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REVIEW

Targeting lipid metabolism for ferroptotic cancer therapy

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Abstract

It has been 10 years since the concept of ferroptosis was put forward and research focusing on ferroptosis has been increasing continuously. Ferroptosis is driven by iron-dependent lipid peroxidation, which can be antagonized by glutathione peroxidase 4 (GPX4), ferroptosis inhibitory protein 1 (FSP1), dihydroorotate dehydrogenase (DHODH) and Fas-associated factor 1 (FAF1). Various cellular metabolic events, including lipid metabolism, can modulate ferroptosis sensitivity. It is worth noting that the reprogramming of lipid metabolism in cancer cells can promote the occurrence and development of tumors. The metabolic flexibility of cancer cells opens the possibility for the coordinated targeting of multiple lipid metabolic pathways to trigger cancer cells ferroptosis. In addition, cancer cells must obtain immortality, escape from programmed cell death including ferroptosis, to promote cancer progression, which provides new perspectives for improving cancer therapy. Targeting the vulnerability of ferroptosis has received attention as one of the significant possible strategies to treat cancer given its role in regulating tumor cell survival. We review the impact of iron and lipid metabolism on ferroptosis and the potential role of the crosstalk of lipid metabolism reprogramming and ferroptosis in antitumor immunity and sum up agents targeting lipid metabolism and ferroptosis for cancer therapy.

Keywords Ferroptosis · Lipid metabolism · Anti-tumor immunity · Ferroptotic cancer therapy

Abbreviations

GPX4	Glutathione peroxidase 4
FSP1	Ferroptosis inhibitory protein 1
DHODH	Dihydroorotate dehydrogenase
FAF1	Fas-associated factor 1
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
LIP	Labile iron pool
LOXs	Lipoxygenases
POR	Cytochrome P450 oxidoreductase
CSCs	Cancer stem cells
TF	Transferrin
TFRC	Transferrin receptor
CTCs	Circulating tumor cells
DMT1	Divalent metal transporter 1
NCOA4	Nuclear receptor coactivator 4
GOT1	Cytosolic aspartate aminotransaminase
HMOX1	Heme oxygenase 1
NFS1	Nitrogenfixation 1
PCBP2	Poly rC binding-protein 2

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AA	Arachidonoyl
AdA	Adrenoyl
ACSL4	Acyl-CoA synthetase long-chain family member 4
PEs	Phosphatidylethanolamines
MUFAs	Monounsaturated fatty acids
POA	Palmitic acid
OA	Oleic acid
ACSL3	Acyl-CoA synthetase long chain family member 3
SFA	Saturated fatty acyl
PUFA ePLs	Polyunsaturated ether phospholipids
LPCAT3	Lysophosphatidylcholine acyltransferase 3
PKCβII	Protein kinase C-βII isoform
PEBP1	Phosphatidylethanolamine-binding protein 1
4-HNE	4-Hydroxynonenal
MDA	Malondialdehyde
CoQ10	Coenzyme Q10
a-TOC	Alpha-tocopherol
CoQ	Ubiquinone
CoQH2	Ubiquinol
Nrf2	Nuclear factor erythroid 2-related factor 2
Sec	Selenocysteine
TFH	Follicular helper T cells
TFAP2C	Transcription factor AP-2γ
SP1	Specific protein 1
GSH	Glutathione
GCL	Glutamate-cysteineligase
BSO	Butionine sulfoximine
GCLC	Glutamic acid cysteine ligase catalytic subunit
BAP1	BRCA1-associated protein 1
CSLCs	Cancer stem cell-like cells
BCSCs	Breast cancer stem cells
CAFs	Cancer-associated fibroblasts
MESH1	Metazoan SpoT Homolog 1
ER	Endoplasmic reticulum
AIFM2	Apoptosis-inducing factor mitochondria-associated 2
AIF	Apoptosis inducing factor
NDH-2	Type 2 NADH ubiquinone oxidoreductase
IPP	Isopentenyl pyrophosphate
BH4	Tetrahydrobiopterin
DHFR	Dihydrofolate reductase
BH2	Dihydrobiopterin
GCH1	GTP-dependent cyclohydrolase 1
iPLA2β	Calcium-independent phospholipase A2β
27HC	27-Hydroxycholesterol
SQS	Squalene synthase
SQLE	Squalene monooxygenase
ACSF2	Acyl-CoA synthetase family member 2
CS	Citrate synthase
SCD1	Stearoyl-CoA desaturase 1
FADS2	Acyl-CoA 6 desaturase
CSCs	Cancer stem cells
SREBPs	Sterol regulatory element binding proteins
BCAT2	Branched-chain amino acid aminotransferase 2
AMPK	AMP-activated protein kinase
LKB1	Liver kinase B1
FAT	Fatty acid translocase
LDs	Lipid droplets
DGATi	Diacylglycerol acyltransferase inhibitor
TPD52	Tumor protein D52
HILPDA	Hypoxia inducible lipid droplet-associated
DAMPs	Damage associated molecular patterns
VLDLRs	Very low-density lipoproteins
LDLRs	LDL receptors
LSRs	Ipolysis-stimulating receptors
ACLY	ATP-citrate lyase
ACSS2	Acyl-CoA synthetase short chain family member 2
ACC	Acetyl-CoA carboxylase
USP22	Ubiquitin-specific enzyme 22
FADS	FA desaturase
ELOVL	Elongating very long-chain fatty acid enzyme
GCs	Gastric cancer cells
HMGCRs	HMG-CoA reductases
SQLE	Squalene epoxidase
ALCLs	Anaplastic large cell lymphomas
EMT	Epithelial-mesenchymal transition
FAO	Fatty acid oxidation
TAGs	Triacylglycerols
CEs	Cholesteryl esters
DGAT1	Diacylglycerol-acyltransferase 1
MGL	Monoacylglycerol lipase
ATGL	Lipase fat triglyceride lipase
HSL	Hormone-sensitive lipase
TME	Tumor microenvironment
STAT3	Transcription 3
ALOX15	Arachidonic acid lipoxygenase 15
STAT1	Transcription 1
PGE2	Prostaglandin E2
cDC1	Conventional type 1 dendritic cells
NK	Natural killer
OXPLs	Oxidized phospholipids
TLR2	Toll-like receptor 2
iNOS	Inducible nitric oxide synthase
MZ	Marginal zone
ICD	Immunogenic cell death
HMGB1	High mobility histone B1
AGER	Advanced glycosylation end-product specific receptor
PDT	Photodynamic therapy

BMDCs	Bone marrow-derived dendritic cells
TAMs	Tumor associated macrophages
HCC	Hepatocellular carcinoma
2D	Two-dimensional
3D	Three-dimensional
NSCLC	Non-small cell lung cancer
BetA	Betulinic acid
SCLC	Small-cell lung cancer
HDLNPs	HDL-like nanoparticle
SCARB1	Scavenger receptor class B member 1
INSIG1	Insulin induced gene 1
HMGCS1	HMG-CoA synthase 1
IKE	Imidazole-ketone-erastin

Introduction

Owning a sharp sword only after decade' grinding. It has been exactly ten years since Dixon et al. proposed the term ferroptosis in 2012 [1] and the basic metabolism of ferroptosis has gradually been studied clearly and thoroughly. Ferroptosis is an iron-dependent regulated cell death characterized by lipid peroxidation, which can be apparently distinguished from other types of programmed cell death by virtue of its differences in molecular mechanism and cell morphology [2]. The driving of ferroptosis is limited by intracellular ferroptosis defense system, i.e., the antioxidant systems including glutathione peroxidase 4 (GPX4) [3], ferroptosis inhibitory protein 1 (FSP1) [4, 5], dihydroorotate dehydrogenase (DHODH) [6] and other antioxidants. Recently, Fas-associated factor 1 (FAF1) was found to assemble a globular structure to isolate free polyunsaturated fatty acids (PUFAs) into a hydrophobic core to protect cells from ferroptosis triggered by peroxidation of PUFAs [7]. When the intracellular ferroptosis defense system is disrupted, ferroptosis is triggered. In most tumor types, the disruption of the antioxidant defense system is fatal to cancer cells. Therefore, there are increasing reports that ferroptosis is associated with the tumor therapy [8].

Carcinogenesis is caused by the accumulation of prooncogenes mutations, which arouse aberrant activation of multiple signaling pathways and reprogram multiple metabolic responses of cancer cells in response to rapid cell proliferation. Metabolic reprogramming of tumor cells not only accelerates cancer progression, but also confers invasiveness, metastatic ability and resistance to antitumor drugs [9]. In addition, cancer cells have a unique ability to adapt to different environments. A typical example is the metabolic flexibility of cancer cells that allows them to escape oxidative stress and survive stubbornly. Reprogramming of lipid metabolism is one of the main features of cancer cells and major factors of tumorigenesis and metastasis [10]. Strikingly, an increasing number of metabolic pathways including lipid metabolism can ultimately converge on ferroptosis [11]. Altering the levels of lipid metabolism-related enzymes to reduce polyunsaturated fatty acid peroxidation can prevent cancer cell ferroptosis from lipotoxicity. Considering that some malignancies, such as renal clear-cell carcinomas, sarcomas and diffuse large B-cell lymphomas, are seemingly susceptible to ferroptosis [3, 12, 13], which may serve as a target vulnerability in these types of cancer [14]. Importantly, ferroptosis inducers (RSL3 and ML210) may be sufficient to deplete drug-tolerant persister tumor cells that survive chemotherapy or targeted therapy [15]. Further, recent research indicated that ferroptosis and lipid metabolism are involved in cancer immune responses. For instance, the combination of IFNγ derived from $CD8^+$ T cells and fatty acids can render sensitivity to ferroptosis in cancer cells [16]. Thus, these emerging studies of ferroptosis highlight the potential therapeutic promise of targeting ferroptosis in cancer.

Here, we summarized the metabolic basis of ferroptosis and discussed the impact of the crosstalk between lipid metabolism reprogramming and ferroptosis in the tumor immune microenvironment. Finally, we summed up agents targeting lipid metabolism for ferroptotic cancer therapy.

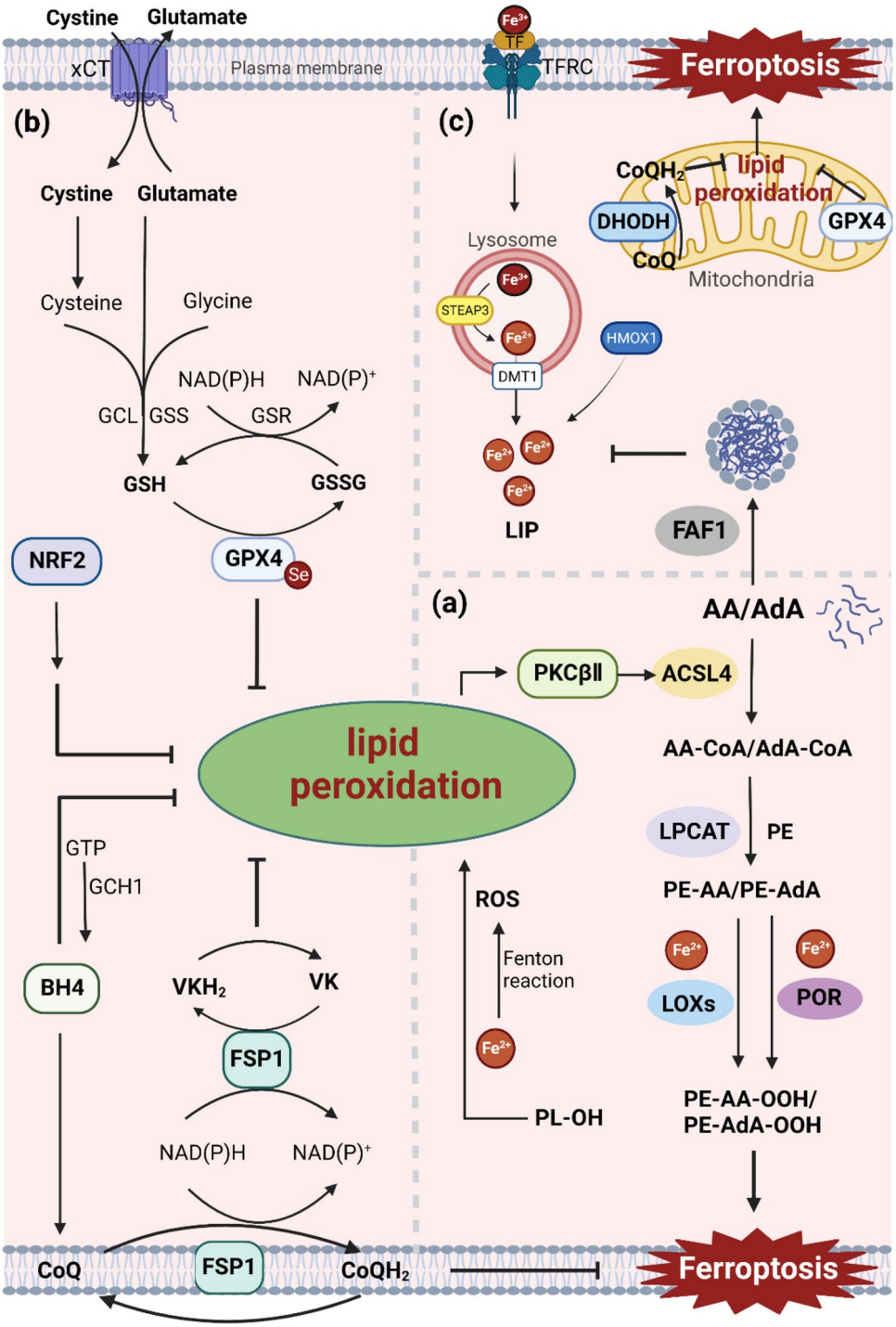
The metabolic basis of ferroptosis

Two key biochemical markers of ferroptosis are iron and lipid reactive oxygen species (ROS) accumulation, which can trigger membrane oxidative damage during ferroptosis [1]. Generally, iron metabolism and fatty acid metabolism affect iron and lipid peroxidative accumulation [17, 18]. The oxidative damage of cell membranes promotes ferroptosis due to accumulation of iron and lipid peroxidation, whereas intracellular antioxidant systems can counteract ferroptotic stress. Therefore, the regulation of ferroptosis depends on two core molecular mechanisms of oxidative damage and antioxidant defense.

Iron metabolism

It is known that iron, an important element of life, is indispensable for cell growth. Nevertheless, since involving in the formation of free radicals and the propagation of lipid peroxidation, iron can display cytotoxic effect. Increasing evidence indicates that modulating intracellular iron absorption, storage and distribution exert influence on ferroptosis susceptibility.

Ferroptotic death can be triggered by iron dependent non-enzymatic and enzymatic lipid peroxidation. The accumulation of intracellular iron, mainly including ferrous (Fe^{2+}), generates the labile iron pool (LIP), which catalyzes the formation of free radicals through the Fenton reaction and



trigger non-enzymatic lipid peroxidation (Fig. 1). In terms of molecular mechanism, the Fenton reaction catalyzes the reaction of Fe^{2+} with hydrogen peroxide (H_2O_2) to generate highly reactive hydroxyl radicals ($OH^{\cdot}$) and ferric iron (Fe^{3+}) [19]. There is a redox cycle, known as the Haberweis reaction, in which Fe^{3+} is reduced to regenerate Fe^{2+} by reacting with superoxide radicals ($O_2^{\cdot-}$) [20, 21]. Both lipoxygenase (LOXs) and cytochrome P450 oxidoreductase (POR), as the heme iron-free enzymes, mediate enzymatic lipid peroxidation, which are tightly dependent on Fe^{2+} (Fig. 1). Although lipid peroxidation has long been thought to be triggered by hydroxyl radicals generated by the Fenton reaction between hydrogen peroxide and Fe^{2+} (from LIP). However, some researchers recently believe that the highly lipophilic environment of lipid bilayer may give rise to the distance between highly active hydroxyl radical and/or Fe^{2+}

◂**Fig. 1** Mechanisms of ferroptosis and against lipid peroxidation. A schematic chart showing that ferroptosis is executed by lipid peroxidation, a process dependent on PUFAs (e.g., AA and AdA), metabolites reactive oxygen species, and the metallic element iron. **a** Mechanisms of ferroptosis. As key catalytic factors of ferroptosis, ACSL4 and LPCAT3 catalyze the production of AA-PE/AdA-PE. PKCβII can act as a lipid peroxidation sensor, and further phosphorylation of ACSL4 by activated PKCβII can amplify the effect of lipid peroxidation. The occurrence of lipid peroxidation occurs both enzymatically and non-enzymatically. LOXs and POR can catalyze enzymatic lipid peroxidation in a Fe^{2+}-dependent manner. Non-enzymatic lipid peroxidation is a free radical-driven chain reaction, and ROS generated by the iron-dependent Fenton reaction can trigger the peroxidation of polyunsaturated fatty acids. **b** Antioxidant mechanisms against lipid peroxidation. GPX4 can prevent lipid peroxidation by reducing PL-OOH to nontoxic PL-OH. Glutathione is a cofactor of GPX4, and xCT can mediate the uptake of cystine required for GSH to synthesize GPX4. FSP1 can inhibit lipid peroxidation by reducing oxidized CoQ to $CoQH_2$ in a GSH-independent manner. FSP1-dependent non-canonical vitamin K cycle is a ferroptosis suppressor to protect potently cells from lipid peroxidation. BH4 is an effective antioxidant against lipid peroxidation in a GPX4 and FSP1 independent manner. In addition, as a key transcription factor of cellular antioxidant response, Nrf2 can block lipid peroxidation by upregulating various ferroptosis inhibitory molecules. **c** Iron metabolism and antioxidant mechanisms of ferroptosis. Transferrin and TFRC are involved in Fe^{3+} transport. STEAP3 mediates the reduction of Fe^{3+} to Fe^{2+} and DMT1 mediates the transport of Fe^{2+} to the cytoplasm LIP, thereby triggering lipid peroxidation. The overexpression of HMOX1 increases LIP and promotes ferroptosis. Mitochondrial DHODH prevents lipid peroxidation by reducing CoQ to $CoQH_2$, which is parallel to antioxidant mechanisms of mitochondrial GPX4. A newly discovered ferroptosis Blocking molecule, FAF1, sequesters the free PUFAs into a spherical structure to block the contact of PUFAs with iron to prevent ferroptosis. (*GPX4* glutathione peroxidase 4; *Se* Selenium; *FSP1* ferroptosis inhibitory protein 1; *DHODH* dihydroorotate dehydrogenase; *FAF1* Fas-associated factor 1; *LIP* labile iron pool; *TF* transferrin; *TFRC* transferrin receptor; *DMT1* divalent metal transporter 1; *HMOX1* heme oxygenase 1; *STEAP3* six-transmembrane epithelial antigen of prostate 3; *ROS* reactive oxygen species; *LOXs* lipoxygenases; *POR* cytochrome P450 oxidoreductase; *AA* arachidonoyl; *AdA* adrenoyl; *ACSL4* acyl-CoA synthetase long-chain family member 4; *PEs* phosphatidylethanolamines; *LPCAT3* lysophosphatidylcholine acyltransferase 3; *PKCβII* protein kinase C-βII isoform; *VK* vitamin K; VKH_2 vitamin K hydroquinone; *BH4* tetrahydrobiopterin; *xCT* cystine-glutamate transporter; *GSH* reduced glutathione; *GSS* Glutathione synthetase; *GSR* Glutathione Reductase; *GCL* glutamate-cysteineligase; *GSSG* oxidized glutathione; *GCH1* GTP-dependent cyclohydrolase 1; *GTP* Guanosine triphosphate; *Nrf2* nuclear factor erythroid 2-related factor 2; *CoQ10* coenzyme Q10; *CoQ* ubiquinone; $CoQH_2$ ubiquinol; *PL-OH* Phospholipid alcohol; *PE-AA-OOH* phosphatidylethanolamine-arachidonoyl-hydroperoxide; *PE-AdA-OOH* phosphatidylethanolamine-adrenoyl-hydroperoxide)

and membrane polyunsaturated fatty acid is not close enough to react. Consequently, the role of hydroxyl radical in initiating lipid peroxidation may be questioned [22].

Maintenance of intracellular iron homeostasis is one of the key factors regulating ferroptosis sensitivity. For instance, cancer stem cells (CSCs) have higher levels of labile iron due to increased iron input and decreased iron output, which increases the sensitivity of CSCs to Fenton response-mediated ferroptosis [23]. The liver produces transferrin (TF), which regulates iron homeostasis through the transferrin receptor (TFRC) expressed in most tissues. Fe^{3+} enter cells through TF and TFRC complexes to form endosomes, and subsequent acidification can release iron from TF to increase LIP when endosomes form functional lysosomes [24] (Fig. 1). Paradoxically, the lipogenesis regulator SREBP2 induces transcription of the iron carrier TFs, and endogenously expressed TFs reduces intracellular iron pools and lipid peroxidation, thereby conferring resistance to drug-induced ferroptosis in circulating tumor cells (CTCs) [25]. Hence, melanoma CTCs with high endogenous expression of TF appear to hijack liver-specific genes to regulate LIP availability and ferroptosis sensitivity to overcome oxidative stress during metastasis. Fe^{3+} is blocked by STEAP3 (six-transmembrane epithelial antigen of prostate 3) and reduced to Fe^{2+}, which is transferred from the vesicle lumen to the cytoplasmic LIP via divalent metal transporter 1 (DMT1) [26] (Fig. 1). Depletion or inhibition of the transferrin receptor can counteract the susceptibility to ferroptosis. Nuclear receptor coactivator 4 (NCOA4)-mediated lysosomes accumulate large amounts of iron by degrading FTH, known as ferritinophagy [27]. Silence of NCOA4 or inhibition of lysosomal activity inhibits ferroptosis [28–30]. According to current reports, cytosolic aspartate aminotransaminase (GOT1) increases in the labile iron pool via ferritinophagy, thus increasing the susceptibility of pancreatic cancer cells to ferroptosis [31]. In addition, heme can enter the cytoplasm through FLVCR2, SLC48A1 or SLC46A1, and subsequently can be decomposed into carbon monoxide, biliverdin and Fe^{2+} by heme oxygenase 1 (HMOX1). Moderate upregulation of HMOX1 can protect cells from oxidative damage due to the antioxidant activity of HMOX1, whereas the overexpression of HMOX1 increases LIP and thus promoting ferroptosis [32, 33] (Fig. 1). Intracellular excess iron is stored by binding with ferritin, which is composed of FTH (ferritin heavy chain) and FTL (ferritin light chain). Nitrogenfixation 1 (NFS1), a [Fe–S] cluster biosynthetic enzyme, protects cells from ferroptosis. Inhibition of NFS1 activity stimulates the expression of TFRC and inhibit FTH1 resulting in activation of iron starvation response, which raises the susceptibility of lung cancer cells to ferroptosis [34]. The expression of pentapeptide protein prominin2 is increased in drug-resistant cells, which stimulates the formation of ferritin-containing multivesicular bodies/exosomes and transporting iron out of cells, thereby suppressing toxicity of lipid peroxidation [35]. Ferroportin (FPN), as the sole iron transmembrane exporter, regulates intracellular iron concentration, thus affecting the sensitivity of ferroptotic cell death [36–40]. As macromolecular ligands for cytosolic iron, the Poly rC Binding-Protein 2 (PCBP2) directs

cytosolic iron to FPN for export, and PCBP2 depletion impaired FPN-mediated iron efflux in some cell types [41].

Lipids metabolism in ferroptosis

Lipids are indispensable for the formation of cell membranes, the storage of energy in organisms and the signal transduction [42, 43]. Importantly, lipids metabolism affects cellular lipotoxicity and is also one of the metabolic bases of ferroptosis in addition to iron metabolism.

The roles of fatty acids in ferroptosis

Ferroptosis can be directly driven by the propagation of lipid peroxides. There are great differences in different types of fatty acids as substrates to drive cells sensitivity to ferroptosis [44]. According to the degree of saturation of fatty acids, fatty acids are classified as saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), among which PUFA and MUFA mainly regulate ferroptotic cell death [45, 46].

PUFA is an important inducer for ferroptosis. PUFAs on the cell membrane, which are prone to be attacked by reactive oxygen species (ROS) due to the weak C–H bond at the diallyl position, can induce lipid peroxidation [1, 47, 48]. It is worth noting that the major substrate for lipid peroxidation-induced ferroptosis is esterified PUFAs, not free PUFAs. Arachidonoyl (AA) and adrenoyl (AdA), as PUFAs, are proved to be the major catalytic substrates of acyl-CoA synthetase long-chain family member 4 (ACSL4), and oxidation of phosphatidylethanolamines (PEs) containing AA or AdA can directly act as ferroptotic signals [47] (Fig. 1). Exogenous PUFAs replace peroxidated PUFAs in membrane phospholipids to prevent ferroptosis. However, ferroptosis is induced by blocking cystine uptake or directly inhibiting GPX4 in mammalian cells, and the addition of exogenous PUFAs, including arachidonic acid, can enhance this lethal process [49, 50]. Lysophosphatidylserine lipase ABHD12 and phospholipase A_2 hydrolyze PUFAs on phospholipids to avoid lipotoxicity [51]. Genome-wide CRISPR–Cas9 suppressor screens and lipidomic profiling confirms that peroxisomes synthesize polyunsaturated ether phospholipids (PUFA ePLs) as substrates for lipid peroxidation and unique functional lipids can dynamically regulate the susceptibility to ferroptosis in cancers, neurological and cardiac diseases [52].

Unlike PUFA for ferroptosis, MUFA has anti-ferroptotic effect. Exogenous MUFAs, such as exogenous palmitic acid (POA) and oleic acid (OA), inhibit drug-induced ferroptosis [53, 54]. This is mainly due to the activation of exogenous MUFA by ACSL3, which causes MUFA to replace PUFA located on the plasma membrane, thereby reducing the sensitivity of plasma membrane lipids to oxidation [53]. Increased ratios of MUFA acyl side chain to SFA acyl side chain and MUFA to PUFA in cancer cell membrane reduce lipotoxicity and susceptibility to ferroptosis [55]. OA reduces the amount or density of oxidizable PUFAs in the membrane to suppress lipid peroxidation [54]. Metastatic melanoma cells uptake peripheral OA during lymphatic metastasis to avoid ferroptosis to form distant metastasis [53]. However, studies have recently found that POA and OA in peripheral blood enhance tumor ferroptosis induced by the combination of IFNγ and arachidonic acid through inducing ACSL4 expression [16]. Mass spectrometry analysis of phospholipids has validated that OA in peripheral blood mainly affected the composition of phospholipids containing AA acyl chains, resulting in increased lipid species of key arachidonic acid-bound PE and PC in tumor cells [16].

The process of lipid peroxidation

AA and AdA are polyunsaturated fatty acids prone to lipid peroxidation, which depend on the integration of ACLS4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3) into the membrane [47]. ACSL4 converts *de novo* synthesized long-chain fatty acids (AA or AdA) to AA-CoA or AdA-CoA, which are susceptible to drive lipid peroxidation [47, 56] (Fig. 1). LPCAT3 catalyzes the re-esterification of AA-CoA or AdA-CoA to phosphatidylethanolamine to form PE-AA or PE-AdA [1, 47] (Fig. 1). However, the pharmacological or genetic damage of LPCAT3 partially but incompletely protects cells from ferroptosis, which is primarily provoked by the bidirectional changes brought about by the inhibition of C20:4 phospholipids and corresponding increases in C22:4 phospholipids [57]. It may hint that synergistic disruption of LPCAT3 and ELOVL5, converting the excess C20:4-CoA to C22:4-CoA, furnish greater protection from ferroptosis [57]. In contrast, disruption of ACSL4 alone has showed better ferroptotic protection than LPCAT3 loss [56]. It seems to explain why ACSL4 rather than LPCAT3 is increasingly appreciated as the target of ferroptosis-related studies. ACSL4 is suppressed by integrin subunits α6 and β4 owing to activate Src and STAT3, thereby increasing breast cancer cells resistant to ferroptosis. Conversely, transcription factors in the Hippo pathway, such as YAP1, upregulate the expression of ACSL4 to promote ferroptosis in cancer cells [58, 59]. And ACSL4 may serve as a novel prognostic biomarker in breast cancer patients receiving neoadjuvant chemotherapy [60]. Although the key role of ACSL4 in ferroptosis has been continuously demonstrated, the molecular mechanisms that ACSL4 senses lipid peroxidation during ferroptosis remain unclear. Some researchers have proposed that once lipid peroxides are formed, the ROS signal will be further amplified [61, 62]. More recently, study from Zhou et al. further indicates that protein kinase C-βII isoform (PKCβII) can serve as a lipid peroxidation sensor. The

signal of lipid peroxidation activates PKCβII, which leads to phosphorylation of ACSL4 and thus rapidly amplifing lipid peroxidation to induce ferroptosis [63] (Fig. 1).

LOXs mediates enzymatic lipid peroxidation in a controlled manner to generate various lipid hydroperoxides, such as PE-AA-OOH or PE-AdA-OOH [47] (Fig. 1). Phosphatidylethanolamine-binding protein 1 (PEBP1), a RAF kinase inhibitory protein, binds to LOX15 to form a complex to alter the substrate specificity of LOX15. HK2 cells overexpressed PEBP1 enhances susceptibility to RSL3-induced ferroptosis whereas KD PEBP1 in HAEC and HT22 cells decreases ferroptotic cell death. It is further found that PEBP1 can bind free AA to promote LOX15-catalyzed AA-PE oxidation [64]. Enzymatic lipid peroxidation has been previously thought to highlight the involvement of LOXs, mainly the LOX5/12/15 subfamily, which dependents on Fe^{2+} to catalyze lipid peroxidation [13, 64, 65] (Fig. 1). Through CRISPR/Cas9-mediated suppressor screens, Zou et al. subsequently have found that POR is likewise a key oxidoreductase in ferroptotic death. POR promotes enzymatic lipid peroxidation due to facilitate the cycling between Fe^{2+} and Fe^{3+} in the heme component of cytochrome P450 [50] (Fig. 1). Non-enzymatic lipid peroxidation is a free radical-driven chain reaction in which reactive oxygen species (ROS) generated by the iron-dependent Fenton reaction trigger the oxidation of polyunsaturated fatty acids (Fig. 1). In non-enzymatic lipid peroxidation, free radicals, such as $OH^{\cdot}$, extract hydrogen from phospholipids (PL-H) on the membrane to form carbon-centered phospholipids ($PL^{\cdot}$), which reacts with molecular oxygen (O_2) to form highly reactive phospholipid peroxyl radicals ($PLOO^{\cdot}$). And $PLOO^{\cdot}$ continues to extract hydrogen from PL-H to produce phospholipid hydroperoxide (PLOOH) and additional $PL^{\cdot}$. PLOOH forms $HO^{\cdot}$ and PL-alkoxy radicals ($PL\text{-}O^{\cdot}$) in the presence of ferrous iron (Fe^{2+}) to promote lipid peroxidation, while additional $PL^{\cdot}$ reacts with O_2 again [66]. PLOOH inactivates protein cross-linking owing to produce harmful 4-hydroxynonenal (4-HNE) or malondialdehyde (MDA). Through Fenton chemistry, PLOOH forms $PL\text{-}O^{\cdot}$, which reacts with PL-H to further promote the chain reaction of lipid peroxidation. Peroxidation of lipids and the presence of 4-HNE or MDA synergistically alter membrane stability and permeability, resulting in ferroptosis [67].

Although the process of lipid peroxidation has been gradually studied, the exact mechanism that mediates ferroptosis in cells remains unclear. In the past, it has been indicated that extensive lipid peroxidation may alter the chemistry and geometry of lipid bilayers. The accumulation of lipid peroxides begets the formation of membrane pores that alter membrane permeability, and these changes ultimately affect cells survival [68, 69]. Another point of view suggests that lipid cross-linking incurs the destruction of membrane properties and the oxidative damage to biomacromolecules and cellular structures triggered by ROS derived from PUFA-PL, resulting in the loss of membrane integrity [70]. In addition, the precise cell membranes such as those in mitochondria, endoplasmic reticulum, peroxisomes, lysosomes, and plasma membranes, involved in lipid peroxidation during ferroptosis are currently unknown [59], which are needed future studies.

Antioxidant mechanisms against lipid peroxidation

The existence of antioxidant systems can combat the cytotoxicity related to ferroptosis, there are multiple ways in cells to terminate the chain reaction of lipid peroxidation (Fig. 1). Among others, GPX4 reduces PLOOH to a non-reactive lipid alcohol (PL–OH) [3, 47, 56]. FSP1 can inhibit lipid peroxidation in a GSH-independent manner via coenzyme Q10 (CoQ10), alpha-tocopherol (a-TOC) and non-canonical vitamin K cycle [4, 5]. Mitochondrial DHODH and mitochondrial GPX4, but not cytoplasmic GPX4 or FSP1, inhibit $PLOO^{\cdot}$ in the inner mitochondrial membrane due to reduce ubiquinone (CoQ) to ubiquinol ($CoQH_2$) [6]. Recently, it was reported that FAF1 may act upstream of GPX4 to prevent ferroptosis by limiting the peroxidation of free AA [7]. In addition, nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor in cellular antioxidant responses, upregulates various ferroptosis-inhibiting molecules to block ferroptosis.

GPX4 pathway

The most classical pathway in the defense system against lipid peroxidation is mediated by GPX4 that serves as a negative regulator of ferroptosis [71] (Fig. 1). Selenium and GSH are essential components for the expression and activity of GPX4 [3, 72, 73] (Fig. 1). Selenium increases the activity of GPX4 through the selenocysteine (Sec) residue at 46 (U46) during GPX4 synthesis [72]. Acetyl-CoA is converted to isopentenyl pyrophosphate (IPP) via the mevalonate pathway, which results in the addition of a selenocysteine residue to the catalytic center of GPX4 to activate GPX4, thereby inhibiting ferroptosis [74]. Recent research has shed light on selenium supplementation enhanced the expression of GPX4 in T cells to get a rise out of ferroptosis, thereby increasing the number of follicular helper T cells (TFH) and further promoting the antibody response [75]. At the transcriptional level, selenium supplementation activates the inducible transcription factor AP-2γ (TFAP2C) and specific protein 1 (SP1) to upregulate GPX4 expression [76]. Notably, SP1, is also a key transcription factor for ACSL4, binds to the ACSL4 promoter region to increase ACSL4 transcription. Considering the opposite effects of GPX4 and ACSL4, it can be speculated that SP1 may play a dual role in regulating ferroptotic damage [77]. The main reducing force donor of GPX4 is glutathione (GSH), an important

molecule in cells to resist peroxidative stress, which is essential for preventing ferroptosis [3]. Metabolomic analysis of cancer has revealed that the level of glutathione is elevated in majority of tumors [78]. Glutamate-cysteine ligase (GCL) is the rate-limiting enzyme in the glutathione biosynthetic pathway, and Butionine sulfoximine (BSO), a GCL inhibitor, has been discovered to induce ferroptosis in cancer cells [79]. Cystine/glutamate anti-transporter xCT, also known as system xCT, consists of two subunits SLC7A11 and SLC3A2, which transports L-cystine into cells and export L-glutamine [1, 80] (Fig. 1). Since cystine is a dimer of cysteine, which is a crucial component of GSH synthesis, the uptake of cysteine plays an important role in GSH synthesis. Several findings indicate that intracellular cystine and cysteine deficiency can undergo ferroptosis by affecting GSH content and glutamate accumulation [1, 81, 82]. Neuroblastoma with high expression of the oncogene MYCN has been found to be highly dependent on cysteine, and blocking cysteine promotes cancer cells ferroptosis and remarkably inhibits tumor growth [83]. Strikingly, recent study has found that glutamic acid cysteine ligase catalytic subunit (GCLC) synthesizes glutamyl dipeptide, leading to glutamate accumulation to prevent ROS production and ferroptosis in non-small cell lung cancer cells under cystine starvation [84]. P53, a tumor suppressor gene with broad and powerful functions, and BRCA1-associated protein 1 (BAP1) both can transcriptionally repress SLC7A11 expression and reduce GSH synthesis to promote tumor ferroptosis [85, 86]. The p53-SLC7A11 axis can also promote ferroptosis in a GSH-independent manner [87]. SLC7A11 is activated by the stem cell transcription factor SOX2 and upregulates in lung cancer stem cell-like cells (CSLCs) [88]. Mutations in the SOX2 binding site of SLC7A11 gene promoter reduce SLC7A11 expression and confer sensitivity to ferroptosis in lung cancer cells. SLC7A11 is highly expressed due to DKK1 secreted by breast cancer stem cells (BCSCs), which protects metastatic tumor cells from lipid peroxidation and ferroptosis [89]. However, in human pancreatic cancer, SLC7A11 is highly expressed in cancer-associated fibroblasts (CAFs) rather than tumor cells. In vivo and in vitro experiments have revealed that genetic ablation of SLC7A11 in pancreatic cancer cells alone has no effect on tumor growth, while stable knockout of SLC7A11 in human pancreatic cancer cells as well as in CAFs is required to diminish tumor growth, metastatic spread and fibrosis [90].

In addition, NADPH is not only involved in the formation of antioxidant systems including GPX4 and FSP1 (Fig. 1), but also affects the mevalonate pathway and fatty acid synthesis and elongation, which places NADPH as a key factor in protecting against lipid peroxidation and ferroptosis. Depletion of NADPH promoted ferroptotic cell death and NADPH can be used as a biomarker to measure the sensitivity of various cancer cell lines to ferroptosis [91] Cytoplasmic NADPH phosphatase (MESH1) depletion confers ferroptosis resistance by maintaining NADPH and GSH levels [92]. Further exploration shows that NADPH levels regulated by MESH1 might trigger endoplasmic reticulum (ER) stress and integrative stress responses as another mechanism to determine ferroptosis [93].

FSP1 pathway

For a long time, GPX4 has been considered to as the only ferroptosis defense system. However, studies have found that the sensitivity of different cell lines to GPX4 inhibitor-induced ferroptosis varies widely, suggesting that other ferroptosis defense systems may exist in cells [12]. FSP1, formerly known as flavoprotein apoptosis-inducing factor mitochondria-associated 2 (AIFM2), is found to parallel GPX4 to inhibit ferroptosis [4, 5] (Fig. 1). In the past, apoptosis inducing factor (AIF) and FSP1 were identified as type 2 NADH ubiquinone oxidoreductase (NDH-2) enzymes in mammalian mitochondria, suggesting a possible interaction between FSP1 and ubiquinone [94]. In addition, coenzyme Q10 has been pointed to significantly reduce the susceptibility of cells to ferroptosis, but the study failed to clarify the underlying molecular mechanism [95]. The mevalonate pathway produces coenzyme Q10 and IPP, which can diminish ferroptosis [74]. FSP1, mainly located in lipid droplets and the plasma membrane, is an NAD(P)H-dependent oxidoreductase that NAD(P)H catalyzes the regeneration of non-mitochondrial coenzyme Q10, thereby attenuating lipid peroxidation (Fig. 1). Extra-mitochondrial ubiquinone is reduced from CoQ10 by FSP1, which can either directly capture lipid free radicals or indirectly act as an antioxidant by recycling α-tocopherol [11]. The CoQ-FSP1 axis is a critical downstream effector of the KEAP1-NRF2 pathway and mediates ferroptosis defense in KEAP1-inactivated lung cancer [96]. Recently, Marcus Conrad et al. have found that FSP1 mediates the reduction of vitamin K (VK) to vitamin K hydroquinone (VKH_2) to involve in non-canonical vitamin K cycling and lead to cell protection against lipid peroxidation and ferroptosis [97] (Fig. 1).

DHODH pathway

Since the newly discovered ferroptosis inhibitor FSP1 reduces CoQ to $CoQH_2$ on the cell membrane, $CoQH_2$ is shown to act as a free-radical-trapping antioxidant to block lipid peroxidation and inhibit ferroptosis [4, 5]. Subsequently, Mao et al. have revealed for the first time that the DHODH-$CoQH_2$ system localized to the inner mitochondrial membrane is independent of FSP1 and GPX4 [6]. DHODH, an enzyme previously found to catalyze the synthesis of pyrimidine nucleotides, catalyzes CoQ to $CoQH_2$ in the inner mitochondrial membrane to prevent lipid peroxidation

(Fig. 1). Furthermore, mitochondrial GPX4 and DHODH are shown to constitute two major defense checkpoints in mitochondria for detoxifying lipid peroxides (Fig. 1). When mitochondrial GPX4 is inactivated, DHODH-mediated $CoQH_2$ production is subsequently enhanced to neutralize lipid peroxidation and prevent ferroptosis in mitochondria [6]. Therefore, mitochondrial GPX4 and DHODH can compensate each other to against mitochondrial lipid peroxidation, whereas cytosolic GPX4 and plasma membrane FSP1 cannot compensate for each other hinder ferroptosis. Additionally, as another mitochondrial enzyme, complex I can also generate $CoQH_2$, but the inhibition of complex I does not appear to have a sustained effect on the sensitivity to erastin-induced ferroptosis [98]. Therefore, there remains a need to elucidate in regulating ferroptosis for the role of complex I.

FAF1 pathway

FAF1, originally identified as a tumor suppressor, binds to β-catenin to promote proteasomal degradation of β-catenin in the absence of fatty acids [99–101]. Cui S et al. have subsequently demonstrated that even in the absence of a GPX4 inhibitor, FAF1 deletion sensitizes cells to ferroptosis when exposes to physiological levels of PUFAs [7]. And KO FAF1 mice is susceptible to develop hepatic injury when consuming AA-enriched diet [7]. Mechanistically, FAF1 mediates ferroptosis suppression via sequestering free PUFAs to the hydrophobic core to limit free PUFAs access to Fe^{2+} (Fig. 1). In general, both FAF1 and free PUFAs are present in the cytoplasm, and FAF1 chelates PUFAs into the hydrophobic core of the FAF1-PUFA complex, leading PUFAs less accessible to Fe^{2+} to trigger peroxidation. However, in the absence of FAF1-mediated protection, AA is susceptible to Fe^{2+}-mediated peroxidation. Unlike lipoxygenase-catalyzed lipid peroxidation, the increased production of the ferroptotic metabolites HETEs due to FAF1 deficiency is not site-specific. GPX4-mediated detoxification response is needed to $FAF1^{-/-}$ cells, which are more sensitive to RSL3 (GPX4 inhibitor), especially when $FAF1^{-/-}$ cells are treated with AA [7]. The FAF1-PUFA complex can not only stabilize β-catenin to promote cell proliferation [101], but also protect cells from lipid peroxidation by limiting PUFA exposure to Fe^{2+} [7]. However, it remains unclear how exactly AA is packaged into the FAF1-AA complex and whether FAF1 is inhibited to avoid lipid peroxidation through other mechanisms mediated by other domains of the protein, which are needs to be further research.

Other antioxidant pathways

Tetrahydrobiopterin (BH4), an antioxidant that traps lipid peroxidized free radicals, antagonizes ferroptosis in a GPX4- and FSP1-independent manner [11, 70, 102] (Fig. 1). BH4 degrades phospholipids containing two PUFA tails by directly capturing antioxidant free radicals [70]. Dihydrofolate reductase (DHFR) converts dihydrobiopterin (BH2) into BH4 to achieve BH4 regeneration. Genetic or pharmacological blockade of DHFR and inhibition of GPX4 synergistically increase susceptibility to ferroptosis [102]. GCH1 (GTP-dependent cyclohydrolase 1) initiates the synthesis of BH2 and tetrahydrobiopterin BH4 to synthesize CoQ 10 *de novo*, thereby promoting resistance to ferroptosis [70] (Fig. 1). Paradoxically, Soula et al. have found that the combination of BH4 or BH2 + DHFR and CoQ10 do not show any synergy in liposome assays. Meanwhile, they fail to find any scoring genes encoding enzymes involved in CoQ10 metabolism in the BH2 rescue CRISPR screen and further find a synergistic effect between BH4 and tocopherol [102]. The Keap1-Nrf2-ARE signaling pathway is one of the most important cellular defense systems against oxidative stress damage. As a vital transcription factor of the cellular antioxidant response, Nrf2 has been increasingly shown that it may be involved in the regulation of ferroptosis [103–105] (Fig. 1). Although cancer cells produce large amounts of ROS, NRF2 overexpression can decline ROS-induced lipid peroxidation. Inactivation of KEAP1 (tumor suppressor gene) prevents NRF2 from being ubiquitinated and degraded to escape lipid peroxidative stress [106]. KEAP1 mutation or deletion in lung cancer cells upregulates FSP1 expression through NRF2, resulting in ferroptosis resistance and radio resistance [96]. More importantly, NRF2 induce the expression of xCT and GPX4 of the GSH antioxidant system [107, 108]. And NRF2 increases NADPH regeneration to protect cells from lipid peroxidation, while NRF2 activation regulates iron-regulated genes (including those involved in iron storage, iron export, heme synthesis, and hemoglobin catabolism) to hinder ferroptosis [107, 109]. In addition, 15-HpETE-PE is a critical signaling molecule for ferroptotic cell death, and calcium-independent phospholipase A2β (iPLA2β) is found to play an anti-ferroptosis function due to remove ferroptotic oxidized phospholipid 15-HpETE-PE in cell membrane. iPLA2β is a key regulator of p53-driven ferroptosis, and iPLA2β-mediated detoxification of lipid peroxides in a GPX4-independent manner is sufficient to inhibit p53-driven ferroptosis under ROS-induced stress [110]. Besides, other natural antioxidants including vitamin E, thioredoxin and mitoxone have also been indicated to block lipid peroxidation [25, 111–113].

Reprogramming of lipid metabolism and ferroptosis in cancer

Cancer cells need active metabolic reprogramming, such as lipid metabolism reprogramming, to meet rapid proliferation. However, lipid metabolism reprogramming may confer

lethal cytotoxicity related to ferroptosis. It is commonly reported that ferroptosis is regulated by lipid metabolism reprogramming in cancers. It seems that cancer cells have unique tricks in how to mobilize rapid lipid metabolism to meet their own needs while preventing cellular lipotoxicity. More importantly, there has been increased focus on ferroptotic cancer cells that can release damage associated molecular patterns (DAMPs) to affect immune cells.

Lipid metabolism reprogramming in cancer

Reprogramming of lipid metabolism, is considered a hallmark of cancer, supports tumorigenesis and cancer progression [10, 114]. Tumor cells mobilize lipid to obtain energy, synthesize biofilm components, and transmit signaling molecules for cell survival, proliferation, invasion, and metastasis [10]. Lipid reprogramming in cancer cells is mainly manifested in alterations about lipid (fatty acids and cholesterol) uptake, de novo lipogenesis (including FA activation, FA desaturation and fatty acid chain elongation), fatty acid oxidation, lipid droplet storage and degradation pathways [114–116] (Fig. 2). In addition, lipid metabolism reprogramming may contribute to evading programmed cell death including ferroptosis to promote cancer progression.

Uptake of lipids

Highly proliferative cancer cells exhibit increased uptake of exogenous free fatty acids and lipoproteins [117]. The fatty acids uptake of cancer cells is increased through high expression of fatty acid protein transporters including CD36 (FA translocase), SLC27 (FA transporter family), FABPs (plasma membrane FA binding proteins) [118] (Fig. 2a). High expression of CD36 is involved in the metastasis of oral squamous cell carcinomais and is associated with poor prognosis in cancers including breast cancer, ovarian cancer, gastric cancer [119]. Cholesterol and VLDL are processed into LDL in the blood. Cholesterol-rich lipoproteins are taken up due to very low-density lipoproteins (VLDLRs), LDL receptors (LDLRs), and lipolysis-stimulating receptors (LSRs) overexpression in cancer cells (Fig. 2a). Upregulation of LDLRs is positively associated with poor prognosis in patients with small cell lung cancer, breast cancer and pancreatic cancer [120–122]. Cancer cells increase the uptake of exogenous fatty acids by LDLR, FATP, CD36 and other mechanisms that increase the intracellular fatty acid pool, which results in the plasma membrane exhibiting increased ratio of MUFA side chains to SFA side chains and increased ratio of MUFA to PUFA, thereby reducing lipotoxicity and ferroptosis [55] (Fig. 2a). Deprivation of lipoproteins in the culture medium of lymphoma cells induces ferroptosis, and sensitivity of ferroptosis is increased by targeted reduction of cholesterol uptake in cholesterol-addicted lymphoma cells [123]. Cancer cells enhance lipid uptake and/or lipid biosynthesis in the context of chronic exposure to 27-hydroxycholesterol (27HC) to inhibit cancer cell ferroptotic death and promote tumorigenesis and metastasis [124].

Synthesis of lipids

In addition to increasing the uptake of exogenous lipids, cancer cells respond to their high metabolic mainly demands by activating adipogenesis, which relies on high expression of lipid synthases. Since the major substrate for *de novo* synthesis of fatty acids and cholesterol is acetyl-CoA, intracellular acetyl-CoA levels are likewise one of the key factors in lipid synthesis [119]. Acetyl-CoA is upregulated by overexpressing acetyl-CoA synthases including ATP-citrate lyase (ACLY) and Acyl-CoA synthetase short chain family member 2 (ACSS2) in tumor cells (Fig. 2b). Reduction of ACLY expression reduces the survival, proliferation, invasion and metastatic capacity of various types of cancer cells and affects cancer-related processes such as colorectal, lung and breast cancer [125]. And the expression of fatty acid synthase also affects the lipid synthesis of cancer cells. For instance, ACC is the rate-limiting enzyme for fatty acid synthesis, and ACC1 (the cytoplasmic enzyme) is overexpressed in various human cancers including breast, prostate, adenocarcinoma and liver cancer [119]. Energy stress activates AMPK, which subsequently phosphorylates ACC to reduce polyunsaturated fatty acid synthesis to inhibit ferroptosis [126]. ACC and ACLY are upregulated by ubiquitin-specific enzyme 22 (USP22) in hepatocellular carcinoma to promote *de novo* fatty acid synthesis and promote tumorigenesis, which may provide new ideas for targeting lipid synthesis in the treatment of liver cancer [127]. Palmitic acid, the major product of *de novo* lipogenesis, is synthesized and catalyzed by ACC and FASN [128] (Fig. 2b). FASN overexpression is found in many epithelial cancers and their precancerous lesions, which may be associated with a high risk of cancer recurrence and death. Cancer cells desaturate palmitate by high expression of SCD or FA desaturase (FADS), and/or extend FA by high expression of elongating very long-chain fatty acid enzyme (ELOVL), which produces other FA species, including stearate and oleate [10, 55] (Fig. 2b). ELOVL5 and FADS1 are upregulated in mesenchymal-type gastric cancer cells (GCs) to promote ferroptosis, while DNA methylation results in ELOVL5 and FADS1 silencing to render intestinal-type GCs resistant to ferroptosis [129]. Ectopic SCD expression promotes EMT, which is likewise closely associated with poor prognosis in colorectal and breast cancer [130]. SCD1 is upregulated by lactate and engender MUFAs, which contributes to liver cancer cells

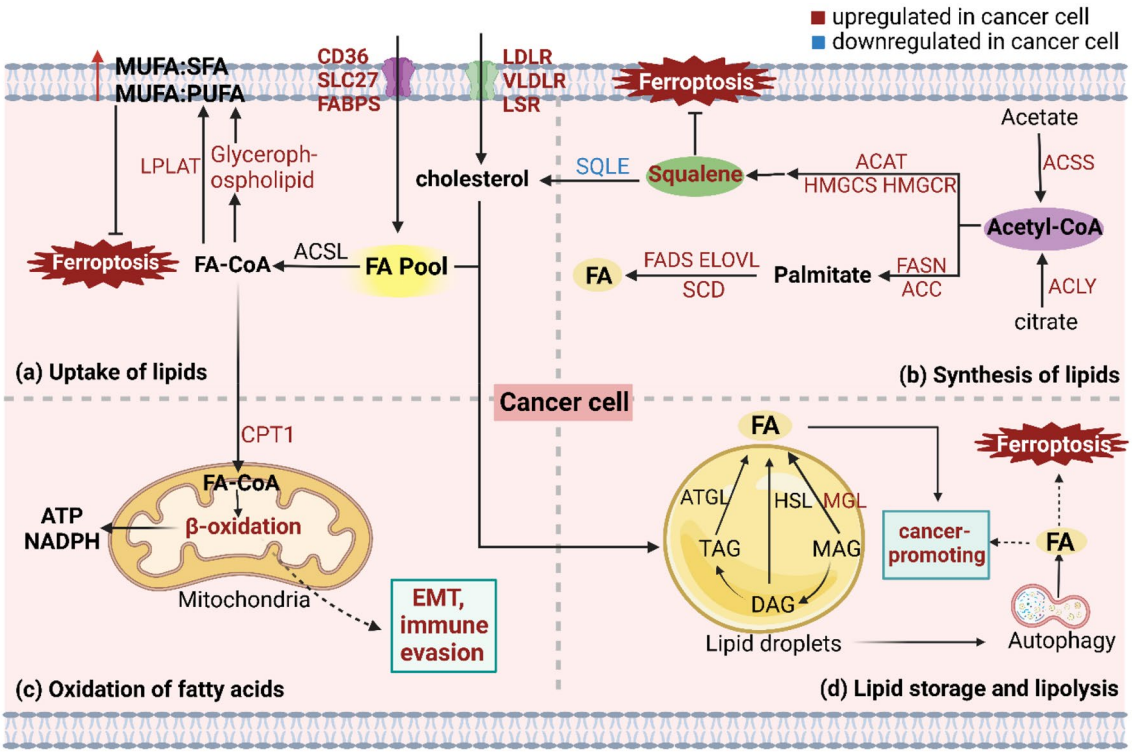


Fig. 2 Lipids metabolism reprogramming in cancer cell. **a** Uptake of lipids Cancer cells increase FAs uptake by overexpressing CD36, SLC27, and FABPs. Cholesterol-rich lipoproteins can be taken up by VLDLR, LDLR, and LSR. The uptake of FAs through LDLR, FATP, CD36 and other mechanisms in cancer cells that increase the intracellular FA pool, which results in the plasma membrane exhibiting increased ratio of MUFA side chains to SFA side chains and increased ratio of MUFA to PUFA, thereby preventing ferroptosis. The increase of glycerophospholipids can maintain membrane homeostasis. **b** Synthesis of lipids Cancer cells can synthesize more acetyl-CoA by overexpressing the lipids ACSS and ACLY. Palmitic acid is the main product of *de novo* lipogenesis, catalyzed by FAs synthases including ACC and FASN. Cancer cells produce other FAs by overexpressing SCD or FADS to desaturate palmitic acid, and/or by overexpressing ELOVL to prolong FAs. High expression of cholesterol synthesis enzymes including HMGCS and HMGCR can promote cancer development. SQLE is reduced due to cholesterol accumulation to accelerate rectal cancer progression. Accumulation of squalene protects lymphoma cells from ferroptosis. **c** Oxidation of fatty acids FAO is overactive in many cancers. In MCF-7, FAO can generate more ATP and increase NADPH levels to attenuate ROS toxicity. FAO is increased to promote EMT in CSCs. Radiation-resistant glioblastoma multiforme cells increase FAs uptake and CPT1A and CPT2 expression to increase subsequent FAO and tumor immune evasion. **d** Lipid storage and lipolysis Excess lipids in cancer cells can be stored in LDs in the form of MAG, DAG and TAG to prevent lipotoxicity. Highly aggressive cancer cells express high levels of MAG to lipoprotein free FAs. Tumor cells increase intracellular free FAs through autophagy to promote ferroptosis and inhibit tumor growth. With nutritional deficiencies, lipophagy can play a role in promoting cancers by mobilizing FAs for subsequent catabolic and anabolic processes. (*FA* fatty acids; *VLDLRs* very low-density lipoproteins; *LDLRs* LDL receptors; *LSRs* ipolysis-stimulating receptors; *ACSL* acyl-CoA Synthetase Long Chain Family Membe; *ACLY* ATP-citrate lyase; *ACSS* acyl-CoA synthetase short chain family member; *ACC* acetyl-CoA carboxylase; *FADS* FA desaturase; *ELOVL* elongating very long-chain fatty acid enzyme; *HMGCR* HMG-CoA reductases; *HMGCS* 3-Hydroxy-3-Methylglutaryl-CoA Synthase; *ACAT* acyl-CoA cholesterol acyltransferase; *SQLE* squalene epoxidase; *FAO* fatty acid oxidation; *TAG* triacylglycerols; *MGL* monoacylglycerol lipase; *ATGL* lipase fat triglyceride lipase; *HSL* hormone-sensitive lipase; *LPLAT* Lysophospholipid acyltransferase)

resist oxidative stress-induced lipid peroxidation [131]. In addition, cholesterol biosynthetic enzymes are involved in regulating the growth and metastasis of cancer cells [132]. For example, knockdown of HMG-CoA reductases (HMGCRs), the first rate-limiting enzyme for cholesterol synthesis, inhibits cancer development. Squalene epoxidase (SQLE), the second rate-limiting enzyme for cholesterol synthesis, is reduced by cholesterol accumulation, which accelerates rectal cancer progression and metastasis [133] (Fig. 2b). Loss of SQLE expression has been reported to result in accumulation of the upstream metabolite squalene, which protects Anaplastic Lymphoma Kinase positive (ALK+) anaplastic large cell lymphomas (ALCLs) from ferroptosis [134] (Fig. 2b).

Adipogenesis is transcriptionally regulated by sterol regulatory element binding proteins (SREBPs), which are master transcription factors of lipids metabolism [119]. SREBP1 overexpression contributes to promoting epithelial-mesenchymal transition (EMT) to accelerate breast cancer growth and metastasis [135]. Ammonia, as a key activator

of SREBP1, stimulates SCAP-Insig protein complex dissociation to induce SREBP1 activation and lipid synthesis, thereby promoting lung and brain tumor growth in mice [136].

Oxidation of fatty acids

Accumulating evidence supports the idea that fatty acids oxidation related proteins are overexpressed or active in cancers, such as triple-negative breast cancer and glioma [137]. Cancer stem cells are characterized by elevated levels of mitochondrial ROS, which promotes EMT through fatty acid β-oxidation, thereby enhancing tumor invasion and metastasis [138] (Fig. 2c). The increase in CD47 expression reported in radioresistant glioblastoma multiforme cells is fuelled by an enhanced fatty acid oxidation (FAO), facilitated by fatty acid uptake and high expression of CPT1A and CPT2(mitochondrial FAO metabolizing enzymes) (Fig. 2c). Besides, it is observed that macrophages phagocytosed tumor cells decreased with low doses of palmitate, and the combination of FAO inhibitors and anti-CD47 antibodies can improve the tumor control effect of the relapsed glioblastoma multiforme mouse model after radiotherapy [139]. Additionally, mitochondria, as master regulators of oxidative phosphorylation, is a major source of ROS and can impel ferroptotic death in a variety of cells. Mitochondrial fatty acid β-oxidation induces the production of lipid peroxides during ferroptosis [74]. A study of clear cell renal cell carcinoma has revealed that inhibition of β-oxidation leads to reduced fatty acid metabolism, which prevents lipid peroxidation and ferroptosis through the GSH/GPX pathway [140].

Lipid storage and lipolysis

LDs is a lipid storage organelle mainly composed of neutral lipids such as triacylglycerols (TAGs) and cholesteryl esters (CEs) (Fig. 2d). SREBP is activated to store excess cholesterol and fatty acids into LDs [141, 142]. In cancer cells, excess FAs is stored in LDs in the form of triacylglycerols and sterol esters, which can maintain lipid homeostasis and prevent lipotoxicity [10, 143] (Fig. 2d). For instance, to attenuate outcome of cytotoxicity from overactive FAO, Glioblastoma cells highly express diacylglycerol-acyltransferase 1 (DGAT1) to produce triglycerides, which are stored in lipid droplets to reduce ROS stress [142]. In breast cancer cells MCF-7, LDs act as substrates for β-oxidation to generate ATP to restore the reoxygenation process after hypoxia, while β-oxidation leads to an increase in NADPH levels to reduce ROS toxicity [144]. Inhibition of lipid storage leads to elevated ROS levels and impairs tumorigenesis in vivo [144, 145]. Autophagy degrades lipid droplets and lipolytic fatty acids to increase intracellular fatty acids (Fig. 2d). Cancer cells increase intracellular free fatty acid levels through lipophagy, which promotes tumor suppression through ferroptosis, ROS production, and ER stress [146–148] (Fig. 2d). However, lipophagy exerts a tumor-promoting effect by mobilizing fatty acids for subsequent catabolic and anabolic processes under nutrient deprivation [149] (Fig. 2d). Monoacylglycerol lipase (MGL), lipase fat triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) regulate lipolysis (Fig. 2d). Highly invasive cancer cells express high levels of MGL to release free fatty acids through lipolysis, resulting in the production of diversified lipid networks to promote tumor signaling molecules and further contribute to tumor survival, growth and migration [150] (Fig. 2d). Recent studies have found that peroxisomal β-oxidation, as an intracellular fatty acid sensor, regulates lipolysis through ATGL ubiquitination [151].

Taken together, it can be concluded that lipid metabolism reprogramming is closely related to cancer progression. Importantly, lipid metabolism disorders may affect the lipotoxicity of cancer cells and ferroptotic cell death, thereby regulating cancer progression.

Dysregulation of lipid metabolism processes affect ferroptosis

Lipid metabolism modulates ferroptosis sensitivity through multiple pathways. Intracellular lipid synthesis, uptake, storage, and degradation processes are tightly and finely regulated, and dysregulation of these processes can affect ferroptosis sensitivity. For instance, dysregulation of cholesterol homeostasis is implicated in ferroptosis resistance and increases tumorigenicity and tumors metastasis. The uptake and/or biosynthesis of lipid is increased in cancer cells upon chronic exposure to 27HC, and thus arousing upregulation of GPX4 to avoid ferroptosis to promote tumorigenesis and metastasis [124]. Inhibition of the activity of squalene synthase (SQS) or SQLE involved in cholesterol synthesis prevents ferroptosis [134]. In contrast, HMG-CoA reductase, the rate-limiting enzyme for cholesterol synthesis, is inhibited by statins to enhance ferroptosis [95]. The knockdown of Acyl-CoA synthetase family member 2 (ACSF2) and citrate synthase (CS) which are involved in fatty acid synthesis and activation blocked erastin-induced ferroptosis [1]. Drug inhibition or gene ablation of SCD1 and acyl-CoA 6 desaturase (FADS2) involved in fatty acid desaturation can promote ferroptosis in ascites-derived ovarian cancer cells, thereby delaying tumor growth and formation of CSCs and reducing of platinum resistance [152]. As the regulator of adipogenesis, SREBPs master regulatory switch of lipid homeostasis, appear to play a dual role in regulating ferroptosis. On the one hand, SREBP1 activation stimulates the transcription of key enzymes in the lipid synthesis pathway, and genetic or drug ablation of SREBP1 induces

ferroptosis [153]. SCD1 is a major downstream factor in SREBP1-mediated ferroptosis resistance. Pharmacological inhibition of SCD1 sensitizes cancer cells to RSL3-induced ferroptosis, and CRISPR/Cas9-mediated knockdown of SCD1 also increases cell sensitivity to ferroptosis [153]. In vitro and in vivo evidence have confirmed that uptake of lactate from the tumor microenvironment by hepatoma cells promotes ATP production and AMPK inactivation, and subsequently upregulates SREBP1 and SCD1 to increase the production of anti-ferroptotic MUFA [131]. Activation of the PI3K-AKT-mTORC1 signaling pathway confers breast cancer cells resistance to ferroptosis by upregulating SREBP1-mediated MUFAs [153]. SREBP2 directly induces transcription of the siderophore TF to reduce LIP, thereby rendering insensitivity to ferroptosis [25]. On the other hand, partially, ferroptosis inducers (erastin, sorafenib or sulfasalazine) inhibit the expression of BCAT2 (branched-chain amino acid aminotransferase 2) through the ferritinophagy-AMPK-SREBP1 pathway to promote ferroptosis in liver cancer, which may provide a potential therapeutic strategy for overcoming sorafenib resistance [154]. Additionally, under conditions of energy stress, AMP-activated protein kinase (AMPK) reduces PUFA synthesis via acetyl-CoA carboxylase (ACC) to prevent fatty acids peroxidation [126]. Liver kinase B1 (LKB1) is the major upstream kinase of AMPK. LKB1-AMPK axis negatively regulates ferroptosis by inhibiting fatty acid synthesis [155]. Since fatty acids is rich in the tumor microenvironment, CD36 (also known as fatty acid translocase (FAT)) mediates fatty acids uptake to induce lipid peroxidation and ferroptosis, resulting in impairing the antitumor effect of $CD8^+$ T cells [156, 157]. In acidic cancer cells, omega-6 (n-6) and omega-3 (n-3) PUFAs preferentially accumulate in LDs to buffer excess PUFA, which can be blocked by using DGATi (diacylglycerol acyltransferase inhibitor) to increase tumor ferroptosis and improve the antitumor effect [145]. Tumor protein D52 (TPD52) is required for neutral lipid accumulation and storage in cultured cells [158], and TPD52 overexpression in hepatoma cells contributes to LDs accumulation to reduce RSL3-induced ferroptosis [148]. In addition, LDs are broken down by autophagy [159, 160], and lipophagy-mediated the degradation of intracellular LDs rebates lipid storage to undergo ferroptosis [148]. Hypoxia, a hallmark feature of the tumor microenvironment, induces HIF-1α-dependent LDs accumulation [144]. Under hypoxic conditions, high HIF1α expression in HT-1080 fibrosarcoma cells results in increased expression of fatty acid-binding proteins 3 and 7 to promote fatty acid uptake and boost lipid storage capacity, thereby avoiding ferroptosis [161]. On the contrary, in kidney cancer-derived cells, activation of EPAS1 (also known as HIF2α) increases PUFAs production by upregulating the expression of hypoxia inducible lipid droplet-associated (HILPDA) to promote ferroptotic cell death [12]. However, HIF2α is activated by adipokine chemerin in clear cell renal cell carcinoma, which inhibits fatty acid oxidation to prevent ferroptosis [162]. Altogether, in the tumor microenvironment, HIF-mediated signaling appears to have a dual role in affecting cancer cell ferroptosis via regulating lipid homeostasis.

Crosstalk between lipids metabolism and ferroptosis reshapes anti-tumor immune microenvironment

In the tumor microenvironment (TME), cancer cells interact with other cells including immune cells and fibroblasts to regulate the tumor immune response. Among others, the role of the crosstalk between ferroptosis and lipid metabolism in regulating anti-tumor immunity has gradually attracted people's attention and research.

CAFs are one of the most abundant cells in the TME, and the release of lactate from tumor cells and CAFs results in the formation of an acidic pH 5.5–6.6 environment in the TME [163] (Fig. 3b). n-3 and n-6 PUFAs selectively induces ferroptosis in cancer cells under acidic tumor environment conditions [145] (Fig. 3a). Prof. Jun Yan et al. has found that tissue-resident macrophages in the pre-metastatic microenvironment upregulate the immunosuppressive molecule PD-L1 and produce large amounts of lactate when induced by exosomes secreted by primary tumor cells, which establishes an immunosuppression microenvironment to promote tumor metastasis [164]. Not only does extracellular lactate serve as one of the main carbon sources for lipid biosynthesis, but lactate can regulate the production of various lipid substances via AMPK and activator of transcription 3 (STAT3) [165]. Lactate in the TME produces MUFA through the HCAR1/MCT1-SREBP1-SCD1 pathway and inhibit ACSL4, thereby synergistically reducing the susceptibility of hepatoma cells to ferroptosis [131] (Fig. 3a). CAFs in the TME release exosomal miR-522, which targets arachidonic acid lipoxygenase 15 (LOX15) and blocks ferroptosis caused by lipid ROS accumulation in gastric cancer cells [166] (Fig. 3a, b). CAFs releases cysteine and GSH to nearby ovarian cancer cells to protect cells from chemoresistance-induced oxidative stress [167]. However, effector $CD8^+$ T cells produce IFNγ, which reduces cysteine and GSH release by downregulating SLC7A11 and SLC3A2 in CAFs, which leads to oxidative stress in ovarian cancer cells [167]. IFNγ produced by activated $CD8^+$ T cells inhibits the expression of SLC7A11 in cancer cells by activating transducer and activator of transcription 1 (STAT1), which triggers ferroptosis in tumor cells and contributes to improve the anti-tumor efficacy of immunotherapy [168] (Fig. 3a, c). Additionally, TGFβ1, is released by many cell types including macrophages, promotes tumor cells ferroptosis

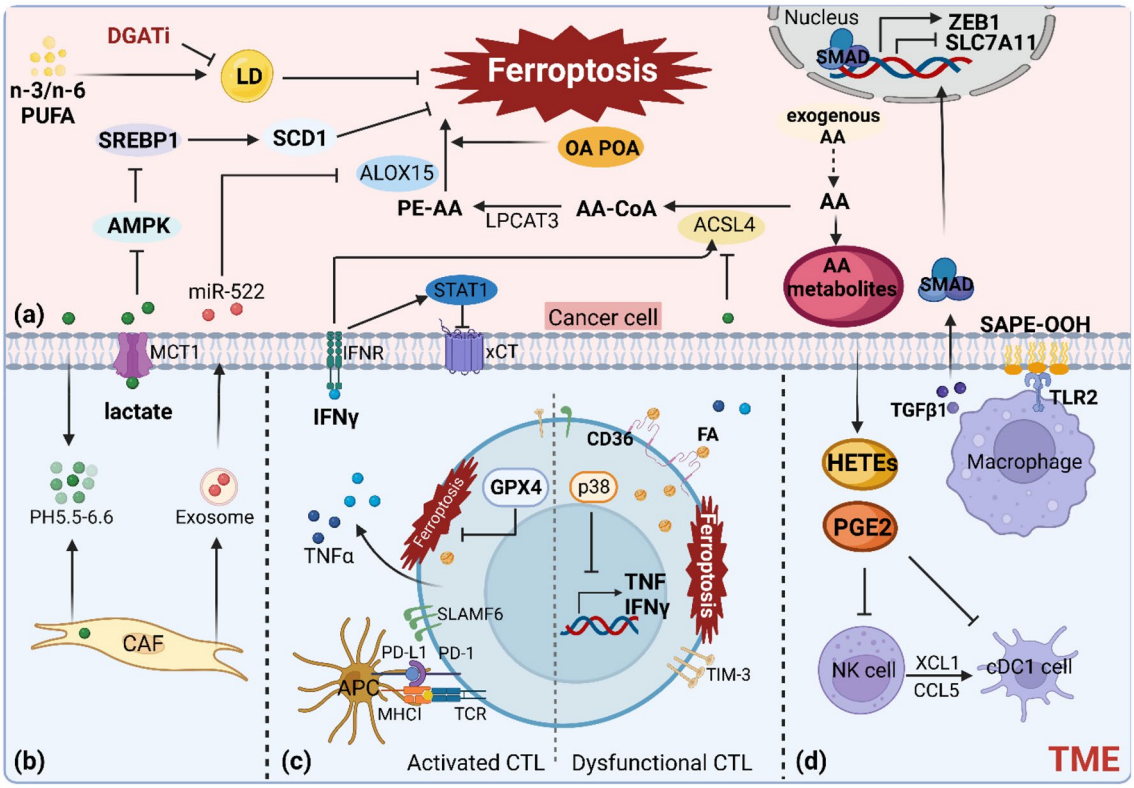


Fig. 3 Crosstalk between lipid metabolism and ferroptosis reshapes anti-tumor immune microenvironment. **a** Lactate can inhibit ferroptosis in liver cancer cells by inhibiting ACSL4 and HCAR1/MCT1-SREBP1-SCD1 pathways. n-3 and n-6 PUFA preferentially accumulated in LDs of acidic cancer cells, and DGATi could prevent the formation of LDs, thereby promoting cancer cell ferroptosis. miR-522 can target ALOX15 and block lipid peroxidation in gastric cancer cells. IFNγ activates STAT1 to inhibit the expression of SLC7A11, thereby triggering ferroptosis in cancer cells. It was recently found that IFNγ synergize with arachidonic acid to render sensitivity to ferroptosis via ACSL4 in cancer cells, and palmitoleic acid and oleic acid can promote IFNγ plus AA-induced ACSL4-dependent ferroptosis. TGFβ1 promotes ferroptosis and tumor phenotype by activating SMAD signaling in tumor cells, which mediates transcriptional repression of SLC7A11 and activation of ZEB1. **b** The release of lactate from cancer cells and CAFs results in an acidic (pH 5.5–6.6) environment in the TME. CAFs mediate the blockade of ferroptosis in cancer cells by releasing exosomal miR-522. **c** Dysfunctional SLAMF6^{-} PD-1^{+} TIM-3^{+} CD8^{+} T cells promote fatty acid uptake and induce ferroptosis by overexpressing CD36, and activation of P38 kinase inhibits IFNγ and TNFα production. Overexpression of GPX4 inhibits ferroptosis leading to the release of IFNγ and TNFα to promote CD8^{+} T cell function. **d** Some AA/AdA metabolites (e.g., HETEs, PGE2) released by ferroptotic cancer cells. HETEs can activate antitumor immunity, while PGE2 inhibits cDC1 and NK cells to promote immune escape of colon cancer cells. Oxidized phospholipids (SAPE-OOH) on the surface of ferroptotic cancer cells act as an eat-me signal to mediate phagocytosis via TLR2 on macrophage membranes. (*PUFA* polyunsaturated fatty acid; *AA* arachidonoyl; *POA* palmitic acid; *OA* oleic acid; *TME* tumor microenvironment; *STAT3* signal transducer and activator of transcription 3; *ALOX15* arachidonic acid lipoxygenase 15; *STAT1* transcription 1; *SCD1* stearoyl-CoA desaturase 1; *AMPK* AMP-activated protein kinase; *LDs* lipid droplets; *DGATi* diacylglycerol acyltransferase inhibitor; *PGE2* prostaglandin E2; *HETEs* 12-Hydroxyeicosatetraenoic acids; *MCT1* The monocarboxylate transporter 1; *xCT* cystine-glutamate transporter; *p38* mitogen-activated protein kinase; *cDC1* conventional type 1 dendritic cells; *NK* natural killer; *OXPLs* oxidized phospholipids; *TLR2* toll-like receptor 2; *CAF* cancer-associated fibroblasts; *CTL* cytotoxic T lymphocyte(CD8^{+} T cell); *APC* antigen presenting cell)

by activating SMAD signaling that mediates transcriptional repression of SLC7A11 and activation of ZEB1 to promote tumor phenotype [17, 169] (Fig. 3a, d). Recently, Professor Jianjian Li et al. have shown that lipid metabolism reprogramming not only enhances the radio resistance of glioblastoma multiforme tumor cells, but also facilitates the immune escape of anti-macrophages through the high expression of CD47 (anti-macrophage phagocyte membrane protein), leading to the malignant phenotype of the tumor [139]. In vitro and in vivo experiments have demonstrated increased fatty acid uptake in radioresistant glioblastoma multiforme cells, and subsequent fatty acid oxidation regulates CD47 expression via citrate-acetyl-CoA-RelA to promote the creation of a microenvironment for immune escape. This is the first time to reveal the cross-linking of tumor fatty acid oxidative metabolism and immune escape, and may provide a new concept for metabolic combined radioimmunotherapy. Dysfunctional CD8^{+} T cells overexpressing

CD36 promotes the uptake of fatty acids accumulated in the TME and predisposes cells to undergo lipid peroxidation and ferroptosis, which leads to reduced IFNγ and TNFα production and impaired antitumor capacity [156, 157] (Fig. 3a, c). IFNγ released by $CD8^+$ T cells cooperates with fatty acids (AA, POA or OA) to sensitize tumor cells to ferroptosis through ACSL4 [16] (Fig. 3a, c). Conversely, ferroptotic cancer cells affect immune cells by releasing various oxidized lipid metabolites. Some AA/AdA metabolites such as 15 HpETE PE, 15-HETE, 12-HETE and 5-HETE released from ferroptotic cancer cells can activate antitumor immunity [170, 171], while ferroptotic cancer cells release other lipids such as prostaglandin E2 (PGE2) inhibits the immune function of conventional type 1 dendritic cells (cDC1), natural killer (NK) cells and cytotoxic T cells to promote the immune escape of colon cancer cells [172] (Fig. 3d). Previous reports have shown that PSs and oxPSs are eat-me signals involved in the phagocytosis of apoptotic cells, while the eat-me signal associated with ferroptotic cells may be oxPE. Subsequently, AA oxidation products and oxidized phospholipids (OXPLs) are considered to be released from ferroptotic cells as potential immunomodulatory signals [171]. Recently, Luo et al. have demonstrated that oxidized phospholipids (1-stearoyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine) (SAPE-OOH) on the surface of ferroptotic cells, as an eat-me signal, are detected by recognition by macrophage membrane receptor TLR2 (Toll-like receptor 2), which mediates phagocytosis to clear ferroptotic cells (Fig. 3d). However, whether oxPSs are also involved in phagocytic signaling in ferroptotic cells remains unclear and needs to be further confirmed in future studies [173]. Furthermore, 27HC, a metabolite of cholesterol, promotes breast cancer metastasis by increasing polymorphonuclear neutrophils and γδ-T cells and reducing the number of cytotoxic $CD8^+$ T lymphocytes [174]. 27HC-resistant cancer cells have increased lipid uptake and/or lipid synthesis, which inhibits ferroptosis by overexpressing GPX4 [124].

In addition, the susceptibility to ferroptosis is significantly different between macrophage subsets and other immune cell subsets. Mechanistically, since pro-inflammatory M1 macrophages highly express inducible nitric oxide synthase (iNOS), which have more nitric oxide radicals ($NO^{\cdot}$) to inhibit RSL3-mediated ferroptosis. In contrast, anti-inflammatory M2 macrophages have low iNOS expression and are more sensitive to ferroptosis [175]. Fatty acids and lipid droplets are increased in B1 and marginal zone (MZ) B cells with high CD36 expression, resulting in greater susceptibility to lipid peroxidation and affecting B cell immune responses. It is observed that knockdown of GPX4 in B1 and MZ B cells trigger ferroptosis, while follicular B cells fail to induce lipid peroxidation due to loss of GPX4 [176].

Altogether, it is concluded that lipid metabolism in ferroptotic cancer cells regulates the function and phenotype of infiltrating immune cells in the TME, and TME generally affects how cancer cells and immune cells utilize lipids. Given that lipids metabolism in the TME modulates cancer cells and immune cells to ferroptosis sensitivity, ferroptosis-mediated anti-tumor immunity may be promoted via coordinating fatty acids in the TME.

Immunogenic cell death (ICD) is a functionally distinct mode of response involving the induction of organelle and cellular stress accompanied by the release of large amounts of DAMPs [177], which strongly stimulates immune responses and greatly improve cancer resistance to immunotherapy [178, 179]. Multiple key DAMPs including high mobility histone B1 (HMGB1) and ATP have been found to be involved in tumor immunogenic cell death. It is confirmed that HMGB1 is released by ferroptotic cell death, which promotes the inflammatory response of macrophages by binding to advanced glycosylation end-product specific receptor (AGER), thus supporting tumor growth [180]. Inhibition of HMGB1 release by genetic ablation or autophagy drugs blocks ferroptosis-mediated inflammatory responses. Additionally, photodynamic therapy (PDT) induces cancer cell death and releases calreticulin, HMGB1, and ATP, which are efficiently phagocytosed by bone marrow-derived dendritic cells (BMDCs) to activate BMDCs [181]. However, this process can be blocked by inhibitors of apoptosis and ferroptosis, but not necroptosis, suggesting a relationship between PDT-mediated immunogenic cell death and ferroptosis [181]. Early work has showed that ferroptotic cancer cells are also thought to be potentially immunogenic [171]. Subsequent study of Dmitri V Krysko et al. has demonstrated for the first time that ferroptosis is an immunogenic cell death [182]. They have confirmed that early ferroptotic cancer cells induce BMDCs activation and maturation and induce effective antitumor immunity, while late ferroptotic cancer cells fail to induce BMDCs differentiation by releasing HMGB1 and ATP [182]. Since oxidized phospholipids produced by 12/15-LOX serve as substrates for key proteins required for autophagy and HMGB1 is released in an autophagy-dependent manner, it is thought that the interaction of lipid metabolism and ferroptosis may affect the release of HMGB1 to regulate tumor immunity [183]. However, this may require more experimental data in the future to support this conjecture. Furthermore, $KRAS^{G12D}$, as a DAMP, is released by ferroptotic pancreatic cancer cells and is AGR-mediated uptake in macrophages, resulting in M1 polarization to M2 phenotype and promoting tumor growth [184] (Fig. 4). 8-OHG, a major product of oxidative DNA damage and one of the known DAMPs, has been shown to be released by high iron levels or GPX4-deficient ferroptotic pancreatic ductal adenocarcinoma and lead to macrophage polarization [185]. Use of liproxstatin-1 (ferroptosis inhibitor), clophosome-mediated macrophage depletion, or pharmacological and genetic inhibition of the 8-OHG-TMEM173

pathway block the interferon gene protein stimulator-mediated DNA sensor pathway in TAMs, thereby reducing the infiltration and M2 polarization of TAMs [185] (Fig. 4). Taken together, various signals released by ferroptotic cancer cells may have different effects on different immune cells, which leads to the possibility that ferroptotic cancer cells may become a double-edged sword for anti-tumor immunity.

Cancer therapy targeting lipid metabolism and ferroptosis

There are currently multiple approaches to treat cancer by targeting the vulnerabilities of various cellular metabolisms, including fatty metabolism. Ferroptosis, which is closely related to lipid metabolism, has also been reported as a potential tumor therapeutic target.

Targeting lipid metabolism enzymes for cancer therapy

Unlike normal cells, which take up fatty acids from exogenous food, lipid synthesis is the primary means of lipid source for tumor cells. Since tumor cells rely on *de novo* synthesis of lipids to grow and proliferate, it can be speculated that tumor development is susceptible to enzymes involved in lipid synthesis and many metabolic enzymes of lipid synthesis have also been confirmed as targets for tumor therapy [9, 119].

Acetyl-CoA is a key substrate for the *de novo* synthesis of fatty acids and acetyl-CoA can be produced by ACLY catalyzing citric acid or by converting acetate through ACSS2. Inhibitors of ACLY have been reported to exhibit antitumor efficacy in xenograft models of prostate and lung cancer [186]. However, complete inhibition of ACLY activity requires relatively high drug concentrations, which may be one of the limitations of ACLY-targeted cancer therapy [10]. In a hepatocellular carcinoma model, ACSS2 knockout did not result in any phenotypic defects in mice. Meanwhile, ACSS2 knockout mice had significantly reduced triple-negative breast cancer growth [187, 188]. Mechanistically, inhibition of ACSS2 may exert beneficial antitumor effects. ACC and FASN are the key enzymes that catalyze the production of palmitic acid. In vivo experiments have showed that ACC inhibitors ND-646 and ND-654 respectively inhibits the growth of mouse lung tumors and rat hepatocellular carcinoma (HCC) [189, 190]. Consistent with the anticancer effects of ND-646 and ND-654, the ACC inhibitor-TOFA also reduces MYC-driven renal tumors [191]. It is worth

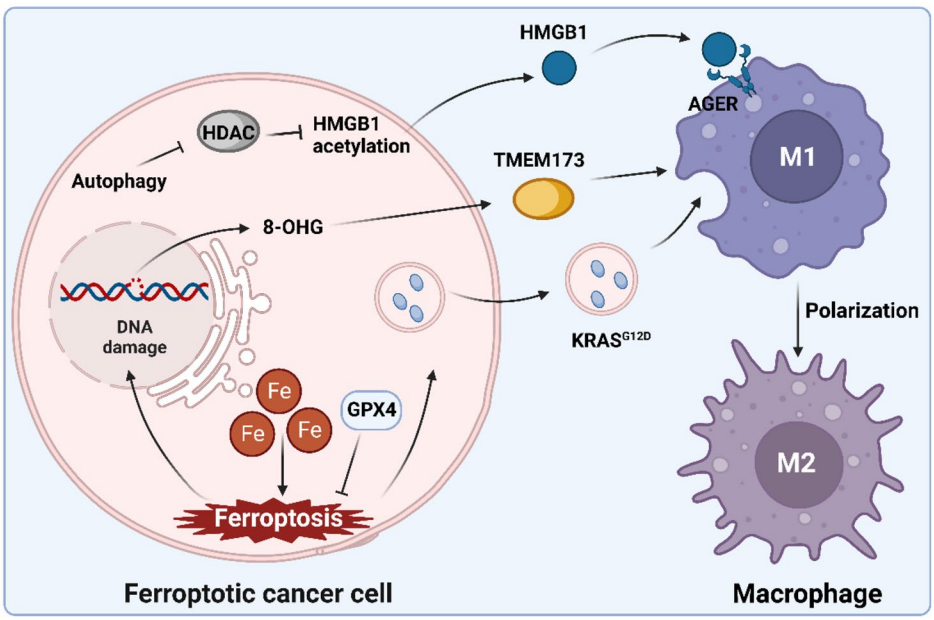


Fig. 4 DAMPs release from ferroptotic cancer cells modulate immune responses. Ferroptotic cancer cells can release three classes of DAMPs, including HMGB1, $KRAS^{G12D}$, and 8-OHG. HMGB1 is released from ferroptotic cancer cells and binds to AGER to promote macrophage inflammatory response and tumor growth. Ferroptotic pancreatic cancer cells release $KRAS^{G12D}$, which is taken up by AGR-mediated macrophages and induces macrophage polarization from M1 to M2 phenotype. 8-OHG, a major product of oxidative DNA damage, was shown to be released at high iron levels or in GPX4-deficient ferroptotic pancreatic ductal adenocarcinomas and ultimately induce macrophage polarization. (*DAMPs* damage associated molecular patterns; *GPX4* glutathione peroxidase 4; *HDAC* histone deacetylase; *HMGB1* high mobility histone B1; *AGER* advanced glycosylation end-product specific receptor; *8-OHG* 8-hydroxyguanosine; *TMEM173* transmembrane protein 173; *M1* classically activated macrophage; *M2* alternatively activated macrophage)

mentioning that ND-630, as a more potent ACC inhibitor, is currently undergoing Phase I clinical testing [119]. FASN is increasingly appreciated as a therapeutic target of lipid metabolism. In vivo breast cancer xenograft as well as two-dimensional (2D) and three-dimensional (3D) breast cancer is inhibited by the FASN inhibitors AZ22 and AZ65[192]. Orlistat, an approved weight loss drug, is also a FASN inhibitor, but its antitumor efficacy is weak. Although the FASN inhibitor C75 has an anti-tumor effect, its lack of efficacy and side effects make it impossible to enter the clinic [9]. The next-generation FASN inhibitor TVB-2640 has shown promising antitumor potential in colorectal and breast cancer models and is currently in clinical tests of multiple solid tumors [193, 194]. Other FASN inhibitors TVB-3664 or TVB-3166 in combination with taxanes were found to improve efficacy in non-small cell lung cancer (NSCLC) xenograft models [195]. SCD generates MUFAs through desaturation, and SCD inhibitors including SSI-4, MF-438 and betulinic acid (BetA) have been shown to inhibit the growth of cancer stem cells [10]. In addition, drugs targeting cholesterol synthesis such as statin family drugs have also been developed. Paradoxically, clinical trial results have suggested that statin therapy prolongs survival in patients with multiple myeloma, metastatic pancreatic cancer and colorectal cancer treated in combination with chemotherapy, whereas adding simvastatin or pravastatin fail to improve the effect of standard chemotherapy in patients with metastatic colorectal cancer, gastric cancer, HCC or small-cell lung cancer (SCLC) [119]. Further, it is confirmed that the anticancer effects of statins are dose- and time-dependent through clinical data analysis [196]. Thus, statins as adjuvant therapy to improve the effect of cancer treatment needs more clinical tests to confirm.

Potential anti-tumor effect targeting fatty acids to induce ferroptosis

The discovery of ferroptosis offers train of new thought for targeting lipid metabolism to treat cancer. In cancer, ferroptotic stress is susceptible to fatty acids metabolism and species. Since the PUFA synthesis-related enzymes ELOVL5 and FADS1are silenced by DNA methylation, intestinal-type gastric cancer cells fail to generate AA and AdA from linoleic acid, and the supplementation of AA can restore the sensitivity to ferroptosis [129]. PUFA dihomogamma-linolenic acid intake appears to trigger ferroptosis in C. elegans and human tumor cells [197], and adding PUFAs to nanoparticles has been shown to improve the therapeutic effect of anticancer drugs [198]. Intravenous injection of omega-3 PUFA or feeding diets supplemented with omega-3 PUFA in mice with malignant tumors, PUFA exerts significant anti-tumor effect [197, 199, 200]. Recent findings had verified that increasing dietary intake of n-3 and n-6 PUFAs promoted acidosis-driven induction of ferroptosis to exert global antitumor effects [145]. Therefore, dietary polyunsaturated fatty acids may serve as a selective adjunctive anti-tumor modality, which may be an effective supplement to pharmacological methods or means of treating cancer. Doll et al. mechanistically found that exogenous AA can promote RSL3-induced ferroptosis through ACSL4 [56]. More recently, further study has shown that supplementing low dose AA as the substrate of ACSL4 and combining with the use of PD-L1 blocker can induce tumor cells ferroptosis to promote tumor immunity in vivo and the therapeutic effect of checkpoint blocking [16]. Furthermore, immunotherapy can promote ferroptotic cell death to render tumor radiotherapy sensitivity [201]. Ferroptosis is gradually considered as an important mechanism of radiotherapy mediated tumor inhibition and radiotherapy resistance [202]. Radiotherapy can induce the expression of ACSL4 and toxic lipid peroxidation accumulation, leading to ferroptotic stress [203]. ACSL4 ablation significantly eliminates radiotherapy-induced ferroptosis and enhances tumor radiation resistance. LOX12, which mediates AA metabolism, is inhibited to endow human prostate cancer cells with radiosensitivity, and the cytotoxic effect of ionizing radiation is susceptible to LOX12 derived bioactive lipids regulation [204]. All together, these results demonstrate that LOX12 and ACSL4 mediated ferroptosis pathway may be involved in radioresistance regulation. The crosstalk between ferroptosis and lipid metabolism may highlight a novel strategy for tumor radiosensitization.

Additionally, increased levels of exogenous MUFAs can allow cancer cells to escape ferroptosis [54]. Cancer cell plasma membranes exhibit elevated MUFA and SFA ratios as well as MUFA and PUFA ratios to reduce lipotoxicity and ferroptosis [55]. The lymphatic system protects cancer cells from ferroptosis by increasing ACSL3-dependent oleic acid (MUFA) production, thereby promoting melanoma metastasis [53]. KRAS-driven lung cancers express high ACSL3 expression to drive cancer cells into a ferroptosis-resistant cell state [205]. Inactivation of ACSL3 attenuates the production of MUFA to render cells susceptible to radiotherapy-induced ferroptosis and enhance tumor radiosensitization [201]. A significant correlation of low ACSL3 expression with sensitivity to ferroptosis-inducing agents was observed in various cancer cells, which may herald potential antitumor efficacy of targeting ACSL3 [54]. Sorafenib, a multikinase inhibitor, can disrupt SCD1-mediated MUFAs biosynthesis to kill liver cancer cells [206]. And a study of ovarian cancer using SCD1 inhibitors revealed that suppression of SCD1 simultaneously triggers two death pathways-apoptosis and ferroptosis, which may imply that SCD1 is one of the effective targets for antitumor therapy [207]. Therefore, it appears that inhibition of MUFAs uptake, activation or *de novo* synthesis may contribute to enhancing the lethality of existing

ferroptotic drugs against tumor cells. In addition, HDL-like nanoparticle (HDLNPs) can activate the expression of *de novo* cholesterol synthesis genes, including DHCR7 (dehydrocholesterol reductase), INSIG1 (insulin induced gene 1), HMGCS1 (HMG-CoA synthase 1) and downregulate GPX4, thereby rendering ferroptosis to reduce tumor cells survival in mouse lymphomas [123].

Anticancer therapeutic potential of ferroptotic agents

Ferroptosis, is shown to be involved in tumor suppression, has been identified as one of the causes and therapeutic targets for cancers, including non-small cell lung cancer, liver cancer, breast cancer, pancreatic cancer [208]. Quite a considerable number of ferroptotic agents have been developed as potential treatments for cancer, some of which are in the research stage, while others are clinically tested and become FDA-approved drugs (Table 1). It has been found that for the purpose of adapting to lipid-induced metabolic stress, cancer cells stabilize GPX4 expression and increase the activity of GPX4-dependent antioxidant systems to avoid ferroptotic cell death, and abrogation of GPX4 is lethal for most cancer cells [124]. In general, GPX4 can be inactivated by direct or indirect targeting. For instance, ML162 and withaferin A directly inactivate GPX4, leading to tumor ferroptosis [209, 210], and Abramycin can also directly suppress GPX4 [208]. Altretamine, an FDA-approved anticancer drug, was initially developed for the treatment of ovarian cancer and was subsequently shown to trigger ferroptosis by inhibiting GPX4 [211]. Studies have reported that RSL3 inhibits the activity of GPX4 to render tumor ferroptosis and attenuate the growth of fibrosarcoma in mice [3, 212]. Targeting GPX4 as a possible therapeutic strategy for drug-tolerant persister tumor cells. The loss of GPX4 in drug-tolerant persister tumor cells with can confer susceptibility to ferroptotic death and prevent tumor relapse in vivo [15]. However, since adult mice with GPX4 gene deletion is lethal, further studies are needed to validate whether GPX4 inhibitors are appropriate in the clinical environment to prevent cancer relapse [15]. FIN56, a specific inducer of ferroptosis, has been shown to promote the degradation of GPX4 as well as activate SQS to deplete coenzyme Q10, which together sensitize cancer cells to ferroptosis [95]. In addition, intracellular GSH depletion can indirectly lead to decreasing GPX4 activity. The antioxidant GSH has been confirmed as one of the important targets for inducing tumor ferroptosis. BSO has been reported to reduce mouse mammary tumor burden by inhibiting GSH synthesis [79, 213]. Cystine and cysteine serve as important substrates for GSH synthesis, preclinical models demonstrated that as an engineered enzyme, cyst(e)inase degrades cystine and cysteine and combines with checkpoint blockade to enhance synergistically T cell-mediated antitumor immunity and induce tumor

Table 1 Anticancer therapeutic potential of ferroptotic agents targeting lipid metabolism

Agents	Targets	Cancer types	References
Altretamine	GPX4	Osteosarcoma, lymphoma	[211]
Withaferin A	GPX4	Neuroblastoma	[209]
(1 S,3R)-RSL3	GPX4	Fibrosarcoma	[3, 212]
DPI7/ DPI10, ML162, ML210, DPI12-13, DPI17-19	GPX4	Fibrosarcoma, lung adenocarcinoma, melanoma, renal cell carcinoma, colon cancer cell, pancreatic cancer	[3, 49, 212]
FIN56	GPX4/ squalene synthase	Fibrosarcoma	[95, 221]
Cisplatin	GSH	Colon cancer, non-small cell lung cancer	[214]
Sulfasalazine	SLC7A11	Fibrosarcoma, pancreatic cancer, breast cancer,	[1, 215, 216]
Sorafenib	SLC7A11/SCD1	Hepatocellular carcinoma, liver cancer	[206, 217]
Erastin	SLC7A11	Cervical carcinoma, ovarian cancer	[219, 220]
Piperazine erastin (PE)	SLC7A11	Fibrosarcoma	[3]
Imidazole ketone erastin (IKE)	SLC7A11	Lymphomas	[218]
Buthionine sulfoximine (BSO)	Glutamate-cysteine ligase	Fibrosarcoma, breast cancer	[3, 213]
BAY 87-2243	Mitochondrial complex I	Melanoma	[226]
Statins (fluvastatin, lovastatin, simvastatin)	HMG-CoA reductase	Fibrosarcoma, high-mesenchymal state cancer cells	[49, 95]
Diacylglycerol acyltransferase inhibitors (DGATi)	Lipid droplets	Colorectal cancer	[145]
$FINO_2$	Lipid/Fe^{2+}	Fibrosarcoma, renal cancer	[221]

cell ferroptosis [168]. Depletion of GSH and inactivation of GPXs are induced by cisplatin to trigger ferroptosis in A549 and HCT116 cells, and the combination therapy of erastin and cisplatin synergistically enhances the antitumor effect [214]. The system XC is essential for the synthesis of GSH, and its inhibitors including sulfasalazine, Sorafenib (FDA-approved drug) provide significant benefit in treating a variety of cancers [215–217]. In a diffuse large B cell lymphoma xenograft model, imidazole-ketone-erastin (IKE) can slow tumor growth by inhibiting the system xc and leading to GSH depletion and ferroptosis [218]. Erastin, which also inhibits the system XC, is found to reverse cervical cancer xenograft tumors and inhibit ovarian tumor growth [219, 220]. And erastin renders lung cancer cells sensitivity to cisplatin, thus triggering ferroptosis [214]. Unlike other GPX4 inhibitors such as erastin, $FINO_2$ fails to deplete GSH to induce ferroptosis by inhibiting the system XC [221]. Having validated that $FINO_2$ increases multiple PE species and a more diverse phospholipid oxidation than erastin in HT-1080 cells. $FINO_2$ directly oxidizes Fe^{2+} and indirectly inactivates GPX4 to confer ferroptosis sensitivity in fibrosarcoma [221]. Although it is demonstrated that $FINO_2$ is not a GPX4 ligand and fail to reduce GPX4 protein levels, the mechanism by which $FINO_2$ causes GPX4 inactivation remains unclear. Immunotherapy blocking PD-L1 activated $CD8^+$ T cells, indicating that the subsequent release of IFNγ downregulates SLC3A2 and SLC7A11 (two subunits of the system XC) to promote tumor cells lipid peroxidation [168]. Ferroptosis inducers inactivates SLC7A11 (such as erastin and sulfasalazine) or GPX4 (such as RSL3, ML162 and FIN56), which render radioresistant tumor cells and xenograft tumors sensitivity to IR [203]. Importantly, SLC7A11 is synergistically inhibited by radiotherapy-activated Ataxia-Telangiectasia mutated gene and IFNγ released by immunotherapy-activated $CD8^+$ T cells, resulting in decreased cystine uptake and enhanced tumor cells ferroptosis, which may become a new strategy for tumor radiotherapy and immunotherapy sensitization [201]. RSL3 and IKE synergize with radiation therapy to promote lipid peroxidation in cell lines of various tumor types including HT-1080 cells, which may likewise validate that ferroptosis inducers may act as effective radiosensitizers [222].

Conclusions and perspectives

It has long been intrigued by ferroptosis, as an emerging cell death method, in cancer research. The increasing knowledge of ferroptosis has suggested that ferroptosis appears to be considered as a potential target for anti-tumor therapy. Some malignant tumor cells have been demonstrated to confer resistance to ferroptosis, while several ferroptotic cancer cells can promote cancer progression by releasing DAMPs that lead to the polarization of TAMs. In addition, ferroptosis has a dual role in the immune response. On the one hand, ferroptosis suppresses the process of the immune system against pathogenic bacteria by reducing the number of T cells and B cells [223]. On the other hand, T cells enhance the effect of tumor immunotherapy by secreting IFNγ to promote cancer cell ferroptosis [16, 168]. How to make good use of ferroptosis as a new target to enhance tumor immunotherapy is still one of the directions that researchers need to work on. More research in the future remains a need for unraveling the mystery of the more molecular mechanisms involved in ferroptosis, and a full understanding of ferroptosis regulatory network might pave the way for the development of effective cancer treatment strategies targeting ferroptosis.

Targeting lipid metabolic pathways has emerged as one of the promising anti-cancer strategies. Tumor cells, especially CSCs, exhibit lipid metabolism reprogramming and iron addiction, which can affect the susceptibility of multiple cancer cells to ferroptosis. Notably, lipid metabolism and ferroptosis can affect the communication between cancer cells and immune cells in the tumor microenvironment. Cancer cells inhibit the function of immune cells by releasing lipid metabolites, while immune cells regulate the lipid metabolism of tumor cells to increase the sensitivity of tumor cells to ferroptosis, thereby inhibiting tumor growth. In addition, lipid metabolic rewiring can boost the functional specialization of Treg cells in tumors [224] and T cell senescence in the tumor microenvironment is associated with lipid metabolism reprogramming [225]. It is recently found that enhanced fatty acids metabolism in glioblastoma multiforme mediates tumor immune escape via CD47 [139]. Taken together, these reveal that targeting lipid metabolism may further improve the efficacy of cancer immunotherapy and provide a new target for tumor immunotherapy.

Collectively, targeting lipid metabolism and ferroptosis may become one of the effective antitumor strategies. The complexity between lipid metabolism reprogramming, ferroptosis and tumor immunity in the tumor microenvironment throws light on future research directions. That is, there is a need to delve into not only the mechanisms of lipid metabolism networks and ferroptosis, but also the impact of interacting pathways in the TME on tumor progression and therapeutic response, in particular the tumor immunotherapy.

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Declarations

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