Review

Targeting the Macrophage-Ferroptosis Crosstalk: A Novel Insight into Tumor Immunotherapy

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Abstract

Ferroptosis is an emerging form of non-apoptotic, regulated cell death that is mechanistically dependent on aberrant iron accumulation and excessive lipid peroxidation. Further evidence indicates that ferroptosis plays a crucial role in the efficacy of tumor immunotherapy. Ferroptosis is often constrained by tumor-associated macrophages (TAMs), and this poses a challenge to clinicians aiming to exploit the potency of immunotherapy to treat various forms of cancer. Current advances revealed a dual character to TAMs in regulating tumor ferroptosis. Specifically, some signaling molecules released from cells undergoing ferroptosis can exert effects on TAM polarization. In this review, we summarize the currently characterized mechanisms of macrophage-ferroptosis crosstalk, discuss how macrophage-ferroptosis crosstalk affects the outcome of tumor immunotherapy, and provide an overview of current advances that seek to leverage this crosstalk to improve cancer immunotherapy efficacy. Despite the fact that further efforts are still required to achieve a more comprehensive understanding of the mechanisms that control this signaling, targeting macrophage-ferroptosis crosstalk has clear potential for reversing immunotherapeutic resistance and may shed light on new therapeutic strategies to overcome some advanced and metastatic malignancies.

Keywords: macrophage; ferroptosis; tumor; immunotherapy; metastasis

1. Introduction

Tumors constantly evolve to meet the demands of their surrounding stromal and immune cells, forming a basis for an intricate, and complex network of cellular and molecular interactions termed the tumor immune microenvironment (TIME). In the early stages of tumor progression, the TIME exerts an anti-neoplastic effect on the developing neoplasm, but later serves as an accomplice in promoting tumor growth, metastasis, and therapeutic resistance. Thus, the TIME presents a challenge to effective tumor management [1–4]. To reshape TIME to favor its tumor-suppressive capacities, immunotherapy has emerged as a promising strategy for some refractory malignancies, most notably evidenced by its approval to treat advanced melanoma in 2011 [5]. Despite manifold targets and mechanisms, most existing immunotherapies share a common tumor-killing ability by triggering regulated cell death (RCD) [6]. Ferroptosis, an iron-dependent and lipid-peroxide-driven form of RCD [7], exerts a prominent effect during immunotherapy [8].

First discovered when studying erastin-induced cell death in 2012, ferroptosis has aroused ongoing interest owing, in part, to its property of selective tumor scavenging [9,10]. Unlike other forms of RCD, ferroptosis does not rely on the caspase system, and demonstrates unique morphological characteristics including a condensed mitochondrial membrane, vanished mitochondria cristae, and a ruptured outer mitochondrial membrane. However, retention of a relatively intact nucleus occurs during ferroptosis [11]. Aberrant iron accumulation plays an essential role in initiating ferroptosis through a Fenton reaction and iron-activated enzymes, whereas excessive lipid peroxidation products eventually lead to the oxidative destruction of intracellular biomembranes [12]. Although many signaling molecules are characterized as participating in regulation of ferroptosis, the endogenous antioxidant glutathione peroxidase 4 (GPX4), which is widely expressed and requires glutathione (GSH) to reach its optimal activity, is viewed as a key controlling molecule in preventing the activation of ferroptosis during both physiological and pathophysiological conditions [10]. Intriguingly, CD8+ T cell-mediated ferroptosis is widely observed in most tumor cells during immunotherapy treatment, revealing potential therapeutic values for ferroptosis in promoting cell killing during tumor immunotherapy [8,13,14].

Another key factor influencing the efficacy of tumor immunotherapy is tumor-associated macrophages (TAMs). It is well accepted that TAMs function as a double-edged sword within the TIME [15]. This range in TAM function owes to two distinct cell polarizations, defined as the clas-

sic phenotype (termed M1) and the alternative phenotype (termed M2), which have opposing functions in tumor progression. M1 macrophages function in antigen presentation, induce inflammatory responses, scavenge pathogenic microorganisms, and exert anti-neoplastic effects within the TIME [16,17]. In contrast, M2 macrophages are able to limit the inflammatory response and contribute to tumor progression by stimulating proliferation, angiogenesis, and metastasis [18]. Notably, M2-like TAMs are highly associated with therapeutic resistance and are widely viewed as providing a barrier to effective tumor immunotherapy [19,20].

Intriguingly, TAMs and ferroptosis share an intricate crosstalk signaling network as compelling evidence from integrative bioinformatic analyses highlights their intimate association at many levels. Hence, it is of great necessity to profile and interpret their interplay in a more comprehensive view. Herein, we endeavor to highlight and integrate the sophisticated crosstalk pathways between TAMs and tumor ferroptosis, and subsequently discuss how their crosstalk affects the outcomes of tumor immunotherapy. Finally we seek to summarize current advances associated with macrophage-ferroptosis crosstalk in tumor elimination in anticipation that this will shed light on new therapeutic strategies for as-yet undruggable malignancies.

2. Ferroptosis within the TIME

Ferroptosis starts with aberrant iron metabolism and excessive lipid peroxidation, and ends with disrupted lipid bilayers [6]. Physiologically, extracellular Fe^{3+} ions are captured by transferrin and reduced into Fe^{2+} inside the cell, while Fe^{3+} ions are exported through solute carrier family 40 member 1 (SLC40A1) [21]. Only a physiological level of Fe^{2+} ions are freely involved in various biological processes, whereas excess Fe^{2+} ions are sequestered in ferritins. As a result, ferritin dysfunction leads to excessive release of Fe^{2+} ions, which can, in turn, activate iron-dependent lipid peroxidases and contribute to the generation of reactive oxygen species (ROS) [22,23]. In this scenario, polyunsaturated fatty acids (PUFAs) within lipid bilayers will be oxidized to PUFA-OOHs, and such lipid peroxide moieties result in irreversible membrane damage and eventually trigger ferroptosis (Fig. 1).

Within the TIME, ferroptosis is co-regulated by intracellular and extracellular pathways. The pivotal intracellular system in regulating ferroptosis is the system Xc^-/glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis [24]. The system Xc^- is a transmembrane heterodimer composed of a light chain xCT (encoded by SLC7A11) and a heavy chain 4F2 (encoded by SLC3A2) [25]. As an amino acid antiporter, system Xc^- plays a pivotal role in uptaking cystine and exporting glutamate in mammalian cells, thus providing necessary precursors for GSH biosynthesis [25]. With a reductive sulfhydryl structure, GSH could scavenge excessive ROS and detoxify lipid hydroperoxides

in the presence of GPX4, a dedicated antioxidant enzyme using GSH as the deoxidative cofactor [26]. Intriguingly, multiple inducers of ferroptosis work by blocking system Xc^- and GPX4 degradation, thus leading to overproduction of ROS and lipoperoxides [6]. For example, a small molecule termed erastin can prevent cystine uptake by directly inhibiting SLC7A11 resulting in a decrease in GSH generation [9]. Furthermore, erastin can trigger ferroptosis through multiple system Xc^--independent pathways [27]. One such mechanism is to induce opening of the voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane. This leads to increased mitochondrial metabolism and excessive mitochondrial-associated ROS. In addition, erastin can upregulate acyl-CoA synthetase long chain family member 4 (ACSL4) to regulate lipid metabolism. Of note, erastin-induced ROS overproduction can indirectly activate p53 and promote ferroptosis as well [27]. However, some GSH-independent molecules, like ferroptosis suppressor protein 1 (FSP1), are also found to mediate tumor ferroptosis, although the underlying mechanisms remain elusive [28].

Beyond intracellular mediators, ferroptosis within the TIME is principally induced by CD8+ T lymphocytes. In 2019, Wang *et al*. [14] first reported that CD8+ T cells can induce tumor ferroptosis as a result of immunotherapy by producing IFN-γ. These investigators found that IFN-γ released from CD8+ T cells can activate the janus kinase/signal transducer and activator of transcription 1 (JAK/STAT1) pathway. Once recognized by the receptor of IFN-γ (IFN-γR), IFN-γ will trigger JAK-mediated phosphorylation of IFN-γR, which subsequently leads to the recruitment of STAT1 and formation of STAT1 homodimers [29,30]. Then the STAT1 homodimers are translocated into the nucleus where they could bind to the transcription region of SLC7A11 and suppressing system Xc^-. Furthermore, IFN-γ can lead to high mitochondrial oxidative status and increased mitochondrial-derived ROS, implying that IFN-γ may disrupt the mitochondrial metabolism [31]. This is probably caused by IFN-γ-induced nitro-oxidative stress via STAT1/NF-κB/NOS2 axis, though the exact mechanism still remains unknown [31,32]. Apart from this mechanism, Liao's team discovered that IFNγ stimulates ACSL4 to promote incorporation of arachidonic acid into into C16 and C18 acyl chain-containing phospholipids (Fig. 2). These modified phospholipids are more sensitive to oxidative damage and thereby enhance tumor sensitivity to ferroptosis [33,34]. Additionally, IFNγ can also enhance the tumor-eliminating potential of CD8+ T cells in a wide range of malignancies, suggesting a positive feedback between CD8+ T cells and IFNγ [35]. Nonetheless, it requires further investigation whether CD8+ T cells could trigger ferroptosis in a IFN-γ-independent manner. Regardless, the anti-tumor efficiency of CD8+ T cells can be remarkably affected by the TIME, which makes it difficult to trigger ferroptosis in certain immunologically silent and
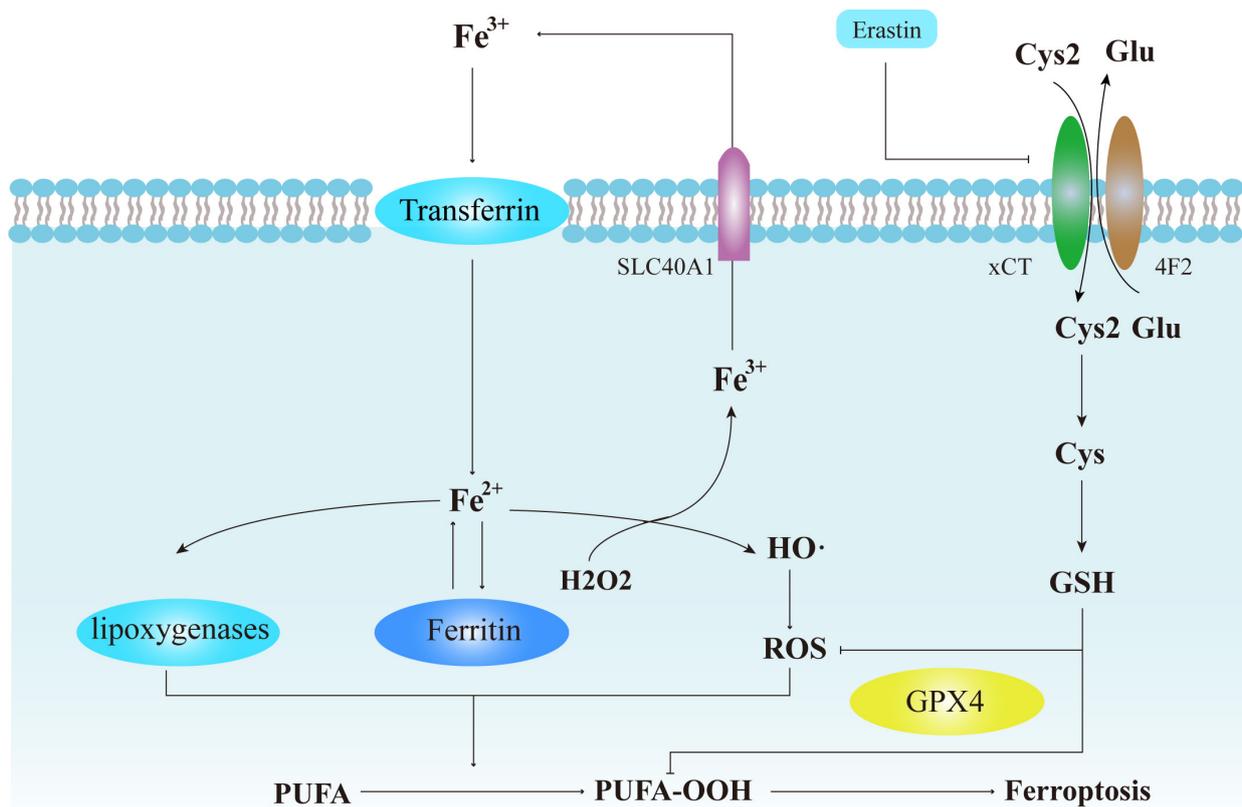
Fig. 1. Cellular events in the regulation and process of ferroptosis. Dysfunction within iron metabolism leads to excessive release of free intracellular Fe^{2+} ions, which subsequently produce ROS through the Fenton reaction or via enzyme activation. These strong oxidative radicals can, in turn, oxidize PUFAs into lipoperoxides (*i.e.*, PUFA-OOHs) resulting in the destruction of the lipid bilayer composition of cellular biomembranes. The system Xc^--GSH-GPX4 axis is the core intracellular antioxidant system against ferroptosis, in which the system Xc^- (composed of xCT encoded by SLC7A11 and 4F2 encoded by SLC3A2) imports cystine and exports glutamate at the ratio of 1:1. Once transferred into the cell, cystine is rapidly reduced into cysteine and is used to produce GSH for the GPX4-dependent reductive reaction, thereby scavenging free ROS and PUFA-OOHs. Of note, Erastin can block the uptake of cystine by disabling the function of SLC7A11. Cys, cysteine; Cys2, cystine; Glu, glutamate; GPX4, glutathione peroxidase 4; GSH, glutathione; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC40A1, solute carrier family 40 member 1; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11.

lymphocyte-depleted cancer subtypes [36]. Therefore, it is of great importance to determine the hub orchestrators that regulate the immunological competence of the TIME as a means to develop novel strategies to enhance the therapeutic effects of ferroptosis-dependent cancer treatment in clinical practice.

3. Detailed Mechanisms of Macrophage-Ferroptosis Crosstalk

To date, TAMs are well recognized as a predominant regulator within the TIME and whose functional status is prone to remodeling by exogenous signals due to the wide distribution of diverse signal receptors on their cell surface [37]. It has been well-established that macrophages are able to trigger ferroptosis via multiple signaling pathways, and, in turn, ferroptotic products can regulate the

polarization of TAMs [6,38,39]. These findings imply an underlying functional existence of macrophage-ferroptosis crosstalk which may influence the efficacy of tumor immunotherapy. Therefore, it is necessary to fully delineate macrophage-ferroptosis crosstalk to provide critical insight into factors that can influence the therapeutic effects of immunotherapy.

3.1 Dual Effects of Macrophage on Ferroptosis

The two distinct TAM differentiation states govern TAM effects on tumor ferroptosis. As a major anti-tumor effector within the TIME, M1 macrophages can promote tumor ferroptosis by enhancing tumor vulnerability to oxidative damage and activating a tumor-eradicating immune response within the TIME [40]. Recent studies have suggested the existence of at least three different mediators in this process, including CD8+ cytotoxic T lymphocytes
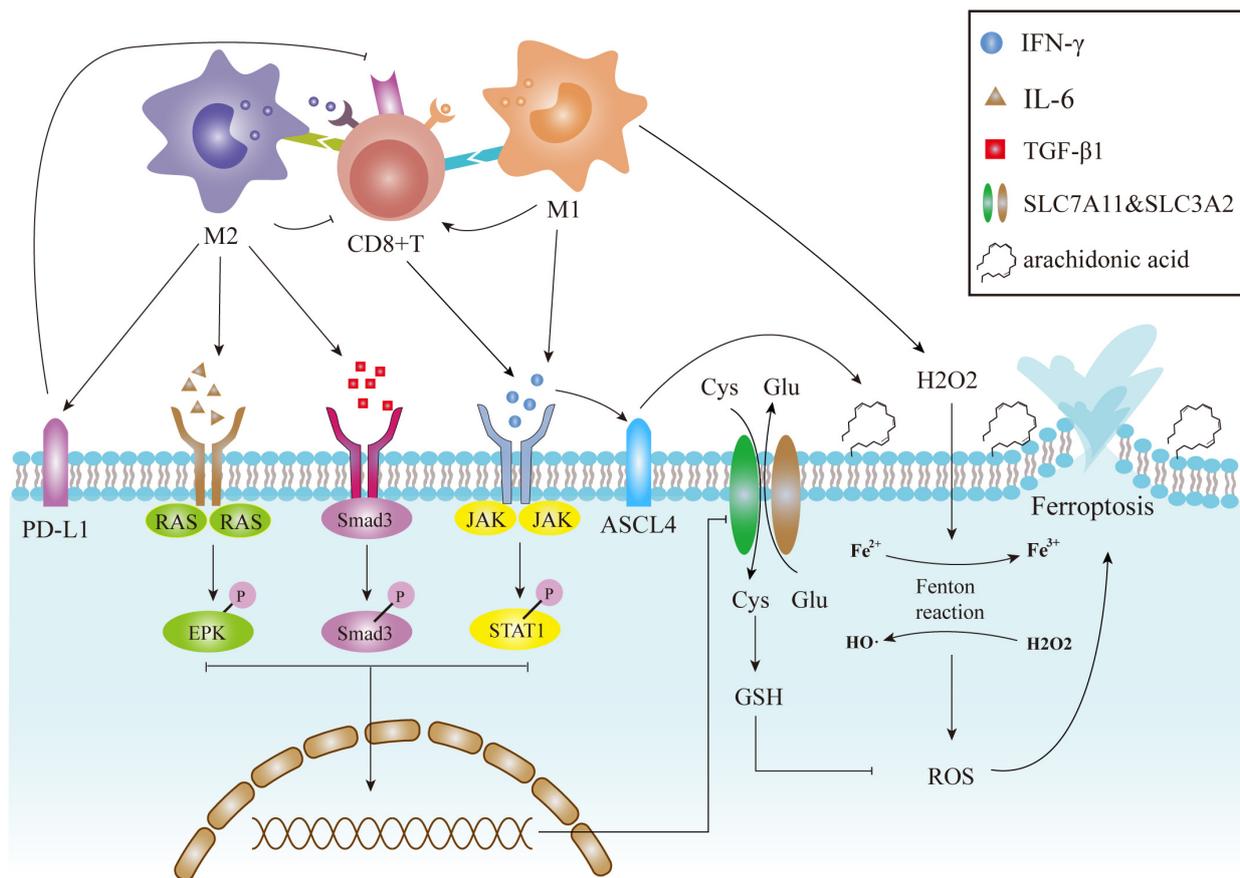
Fig. 2. Dual effects of TAMs on ferroptosis. M1-like TAMs can trigger tumor ferroptosis through at least three distinct mechanisms: activation of CD8+ CTLs, release of proinflammatory cytokines, and providing peroxides to accelerate Fenton reactions. The former two pathways downregulate the expression of SLC3A2 and SLC7A11 at the transcriptional level, resulting in downregulation of an endogenous anti-ferroptosis system. The latter mechanism contributes to excessive ROS production which, in turn, promotes tumor ferroptosis. M2-like TAMs can indirectly suppress ferroptosis either by inactivating CTLs or by upregulating the expression of oncogenic PD-L1. JAK, Janus kinase; STAT1, signal transducer and activator of transcription 1; Smad2, small mothers against decapentaplegic homolog 2; Smad3, small mothers against decapentaplegic homolog 3; Smad4, small mothers against decapentaplegic homolog 4; RAS, rat sarcoma viral oncogene homolog; SLC3A2, Solute Carrier Family 3 Member 2; SLC7A11, Solute Carrier Family 7 Member 11; PD-L1, programmed cell death 1 ligand 1.

(CTLs), various cytokines, and peroxides resulting from the respiratory burst (Fig. 2) [41,42].

The CTL-mediated pathway is considered to have a major contribution to initiating tumor ferroptosis. It is well established that M1 macrophages utilize cell contact-dependent signaling to activate CTLs [43], which plays a crucial role in triggering ferroptosis during tumor immunotherapy. As discussed above, interferon γ (IFNγ) from activated CD8+ CTLs can downregulate the expression of SLC3A2 and SLC7A11, the two subunits of glutamate-cysteine anti-transporter, though the JAK/STAT1 signaling pathway [14]. This disables the GSH-dependent antioxidant system and eventually results in excessive lipid peroxidation and activation of ferroptosis [9]. Notably, IFN-γ-activated *ACSL4* could promote the incorporation of arachidonic acid into tumor phospholipids, enhancing the susceptibility of phospholipid to ox-

idative damage [33,34]. M1 macrophages can also directly release peroxides, such as H_2O_2, during the respiratory burst [44,45], thus accelerating the intracellular Fenton reaction and consequential creation excessive reactive oxygen species (ROS) which also promote tumor ferroptosis [46]. Since Fe^{2+} is an indispensable catalyst for the Fenton reaction, small amounts of peroxide from M1 macrophages appears to make no impact on the activation of tumor ferroptosis without coordinating excessive iron accumulation.

Although bioinformatic analyses have identified a significant negative correlation between tumor ferroptosis and M2 infiltration [39,47–52], there are few studies exploring the direct effects of M2 macrophages on tumor ferroptosis. Instead, M2 macrophages are more likely to play an indirect role in regulating ferroptosis by disrupting the ferroptosis-promoting function of CTLs [53]. It is well documented that M2 macrophages can prevent the recruit-

ment and activation of CTLs via the inhibition of numerous chemokines such as C-X-C motif chemokine ligand 9 (CXCL9), C-X-C motif chemokine ligand 10 (CXCL10) and C-X-C motif chemokine ligand 12 (CXCL12) [54,55]. Together, these molecules disable major mechanisms that promote tumor ferroptosis during immunotherapy. In addition, M2 macrophages can enhance tumor-derived resistance to ferroptosis by upregulating the expression of PD-L1 on neoplastic cells [56,57], which can engage with PD-1 to initiate programmed cell death in CTLs [53,58]. Furthermore, Xu and colleagues, using a combination of *in silico* and *in vitro* experimental approaches, recently identified a novel molecular matrix remodeling-associated protein termed MXRA8, which can decrease the level of intracellular ferrous iron (Fe^{2+}) and lipid peroxidation, meanwhile elevating the infiltration of M2 macrophages in the glioma cells [59].

It is noteworthy that some M2-associated cytokines may serve to promote ferroptosis. For example, TGF-β1 can activate NADPH Oxidase 4 (NOX4) which can transport electrons from NADPH to O_2 and thus generate ROS [60]. Moreover, it was reported that TGF-β1 can activate Smad3 to downregulated the expression of SLC7A11 [61]. Although there was no evidence that Smad3 could specifically bind to SLC7A11, presumably Smad3 may affect the stability of xCT via ubiquitination and degradation. Another M2-associated cytokine, IL-6, can disrupt iron homeostasis by stimulating the generation of hepcidin via JAK/STAT3 pathway, which can bind to the transmembrane iron exporter resulting in iron accumulation [62,63]. In addition, IL-6 can activate extracellular regulated protein kinase (ERK) signaling to repress the expression of xCT [64], which was further supported by the observation of increased phosphorylated ERK in IL-6-treated HeLa cells [65]. Nonetheless, how the phosphorylated ERK mediates the expression of xCT requires further exploration [64]. Such anti-tumor effects of M2-like TAMs broadens our perspective of the functions exerted by M2-like TAMs in tumor progression, and may inspire novel ideas for TAM-targeting therapy in the future [66]. Despite all these developments, the profile of M2-derived effects on CTLs still remains largely unexplored, and calls for further investigation into the details of crosstalk signaling are clearly warranted.

In summary, M1 macrophages function in the activation of tumor ferroptosis through both direct and indirect mechanisms, whereas M2 macrophages principally act by opposing inactivation of CTLs in TIME. Despite the need for more information to fully appreciate the intricacies of these signaling pathways, there is little doubt that TAMs play a vital role in regulating tumor ferroptosis. This supports the emerging view of TAMs are valuable targets to increase neoplastic sensitivity to ferroptosis-inducing immunotherapy.

3.2 Association between Ferroptosis-Related Genes and TAMs

While macrophages are involved in the regulation of ferroptosis, ferroptosis is also capable of affecting macrophage polarization through several mechanisms. Current advances in bioinformatics have highlighted significant correlations between ferroptosis-related genes (FRGs) and TAM infiltration in several malignancies. Such advances were possible with the assistance of newly-emerging algorithms such as Cibersort, TIMER, quanTIseq and xCell (Fig. 3). Generally speaking, ferroptosis-promoting FRGs are more likely to serve in an anti-oncogenic capacity, while ferroptosis-blocking FRGs are predisposed to contribute to tumor progression, and thereby may be linked to TAM infiltration. For example, ferroptosis-promoting FRGs such as *HIF1A*, *SLC7A11*, *GPX4*, *FTH1* are highly associated with poor prognosis as well as TAM infiltration in ovarian cancer. Other ferroptosis-promoting FRGs, including *FGFR3*, *CDGSH* and *CISD1*, which are directly involved in either iron storage or inhibiting iron uptake, are also associated with an increased proportion of tumor-infiltrating macrophages in bladder cancer [39,67–71]. The ferroptosis driver *SOCS1* and suppressor *FTH1* correlate with M1 and M2 infiltration, respectively, in head and neck squamous cell carcinoma (HNSCC) [39] which implies the probability of ferroptosis-mediated macrophage polarization within the TIME. Moreover, some ferroptosis-associated lncRNAs are also implicated in TAM infiltration in hepatocellular carcinoma [68]. In conclusion, many differentially expressed FRGs and lncRNAs are highly associated with tumor prognosis, clearly indicating the potential involvement of ferroptosis-related signals in tumor progression [39,69–71]. However, further studies are required to identify the specific effect of FRGs on TAM polarization.

3.3 Dual Effects of Ferroptotic Products on TAM Polarization

Recent studies of damage-associated molecular patterns (DAMPs) have revealed one of the feasible means to mediate ferroptosis-related TAM polarization at the molecular level. By definition, DAMPs are an array of molecular products from damaged tissues, whose counterparts, the pattern recognition receptors (PRRs), are located on the surface of macrophages. PRRs function to interpret the messages delivered by DAMPs and produce responses to tissue damage [72]. Interestingly, different DAMPs released by tumor cells undergoing ferroptosis may convey completely distinct messages, either as an "eat-me" signal or as a "save-me" signal, depending on the specific type of DAMPs and neoplastic subtypes (Fig. 4).

The "eat-me" DAMPs allow navigated immune clearance of ferroptotic cells and promote anti-tumor immunity. For example, 1-steaoryl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine (SAPE-OOH), one of the oxygenated lipid products released from cells undergoing fer-
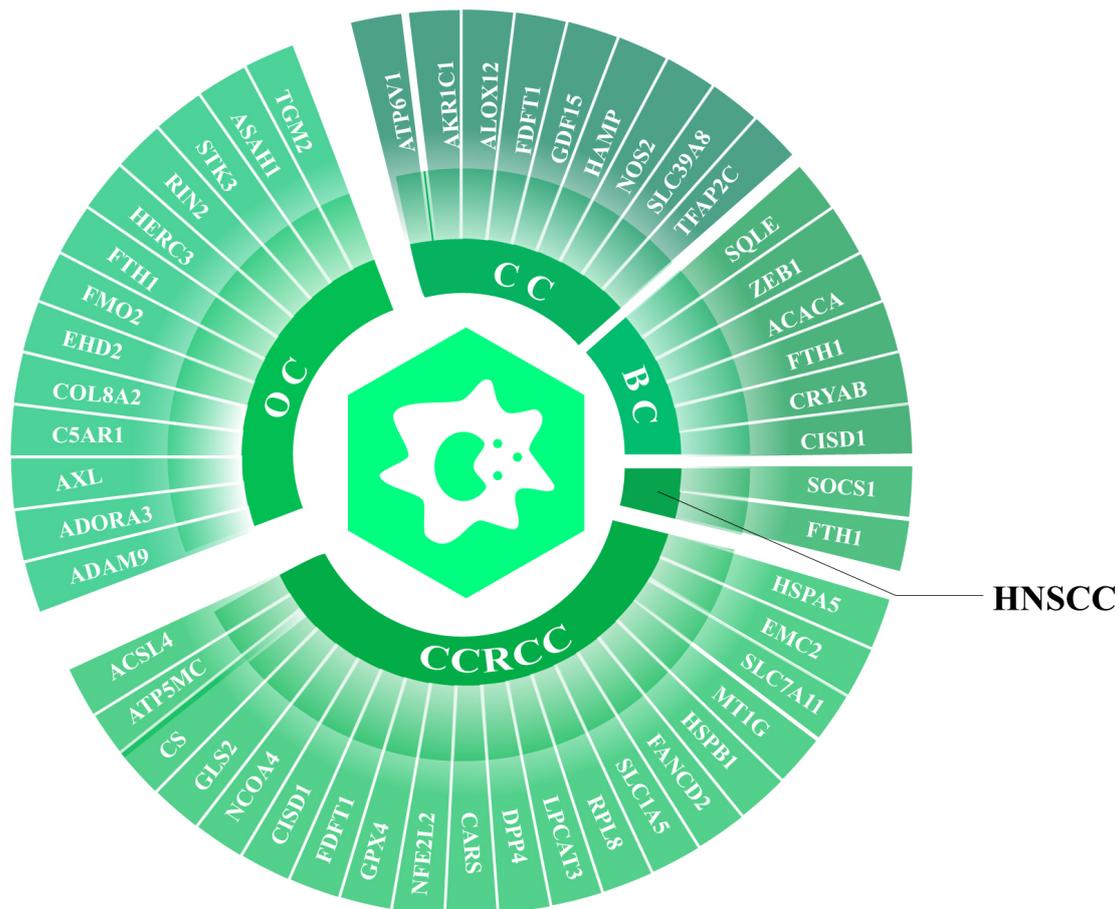
Fig. 3. Ferroptosis-related genes (FRGs) in different tumors are associated with TAM infiltration. Integrative analysis with bioinformatic tools highlight comprehensive differentially expressed FRGs that are associated with TAM infiltration in different cancers. OC, ovarian cancer; CCRCC, clear cell renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; BC, bladder cancer; CC, colorectal cancer.

roptosis, serves as an "eat-me" DAMP by interacting with toll-like receptor 2 (TLR2) on macrophages. Within the context of ovarian cancer, this event has been shown to promote M1 activation [73]. Another important "eat-me" DAMP is high mobility group box 1 (HMGB1), whose release relies on ferroptosis-related autophagy [72]. HMGB1 can not only promote M1 polarization but also can up-regulate advanced glycosylation end product-specific receptor (AGER)-mediated TNF-α secretion in TAMs in bladder cancer [74]. Curiously, additional studies underscore the indispensable role for autophagy-related genes like autophagy-related 5 (ATG5) and autophagy-related 7 (ATG7) in this process, indicating a significant role for autophagy in regulating HMGB1 [74].

Alternatively, the "save-me" DAMPs initiate a repair process in neoplastic tissues, resulting in immunosuppression within the TIME and enhanced resistance to ferroptosis [8]. It was reported that ferroptotic cells in pancreatic ductal adenocarcinoma (PDAC) can package an oncogenic form of the protein KRAS^{G12D} into exosomes, which are subsequently retrieved by AGERs on TAMs and activate STAT3-

mediated M2 polarization in the TIME [38]. Interestingly, autophagy is also required for the formation of these exosomes. Another DAMP produced by oxidative DNA damage termed 8-hydroxy-2'-deoxyguanosine (8-OHG), was found to activate transmembrane protein (TMEM173) and a downstream DNA sensor pathway. In turn, these events promote TAM infiltration thus favoring PDAC tumorigenesis. In contrast, 4-hydroxynonenal (4-HNE), another lipid peroxidation product similarly emitted by ferroptotic cells, fails to trigger the same events as 8-OHG [75]. This presents a paradox as the TMEM173/STING DNA-sensing pathway generally activates a strong type I interferon response resulting in M1 activation and tumor eradication [76,77]. However, since the TMEM173/STING pathway can directly increase the genetic instability of neoplastic cells and as this, in turn, can increase the frequency of genetic variation and create tumor subgroups with stronger adaptability [78], the long-term effects of 8-OHG may result in enhanced tumor resistance to ferroptosis.

Notably, ferroptosis is often accompanied by autophagy, which plays an essential role in regulating fer-
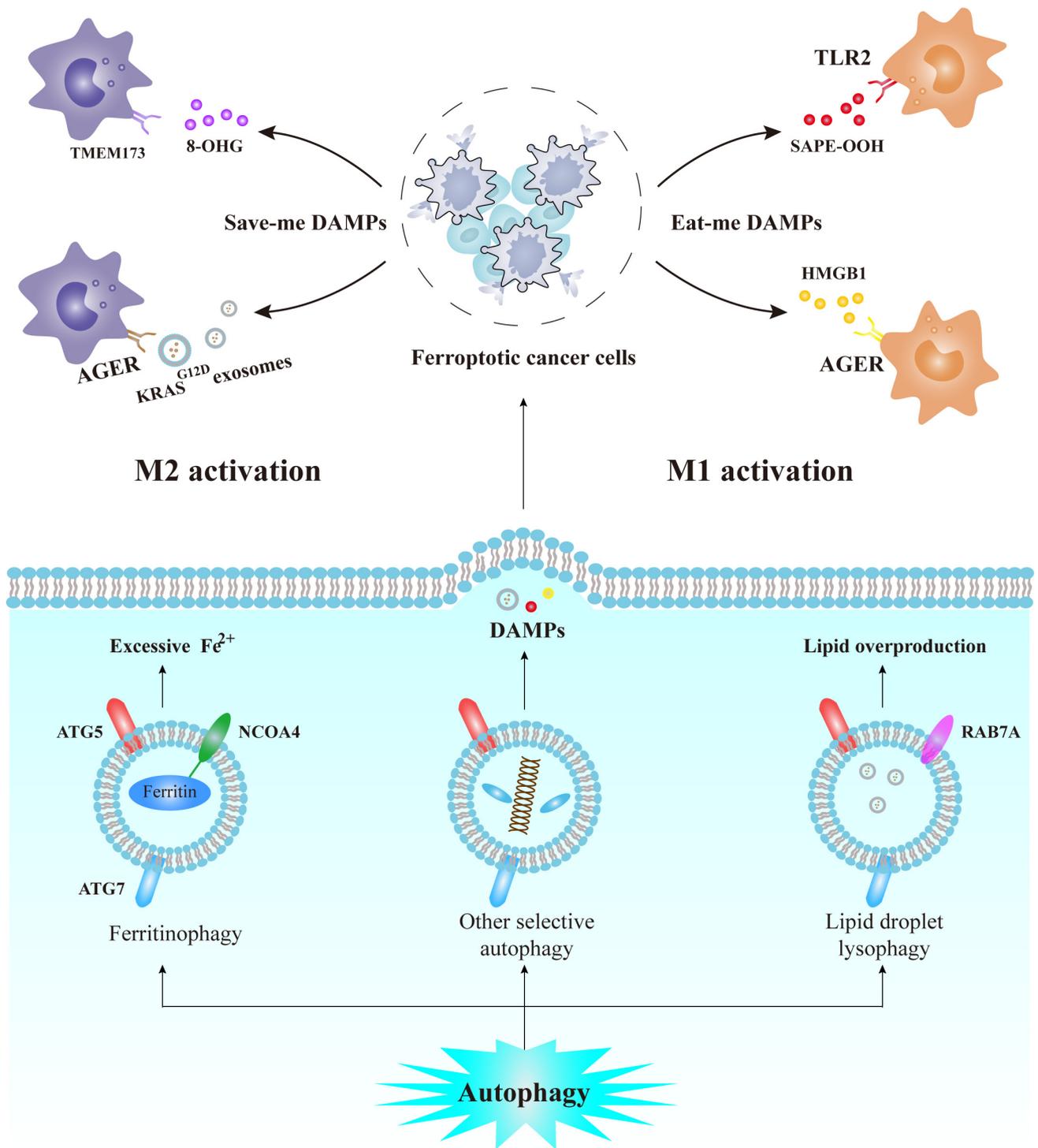
Fig. 4. Relationship between selective autophagy, tumor ferroptosis, ferroptotic DAMPs, and the TAM polarization. The NCOA4-mediated ferritinophagy and the RAB7A-mediated lysophagy of lipid droplets could provide labile Fe^{2+} ions and excessive lipids for ferroptosis, while selective autophagy of other components may involve in DAMP production. Once released from ferroptotic cancer cells, the "eat-me" DAMPs (*e.g.*, SAPE-OOH and HMGB1) are recognized by corresponding PRRs (TLR2 and HMGB1) and favor M1 polarization. The "save-me" DAMPs (*e.g.*, KRAS^{G12D} and 8-OHG) can mediate M2 polarization in a similar fashion in PDAC. SAPE-OOH, 1-steaoryl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine; TLR2, toll-like receptor 2; HMGB1, high mobility group box 1; KRAS, Kirsten rat sarcoma vital oncogene; AGER, advanced glycosylation end-product specific receptor; TMEM173, transmembrane protein; 8-OHG, 8-hydroxy-2′-deoxyguanosine; NCOA4, nuclear receptor coactivator 4; RAB7A, Ras-related protein rab-7a.

roptosis (Fig. 4). Some ferroptosis-associated DAMPs, including HGMB1 and 8-OHG, originate from the autophagy of specific cellular components, whereas knockout of autophagy-dependent genes, such as ATG5 and ATG7, will inhibit the release of DAMPs [38,79]. Further, the selective autophagy of ferritin and lipid droplets will release dramatic amounts of labile iron and lipoperoxides, thus providing a significant pool of molecules to trigger ferroptosis. For example, ferritin can specifically bind to the C-terminus of nuclear receptor coactivator 4 (NCOA4) which will subsequently be trafficked into autophagosomes [80]. Similarly, ras-related protein Rab-7a (RAB7A) can contribute to lipid phagocytosis by recruiting lipid droplets for delivery into lysosomes [81]. Of note, some classical autophagy-associated molecules can inactivate the core components of the intracellular antioxidant system in an autophagy-independent manner. Specifically, AMPK-mediated Beclin 1 (BECN1) phosphorylation can trigger the formation of the BECN1/SLC7A11 complex and inhibit the transport activity of system Xc$^-$ in cancer cells [82]. However, whether and how TAMs can regulate tumor ferroptosis by selectively mediating autophagy remains unclear.

In sum, the core mechanism of ferroptosis-mediated macrophage polarization can be summarized into three basic steps: (1) DAMPs are produced by cells undergoing ferroptosis; (2) DAMPs are released from cells in a specific form; (3) DAMPs are ultimately uptaken by macrophages to induce a series of phenotypic alterations (Fig. 5). On the basis of these three steps, we can develop a series of therapeutic strategies to favor the "eat-me" DAMPs and suppress the "save-me" DAMPs. It is noteworthy that autophagy is vital in the production of some DAMPs, and that exosomes can serve as a crucial DAMP carrier for tumor/macrophage communication. Thus, targeting autophagy-related signaling molecules, as well as the formation of exosomes, may also contribute to resetting DAMP release in immunotherapy.

3.4 Immunogenic Ferroptosis and DAMPs

Ferroptosis is a necrotic process accompanied by oxidative damage and autophagic degradation, and which generates a multitude of compounds with strong immunogenicity and adjuvanticity [83]. Accumulating evidence has established that ferroptotic tumor cells are abundant sources of DAMPs such as HMGB1, ATP and HSP90, which could induce activation and maturation of the antigen-presenting cells (APCs) and lead to secondary secretion of proinflammatory cytokines [84]. Conversely, inhibiting either the release of DAMPs or blocking binding to PRRs will result in dysregulation of anti-tumor CTLs within the TIME [85]. Thus, these findings suggest that ferroptosis exhibits hallmarks of immunogenic cell death (ICD), and plays a crucial role in activating cancer-killing immune responses within the TIME.

Ferroptosis exerts immunostimulatory effects mainly through DAMP production and major forms of ferroptotic DAMPs can vary in a time-dependent way. For example, early in the process of ferroptosis, cells produce higher levels of HMGB1 but at later stages, feroptotic cells tend to generate more oxidized lipids. These oxidation products decrease phagocytosis and antigen cross-presentation by dendritic cells [86]. Such a distinct immunogenic propensity between early and late ferroptotic cells is presumably because ferroptosis-associated autophagy may be the dominant biological event during the early stages of ferroptosis, but at later stages this may be replaced by ROS generation and lipid peroxidation. Other than different temporal stages of ferroptosis, different cancer cell types appear to have preferences for a specific type(s) of ferroptotic DAMPs, such as the PDAC-specific KRAS^{G12D} mutant and SAPE-OOH in ovarian cancer. Although, as we have discussed above, the reason for such a preference is not yet understood. Although a few observations point towards a potential tendency for specific ferroptotic DAMPs to function coordinately with different types of ferroptotic inducers (such as the RSL3-induced ATP release) [83], no evidence has been gathered that indicates a specific association between inducers of ferroptosis and ferroptotic byproducts.

Immunostimulatory efficiency relies on the specific type of byproduct produced by cells undergoing ferroptosis. Generally speaking, cytokines are more effective than DAMPs as they function at lower concentrations, generally at the picogram level [87]. Owing to the similarities between cytokines and DAMPs, Yatim et al. [88] proposed that cytokines can be seen as inducible DAMPs (iDAMPs), and both DAMPs and iDAMPs are required for efficient immune activation. However, most iDAMPs are stimulated by DAMPs in the later stages of activation; therefore, DAMPs play a vital role in early immune activation. Of the various ferroptotic DAMPs, HMGB1 demonstrates higher immunostimulation efficiency and enhanced stability in the extracellular environment compared with ATP, which is rapidly depleted after 24 h of ferroptosis induction [86]. However, Elliott et al. [89] discovered abolishment of APC recruitment when ATP fails to bind to the purinergic receptors, suggesting that ATP plays an indispensable role in activation anti-tumor immunity. Additionally, calreticulin exposure is also required for immunostimulation during the triggering of ferroptosis-like cell death exhibited by TRAMP-C1 cells [90]. Taken together, these findings revealed at least three ferroptotic DAMPs, namely HMGB1, ATP and calreticulin, are essential in mediating the activation of anti-tumor immunity.

Finally, different PRR pathways have been characterized as having distinct effects. In general, DAMPs have higher affinity to TLRs [91], which can accept a wide range of ligands and activate serval classical signaling pathways to promote innate immunity. Some PRRs can activate specific pathways to exert distinct effects. For example, CRT and HSPs can bind to LRP1 and drive immunogenic
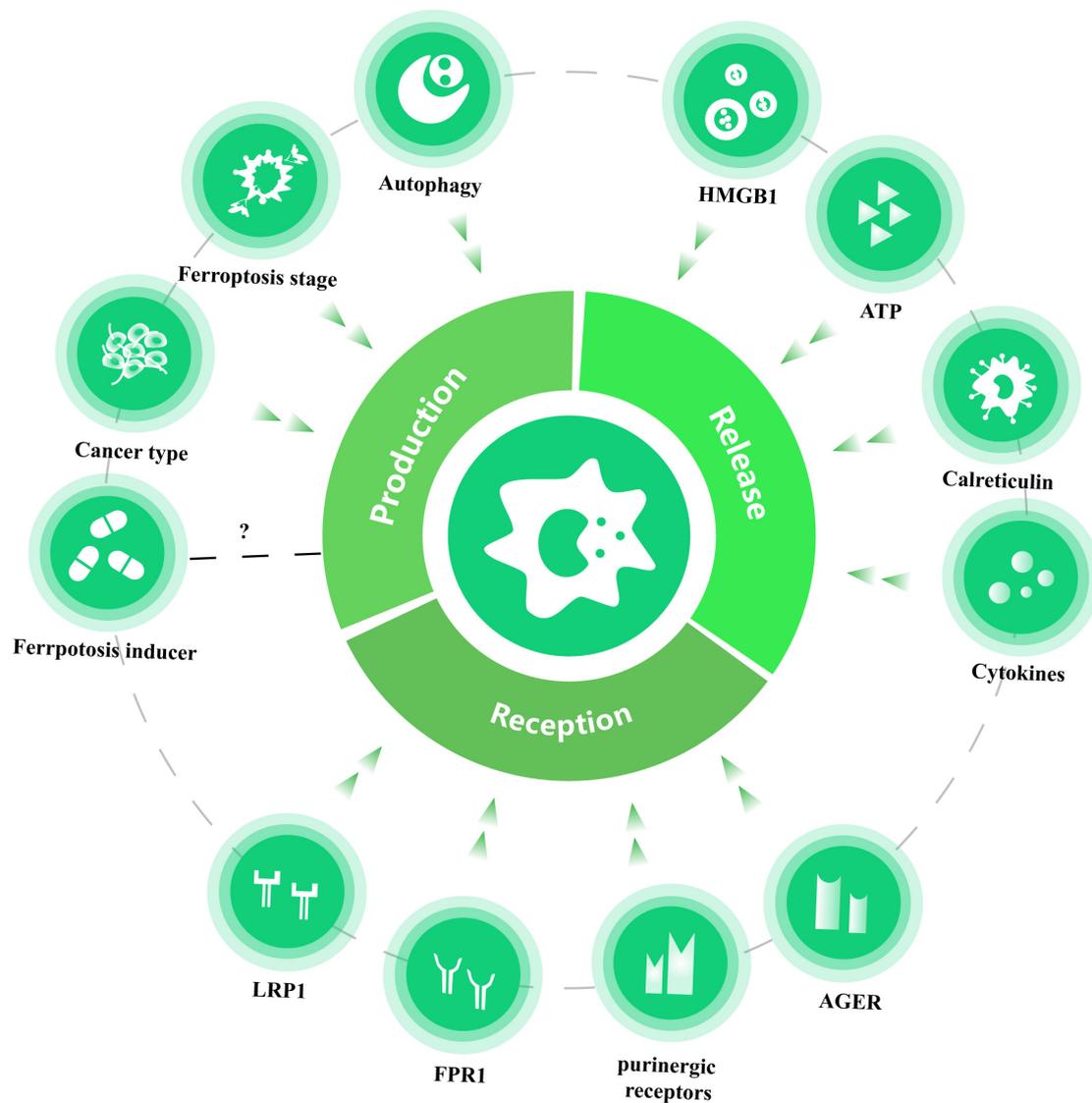
Fig. 5. Three basic steps of DAMP-mediated TAM activation and the factors affecting the immunogenic property of ferroptotic tumor cells. Ferroptotic cancer cells exert the immunostimulatory effects to activate TAMs by the production, release and TAM recognization of DAMPs (taking cytokines as a special kind of inducible DAMPs). Factors affecting DAMP production could largely impact the type of ferroptotic DAMPs, and different types of DAMPs and PRRs will activate distinct signaling pathways, thereby determining the immunogenic property of ferroptosis. Of note, it is still unclear whether the type of ferroptosis inducers could impact DAMP production. PD-L1, programmed cell death 1 ligand 1; CTL, Cytotoxic T Lymphocyte; LRP1, low density lipoprotein receptor-related protein 1; FPR1, formyl peptide receptor 1; HMGB1, high mobility group box 1; AGER, advanced glycosylation end-product specific receptor.

phagocytosis [92,93], while ATP can stimulate inflammasomes through purinergic receptors [85]. Notably, certain immunostimulatory DAMPs do not signal through PRRs but rather bind to other immunostimulatory receptors like purinergic P2 receptors, low density lipoprotein receptor-related protein 1 (LRP1), formyl peptide receptor 1 (FPR1), or AGRE to propagate danger signals [94]. Conversely, some DAMPs may not always act as danger signals but as "bystanders". For example, HSP90 does not exert any immunogenic effects despite being commonly exposed on the surface of cancer cells [95]. Taken together, ferroptosis is an indispensable part of ICD, and presents a promising therapeutic strategy by targeting ferroptotic DAMPs and relevant immune signaling pathways to enhance immunogenic effects and improve cancer immunotherapy (Fig. 5).

4. Macrophage-Ferroptosis Crosstalk and Immunotherapeutic Tolerance

Since the initial approval of anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) for clinical use in melanoma patients in 2011, immune checkpoint inhibitors (ICIs) have been a predominant strategy for treating some advanced malignancies [96,97]. One of the most widely-used ICIs, anti-PD-L1 antibody, blocks
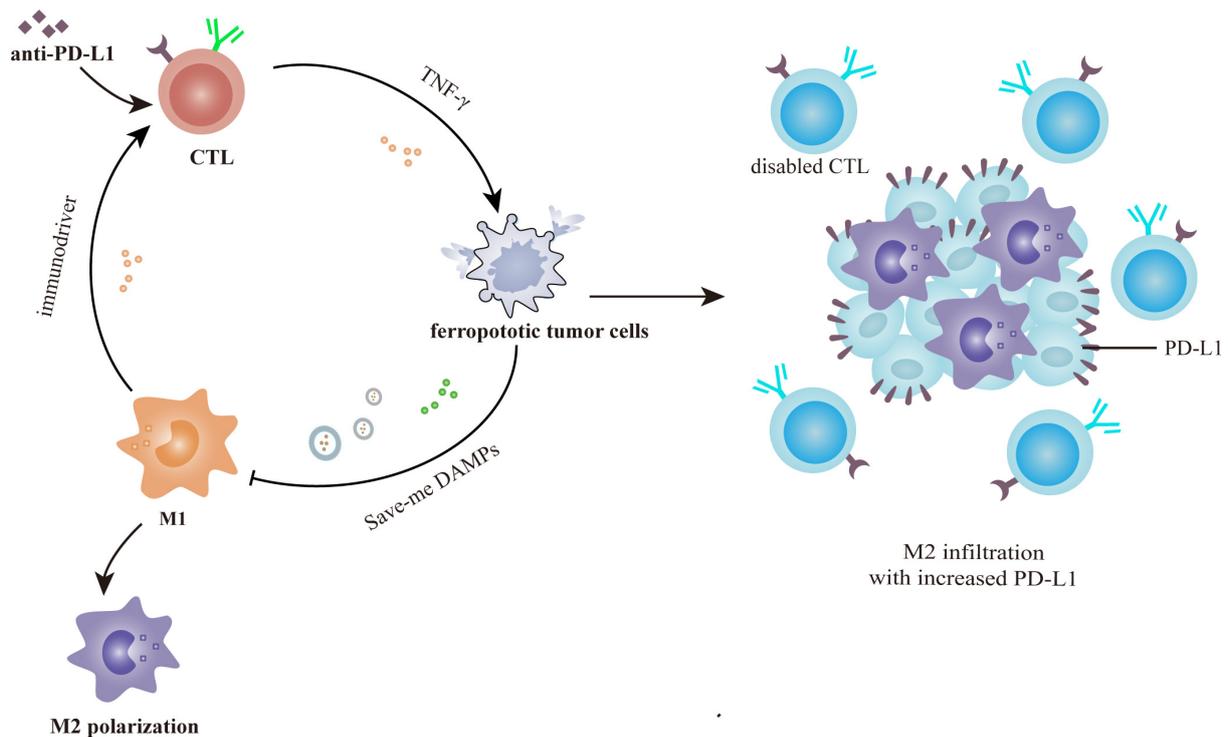
Fig. 6. Immunotherapeutic tolerance caused by the macrophage-ferroptosis crosstalk. Tumor resistance to anti-PD-L1 antibody derives from negative feedback signaling between ferroptotic cells and macrophages. Anti-PD-L1 immunotherapy causes intensive tumor ferroptosis in the early stage, which in return promotes M2 infiltration and tumorigenic PD-L1 expression via the "save-me" DAMPs. This may account for the iron-induced resistance of advanced PDAC to immune checkpoint inhibitors.

PD-L1, a CTL inhibitor expressed on neoplastic cells. This approach exploits the anti-tumor potential inherent in CTLs and included in this response is promotion of tumor ferroptosis [98]. ICIs were once considered to be the ultimate solution to metastatic malignancies until drug tolerance was reported in clinical cohorts [99,100]. It is well recognized that many of the intrinsic properties of tumors including tumor heterogeneity, tumor mutation burden, and metabolic reprogramming are associated with the therapeutic effects of ICIs [101]. Just as clearly, TIME components, especially TAMs, play a crucial role in tumor resistance to ICIs. Various cytokines from TAMs can both disable and deplete CD8+ T cells as well as interact with tumor cells resulting in metabolic reprogramming and even promote irreversible alterations in the cell's genetics [102]. Such typical changes include overexpression of oncogenic ICIs and insensitivity to immunogenic cell death [103,104]. Notably, a predominant population of M2-like TAMs is observed in tissue samples taken from non-responders to immunotherapy, indicating that M2-like TAMs may play a central role in contributing to cancer-acquired resistance to immunotherapy [105,106]. However, some drug-resistant tumor cells undergoing epithelial-mesenchymal transition (EMT) may display heightened sensitivity to ferroptosis due to GPX4 system downregulation and the activation of inflammatory pathways that occur during EMT [107].

On basis of these findings, we can propose a hy-pothesis to account for the cancer-acquired immunotherapeutic tolerance stemming from macrophage-ferroptosis crosstalk. Specifically, in the early therapeutic stages, anti-PD-L1 therapies can alert a significant number of CTLs in a very short time, and this can activate a potent tumor ferrop-totic response [14]. This response may lead to a predom-inant release of "save-me" DAMPs and thereby promote an overwhelming accumulation of M2 macrophages within the TIME. These dominant M2 macrophages can, in the long term, elevate the expression of tumorigenic PD-L1 and activate feedback signaling to suppress CTL-mediated fer-roptosis during immunotherapy (Fig. 6) [20,108,109]. Al-though such negative feedback may slow down as tumor resistance to ferroptosis gradually develops, it will be ir-reversible once therapeutic resistance is rooted within the genome of the cancer cells [104]. This may be an im-portant cause for iron-induced immunotherapeutic resis-tance in PDAC [38,110]. However, given the cancer type-dependent property of DAMP production, whether such a mechanism of immunologic tolerance exists in other types of malignancies is still unclear. While further efforts are clearly required to veraciously test this hypothesis, it is very likely that the macrophage-ferroptosis axis can provide key insight into mechanisms that govern the development of immunotherapeutic resistance. Rebalancing macrophage-ferroptosis crosstalk to favor M1 macrophage polarization may provide a necessary conceptual framework to under-

Table 1. Summary of the four types of ferroptosis-inducing agents.

Type	Agent	Mechanism	Application	References
Type I	erastin	inhibits system Xc$^-$; targets VDAC, ACSL4 and p53	preclinical experiments	Dixon *et al*. [9]
	sorafenib	inhibits system Xc$^-$	clinical treatement for several advanced cancers	Sun *et al*. [115]
	sulfasalazine	inhibits system Xc$^-$	clinical treatement for lymphoma, SCLC and PC	Gout *et al*. [116]
Type II	RSL3	inactivates GPX4	preclinical experiments	Sui *et al*. [111] Yang *et al*. [117]
	altretamine	inactivates GPX4	clinical treatement for OC	Woo *et al*. [112]
Type III	FIN56	depletes GPX4 and CoQ10	preclinical experiments	Sun *et al*. [118]
	statins	depletes GPX4 and CoQ10	undergoing clinical trials for HCC and AML	Viswanathan *et al*. [119]
Type IV	FINO2	increases the level of labile iron; inactivates GPX4	preclinical experiments	Gaschler *et al*. [113]
Others	ferroptocide	depletes thioredoxin	preclinical experiments	Llabani *et al*. [114]

CC, Hepatocellular carcinoma; AML, Acute myeloid leukemia; SCLC, small-cell lung cancer; OC, ovarian cancer; PC, prostate cancer.

stand, and ultimately overcome, the current therapeutic resistance dilemma.

5. Ferroptosis Inducers in Clinical and Preclinical Trails

Recently, drugs targeting ferroptosis have shown promise as effective anti-cancer therapeutics. Currently, ferroptosis inducers can be divided into 4 types based on targets and mechanisms (Table 1, Ref. [9,111–119]). Type I ferroptosis inducers directly bind to subunits of system Xc$^-$ and inhibit cystine import into the cell. The most employed type I inducer is erastin, which was the first identified as an inducer of ferroptosis inducer. This small compound was found in a screen for selective tumor-killing agents for RAS-mutation bearing cancer cells, but was later found to mediate a novel form of necrotic RCD termed ferroptosis [9]. Erastin is a multifunctional ferroptosis inducer that not only inhibits cystine transport by system Xc$^-$, but can also target VDAC, ACSL4, and p53 as discussed above [27]. Despite its efficiency in triggering ferroptosis, erastin has poor water solubility and stability within physiological environments, rendering it unqualified for clinical application [27].

Sorafenib is currently the FDA-approved ferroptosis inducer for treatment of certain advanced cancers [120]. Unlike other type I ferroptosis inducers, sorafenib acts as a multi-kinase inhibitor which inactivates kinases essential for system Xc$^-$ activity [121]. Compared to erastin, sorafenib has favorable potency and appropriate pharmacokinetic properties. Another clinically approved agent, termed sulfasalazine, can inhibit system Xc$^-$ in a similar manner as erastin. However, since the correlation between sulfasalazine's molecule structure and pharmacological effects still remains unclear, it has yet to be determined whether sulfasalazine's major therapeutic effects rely on ferroptosis induction or occur through other mechanisms [122].

Type II ferroptosis inducers inhibit the cellular antiox-

idant system by directly inactivating GPX4, and drugs of this type include RSL3 and altretamine. Of these, RSL3 is widely used as a complement to erastin in parallel experimental designs [111], while altretamine is clinically approved for treating ovarian cancer [112]. Slightly different from type II ferroptosis inducers, the type III ferroptosis inducers deplete GPX4 by mediating the degradation of GPX4 and CoQ10, and drugs of this type are FIN56 and the statins. It remains unclear whether GPX4 depletion is caused by statins or via statin-mediated decreases in cholesterol [6]. Further, type IV ferroptosis inducers can accelerate lipid peroxidation by increasing cellular levels of labile iron. Of note, FINO2, a type IV ferroptosis inducer, can synergistically trigger the oxidation of labile iron and inactivation of GPX4 [113]. Finally, some atypical ferroptosis inducers can target the non-classical pathways that trigger ferroptosis. One such drug is ferroptocide which targets thioredoxin to produce excessive ROS [114]. Taken together, this evidence indicates that targeting ferroptosis can provide an innovative and promising therapeutic strategy for malignant tumors as a complement to traditional chemotherapy.

6. Promoting Tumor Ferroptosis with M2-to-M1 Reprogramming

TAMs are enriched with diverse types of signaling receptors that are sensitive to glycolipids and cytokines present within the TIME, and these provide TAMs with great metabolic and functional plasticity [123,124]. It is well undeerstood that macrophage polarization is a reversible process with modulators from the local microenvironment intervening in the reprogramming process at multiple levels [125,126]. To reprogram M2-like TAMs to favor activation of tumor ferroptosis, a series of bioengineered nanoparticles was developed to target various pathways. In brief, currently-developed nanoparticles targeting TAM repolarization can be divided into three main subtypes:
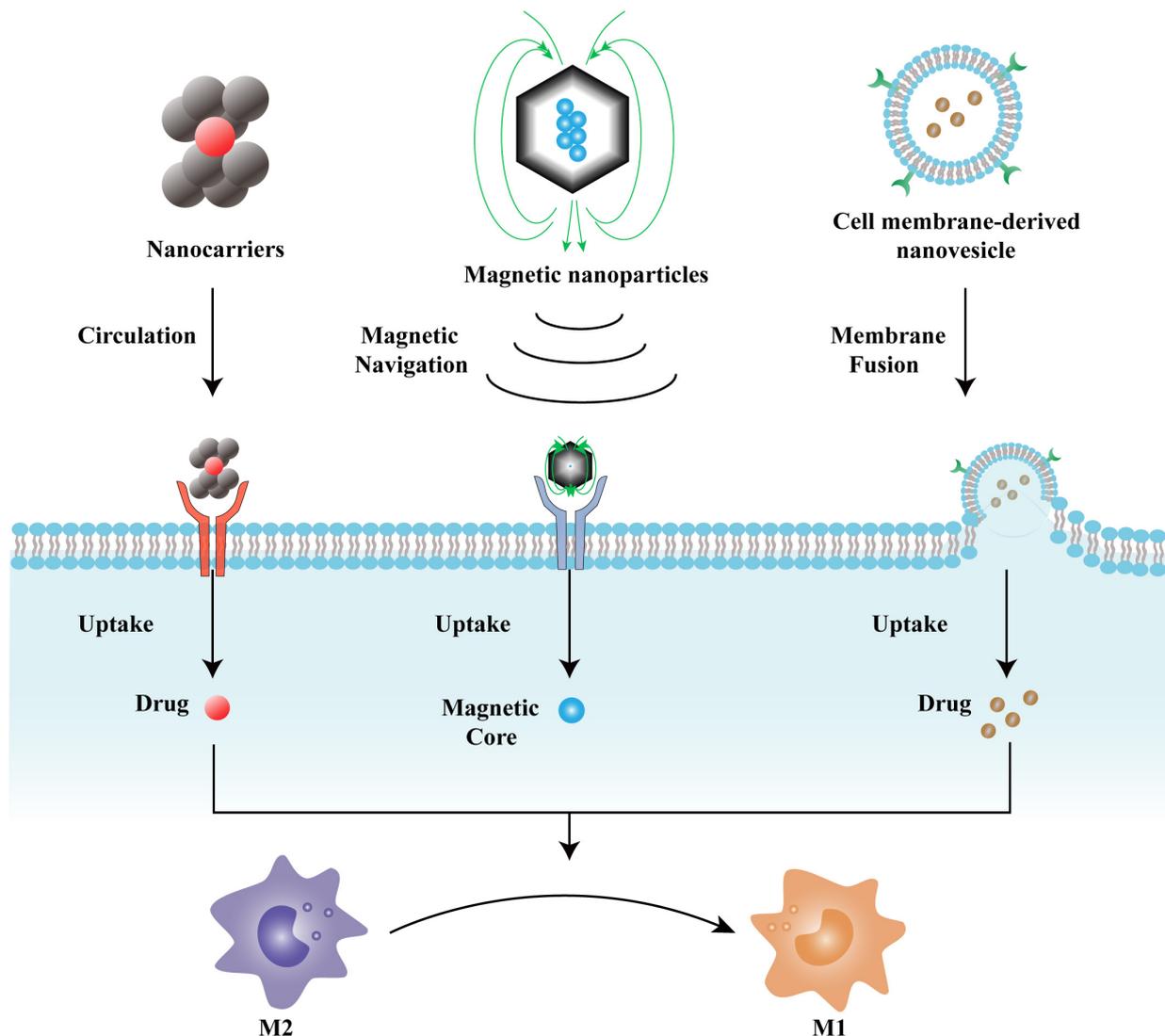
Fig. 7. Structural and functional characteristics of TAM repolarization-targeting nanoparticles. Nanocarriers can be specifically recognized and uptaken by TAMs, where the drug molecules are released to exert their effects. Magnetic nanoparticles can be efficiently delivered via magnetic navigation and can be captured through coat/receptor interaction. Cell membrane-derived nanovesicles are naturally compatible with the structure of lipid bilayers, and, as such, can be easily uptaken by TAMs.

nanocarriers, magnetic nanoparticles, and cell membrane-derived bionic nanoparticles (Fig. 7).

Nanocarriers work by targeted drug delivery or tumor-killing nano-scale effects such as cytotoxic photodynamic and photothermal effects [127,128]. These drugs are usually designed with unique geometrical structures which can be specifically recognized and uptaken by TAMs rather than by other normal tissues, thereby exhibiting low general cytotoxicity and high biocompatibility [129,130]. For example, Fu and colleagues [131] developed a novel nanoparticle using a polymer of poly (styrene-co-maleic anhydride) (PSMA), and a polymer of poly [2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene] (PPV). This nanoparticle exhibited high affinity for TAMs and can repolarize TAMs into the tumoricidal M1 phenotype, likely owing to its lipopolysaccharide-like structure. In addi-

tion, by taking advantage of the acidic metabolic feature of the TIME, Xiao's team [132] ingeniously designed a micellar nanodrug with M2-targeting peptides hidden in the pH-sheddable polyethylene glycol (PEG) corona so that the repolarizing drugs inside in nanoparticle can only target macrophages within the TIME. Furthermore, Qian *et al.* [133] developed an efficient siRNA and CpG oligonucleotide (ODN) delivery system that facilitates TAM remodeling by directly silencing M2 macrophage-related genes by using a nucleic acid step-wise, self-assembly technique. Inspiringly, CpG-siRNA-tFNA could effectively trigger proinflammatory cytokine secretion and activate NF-kB signal pathway, thus inducing dramatic antitumor immune responses in 4T1-bearing mice.

Magnetic nanoparticles with functional coatings are the next-generation version of traditional nanocarriers.

These nanoplatforms are endowed with integrative functions such as magnetic navigation-based targeted delivery, nano-scale therapeutic effects, and use in magnetic resonance imaging [134–136]. Iron oxide-based magnetic nanoparticles can be released as free iron ions which can subsequently directly activate tumor ferroptosis [136, 137]. In 2020, Rao's group [138] developed novel magnetic nanoparticles coated with genetically engineered cell-membranes (gCM-MNs) which can precisely target the TIME through the guidance of magnetic navigation. Not only can gCM-MNs block the CD47-SIRPα pathway which participates in tumor immune evasion, but they can also promote TAM reprogramming within the magnetic core. Furthermore, the engineered cell-membrane shell can protect the magnetic nanoparticles from immune clearance, thereby enhancing their systemic circulation and tumor accumulation.

Composed of phospholipid bilayers, saccharides, and proteins, the cell membrane is naturally compatible with the *in vivo* environment and possesses a remarkable affinity to homogeneous cells [139]. Therefore, cell membrane-derived bionic nanoparticles are the current optimal nanoplatform for targeted therapy. Of note, some M1-derived exosome mimics can simultaneously act as both an M2 repolarizer and ferroptosis inducer, providing an ideal biomaterial to achieve the perfect combination of these two anti-cancer properties. The case in point is CCR2(+)-Fe-M1-nanovesicles (Nvs), which are bioengineered with up-regulated C-C motif chemokine receptor 2 (CCR2) expression and are loaded with Fe_3O_4 nanoparticles [140]. Acting through the CCR2-CCL2 axis, CCR2(+)-Fe-M1-Nvs can be recruited to metastatic sites, where Fe_3O_4 nanoparticles and M1-related modulators synergistically facilitate tumor ferroptosis by increasing TAM repolarization. Moreover, Wei *et al*. [141] developed mannose-modified macrophage-derived microparticles that with loaded metformin that can both reset TAM polarization as well as enhance the performance of anti-PD-L1 therapy. Similarly, a cancer cell membrane-camouflaged gold nanocage loaded with doxorubicin and l-buthionine sulfoximine can synergistically evoke both effective ferroptosis and TAM repolarization [142].

Despite their great promise, there are great challenges to the clinical translation of these nanoparticles. For one, it is hard to guarantee the specificity of observed therapeutic effects in large-scale clinical cohorts due to individual variation and tumor heterogeneity. For another, techniques used to prepare nanomedicines in the lab must be improved to meet the demands and requirements for large-scale production [143]. In this context, more effort is needed in the field of translational medicine to equip these nanodrugs with critical properties such as stable therapeutic effects and higher biosafety.

7. Conclusions and Perspectives

Despite great progress made in exploring independent roles of TAMs and ferroptosis in tumor immunotherapy, there are few studies focused on the integrative effects of macrophage-ferroptosis crosstalk in tumor immunotherapy. In fact, TAMs and ferroptosis are coordinately regulated, and thus co-regulate response to tumor immunotherapy. In this review, we profiled the molecular landscape of macrophage-ferroptosis crosstalk in the TIME with a focus on the different roles of M1 and M2-like TAMs. We also discussed the significant roles for macrophage-ferroptosis crosstalk in immunotherapeutic tolerance, and summarized the latest advances in treatment strategies that seek to leverage ferroptosis and TAM repolarization. Although these combined strategies have demonstrated dramatic anti-tumor effect, related clinical studies are still in their infancy and the detailed mechanisms governing macrophage-ferroptosis crosstalk still remain largely unexplained. Thus, further efforts are needed to better understand the signaling network that links TAMs and ferroptosis, and to promote the clinical translation of treatment strategies that seek to leverage macrophage-ferroptosis signaling for clinical benefit. We believe that synergistic strategies that target macrophage-ferroptosis crosstalk will dramatically improve the clinical application of tumor immunotherapy in the future.

Author Contributions

ZZ and WY together conceptualized the idea. BX and NH collected reliant literatures. ZZ integrated useful information and wrote the manuscript. ZG and WB created the figures. BS and WY offered advice on polishing the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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