Targeting ferroptosis for cancer therapy: exploring novel strategies from its mechanisms and role in cancers

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Abstract: Ferroptosis is a novel form of non-apoptotic regulated cell death (RCD), with distinct characteristics and functions in physical conditions and multiple diseases such as cancers. Unlike apoptosis and autophagy, this new RCD is an iron-dependent cell death with features of lethal accumulation of reactive oxygen species (ROS) and over production of lipid peroxidation. Excessive iron from aberrant iron metabolisms or the maladjustment of the two main redox systems thiols and lipid peroxidation role as the major causes of ROS generation, and the redox-active ferrous (intracellular labile iron) is a crucial factor for the lipid peroxidation. Regulation of ferroptosis also involves different pathways such as mevalonate pathway, P53 pathway and p62-Keap1-Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. Ferroptosis roles as a double-edged sword either suppressing or promoting tumor progression with the release of multiple signaling molecules in the tumor microenvironment. Emerging evidence suggests ferroptosis as a potential target for cancer therapy and ferroptosis inducers including small molecules and nanomaterials have been developed. The application of ferroptosis inducers also relates to overcoming drug resistance and preventing tumor metastasis, and may become a promising strategy combined with other anticancer therapies. Here, we summarize the ferroptosis characters from its underlying basis and role in cancer, followed by its possible applications in cancer therapies and challenges maintained.

Keywords: Cancer; ferroptosis; immune; tumor microenvironment

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Introduction

In multicellular organisms, cell death is an indispensable homeostatic mechanism to maintain tissue morphology and function (1). Cells may die from a biologically uncontrolled process called accidental cell death (ACD), or regulated cell death (RCD) that involves closely coordinated signal cascades with tight structure and dedicated molecular mechanisms (2). The form of cell death included three categories historically: apoptosis, autophagy, and necrosis (3). Apoptosis is the traditionally well-known RCD. However,
drugs targeting apoptosis appear to be challenged with the occurrence of drug resistance and immune evasion in cancer treatment (4,5).

Ferroptosis was firstly described as an iron-dependent form of non-apoptotic RCD induced by erastin in 2012, featured with excess reactive oxygen species (ROS) generation and lipid peroxidation (2). Unlike apoptosis and autophagy, ferroptosis is iron-dependent, with specific characteristics of cytological changes such as the rupture of outer mitochondrial membrane, small mitochondria with the condensed mitochondrial membrane, and a vanishing or decrease of mitochondria cristae (6-8). Based on the original studies of cell death, ferroptosis is markedly different from the other RCD types such as apoptosis and autophagy at levels of cell morphology, biochemical features, and regulations (Table 1) (9-11). Ferroptosis induction is associated with multiple disease occurrence, including immune system (nonalcoholic steatohepatitis), brain (stroke and intracerebral hemorrhage), neurodegenerative [Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD)], heart (heart failure), and blood diseases (leukemia) (7,12). Inhibiting ferroptosis has been identified as a potential prevention or therapeutic strategies for some of these diseases.

Beyond these findings, ferroptosis has recently gained much importance in cancer treatment, and emerging evidence shows that ferroptosis influences a growing number of oncogenic pathways. For example, P53 regulation promotes tumor cell ferroptosis but also decreases tumor metastases to blood, lung, and liver. Viswanathan and colleagues contended the contribution of ferroptosis to drug resistant phenomenon and cancer immunotherapeutic efficacy (13-15). Therefore, targeting ferroptosis might become a prospective strategy for cancer therapy, and its role in cancer-associated immune environment is worth deep exploration. In this review, we focus on the basic metabolisms and regulation of ferroptosis, its characteristics in cancer, and current research progress of ferroptosis-targeted therapies.

### Basis of ferroptosis

The complicated interplay of iron, cysteine and lipid metabolism takes an important role in ferroptosis (Figure 1).

The most prominent character of ferroptosis is ROS generation, mainly caused by iron metabolism disorders (7). The endosomal uptake of circulated iron (Fe$^{3+}$) is mediated by its binding to transferrin (TF) and transferrin receptor 1 (TFR1). Iron Fe$^{3+}$ is deoxidized to iron Fe$^{2+}$, under the catalysis of iron oxide reductase named six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and ultimately release into labile iron pool (LIP), due to Fe$^{2+}$'s characteristics of high solubility and transfer electron capability. Increasing formation of LIP may trigger the Fenton reaction [the process of ROS generation mediated by interaction between Fe$^{2+}$ and hydrogen peroxide (H$_2$O$_2$)], which may result in iron poisonous (16). Compared with RAS un-mutated ferroptosis-insensitive cells, RAS-mutated ferroptosis-sensitive cells increased the expression of TFR1 and decreased the expression of ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1) in the iron-storage protein subunits. This suggests

<table>
<thead>
<tr>
<th>Type of cell death</th>
<th>Cell morphology</th>
<th>Biochemical features</th>
<th>Key regulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferroptosis</td>
<td>Small mitochondria with a condensed mitochondrial membrane, vanishing or reduction of mitochondria cristae, and rupture of outer mitochondrial membrane</td>
<td>Iron loading, ROS accumulation, System X$_c^-$ inhibition with reduced GSH, GPX4 inhibition</td>
<td>Positive: p53, Ras, VDAC2/3, TFR1, NOX; Negative: SLC7A11, GPX4, NRF2, HSPB1</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Plasma membrane blebbing; reduction of cellular and nuclear volume; nuclear fragmentation; and chromatin condensation</td>
<td>Activation of caspases and proapoptotic Bcl-2 family proteins, oligonucleosomal DNA fragmentation, exposure of Plasma membrane rupture, dissipation of dissipation</td>
<td>Positive: pro-apoptotic Bcl-2 family proteins (Bax, Bak), p53; Negative: anti-apoptotic Bcl-2 family proteins (Bcl-2, Bcl-XL)</td>
</tr>
<tr>
<td>Autophagy</td>
<td>(Double-membraned) autolysosome accumulation, cytoplasmic vacuolization</td>
<td>Conversion from LC3-I to LC3-II, degradation of p62Lck, Beclin-1 dissociation from Bcl-2/XL</td>
<td>Positive: Beclin 1, ATG family proteins (ATG5, ATG7)</td>
</tr>
</tbody>
</table>
Mechanisms of ferroptosis. Excess iron is regarded as an important factor for ferroptosis. The circulating iron (Fe$^{3+}$) combined with transferrin (TF) enters cells mediated by transferrin receptor (TFR). Under the catalysis of iron oxide reductase STEAP3, Fe$^{3+}$ can be deoxidized to Fe$^{2+}$ and ultimately, releasing it into labile iron pool (LIP) mediated by DMT1. LIP consists of iron from endosomal uptake of circulated iron and ferritin degradation (ferritinophagy). System Xc-mediate the uptake of cysteine (Cys2). Cys2, glutamate (Glu) and glycine (Gly) are materials of glutathione (GSH), which is an important antioxidant in cells. Transsulfuration pathway may also increase the level of cysteine transformed from methionine (Met). Cysteine can be imported directly by alanine-serine/cysteine transporter (system ASC) under reducing conditions. The uptake of free PUFAs such as arachidonic acid (AA) or adrenoxyl (AdA) mediated by fatty acid translocase (FAT) and fatty acid transport protein (FATP) can be converted to membrane phospholipids by enzyme acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), which is important to ROS generation. PE-PUFAs can be oxidized to PE-PUFAs-OOH by lipoxygenases (LOXs), leading to ferroptosis. GPX4 roles as a protector to transfer PE-PUFAs-OOH to PE-OH. CoQ10, coenzyme Q10; DMT1, divalent metal transporter 1; FPN, ferroportin; Gln, glutamine; HAMP, hepcidin antimicrobial peptide; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IREB2, iron-responsive element binding protein 2; NCOA4, Nuclear receptor coactivator 4; STEAP3: six-transmembrane epithelial antigen of the prostate 3.

that increasing iron intake and reducing iron storage may cause iron overload, in the end, leading to ferroptosis (17). Thus, intracellular iron metabolism homeostasis regulates ferroptosis process. Cancer cells become more vulnerable to iron toxicosis and ROS accumulation than noncancerous cells with a powerful iron dependency characteristic, making it possible for application of ferroptosis inducers in cancer therapy (18,19).

**System Xc$^{-}$ inhibition or enzyme glutathione peroxidase 4 (GPX4) inactivation can prompt ferroptosis as well. Antiporter system Xc$^{-}$ functioned to mediate the transmembrane exchange of extracellular cystine (Cys2) and intracellular glutamic acid (Glu) (20). The uptake of Cys2 is required for glutathione (GSH) formation, which is an important antioxidant interacting with GPX4 (21). The peroxidation of polyunsaturated fatty acids (PUFAs) is an important contributor for ferroptosis. Free PUFAs can be transformed into phosphatidylethanolamine (PE)-PUFAs-OOH finally through three important enzymes including acyl-CoA synthetase long-chain family member 4 (ACSL4),
Figure 2 Ferroptosis modulation in tumor. Small molecules such as erastin, sorafenib, glutamate, and sulfasalazine induce ferroptosis by inhibiting system Xc- and impeding cysteine uptake, which could result in a subsequent decline of glutathione and a decrease of cells’ antioxidative ability. mucin 1 C-terminal (MUC1-C) binds with CD44v to promote stability of the system Xc-. The cysteine level can also be supplemented by cellular methionine via the sulphur-transfer pathways. GPX4 can prevent ferroptosis by suppressing cellular lipid peroxides and the mevalonate (MVA) pathway is crucial for its maturation and the products of it (IPP and CoQ10) can promote synthesis of GPX4. Treatment FIN56 modulates squalene synthase (SQS) to reduce CoQ10. Ferroptosis inducer RSL3 can suppress GPX4 directly to regulate ferroptosis. The p62-Keap1-Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway is able to regulate Nrf2-targeted genes such as heme oxygenase-1 (HO-1), ferritin heavy chain 1 (FTH1), and NAD(P)H: quinone oxidoreductase 1 (NQO1) against ferroptosis. CISD1, PHKG2, and IREB2 are important in regulating iron metabolism and ferroptosis. Ironchelators can inhibit ferroptosis. The HSPB1 also impedes ferroptosis by inhibiting increase of intracellular iron. In addition, p53 also regulate ferroptosis through inhibiting SLC7A11 and promoting lipid peroxides production. BSO, buthionine sulfoximine; FTH1, ferritin heavy chain 1; HSP, heat-shock protein; HO-1, heme oxygenase-1; MUC1-C, mucin 1 C-terminal; MVA, mevalonate; NQO1, NAD(P)H: quinone oxidoreductase 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2; SQS, squalene synthase.

lysophosphatidylcholine acyltransferase 3 (LPCAT3) and lipoxygenases (LOXs) (22).

Apart from the mechanisms discussed above, there are several other pathways involved in ferroptosis (Figure 2). In mevalonate (MVA) pathway, the activity of FIN56-targeted protein squalene synthase (SQS) reduces the idebenone level in cells, therefore decreasing the cellular antioxidation activity (23). Nuclear factor (erythroid-derived 2) like 2 (Nrf2) is a regulator in the iron metabolism, and Nrf2 activation was reported capable of inhibiting ferroptosis in hepatocellular carcinoma cells (24). The famous tumor suppressor P53 also plays an essential role in ferroptosis regulation. Other pathways such as the sulphur-transfer pathway, heat shock factor-1 (HSF1)-heat shock protein beta-1 (HSPB1) pathway, and mucin 1 C-terminal (MUC1-C)/system Xc- (xCT) also contribute to ferroptosis regulation (Figure 2) (6). Further, evaluation of ferroptosis-related molecules provides diverse approaches to monitor the ferroptosis process in-vitro and in-vivo (Tables 2, 3).

Hallmarks of ferroptosis in cancer
Role of ferroptosis in tumor suppression
Tumor suppressor P53 inactivation is very common in
<table>
<thead>
<tr>
<th>Reagents</th>
<th>Mechanisms</th>
<th>Formula</th>
<th>In-vitro</th>
<th>In-vivo</th>
<th>Refs</th>
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<tbody>
<tr>
<td>Erastin</td>
<td>System Xc&lt;sup&gt;-&lt;/sup&gt;</td>
<td>C&lt;sub&gt;30&lt;/sub&gt;H&lt;sub&gt;31&lt;/sub&gt;CIN&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>BJeLR, HT1080, Calu-1, A-673, Hela, 143B p0 and p+ cell</td>
<td>NA</td>
<td>(25,26)</td>
</tr>
<tr>
<td>Imidazole ketone erastin</td>
<td>System Xc&lt;sup&gt;-&lt;/sup&gt;</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>SUDHL-2/5/6/, SUDHL-7/5/9/, SUDHL-10/16, LY-7/9/18, HT-1080, DOHH-2, HBL-1, U2932, A4/FUK, WSU-NHL, Karpas422, A3/KAW, RIVA, U937</td>
<td>SUDHL-6</td>
<td>(27)</td>
</tr>
<tr>
<td>Piperazine erastin</td>
<td>System Xc&lt;sup&gt;-&lt;/sup&gt;</td>
<td>C&lt;sub&gt;30&lt;/sub&gt;H&lt;sub&gt;31&lt;/sub&gt;CIN&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>HT-1080, BJeLR, DRD59</td>
<td>NA</td>
<td>(25,28)</td>
</tr>
<tr>
<td>RSL3</td>
<td>GPX4</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>BJeLR, HT1080, A549, Calu-1, HCT116, MIA PaCa-2, KBM7</td>
<td>NA</td>
<td>(17,29)</td>
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<tr>
<td>DPI7</td>
<td>GPX4</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>KBM7</td>
<td>NA</td>
<td>(29)</td>
</tr>
<tr>
<td>FIN56</td>
<td>GPX4</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>BJeLR, HT-1080</td>
<td>NA</td>
<td>(23,30)</td>
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<tr>
<td>FINO2</td>
<td>GPX4</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>HT-1080</td>
<td>NA</td>
<td>(30)</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Buthionine sulfoximine</td>
<td>GSH depletion</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>BJeLR, HCT116/A549</td>
<td>NA</td>
<td>(28,31)</td>
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<tr>
<td>Acetaminophen</td>
<td>GSH depletion</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>HepG2/primary mouse hepatocytes</td>
<td>NA</td>
<td>(32)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>System Xc&lt;sup&gt;-&lt;/sup&gt; inhibitor</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>BJeLR, HT1080, Calu-1, DU-145</td>
<td>HT-1080, F98</td>
<td>(25,31)</td>
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<tr>
<td>Sorafenib</td>
<td>system Xc&lt;sup&gt;-&lt;/sup&gt; inhibition</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>HT1080, Calu-1, DU-145, Huh7, ACHN cells</td>
<td>Huh7, Nude mice</td>
<td>(31,33-36)</td>
</tr>
<tr>
<td>Artesunate</td>
<td>GSH depletion</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>PDAC cell lines</td>
<td>NA</td>
<td>(35)</td>
</tr>
<tr>
<td>Lanperisone</td>
<td>System Xc&lt;sup&gt;-&lt;/sup&gt;</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>K-ras&lt;sup&gt;22,33&lt;/sup&gt;-transformed MEFs</td>
<td>Nude mice</td>
<td>(37)</td>
</tr>
<tr>
<td>Piperazine erastin</td>
<td>system Xc&lt;sup&gt;-&lt;/sup&gt;</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>BJeLR</td>
<td>NA</td>
<td>(28)</td>
</tr>
<tr>
<td>1S,3R-RSL3</td>
<td>GPX4</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>HT-1080, 143B; B16; COHBR1; BT474, PC9</td>
<td>BJeLR, HT-1080</td>
<td>(14,25,28,38)</td>
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<td>Cisplatin</td>
<td>GSH, partially inhibited by DFO, Fer-1, Z-VAD-FMK</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>A549, HCT116</td>
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<td>(39)</td>
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<tr>
<td>Ferrous ammonium sulfate</td>
<td>Iron loading</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;FeN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>IMR-32</td>
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<td>(40)</td>
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<tr>
<td>Ferric ammonium citrate</td>
<td>Iron loading</td>
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<td>HT-1080</td>
<td>NA</td>
<td>(41)</td>
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<td>Haemin</td>
<td>Iron loading</td>
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<td>IMR-32, THP-1, THP-1</td>
<td>NA</td>
<td>(41,42)</td>
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<tr>
<td>Siramesine+ lapatinib</td>
<td>Increase the iron level by upregulating TF and down regulating of FPN-1</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MDA MB231, MCF-7, ZR-75, SKBr3</td>
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<td>(43)</td>
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<td>BAY 11-7085</td>
<td>Increase in LP by HMOX1</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MCF-7, MDAMB-468, MDA-MB-231, A549, SKBR3, SKOV3</td>
<td>NA</td>
<td>(44)</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Upregulation of ACSL-4 in Kras mutant CRC cells</td>
<td>C&lt;sub&gt;32&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;CIN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CT-116, DLD-1</td>
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<td>(45)</td>
</tr>
<tr>
<td>Reagents</td>
<td>Mechanisms</td>
<td>Formula</td>
<td>In-vitro</td>
<td>In-vivo</td>
<td>Refs</td>
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<tr>
<td>Trolox</td>
<td>Lipophilic antioxidants</td>
<td>C_{14}H_{18}O_{4}</td>
<td>HT1080, PUFA-oxidation-induced death model on S. cerevisiae; Wild-type and Bax/Bak DKO MEFs; HT1080, Calu-1, BJeLR</td>
<td>NA</td>
<td>(25,46)</td>
</tr>
<tr>
<td>Cycloheximide</td>
<td>Protein synthesis</td>
<td>C_{10}H_{24}NO_{4}</td>
<td>HT1080, Calu-1, BJeLR, Wild-type and Bax/Bak DKO MEFs</td>
<td>NA</td>
<td>(25)</td>
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<td>Ebs</td>
<td>Oxidative pathway</td>
<td>C_{10}H_{16}NOSe</td>
<td>HT1080, Calu-1, BJeLR, GPX4-deficient T cells</td>
<td>NA</td>
<td>(25,47)</td>
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<tr>
<td>Aminooxyacetic acid</td>
<td>Fatty-acid synthesis</td>
<td>C_{10}H_{20}O_{3}</td>
<td>HT1080, BJeLR</td>
<td>NA</td>
<td>(25)</td>
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<td>B-mercaptoethanol</td>
<td>Cystine uptake</td>
<td>C_{9}H_{18}SO</td>
<td>HT1080</td>
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<td>(25)</td>
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<td>Ciclopiroxolamine</td>
<td>Intracellular iron</td>
<td>C_{12}H_{22}NO_{3}</td>
<td>HT1080</td>
<td>OHSC</td>
<td>(25,46)</td>
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<td>Diphenylene iodonium</td>
<td>NOX</td>
<td>C_{10}H_{8}I</td>
<td>HT1080, Calu-1</td>
<td>NA</td>
<td>(25)</td>
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<td>GKT137831</td>
<td>NOX1/4</td>
<td>C_{21}H_{16}ClN_{2}O_{4}</td>
<td>HT1080/Calu-1</td>
<td>NA</td>
<td>(25)</td>
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<tr>
<td>6-aminonicotinamide</td>
<td>NADPH-generating pentose phosphate pathway</td>
<td>C_{6}H_{12}N_{3}O</td>
<td>HT1080, Calu-1, BJeLR</td>
<td>NA</td>
<td>(25)</td>
</tr>
<tr>
<td>Butylated hydroxytoluene (BHT)</td>
<td>Oxidative pathway</td>
<td>C_{10}H_{20}O</td>
<td>HT1080, BReLR</td>
<td>GPX4-deficient T-cell mice</td>
<td>(17,26,47)</td>
</tr>
<tr>
<td>α-tocopherol (vitamin E)</td>
<td>Oxidative pathway</td>
<td>C_{29}H_{50}O_{2}</td>
<td>BReLR</td>
<td>NA</td>
<td>(25)</td>
</tr>
<tr>
<td>β-carotene</td>
<td>Oxidative pathway</td>
<td>C_{40}H_{56}</td>
<td>HT1080</td>
<td>NA</td>
<td>(28)</td>
</tr>
<tr>
<td>Glutathione</td>
<td>Oxidative pathway</td>
<td>C_{10}H_{17}N_{2}O_{3}</td>
<td>HT1080</td>
<td>NA</td>
<td>(28)</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Oxidative pathway</td>
<td>C_{9}H_{18}NO_{3}</td>
<td>HT1080</td>
<td>NA</td>
<td>(29)</td>
</tr>
<tr>
<td>2,3-bipyridyl</td>
<td>Intracellular iron</td>
<td>C_{12}H_{22}N_{2}</td>
<td>Wild-type and Bax/Bak DKO MEFs</td>
<td>NA</td>
<td>(29)</td>
</tr>
<tr>
<td>Deferoxamine mesylate</td>
<td>Intracellular iron</td>
<td>C_{25}H_{48}NO_{2} • CH_{3}O_{2}S</td>
<td>BJeLR</td>
<td>NA</td>
<td>(17)</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>Fenton reaction</td>
<td>C_{20}H_{30}N_{2}O_{4}</td>
<td>Wild-type and Bax/Bak DKO MEFs, HT1080, Calu-1</td>
<td>NA</td>
<td>(25)</td>
</tr>
<tr>
<td>SU6656</td>
<td>SRC kinase</td>
<td>C_{9}H_{12}N_{2}O_{3}</td>
<td>HT1080</td>
<td>NA</td>
<td>(17)</td>
</tr>
<tr>
<td>U0126</td>
<td>MEK1/2</td>
<td>C_{12}H_{24}N_{2}O_{3}</td>
<td>Wild-type and Bax/Bak DKO MEFs, HT1080</td>
<td>NA</td>
<td>(17,25)</td>
</tr>
<tr>
<td>Ferrostatin-1</td>
<td>ROS from lipid peroxidation</td>
<td>C_{12}H_{18}N_{2}O_{2}</td>
<td>HT1080, OHSC, Rat corticostriatal brain slice, PVL model, AKI model, Huh7</td>
<td>NA</td>
<td>(25,34,46)</td>
</tr>
<tr>
<td>Liproxstatin-1</td>
<td>ROS from lipid peroxidation</td>
<td>C_{9}H_{14}CIN_{2}</td>
<td>HRPTEpCs, GPX4^{−/−} cells</td>
<td>GPX4^{−/−} mice</td>
<td>(48)</td>
</tr>
<tr>
<td>SSRS11-92</td>
<td>ROS from lipid peroxidation</td>
<td>C_{18}H_{20}N_{2}O_{4}</td>
<td>NA</td>
<td>NA</td>
<td>(46)</td>
</tr>
<tr>
<td>SRS 16-86</td>
<td>ROS from lipid peroxidation</td>
<td>C_{12}H_{24}N_{2}O_{2}</td>
<td>HT1080/NIH 3T3</td>
<td>IRI mice model</td>
<td>(49)</td>
</tr>
<tr>
<td>Zileuton</td>
<td>5-LOX</td>
<td>C_{11}H_{12}N_{2}O_{3}</td>
<td>HT22</td>
<td>NA</td>
<td>(50)</td>
</tr>
<tr>
<td>SB202190</td>
<td>p38</td>
<td>C_{9}H_{18}N_{2}OF</td>
<td>HL-60</td>
<td>NA</td>
<td>(51)</td>
</tr>
<tr>
<td>SP600125</td>
<td>JNK</td>
<td>C_{6}H_{11}N_{2}O</td>
<td>HL-60, HD model</td>
<td>NA</td>
<td>(46,51)</td>
</tr>
</tbody>
</table>
Figure 3 Role of ferroptosis in cancer. AA, arachidonic acid; AdA, adrenaline; ACSL4, acyl-CoA synthetase long-chain family 4; cDC1, type 1 dendritic cell; CAF, cancer-associated fibroblast; DMT1, divalent metal transporter 1; DAMP, damage-associated molecular pattern; HETE, hydroxyeicosatetraenoic acid; HMGB1, high mobility group box 1; FPN, ferroportin; LF, lactoferrin; LIP, labile iron pool; LCN, lipocalin; LPCAT3, lysophosphatidylcholine acyltransferase 3; NTBI, non-transferrin-bound iron; NCOA4, nuclear receptor coactivator 4; NK cell, natural killer cell; PE, phosphatidylethanolamine; PTGS2, prostaglandin-endoperoxide synthase 2; SCARA5, scavenger receptor A member 5; TF, transferrin; TFR1, transferrin receptor 1; TAM, tumor-associated macrophage; TME, tumor microenvironment.

Role of ferroptosis in tumor promotion and tumor evasion

Ferroptotic cancer cells can release oxidized lipid mediators, which might regulate antitumor immunity (Figure 3). Eicosanoids such as 5-hydroxyeicosatetraenoic acid (5-HETE), 11-HETE and 15-HETE released from ferroptotic cells can induce GPX4 depletion and affect anti-tumor immunity (48). GPX4 inactivation was reported associated with ferroptosis promotion of T cells. The lower GPX4 activity is, the more pro-inflammatory lipid mediators such as 5-HETE and leukotriene B4 (LTB4) produced (57,58), whereas LTB4, a kind of pro-inflammatory leukotriene, is crucial to carcinogenesis. Beyond free eicosanoids, esterified eicosanoids also role in immune response. Oxidized phosphatidylcholine was reported to inhibit DC maturation through Nrf2 activation and suppress the differentiation of T helper 17 (TH17) cells (59). Moreover, PUFA triacylglycerols and free PUFAs can cause inaccurate cross-presentation and defective immune responses.
antitumor immunity (60).

With further deeper studies, prostaglandins (PGs) have been regarded as significant immune regulators. Ferroptotic tumor cells were reported to associate with the increase of the release of prostaglandin E2 (PGE2), which acts as a main immunsuppressive factor and can affect anti-tumor immunity (Figure 3) (28). A study argued that PGE2 could downregulate chemokine receptors to block classical type I dendritic cells (cDC1s) directly as well as inhibit natural killer (NK) cells to secrete chemokines CC chemokine ligand 5 (CCL5) and chemokine lymphotactin (XCL1), so cDC1 accumulation was suppressed in tumor site. Additionally, PGE2 also functions in acquired immune system. Cytotoxic T cell action can be inhibited directly by PGE2 (61). Kurtova's study demonstrated a new mechanism of tumor cells' resistance to cytotoxic chemotherapy. They found under the treatment of chemotherapy, the PGE2 was released, which contributed to the repopulation of tumor cells (62).

**Association of ferroptosis with players (macrophages and lymphocytes) in tumor microenvironment (TME)**

Iron metabolism impacts the TME greatly and tumor cells contain more iron than normal cells (63). Malignant cells usually uptake iron mediated by TFR1. TFR1 overexpression has been observed in diverse cancers. The increase of labile iron in cancer cells is a double-edged sword, because it can facilitate DNA replication to accelerate tumor progression (64), but can also lead to ferroptosis (25). The number and/or the distribution of tumor-associated macrophages (TAMs) may link to prognosis in potential malignant diseases (65). In most tumors, M2-polarized TAMs act as “iron-donators” that may promote cancer progression (66). Ferroportin (FPN-1) is a well-known cellular iron exporter, which can be regulated by hepcidin antimicrobial peptide (HAMP) (67). The cellular iron of M2-polarized TAMs is decreased in TME and the expression of FPN-1 is increased, thereby providing iron for tumor cells (68). However, an opposite viewpoint of TAM's role in cancer immune system was presented in a murine lung carcinoma model. This group demonstrated the hemolysis in the TME transformed the M2-polarized TAMs into M1-polarized TAMs, which functioned in inducing anti-cancer activity (69). Therefore, TAMs can both promote and suppress tumor progression. The association between lymphocytes and ferroptosis has also been studied. An elegant study from Wang's group in the ID8 ovarian tumor bearing mice model demonstrated the treatment of programmed death-ligand 1 (PD-L1) inhibitors can increase lipid ROS in CD45-IDB cells and suppress tumor progression. Their further study in erastin-resistant ID8 cells showed cells' insensitivity to anti-PD-L1 inhibitors, suggesting ferroptosis was involved in antitumor activity of immunotherapy. Besides, the cytokine interferon gamma (IFN-γ) released by CD8+ T cells could down-regulate the system Xc’ expression in ferroptosis (Figure 3) (14).

**Hepcidin-ferroportin in ferroptosis of cancers**

Hepcidin and FPN1 constitute the vital regulator of the systemic iron homeostasis (63). As the negative regulator of protein FPN-1, hepcidin inhibits the release of iron from macrophages and intestinal mucosal cells into circulation. Systemic hepcidin is increased in patients with cancers such as prostate cancer (70), upper gastrointestinal tract tumors (71), breast cancer (72), and non-Hodgkin's lymphoma (73). Elevated plasma hepcidin could cause iron accumulation in cancer cells through degrading FPN-1, which would promote tumor progression by activating NF-κB and Wnt signal pathways (74,75). Besides, FPN-1 knockdown in neuroblastoma cells could accelerate erastin-induced ferroptosis with increased iron-dependent ROS accumulation. Pancreatic cancer cells treated with ruscogenin were also observed elevated intracellular iron, ROS generation, and ferroptosis by downregulating FPN-1 and upregulating TF (76). Thus, regulator hepcidin-ferroportin plays an important role in iron homeostasis and ferroptosis in cancers.

**MicroRNAs (miRNAs) in ferroptosis of cancers**

miRNAs are a class of small non-coding RNA molecules, which can regulate the posttranscriptional gene expression. The important role of miRNAs in regulating iron homeostasis has been reviewed well before (77), including regulating proteins that control the iron export, import and storage. Based on this, emerging evidence suggests associations between different miRNAs and ferroptosis. For example, miR-137 was reported to regulate ferroptosis negatively in melanoma cells by regulating glutamine transporter SLC1A5 directly (78). Besides, cancer-associated fibroblasts could inhibit ferroptosis in tumor cells by secreting the exosomal miR-522, in which the lipid-ROS accumulation was blocked (79). The miR-4715-3p (80), miR-103a-3p (81), and miR-6852 (82) were also identified.
as regulators in ferroptosis in upper gastrointestinal, gastric, and lung cancers respectively. Thus, miRNAs play important roles in iron metabolisms and ferroptosis.

**Therapeutic strategies targeting ferroptosis**

**Small molecules to induce ferroptosis in cancer**

System Xc\(^{−}\) determines the survival and growth of a large part of tumor cells to a certain extent, making it a possible target for cancer treatment.

Erastin is famous for its function directly inhibiting system Xc\(^{−}\) to reduce the GSH level and induce ferroptosis. An interesting phenomenon was observed in Dixon’s study in 2012 that erastin triggered the ROS accumulation in NRAS-mutant HT-1080 fibrosarcoma cells. Cell death was suppressed when adding iron chelator deferoxamine, which suggested erastin could induce ferroptosis (25). Further study has proved the importance of RAF/MEK/ERK signaling pathway in erastin-triggered ferroptosis in RAS-mutated cancer (7). Erastin derivatives such as piperazine erastin and imidazole ketone erastin (IKE) were developed to overcome the shortcomings of erastin such as poor water-solubility and unstable metabolism in-vivo. A study in the SUDHL6 xenograft animal model showed IKE was successfully used in the treatment of diffuse large B cell lymphoma (DLBCL) (27).

Another ferroptosis inducer is sorafenib, which is a multi-kinase inhibitor in therapy of cancers including advanced renal cell carcinoma, thyroid carcinoma and hepatocellular carcinoma. The cytotoxicity of sorafenib to hepatocellular carcinoma was removed when treated with iron chelator (33). However, resistance to sorafenib has emerged in some cancer cell lines. For example, sorafenib-induced ferroptosis was inhibited in hepatocellular carcinoma cells with retinoblastoma (Rb) protein (34). The anti-inflammatory drug sulfasalazine (SAS) (brand name Salazopyrin, Sulazine, Azulfidine, etc.) can role as a ferroptosis inducer as well. In glioma cells, sulfasalazine can lead to ferroptosis by inhibiting system Xc\(^{−}\) (83).

Some cancer cells induce ferroptosis by the transulfuration pathway instead of system Xc\(^{−}\), and GPX4 inactivation can eradicate these tumor cells. One example is (1S, 3R) -RSL, which induces ferroptosis by direct GPX4 inhibition. Another is FIN56, a specific inducer for ferroptosis as a GPX4 degradation promotor (23).

Beyond inhibition of system Xc\(^{−}\) and GPX4, ferroptosis can also be induced by increasing LIP. For example, molecular BAY 11-7085 could induce ferroptosis through the Nrf2-SLC7A11-HO-1 pathway, and overexpression of heme oxygenase-1 (HO-1) that is encoded by HMOX1 has been observed in MDA-MB-231 breast cancer cells and DBTRG-05MG glioblastoma cells (44). Increased TF expression and decreased FPN-1 expression could also mediate ferroptosis using siramesine and lapatinib (43). In addition, autophagy also contributes to inducing ferroptosis by degrading ferritin in cancer cells. The cargo receptor nuclear receptor coactivator 4 (NCOA4) is important in the autophagic turnover of the ferritin in ferroptosis. In pancreatic cancer cells, overexpression of NCOA4 via gene transfection inhibited FIH1 expression and promoted erastin-induced ferroptosis (84). Further studies are needed to explore novel molecules targeting NCOA4 in ferroptosis to treat cancer. Beyond these small molecules, more are involved in ferroptosis induction (Table 2).

**Nanoparticle inducers of ferroptosis in cancer**

Nanotechnology applications have attracted much attention with specific physicochemical properties recently (Table 4).

Most nanomaterials such as iron-containing nanoparticles are based on Fenton reaction. Chen and colleagues developed a tumor-targeted nanoparticle named α-enolase targeting peptide modified Pt-prodrug loaded FeO\(_{3}\) nanoparticles (ETP-PtFeNP). Tumor cells treated with ETP-PtFeNP were observed increased ROS generation, enhanced immunogenicity and strong anti-tumor immune response (99). Additionally, a novel nanoparticle called SRF@FeIIITA (SFT) was reported important in inhibiting tumor progression. By loading methylene blue (MB) into SFT through depositing tannic acid (TA) and Fe\(^{3+}\) onto SRF nanocrystal, the combination therapy of photodynamic therapy (PDT) and ferroptosis succeeded (95).

Nanomaterials can also induce ferroptosis through GSH metabolism. The arginine-capped manganese silicate nanobubbles (AMSNs) were developed with a high efficiency of GSH depletion, based on the high ratio of surface area to volume (96). Further *in-vivo* study indicated AMSNs could help suppress Huh7 xenograft tumor growth by downregulating GPX4. This could be inhibited by ferroptosis inhibitor liproxstatin-1.

**Ferroptosis modulation for tumor sensitization to anticancer therapies**

Drug resistance becomes a major challenge in...
<table>
<thead>
<tr>
<th>Nanoparticle inducers</th>
<th>Mechanism</th>
<th>in-vitro</th>
<th>in-vivo</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferumoxytol</td>
<td>increase Fe(^{3+}) or Fe(^{2+}), generate highly toxic ROS</td>
<td>MMTV-PyMT, MDA-MB-468, HT1080, RAW264.7, human dermal fibroblasts (ATCC, PCS-201-012), HUVECs</td>
<td>FVB/N mice</td>
<td>(85)</td>
</tr>
<tr>
<td>FePt-NP2</td>
<td>ROS generation induced by released cisplatin and Fe(^{3+}/Fe^{2+})</td>
<td>A2780, ACP cells</td>
<td>H22 cancer model</td>
<td>(86)</td>
</tr>
<tr>
<td>IO-LAHPIPs</td>
<td>generation of O(_2) via a chemical reaction between LAHP and catalytic ions (i.e., Fe(^{3+})) by the Russell mechanism.</td>
<td>U87MG, OVCAR-8</td>
<td>Nude mice</td>
<td>(87)</td>
</tr>
<tr>
<td>Fe(_3)O(_4)@PLGA NPs</td>
<td>providing O(_2) for echogenic reflectivity and •OH as the therapeutic ROS</td>
<td>HeLa cells</td>
<td>HeLa cell carcinoma tumor-bearing nude mice</td>
<td>(88)</td>
</tr>
<tr>
<td>AFeNPs</td>
<td>overproduced H(_2)O(_2), increase iron in tumor</td>
<td>MCF-7</td>
<td>4T1 tumor-xenografted mouse</td>
<td>(89)</td>
</tr>
<tr>
<td>MON-p53</td>
<td>iron loading, inhibit system X(_c)^− (ferroptosis+ apoptosis)</td>
<td>HT-1080, 4T1, SCC-7</td>
<td>HT-1080</td>
<td>(15)</td>
</tr>
<tr>
<td>FePt/GO CNs</td>
<td>increased Fe, ROS accumulation</td>
<td>MCF-7, L02, HeLa, HepG2, BRL 3A</td>
<td>balb/c mice bearing 4T1 tumors</td>
<td>(90)</td>
</tr>
<tr>
<td>αMSH-PEG-Cdot particles</td>
<td>iron uptake, suppression of glutathione, and accumulation of lipid ROS</td>
<td>M21, BxPC3</td>
<td>786-O, HT-1080 xenograft models</td>
<td>(91)</td>
</tr>
<tr>
<td>ZVI NPs</td>
<td>iron loading, ROS accumulation, lipid peroxidation</td>
<td>OC2, KOSC-3, OEC-M1, SCC9, HSC-3, SAS</td>
<td>SAS</td>
<td>(92)</td>
</tr>
<tr>
<td>FeCO-DOX@MCN</td>
<td>iron loading, ROS level increase, GSH depletion, GPX4 inactivation</td>
<td>MCF-7, A549, HeLa</td>
<td>MCF-7</td>
<td>(93)</td>
</tr>
<tr>
<td>DGU:Fe/Dox</td>
<td>Dox release triggered by NIR, iron loading, ROS accumulation, downregulation of GPX4 and ACSL4</td>
<td>4T1, J774A.1</td>
<td>4T1</td>
<td>(94)</td>
</tr>
<tr>
<td>SRF@Fe(^{3+})TA</td>
<td>system Xc(^-) inhibition, iron loading, ROS accumulation</td>
<td>4T1, HT-1080, Hep G2, CT26</td>
<td>4T1</td>
<td>(95)</td>
</tr>
<tr>
<td>AMSNs</td>
<td>ROS accumulation, GSH depletion</td>
<td>Huh7</td>
<td>Huh7, MDA-MB 231</td>
<td>(96)</td>
</tr>
<tr>
<td>LDL-DHA</td>
<td>ROS accumulation, GSH depletion</td>
<td>PLC/PRF/5, HepG2 (Human), H4IE(Rat)</td>
<td>HepG2</td>
<td>(97)</td>
</tr>
<tr>
<td>Pa-M/Ti-NCs</td>
<td>iron loading, ROS accumulation</td>
<td>B16F10, 4T1</td>
<td>B16F10, 4T1</td>
<td>(98)</td>
</tr>
</tbody>
</table>
chemotherapy treatment. Hopefully, ferroptosis inducers may help to overcome this drug resistance (24), and combining ferroptosis agonists with chemotherapy drugs may become a novel strategy to cancer treatment. Persister cells refer to the cancer cells that remain its life after several rounds of chemotherapy drugs (100). Down-regulated Nrf2-targeted genes were shown in these cancer cells, while inhibition of intracellular NF2 and hippo signaling pathway can accelerate ferroptosis (101). Besides, decreased levels of GSH and nicotinamide adenine dinucleotide phosphate (NADPH) are observed in persister cells. Persister cells tend to be more sensitive to lipid peroxidation, and GPX4 inhibitors are proved lethal in persister cells. Thus, the ferroptosis inducers may be promising to overcome these cells’ drug resistance.

**Ferroptosis-associated antitumor combination therapy**

Few studies have reported the combination of ferroptosis inducers with other anti-tumor therapies for clinical treatment. Many studies remain in the experimental stage. Iron-sulfur cluster biosynthetic enzyme NFS1 is important to cancer cells when the oxygen concentration is above 3–8% in most tissues. And high expression of it is often found in well-differentiated adenocarcinomas. The study of Alvarez SW’s group suggested that inhibition of NFS1 cooperated with suppression of cysteine transport to induce tumor cell ferroptosis (102). Although some tumors are resistant to certain chemotherapy drugs, they are very sensitive to ferroptosis inducers. For example, pancreatic cancer cells are shown to be resistant to chemotherapy-induced apoptosis, but have great sensitivity to artemisinin-induced ferroptosis (103). Therefore, ferroptosis inducers turn out to be a promising strategy for cancer therapies.

**Targeting ferroptosis: potential way to prevent tumor metastasis**

Clinical treatment of tumor metastasis seems complicated possibly because of tumor heterogeneity, activity of oncogenes, epithelial-mesenchymal transition (EMT), and the microenvironment of the metastatic sites (104). Cancer metastasis can be inhibited by high intracellular oxidative stress. Hence, targeting ferroptosis may become a promising way to prevent metastasis.

Nanoparticles may offer enormous advantages to treat cancer metastasis because of their relatively low risk compared with locally injected agents (105). Based on coordination between ferric iron (Fe$^{3+}$) and tannic acid (TA), p53 plasmid-encapsulated metal–organic network (MON-p53) was developed. Treatment of MON-p53 could suppress cancer cell migration in a wound healing assay in-vitro (15), indicating that MON-p53 might inhibit tumor metastasis. Mesenchymal cancer cells are easily metastatic and prone to be resistant to anticancer treatments (13). Increased cell sensitivity to chemotherapy drugs can also reduce cancer metastasis to some extent. Antagonizing NF2-YAP pathway allows the promotion of ferroptosis by up-regulating ferroptosis modulators such as ACSL4 and transferrin receptor (TFRC) (101). This provides a novel insight that mesenchymal or metastatic property cancer cells are highly sensitive to ferroptosis.

**Conclusions**

Ferroptosis is a new form of RCD, characterized by lethal ROS accumulation and over production of lipid peroxidation, which relates closely to excess iron loading, GSH depletion as well as lipid peroxidation. An important peroxidase GPX4 can protect cells from ferroptosis and inactivation of GPX4 will lead to ROS accumulation. Ferroptosis can also be regulated by pathways including mevalonate pathway, P53 pathway and Nrf2. Researchers have increasingly explored the role of ferroptosis in TME. Tumor cells are proved to contain more intracellular iron than normal cells, related to the over-expression of TFR and iron supply of macrophages. Ferroptosis roles as a double-edged sword in tumor development because ferroptotic cancer cells release a variety of signaling molecules either to inhibit tumor growth or to promote tumor proliferation. The role of these signals released from ferroptotic cancer cells in TME remains further investigation.

Appropriate drug type and dose of ferroptosis inducers have a certain therapeutic effect on different types of tumors, making ferroptosis inducers prospective to treat cancer. A vast majority of studies on ferroptosis inducers are still in the experimental phase. Interestingly, ferroptosis is applicable to those tumor cells that are less sensitive to chemotherapy, radiotherapy, and other treatments.

However, some considerations should be taken into account for treating cancers based on ferroptosis. Ferroptosis is identified related to various pathological cell deaths and the occurrence of many diseases. Degenerative pathological changes may occur due to the reduced ability to repair lipid peroxidation (106). Therefore,
ferroptosis is extremely complex in human health and diseases. Ferroptosis inducers can not only treat cancer, but also promote cancer and other diseases. The specificity and optimal dose of ferroptosis inducers need further exploration, so damages to normal cells can be reduced. In addition, the heterogeneity and replasticity of tumor cells affect their sensitivity to ferroptosis inducers differently, and the specific functions of signals released from ferroptotic cancer cells in TME has not been determined.

With deeper understanding of ferroptosis and its relationship with cancers, the mystery of ferroptosis will be gradually unveiled in the near future.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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