.

Within the TME, CD8<sup>+</sup> T cells activated by immunotherapy are found to increase melanoma cells' sensitivity to ferroptosis via IFN- $\gamma$  production [46, 47]. However, CD8<sup>+</sup> T cells are also more prone to ferroptosis than melanoma cells [68]. CD36 enhances the sensitivity of tumor-infiltrating CD8<sup>+</sup> T cells to ferroptosis and impairs their anti-tumor capabilities [151, 153], whereas Treg cells use GPX4 to resist ferroptosis and maintain immunosuppression [159]. Interestingly, Tc9 cells in melanoma are more resistant to ferroptosis than Tc1 cells and exhibit stronger anti-tumor abilities [155, 156]. Thus, inducing ferroptosis in melanoma can have mixed effects on the TME.



## 5.2 | Breast cancer

Similarly, several studies have observed that ferroptotic breast cancer cells can release DAMPs [77, 82, 85], leading to the phenotypic maturation of DCs [82, 85]. Furthermore, ferroptotic breast cancer cells enhance the infiltration of anti-tumor immune cells [86], improve the immune microenvironment phenotype [56, 58, 85, 118, 121], and enhance the therapeutic efficacy of ICIs [56]. Ferroptosis induction in breast cancer cells also activated persistent anti-tumor immune memory [121]. Additionally, ferroptotic breast cancer cells expose SAPE-OOH as an “eat me” signal, promoting their engulfment by macrophages [108]. These findings suggest that ferroptosis in breast cancer contributes to immune activation and enhances anti-tumor immune responses.

In breast cancer, the induction of ferroptosis can promote the polarization of TAMs towards an anti-tumor M1 phenotype [168, 169]. However, MDSCs in breast cancer display resistance to ferroptosis, which is attributed to the expression of ASAH2 [71]. The impact of ferroptosis on other immune cells within the breast cancer microenvironment requires further investigation to elucidate its role comprehensively.

## 5.3 | HCC

Ferroptotic HCC cells can also promote the release of DAMPs, including HMGB1, ATP, and CRT [52, 80, 81, 83], suggesting that ferroptosis enhances the immunogenicity of HCC. Furthermore, ferroptotic HCC cells can induce DC maturation [83], improve the immune microenvironment by increasing the frequency of anti-tumor immune cells [49, 51, 52], and augment the efficacy of ICIs in vivo [49, 51, 52], which all indicate that ferroptosis activates anti-tumor immunity in HCC. Additionally, stimulation of ferroptosis has also been found to drive the M1 polarization of TAMs [166, 170]. Furthermore, the role of Runx1 in inhibiting ferroptosis and promoting the polarization of MDSCs has been identified, suggesting it as a potential target for immunotherapy [172]. In summary, there's evidence of ferroptosis playing a role in bolstering anti-tumor immunity within HCC. However, direct evidence on the effects of ferroptosis on immune cells in the TME of HCC remains scarce. Further research is needed to uncover the impact of ferroptosis on various immune cells in the TME, such as whether it adversely affects anti-tumor CD8<sup>+</sup> T cells or NK cells, thereby hampering anti-tumor immunity. This will help clarify the potential of combining ferroptosis-targeted treatment with immunotherapy in HCC.

## 5.4 | Pancreatic cancer

In pancreatic cancer cells, ferroptosis has been found to promote the release of HMGB1 and DCN, enhancing anti-tumor immunity [63, 74]. However, in KRAS-mutated pancreatic cancer cells, two immunosuppressive substances, 8-OHG and KrasG12D, have been discovered [65, 66]. These substances can polarize macrophages towards a pro-tumor M2 phenotype, stimulating tumorigenesis and growth in pancreatic cancer [65, 66]. Nevertheless, it has also been observed that ferroptosis in pancreatic cancer cells can improve the immune microenvironment by increasing the frequency of anti-tumor immune cells, such as CD8<sup>+</sup> T cells and NK cells within the TME, and reducing the frequency of immunosuppressive cells like Tregs and MDSCs [57, 110]. Additionally, the level of IFN- $\gamma$  in the TME also increased correspondingly, leading to an elevated expression of PD-L1 on the surface of tumor cells [57]. This increase has been verified to enhance the efficacy of ICIs in vivo [57]. Further research is needed to elucidate the role of ferroptosis in anti-tumor immunity, specifically in KRAS-mutated pancreatic cancer cells. Currently, there are no direct reports on the relationship between immune cells in pancreatic cancer TME and ferroptosis. It remains uncertain whether inducing ferroptosis affects immune cells in pancreatic cancer, subsequently influencing anti-tumor immunity. In summary, the role of ferroptosis in anti-tumor immunity in pancreatic cancer is ambiguous: it might either promote or inhibit the process, possibly contingent upon specific conditions like the status of the KRAS mutation [65, 66]. Given that pancreatic cancer inherently exhibits low immunogenicity [188], more research is essential to elucidate the intricate relationship between ferroptosis and anti-tumor immunity in this context. Unraveling the effects of ferroptosis on immune cells within the TME and understanding the conditions and mechanisms whereby ferroptosis exerts varying impacts on anti-tumor immunity could pave the way for enhancing the efficacy of ICIs in treating pancreatic cancer.

## 5.5 | Lung cancer

Ferroptosis in lung adenocarcinoma has been observed to promote the release of DAMPs, which enhances the immunogenicity of the tumor [76, 79]. This improved immune cell infiltration or activation, ultimately enhancing the immune microenvironment [48, 50, 79, 119]. Furthermore, ferroptosis synergized with ICIs in the treatment of lung adenocarcinoma [48, 50]. In ferroptotic large cell lung cancer, activation of the immune system and enhanced tumor killing have also been observed [119].

In lung adenocarcinoma, CD8<sup>+</sup> T cells activated by immunotherapy kill tumors via ferroptosis and synergize with AA [47]. A research also shows that M2 TAMs in lung cancer were more sensitive to ferroptosis than M1 TAMs, and ferroptosis induction can effectively repolarize TAMs towards the M1 phenotype [134]. These findings are reinforced by studies using ferroptosis-promoting nanomedicines in lung cancer [119, 165].

## 5.6 | Colon cancer

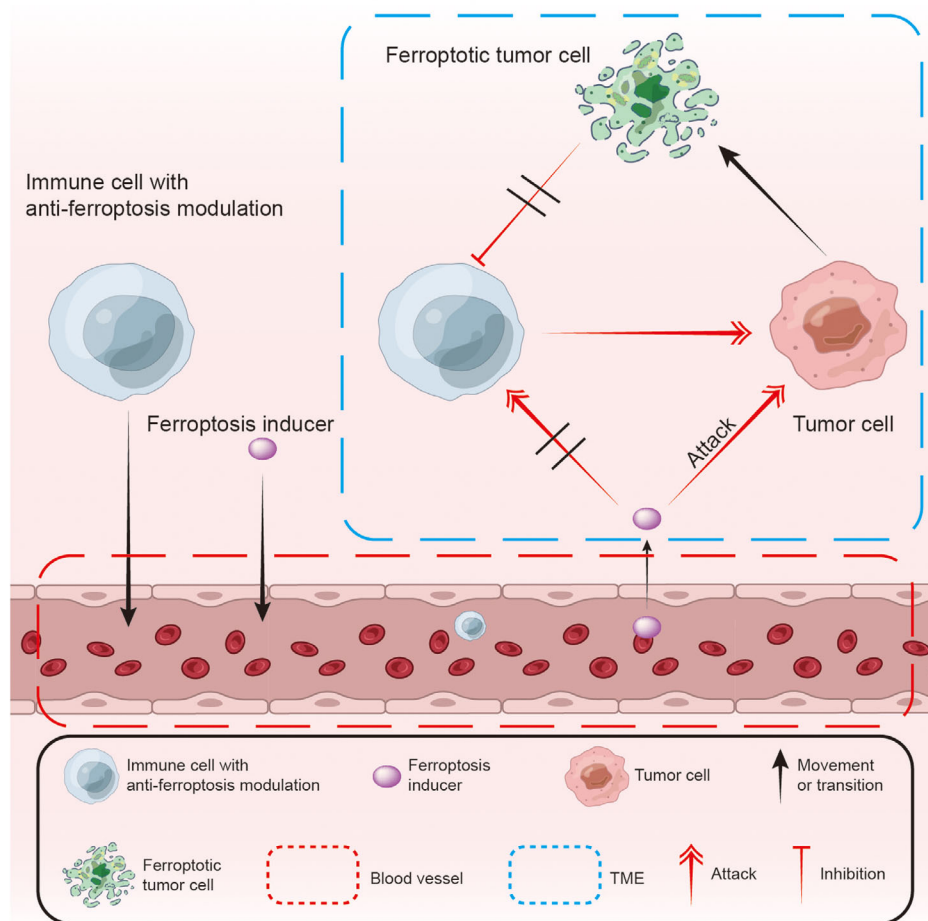
Similar to other tumor types discussed in this section, ferroptotic colon cancer cells can enhance the release of HMGB1 and the exposure of CRT, thereby amplifying the immunogenicity of colon cancer [54, 75]. These ferroptotic cells can also promote DC maturation, improving the immune microenvironment by increasing the frequency of anti-tumor immune cells and increasing the release of IFN- $\gamma$  by T cells [54, 75]. Ferroptosis induction can also notably enhance the efficacy of ICIs [75]. Interestingly, this enhanced effect was absent in immunodeficient mice, suggesting that the effect of ferroptosis on colon cancer partly relies on the activation of anti-tumor immunity [75]. Moreover, a synergistic effect between immune-activated CD8<sup>+</sup> T cells and AA has also been observed, promoting ferroptosis in cancer cells and enhancing anti-tumor immune function [47]. However, it should be noted that both CD8<sup>+</sup> T cells and Tregs in colon cancer exhibited high sensitivity to GPX4 inhibition-induced ferroptosis [68, 159] while tolerating inhibition of the Xc<sup>-</sup> system [146, 159]. Additionally, CD36 expression on CD8<sup>+</sup> T cells has been found to increase their sensitivity to ferroptosis, leading to the inhibition of their function [153]. Furthermore, ASAH2 has been identified as a mediator of MDSC resistance to ferroptosis. Inhibition of ASAH2 can restore MDSC sensitivity to ferroptosis, thereby enhancing immune-mediated tumor killing [71]. In summary, in colon cancer, there exists a synergistic relationship between ferroptosis and anti-tumor immunity. Notably, a recent research has revealed that the knockdown of N-acetyltransferase 10 led to ferroptosis in colon cancer cells by decreasing the stability and expression of FSP1 mRNA, subsequently inhibiting the initiation and progression of colon cancer [189]. Given ferroptosis's proficiency in eliminating drug-resistant tumor cells [18, 145], the combination of ferroptosis-targeted therapy and immunotherapy may offer significant therapeutic potential in colon cancer.

In other types of tumors, the existing research on the interplay between ferroptosis and anti-tumor immunity is relatively scattered, and therefore, it is not further elaborated here. The conclusions drawn from a few specific tumor types still need to be validated in other types

of tumors to enhance their universality across different cancers.

## 6 | PERSPECTIVES

Immunotherapy and ferroptosis, new focal points in cancer treatment and regulatory cell death research, have been the subject of widespread study since their inception. Since the discovery that ferroptosis induction is one of the mechanisms of anti-tumor immunity and can enhance the efficacy of immunotherapy [46, 47], more and more researchers have devoted themselves to the research of combined use of both for synergistic anti-cancer treatment. Despite recent studies suggesting that ferroptosis may suppress anti-tumor immunity and attenuate its therapeutic effect, enthusiasm and investigation in this domain persist unabated. There is ongoing debate about the interaction between ferroptosis and anti-tumor immunity. Our literature review reveals a relatively higher amount of direct evidence supporting ferroptosis' role in promoting anti-tumor immunity. Despite potential publication bias and study heterogeneity, the direct evidence suggesting ferroptosis inhibits anti-tumor immunity is comparatively scant. The evidence that does exist primarily focuses on localized and mechanistic analysis. While this helps broaden our understanding of molecular pathways and potential treatment targets, it overlooks the influence of external complex factors, thus providing a less accurate reflection of the true situation. One study notably asserts that ferroptosis does not induce ICD using a prophylactic vaccination model [64]. This study by Wiernicki et al. [64], using a doxycycline-inducible knockdown of GPX4, allowing for synchronous and complete cell death induction, contradicts Efimova et al.'s conclusions [59], asserting that ferroptotic cancer cells are non-immunogenic. However, this conclusion drawn by Wiernicki et al. [64] may not accurately mirror real-world scenarios of targeting ferroptosis treatment, as ferroptosis stages in different cancer cells cannot be identical. Thus, in contrast, Efimova et al. [59] research, which assesses the immunogenicity of cancer cells after a period of treatment with ferroptosis inducers, might be more representative of actual clinical scenarios. Clinically, it's improbable to achieve a situation, as described by Wiernicki et al. [64], where all cancer cells are synchronously and completely induced into the same stage of ferroptosis using a specific experimental method. Furthermore, relying on a single study investigating one tumor type is insufficient due to tumor heterogeneity. Hence, findings derived from one type of tumor may not apply to others, warranting additional studies for validation. Contrastingly, there is substantial direct evidence suggesting that ferroptotic cancer cells can



**FIGURE 6** Possible combinations of ferroptosis-targeted therapy with adoptive cell therapy. Although inducing ferroptosis can effectively kill tumor cells, it may also impair anti-tumor immunity and affect the efficacy of ferroptosis-targeted therapy. Therefore, combining adoptive reinfusion of anti-tumor immune cells after anti-ferroptosis modulation with ferroptosis inducers may play a more effective therapeutic role. This approach not only maintains the killing effect of the ferroptosis inducer on tumors but also reduces damage to anti-tumor immunity, thereby improving the curative effect of combined ferroptosis-targeted therapy and immunotherapy. Abbreviations: TME: tumor microenvironment

enhance anti-tumor immunity, albeit without clear mechanistic explanations. This body of evidence encompasses various tumor types, thereby enhancing the universality and credibility of the hypothesis that ferroptosis in cancer cells can promote anti-tumor immunity.

Despite potential shortcomings, such as the possibility of drugs acting through non-ferroptotic pathways, incomplete elimination of drugs' direct impact on anti-tumor immunity, and a lack of key evidence, such as prophylactic vaccination models, the preponderance of evidence leads us to hypothesize that the overall effect of ferroptotic cancer cells on anti-tumor immunity may vary with tumor types and specific environments, but generally, its promotion of anti-tumor effects outweighs the inhibitory effects. However, there remains a necessity for further research to gather more evidence and elucidate underlying mechanisms. This will help identify specific conditions

where ferroptosis promotes or inhibits anti-tumor immunity and devise strategies to maximize its beneficial effects while minimizing any negative consequences in the future.

For immune cells, the direct impact of ferroptosis-inducing drugs on them is an unavoidable problem. The ferroptosis and related functional decline of anti-tumor immune cells may play an important role in part of the immune suppression mediated by ferroptosis. However, as described in the main text, the key molecules and signaling pathways that mediate the sensitivity of different immune cells to ferroptosis may vary, providing possibilities for targeted treatment of ferroptosis and even using ferroptosis to kill immune-suppressing cell groups. Furthermore, combining anti-ferroptosis modification of anti-tumor immune cells with ferroptosis treatment may be a feasible method (Figure 6).

In addition to the potential immune suppression effect mediated by the direct impact of ferroptosis-inducing drugs on immune cells, the special lipid metabolism of ferroptotic cancer cells, which undergoes lipid peroxidation [11], may also play an important role in inhibiting anti-tumor immunity. Its lipid peroxidation-related metabolic products and activation of the COX-2 pathway [5] may produce a variety of immune regulatory mediators. However, apart from PGE2, direct evidence linking other products to ferroptosis-mediated anti-tumor immunity is still lacking, although the regulation of tumor immunity by substances such as PGD2 has been reported in some studies [101, 102]. Further research on this metabolic pathway and its products may further clarify the immune suppression mechanism mediated by ferroptosis. In addition, it has been observed that KRAS mutant pancreatic cancer cells can release special DAMP, including KRASG12D and 8-OHG, during ferroptosis, leading to the M2 polarization of macrophages, which in turn promoted tumor growth [65, 66], suggesting that the impact of ferroptosis on anti-tumor immunity may depend on the specific context. In tumors with different histological types and genotypes, there may be unique pathways in which ferroptosis exerts an immunosuppressive effect. However, whether there are similar mechanisms in other types of tumors and different genotypes remains unclear. Moreover, DAMPs, which serve as a hallmark of ICD and are indicative of enhanced anti-tumor immunity, can also promote immune suppression through specific mechanisms [49, 138], highlighting that the release of DAMPs and other characteristics can only serve as indirect evidence for identifying ICD, and the gold standard is still the prophylactic vaccination model.

As for whether ferroptotic cancer cells are immunogenic, it may also affect their treatment strategy. For example, in immunotherapy, the immune phenotype of TME needs to be considered. The TME can be categorized into three distinct immunophenotypes based on the distribution of infiltrating immune cells. These include the inflamed type, immune-altered type, and immune-desert type [190–192]. In the immune-desert type, tumors lack immune cell infiltration due to a lack of immunogenicity. If ferroptosis is an ICD, inducing cancer cell ferroptosis can promote immune cell infiltration and enhance the efficacy of immunotherapy [193]. If ferroptosis does not qualify as an ICD, this strategy lacks a theoretical foundation. At present, although there is a lot of evidence suggesting that ferroptotic cancer cells can release DAMP, the most critical evidence of the prophylactic vaccination model remains insufficient. Therefore, further relevant research is still required.

## 7 | CONCLUSIONS

In conclusion, the relationship between ferroptosis and anti-tumor immunity is complex. While the overall effect of ferroptotic cancer cells on anti-tumor immunity might differ based on tumor types and specific environments, it's generally believed that its promotive effects on anti-tumor activities overshadow the inhibitory ones. More research is still needed to elucidate the immunogenicity of ferroptotic cancer cells, the effect of ferroptosis on immune cells, and the interaction between ferroptotic cells and anti-tumor immunity to further elucidate the regulatory role of ferroptosis in anti-tumor immunity and its underlying mechanisms. This will help to clarify the feasibility and potential drawbacks of ferroptosis-targeted therapy in the treatment of tumors and provide a translational basis for selecting different combination strategies of ferroptosis-targeted therapy and immunotherapy for different types of tumors.

## DECLARATIONS

### AUTHOR CONTRIBUTIONS

JM and YCZ designed and prepared the manuscript. YCZ and LQS drew and revised the figures. All authors contributed to the initial draft and offered valuable insights during discussions about the manuscript's concepts. All authors were involved in revising the article. All authors have read and given their approval for the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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