communications biology

Review article

https://doi.org/10.1038/s42003-024-07180-8

Ferroptosis as a new tool for tumor suppression through lipid peroxidation

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As a newly defined type of programmed cell death, ferroptosis is considered a potent weapon against tumors due to its distinct mechanism from other types of programmed cell death. Ferroptosis is triggered by the uncontrolled accumulation of hydroperoxyl polyunsaturated fatty acid-containing phospholipids, also called lipid peroxidation. The lipid peroxidation, generated through enzymatic and non-enzymatic mechanisms, drives changes in cell morphology and the destruction of membrane integrity. Here, we dissect the mechanisms of ferroptosis induced enzymatically or non-enzymatically, summarize the major metabolism pathways in modulating lipid peroxidation, and provide insights into the relationship between ferroptosis and tumor suppression. In this review, we discuss the recent advances of ferroptosis in tumor microenvironments and the prospect of potential therapeutic application.

In 2012, Dixon et al. found that the inhibition of cystine uptake by either the cystine/glutamate antiporter (system xc^-) inhibitor erastin, or by raising cellular glutamate concentration can lead to an iron-dependent oxidative stress-driven cell death, which they termed ferroptosis[1]. Afterward, the core regulatory role of glutathione peroxidase 4 (GPX4) in modulating cell sensitivity to ferroptosis was identified[2]. Actually, the involvement of different GPX4 isoforms in protecting against oxidative stress-induced cell death had been reported earlier. GPX4 possesses three physiological isoforms located at distinct cellular compartments: nuclear (nGPX4), cytoplasm (cGPX4), and mitochondria (mGPX4). nGPX4 is responsible for the structural integrity of mammalian sperm chromatin[3,4]. cGPX4 is the one we commonly investigated, which serves as a critical factor against lipid peroxidation[5,6]: *Gpx4* knockout causes embryonic lethality; tissue-specific *Gpx4*-deficient mice demonstrate a series of pathological phenomena, including acute hepatic injury, neurodegeneration phenotype, and immunity failure[5,7–9]. In addition, mGPX4 also limits cell death induced by mitochondrial reactive oxygen species (ROS)[10]. Thus, as a housekeeping gene, GPX4 appears to be a cornerstone for maintaining cellular homeostasis. Interestingly, according to Nomenclature Committee on Cell Death, the official definition of *ferroptosis* is "A form of regulated cell death initiated by oxidative perturbations of the intracellular microenvironment that is under constitutive control by GPX4 and can be inhibited by iron chelators and lipophilic antioxidants"[11], from which the concept of ferroptosis expends to the three major modulating pathways: oxidative stresses, lipid peroxidation, and ferroptosis defense pathways (Fig. 1).

The phospholipids containing polyunsaturated fatty acyl moieties (PUFA-PLs) are the major substrates for lipid peroxidation, which have been repeatedly reported to be involved in human diseases, especially cancer[12]. Nevertheless, with the development of lipidomics and phospholipidomics techniques, more and more types of lipids with crucial roles in ferroptosis have been revealed[13]. This review summarizes the mechanisms by which cells, through remodeling fatty acid (FA) diversity and the metabolism of PUFA-PLs and MUFA-PLs (phospholipids containing monounsaturated fatty acyl moieties), modulate the synthesis of specific phospholipids to dictate cell sensitivity to lipid peroxidation. Moreover, we focus on providing insights into the mechanism of lipid peroxidation through enzymatic and non-enzymatic routes and describe their critical roles in tumor suppression, tumor microenvironment (TME), and tumor therapy[14].

Ferroptosis defense systems parallel with the GSH/GPX4 pathway

Since the discovery of ferroptosis, numerous studies have revealed that the regulation of cystine uptake and GSH synthesis determines cell vulnerability to ferroptosis[15–18] (Fig. 2). The mechanisms of ferroptosis suppression are extensively studied; several fundamental metabolic pathways, beyond the initially discovered GSH/GPX4 axis, play essential roles in lipid peroxidation elimination and ferroptosis defense. Most importantly, the different dependence of tumor cells on the anti-ferroptosis pathways provides us with more choices in tumor therapy by targeting the cell vulnerability to

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ferroptosis (Fig. 2). We briefly summarize the basic mechanisms of anti-ferroptosis pathways, which act in a GPX4-independent manner. The readers are referred to the review[19] for detailed mechanisms of these pathways we introduced here.

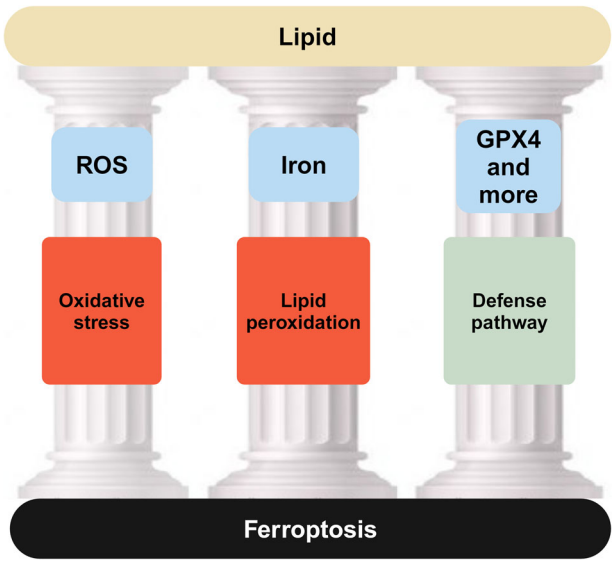

Fig. 1 | Major pathways in modulating ferroptosis. Oxidative stresses, lipid peroxidation, and ferroptosis defense pathways are three fundamental characteristics of ferroptosis. The ROS stresses generated by hydroxyl radicals or alkoxyl radicals initiate lipid peroxidation in the presence of iron. Ferroptosis defense pathways, including GPX4 or multiple GPX4-independent pathways, eliminate the peroxidized lipids and protect the cells from ferroptosis. The balance between pro- or anti-lipid peroxidation determines the cell fate and influences pathological diseases. ROS, reactive oxygen species; GPX4, glutathione peroxidase 4. Created with BioRender.com.

CoQ_{10}

CoQ_{10}, also called ubiquinone, is a well-known intermediate metabolite participating in the electron transport chain (ETC) by transporting electrons from complexes I and II to complex III[20]. CoQ_{10} reduction-mediated anti-ferroptosis effect is the earliest reported pathway as the second-line ferroptosis defense independent of GPX4[21,22]. The ferroptosis suppressor protein 1 (FSP1), encoded by the *AIFM2* gene, reduces the oxidized form of CoQ_{10} using reduced nicotinamide adenine dinucleotide (phosphate) (NAD(P)H). As a type of radical-trapping antioxidant (RTA), reduced CoQ_{10} directly reacts with and transfers the electron to peroxidized phospholipids to eliminate the excessive lipid peroxidation and subsequently inhibit ferroptosis[21,22]. Additional study revealed that the FSP1-mediated CoQ_{10} mainly happens at the plasma membrane, while another CoQ_{10} reductase, dihydroorotate dehydrogenase (DHODH), can also catalyze the reduction reaction of CoQ_{10} to prevent the accumulation of lipid peroxidation in mitochondria[10]. These studies highlight the defensive role of CoQ_{10} in different subcellular compartments. Both FSP1 and DHODH are valuable targets in tumor treatment: FSP1 expression positively correlates with ferroptosis resistance across multiple cancer cell lines[23]; DHODH inhibitor, brequinar, selectively suppresses the growth of tumors with low expression of GPX4 by inducing ferroptosis[10]. It is worth noting that Doll et al. identified iFSP1 (FSP1 inhibitor) as a potent drug in achieving anti-tumor effects[22]. Nakamura et al. recently identified a novel FSP1 inhibitor that impairs tumor growth through inducing phase separation of FSP1[24]. KRAS hijacks the FSP1/CoQ_{10} ferroptosis defense pathway and facilitates the initiation of tumor[25,26]. More and more studies indicate therapeutic strategies targeting FSP1/CoQ_{10} or DHODH/CoQ_{10}-mediated ferroptosis resistance in cancers.

Vitamin K

As an ancient vitamin, vitamin K was first identified around 1929[27]. In the following decades, vitamin K had been proven to be associated with blood coagulation through canonical vitamin K metabolism[28]. Although the potential of vitamin K in anti-oxidative stress was reported earlier[29], Mishima et al. first provided a deeper understanding of FSP1-mediated non-canonical

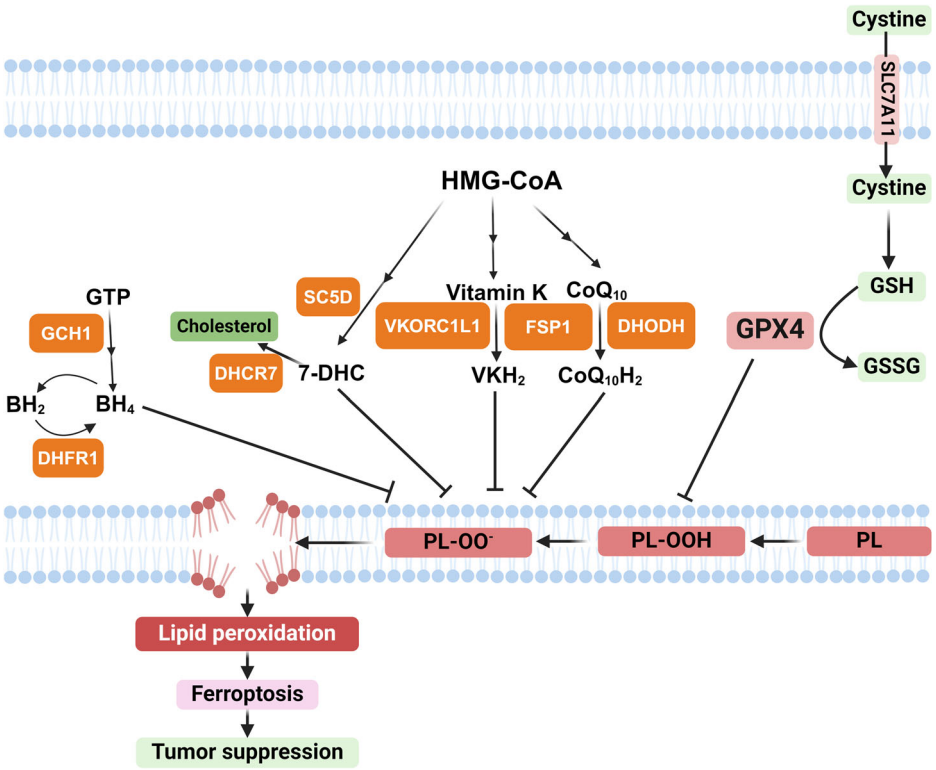

Fig. 2 | The defense pathways of ferroptosis. Schematic overview of the discovered defense systems of ferroptosis. SLC7A11 works as a transporter to uptake cystine, which is critical for GSH synthesis. GPX4 converts PLOOH to an alcohol form of phospholipids by utilizing GSH. FSP1 or DHODH inhibits peroxidized lipids via reducing CoQ_{10} to its reduced form, $CoQ_{10}H_2$. VKORC1L1 or FSP1 protects cells from ferroptosis by generating reduced vitamin K (VKH_2). In addition, 7-DHC, synthesized by SC5D, suppresses lipid peroxidation. DHCR7 contributes to ferroptosis regulation through metabolizing 7-DHC to cholesterol. Synthesis of BH_4, the other type of radical trapping antioxidant, is catalyzed by GCH1 and recycled by DHFR from BH_2. SLC7A11, solute carrier family 7 member 11; GSH, glutathione; PLOOH, phospholipid hydroperoxides; CoQ_{10}, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; DHODH, dihydroorotate dehydrogenase; VKORC1L1, vitamin K epoxide reductase complex subunit 1 like 1; 7-DHC, 7-dehydrocholesterol; SC5D, sterol-C5-desaturase; DHCR7, 7-dehydrocholesterol reductase; GCH1, GTP cyclohydrolase 1; DHFR, dihydrofolate reductase; BH_2, dihydrobiopterin; BH_4, tetrahydrobiopterin. Created with BioRender.com.

Box 1 | Open questions of ferroptosis research

1. What are the new types of lipid peroxidation substrates? Phosphatidylcholine and phosphatidylethanolamine have been reported as lipid peroxidation substrates during ferroptotic cell death; however, whether low-abundance lipids also play essential roles in inducing ferroptosis requires further investigation. The relationship between specific types of lipid peroxidation and tumor suppression is largely unrevealed.
2. What happens to the subcellular organelles during the ferroptotic processes? Lipid peroxidation happening at the plasma membrane is undoubtedly the limiting one in ferroptosis. Mitochondria and endoplasmic reticulum (ER) also contribute to the initiation of ferroptosis. Exploring the dynamic interplays among membrane-containing organelles will provide additional insights into the regulation of ferroptosis and tumor suppression.
3. Can ferroptosis be induced explicitly in tumors without affecting normal tissues? GPX4 is the most crucial switch in ferroptosis. Inactivation of GPX4, the housekeeping gene, inevitably causes damage to normal cells. The discovery of tumor-specific ferroptosis inducers that can effectively kill tumor cells without affecting normal cells is urgently needed.
4. What is the physiological ferroptosis inducer(s) for tumor suppression under immunocompetent conditions? The converse effects of ferroptosis inducers in treating tumors with or without a complete immune system discourage the application of ferroptosis in tumor therapy. Since ferroptosis is a type of cell death triggered by oxidative stresses, further studies are required to investigate how to induce tumor cell ferroptosis without any ferroptosis inducers by taking advantage of the oxidative stresses occurring during tumorigenesis.

vitamin K metabolism in modulating cells' sensitivity to ferroptosis[30–32]. The researchers identified FSP1 as an undescribed vitamin K reductase that sustains vitamin K hydroquinone (VKH_2) levels for ferroptosis defense. Moreover, Yang et al. identified that vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1), the vitamin K reductase among canonical vitamin K metabolism, can also repress ferroptosis by maintaining the reduced form of vitamin K[33]. Additionally, VKORC1L1 is a novel target of tumor suppressor p53. This study underscores the correlation between *p53* mutations and high VKORC1L1 expression in multiple types of cancers and repurposes the traditional anti-coagulant drug, warfarin, in cancer therapy[33,34]. The ferroptosis-suppressing roles of canonical and non-canonical vitamin K metabolisms endow ancient vitamin K with a novel function and elevate the investigation of vitamin K reductase to an emerging stage.

BH_2/BH_4

The GTP cyclohydrolase 1/tetrahydrobiopterin ($GCH1/BH_4$) axis acts as the other GPX4-independent defense pathway to prevent cells from ferroptotic cell death. GCH1 is the rate-limiting enzyme of BH_4 synthesis[35]. Through CRISPR-Cas9 activation screening, Kraft et al. identified GCH1 as a ferroptosis repressor. Mechanistically, BH_4 is an effective RTA that can inhibit ferroptosis through the same mechanism as reduced CoQ_{10}[36,37]. Moreover, after the reaction of BH_4 with peroxidized phospholipids, BH_4 is regenerated again by dihydrofolate reductase (DHFR) using NADH as cofactor[37]. Kraft et al. also found a negative correlation of GCH1 levels with ferroptosis sensitivity, particularly in breast and kidney cancers[36].

Other metabolic pathways

Several reports indicate other ferroptosis defense mechanisms independent of the aforementioned pathways. For example, retinoids, including retinol and its derivatives (retinal and retinoic acid), suppress ferroptosis, while retinol saturase (RETSAT)-mediated retinoid metabolism can abrogate the ferroptosis-protective effects[38]. It is reported that amino acid oxidase interleukin 4 induced 1 (IL4i1) produces indole-3-pyruvate, which suppresses ferroptosis by direct free radical-scavenging ability or through the activation of an anti-oxidative gene expression program[39]. The phospholipase A2 group VI (iPLA2β) suppresses ferroptosis by removing oxidized PUFA tails from PLs, suggesting the importance of PUFA chain remodeling in suppressing ferroptosis[40,41]. Although glutamine has been shown to have pro-ferroptotic capacities in ferroptosis induction through glutaminolysis[42], under certain conditions, glutamine is also required for ferroptosis defense. Xiao et al. clarified the importance of exogenous glutamine in the detoxification of ROS in pancreatic cancer cells[43]. In addition, Mukhopadhyay and colleagues found that glutamine is responsible for KRAS-driven pancreatic cancers in an NRF2-dependent manner[44]. It is worth exploring whether other endogenous metabolites and related metabolisms can inhibit ferroptosis by acting as RTAs or modulators of genes that regulate ferroptotic stresses.

Lipid peroxidation and ferroptosis

How does lipid peroxidation happen? To answer the question, researchers have been engaged in exploring the connection between oxidative stresses and lipid metabolism. As early as 2016, Yang et al. first raised the point that the contents of PUFA-phosphatidylcholine (PC) were depleted upon ferroptosis induced by system xc^- inhibitor[45]. Afterward, in 2017, by using the redox phospholipidomics, Doll et al. and Kagan et al. revealed that the only type of PUFA-containing phospholipids, phosphatidylethanolamine (PE), are the main substrates for lipid peroxidation upon the treatment of GPX4 inhibitors[46,47]. These studies inspired researchers to investigate the regulatory mechanisms of specific types of phospholipids and the contents of PUFAs during oxidative stresses and ferroptosis induction (Box 1). In this part, we summarize the distinct mechanisms of lipid peroxidation and describe the metabolisms involving lipid peroxidation.

Distinct mechanisms of lipid peroxidation

The lipid peroxidation of PUFA-PLs is triggered by either the non-enzymatic Fenton reaction or enzymes, such as lipoxygenases (ALOXs), both of which are iron-dependent (Fig. 3).

Fenton reaction generates highly reactive alkoxyl and/or hydroxyl radicals by decomposition of hydrogen peroxide using ferrous iron (Fe^{2+}). The generation of hydroperoxide phospholipids (PLOOHs) by non-enzymatical Fenton reaction can be divided into three steps: initiation, propagation, and termination. The hydroxyl radicals attack the two carbon-carbon double bonds of PUFA-PLs, remove a hydrogen atom, and generate a phospholipid radical (PL•). Then, PL• reacts with oxygen to generate a phospholipid peroxyl radical (PLOO•). At the propagation step, PLOO• reacts with the nearby PUFA-PL to produce PLOOH and the other PL•. Hence, without termination by GPX4 or the aforementioned anti-ferroptosis metabolites, the PLOOH will propagate uncontrollably and eventually cause the destruction of plasma/organelles' membranes and cell rupture. Due to the requirement of PUFA-PLs as substrate, the autoxidation-mediated ferroptosis initiation and execution is tightly regulated by the content of membrane polyunsaturated or monounsaturated fatty acyl moieties in phospholipids. Thus, it is very likely that long-chain-fatty-acid-CoA ligase 4 (ACSL4)-dependent PUFA-PE generation and non-enzymatic Fenton reaction are responsible for the basal level of lipid peroxidation, while GPX4 maintains redox homeostasis through detoxifying the peroxidized lipids. Whenever GPX4 loses its ability to eliminate lipids peroxidation, the balance is broken, and cells die without the ferroptosis inhibitors. In this case, it is understandable that one major obstacle to the application of GPX4 inhibition in clinical cancer therapy is the

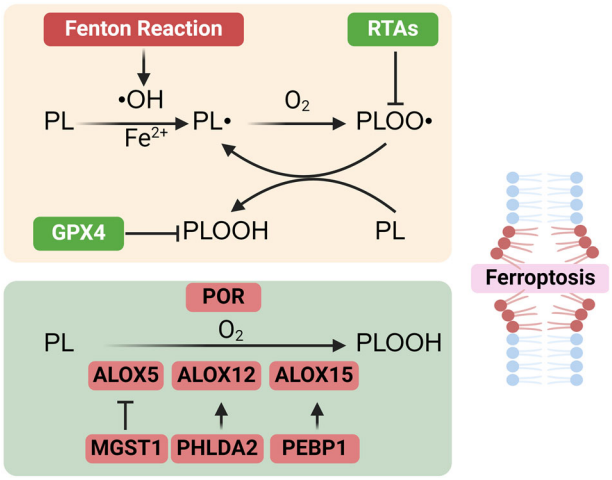

Fig. 3 | Mechanisms of lipid peroxidation. Fenton reaction produces hydroxyl radicals that can attack PLs and generate PL•. Then, PL• reacts with oxygen to produce PLOO•, which propagates to the nearby PL to produce PLOOH and the other PL•. POR is considered as an executioner for ferroptosis. Lipoxygenase family proteins, ALOX5, ALOX12, or ALOX15, regulated by MGST1, PHLDA2, or PEBP1, respectively, are critical for enzymatic lipid peroxidation and ferroptosis. RTAs, radical-trapping antioxidants; PLs, phospholipids; PL•, phospholipid radicals; PLOO•, phospholipid peroxyl radicals; POR, cytochrome P450 reductase; MGST1, microsomal glutathione S-transferase 1; PHLDA2, pleckstrin homology like domain family A member 2; PEBP1, phosphatidylethanolamine binding protein 1. Created with BioRender.com.

opposite outcomes in tumor growth when inhibiting GPX4 in tumor cells or immune cells.

Oxidative stress is a primary characteristic of ferroptosis, as mentioned above. For example, mitochondrial respiration or enzymes, such as NADPH oxidases (NOXs) and cytochrome P450 oxidoreductase (POR), can initiate lipid peroxidation by producing superoxide or hydrogen peroxide[48,49]. The anti-oxidative factor sirtuin 3 (SIRT3) counteracts ferroptosis by eliminating cellular ROS[50]. Of note, ALOX family proteins are iron-containing enzymes that catalyze the dioxygenation of PUFAs to produce FA hydroperoxides[51]. Recently, the function of ALOXs in directly oxygenating PUFA-PLs has been revealed. Shah et al. found that overexpression of lipoxygenases, including ALOX5, ALOX12, and ALOX15, increases cell sensitivity to ferroptosis[52]. Loss of ALOXs decreases the cell sensitivity to erastin, but not RSL-3 treatment, indicating the involvement of ALOXs in initiating ferroptosis in a distinct pathway from GPX4 inhibition[45,52]. Subsequent evidence confirmed that ALOX15 promotes lipid peroxidation by forming an enzymatic complex with phosphatidylethanolamine binding protein 1 (PEBP1) to generate a death signal, 15-hydroperoxy-arachidonic acid-PE, to initiate ferroptosis[53,54]. ALOX12-mediated ferroptosis relies on its interaction with a phospholipid-binding protein, pleckstrin homology like domain family A member 2 (PHLDA2)[55]. In addition, ALOX5-mediated ferroptosis upon ROS stress plays a critical role in Huntington's disease[56]. Kuang et al. identified microsomal glutathione S-transferase 1 (MGST1) as a negative regulator of ferroptosis through binding with ALOX5, associated with the progression of pancreatic cancer[57]. Collectively, PUFA-PLs are the common substrates for lipid peroxidation induced by distinct pathways, emphasizing the importance of ferroptosis regulation under either homeostasis or stress conditions.

PUFA-PL metabolism and ferroptosis

ACSL4 ligates free arachidonic acid (AA) with CoA to generate AA-CoA. With the help of lysophosphatidylcholine acyltransferase 3 (LPCAT3), AA is linked to one side chain of phospholipids to generate AA-PLs[58,59]. AA-PLs are the major types of PUFA-PLs in lipid peroxidation (Fig. 4). It is interesting that almost all CRISPR-Cas9 screens in ferroptosis research identified *ACSL4* as the top gene selected by GPX4 inhibitors (such as RSL-3, ML162, and ML210), indicating that ACSL4 is the predominant enzyme required for GPX4 inhibition-induced ferroptosis[33,60–62]. Specifically, PE-containing AA or adrenic acid (AdA) chains (referred to 18:0/20:4-PE and 18:0/22:6-PE) were identified as ferroptotic signals[46,47]. Phadnis et al. described that the Lands cycle enzyme membrane bound O-acyltransferase domain containing 7 (MBOAT7) cooperates with ACSL4 to promote the incorporation of AA into phosphatidylinositol (PI), highlighting the other specific type of PUFA-PL, PUFA-PI, drives ferroptosis susceptibility in ovarian and renal carcinoma cells[63]. In line with these studies, a systemic analysis of oxidized phospholipids during different types of cells confirmed that PE oxidation is the major executioner in ferroptosis[64]. More evidence suggests that the phospholipids containing double PUFA tails drive ferroptosis. Stockwell's lab recently revealed that PC with rare double PUFA tails (PC-$PUFA_2$s) is a fuse of ferroptosis. PC-$PUFA_2$s interact with the ETC in mitochondria to promote the generation of cellular ROS, hence initiating ferroptosis, particularly in aging and Huntington's disease[65]. Consistently, Kagan's lab reached the same conclusion that PE-$PUFA_2$s drive ferroptosis with higher potency than PE lined with single PUFA[66].

It is worth noting that PUFA-PL demonstrates a tumor-suppressive role under certain conditions. Peroxidation of n-3 and n-6 triglycerides at lipid droplets induces ferroptosis and exerts significant anti-tumor effects under acidosis, which emphasizes the importance of a combination of diacylglycerol acyltransferase (DGAT) inhibitors and n-3/n-6 long-chain PUFA-rich diet in killing tumors[67]. Consistently, using CRISPR screening, Zou et al. identified that hypoxia-inducible factor 2 alpha (HIF2α) is responsible for ferroptosis susceptibility through activating lipid droplet-associated protein (HILPDA) to enrich polyunsaturated lipids. This study indicated the vulnerability of kidney and ovary-originated clear cell carcinoma to GPX4 inhibitors[60]. ACSL1 incorporates α-eleostearic acid (αESA) into neutral lipids to trigger ferroptosis independent of GPX4 inhibition. Supplement of αESA through oral administration of tung oil restrains tumor growth and metastasis[68].

MUFA-PL metabolism and ferroptosis

MUFA-PL inhibits cell vulnerability to ferroptosis by reducing PUFA-PL contents dependent on ACSL3[69] (Fig. 4). KRAS-mutated lung cancer cells modulate ACSL3 expression to remodel MUFA-PL metabolism and tumor growth[70]. Another tumor-promoting mechanism of MUFA-PL was described in metastasizing melanoma: the lymphatic environment with higher levels of oleic acid protects cancer cells from ferroptosis dependent on ACSL3 and increases lymph nodes' ability to form metastatic tumor[71]. In addition, Vriens et al. found that cancer cells utilize an alternative fatty acid desaturation pathway, which desaturates palmitate to sapienate to facilitate cell proliferation by supporting membrane synthesis, thus indicating the metabolic plasticity of cancer[72]. Indeed, deficiency of fatty acid desaturase (FADS1) protects mesenchymal-type gastric cancer cells from ferroptosis by inhibiting producing AA and AdA, further proving the importance of MUFA-PUFA competition as the checkpoint in determining cell ferroptosis sensitivity[73]. FADS1/2 controls lipid metabolism and ferroptosis susceptibility in triple-negative breast cancer[74]. FADS2-mediated highly unsaturated FA biosynthesis sensitizes cells to ferroptosis and restricts hepatitis C virus (HCV) replication[75].

Recently, Liang et al. found that phospholipid-modifying enzymes, Membrane Bound O-Acyltransferase Domain Containing 1 and 2 (MBOAT1 and MBOAT2), suppress ferroptosis independently of GPX4 through remodeling the cellular MUFA-PE profile. MBOAT1/2 acts as transcriptional targets of sex hormone receptors to regulate estrogen receptor (ER)-positive breast cancer and androgen receptor (AR)-positive prostate cancer growth[76]. Conversely, 2,4-dienoyl-CoA reductase 1 (DECR1) is a negatively regulated target of AR. DECR1 mediates PUFA remodeling to enhance mitochondrial oxidative stress and promote lipid peroxidation, suggesting another example of ferroptosis induction by targeting AR signaling in human cancers[77,78]. Li et al. identified that lysophosphatidylcholine acyltransferase 1 (LPCAT1) promotes membrane

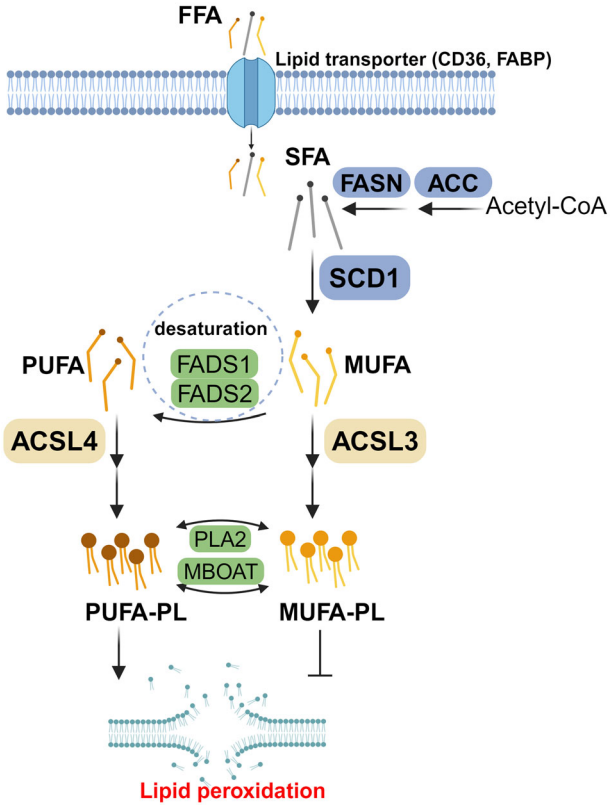

Fig. 4 | The role of lipid metabolism in ferroptosis. De novo lipogenesis is initiated by ACC, which metabolizes acetyl-CoA to malonyl-CoA. SFA is synthesized after a series of reactions catalyzed by FASN. SFA is then desaturated to MUFA by SCD1. Meanwhile, FADS1 or FADS2 is responsible for fatty acid desaturation dependent on substrate specificity. ACSL3 or ACSL4 acylates MUFA or PUFA, respectively, and further promotes the production of MUFA-PL or PUFA-PL to regulate the cell sensitivity to ferroptosis. Extracellular FA can be uptake via CD36 or FABP. ACC, acetyl-CoA carboxylase; SFA, saturated fatty acid; FASN, fatty acid synthase; MUFA, monounsaturated fatty acid; SCD1, stearoyl-CoA desaturase; FADS, fatty acid desaturases; ACSL, long-chain-fatty-acid-CoA ligase; PUFA, polyunsaturated fatty acid; PL, phospholipid; FABP, fatty acid-binding proteins. Created with BioRender.com.

phospholipid saturation via the Lands cycle for lipid remodeling in ferroptosis evasion and tumor progression[79].

Fatty acid metabolism and ferroptosis

De novo synthesis of saturated FA (SFA) and MUFA in cells is critical for cell growth. Starting from acetyl-CoA carboxylation, palmitic acid (C16:0) or stearic acid (C18:0) is generated after a series of reactions catalyzed by fatty acid synthase (FASN). Stearoyl-CoA desaturase-1 (SCD1) desaturates palmitoyl-CoA or stearoyl-CoA to form MUFAs, palmitoleic acid (C16:1) and oleic acid (C18:1), respectively. Expression of FASN, SCD1, and acetyl-CoA carboxylase (ACC) are critical in determining ferroptosis sensitivity (Fig. 4). The hijack of de novo lipogenesis and subsequent ferroptosis defense by oncogenic signaling are well-established. FASN protects KRAS-mutated lung cancer cells from ferroptosis by remodeling oxidized phospholipids, including PC[80]. Suppression of SCD1 sensitizes ovarian cancer cells to ferroptosis[81]. Cancers carrying the hyperactive mutation in the PI3K-AKT-mTOR signaling pathway are resistant to ferroptosis through sterol regulatory element-binding protein 1 (SREBP1) and its transcriptional target, SCD1[82]. Circulating melanoma cells shows upregulation of the lipogenesis pathway compared to primary melanoma cells. The lipogenesis regulator SREBP2 mediates ferroptosis defense through transcriptionally activating the expression of SCD1, which is tightly involved in resistance to BRAF inhibitors and melanoma progression[83]. Although AMPK has a context-dependent role in regulating ferroptosis, AMPK-mediated ACC phosphorylation and subsequently FA synthesis contribute to the protection effects upon GPX4 inhibition[84–86].

Besides FA synthesis, the uptake of FA plays an essential role in ferroptosis modulation. Deficiency of CD36, fatty acid transporters, reduce FA uptake and restrains cancer progression in prostate cancer[87]. In intratumoral $CD8^+$ T cells, CD36-mediated uptake of FAs increases lipid peroxidation and ferroptosis levels and impairs their anti-tumor ability by reducing cytotoxic cytokine production[88]. These studies proposed the combination of CD36 antibodies with anti-tumor drugs as a potent way of tumor suppression. On the other hand, Sun et al. identified a FA-binding protein, fatty acid binding protein 5 (FABP5), as a ferroptosis suppressor. Ablation of FABP5 sensitizes hepatocellular carcinoma (HCC) cells to ferroptotic cell death, thus providing an efficient way to HCC suppression[89].

Other lipid metabolism and ferroptosis

The plasmalogen form of PE (ether PE), which represents 50% of total PE, is associated with the vulnerability of ferroptosis induced by inhibiting GPX4[61,90,91]. These studies highlight the importance of peroxisomes in ether phospholipid synthesis and ferroptosis[61].

Although the direct involvement of cholesterol in ferroptosis regulation is not reported, cholesterol metabolism is indeed critical in ferroptosis and tumor progression[92]. Notably, the CoQ_{10} and vitamin K synthesis are closely dependent on the intermediate metabolites during cholesterol synthesis, further emphasizing the importance of cholesterol metabolism in ferroptosis modulation[93,94]. The rate-limiting enzymes of mevalonate pathways, including squalene monooxygenase (SQLE) and 7-dehydrocholesterol reductase (DHCR7), are essential in ferroptosis regulation and tumor growth. ALK^+ anaplastic large cell lymphoma cells are highly dependent on cholesterol uptake upon the deficiency of SQLE. Loss of SQLE-driven dysregulation of cellular lipid metabolism leads to resistance to ferroptosis and further promotes tumor growth[95]. A system analysis of cholesterol metabolism-mediated ferroptosis defense showed that dual inhibition of CoQ_{10} and squalene biosynthesis completely abrogates the anti-ferroptosis effects of cholesterol metabolism[96]. Consistent with this study, inhibition of vitamin K synthesis has similar effects[33]. Freitas et al. and Li et al. found that the metabolite 7-dehydrocholesterol (7-DHC), generated by sterol-C5-desaturase (SC5D), can directly clear the peroxidized lipids by acting as RTAs; however, DHCR7 metabolizes 7-DHC to cholesterol and sensitizes cells to ferroptosis[97,98]. Furthermore, Li et al. identified several proteins that participate in cholesterol biosynthesis also regulate cell vulnerability to ferroptosis, such as methylsterol monooxygenase 1 (MSMO1), cytochrome P450 family 51 subfamily A member 1 (CYP51A1), and emopamil binding protein (EBP)[97,98].

Iron and ferroptosis

Iron is the fundamental factor in ferroptosis, highlighting the importance of iron manipulation in regulating cells' susceptibility to ferroptosis induction. Modulation of iron metabolism, including iron uptake, usage, storage, and export, provides compelling paths during tumor suppression. Enhancement of iron uptake by transferrin or Transferrin Receptor protein 1 (TfR1) sensitizes cells to ferroptosis and has been identified as a biomarker during the progression of ferroptosis[42,99]. Aberrant Neurofibromin 2 (NF2)/Yes-associated protein (YAP)-mediated upregulation of TfR1 dictates the sensitivity of ferroptosis to malignant mesothelioma and could predict the responsiveness of cancer cells to therapy[100]. Ferritinophagy is a selective process of autophagy that releases iron via nuclear receptor coactivator 4 (NCOA4)[101–103]. Targeting NCOA4-mediated ferritinophagy has been shown to play a pro-ferroptotic role during tumor regression[104]. NCOA4 induction and defective GPX4 expose BRCA1-deficient cancers to ferroptosis, providing a novel cancer-treating method by synergizing GPX4 inhibitor with canonical PARP inhibitor[105]. Indeed, oncogenic signaling, such as NRF2/HERC2/VAMP8 axis or AKT/TRPML1/ARL8b, abrogates intracellular iron accumulation and facilitates aberrant tumor progression[106,107]. Accumulating evidence indicates that the imbalance of

iron metabolism is targetable during cancer therapy. Withaferin A promotes the expression levels of heme oxygenase 1 (HMOX1) in an NRF2-dependent manner. Thus, increased intracellular labile Fe^{2+} upon excessive HMOX1 induces ferroptosis sufficiently[108]. Breast cancer cells hijack metal-regulatory transcription factor 1 (MTF1) and remodel iron storage (ferritin heavy and light chain, FTH1 and FTL) and export (ferroportin, FPN1) expression to escape ferroptosis[109]. Collectively, understanding how iron contributes to ferroptosis and applying the iron modulation paths may reveal new ways to intervene in tumors.

The role of ferroptosis in cancer

Induction of ferroptosis not only directly suppresses tumors but also participates in immune responses, both of which are critical for the implication of ferroptosis in cancer. In this part, we present the details of ferroptosis-mediated tumor suppression and navigate the complex role of ferroptosis in modulating anti-tumor immunity. Furthermore, we introduce the current advances in ferroptosis-based therapeutics and clinical trials.

Ferroptosis promotes tumor suppression

We and other labs have proved the ALOX family proteins are powerful weapons in ferroptosis induction and tumor regression. ALOX12 participates in p53-mediated tumor suppression independent of GPX4/ACSL4 ferroptosis pathway[110,111]. In line with this, Yang et al. identified phospholipid-binding protein, PHLDA2, as a key factor in inducing ferroptosis and tumor suppression upon high levels of ROS[55]. In contrast to the ferroptosis induced by GPX4 inhibitors, PHLDA2-mediated ferroptosis is neither ACSL4-dependent nor acts through canonical PUFA-PE peroxidation but is critical for p53-mediated ferroptosis[112]. Through redox phospholipidomics, Yang et al. identified that GPAT3 (glycerol-3-phosphate acyltransferase 3) catalyzes the synthesis of PUFA-phosphatidic acid (PA) and contributes to its peroxidation by ALOX12/PHLDA2 complex[55]. More recent work demonstrated that ALOX5 deficiency results in ferroptosis escape and the progression of bladder cancer[113]. In addition, Bi and colleagues identified polyamine-mediated ferroptosis induction through modulating oxidative stresses[114].

Although ACSL4 presents a core role in GPX4 inactivation-induced ferroptosis, which has been proven to be targetable in acute organ injury, such as ischemia/reperfusion (I/R)-induced acute kidney injury (AKI)[115,116], the tumor suppressive role of ACSL4 is still contradictable. By using the liver cancer model, Grube et al. found that ACSL4-dependent ferroptosis surprisingly represents no tumor-suppressive effect but rather promotes liver cancer progression[117]. On the other hand, while ACSL4 has no tumor-suppressive effects in immunodeficient mouse models, ACSL4 is indeed required for tumor suppression in immunocompetent mouse models, especially in the presence of AA and interferon-gamma (IFNγ)[118]. It now seems clear that ACSL4, but not ALOXs, plays a role in the ferroptotic cell death downstream of GPX4. Losing ACSL4 abrogates the spontaneous ferroptotic cell death caused by GPX4 knockout[40,55,110], while the generation of *Alox15/Gpx4* double knockout mice fails to rescue *Gpx4*-loss-induced embryonic lethality, kidney failure, and T cell dysfunction[5,119,120]. Based on these observations, we speculate that oxidative stress-induced ferroptosis is another potential way in tumor therapy without any ferroptosis inducers at physiological conditions.

Tumor microenvironment and ferroptosis

Recent research has reported the close relationship between ferroptosis and anti-tumor immunity. It is well-accepted that ferroptotic tumor cells could modulate the immune response, while ferroptotic immune cells affect the function of cytotoxic cells, antigen presentation, and inflammatory response, etc. In this part, we briefly discuss the recent advances of ferroptosis in immune response and the crosstalk between tumor microenvironment and ferroptosis (Fig. 5).

T cells and ferroptosis

It is well-established that $CD8^+$ T cell-induced ferroptosis contributes to cancer immunotherapy. Activated $CD8^+$ T cells release IFNγ to suppress the

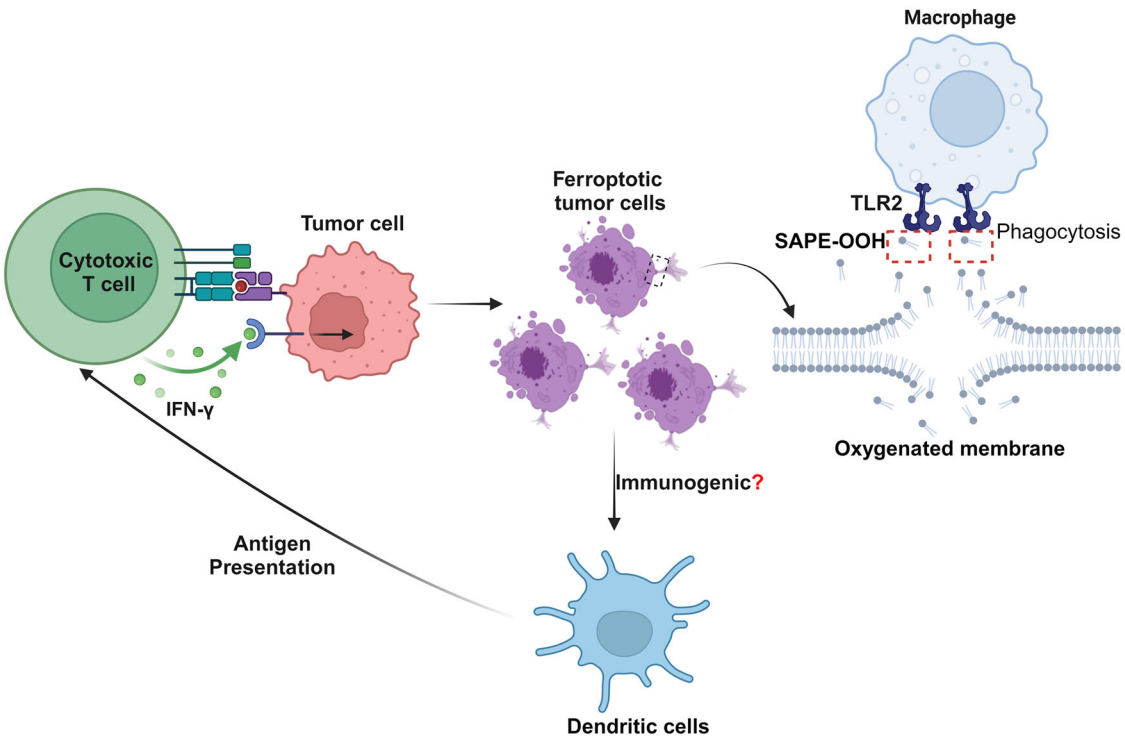

Fig. 5 | Tumor microenvironment and ferroptosis. T cells kill tumors by inducing ferroptotic cell death in tumor cells. T cells secret IFNγ to modulate SLC7A11 or ACSL4 expression. With the collaboration of endogenous arachidonic acid, the tumor cells undergo lipid peroxidation and ferroptosis. The ferroptotic signals, SAPE-OOH, could be recognized by TLR2 and trigger the phagocytosis by macrophage. Whether the ferroptotic tumor cells are immunogenic is undetermined now. TLR2, toll-like receptor 2. Created with BioRender.com.

expression of SLC3A2 and SLC7A11 and the uptake of extracellular cystine into tumor cells[18]. T cell-mediated anti-tumor immunity promotes lipid peroxidation and ferroptosis in cancer cells[121]. Ferroptosis has also been implicated during radiotherapy. Radiotherapy collaborates with IFNγ to decrease the expression of SLC7A11 and induce the ferroptosis of tumor cells[122].

How T cells escape from inner ferroptotic stresses determines their anti-tumor capacities. Activated PGE2 impairs IL-2-mTOR adaptation and PGC1α transcriptional repression, subsequently promoting tumor-infiltrating lymphocyte death via ferroptosis[123]. The uptake of oxidized lipids into T cells by receptor CD36 causes lipid peroxidation and ferroptosis. Ablation of CD36 in $CD8^+$ T cells enhances the antitumor effects and increases the efficacy of immunotherapy[88,124]. Ping et al. reported that phospholipid phosphatase 1 (PLPP1), which possesses the synthesizing capacities of PC and PE, is required for ferroptosis resistance and anti-tumor abilities of $CD8^+$ T cells. Loss of PLPP1 impairs anti-tumor immunity and promotes T cell death by ferroptosis[125]. On the contrary, GPX4 prevents T regulatory (T_{reg}) cells' lipid peroxidation and ferroptosis to sustain T_{reg} cell activation. Ferroptosis induced by deficiency of GPX4 in T_{reg} cells suppresses tumor growth and promotes anti-tumor immunity[126]. These regulatory mechanisms suggest the complex role of ferroptosis within the tumor microenvironment and its interplay with anti-tumor immunity.

Macrophages and ferroptosis

In addition to T cells, the crosstalk between macrophage subsets and ferroptosis is critical during anti-tumor immunity. Wen et al. found that HMGB1, a type of DAMP released by ferroptotic cells, stimulates the inflammation in macrophages[127]. Toll-like receptor 2 (TLR2) on macrophages interacts with the well-known ferroptotic signals, SAPE-OOH, and improves the efficiency for macrophages to engulf ferroptotic cells[128]. On the other hand, peroxidation in TME macrophages impairs their ability to eliminate ferroptotic tumor cells by phagocytosis, thus causing tumor resistance to ferroptosis therapy[129]. Indeed, high CXCL16-expressed islet macrophages demonstrate the scavenging effects of oxidized low-density lipoproteins and maintain tissue homeostasis by modulating the differentiation of pathogenic $CD8^+$ T cells[130].

On the other hand, ferroptosis plays a vital role in shaping the macrophages. Iron overload activates hepatic M1 macrophages, indicating the critical role of iron in controlling the balance between M1/M2 macrophage polarization and macrophage-driven inflammation[131]. In comparison to M2 macrophages, the M1 type exhibits higher resistance to ferroptosis due to the inducible nitric oxide synthase (iNOS)/NO•-mediated ferroptosis defense system, thus creating a pro-inflammatory tumor microenvironment. The anti-ferroptotic activity of iNOS may depend on the ability of NO•: NO• interfered with 15LOX/PEBP1 activity by competing with the 15LOX-2 catalytic site[132,133].

Neutrophils and ferroptosis

Neutrophils are responsible for tumor cell killing in glioblastoma mouse model[134]. Neutrophils induce iron-dependent accumulation of lipid peroxides within tumor cells by transferring myeloperoxidase-containing granules into tumor cells[134]. Interestingly, Zhao et al. reported that tumor-infiltrating neutrophils are resistant to ferroptosis through aconitate decarboxylase 1 (Acod1)-mediated Nrf2 activation and ferroptosis defense. During breast cancer metastasis, Acod1 ablation boosts anti-tumor T cell immunity through abrogating tumor-infiltrating neutrophils activities[135]. However, Kim et al. challenged the existing opinion and found that ferroptosis inducers, such as imidazole ketone erastin (IKE), promote tumor growth in immunocompetent mouse models[136]. Mechanistically, spontaneous ferroptosis of pathologically activated neutrophil myeloid-derived suppressor cells (PMN-MDSCs) can release oxygenated lipids to restrain the activation of T cells. Thus, ferroptosis inhibitors efficiently limit the ferroptosis of PMN-MDSCs and maintain the activities of T cells for tumor suppression[136]. Likewise, the differences among these studies indicate that the role of TME regulated by ferroptosis is complicated, thus the ferroptosis happening in tumor immunity is in a context manner.

Dendritic cells and ferroptosis

Additionally, a recent study also indicated that ferroptotic cancer cells lack immunogenicity, which impedes antigen presentation to dendritic cells (DCs) and hinders therapeutic applications of ferroptosis[137,138]. This phenomenon is unsurprising because the immune-inhibitory effects of well-known ferroptotic cell death signals have already been reported[123,139–141]. However, a contradictory conclusion was reached by Efimova and colleagues: they found ferroptotic cells are immunogenic and can sufficiently promote the maturation of DCs[142]. The different conclusions may be caused by different experimental conditions, for the most part, the degree of ferroptotic cells induced by ferroptosis reagents during the immune response.

Targeting ferroptosis therapeutically and clinically

As we discussed above, the ferroptosis regulation of immune cells affects the outcomes of tumor suppression. It remains unclear how to target tumor cells only without affecting immune cells in the TME during tumor therapy. N6F11, a recently identified GPX4 degrader, can selectively eliminate GPX4 proteins in tumor cells but not T cells, DCs, or natural killer cells. N6F11 shows potent anti-tumor capacities in mouse pancreatic tumor models, highlighting the importance of discriminately inducing ferroptosis in TME[143].

Combinations of ferroptosis induction with well-established therapies are another way to treat tumors. The pharmacological combination of immunotherapy and ferroptosis has been explored, such as triple-negative breast cancer[144,145]. Jiang et al. demonstrated that high expression of tyrosine-protein kinase receptor TYRO3 restrains the ferroptotic cell death of tumor cells induced by anti-PD1/PDL1 therapy, suggesting the combination of TYRO3 inhibition and anti-PD1/PDL1 therapy in cancer therapy through ferroptosis induction[146]. Furthermore, delicate nanoparticles somehow provide better solutions, particularly through modulating immune response[147,148]. Recently, a new approach, called ultrathin manganese (Mn)-based nanoplatform, has been proposed to mutually reinforce the ferroptosis and systemic immunity via targeting SLC7A11[149]. A biomimetic ferroptosis inducer (D@FMN-M) promoted the ferroptosis of both M2-type tumor-associated macrophages (TAM) and tumor cells to enhance the efficacy of immunotherapy, providing a strategy against the TAM infiltration-mediated immunosuppressive TME[150]. Overall, based on the mechanism studies of ferroptosis, the development of ferroptosis therapeutics will provide more options for cancer treatment.

Given that ferroptosis is a powerful weapon against ferroptosis, accumulating clinical trials are applying pharmacological approaches to treating cancers by targeting critical ferroptosis-regulating processes. Below, we summarize the clinical-grade anti-tumor molecules targeting ferroptosis indicated at ClinicalTrail. gov. (Table 1).

Prospective

Ferroptosis is a type of cell death driven by metabolism alteration. Oxidative stress, lipid peroxidation, and diverse surveillance pathways are the main characteristics of ferroptotic cell death. Given the fact that tumor cells rewire their metabolisms (high levels of ROS, overloaded iron, and accumulation of PUFA, etc.) for rapid proliferation and ferroptosis evasion, targeting tumor ferroptosis vulnerability presents exciting opportunities for tumor suppression. It is evident that GPX4 contributes most to the ferroptosis defense and provides a straightforward approach to induce ferroptosis in therapy-resistant tumors[151]. Indeed, Magtanong et al. found that although ferroptosis is inevitably through excessive lipid peroxidation, the regulation of ferroptosis sensitivity is context-specific[152]. ACSL4 is indispensable for the ferroptosis induced by GPX4 inhibitors; however, the critical regulators of the ferroptosis under distinct conditions are still unclear. Thus, the identification of the ferroptosis regulators upon stresses is emerging but still warrants further exploration. First, the underlying mechanism of ferroptotic cell death is still elusive, particularly the crosstalk between different subcellular

Table 1 | Summary of molecules targeting ferroptosis clinically

Agent	Mechanism	Targeted Cancer	NCT Number	Phase	Status (10/8/2024)
Auranofin	Increase ROS[154]	Ovarian Cancer	NCT03456700	II	Active, not recruiting
		Non-Small Cell Lung Cancer	NCT02126527	I	Withdrawn
		Glioblastoma	NCT02770378	I, II	Completed
		Recurrent non-small cell lung cancer or small cell lung cancer	NCT01737502	I, II	Completed
		Chronic lymphocytic leukemia (CLL)	NCT01419691	II	Completed
		Recurrent epithelial ovarian; primary peritoneal, or fallopian tube cancer	NCT01747798	Early Phase I	Completed
Brequinar	DHODH inhibitor[10]	Acute myeloid leukemia	NCT03760666	I, II	Terminated
Buthionine sulfoximine	GCLC inhibitor; GSH depletion[155]	Neuroblastoma	NCT00002730	I	Completed
Sulfasalazine	SLC7A11 inhibitor[156]	Metastatic Colorectal Cancer	NCT06134388	III	Recruiting
		Glioma; glioblastoma; recurrent glioblastoma	NCT04205357	I	Completed
		Breast cancer; chronic pain due to malignancy	NCT03847311	II	Completed
Withaferin A	GPX4 inhibition and HMOX1 activation[108]	Recurrent ovarian cancer	NCT05610735	I and II	Recruiting
Nanoparticle-Loaded Iron [CNSI-Fe(II)]	Iron overload and increase ROS[157]	Advanced Solid Tumor	NCT06048367	I	Recruiting

organelles[153]. Understanding the ferroptosis processes at the single-cell level has emerged. Most importantly, rethinking the critical role of oxidative stress in triggering ferroptosis could provide us with additional choices in tumor therapy. It is likely that the context of TME affects the outcome of ferroptosis. Whether the ferroptosis of immune cells, especially neutrophils and DCs, is immunosuppressive or immunogenic should be discussed carefully. The contradictory effects of ferroptosis during anti-tumor immunity prompt us to think more about the alternative way of applying ferroptosis in tumor suppression. Leveraging the high levels of ROS in tumor cells and applying the enzyme complexes-dependent ferroptosis could be the other way we should explore in the future.

Received: 11 June 2024; Accepted: 31 October 2024;
Published online: 09 November 2024

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Acknowledgements

This work was supported by Soochow University Research Development Funds under NH24900724 to X.Y.

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Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s42003-024-07180-8.

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Peer review information *Communications Biology* thanks Cheng Zhan, Archita Venugopal Menon and Kunlong Duan and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editors: Mengtan Xing and Manuel Breuer. [A peer review file is available].