INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Ferroptosis-Targeting Drugs In Cancer Therapy

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ARTICLE INFO

Published: 10 Sept. 2026
Keywords:
cancer, ferroptosis, immune, tumour microenvironment
DOI:
10.5281/zenodo.22686856

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) pathways. Ferroptosis roles as a double-edged sword either suppressing or promoting tumour progression with the release of multiple signalling molecules in the tumour 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 tumour metastasis and may become a promising strategy combined with other anti-cancer 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.

INTRODUCTION

In multicellular organisms, cell death is an indispensable homeostatic mechanism to maintain tissue morphology and function. Cells may die from a biologically uncontrolled process called

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

accidental cell death (ACD), or regulated cell death (RCD) that involves closely coordinated signal cascades with tight structure and dedicated molecular mechanisms. The form of cell death included three categories historically: apoptosis, autophagy, and necrosis. 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.

Ferroptosis was firstly described as an iron-dependent form of non-apoptotic RCD induced by elastin in 2012, featured with excess reactive oxygen species (ROS) generation and lipid peroxidation. 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 . 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*) . Ferroptosis induction is associated with multiple disease occurrence, including immune system (non-alcoholic steatohepatitis), brain (stroke and intracerebral haemorrhage), neurodegenerative [Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD)], heart (heart failure), and blood diseases (leukaemia). Inhibiting ferroptosis has been identified as a potential prevention or therapeutic strategies for some of these diseases.

Table 1. Cell morphology, biochemical features, and key regulators of ferroptosis, apoptosis, necroptosis.

Type of cell death	Cell morphology	Biochemical features	Key regulators
Ferroptosis	Small mitochondria with a condensed mitochondrial membrane, vanishing or reduction of mitochondria crista, and rupture of outer mitochondrial membrane	Iron loading, ROS accumulation, System X_c^- inhibition with reduced GSH, GPX4 inhibition	Positive: p53, Ras, VDAC2/3, TFR1, NOX; Negative: SLC7A11, GPX4, NRF2, HSPB1
Apoptosis	Plasma membrane blebbing; reduction of cellular and nuclear volume; nuclear fragmentation; and chromatin condensation	Activation of caspases and proapoptotic Bcl-2 family proteins, oligonucleosomal DNA fragmentation, exposure of Plasma membrane rupture, dissipation of dissipation	Positive: pro-apoptotic Bcl-2 family proteins (Bax, Bak), p53; Negative: anti-apoptotic Bcl-2 family proteins (Bcl-2, Bcl-XL)
Autophagy	(Double-membraned) autolysosome accumulation, cytoplasmic vacuolization	Conversion from LC3-I to LC3-II, degradation of p62Lck, Beclin-1 dissociation from Bcl-2/XL	Positive: Beclin 1, ATG family proteins (ATG5, ATG7)

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 tumour cell ferroptosis but also decreases tumour metastases

to blood, lung, and liver. Viswanathan and colleagues contended the contribution of ferroptosis to drug resistant phenomenon and cancer immunotherapeutic efficacy.

Basis of ferroptosis

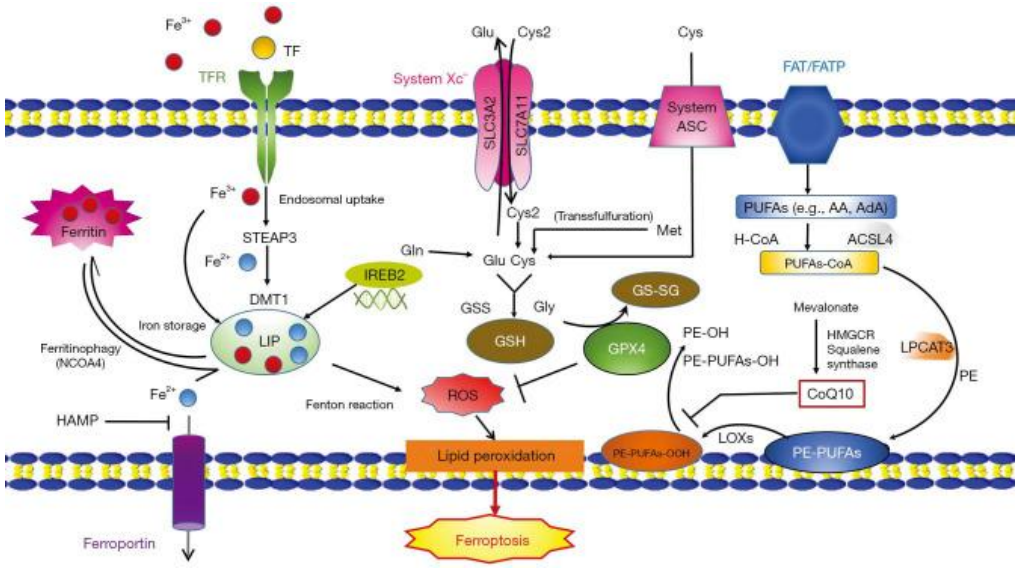

Figure 1. The complicated interplay of iron, cysteine and lipid metabolism takes an important role in ferroptosis

Mechanisms of Ferroptosis. Excess irons are regarded as an important factor for ferroptosis. The circulated 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 cystine (Cys2). Cys2, glutamate (Glu) and glycine (Gly) are materials of glutathione (GSH), which is an important antioxidant in cells. Transsulfurylation 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 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, ferroprotein; 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.

The most prominent character of ferroptosis is ROS generation, mainly caused by iron metabolism disorders . 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_2O_2)], which may result in iron poisonous . 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. 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 anti-oxidation activity. 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. The famous tumour 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*) . Further, evaluation of ferroptosis-related molecules provides diverse approaches to monitor the ferroptosis process *in-vitro* and *in-vivo* (*Tables 2,3*).

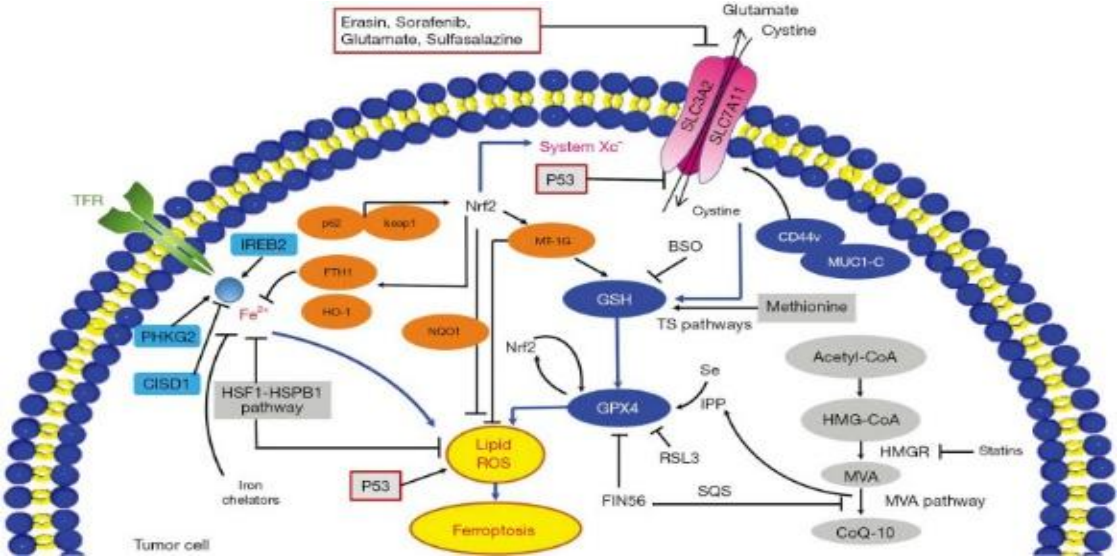

Figure 2:ferroptosis regulation

Ferroptosis modulation in tumour. Small molecules such as elastin, 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' anti-oxidative 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 hemi 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. Iron chelators 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, hemi 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.

Table 2. Ferroptosis inducers.

Reagents	Mechanisms	Formula	*In-vitro*	*In-vivo*	Refs
Erastian	System Xc^-	$C_{30}H_{31}ClN_4O_4$	BJeLR, HT1080, Calu-1, A-673, Hela, 143B p0 and p+ cell, HT1080, Calu-1, A-673, Hela, 143B p0 and p+ cell	NA	(25,26)
Piperazine erastin	System Xc^-	$C_{35}H_{41}ClN_6O_4$	HT-1080, BJeLR, DRD59	NA	(25,28)
RSL3	GPX4	$C_{23}H_{21}ClN_2O_5$	BJeLR, HT1080, A549, Calu-1, HCT116, MIA PaCa-2, KBM7, HT1080, A549, Calu-1, HCT116, MIA PaCa-2, KBM7	NA	(17,29)

Table 3. Ferroptosis inhibitors.

Reagents	Mechanisms	Formula	*In-vitro*	*In-vivo*	Refs
Bmercaptoethanol	Cystine uptake	C_2H_6SO	HT1080	NA	(25)
Ciclopirox olamine	Intracellular iron	$C_{12}H_{17}NO_2$	HT1080	OHSC	(25,46)
GKT137831	NOX1/4	$C_{21}H_{19}ClN_4O_2$	HT1080/Calu-1	NA	(25)
		$C_6H_7N_3O$	HT1080, Calu-1, BJeLR	NA	(25)

Hall marks of ferroptosis in cancer

Role of ferroptosis in tumour suppression:

Tumour suppressor P53 inactivation is very common in cancers. The anti-tumour activity of P53 was thought to drive cell senescence, cell cycle arrest and apoptostraditionally. These years, P53 has been explored to be essential in some other activities to suppress tumour progression (53,54). In the study of Jiang's group, the acetylated defective mutant TP533KR lost its function to induce cell senescence, cell cycle arrest and apoptosis, while the function of ferroptosis-induction was still kept. The cancer progression was depressed through the inhibition of Cys2 uptake and elevation of tumours' sensitivity to ferroptosis by repressing the SLC7A11 expression (55). Additionally, evidence has shown a high release of mobility group box 1 (HMGB1) in ferroptosis. We may conjecture that ferroptotic tumour cells might be immunogenic (56). Release of damage-associated molecular patterns (DAMPs) can trigger Toll-like receptor 4 (TLR4) signals in ferroptotic cell death. Such phenomena have been observed in the attraction of neutrophils and dendritic cells (DCs), thus activating the innate immune system.

Role of ferroptosis in tumour promotion and tumour 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-tumour immunity. 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, 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.

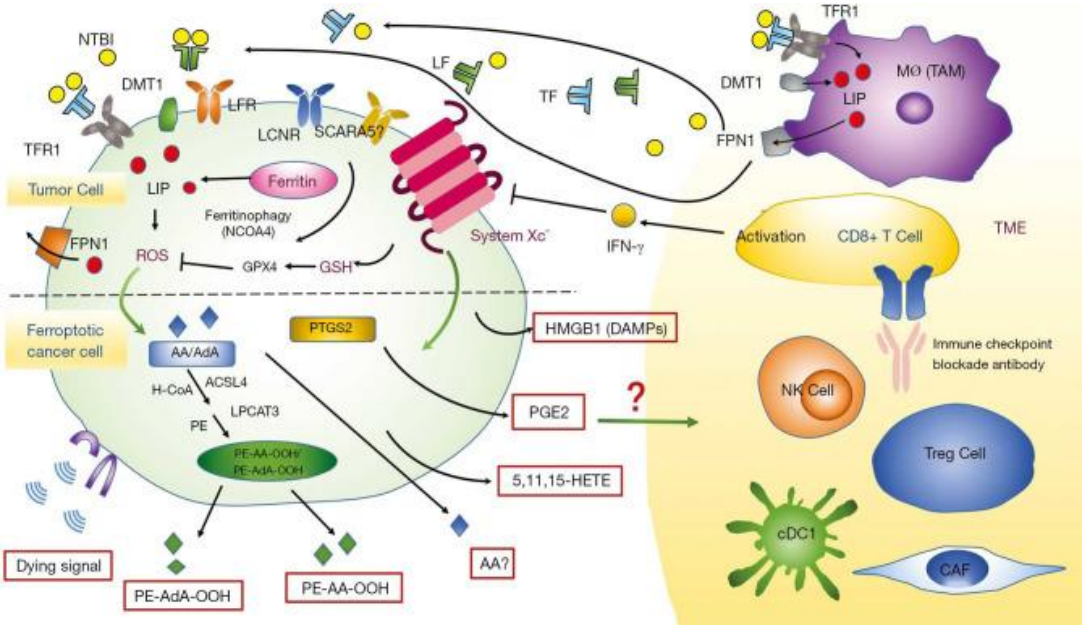

Figure 3. Regulate antitumor immunity

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, hydroxy eicosatetraenoic 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, tumour-associated macrophage; TME, tumour microenvironment.

Iron Metabolism

Iron is an indispensable and most abundant trace element in the body, and it participates in many important physiological and biochemical functions in the body. Iron is the main raw material for the synthesis of haemoglobin and myoglobin. It not only participates in the biosynthesis of DNA and ATP but is also an important electron transport

chain in mitochondria and a cofactor of metalloproteinases . Under normal conditions, the body maintains the homeostasis of iron through food sources of iron and the "iron cycle" (a process in which aging red blood cells release iron ions under the action of heme oxygenase, and macrophages re-engulf and recycle iron). The hepcidin synthesized and secreted by the liver directly regulates the level of serum iron, while the regulation of iron homeostasis in the body's cells is mainly played by the iron responsive element, the hepcidin system. The trivalent iron ion (Fe3+) in the peripheral circulation combines with transferrin to form a complex and then binds to the transferrin receptor on the cell membrane and enters the endosomes in the cell.

Regulation of lipid metabolism pathway

Accumulations of PLOOH is the hallmark of ferroptosis. Lipid metabolism is closely related to cell vulnerability to ferroptosis. PLOOH can accumulate in both enzymatic and nonenzymatic ways. Dull et al.'s study revealed that ACSL4 is an essential component for ferroptosis execution. ACSL4 functions in converting long chain-PUFAs to acyl-CoA, subsequently participating in producing PLOOH in an enzymatic way. Ye et al. Ribosylation factor 6 (ARF6) overcame gemcitabine Resistance in pancreatic cancer by inducing ferroptosis. In addition, several LOXs have been reported to Be able to oxygenate PUFAs directly in a nonenzymatic Way, thereby mediating ferroptosis . Zhang et al. Showed that arachidonate lipoxygenase 15 (ALOX15), A LOX member, was closely linked with the suppression of ferroptosis in gastric cancer. Downregulation of microRNA-522, which promotes ALOX15 expression, provides novel methods to enhance cisplatin/paclitaxel sensitivity in gastric cancer by inducing ferroptosis.

Therapeutic strategies targeting ferroptosis

Potential compounds to target ferroptosis based cancer therapy:

Ferroptosis can be induced by suppressing antioxidant defence components such as systems Xc–, GSH, and GPX4, or by precisely controlling various endogenous elements like intracellular iron concentration and PUFA-containing phospholipids.74 Up till now, the potential effectiveness of a variety of naturally occurring substances and clinically utilized medications in inducing ferroptosis has been investigated. While some of these drugs are already FDA-approved, others are still in the preclinical and clinical trial stages (Table 1). Here, we are reminded of the substances already on the market for various purposes that could be converted to ferroptosis-based cancer therapy.

Potential compounds to target intracellular iron levels

One of the key characteristics of ferroptosis is iron overload. The following is a description of the medications and substances that cause ferroptosis by raising the amount of iron within cells: salinomycin, artesunate, neratinib, lapatinib+siramesine, and ruscogenin are some of these agents.

Salinomycin

A polyether ionophore molecule called salinomycin was discovered from the bacterium Streptomycin albus. It exhibits a broad spectrum of antibacterial activity against viruses, gram-positive bacteria, fungi, and parasites. Salinomycin has antitumor effects that significantly reduce the growth of breast tumours in the mice xenograft model,76 according to a 2009 study by Gupta et al.Studies have shown that salinomycin dramatically reduces the ability of docetaxel-resistant prostate cancer cells to form

colonies.77 Additionally, the resistance of ovarian cancer cells to chemotherapy medicines based on platinum is substantially eliminated by salinomycin and its derivatives. By focusing on the hypoxia-inducible factor 1-α (HIF-1α)/vascular endothelial growth factor (VEGF) signaling pathway, salinomycin significantly inhibits the angiogenesis and development of breast cancer cells.

80Tumor cells treated with salinomycin have been shown to undergo apoptosis and autophagy caused by endoplasmic reticulum (ER) stress.81-82 Additionally, it has been discovered that salinomycin increases intracellular ROS levels and downregulates NRF2 expression, hence improving the radiosensitivity of nasopharyngeal cancer cells.83Salinomycin treatment for colon cancer cells may cause ROS production and mitochondrial dysfunction. Researchers have discovered that administering salinomycin and AM5 to cancer stem cells prevents iron transport from the lysosome lumen to the cytosol. This, in turn, causes cytosolic iron depletion, which is shown by ferritin degradation and an increase in IREB2 and TfR.85-86By causing lipid peroxide buildup and inducing ferroptosis, delivery of salinomycin-loaded gold nanoparticles (SalAuNPs) to breast cancer stem cells can efficiently kill tumour cells.

Potential compounds to target system Xc-, GSH, And GPX4

Sorafenib

NEXAVAR, commonly known as sorafenib, is an oral bioavailable multitarget kinase inhibitor that is being used to treat patients with thyroid, liver, and advanced renal cell carcinoma.119 By targeting Raf serine/threonine kinases and various cell surface receptor tyrosine kinases, such as VEGFR1-3, PDGFRβ, cKitprotein, FMSlike tyrosine kinase 3 (FLT3), and platelet derived growth factor receptor β (PDGFRβ)derived growth factor receptor β (PDG-FRβ), sorafenib is able to exert its antineoplastic activity.120 It has been discovered that sorafenib not only causes apoptosis but also activates autophagy in cancer cells.121-122 Additionally, it has been discovered by researchers that sorafenib's anti-cancer effect can also be mediated by ferroptosis induction, which is separate from its conventional kinase inhibitory function.123-124 By inhibiting system Xc and subsequently depleting

GSH, sorafenib mechanistically causes ferroptosis.125 Furthermore, research indicates that sorafenib-mediated ferroptosis is also modulated by the expression of a few genes, such as NRF2, retinoblastoma (RB), and MT-1G.126-127 In hepatocellular carcinoma cells, sorafenib-induced ferroptotic cell death is negatively regulated by MT-1G, a transcriptional NRF2 target gene, which inhibits GSH depletion-mediated lipid peroxidation.126 Significantly, sorafenib's anticancer effectiveness is enhanced by decreasing MT-1G both *in vitro* and *in vivo*.

Potential compounds to target HMG-CoA Reductase

Statins (Fluvastatin, Pravastatin, Lovastatin, Simvastatin)

Known for their ability to decrease cholesterol, statins are frequently administered to patients with hypercholesterolemia. Mechanistically, statins inhibit HMG-CoA reductase, an essential enzyme involved in the mevalonate pathway-mediated production of cholesterol, IPP, and CoQ10.186 Numerous accounts exist on encouraging attempts to treat cancer with statins.186 Statins have been shown to promote apoptosis in tumour cells and mediate cell cycle G1/S-phase arrest. According to a paper, statins work in concert to enhance

sorafenib's antitumor activity in vitro.188 Furthermore, in comparison to control groups, the combination of simvastatin with lipid nano emulsions paclitaxel considerably reduces the tumour growth and metastatic rate of melanoma-bearing animal models. Accordingly, statins may decrease intracellular GPX4 levels and increase lipid peroxidation in a manner that is dose- and time-dependent, according to Viswanathan et al.

Potential compounds to target SCD1 and ACSL4

MF-438, CAY10566, and A939572

SCD1, an enzyme linked to the endoplasmic reticulum, is essential for the transformation of saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs). It's interesting to note that a rise in cellular MUFA concentration and overexpression of SCD1 have been seen in a number of cancer types. SCD1 may be a viable target for antitumor therapy since, as a wealth of data over the last ten years has demonstrated, it zl. lays a remarkable role in encouraging tumour growth and metastasis.191 According to Pisanu et al., pharmacological targeting of SCD1 with MF-438 dramatically increases the cisplatin susceptibility of lung cancer stem cells.192 More research is required to determine the exact underlying mechanism by which SCD1 inhibition inhibits tumour growth. SCD1 inhibition induced by MF-438 and CAY1-0566 inhibits tumour cell growth and chinitiates apoptosis.193 Moreover, administering CAY1-0566 to hepatocellular carcinoma cells induces autophagy via AMP-activated protein kinase (AMPK).194 By suppressing YAP/TAZ activity, MF-438 has been demonstrated to eliminate lung cancer cells' capacity to form spheres.195 Further more, A939572-inhibiting SCD1 prevents tumour cell migration that is driven by cancer-associated fibroblasts (CAF).196 The ferroptosis is maintained by suppressing SCD1, which lowers MUFA and CoQ10 levels. According to Tesfay and colleagues, administering SCD1 inhibitors to ovarian cancer cells causes an increase in lipid peroxidation and ferroptosis-mediated cell death, which is prevented when Fer-1 and oleic acid are present. Furthermore, erastin, RSL3, and SCD1 inhibitors work in concert to suppress tumour growth *in vivo and in vitro*.

Nanoparticle inducers of ferroptosis in cancer

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

Table 4

Nanoparticle inducers	Mechanism	*In-vitro*	*In-vivo*	Refs
Ferumoxytol	increase Fe^{3+} or Fe^{2+}, generate highly toxic ROS	MMTV-PyMT, MDA-MB-468, HT1080, RAW264.7, human dermal fibroblasts (ATCC, PCS-201–012), HUVECs	FVB/N mice	(85)
FePt-NP2	ROS generation induced by released $^{+}/Fe^{3+}$	A2780, ACP cells	H22 cancer model	(86)

Most nanomaterials such as iron-containing nanoparticles are based on Fenton reaction. Chen and colleagues developed a tumour-targeted nanoparticle named α-enolase targeting peptide modified Pt-prodrug loaded Fe_3O_4 nanoparticles (ETP-PtFeNP). Tumour cells treated with ETP-PtFeNP were observed increased ROS generation, enhanced immunogenicity and strong anti-tumour immune response. Additionally, a novel nanoparticle called SRF@FeIIITA (SFT) was reported important in inhibiting tumour 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. Nanomaterials can also induce ferroptosis through GSH metabolism.

CONCLUSION

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. Tumour cells are proved to contain more intracellular iron than normal cells, related to the over-expression of TFR on tumour cells and iron supply of macrophages. Ferroptosis roles as a double-edged sword in tumour development because ferroptotic cancer cells release a variety of signalling molecules either to inhibit tumour growth or to promote tumour proliferation.

Appropriate drug type and dose of ferroptosis inducers have a certain therapeutic effect on different types of tumours, 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 tumour cells that are less sensitive to chemotherapy, radiotherapy, and other treatments. 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. Therefore, ferroptosis is extremely complex in human health and diseases.

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HOW TO CITE: K.Malleswaram, Dr. D. Rama Brahma Reddy*, B.Vinay Kumar, Ferroptosis-Targeting Drugs In Cancer Therapy, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 993-1003. https://doi.org/10.5281/zenodo.22686856