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Tumor Cell Ferroptosis as a "Game Changer" in the Tumor Immune Microenvironment

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Abstract: The tumor immune microenvironment (TIME) is a critical determinant of tumor progression, response to treatment, and overall patient prognosis. An intricate network of cellular and molecular interactions within the TIME regulates immune responses against tumors. Recently, ferroptosis, a novel form of regulated cell death characterized by an overload of intracellular iron and lipid peroxidation, has emerged as a significant player in the TIME. Tumor cells are naturally susceptible to ferroptosis, and tumor cells undergoing ferroptosis secrete damage-associated molecular patterns, lipid metabolites, ferroptosis-related proteins, as well as "find me" and "eat me" signals, which interacts with immune cells in the surrounding tumor microenvironment, thus affecting the growth and development of cancer. This review article delves into the role of ferroptosis in modulating the tumor immune landscape, highlighting its potential as a "game changer" in cancer therapy. Ferroptosis in tumor cells can alter the TIME by modulating immune cell infiltration and activation, affecting cytokine and chemokine profiles, and influencing antigen presentation. We dissect the latest findings on the mechanistic interplay between ferroptosis and immune cells, including macrophages, dendritic cells, and T cells. Furthermore, we explore how targeting ferroptosis pathways may pave the way for new therapeutic strategies, particularly in combination with current immunotherapies. This comprehensive review provides insights for researchers and clinicians alike, aiming to harness the potential of ferroptosis to transform the therapeutic landscape of oncology.

1. Ferroptosis vulnerability of cancer cells

Cancer cells are manifested by the reprogramming of energy metabolism as well as the instability and mutations of its genome. First, mitochondrial dysfunction, upregulation of NOX1 and NOX4, as well as alterations of antioxidant enzymes collectively contribute to elevated levels of ROS in cancer tissues. Specifically, mitochondrial malfunction resulting from the damage of its electron transport chain is a rich source of O2 ·- [1]. In addition, despite OXPHOS being the most efficient way of ATP biosynthesis, many cancer cells have undergone a mitochondrial dysfunction-related shift to aerobic glycolysis (known as metabolic reprogramming), wherein they mainly generate ATP from cytosolic aerobic glycolysis coupled to lactate fermentation. This metabolic re-

programming in cancer was famously discovered by Warburg and Cori in the 1920s [2,3] and has been suggested as an early step of carcinogenesis, which can occur before the appearance of a hypoxic tumor environment [4]. Warburg effect is known as a cancer cell means to evade toxic levels of ROS production, whereas its maintenance requires higher glucose uptake and elevated metabolic activity making tumor cells nevertheless heavily reliant on the antioxidant machinery and maybe even more susceptible to oxidative stress [5]. Therefore, the efficient clearance of accumulated intracellular ROS in proliferative cancer cells is essential for the establishment of tumors [6].

Regarding the metabolic characteristics, therapy-refractory cancer cells in some states may exhibit remarkably high ferroptosis sensitivity [7]. For example, cancer cells with mesenchymal phenotype are featured by ZEB1, ELOVL5, and FADS1 upregulation, which lead to the plethora in PUFAs and a strong reliance on GPX4, and dedifferentiated melanoma cell subtypes became highly susceptible to ferroptosis when PUFAs accumulate and GSH is depleted [7]. Similar to this, certain types of cancer with distinct metabolic traits (e.g., triple-negative breast cancer (TNBC), clear cell renal cell cancer (CCRCC), and non-euroendocrine small cell lung cancer (SCLC)), exhibit unexpected ferroptosis sensitivity. Of note, various defense systems collectively contribute to the suppression of ferroptosis, striking a balance between pro- and anti- ferroptosis systems. Once the balance is upset (i.e., one ferroptosis defense system is inhibited or depleted), cancer cells become highly dependent on other defense mechanisms available, and vulnerable to ferroptosis triggered by other defense mechanisms. For example, TNBC cells may increase PUFA and LIP levels while suppressing the anti-oxidative GPX4-GSH axis, favoring ferroptosis onset [8].

2. Ferroptotic cancer cell as a “game changer” in tumor immune microenvironment

Solid tumors are more than clusters of malignant cells; they are sophisticated “organs” that comprises both cancer cells and non-cancerous cells, especially immune cells, which plays a vital role in maintaining the defense against pathogens, homeostasis of organs, as well as anti-tumor responses. Tumor immune microenvironment (TIME) represents the interactions among malignant and non-malignant cells (e.g., immune cells, the tumor vasculature and lymphatics, fibroblasts, pericytes and adipocytes), which is fueled by a complicated and dynamic molecular network of extracellular enzymes, cytokines and chemokines. The extracellular matrix (ECM), on the other hand, denotes a heterogeneous yet well-organized scaffold of macromolecules, acting as a mechanical framework for these cells and regulator for the molecular signals and enzymes to maintain cell functions.

During the development of tumor cells, specific tumor immune microenvironments are formed, which is a complex environment regulated by multiple factors, including both immune cells and cytokines that promote or inhibit immune responses, whose interplay maintains the stability of the tumor immune microenvironment. When one of those factors changes, leading to a disruption of the microenvironmental homoeostasis, immune cells will be affected accordingly, followed by a re-balance of the overall immune environment [9]. A multitude of factors are known to cause perturbations in TIME, such as oxygen or electrolyte concentration, nutrient levels, environmental pH, or tissue metabolites, etc., which ultimately reshape TIME by inducing the development, differentiation, and proliferation of immune cells. Ferroptotic cancer cells are rich sources of cell damaging products and ferroptosis-specific products, which may interact with immune cells and affect tumor formation, growth, metastasis and sensitivity to anti-cancer therapies [10].

2.1 Damage-associated molecular patterns

Immunogenic cell death (ICD), defined as a cell death method that causes an immunological

response to dead-cell antigens, particularly when they originate from cancer cells, has developed in recent years [11]. This approach was originally proposed in relation to chemotherapy for cancer [12], in light of multiple clinical studies revealing that tumor-specific immune responses might impact the efficacy of anti-cancer therapy employing traditional cytotoxic medicines. These DAMPs may interact with pattern recognition receptors, phagocytosis receptors, RAGE (receptor for advanced glycation end products), toll-like receptor 2 (TLR2), toll-like receptor 4 (TLR4), and purinergic receptors located on the membrane of immune cells to enhance the immune response and cytotoxic T lymphocyte-driven adaptive immunity [13,14]. In a series of in vitro and in vivo studies, Efimova et al. found that early ferroptotic cells (one hour after RSL3) were able to stimulate the maturation of bone marrow-derived dendritic cells (BMDCs), whereas late ferroptotic cells (24 hours after RSL3) were unable to release HMGB1 and ATP and failed to stimulate BMDC differentiation [15].Their findings establish the involvement of ICD-inducing DAMPs after ferroptosis induction and offer the first proof that ferroptosis is in fact a type of ICD. However, it is not yet clear how ferroptotic cancer cells affect antitumor immunity. Therefore, studies into how the immunogenicity of ferroptotic tumor cells affects the efficacy of anticancer therapies have important clinical and scientific ramifications.

A DNA-binding nuclear protein of 215 amino acids, HMGB1 is generated both actively following cytokine stimulation and passively after cell death. It has also been connected to a number of inflammatory illnesses and serves as the model DAMP molecule[16]. As a key protein required for the immunogenicity of cancer cells, HMGB1 is produced by cancer cells during ferroptosis in a manner dependent on autophagy [17]. Wen et al. claim that ferroptotic cells' production of HMGB1 can increase the expression of tumor necrosis factor (TNF) in macrophages. Additionally, a mouse model of experimental pancreatitis was recently created by Liu and colleagues, and the ferroptotic tissue showed an increase in HMGB1 and a leukocyte infiltration.

Additionally, photodynamic therapy (PDT) has been discovered to be a novel catalyst for the ferroptosis of cancer cells, which intriguingly emits CALR/HMGB1/ATP and subsequently promotes the maturation, phagocytosis, and activation of macrophages (146). These studies have emphasized the relationship between ferroptosis and ICD and shed light on the function of ICD induction in enhancing immunity after ferroptosis induction. As a result, ATP and HMGB1 are immunogenic signals that contribute to ferroptosis, which has the potential to reduce immunological tolerance via the CD40-ATP-P2X7 pathway [18,19].

Interleukin-33 (IL-33) is a member of the IL-1 family and is first thought to function as an alarmin in mucosal immunity. Martin-Sanchez and colleagues found an increase in IL-33 in the kidney and plasma of an acute kidney injury murine model experiencing ferroptosis, which can be inhibited by a ferroptosis inhibitor, giving important evidence that ferroptosis occurred in a mouse model of acute renal injury [20] . Because of its substantial pro-inflammatory action on its release, IL-33 is considered a specific necroptotic DAMP [21].

Calreticulin (CALR) is an important component of the peptide-loading complex (PLC), a transitory, multisubunit membrane complex in the endoplasmic reticulum (ER) that coordinates peptide translocation with proper MHC Class I molecule loading [22]. CALR is known to be released from the plasma membrane when cells are stressed or dying, and it governs the interaction between stressed or dying cells and immune cells in addition to playing a vital role in reticular homeostasis and antigen presentation [23]. The so-called "adjuvanticity," or the capacity of stressed or dying cells to stimulate immune cells by producing adjuvant-like signals, is also known to be regulated by CALR [13]. Calreticulin exhibits a strong antitumor effect in ferroptotic cancer cells by moving to the cell surface and increasing the efficiency of phagocyte phagocytosis. These results are consistent with the idea that ferroptotic cells can release signals that allow immune cells to locate them.

Some DAMP combinations, which are relevant to both ferroptotic and apoptotic ICD, such as annexin A1 secretion, type-1 interferon release, and calreticulin surface exposure, may be shared by various ICD [13], and further research is required to clarify the comprehensive DAMP secretion mode of ferroptotic ICD. It has been proposed, however, that particular modes of DAMP release that have not yet been defined may be implicated in different types of ICDs. It is therefore vitally needed to pay much attention on the hypothesis that different cell death patterns, such as apoptosis, ferroptosis, and necrosis, may cause ICD via multiple pathways despite sharing just a small portion of DAMPs. Henceforth, ferroptosis is proposed as a potential type of immunogenic cell death in light of the aforementioned [18,19,24]. In contrast to other cell death modes, such as apoptosis or necroptosis, ferroptotic cancer cells were found to be unable to elicit immune protection despite DAMP and cytokine production, and ferroptotic DCs failed to resist tumor formation, suggesting that ferroptosis had a detrimental effect on the adaptive immune response and antigen-presenting cells, which may have an impact on cancer immunological treatments and limit the potential therapeutic applications of ferroptosis [25]. To further comprehend ferroptosis' role in cancer treatment, more study is required to determine experimentally whether it is immunogenic.

2.2 Oxidized lipids

Ferroptotic cells generate a variety of oxidative by-products of arachidonic acid (AA), which may serve as potential cues to regulate lipid mediators and antitumor immunity [19]. In order to modulate the immune response against malignancies, lipoxygenase, or LOX, a ferroptotic signal, is crucial for the oxidation of esterified PUFAs [26]. It also induces the release of comparable signals from ferroptotic cells. When GPX4 is depleted, ferroptotic cells in particular can emit eicosanoids such 5-HETE, 11-HETE, and 15-HETE [27]. Increased GPX4 activity reduces pro-inflammatory activity produced by the NF-κB pathway in cells activated by TNF or IL-1 and prevents the production of pro-inflammatory lipid mediators like LTB4, which is essential for carcinogenesis [28].

Either through the direct catalysis of lipoxygenase on SN-2 fatty acids or through the re-esterification of free eicosanoids, a family of substances referred to as esterified eicosanoids are produced [29]. Growing interest in its biological function has led to speculation that it may function similarly to free eicosanoids, which act as immunoregulatory signaling molecules. After examining the lipid components of the ferroptotic cells, it was discovered that a variety of doubly and triply oxidized arachidonic acids, including albumin phosphatidylethanolamine (PE), may be produced under the catalysis of arachidonic acid 15-lipoxygenase (ALOX15) [30,31]. Previous research has employed lysophospholipids, a form of PE hydrolysis product, to explain why apoptotic cells attract APC [32]. Additionally, it has been shown that increasing the amount of AA given to cancer cells undergoing ferroptosis accelerated the production of eicosanoids, which in turn improved antitumor immunity [19]. Esterified eicosane also plays a role in the immunological response. ALOX-15 generated droplets have been demonstrated to have an impact on several immunological processes, including dendritic cell (DC) maturation and adaptive immune responses. By stimulating the transcription factor Nrf2, oxidized phosphatidylcholine prevented DC maturation and prevented the differentiation of T helper 17 (TH17) cells [33].

2.3 Protein products

As was already noted, cells going through ferroptosis secrete certain proteins that have been found to promote tumor growth by suppressing immune cells. Given that the expression of KRAS in TAMs is inversely linked with the clinical outcome of pancreatic cancer [34], it is a promising target protein for tumor immunotherapy. It has been demonstrated that ferroptotic cancer cells emit a significant amount of mutant KRAS protein, or $KRAS^{G12D}$, which macrophages can ingest using

RAGE (an advanced glycation end-product that is anchored in the cell membrane as a particular receptor) [34,35]. $KRAS^{G12D}$ has an anti-tumor effect on macrophages by inducing fatty acid oxidation and promoting the polarization of tumor-associated macrophages to the M2 phenotype [34]. Recently, Stearoyl-CoA desaturase-1 (SCD1) and fatty acid binding protein (FABP4) are implicated in the recurrence of tumors by reducing the sensitivity of cancer cells to ferroptosis, according to a recent study [36]. SCD1 released from cancer cells promotes MUFA biosynthesis, and FABP4 enhances the generation of lipid droplets under hypoxic conditions, both of which prevents tumor cells from undergoing ferroptosis and promotes tumor migration [36].

2.4 Prostaglandin E2

As discussed before, AA is converted into a range of lipid metabolites upon activation, including prostaglandin E (PGEs) via cyclooxygenases (COXs) and hydroxydodecanoic acids (HETEs) via LOXs [26]. Importantly, it has been demonstrated that prostaglandin E2 (PGE2), a bioactive lipid modulator, has a wide range of biological effects on anti-tumor immunity [37-39]. PGE2 prevents natural killer (NK) cells from producing the chemokines CC chemokine ligand 5 (CCL5) and chemokine lymphotactin as well as from accumulating classical type 1 dendritic cells [39-41]. Furthermore, PGE2 specifically inhibits the activity of cytotoxic T cells, which can have an impact on adaptive immunity [42].

Cancer cells in ferroptotic state may affect tumor immunity by secreting PGE2. The formation of PGE2 during chemotherapy, which might be inhibited by PGE2 inhibition, boosted a tumor's resistance to treatment, according to a recent study [43]. Contrarily, chemotherapy-treated tumor cells would produce more PGE2, which would in turn boost the growth of tumor cells that are previously vulnerable to ferroptosis. With such presumptions, it becomes difficult to balance the immunosuppressive effects of PGE2 produced by ferroptosis-sensitive cells with the anticancer immunological responses brought on by ferroptosis [29,44,45].

2.5 "Find me" and "eat me" signals

Previous study showed that apoptotic cells may release a range of signals when they die, including "find me" and "eat me" signals that help immune cells communicate with apoptotic cells [46]. Recent studies have demonstrated a similar crosstalk between ferroptotic cells and immune cells, in which ferroptotic cells generate a "find me" signal that involves lipid mediators and can help immune cells locate ferroptotic cells that are dead or dying. Such signals can help macrophages identify and effectively eat ferroptotic cancer cells in vitro [47]. For example, 1-steaoryl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine (SAPE-OOH) is found to be a "eat me" signal on the surface of ferroptotic cell membranes that boosted macrophage phagocytic activity by targeting TLR2 [48]. Nonetheless, few studies reported the biosynthesis and immunoregulatory role of ferroptotic "find me" and "eat me" signals, although these signals in apoptosis have already been intensively studied.

3. Conclusions and future perspectives

Cancer cells are more vulnerable to ferroptosis due to elevated ROS levels [1]. Ferroptotic cancer cells feature morphological, biological, genetic and protein alternations, which has been intensively studied in a multitude of previous studies. Considering the extraordinary complexity and heterogeneity of TIME, it is of necessity to investigate the impact ferroptosis cancer cells have on immune cells in the TIME. Collectively, we propose that cancer cell ferroptosis may promote at least four possible outcomes in the TIME: (A)promote immunogenicity by secreting DAMPs as a

potential ICD; (B) mediate the maturation and differentiation of immune cells by releasing immuno-modulatory signaling lipid molecules; (C) upregulate and release proteins which suppress the function of immune cells; (D) regulate both natural and acquired immunity by secreting PGE2, (E) promote the engulfment of ferroptosis cells by macrophages due to the release of "find me" and "eat me" signals (refer to **Figure 1**). Nevertheless, there is still a lack of corresponding research to clarify whether there are differences in the substances secreted by ferroptotic cancer cells induced by different FINs. Future studies are also required to distinguish the chemicals released by different types of cancer cell undergoing ferroptosis. Considering that cancer cell ferroptosis has the possibility to change the "game" or even turn the situation around, thus, it will be of great necessity in future work to not only develop ferroptosis-inducing drugs, but also further illuminate the impact ferroptotic cancer cells have on the surrounding TIME, in order to fully harness the potential of ferroptosis for cancer treatment.

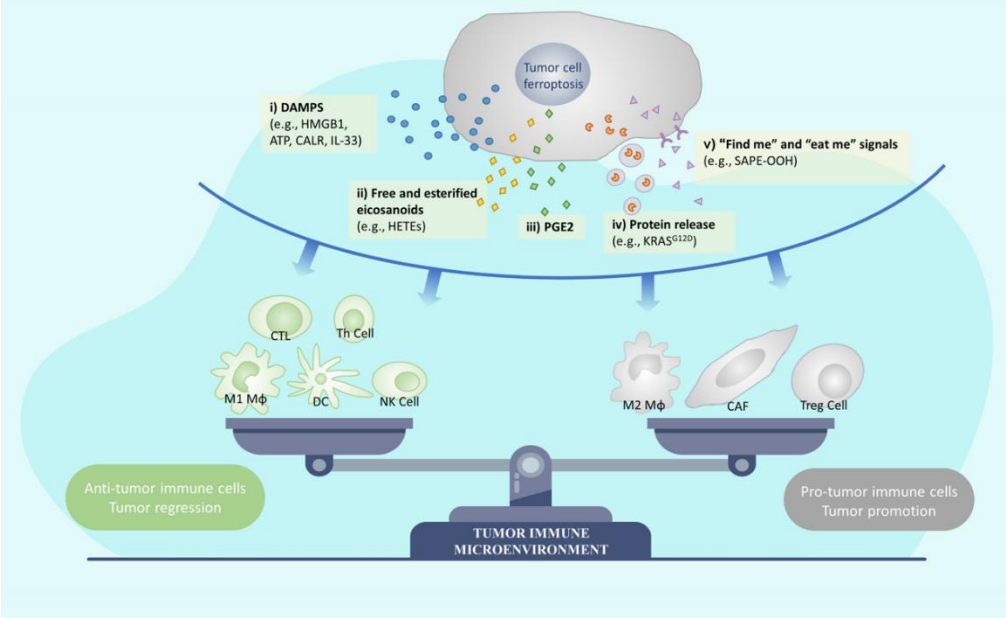

Figure 1: Tumor cell ferroptosis as a "game changer" in the tumor immune microenvironment.

Author Contributions

Z.W. took the lead in writing the manuscript. D.L. and Z.W. discussed the contents and edited the manuscript. Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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