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Review

Emerging mechanisms and applications of ferroptosis in the treatment of resistant cancers

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ABSTRACT

The development of chemotherapy drugs has promoted anticancer treatment, but the effect on tumours is not clear because of treatment resistance; thus, it is necessary to further understand the mechanism of cell death to explore new therapeutic targets. As a new type of programmed cell death, ferroptosis is increasingly being targeted in the treatment of many cancers with clinical drugs and experimental compounds. Ferroptosis is stimulated in tumours with inherently high levels of ferrous ions by a reaction with abundant polyunsaturated fatty acids and the inhibition of antioxidant enzymes, which can overcome treatment resistance in cancers mainly through GPX4. In this review, we focus on the intrinsic cellular regulators against ferroptosis in cancer resistance, such as GPX4, NRF2 and the thioredoxin system. We summarize the application of novel compounds and drugs to circumvent treatment resistance. We also introduce the application of nanoparticles for the treatment of resistant cancers. In conclusion, targeting ferroptosis represents a considerable strategy for resistant cancer treatment.

1. Introduction

Although our understanding of drug therapy has increased greatly in recent decades [1,2], cancer continues to be a major public health problem with few effective treatment options, treatment resistance and high mortality worldwide [3].

The primary mechanism of drug therapy is the induction of apoptosis, which has made tremendous contributions to cancer treatment [4]. However, cancer cells can often develop mechanisms to prevent apoptosis through drug-resistant phenotypes and increasing survival-promoting signals [5,6]. It is necessary to explore other forms of cell death to address drug resistance. In recent years, studies have shown that the induction of ferroptosis in cancer cells is expected to be a new cancer therapy strategy [7,8] and aim accelerate the clinical application of ferroptosis in cancer treatment [9].

Ferroptosis is a destructive form of passive cell death that is closely linked to drug-resistant diseases [10]. The initiation of ferroptosis requires the accumulation of intracellular reactive oxygen species (ROS) in an iron-dependent manner [8]. Studies in the past several decades have shown that increased intracellular ROS play important roles in cancer tumorigenesis, angiogenesis, invasion, metastasis, and chemoresistance [11,12]. Moreover, advanced cancer cells often exhibit a variety of genetic changes and elevated oxidative stress, which indicates that these cancer cells can be preferentially eliminated by using agents to either increase ROS generation or inhibit antioxidant defence [13,14]. The upregulation of antioxidant capacity to adapt to oxidative stress in cancer cells can promote cancer progression and treatment resistance [15,16].

Glutathione peroxidase 4 (GPX4) plays a major antioxidant role in cancer resistance. Hangauer et al. showed that mesenchymal cancer cells with high resistance to therapy were dependent on GPX4, which was also necessary for tumour recurrence in a melanoma xenograft model [17]. However, GPX4 is not the only key regulator through which cancer cells avoid ferroptosis. Recently, both Bersuker et al. and Doll et al. identified ferroptosis effector protein 1 (FSP1) as a novel coenzyme Q_{10} (CoQ_{10}) plasma membrane oxidoreductase that protects cells from glutathione (GSH)-independent ferroptosis [7,18], which suggested that cancer escape from ferroptosis may be regulated by many antioxidation mechanisms, and targeting these proteins can be a therapeutic strategy for cancer treatment.

In this review, we give a brief introduction to the mechanism of ferroptosis. We present the factors that inhibit ferroptosis in treatment-

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resistant cancers and the use of diverse clinical agents that participate in the treatment of cancer. Additionally, we discuss the application of ferroptosis induction in combination with other technologies, such as nanoparticles, in cancer therapy. In conclusion, targeting ferroptosis in persistent cancer cells presents a therapeutic opportunity to treat resistant cancers.

2. Main pathways involved in the execution of ferroptosis

The development of ferroptosis is a new field in cancer treatment and includes the development of the lethal ferroptosis drugs RSL3 and erastin (Fig. 1). Ferroptosis is mainly caused by abnormal increases in iron-dependent lipid oxygen free radicals and imbalances in the redox balance of cells, which brings new hope for the development of chemotherapy and the treatment of resistant cancers [19]. Ferroptosis can be controlled by GPX4, ferrous iron and lipid metabolism, as previously reported. Generally, ferroptosis involves the loss of GPX4 and excessive ferrous iron, which induce an increase in lipid peroxide-mediated cell death.

2.1. GSH

GSH metabolism is mediated by system X_C^-, which is connected by the disulfide-linked heterodimers SLC7A11 (xCT) and SLC3A2 (4F2hc, or CD98hc), which form the extracellular oxidized forms of cysteine; cystine enters the cells and exchange intracellular glutamate, which is excluded [20]. The suppression of system X_C^- can promote ferroptosis (Table 1). As a precursor of GSH synthesis, cystine plays an important role in the regulation of ferroptosis. Preliminary observations indicated that cystine deprivation inhibited cell growth [21,22], and this type of cell death could be inhibited by lipophilic antioxidants and iron chelators [22–25]. Inhibiting the entry of cystine results in decreased intracellular GSH levels [7,26], and the depletion of cysteine or cystine induced ferroptosis in pancreatic ductal adenocarcinoma (PDAC) [27]. In addition, glutamate metabolism (glutaminolysis) is necessary for ferroptosis caused by cystine deprivation [28]. P53 can induce glutaminase 2 (GLS2) expression to favour glutaminolysis, which promotes ferroptosis through the accumulation of glutamate [29] (Fig. 2a).

GSH can be stimulated as a cofactor of selenium-dependent GPX4 to reduce lipid hydroperoxides [30,31]. Therefore, the inactivation of GPX4 can be achieved by targeting the consumption of GSH [7,32,33]. In addition, the mevalonate pathway is involved in the synthesis of GPX4 and antioxidant reactions. Isopentenyl pyrophosphate (IPP), a direct metabolite of mevalonate, is essential for cholesterol biosynthesis and selenocysteine (Sec)-tRNA and CoQ_{10} production [34] (Fig. 2b).

Nicotinamide adenine dinucleotide phosphate (NADPH), which is involved in the synthesis of GSH, can predict sensitivity to ferroptosis-inducing compounds and is essential for maintaining intracellular GSH levels [35,36]. Further transcriptome analysis revealed that NADPH was produced by the pentose phosphate pathway (PPP). Studies have shown that the inhibition of the PPP and two PPP enzymes (glucose-6-phosphate dehydrogenase (G6PD) and phosphoglycerate dehydrogenase (PGD)) can inhibit erastin-induced ferroptosis in lung cancer cells [7]. However, the PPP can also provide NADPH for NADPH oxidases (NOXs), thus promoting ROS production and ferroptosis in colorectal cancer cells [37].

2.2. Ferrous iron

Iron ions are involved in lipid peroxidation and have been identified as novel players in ferroptosis [19]. Iron regulatory protein (IRP) controls iron metabolism genes post-transcriptionally through the iron-responsive element (IRE)-IRP system and plays a critical role in controlling iron homeostasis in cells [38]. These iron metabolism genes include ferritin heavy peptide 1 (FTH1), ferritin light chain (FTL), transferrin (TF, TRF), transferrin receptor (TFRC), ferroportin (FPN, SLC40A1) and divalent metal transporter 1 (DMT1) [39].

TF, an iron binding serum protein, can be taken into the cell through endocytosis mediated by transferrin receptor 1 (TfR1) [40]. In addition, the ZRT/IRT-like protein (ZIP) family transporters ZIP8 and ZIP14 were recently identified as crucial for transporting non-transferrin bound iron (NTBI) after the reduction of NTBI by prion protein (PRNP) [41,42]. TF is an important component of iron-dependent cell death. Gao et al. showed that adding holo-transferrin as an iron carrier protein in Bax/-Bak double-knockout cells can induce ferroptosis [28]. In addition, Feng et al. indicated that TfR1 carrying iron into cells can function as a specific ferroptosis marker [43]. TF-TfR1 binding induces internalization to an acidic endosome, and then Fe^{3+} is released from TF and transformed to Fe^{2+} by six-transmembrane epithelial antigen of prostate 3 (STEAP3) [44]. Finally, Fe^{2+} is transported in the cytoplasm by DMT1 or ZIP8/14 (Fig. 2c). Knockdown of FPN accelerates erastin-induced ferroptosis in neuroblastoma cells by increasing iron-dependent lipid ROS accumulation [45]. HSPB1 can mediate iron uptake by downregulating TfR1, and HSPB1 overexpression slows the endocytosis and circulation of TF [46].

Ferritin is the main iron storage protein in cells; the utilization of iron ions occurs nuclear receptor coactivator 4 (NCOA4)-mediated autophagy of ferritin, and NCOA4-mediated ferritinophagy (autophagic degradation of ferritin) is involved in erastin-induced ferroptosis [47,48]. Prominin2 mediates the formation of ferritin-containing multivesicular bodies (MVBs) and exosomes that transport iron out of breast carcinoma cells [49] (Fig. 4g). In contrast, phosphatase kinase G2 (PHKG2) regulates iron availability to lipoxygenase enzymes, which in

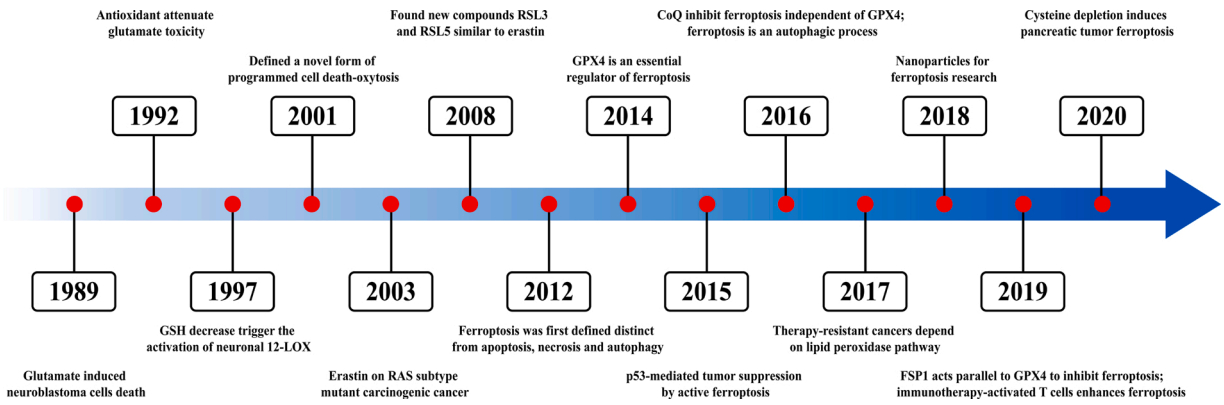

Fig. 1. The development of ferroptosis in cancer research.
The key development of ferroptosis in cancer research including the discovery of important regulatory factors, such as lipoxygenases 12 (LOX12), glutathione peroxidase 4 (GPX4), coenzyme Q_{10} (CoQ_{10}) and ferroptosis effector protein 1 (FSP1), the synthesis of ferroptosis inducers such as 1S,3R-RSL3 (RSL3) and RSL5 and the relationship of ferroptosis with other fields such as immunity, autophagy and cancer resistance.

Table 1
Modulation of ferroptosis in cancer research.

Factors GSH	Protein	Function	Modulatory Effect	Cancers	Refs
SLC7A11	Solute carrier family 7 member 11	Subunit of system X_C^- to import cystine in the cell	Inhibition induces ferroptosis	LUAD, fibrosarcoma	[7]
TP53	Tumor protein P53	Regulate cell cycle arrest, apoptosis, senescence, DNA repair, metabolism	Inhibit cystine uptake and sensitizes cells to ferroptosis by repressing SLC7A11 and induced GLS2	NSCLC, BRCA, osteosarcoma	[62]
IFN_γ	Interferon γ	Triggers a cellular response to viral and microbial infections	Derived from $CD8^+$ T cells and promote ferroptosis by suppress SLC7A11	Melanoma, fibrosarcoma, ovarian cancer	[63, 64]
BECN1	Beclin1	Regulates autophagy and proteins metabolism	Promote ferroptosis by blocking SLC7A11	CRC, PAAD, LUAD, fibrosarcoma, cervical carcinoma	[65]
ATF3	Activation transcription factor 3	Involved in the complex process of cellular stress response	Repressing SLC7A11 expression and promote erastin induced ferroptosis	COAD, PRAD, fibrosarcoma, osteosarcoma	[66]
ATM	Ataxia- Telangiectasia mutated gene	Regulate p53 BRCA1, CHK2, RAD 9/17, NBS1	Activate by radiotherapy and promote ferroptosis by suppress SLC7A11	Melanoma, fibrosarcoma, ovarian cancer	[64]
GCL	Glutamate-cysteine ligase	Enzyme involved in GSH synthesis	Inhibition induces ferroptosis	DLBLC, RCC, fibrosarcoma osteosarcoma	[32]
NADPH	Nicotinamide adenine dinucleotide phosphate	Reduce oxidized glutathione to GSH	Knockdown sensitizes erastin, RSL3, FIN56 induced ferroptosis	RCC, LUAD, PRAD, CRC, PAAD, BRCA, fibrosarcoma melanoma, sarcoma, osteosarcoma	[36]
CARS	Cysteinyl-tRNA synthetase	Synthetases translation tRNA	Knockdown suppresses erastin induced ferroptosis by activation of transsulfuration	RMS, PAAD, PHCC, fibrosarcoma, osteosarcoma	[67]
CBS	Cystathionine-b- synthase	Converts homocysteine to cystathionine	Knockdown sensitizes erastin induced ferroptosis in CARS knockdown cells	PAAD, PHCC fibrosarcoma rhabdomyosarcoma, osteosarcoma	[67]
ABCC1/ MRP1	ATP binding cassette/ multidrug-resistance protein 1	Mediates GSH and chemotherapeutics efflux from cells	Overexpression sensitizes to erastin2, cyst(e)inase, RSL3, ML162 induced ferroptosis	NSCLC, osteosarcoma, fibrosarcoma, glioblastoma	[68]
GLS2	Glutaminase 2	Catalyzes the hydrolysis of glutamine to glutamate and ammonia	Promote ferroptosis by excessive glutamate to inhibit cysteine	NSCLC, BRCA, osteosarcoma, gastric cancer	[69, 70]
CHAC1	ChaC glutathione specific γ-glutamylcyclotransferase 1	Transferase activity, transferring acyl groups	Degrade GSH enhances cystine-starvation-induced ferroptosis	TBNC	[71]

Ferrous iron	Protein	Function	Modulatory Effect	Cancers	Refs
TF	Transferrin	Iron-binding serum protein	Silencing decreases siramesine and lapatinib induced ferroptosis	BRCA	[72]
TfR1/ TFRC	Transferrin receptor 1	Cellular transferrin-iron uptake	Knockdown suppresses amino acid/cystine deprivation, erastin induced ferroptosis	LUAD, COAD, PAAD, fibrosarcoma	[28, 48,73]
HO1/ HMOX1	Heme oxygenase 1	Catalytic degradation of heme to biliverdin, carbon monoxide and Fe^{2+}	Knockdown suppresses withaferina, erastin, BAY 11-7058 induced ferroptosis	Neuro- blastoma	[74]
IREB2	Iron response element-binding protein 2	Regulating the translation and stability of mRNAs that affect iron homeostasis upon iron depletion	Knockdown suppresses ferroptosis induced by erastin, amino acid/cystine deprivation in fibrosarcoma	LUAD, fibrosarcoma	[7,48]
NCOA4	Nuclear receptor coactivator 4	Cargo receptor mediating ferritinophagy	Knockdown suppresses ferroptosis	LUAD, fibrosarcoma	[48]
PHKG2	Phosphorylase kinaseγ2	Regulation of iron availability to lipoxygenase enzyme	Knockdown suppresses erastin induced ferroptosis	RCC, fibrosarcoma, osteosarcoma	[33]
ACO1/ IREB1	Aconitase 1/ iron-responsive element-binding protein 1	Control cellular iron ion homeostasis	Knockdown suppresses cystine deprivation induced ferroptosis	LUAD, fibrosarcoma	[48]
FTH1& FTL	Ferritin	Concentrates intracellular iron in a mineralized, redox-inactive form	Knockdown enhances erastin, sorafenib induced ferroptosis in LIHC	LIHC, PAAD fibrosarcoma	[47, 73,75]
FPN/ SLC40A1	Ferroportin-1/ solute carrier family 40 member 1	The only known cellular iron efflux pump	Knockdown accelerated erastin induced ferroptosis	CRC, neuro- blastoma	[45, 74,76]
DMT1/ SLC11A2	Divalent metal transporter 1	Transporting transferrin-bound iron from the endosome to the cytoplasm	Inhibition promote lysosomal iron accumulation, production of ROS and ferroptosis	BRCA, CSC	[77, 78]
CP	Ceruloplasmin	Involved in the peroxidation of Fe^{2+} transferrin to Fe^{3+} transferrin	Depletion of CP promoted erastin- and RSL3-induced ferroptosis	LIHC	[79]

Lipid	Regulators	Function	Modulatory Effect	Cancers	Refs
ACSL4	Acyl-CoA synthetase longchain family member 4	Catalyzes the reaction of long-chain fatty acids with coenzyme A to produce esteryl coenzyme A.	Knockdown suppresses erastin, RSL3, GPX4 depletion induced ferroptosis	LIHC, LAML, LCML PRAD, BRCA	[51, 53, 80]
ACSF2	Acyl-CoA synthetase family member 2	Regulation of mitochondrial fatty acid metabolism	Knockdown suppresses erastin induced ferroptosis	LUAD, fibrosarcoma	[7]
CS	Citrate synthase	Regulation of mitochondrial fatty acid metabolism	Knockdown suppresses erastin induced ferroptosis	LUAD, fibrosarcoma	[7]
LPCAT3	Lysophos-phatidylcholine acyltransferase 3	Incorporation of acylated fatty acids into membranes	Knockdown suppresses RSL3 induced ferroptosis	LCML, fibrosarcoma	[52, 80]
ACACA	Acetyl-CoA carboxylase alpha	Converts acetyl-CoA to malonyl-CoA, the rate-limiting step in fatty acid synthesis	Inhibition suppresses FIN56 induced ferroptosis	LCML, LUAD, fibrosarcoma	[80, 81]

(*continued on next page*)

Table 1 (*continued*)

Lipid	Regulators	Function	Modulatory Effect	Cancers	Refs
LOX	Lipoxygenases	Catalyzes the dioxygenation of polyunsaturated fatty acids in lipids	Knockout protects IKE, GPX4, RSL3 induced ferroptosis	RCC, PAAD, LUAD, osteosarcoma, fibrosarcoma, renal cancer	[33, 55]
ALOX12	Arachidonic acid 12-lipoxygenase	Acts on different polyunsaturated fatty acid substrates to generate bioactive lipid mediators	Promote p53-mediated ferroptosis and tumour suppression	NSCLC, BRCA, COAD, SCLC fibrosarcoma, melanoma, osteosarcoma,	[82]
SQS/ FDFT1	Squalene synthase/ Farnesyl-diphosphate farnesyl-transferase 1	Responsible for synthesis of squalene and involved in cholesterol synthesis	Knockdown suppresses FIN-56, ML162 induced ferroptosis	LUAD, ALCL fibrosarcoma, osteosarcoma,	[83, 84]
SQLE	Squalene monooxygenase	Catalyzes the conversion of squalene to squalene-2,3- epoxide	Overexpression promote ML162 induced ferroptosis	ALCL, osteosarcoma	[84]
FADS2	Fatty acid desaturase 2	Involved in biosynthesis of highly unsaturated fatty acids	Knockdown suppresses RSL3 induced lipid peroxidation	BRCA, LUAD, PRAD, LIHC	[85]
MDM2, MDMX	MDM2 proto-oncogene	Promote tumor formation by targeting tumor suppressor proteins for proteasomal degradation	Remodeling lipid profile of cells to favor ferroptosis through altering PPARα activity	LIHC, NSCLC, COAD, fibrosarcoma	[86]
SAT1	Spermidine/ spermine N^1-acetyl- transferase 1	Regulate N-acetyltransferase activity and spermidine binding	Transcript by p53 and sensitizes cells to ferroptosis by increased ALOX15	NSCLC, osteosarcoma	[87]
ASCL3	Acyl-CoA synthetase long chain family member 3	Converts exogenous monounsaturated fatty acids (MUFAs) into fatty acyl-CoAs	Knockout attenuates MUFA induced resistance to ferroptosis	LUAD, fibrosarcoma, glioblastoma	[88]
HMGCR	3-hydroxy-3-methyl-glutaryl coenzyme A reductase	Synthesis of mevalonic acid	Inhibition enhances FIN-56 induced ferroptosis	LUAD, osteosarcoma, fibrosarcoma	[81]

Abbreviations: PPARα: Peroxisome proliferator-activated receptor α; CP: Ceruloplasmin; IKE: imidazole keto erastin; LAML: Acute myeloid leukemia; LCML: Chronic myeloid leukemia; NSCLC: Non-small cell lung cancer; ALCL: Anaplastic large cell lymphoma; RCC: Renal cell carcinoma; CRC: Colorectal cancer; LUAD: Lung adenocarcinoma; PAAD: Pancreatic adenocarcinoma; PRAD: Prostate adenocarcinoma; LIHC: Liver hepatocellular carcinoma; BRCA: Breast invasive carcinoma; BDCA: Breast ductal carcinoma; PHCC: Pheochromocytoma; HNC: Head and neck cancer; RMS: Rhabdomyosarcoma; COAD: Colon adenocarcinoma; CSC: Cancer stem cells; ESCA: Esophageal carcinoma; TNBC: Triple negative breast cancer; HNSCC: Head and neck squamous cell carcinoma; OSCC: Oral squamous cell carcinoma; CEAD: Cervical adenocarcinoma; ALL: Acute lymphoblastic leukemia.

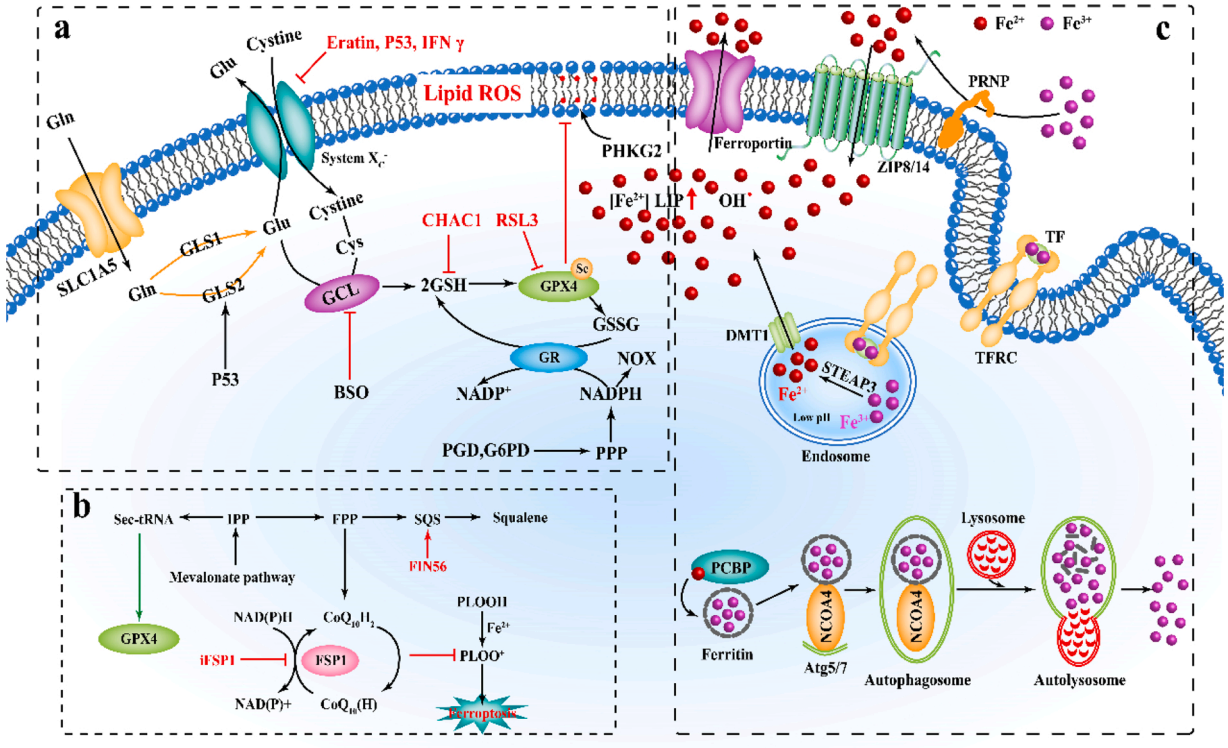

Fig. 2. Main pathway involved in the execution of ferroptosis. a: Glutathione peroxidase 4 (GPX4) as the main protective mechanism of membrane peroxidation which derived from cystine/glutamate-cysteine ligase (GCL)/ glutathione (GSH). b: Coenzyme Q_{10} (CoQ_{10}) as GPX4 independent way to negatively regulate ferroptosis which derived from the transsulfuration pathway. c: The regulation of iron involved in ferroptosis including the transport of ferritin to the cell through the transferrin receptor, the degradation of transferrin in endosome, the conversion of ferric iron to ferrous iron and the degradation of ferritin in the process of autophagy.

turn drive ferroptosis through the peroxidation of polyunsaturated fatty acids (PUFAs) at the bis-allylic position, and PHKG2 silencing may play a role similar to that of iron chelators, such as DFO [33]. BTB domain and CNC homologue 1 (BACH1) is a regulator of haem and iron metabolism that promotes ferroptosis by repressing the transcription of a subset of erastin-induced protective genes [50]. In general, a certain

amount of available ferrous iron is the basis of ferroptosis.

2.3. Lipid peroxidation

Ferroptosis is characterized by iron ion-catalysed peroxidation of PUFA-containing PLs in mammalian cell membranes. Adding PUFAs to cells can promote ferroptosis, while the exchange of PUFAs with deuterated PUFAs will inhibit the occurrence of ferroptosis because the deuterated PUFAs are not easily oxidized [33,51–53]. Therefore, it is believed that lipid peroxidation is the main mechanism of ferroptosis. Lipid peroxidation is a free radical-driven chain reaction that is mainly initiated by activated ROS interacting with PUFAs; hydroxyl radicals (OH·) are the most active ROS, and Fenton reactions are the main source of OH· through hydrogen peroxide (H_2O_2) reacting with ferrous ions (Fe^{2+}) [54] (Fig. 3). Lipoxygenases (LOXs) can catalyse the di-oxygenation of free and esterified PUFAs to produce numerous lipid hydroperoxides [55]. Linoleic acid (LA) and arachidonic acid (AA) are the most abundant PUFAs and can be used as LOX substrates [56]. Acyl-CoA synthetase long-chain member 4 (ACSL4), which preferentially converts AA to acylated AA, is ultimately catalysed by lysophospholipid acyltransferase 3 (LPCAT) [57,58]. E-cadherin (E-cad) suppresses ferroptosis through intracellular Merlin-Hippo signalling to inhibit the upregulation of ACSL4 [59] (Fig. 4f). In addition, phosphatidylethanolamine binding protein 1 (PEBP1), a scaffold protein inhibitor of the protein kinase cascade, was found to directly bind 15-lipoxygenase to PUFAs in the cell membrane to promote ferroptosis [60]. The inhibition or knockdown of LOXs inhibited the occurrence of ferroptosis in mouse neurons cells [8,61](Table 2).

3. Negative regulation of ferroptosis and potential treatment resistance

It is worth noting that some cancer cells have no response to ferroptosis, which suggests that alternative forms of ferroptosis resistance may exist (Fig. 4a-e).

3.1. GPX4

As mentioned above, GPX4 synthesized by GSH plays an important role in antioxidant reduction [32]. Viswanathan et al. described that therapy-resistant cancer cells with high mesenchyme state are dependent on GPX4 [89]. Matthew J et al. established lapatinib-resistant melanoma and breast cancer cells and found that GPX4 was selectively required for drug resistance in cancer cells in response to diverse therapeutics, and the cotreatment of cancer cells with a targeted therapeutic or chemotherapeutic agent together with a GPX4 inhibitor effectively reduced the residually persistent cells [17]. Furthermore, pre- or post-treatment but not cotreatment with GPX4 inhibitors may be sufficient to deplete persistent cells that survive targeted therapy or chemotherapy [17]. Theodossis A et al. examined two breast adenocarcinoma cell lines with two different phenotypes and genotypes and showed that GPX4 expression was higher in cancer cells that were resistant to the ferroptosis inducer buthionine sulfoximine (BSO) and hypericin photodynamic therapy (PDT) than in non-resistant cells [90]. Similarly, Girotti and colleagues found that transfection of GPX4 into non-GPX4-expressing breast cancer cells led to increased resistance to PDT [91]. Doxorubicin (DOX)-induced expression of GPX1 and GPX4 in sarcoma cancer cells promotes resistance to PDT [92]. In addition, supplying cystine for GSH maintenance by SLC7A11 can confer resistance to geldanamycin [93]. Ionizing radiation (IR) or Kelch-like ECH-related protein 1 (Keap1) deficiency-induced SLC7A11 expression promotes radio-resistance by inhibiting ferroptosis [94]. Heat-shock 70-kDa protein 5 (HSPA5) can bind GPX4 and protect against protein degradation, limiting the anticancer activity of gemcitabine by mediating ferroptosis resistance [95]. Depleting GPX4 by curcumin analogues can inhibit the growth of temozolomide-resistant glioblastomas [96].

3.2. CoQ_{10}

FSP1 is completely resistant to lethal peroxidation and ferroptosis in the absence of GPX4 [97]. FSP1 contains both an N-myristoylation

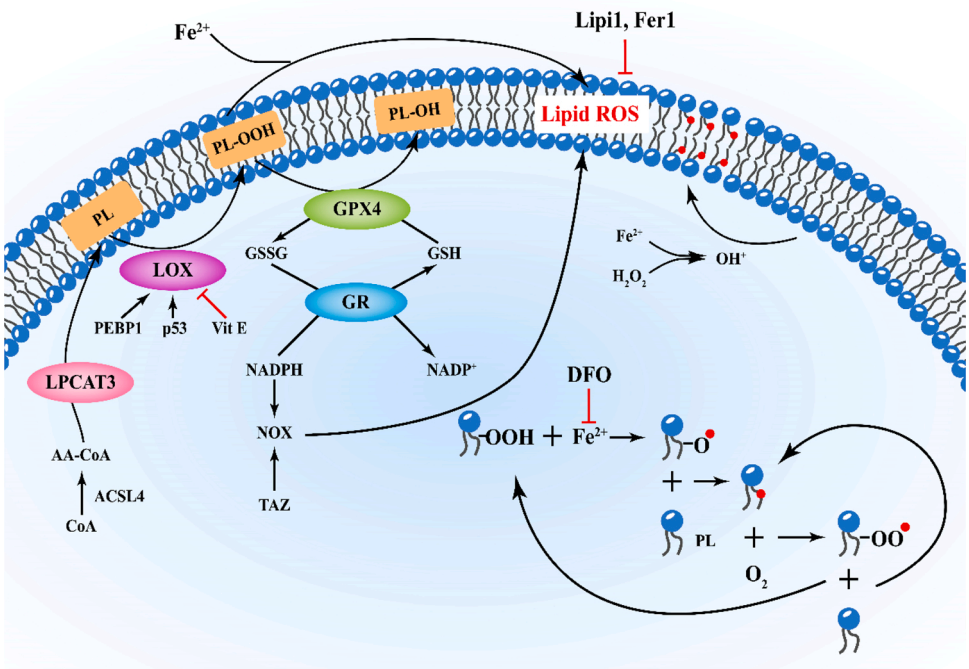

Fig. 3. The regulators of lipid peroxidation in ferroptosis.
The lipid peroxidation involved in the synthesis process of phospholipid hydroperoxide (PLOOH) derived from CoA/ arachidonic acid (AA)-CoA/PL, and ferrous ions-driven reactive oxygen species (ROS) production initiate the oxidation of polyunsaturated fatty acids (PUFAs) chain reaction.

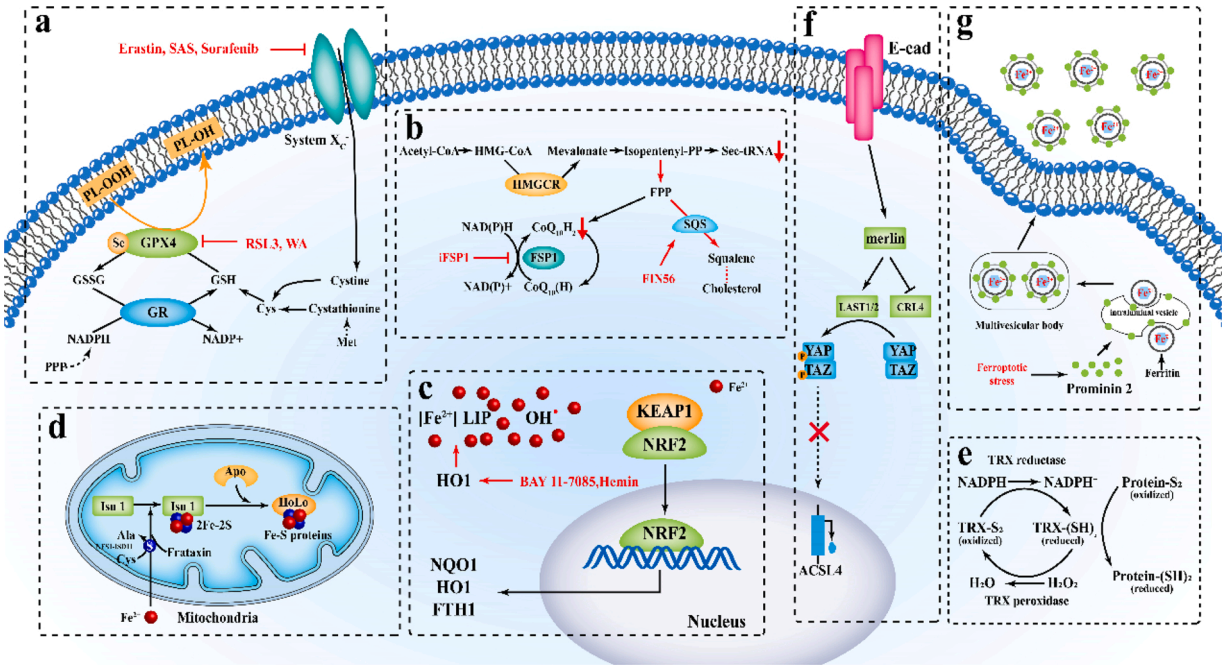

Fig. 4. Negative regulation of ferroptosis and corresponding targets. a, b: Glutathione peroxidase 4 (GPX4)-dependent antioxidation and coenzyme Q_{10} (CoQ_{10}) can play an antioxidant role and potential treatment resistance. c: Nuclear factor erythroid-2-related factor 2 (NRF2) plays an antioxidant role and is involved in cancer resistance through post transcriptional generation of quinone oxidoreductase 1 (NQO1), haem oxygenase 1 (HO1) and ferritin heavy peptide 1 (FTH1). d: Iron sulfur cluster (ISC) regulates the transport of ferrous iron in or out of mitochondria and the synthesis of Fe-S protein to control the homeostasis of ferrous iron cellular. e: Thioredoxin system reduces intracellular oxidation levels by reducing H_2O_2 and sulfur-containing proteins. f: E-cadherin (E-cad) reduces the generation of acyl-CoA synthetase long-chain family member 4 (ASCL4) and promote ferroptosis resistance by activating the Hippo-YAP pathway. g: Exosomes efflux can promote ferroptosis resistance by excreting ferritin and promoting intracellular iron homeostasis.

signal and a flavoprotein oxidoreductase domain, which are needed to recruit FSP1 to plasma membrane-enriched organelles, such as the endoplasmic reticulum (ER) and the Golgi apparatus [98]. Once recruited, FSP1 functions as an NADH-dependent CoQ_{10} oxidoreductase to reduce CoQ_{10} to ubiquinone ($CoQ_{10}H_2$), thereby counteracting lethal lipid peroxidation through radical trapping [18]. CoQ_{10} can act as a lipophilic radical-trapping antioxidant (RTA) that halts the propagation of lipid peroxides [99] and is a type of mobile lipophilic electron carrier and the only carrier for the endogenous synthesis of lipid-soluble antioxidants [100]. Lia et al. showed that mesenchyme subtype ovarian cancer cells were resistant to RSL3-induced ferroptosis through increased expression of stearoyl-CoA desaturase 1 (SCD1)-induced CoQ_{10}, and the use of SCD1 inhibitors combined with ferroptosis inducers could be an effective therapeutic strategy for ovarian cancer cells [101]. Vanessa et al. found that GTP cyclohydrolase-1 (GCH1) and its metabolic derivative tetrahydrobiopterin/dihydrobiopterin (BH4/BH2) promote ferroptosis resistance by controlling the endogenous production of CoQ_{10} [102].

3.3. NRF2

The nuclear factor erythroid-2-related factor 2 (NRF2) antioxidant pathway is one of the key negative regulators of ferroptosis, and NRF2 inhibition increases the anticancer effects of erastin and sorafenib *in vitro* and in xenograft models [75]. After exposure to erastin and sorafenib, p62 inhibited NRF2 degradation and enhanced NRF2 nuclear accumulation by inactivating Kelch-like Keap1 [103]. NRF2 is released from Keap1 and then moves to the nucleus to form a complex by interacting with the small transcriptional coactivator small v-maf avian musculoaponeurotic fibrosarcoma oncogene homologue (Maf) protein (MafG), which binds to the ARE sequence of DNA and transcribes the antioxidant genes quinone oxidoreductase 1 (NQO1), haem oxygenase 1 (HO1, HMOX1) and FTH1 [104]. NRF2 signalling is linked to primary and acquired drug resistance. Hoi et al. showed that ROS-induced NRF2 activation regulated sorafenib resistance by triggering the sonic hedgehog pathway and mediating liver tumour-initiating cell (T-IC) characteristics [105]. The multiple myeloma target drug melphalan induced NRF2 pathway activation and conferred resistance to high-dose melphalan [106]. Temozolomide (TMZ), a glioma and melanoma treatment, can stimulate the induction of NRF2 and drug resistance in cancer cells [107]. RBP5-mediating protein (RMP) promotes the expression of NRF2 and drug resistance by competing for binding to Kelch in intrahepatic cholangiocarcinoma (ICC) cells [108]. NRF2 can mediate drug resistance by the transcription of other factors. Advanced oxidation protein products (AOPPs) can stimulate NRF2 to upregulate the expression of efflux transporters, including ATP binding cassette subfamily B member 1 (ABCB1, P-glycoprotein), ATP-binding cassette (ABC) transporters (ABCC2, multidrug resistance-associated protein 2) and breast cancer resistance protein (ABCG2) [109]. Metallothionein-1 G (MT-1 G), a metalloenzyme transcript stimulated by NRF2, can negatively regulate ferroptosis and is an effective target for the treatment of sorafenib resistance [110,111]. NRF2-mediated production of ribosomal protein S6 (RPS6) could mediate resistance to anti-HER2 drugs [112]. In conclusion, activation of the p62-keap1-NRF2 pathway can protect cancer cells from ferroptosis and provide a target for treating chemoresistant cancer.

3.4. Iron sulfur cluster regulators

The drug resistance phenotype is accompanied by changes in mitochondrial function [113]. The mitochondrial protein iron sulfur cluster (ISC) is critical for redox reactions, iron homeostasis, and enzyme catalysis [114]. ISC biogenesis begins with the removal of sulfur from cysteine via the cysteine desulfurase complex NFS1-ISD11 and the FXN activation process [115]. FXN may be an iron chaperone or an allosteric activator of cysteine binding to NFS1 (cysteine desulfurase) [115].

Table 2
Negative regulation of ferroptosis and potential treatment resistance.

Factors	Protein	Funtion	Modulate Effect	Cancers	Refs
GPX4	Glutathione peroxidase 4	Catalyzes the reduction of hydrogen peroxide, lipid peroxides and functions in the protection of cells against oxidative damage	Therapy-resistant cancer depend on GPX4 and knockout inhibit tumor growth	PAAD, BDCA, BRCA, LUAD, NSCLC, melanoma, fibrosarcoma, leiomyo- sarcoma	[17,89]
NRF2/ NFE2L2	Nuclear factor erythroid 2-related factor 2	Transcript NQO1, HO1, FTH1 as antioxidants	Prevent erastin, sorafenib induced ferroptosis	LIHC, NSCLC, glioblastomas	[75,103,143, 144]
MT-1G	Metallo-thionein-1G	Regulate the antioxidant response	Prevent ferroptosis by blocking GSH depletion	LIHC	[110,111]
ATF4	Activating transcription factor 4	Promote xCT elevation and increased levels of xCT amplifies	Promote temozolomide resistance	Gliomas	[145–147]
CISD2/ NAF-1	CDGSH iron sulfur domain1/nutrient-deprivation autophagy factor-1	Transfer 2Fe-2S cluster to an apo-acceptor protein and iron to mitochondrial	Overexpression conferred resistance to SAS induced ferroptosis	HNC	[126]
TrxR/ TXNRD	Thioredoxin reductase	Oxidoreductase activity, acting on a sulfur group of donors, disulfide as acceptor.	Succinate binds to and activates TrxR2 to confer chemotherapy resistance	CRC	[15,129,148]
CoQ_{10}	Coenzyme Q_{10}	Required for the function of coenzyme Q in the respiratory chain	Lipophilic radical-trapping antioxidant	SCLC, NSCLC, osteosarcoma	[18]
AKRs	Aldo-keto reductases	Regulate oxidoreductase activity and NADP activity.	Degrades the 12/15-LOX-generated lipid peroxides	NSCLC, PRAD, melanoma, fibrosarcoma, osteosarcoma	[26,139]
ALDHs	Aldehyde dehydrogenases	Regulate oxidoreductase activity and aldehyde dehydrogenase (NAD) activity	Inhibition promote toxic aldehyde 4-HNE and ferroptosis	HNSCC, COAD, BRCA, SCLC, ovarian cancer	[141,142]

Abbreviations: SAS: Sulfasalazine; AKR: Aldo-keto reductase; HNSCC: Head and neck squamous cell carcinoma; HNC: Head and neck cancer; SCLC: Small-cell lung cancer; NSCLC: Non-small cell lung cancer; PAAD: Pancreatic adenocarcinoma; BDCA: Breast ductal carcinoma; BRCA: Breast invasive carcinoma; LUAD: Lung adenocarcinoma; LIHC: liver hepatocellular carcinoma; PRAD: Prostate adenocarcinoma.

Maintenance of ISC can protect cells from ferroptosis by regulating iron metabolism, rescuing mitochondrial function and increasing the level of GSH [116]. NFS1 activity is particularly important for maintaining iron-sulfur cofactors and protects lung cancer cells from undergoing ferroptosis in response to oxidative damage [117]. FXN is a key regulator of ferroptosis by modulating iron homeostasis and mitochondrial function, and the suppression of FXN significantly enhanced erastin-induced ferroptosis by repressing proliferation, destroying mitochondrial morphology, and activating iron starvation-induced stress [118,119]. Jing et al. indicated that overexpression of ISCU (iron-sulfur cluster assembly enzyme) significantly attenuated dihydroartemisinin (DHA, DAT)-induced ferroptosis by regulating iron metabolism, rescuing mitochondrial function and increasing the level of GSH [120].

NEET proteins belong to a novel family of iron-sulfur (2Fe-2S) proteins that are defined by a unique CDGSH amino acid sequence in their Fe-S cluster-binding domain and are required for iron regulation and ROS homeostasis in cells [121]. Recent studies have revealed that the NEET proteins CDGSH iron sulfur domain 1 (CISD1) and CISD2 can transfer 2Fe-2S clusters in mitochondria to apo receptor proteins in the cytoplasm (such as anamorsin and IRP1) [122,123], which play critical roles in promoting mitochondrial homeostasis and the proliferation of cancer cells [124]. Werner et al. indicated that CISD1 expression in cytarabine-resistant B-cell acute lymphoblastic leukaemia (ALL) cells was higher than that in parental cells, and the inhibition of CISD1 by NL-1 could effectively target resistant ALL cells [125]. CISD2 overexpression conferred resistance to sulfasalazine (SAS)-induced ferroptosis in head and neck cancer (HNC) cells, which could be reversed by silencing CISD2 or pioglitazone [126]. ISC is a ferroptosis modulator and may be a potential target for improving antitumour activity [118].

3.5. The thioredoxin system

Inhibition of GSH synthesis is not sufficient to promote ferroptosis in some cells, which may be due to the upregulation of the thioredoxin (Txn, Trx, TXN) antioxidant pathway [15,62,93]. Thiol compounds with redox-active sulfhydryl functions are necessary for maintaining a mild redox cellular environment to resist oxidative stress and thereby escape ferroptosis in cancer cells [127], and these compounds include thioredoxin reductase (TrxR, TXNRD), thioredoxin and NADPH [128]. Du et al. showed that $sirt5^{+}$ wild-type V-Kras2 colorectal carcinoma (CRC) cells are resistant to cetuximab through the accumulation of the oncometabolite succinate and TrxR2 activation [129]. Thioredoxin domain containing 17 (TXNDC17) is a novel 14-kDa disulfide reductase in the TXN (thioredoxin) family [130] that can promote BECN1-induced autophagy and induce paclitaxel resistance in ovarian cancer [131]. TXNDC9 was found to confer oxaliplatin resistance by regulating autophagy and apoptosis in colorectal adenocarcinoma cells [132]. Similarly, thioredoxin-related protein of 14 kDa (TRP14) induced autophagy and cisplatin resistance in ovarian cancer cells [133]. The novel ferroptocide compound pleuromutilin has been shown to induce ferroptosis by inhibiting thioredoxin [134]. Pyrimidotriazinedione (35G8) at nanomolar concentrations can induce glioblastoma cell ferroptosis by decreasing thioredoxin-interacting protein 1 (TXNIP) [135]. In general, thiol compounds act as antioxidants, and chemoresistance promoters may be used as ferroptosis targets in further research.

3.6. Metabolism-related enzymes

The efficacy of xCT-targeted therapy has been shown to be diminished by metabolic reprogramming that is involved in ferroptosis resistance. The overexpression of the aldo-keto reductase (AKR) gene in cancer cells renders cancer cells resistant to chemotherapeutic drugs [136]. Chen indicated that the AKR family modulates cisplatin resistance in cervical carcinoma cells [137]. Overexpression of AKR1C confers resistance to erastin by enhancing the detoxification of oxidative

products [26]. AKR1C3 is overexpressed in many cancer types and is involved in resistance to anthracyclines [138]. AKRs can also promote ferroptosis resistance by degrading 12/15-LOX-generated lipid peroxides [139]. Reactive aldehydes can also be detoxified by aldehyde dehydrogenase (ALDH) enzymes, which are linked to cancer progression and treatment resistance. ALDH1 induction has been shown to render lung adenocarcinomas resistant to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), such as erlotinib, and ALDH1 may affect the reactive carbonyl species (RCS)-ROS-metabolic pathway through the ALDH1A1-GPX4-SOD2 axis [140]. The combination of ALDH inhibitors and ferroptosis inducers may provide a promising treatment. Vasodilator oxyfedrine (OXY) can sensitize GSH-depleted resistant cancer cells by covalent inhibition of ALDH enzymes [141]. The combination of dyclonine and sulfasalazine cooperatively suppressed the growth of resistant head and neck squamous cell carcinoma (HNSCC), small cell lung cancer (SCLC), CRC, and breast cancer cells [142]. The identification of effective synergistic combinations of ALDH inhibitors and ferroptosis inducers may provide a novel approach to overcome resistant cancer (**Table 2**).

4. Compound-induced ferroptosis and the treatment of resistant cancers

Tolerance correlates with the induction of known exogenous defence genes and decreases in novel ferroptosis sensitivity biomarkers, suggesting that ferroptosis is a druggable driver of cancer therapy. Currently, a series of strategies have been developed to induce ferroptosis. Some clinical drugs can induce ferroptosis in several cancer cells, supporting the feasibility of using ferroptosis in preclinical and clinical settings for the treatment of resistant cancers (**Table 3**).

4.1. BSO

Buthionine sulfoximine (BSO) is an inhibitor of GSH synthesis that can sensitize neuroblastoma and melanoma to melphalan [184,185]. Studies show that BSO reduces the growth of breast cancer, colon cancer, lymphoma, glioblastoma and NSCLC cells when combined with sulfasalazine (SAS) [15]. In addition, low GSH levels may be a selection marker for the use of BSO in the treatment of kidney cancer and ovarian cancer [149]. In the treatment of drug-resistant tumours, an early study showed that treatment with BSO completely abolished Bcl-2-mediated drug resistance with nonapoptotic cell death in leukaemia cells [186]. Leukaemia cell resistance to imatinib mesylate depends on high Bcr-Abl expression levels but can be reversed by BSO combined with arsenic trioxide (ATO) [187]. Recently, Felisa et al. synthesized a novel folate-targeted PEGylated-BSO conjugate and found that it was effective in sensitizing folate receptor-positive cancer cells to gemcitabine [188]. BSO also increased sulindac sulfide (a nonsteroidal anti-inflammatory drug)-induced cytotoxicity by reversing ABCC1-mediated multidrug resistance (MDR) [189]. The intracellular GSH concentration is a potential molecular marker for cisplatin resistance in glioma, and BSO sensitized glioma cells to TMZ or cisplatin [190]. In the context of adverse effects, pretreatment with BSO can partly reverse the effect of osthole on tamoxifen (TMX)-induced liver injury in mice [191] but can increase the susceptibility of developing embryos to metal toxicity in reproductively active oysters [192].

4.2. Erastin

Erastin, a system X_C^- inhibitor, has been approved for the inhibition of cervical cancer, ovarian cancer, neuroblastoma, RMS and breast cancer cells [45,46,77,150,151]. Two erastin analogues, piperazine and imidazole ketone erastin (IKE), can effectively inhibit tumour growth in fibrosarcoma and diffuse large B-cell lymphoma (DLBCL) [156,157]. Temozolomide (TMZ), a first-line therapeutic drug for glioblastoma multiforme (GBM) patients, can induce xCT expression via the NRF2, ATF4 and cystathionine γ-lyase (CTH, a key enzyme in the trans-sulfuration pathway) activation pathways, and cytotoxicity is significantly enhanced by the combination of TMX with erastin [193]. In acute myeloid leukaemia (AML), erastin enhanced the sensitivity of cells to chemotherapeutic agents when combined with cytarabine or DOX in an RAS-independent manner [194] and reversed ABCB1-mediated docetaxel resistance in ovarian cancer [195]. Erastin can also reverse cisplatin resistance in head and neck cancer cells by inducing ferroptosis and enhancing cisplatin cytotoxicity *in vitro* and *in vivo* [196]. Li et al. indicated that erastin in combination with a low dose of cisplatin effectively inhibited the growth of cisplatin-resistant non-small cell lung cancer (NSCLC) cells [197].

4.3. Sulfasalazine

An FDA-approved drug, the system X_C^- inhibitor sulfasalazine (SAS), can inhibit the growth of pancreatic adenocarcinoma, lung cancer, lymphoma and breast cancer in experimental models [77,198–200]. Previously, Alexander et al. found that constitutive NF-kappaB activity confers gemcitabine resistance to pancreatic cancer cells, which can be strongly diminished by SAS [201]. SAS can eliminate cellular detoxification by interrupting GSH synthesis and enhancing the anticancer activity of cisplatin by increasing drug transport in CRC cells [202]. Cisplatin-resistant hepatocellular carcinoma cells exhibit increased expression of CD44v9, which is related to xCT, and such drug resistance can be resolved by combination treatment with SAS [203]. Ross et al. indicated that the reduction in the miRNA-27a target SLC7A11 contributes to cisplatin resistance in bladder cancer cells, and restoring miRNA-27a expression or treatment with SAS can sensitize cells resistant to cisplatin [204]. SAS also has a strong affinity for human breast cancer resistance protein (hBCRP) compared with that of other drugs, which may promote pharmacodynamics by reducing drug transport [205]. In the context of drug toxicology, SAS can attenuate tamoxifen-induced toxicity in human retinal pigment epithelial cells for ER-positive breast cancer treatment [206], but the side effects of SAS in clinical applications mainly include nausea, dyspepsia, vomiting and headache.

4.4. Artesunate

The efficacy of the antimalarial agent artesunate (ART) was first shown in breast cancer by decreasing cellular GSH levels and the presence of iron-induced ROS generation [207]. ART specifically induced lysosomal iron-dependent ferroptosis in PDAC cells [208]. Activation of the ATF4-C/EBP-homologous protein (CHOP)-CHAC1 pathway by ART has a significant lethal effect in Burkitt's lymphoma [153]. ART can also induce ferroptosis in adult T-cell leukaemia/lymphoma (ATLL) via a caspase-independent lethal pathway [154]. For cancer-resistant treatment, Xenofon et al. indicated that ART reliably induced drug-resistant multiple myeloma cell death through iron-induced ROS and non-caspase-mediated apoptosis [209]. Wang et al. found that ART can protect against carboplatin accumulation-induced drug resistance at a low concentration in NSCLC cells [210]. In addition, ART can impair the increased lysosomal function of resistant cancer cells and potently inhibit paclitaxel-resistant lung cancer and breast cancer cells [211]. These findings suggest that compounds such as ART may target not only GPX4 but also other potential targets. However, ART-mediated killing of cisplatin-resistant HNC cells can simultaneously activate the NRF2-antioxidant response element (ARE) pathway, which contributes to ferroptosis resistance [152]. Therefore, the combination of ART with NRF2 genetic silencing or trigonelline may provide a preferable efficacy. In clinical patients, the use of ART may lead to temporary decreases in peripheral reticulocytes, vomiting, abdominal pain, diarrhoea and other gastrointestinal symptoms.

Table 3
Compounds induced ferroptosis for cancer research.

Compound	Target	Phenotype	Cancer research	Refs
Buthionine sulfoximine (BSO) (1982)	GCL	Inhibited the synthesis of GSH and induced lipid ROS	DLBLC, RCC, fibrosarcoma, osteosarcoma, melanoma, neuroblastoma	[15,149]
Sulfasalazine (2001)	System X_C^-	Death can inhibit by DFO, Fer1 and trolox	SCLC, PAAD, HNC, HNSCC, BRCA, NSCLC, COAD, gastric cancer, lymphoma, fibrosarcoma	[7,77]
Erastin (2003)	System X_C^- &VDAC2/3	Lipid ROS death can inhibit by Fer1, DFO and trolox	DLBLC, RMS RCC, neuroblastoma, fibrosarcoma, osteosarcoma, ovarian cancer, cervical cancer	[45,150,151]
Artesunate (ART) (2011)	Glutathione S-transferase	Lipid ROS death can inhibit by Fer1, DFO and trolox	BRCA, PAAD, ATLL, Burkitt's lymphoma	[152–154]
Glutamate (Glu) (2012)	System X_C^-	Can inhibited by CPX and Fer1	LUAD, fibrosarcoma	[7,28]
Sorafenib (2013)	System X_C^-	lipid ROS death can inhibit by Fer1 and DFO	LIHC, fibrosarcoma	[26,155]
Piperazine erastin (2014)	System X_C^-	Promote lipid peroxidation increased by PTGS2 and can be inhibited by VitE	DLBLC, RCC, fibrosarcoma, osteosarcoma	[32]
Imidazole ketone erastin (IKE) (2015)	System X_C^-	Exerted an antitumor effect by the induction of ferroptosis both *in vitro* and *in vivo*	DLBCL, fibrosarcoma, astrocytoma	[156,157]
BAY 87-2243 (2015)	ND dehydrogenase	Reduced BRAF mutant melanoma mouse xenografts and patient-derived melanoma mouse models	Melanoma	[158,159]
Cyst(e)inase (2017)	L-Cys & CSSC	Depletion of intracellular GSH with no apparent toxicities	PRAD, PDAC, BRCA	[27,160]
PG (2019)	Cysteine	Promote ferroptosis by regulating miR-103a-3p/GLS2 axis	Gastric cancer	[70]
IMCA (2020)	SLC7A11	Decrease SLC7A11 by regulate AMPK/mTOR/p70S6k signaling pathway	CRC	[161]
ACP (2020)	SLC7A11	Induced apoptosis, ferroptosis and suppressed mesenchymal phenotype	Gastric cancer	[162]
1S,3R-RSL3 (2008)	GPX4	Lipid ROS by increase PTGS2 and can inhibited by Fer1, DFO	DLBLC, RCC, LUAD, COAD, PAAD, ALL, LIHC, fibrosarcoma, osteosarcoma	[163–165]
DPI7/ML162, DPI10/ML210 (2012)	GPX4	Nanomolar potencies and 4-23-fold selective	Fibrosarcoma	[166]
DPI2, DPI12-13, DPI17-19 (2014)	GPX4	Prevented tumor growth in xenograft mouse tumor models, death inhibited by DFO and α-Toc	DLBLC, RCC fibrosarcoma, osteosarcoma,	[32]
Altretamine (2015)	GPX4	Cause effect similar to the activity of sulfasalazine	DLBCL, osteosarcoma	[167]
FIN56 (2016)	GPX4, SQS and CoQ_{10}	Derived from CIL56, promotes degradation of GPX4 and can inhibited by DFO, α-Toc	RCC, NSCLC, KIRC, PAAD BRCA, PRAD, CRC, fibrosarcoma, ewing's sarcoma, osteosarcoma, melanoma	[36,81,168]
Lovastatin, simvastatin (2016)	HMG-CoA reductase	Mesenchymal state targeting compounds that cause lipid ROS	LUAD, osteosarcoma, fibrosarcoma	[81,89]
Fluvastatin (2017)	HMG-CoA reductase	Decreased expression of GPX4	LUAD, melanoma, prostate cancer, sarcomas, fibrosarcoma	[89]
$FINO_2$ (2018)	GPX4	Indirectly inhibits GPX4 causing widespread lipid peroxidation	KIRC, fibrosarcoma	[168]
Withaferin A (2018)	GPX4	Caused lipid ROS and can inhibited by DFO, Fer1 and α-Toc	Neuroblastoma	[74]
iFSP1 (2019)	FSP1, CoQ10	Induced ferroptosis in GPX4-knockout cells and sensitized to RSL3-induced ferroptosis	BRCA, SCLC, NSCLC, LIHC, KIRC, RCC, COAD, READ, fibrosarcoma, glioblastoma, melanoma	[97]
ACP (2020)	GPX4	Induced apoptosis, ferroptosis and suppressed mesenchymal phenotype	Gastric cancer	[162]
DHA, DAT (2016)	IRP/IRE	Induced ferroptosis, apoptosis by cell cycle arrest and alters the angiogenic phenotype	HNC, NSCLC, CRC, BRCA, fibrosarcoma	[169,170]
Siramesine, lapatinib (2016)	FPN, lysosomes iron	Induced $FeCl_3$, TF elevated and FPN decrease, death inhibited by DFO and Fer1	BRCA	[72]
Non-thermal plasma (2017)	Lysosomes iron	Increased lysosome content, autophagy for catalytic Fe^{2+} and can inhibited by DFO	Mesothelioma	[171,172]
Salinomycin, AM5 (2017)	Sequestering iron in lysosomes	Lysosomal membrane permeabilization and can inhibited by Fer1	Breast CSC	[173]
$FINO_2$ (2018)	GPX4	Directly oxidizes iron causing widespread lipid peroxidation	KIRC, fibrosarcoma	[168]
HO1, hemin, $(NH4)_2Fe(SO4)_2$ (2018)	Increase the labile Fe^{2+}	Suppressed the growth and relapse rate of neuroblastoma xenografts	Neuroblastoma	[74]
Withaferin A (2018)	Keap1	increase LIP by inactive of Keap1, GPX4 and can inhibited by DFO Fer1 and α-Toc	Neuroblastoma	[74]
BAY 11-7085 (2018)	IκBα	Increase LIP by upregulating HMOX1,death inhibited by Fer1, Lip1	BRCA, LIHC, lung cancer, glioblastoma, ovarian cancer,	[174]
Lanperisone (2011)	Unkonw	Induced ROS that are inefficiently scavenged in KRAS mutant cells	KRAS mutant tumors	[175]
Artemisinin derivatives (2015)	Unkonw	Regulate ferroptosis by TF, TFRC, CP, LTF	NSCLC, RCC, COAD, PRAD, BRCA, glioblastoma, leukemia, ovarian cancer, melanoma	[176]
BV6 (2016)	Unkonw	RSL3/BV6 but not erastin/BV6 cotreatment triggers ferroptosis	ALL	[177]
Haloperidol (2017)	Unknow	Induce ferroptosis by increased the cellular levels of HO-1	LIHC	[178]
Trigonelline (2018)	NRF2	Reversed the ferroptosis resistance of Keap1-silenced and cisplatin-resistant HNC	LIHC, HNC	[110,152,179]
Ungeremine (2019)	Unkonw	Induced ROS and promote ferroptosis	LIHC, AML, COAD, gliomas, breast carcinoma	[180]
Ferroptocide (2019)	TXN	Rapidly and robustly induces ferroptosis	COAD, NSCLC, PAAD ovarian cancer breast cancer	[134]

(*continued on next page*)

Table 3 (*continued*)

Compound	Target	Phenotype	Cancer research	Refs
β-elemene (2020)	Unkonw	Sensitive to KRAS mutant CRC cells by ferroptosis and inhibited EMT	CRC	[76]
Ibuprofen (2020)	NRF2	Downregulation of NRF2 signaling pathway and can inhibited by DFO, Fer1, Lip1	Glioblastoma	[181]
DSF/Cu (2020)	Unkonw	Antitumor through ROS/MAPK and p53-mediated ferroptosis pathways	NPC	[182]
DO264 (2020)	Lyso- and ox- PS lipase $ABHD_{12}$	Enhanced RSL3 induced ferroptosis	Fibrosarcoma	[183]

Abbreviations: CoQ_{10}: Coenzyme Q_{10} ; GPX4: Glutathione peroxidase 4; GSH: Glutathione; HO1: Heme oxygenase-1; ROS: Reactive oxygen species; Fer1: Ferrostatin-1; DFO: Deferoxamine; CPX: Ciclopirox olamine; IKBα: Nuclear factor of k light-chain polypeptide gene enhancer in B cell inhibitor α; KEAP1: Kelch-like ECH-associated protein 1; LIP: Labile iron pool; Lip1: Liproxstatin-1; α-Toc: a-tocopherol; CIL: Caspase-3/7-independent lethal; VitE: Vitamin E; PTGS2: Prostaglandin-endoperoxide synthase 2; SQS: Squalene synthase; GS: Glutathione S-transferase; CSSC: L-Cystine; L-Cys: L-cysteine; PG: Physcion 8-O-β-glucopyranoside; VDACs: Voltage-dependent anion channels; GCL: Glutamate-cysteine ligase; HMGCR: 3-hydroxy-3-methyl-glutaryl-CoA reductase; IMCA: benzopyran derivative 2-imino-6-methoxy-2H-chromene-3-carbothioamide; ACP: Actinidia chinensis Planch; FPN: Ferroportin-1; TXN: Thioredoxin; DSF/Cu: Disulfiram/copper; NPC: Nasopharyngeal cancer; transferrin, TF; FPN: Ferroportin; DHA, DAT: Dihydroartemisinin; CP: Cerulopasmin; LTF: Lactoferrin; PS: Phosphatidylserine; BV6: Smac mimetic; Smac: Second mitochondrial activator of caspases; AM5: ironomycin; HNSCC: Head and neck squamous cell carcinoma; HNC: Head and neck cancer; DLBCL: Diffuse large B cell lymphoma; SCLC: Small-cell lung cancer; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinomas; BRCA: Breast invasive carcinoma; COAD: Colon adenocarcinoma; LUAD: Lung adenocarcinoma; LIHC: Liver hepatocellular carcinoma; PRAD: Prostate adenocarcinoma; KIRC: Kidney renal clear cell carcinoma; RMS: Rhabdomyosarcoma; CSC: Cancer stem cells; KIRC: Kidney renal clear cell carcinoma; COAD: Colon adenocarcinoma; READ: Rectum adenocarcinoma; CRC: Colorectal cancer; PDAC: Pancreatic ductal adenocarcinoma; PAAD: Pancreatic adenocarcinoma; ATLL: adult T-cell leukemia/lymphoma; ALL: Acute lymphoblastic leukemia.

4.5. RSL3

The inhibition of system X_C^- may represent a barrier against effectiveness in some cells, which may be due to the trans-sulfuration pathway and indirect synthesis of GPX4 or other pathways independent of GPX4, such as the TXN antioxidant pathway [15,67]. Therefore, targeting GPX4 with other ferroptosis inducers has become an important direction for the treatment of resistant cancers. RSL3 has been demonstrated to inhibit fibrosarcoma, ALL, LIHC, RMS, CRC, and glioma cells by directly inhibiting GPX4 [32,163,165,212]. Low-concentration RSL3 with paclitaxel (PTX) can significantly inhibit hypopharyngeal squamous carcinoma (HPSCC) cells compared with that of PTX monotherapy [213]. Gemcitabine-resistant pancreatic cancer cells exhibit increased expression of ADP ribosylation factor 6 (ARF6), which can be sensitive to RSL3 [214]. Liu et al. established cisplatin-resistant osteosarcoma cells and found that cotreatment with RSL3 can increase sensitivity by inhibiting the STAT3/NRF2/GPX4 pathway [215]. Daiha et al. reported that RSL3 treatment increased the expression of p62 and NRF2 in cisplatin-resistant cells, which indicated that the multidrug combination needs to be explored for the treatment of resistant cancers [179] **(**Table 4**).**

4.6. Withaferin A

The natural product compound withaferin A (WA) was synthesized by reverse pharmacological analysis of *Withania somnifera* leaves and has gradually been used as a preclinical anticancer drug [216]. Withaferin A can obviously suppress high-risk neuroblastoma compared with etoposide or cisplatin by inactivating GPX4 and a sufficient amount of ferrous iron to induce ferroptosis [74]. The combination of withaferin A and 5-fluorouracil (5-FU) decreases resistant CRC cell viability by inducing ER stress-mediated induction of autophagy and apoptosis [217]. Jade et al. reported that withaferin A combined with cisplatin or pemetrexed is a potential treatment for EGFR-expressing wild-type lung cancer and decreases the occurrence of cisplatin resistance [218]. Withaferin A also promotes mitochondrial dysfunction and inactivation of the PI3K/AKT pathway, which enhances oxaliplatin-induced growth suppression and apoptosis in pancreatic cancer cells [219]. Based on these findings, we can conclude that the inhibition of GPX4 is an important effect of compounds targeting system X_C^- and may provide an opportunity to treat drug-resistant cancers.

4.7. Siramesine

Cancer cells tend to have a higher iron demand than normal cells, which makes them more susceptible to ferroptosis induction through the high expression of the labile iron pool (LIP). Thus, increasing the LIP or iron oxide can be an optimum cancer therapy. Siramesine is a lysosome-destabilizing compound that can promote lysosome membrane permeabilization (LMP), mitochondrial membrane potential loss with ROS release and lipid peroxidation in chronic lymphocytic leukaemia (CLL) cells [220]. Combined treatment of siramesine with lapatinib can induce breast cancer cell ferroptosis by promoting TF expression and decreasing FPN [72]. Similarly, cotreatment with siramesine renders resistant triple-negative breast cancer (TNBC) cells sensitive to CDK4/6 inhibitors [221]. Siramesine can also trigger lysosomal cell death in apoptosis- and multidrug-resistant cancer cells by targeting acid sphingomyelinase (ASM) [222]. However, whether the form of death induced by siramesine in cancer cells is ferroptosis or lysosomal death or the coexistence of multiple forms needs further study.

4.8. Salinomycin

Salinomycin is a monocarboxylic acid polyether antibiotic that is used to effectively kill epithelial cancer stem cells (CSCs) [223]. The salinomycin derivative ionomycin (AM5) exhibits increased effectiveness against breast CSCs by accumulating and sequestering lysosomal iron, which promotes the degradation of lysosomal ferritin and lysosomal membrane permeabilization (LMP), consistent with ferroptosis, in response to the cytoplasmic depletion of iron [173]. Other derivatives, including C20-amination, C1-esterification, C9-oxidation, and C28-dehydration, show great efficiency against breast CSCs by targeting lysosomal iron [224]. In the treatment of resistant cancers, salinomycin can overcome cisplatin resistance by inhibiting cancer stemness in ovarian germ cell tumour-derived cells [225]. The polyether ionophore salinomycin (SAL) and its semisynthetic derivatives significantly overcome resistance to platinum-based drugs in ovarian cancer cells and are more potent than commonly used anticancer drugs such as 5-fluorouracil, gemcitabine, and cisplatin [226]. Docetaxel-resistant prostate cancer cells can be significantly reduced by salinomycin with a decrease in the tumour-initiating CD24- /$CD44^{high}$ population [227]. Interestingly, Piotr et al. reported salinomycin-induced changes in mRNAs and miRNAs involved in drug resistance in endometrial cancer cells, which is an expected result of anticancer treatment and offers new ideas for the clinical treatment of drug-resistant tumours [228]. The use of salinomycin in the clinic may lead to mitochondrial dysfunction, such as

Table 4
Application of ferroptosis for resistant cancer treatment.

Cancers	Resistant drug	Co-treatment	Effect	Cells & Animals	Refs
Small cell lung cancer (SCLC)	SAS	Dyclonine	Induce toxic 4-HNE by inhibit ALDHs in a cooperative with SAS	DMS114	[142]
	SAS	OXY	Promote SAS resistant cancer cells ferroptosis by inhibit ALDH enzymes	DMS114, SBC3	[141, 197]
Non-small cell lung cancer (NSCLC)	Cisplatin	Erastin, sorafenib	Erastin and sorafenib, alone or combined with low dose cisplatin, effectively inhibited the resistant NSCLC	N5CP, xenograft models	[197]
	Erastin	APAP	Promote ferroptosis and apoptosis by regulate NRF2/HO1	A549, H1299, athymic BALB/c nude mice	[234]
	SAS	OXY	Promote SAS resistant cancer cells ferroptosis by inhibit ALDH	A549	[141]
	RSL3	DHA, DOX	Reversed GPX4 inhibition-resistant cancer to ferroptosis	H292	[170]
Colorectal cancer (CRC)	Cisplatin	SAS	Significant induced accumulation of ROS and growth inhibition	HCT116, HT29, LOVO, DLD1	[202]
	Cetuximab	β-elemene and cetuximab	Sensitive to KRAS mutant CRC cells by inducing ferroptosis and inhibiting EMT	HCT116, LOVO, CaCO2	[76]
	SAS	Dyclonine, OXY, ALDH3A1 knockdown	Induce toxic 4-HNE by inhibit ALDHs in a cooperative with sulfasalazine	HCT116	[141, 142]
	RSL3	DHA, DOX	Reversed GPX4 inhibition-resistant cancer to ferroptosis	HCT116, HT29, SW480	[170]
Liver hepatocellular carcinoma (LIHC)	Sorafenib	Trigonelline, MT-1 G knockout	Promoting GSH depletion and lipid peroxidation	Huh7, HepaG2, Hep3B	[110]
Pancreatic cancer	Gemcitabine	RSL3	Abrogation of ARF6 promotes RSL3 induced ferroptosis and mitigates gemcitabine resistance	AsPC-1, PANC-1, BxPC3, SW1990, Capan-1, MIA PaCa	[214]
Breast cancer	SAS	Dyclonine	Induce toxic 4-HNE by inhibit ALDHs in a cooperative with sulfasalazine	4T1	[142]
	RSL3	DHA, DOX	Reversed GPX4 inhibition-resistant cancer to ferroptosis	MDA-MB- 453	[170]
Head and neck cancer (HNC)	Cisplatin	Erastin, SAS, SLC7A11 knockdown	Sensitize resistant HNC cells to cisplatin *in vitro* and *in vivo*	AMC-HN3R/4R/ 9R	[196]
	Cisplatin	Aspirin plus sorafenib	Low-dose aspirin plus sorafenib enhanced the cytotoxicity of cisplatin resistant HNC	Xenograft models	[235]
	Cisplatin, artesunate	Trigonelline	reversed the ferroptosis resistance of cisplatin resistant HNC cells to artesunate	HN2–10, SNU, HN3-cisR, HN4-cisR, HN9-cisR, BALB/c male nude mice (nu/nu)	[152]
	SAS	Pioglitazone, CISD2 knockout	silencing CISD2 or pioglitazone induced sensitized resistant HNC cells to SAS	SUN-1041/ 1066/1076, AMC-HN2-11	[126]
	Cisplatin, RSL3	RSL3, ML-162, trigonelline	inhibiting NRF2-ARE pathway reverse the resistance of GPX4 inhibition	HN3R, HN3-rslR	[179]
Head and neck squamous cell carcinoma (HNSCC)	SAS	Dyclonine	induce toxic 4-HNE by inhibit ALDHs in a cooperative with sulfasalazine	OSC19, HSC-2/3/4, SCC25	[142]
Hypopharyngeal squamous carcinoma (HPSCC)	PTX	RSL3	Enhanced the ferroptosis by upregulating mutant p53 expression	Detroit562	[213]
Oral squamous cell carcinoma (OSCC)	SAS	OXY	Promote resistant cancer cells ferroptosis by inhibit ALDH	HSC-2/3/4, OSC19, SCC25	[141]
Glioblastoma	TMZ	Erastin	Inhibiting cysteine uptake and suppressed CTH activity	A172, U87, T98 G, GBM-N6, GBM-N15	[193]
	TMZ	SAS	SAS treatment can potentiate the efficacy of TMZ resulted in reduced glioma-derived edema	F98, U251, male fisher rats	[236]
	TMZ	ALZ003	inhibited the survival of TMZ-sensitive and -resistant glioblastoma in vitro and in vivo	U87MG, A172, Pt#3, NOD-SCID male mice	[96]
Neuro- blastoma	Etoposide or cisplatin	Withaferin A	Eradicates high-risk neuroblastoma tumors and shows lower relapse rates compared with etoposide.	IMR-32, Kelly, NB69, SH-SY5Y/EP	[74]
Osteosarcoma	Cisplatin	Erastin, RSL3, STAT3 inhibitor	Reactivated ferroptosis by impairing STAT3/ NRF2/ GPX4 signaling	MG63/DDP Saos-2/DDP	[215]
Ovarian cancer	Carboplatin	Activating TAZ-ANGPTL4-NOX2	Elevated lipid ROS induced by erastin	TOV-21 G/ CAOV2, CAOV2 xenograft	[237]
	Docetaxel	Erastin	Restricting the drug-efflux activity of ABCB1 and reverse docetaxel resistance	A2780, Taxol	[195]
	SAS	OXY	Sensitive resistant cancer cells by inhibit ALDH	DMS114, SBC3	[141]
Acute myeloid leukemia (LAML)	Cytarabine, DOX	Erastin	Induced growth inhibition and overcame drug resistance	HL60, Jurkat, THP-1, K562, NB-4	[194]
Fibrosarcoma	RSL3	DHA	Reversed GPX4 inhibition-resistant cancer to ferroptosis	HT1080	[170]

Abbreviations: CTH: cystathionine γ-lyase (CTH); APAP: Acetaminophen; xCT: SLC7A11; ALDHs: Aldehyde dehydrogenases; 4-HNE: 4-hydroxynonenal; SAS: Sulfasalazine; OXY: Oxyfedrine; DOX: Doxorubicin; TMZ: temozolomide; PTX: Paclitaxel; DHA: Dihydroartemisinin.

energy metabolism disorders, and cause muscle damage [229].

4.9. Artemisinin

Artemisinin derivatives such as DHA induce ferroptosis by impinging on IRP/IRE-controlled iron homeostasis to further increase iron and

reverse GPX4 inhibition-induced resistance to ferroptosis in cancer cells [169,170]. DHA treatment could overcome dexamethasone (Dexa) resistance and enhance Dexa efficacy in multiple myeloma (MM) with increased ROS production and cytochrome C translocation [230]. Cotreatment with DHA could effectively restore the anticancer effect of 5-FU against p53-knockout colorectal cancer cells [231]. Other artemisinin derivatives that act as P-glycoprotein (P-gp) inhibitors can reverse MDR towards clinically used anticancer drugs [232]. 10-Phenyltriazoyl artemisinin can suppress paclitaxel-induced overexpression of P-gp and restore the anticancer effect of paclitaxel in colorectal cancer cells [233]. The rare side effect of DHA in clinical patients is the transient decrease in reticulocytes. Overall, promoting iron ions in lysosomes, increasing transcription-induced iron expression and increasing exogenous iron ions can effectively promote ferroptosis for the treatment of resistant cells.

5. Nanoparticles-induced ferroptosis in the treatment of resistant cancers

Nanoparticles exhibit improved therapeutic efficacy due to enhanced cellular uptake and increased intracellular drug accumulation. Wu et al. synthetized BSO/celecoxib@biotin-heparin/heparin/calcium carbonate/calcium phosphate nanoparticles (BSO/CXB@BNPs) by co-loading BSO and celecoxib (CXB) in polymer/inorganic hybrid nanoparticles and found that BSO/CXB@BNPs exhibited great efficacy against drug-resistant tumour cells by downregulating GSH and P-gp compared with that of free drug inhibitors [238]. Similarly, the dual-drug-loaded hybrid nanovesicles containing BSO and the P-gp inhibitor tariquidar (TQR) exhibit significantly stronger cell growth inhibition than DOX mono-drug-loaded nanovesicles [239]. In a human resistant ovarian adenocarcinoma cell model, RSL3 micelles were 30-fold more toxic than activatable control micelles due to the machinery process [240]. Huang et al. indicated that resistant oral cancer cells could attenuate zero-valent iron (ZVI) nanoparticle-induced oxidative stress and GPX reduction but could be sensitized by certain ferroptosis inducers without compromising healthy non-malignant cells [241]. Xiong et al. developed a drug-organic-inorganic self-assembled nanosystem (DFTA) with DOX, $FeCl_3$ and tannic acid (TA), and combined with a laser, this system could significantly inhibit therapy-resistant oestrogen receptor-positive (ER^+) breast carcinoma cells [242].

6. Conclusions and future perspectives

Cancer treatment is still a major challenge for humans. To date, although many effective cancer treatment strategies have been investigated and some of them have been approved for cancer indications, they mainly focus on apoptotic cancer cell death. However, due to the overexpression of apoptosis protein inhibitors and the MDR effect, the role of apoptosis-based treatment strategies in cancer therapy is not well understood. In addition, some RAS-mutated cancers show intrinsic resistance to apoptosis due to endogenous inhibition of apoptosis. Thus, a new form of non-apoptotic PCD, ferroptosis, is characterized by the lethal accumulation of iron-dependent lipid hydroperoxides. In addition, ferroptosis differs from apoptosis in morphology, biochemistry and genetics, which provides a novel treatment strategy for overcoming apoptosis resistance in multidrug resistant cancers.

Since the discovery of ferroptosis, much credible evidence has been obtained in experimental tumour models that ferroptosis has good anticancer efficacy. The vulnerability of therapy-resistant cancers to ferroptosis and the recognition of the FDA-approved drugs SAS, altretamine, and sorafenib and nanoparticles as ferroptosis inducers in cancer create high expectations for therapeutic potential. Considering these advantages, ferroptosis is expected to become a promising cancer treatment strategy, whether alone or in combination therapy, in the near future.

However, there are still many issues that need more clarification. What is the relationship between cancer resistance and ferroptosis? In this article, we have summarised that the antioxidant reduction pathway and metabolism may contribute to the promotion of resistance to ferroptosis, which has also been verified in drug-resistant tumours. These drug-resistant cancers can be treated by coadministration of inducers of ferroptosis or other pathways. However, the deeper mechanism needs to be explored. In addition, specificity and how to control the potential adverse effects of ferroptosis in preclinical and clinical cancer environments requires study. In this context, nanoparticle-induced ferroptosis has potential in cancer research. We can make use of the unique enhanced permeability and retention (EPR) effect of nanoparticles and the effect of synthetic materials that have a strong killing effect on tumours but induce little damage to normal cells. However, more exploration is needed before ferroptosis-based nanomaterials can be used in clinical practice. Real-time diagnostic tools are needed to detect ferroptosis in order to treat drug-resistant cancers to provide a more effective strategy for clinical treatment.

Author contributions

Bowen Li designed the review article and wrote the manuscript, Liang Yang Xueqiang Peng, Qin Fan, Shibo Wei, Shuo Yang, Xinyu Li, Hongyuan Jin, Bo Wu, Mingyao Huang, Shilei Tang and Jingang Liu performed literature collection, Hangyu Li conceived the study and participated in its design. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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References

[1] D. Brunen, R. Bernards, Drug therapy: Exploiting synthetic lethality to improve cancer therapy, Nat Rev Clin Oncol 14 (6) (2017) 331–332.
[2] B. Al-Lazikani, U. Banerji, P. Workman, Combinatorial drug therapy for cancer in the post-genomic era, Nat Biotechnol 30 (7) (2012) 679–692.
[3] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, A. Jemal, X.Q. Yu, J. He, Cancer statistics in China, 2015, CA Cancer J Clin 66 (2) (2016) 115–132.
[4] C. Cerella, C. Grandjenette, M. Dicato, M. Diederich, Roles of Apoptosis and Cellular Senescence in Cancer and Aging, Curr Drug Targets 17 (4) (2016) 405–415.
[5] Z. Su, Z. Yang, L. Xie, J.P. DeWitt, Y. Chen, Cancer therapy in the necroptosis era, Cell Death Differ 23 (5) (2016) 748–756.
[6] M. Ishibashi, H. Tamura, M. Sunakawa, A. Kondo-Onodera, N. Okuyama, Y. Hamada, K. Moriya, I. Choi, K. Tamada, K. Inokuchi, Myeloma Drug Resistance Induced by Binding of Myeloma B7-H1 (PD-L1) to PD-1, Cancer Immunol Res 4 (9) (2016) 779–788.
[7] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, D.N. Patel, A.J. Bauer, A.M. Cantley, W.S. Yang, B. Morrison 3rd, B.R. Stockwell, Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[8] W.S. Yang, B.R. Stockwell, Ferroptosis: Death by Lipid Peroxidation, Trends Cell Biol 26 (3) (2016) 165–176.
[9] Y. Mou, J. Wang, J. Wu, D. He, C. Zhang, C. Duan, B. Li, Ferroptosis, a new form of cell death: opportunities and challenges in cancer, J Hematol Oncol 12 (1) (2019) 34.
[10] D.R. Green, The Coming Decade of Cell Death Research: Five Riddles, Cell 177 (5) (2019) 1094–1107.
[11] S. Galadari, A. Rahman, S. Pallichankandy, F. Thayyullathil, Reactive oxygen species and cancer paradox: To promote or to suppress? Free Radic Biol Med 104 (2017) 144–164.
[12] B. Perillo, M. Di Donato, A. Pezone, E. Di Zazzo, P. Giovannelli, G. Galasso, G. Castoria, A. Migliaccio, ROS in cancer therapy: the bright side of the moon, Exp Mol Med 52 (2) (2020) 192–203.

[13] S. Kwon, H. Ko, D.G. You, K. Kataoka, J.H. Park, Nanomedicines for Reactive Oxygen Species Mediated Approach: An Emerging Paradigm for Cancer Treatment, Acc Chem Res 52 (7) (2019) 1771–1782.
[14] M. Luo, L. Shang, M.D. Brooks, E. Jiagge, Y. Zhu, J.M. Buschhaus, S. Conley, M. A. Fath, A. Davis, E. Gheordunescu, Y. Wang, R. Harouaka, A. Lozier, D. Triner, S. McDermott, S.D. Merajver, G.D. Luker, D.R. Spitz, M.S. Wicha, Targeting Breast Cancer Stem Cell State Equilibrium through Modulation of Redox Signaling, Cell Metab 28 (1) (2018) 69–86, e6.
[15] I.S. Harris, A.E. Treloar, S. Inoue, M. Sasaki, C. Gorrini, K.C. Lee, K.Y. Yung, D. Brenner, C.B. Knobbe-Thomsen, M.A. Cox, A. Elia, T. Berger, D.W. Cescon, A. Adeoye, A. Brustle, S.D. Molyneux, J.M. Mason, W.Y. Li, K. Yamamoto, A. Wakeham, H.K. Berman, R. Khokha, S.J. Done, T.J. Kavanagh, C.W. Lam, T. W. Mak, Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression, Cancer Cell 27 (2) (2015) 211–222.
[16] N. Takahashi, H.Y. Chen, I.S. Harris, D.G. Stover, L.M. Selfors, R.T. Bronson, T. Deraedt, K. Cichowski, A.L. Welm, Y. Mori, G.B. Mills, J.S. Brugge, Cancer Cells Co-opt the Neuronal Redox-Sensing Channel TRPA1 to Promote Oxidative-Stress Tolerance, Cancer Cell 33 (6) (2018) 985–1003, e7.
[17] M.J. Hangauer, V.S. Viswanathan, M.J. Ryan, D. Bole, J.K. Eaton, A. Matov, J. Galeas, H.D. Dhruv, M.E. Berens, S.L. Schreiber, F. McCormick, M.T. McManus, Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition, Nature 551 (7679) (2017) 247–250.
[18] K. Bersuker, J.M. Hendricks, Z. Li, L. Magtanong, B. Ford, P.H. Tang, M. A. Roberts, B. Tong, T.J. Maimone, R. Zoncu, M.C. Bassik, D.K. Nomura, S. J. Dixon, J.A. Olzmann, The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis, Nature 575 (7784) (2019) 688–692.
[19] S. Doll, M. Conrad, Iron and ferroptosis: A still ill-defined liaison, IUBMB Life 69 (6) (2017) 423–434.
[20] J.Y. Cao, S.J. Dixon, Mechanisms of ferroptosis, Cell Mol Life Sci 73 (11-12) (2016) 2195–2209.
[21] H. Eagle, The specific amino acid requirements of a human carcinoma cell (Stain HeLa) in tissue culture, J Exp Med 102 (1) (1955) 37–48.
[22] S. Harvey, S. Hoshino, M. Suzuki, Plasma immunoreactive-growth hormone in domestic fowl: measurement by homologous and heterologous radioimmunoassays, Gen Comp Endocrinol 65 (1) (1987) 92–98.
[23] S. Bannai, H. Tsukeda, H. Okumura, Effect of antioxidants on cultured human diploid fibroblasts exposed to cystine-free medium, Biochem Biophys Res Commun 74 (4) (1977) 1582–1588.
[24] T.H. Murphy, M. Miyamoto, A. Sastre, R.L. Schnaar, J.T. Coyle, Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress, Neuron 2 (6) (1989) 1547–1558.
[25] T.H. Murphy, R.L. Schnaar, J.T. Coyle, Immature cortical neurons are uniquely sensitive to glutamate toxicity by inhibition of cystine uptake, FASEB J 4 (6) (1990) 1624–1633.
[26] S.J. Dixon, D.N. Patel, M. Welsch, R. Skouta, E.D. Lee, M. Hayano, A.G. Thomas, C.E. Gleason, N.P. Tatonetti, B.S. Slusher, B.R. Stockwell, Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis, Elife 3 (2014), e02523.
[27] M.A. Badgley, D.M. Kremer, H.C. Maurer, K.E. DelGiorno, H.J. Lee, V. Purohit, I. R. Sagalovskiy, A. Ma, J. Kapilian, C.E.M. Firl, A.R. Decker, S.A. Sastra, C. F. Palermo, L.R. Andrade, P. Sajjakulnukit, L. Zhang, Z.P. Tolstyka, T. Hirschhorn, C. Lamb, T. Liu, W. Gu, E.S. Seeley, E. Stone, G. Georgiou, U. Manor, A. Iuga, G. M. Wahl, B.R. Stockwell, C.A. Lyssiotis, K.P. Olive, Cysteine depletion induces pancreatic tumor ferroptosis in mice, Science 368 (6486) (2020) 85–89.
[28] M. Gao, P. Monian, N. Quadri, R. Ramasamy, X. Jiang, Glutaminolysis and Transferrin Regulate Ferroptosis, Mol Cell 59 (2) (2015) 298–308.
[29] R. Kang, G. Kroemer, D. Tang, The tumor suppressor protein p53 and the ferroptosis network, Free Radic Biol Med 133 (2019) 162–168.
[30] S.C. Lu, Regulation of glutathione synthesis, Mol Aspects Med 30 (1-2) (2009) 42–59.
[31] L.J. Yant, Q. Ran, L. Rao, H. Van Remmen, T. Shibatani, J.G. Belter, L. Motta, A. Richardson, T.A. Prolla, The selenoprotein GPX4 is essential for mouse development and protects from radiation and oxidative damage insults, Free Radic Biol Med 34 (4) (2003) 496–502.
[32] W.S. Yang, R. SriRamaratnam, M.E. Welsch, K. Shimada, R. Skouta, V. S. Viswanathan, J.H. Cheah, P.A. Clemons, A.F. Shamji, C.B. Clish, L.M. Brown, A. W. Girotti, V.W. Cornish, S.L. Schreiber, B.R. Stockwell, Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (1-2) (2014) 317–331.
[33] W.S. Yang, K.J. Kim, M.M. Gaschler, M. Patel, M.S. Shchepinov, B.R. Stockwell, Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis, Proc Natl Acad Sci U S A 113 (34) (2016) E4966–75.
[34] B. Moosmann, C. Behl, Selenoproteins, cholesterol-lowering drugs, and the consequences: revisiting of the mevalonate pathway, Trends Cardiovasc Med 14 (7) (2004) 273–281.
[35] L.H. Dong, L. Li, Y. Song, Z.L. Duan, S.G. Sun, Y.L. Lin, S.B. Miao, Y.J. Yin, Y. N. Shu, H. Li, P. Chen, L.L. Zhao, M. Han, TRAF6-Mediated SM22alpha K21 Ubiquitination Promotes G6PD Activation and NADPH Production, Contributing to GSH Homeostasis and VSMC Survival In Vitro and In Vivo, Circ Res 117 (8) (2015) 684–694.
[36] K. Shimada, M. Hayano, N.C. Pagano, B.R. Stockwell, Cell-Line Selectivity Improves the Predictive Power of Pharmacogenomic Analyses and Helps Identify NADPH as Biomarker for Ferroptosis Sensitivity, Cell Chem Biol 23 (2) (2016) 225–235.
[37] Y. Xie, S. Zhu, X. Song, X. Sun, Y. Fan, J. Liu, M. Zhong, H. Yuan, L. Zhang, T. R. Billiar, M.T. Lotze, H.J. Zeh 3rd, R. Kang, G. Kroemer, D. Tang, The Tumor Suppressor p53 Limits Ferroptosis by Blocking DPP4 Activity, Cell Rep 20 (7) (2017) 1692–1704.
[38] N. Wilkinson, K. Pantopoulos, The IRP/IRE system in vivo: insights from mouse models, Front Pharmacol 5 (2014) 176.
[39] A.R. Bogdan, M. Miyazawa, K. Hashimoto, Y. Tsuji, Regulators of Iron Homeostasis: New Players in Metabolism, Cell Death, and Disease, Trends Biochem Sci 41 (3) (2016) 274–286.
[40] D.R. Richardson, Mysteries of the transferrin-transferrin receptor 1 interaction uncovered, Cell 116 (4) (2004) 483–485.
[41] J.P. Liuzzi, F. Aydemir, H. Nam, M.D. Knutson, R.J. Cousins, Zip14 (Slc39a14) mediates non-transferrin-bound iron uptake into cells, Proc Natl Acad Sci U S A 103 (37) (2006) 13612–13617.
[42] C.Y. Wang, S. Jenkitkasemwong, S. Duarte, B.K. Sparkman, A. Shawki, B. Mackenzie, M.D. Knutson, ZIP8 is an iron and zinc transporter whose cell-surface expression is up-regulated by cellular iron loading, J Biol Chem 287 (41) (2012) 34032–34043.
[43] H. Feng, K. Schorpp, J. Jin, C.E. Yozwiak, B.G. Hoffstrom, A.M. Decker, P. Rajbhandari, M.E. Stokes, H.G. Bender, J.M. Csuka, P.S. Upadhyayula, P. Canoll, K. Uchida, R.K. Soni, K. Hadian, B.R. Stockwell, Transferrin Receptor Is a Specific Ferroptosis Marker, Cell Rep 30 (10) (2020) 3411–3423, e7.
[44] X. Song, Y. Xie, R. Kang, W. Hou, X. Sun, M.W. Epperly, J.S. Greenberger, D. Tang, FANCD2 protects against bone marrow injury from ferroptosis, Biochem Biophys Res Commun 480 (3) (2016) 443–449.
[45] N. Geng, B.J. Shi, S.L. Li, Z.Y. Zhong, Y.C. Li, W.L. Xua, H. Zhou, J.H. Cai, Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells, Eur Rev Med Pharmacol Sci 22 (12) (2018) 3826–3836.
[46] X. Sun, Z. Ou, M. Xie, R. Kang, Y. Fan, X. Niu, H. Wang, L. Cao, D. Tang, HSPB1 as a novel regulator of ferroptotic cancer cell death, Oncogene 34 (45) (2015) 5617–5625.
[47] W. Hou, Y. Xie, X. Song, X. Sun, M.T. Lotze, H.J. Zeh 3rd, R. Kang, D. Tang, Autophagy promotes ferroptosis by degradation of ferritin, Autophagy 12 (8) (2016) 1425–1428.
[48] M. Gao, P. Monian, Q. Pan, W. Zhang, J. Xiang, X. Jiang, Ferroptosis is an autophagic cell death process, Cell Res 26 (9) (2016) 1021–1032.
[49] C.W. Brown, J.J. Amante, P. Chhoy, A.L. Elaimy, H. Liu, L.J. Zhu, C.E. Baer, S. J. Dixon, A.M. Mercurio, Prominin2 Drives Ferroptosis Resistance by Stimulating Iron Export, Dev Cell 51 (5) (2019) 575–586, e4.
[50] H. Nishizawa, M. Matsumoto, T. Shindo, D. Saigusa, H. Kato, K. Suzuki, M. Sato, Y. Ishii, H. Shimokawa, K. Igarashi, Ferroptosis is controlled by the coordinated transcriptional regulation of glutathione and labile iron metabolism by the transcription factor BACH1, J Biol Chem 295 (1) (2020) 69–82.
[51] S. Doll, B. Proneth, Y.Y. Tyurina, E. Panzilius, S. Kobayashi, I. Ingold, M. Irmler, J. Beckers, M. Aichler, A. Walch, H. Prokisch, D. Trumbach, G. Mao, F. Qu, H. Bayir, J. Fullekrug, C.H. Scheel, W. Wurst, J.A. Schick, V.E. Kagan, J.P. Angeli, M. Conrad, ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition, Nat Chem Biol 13 (1) (2017) 91–98.
[52] V.E. Kagan, G. Mao, F. Qu, J.P. Angeli, S. Doll, C.S. Croix, H.H. Dar, B. Liu, V. A. Tyurin, V.B. Ritov, A.A. Kapralov, A.A. Amoscato, J. Jiang, T. Anthonymuthu, D. Mohammadyani, Q. Yang, B. Proneth, J. Klein-Seetharaman, S. Watkins, I. Bahar, J. Greenberger, R.K. Mallampalli, B.R. Stockwell, Y.Y. Tyurina, M. Conrad, H. Bayir, Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis, Nat Chem Biol 13 (1) (2017) 81–90.
[53] H. Yuan, X. Li, X. Zhang, R. Kang, D. Tang, Identification of ACSL4 as a biomarker and contributor of ferroptosis, Biochem Biophys Res Commun 478 (3) (2016) 1338–1343.
[54] T.C. Chalmers, Prevention of atherosclerotic complications with ketanserin, BMJ 298 (6679) (1989) 1033.
[55] R. Shintoku, Y. Takigawa, K. Yamada, C. Kubota, Y. Yoshimoto, T. Takeuchi, I. Koshiishi, S. Torii, Lipoxygenase-mediated generation of lipid peroxides enhances ferroptosis induced by erastin and RSL3, Cancer Sci 108 (11) (2017) 2187–2194.
[56] H. Kuhn, S. Banthiya, K. van Leyen, Mammalian lipoxygenases and their biological relevance, Biochim Biophys Acta 1851 (4) (2015) 308–330.
[57] D. Hishikawa, T. Hashidate, T. Shimizu, H. Shindou, Diversity and function of membrane glycerophospholipids generated by the remodeling pathway in mammalian cells, J Lipid Res 55 (5) (2014) 799–807.
[58] T. Mashima, H. Seimiya, T. Tsuruo, De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy, Br J Cancer 100 (9) (2009) 1369–1372.
[59] J. Wu, A.M. Minikes, M. Gao, H. Bian, Y. Li, B.R. Stockwell, Z.N. Chen, X. Jiang, Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling, Nature 572 (7769) (2019) 402–406.
[60] S.E. Wenzel, Y.Y. Tyurina, J. Zhao, C.M. St Croix, H.H. Dar, G. Mao, V.A. Tyurin, T.S. Anthonymuthu, A.A. Kapralov, A.A. Amoscato, K. Mikulska-Ruminska, I. H. Shrivastava, E.M. Kenny, Q. Yang, J.C. Rosenbaum, L.J. Sparvero, D.R. Emlet, X. Wen, Y. Minami, F. Qu, S.C. Watkins, T.R. Holman, A.P. VanDemark, J. A. Kellum, I. Bahar, H. Bayir, V.E. Kagan, PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals, Cell 171 (3) (2017) 628–641, e26.
[61] A. Seiler, M. Schneider, H. Forster, S. Roth, E.K. Wirth, C. Culmsee, N. Plesnila, E. Kremmer, O. Radmark, W. Wurst, G.W. Bornkamm, U. Schweizer, M. Conrad, Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death, Cell Metab 8 (3) (2008) 237–248.

[62] L. Jiang, N. Kon, T. Li, S.J. Wang, T. Su, H. Hibshoosh, R. Baer, W. Gu, Ferroptosis as a p53-mediated activity during tumour suppression, Nature 520 (7545) (2015) 57–62.
[63] W. Wang, M. Green, J.E. Choi, M. Gijon, P.D. Kennedy, J.K. Johnson, P. Liao, X. Lang, I. Kryczek, A. Sell, H. Xia, J. Zhou, G. Li, J. Li, W. Li, S. Wei, L. Vatan, H. Zhang, W. Szeliga, W. Gu, R. Liu, T.S. Lawrence, C. Lamb, Y. Tanno, M. Cieslik, E. Stone, G. Georgiou, T.A. Chan, A. Chinnaiyan, W. Zou, CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy, Nature 569 (7755) (2019) 270–274.
[64] X. Lang, M.D. Green, W. Wang, J. Yu, J.E. Choi, L. Jiang, P. Liao, J. Zhou, Q. Zhang, A. Dow, A.L. Saripalli, I. Kryczek, S. Wei, W. Szeliga, L. Vatan, E. M. Stone, G. Georgiou, M. Cieslik, D.R. Wahl, M.A. Morgan, A.M. Chinnaiyan, T. S. Lawrence, W. Zou, Radiotherapy and Immunotherapy Promote Tumoral Lipid Oxidation and Ferroptosis via Synergistic Repression of SLC7A11, Cancer Discov 9 (12) (2019) 1673–1685.
[65] X. Song, S. Zhu, P. Chen, W. Hou, Q. Wen, J. Liu, Y. Xie, J. Liu, D.J. Klionsky, G. Kroemer, M.T. Lotze, H.J. Zeh, R. Kang, D. Tang, AMPK-Mediated BECN1 Phosphorylation Promotes Ferroptosis by Directly Blocking System Xc(-) Activity, Curr Biol 28 (15) (2018) 2388–2399, e5.
[66] L. Wang, Y. Liu, T. Du, H. Yang, L. Lei, M. Guo, H.F. Ding, J. Zhang, H. Wang, X. Chen, C. Yan, ATF3 promotes erastin-induced ferroptosis by suppressing system Xc(.), Cell Death Differ 27 (2) (2020) 662–675.
[67] M. Hayano, W.S. Yang, C.K. Corn, N.C. Pagano, B.R. Stockwell, Loss of cysteinyl-tRNA synthetase (CARS) induces the transsulfuration pathway and inhibits ferroptosis induced by cystine deprivation, Cell Death Differ 23 (2) (2016) 270–278.
[68] J.Y. Cao, A. Poddar, L. Magtanong, J.H. Lumb, T.R. Mileur, M.A. Reid, C. M. Dovey, J. Wang, J.W. Locasale, E. Stone, S.P.C. Cole, J.E. Carette, S.J. Dixon, A Genome-wide Haploid Genetic Screen Identifies Regulators of Glutathione Abundance and Ferroptosis Sensitivity, Cell Rep 26 (6) (2019) 1544–1556, e8.
[69] S. Suzuki, T. Tanaka, M.V. Poyurovsky, H. Nagano, T. Mayama, S. Ohkubo, M. Lokshin, H. Hosokawa, T. Nakayama, Y. Suzuki, S. Sugano, E. Sato, T. Nagao, K. Yokote, I. Tatsuno, C. Prives, Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species, Proc Natl Acad Sci U S A 107 (16) (2010) 7461–7466.
[70] Y. Niu, J. Zhang, Y. Tong, J. Li, B. Liu, Physcion 8-O-beta-glucopyranoside induced ferroptosis via regulating miR-103a-3p/GLS2 axis in gastric cancer, Life Sci 237 (2019), 116893.
[71] M.S. Chen, S.F. Wang, C.Y. Hsu, P.H. Yin, T.S. Yeh, H.C. Lee, L.M. Tseng, CHAC1 degradation of glutathione enhances cystine-starvation-induced necroptosis and ferroptosis in human triple negative breast cancer cells via the GCN2-eIF2alpha-ATF4 pathway, Oncotarget 8 (70) (2017) 114588–114602.
[72] S. Ma, E.S. Henson, Y. Chen, S.B. Gibson, Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells, Cell Death Dis 7 (2016) e2307.
[73] W.S. Yang, B.R. Stockwell, Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells, Chem Biol 15 (3) (2008) 234–245.
[74] B. Hassannia, B. Wiernicki, I. Ingold, F. Qu, S. Van Herck, Y.Y. Tyurina, H. Bayir, B.A. Abhari, J.P.F. Angeli, S.M. Choi, E. Meul, K. Heyninck, K. Declerck, C. S. Chirumamilla, M. Lahtela-Kakkonen, G. Van Camp, D.V. Krysko, P.G. Ekert, S. Fulda, B.G. De Geest, M. Conrad, V.E. Kagan, W. Vanden Berghe, P. Vandenabeele, T. Vanden Berghe, Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma, J Clin Invest 128 (8) (2018) 3341–3355.
[75] X. Sun, Z. Ou, R. Chen, X. Niu, D. Chen, R. Kang, D. Tang, Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells, Hepatology 63 (1) (2016) 173–184.
[76] P. Chen, X. Li, R. Zhang, S. Liu, Y. Xiang, M. Zhang, X. Chen, T. Pan, L. Yan, J. Feng, T. Duan, D. Wang, B. Chen, T. Jin, W. Wang, L. Chen, X. Huang, W. Zhang, Y. Sun, G. Li, L. Kong, X. Chen, Y. Li, Z. Yang, Q. Zhang, L. Zhuo, X. Sui, T. Xie, Combinative treatment of beta-elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation, Theranostics 10 (11) (2020) 5107–5119.
[77] H. Yu, C. Yang, L. Jian, S. Guo, R. Chen, K. Li, F. Qu, K. Tao, Y. Fu, F. Luo, S. Liu, Sulfasalazineinduced ferroptosis in breast cancer cells is reduced by the inhibitory effect of estrogen receptor on the transferrin receptor, Oncol Rep 42 (2) (2019) 826–838.
[78] A.L. Turcu, A. Versini, N. Khene, C. Gaillet, T. Caneque, S. Muller, R. Rodriguez, DMT1 Inhibitors Kill Cancer Stem Cells by Blocking Lysosomal Iron Translocation, Chemistry 26 (33) (2020) 7369–7373.
[79] Y. Shang, M. Luo, F. Yao, S. Wang, Z. Yuan, Y. Yang, Ceruloplasmin suppresses ferroptosis by regulating iron homeostasis in hepatocellular carcinoma cells, Cell Signal 72 (2020), 109633.
[80] S.J. Dixon, G.E. Winter, L.S. Musavi, E.D. Lee, B. Snijder, M. Rebsamen, G. Superti-Furga, B.R. Stockwell, Human Haploid Cell Genetics Reveals Roles for Lipid Metabolism Genes in Nonapoptotic Cell Death, ACS Chem Biol 10 (7) (2015) 1604–1609.
[81] K. Shimada, R. Skouta, A. Kaplan, W.S. Yang, M. Hayano, S.J. Dixon, L.M. Brown, C.A. Valenzuela, A.J. Wolpaw, B.R. Stockwell, Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis, Nat Chem Biol 12 (7) (2016) 497–503.
[82] B. Chu, N. Kon, D. Chen, T. Li, T. Liu, L. Jiang, S. Song, O. Tavana, W. Gu, ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway, Nat Cell Biol 21 (5) (2019) 579–591.
[83] N.S. Hussain, C.S. Specht, E. Frauenhoffer, M. Glantz, K. Harbaugh, Hybrid Neurofibroma-Schwannoma, Cureus 8 (3) (2016) e548.
[84] J. Garcia-Bermudez, L. Baudrier, E.C. Bayraktar, Y. Shen, K. La, R. Guarecuco, B. Yucel, D. Fiore, B. Tavora, E. Freinkman, S.H. Chan, C. Lewis, W. Min, G. Inghirami, D.M. Sabatini, K. Birsoy, Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death, Nature 567 (7746) (2019) 118–122.
[85] K. Vriens, S. Christen, S. Parik, D. Broekaert, K. Yoshinaga, A. Talebi, J. Dehairs, C. Escalona-Noguero, R. Schmieder, T. Cornfield, C. Charlton, L. Romero-Perez, M. Rossi, G. Rinaldi, M.F. Orth, R. Boon, A. Kerstens, S.Y. Kwan, B. Faubert, A. Mendez-Lucas, C.C. Kopitz, T. Chen, J. Fernandez-Garcia, J.A.G. Duarte, A. A. Schmitz, P. Steigemann, M. Najimi, A. Hagebarth, J.A. Van Ginderachter, E. Sokal, N. Gotoh, K.K. Wong, C. Verfaillie, R. Derua, S. Munck, M. Yuneva, L. Beretta, R.J. DeBerardinis, J.V. Swinnen, L. Hodson, D. Cassiman, C. Verslype, S. Christian, S. Grunewald, T.G.P. Grunewald, S.M. Fendt, Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity, Nature 566 (7744) (2019) 403–406.
[86] D. Venkatesh, N.A. O'Brien, F. Zandkarimi, D.R. Tong, M.E. Stokes, D.E. Dunn, E. S. Kengmana, A.T. Aron, A.M. Klein, J.M. Csuka, S.H. Moon, M. Conrad, C. J. Chang, D.C. Lo, A. D'Alessandro, C. Prives, B.R. Stockwell, MDM2 and MDMX promote ferroptosis by PPARalpha-mediated lipid remodeling, Genes Dev 34 (7-8) (2020) 526–543.
[87] Y. Ou, S.J. Wang, D. Li, B. Chu, W. Gu, Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses, Proc Natl Acad Sci U S A 113 (44) (2016) E6806–E6812.
[88] L. Magtanong, P.J. Ko, M. To, J.Y. Cao, G.C. Forcina, A. Tarangelo, C.C. Ward, K. Cho, G.J. Patti, D.K. Nomura, J.A. Olzmann, S.J. Dixon, Exogenous Monounsaturated Fatty Acids Promote a Ferroptosis-Resistant Cell State, Cell Chem Biol 26 (3) (2019) 420–432, e9.
[89] V.S. Viswanathan, M.J. Ryan, H.D. Dhruv, S. Gill, O.M. Eichhoff, B. Seashore-Ludlow, S.D. Kaffenberger, J.K. Eaton, K. Shimada, A.J. Aguirre, S. R. Viswanathan, S. Chattopadhyay, P. Tamayo, W.S. Yang, M.G. Rees, S. Chen, Z. V. Boskovic, S. Javaid, C. Huang, X. Wu, Y.Y. Tseng, E.M. Roider, D. Gao, J. M. Cleary, B.M. Wolpin, J.P. Mesirov, D.A. Haber, J.A. Engelman, J.S. Boehm, J. D. Kotz, C.S. Hon, Y. Chen, W.C. Hahn, M.P. Levesque, J.G. Doench, M.E. Berens, A.F. Shamji, P.A. Clemons, B.R. Stockwell, S.L. Schreiber, Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway, Nature 547 (7664) (2017) 453–457.
[90] T.A. Theodossiou, C.E. Olsen, M. Jonsson, A. Kubin, J.S. Hothersall, K. Berg, The diverse roles of glutathione-associated cell resistance against hypericin photodynamic therapy, Redox Biol 12 (2017) 191–197.
[91] A.W. Girotti, J.M. Fahey, W. Korytowski, Multiple Means by Which Nitric Oxide can Antagonize Photodynamic Therapy, Curr Med Chem 23 (24) (2016) 2754–2769.
[92] C.E. Olsen, K. Berg, P.K. Selbo, A. Weyergang, Circumvention of resistance to photodynamic therapy in doxorubicin-resistant sarcoma by photochemical internalization of gelonin, Free Radic Biol Med 65 (2013) 1300–1309.
[93] Y. Huang, Z. Dai, C. Barbacioru, W. Sadee, Cystine-glutamate transporter SLC7A11 in cancer chemosensitivity and chemoresistance, Cancer Res 65 (16) (2005) 7446–7454.
[94] G. Lei, Y. Zhang, P. Koppula, X. Liu, J. Zhang, S.H. Lin, J.A. Ajani, Q. Xiao, Z. Liao, H. Wang, B. Gan, The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression, Cell Res 30 (2) (2020) 146–162.
[95] S. Zhu, Q. Zhang, X. Sun, H.J. Zeh 3rd, M.T. Lotze, R. Kang, D. Tang, HSPA5 Regulates Ferroptotic Cell Death in Cancer Cells, Cancer Res 77 (8) (2017) 2064–2077.
[96] T.C. Chen, J.Y. Chuang, C.Y. Ko, T.J. Kao, P.Y. Yang, C.H. Yu, M.S. Liu, S.L. Hu, Y. T. Tsai, H. Chan, W.C. Chang, T.I. Hsu, AR ubiquitination induced by the curcumin analog suppresses growth of temozolomide-resistant glioblastoma through disrupting GPX4-Mediated redox homeostasis, Redox Biol 30 (2020), 101413.
[97] S. Doll, F.P. Freitas, R. Shah, M. Aldrovandi, M.C. da Silva, I. Ingold, A. Goya Grocin, T.N. Xavier da Silva, E. Panzilius, C.H. Scheel, A. Mourao, K. Buday, M. Sato, J. Wanninger, T. Vignane, V. Mohana, M. Rehberg, A. Flatley, A. Schepers, A. Kurz, D. White, M. Sauer, M. Sattler, E.W. Tate, W. Schmitz, A. Schulze, V. O'Donnell, B. Proneth, G.M. Popowicz, D.A. Pratt, J.P.F. Angeli, M. Conrad, FSP1 is a glutathione-independent ferroptosis suppressor, Nature 575 (7784) (2019) 693–698.
[98] H.P. Nguyen, D. Yi, F. Lin, J.A. Viscarra, C. Tabuchi, K. Ngo, G. Shin, A.Y. Lee, Y. Wang, H.S. Sul, Aifm2, a NADH Oxidase, Supports Robust Glycolysis and Is Required for Cold- and Diet-Induced Thermogenesis, Mol Cell 77 (3) (2020) 600–617, e4.
[99] M.M. Santoro, The Antioxidant Role of Non-mitochondrial CoQ10: Mystery Solved!, Cell Metab 31 (1) (2020) 13–15.
[100] F.L. Crane, Discovery of ubiquinone (coenzyme Q) and an overview of function, Mitochondrion 7 (Suppl) (2007) S2–7.
[101] L. Tesfay, B.T. Paul, A. Konstorum, Z. Deng, A.O. Cox, J. Lee, C.M. Furdui, P. Hegde, F.M. Torti, S.V. Torti, Stearoyl-CoA Desaturase 1 Protects Ovarian Cancer Cells from Ferroptotic Cell Death, Cancer Res 79 (20) (2019) 5355–5366.
[102] V.A.N. Kraft, C.T. Bezjian, S. Pfeiffer, L. Ringelstetter, C. Muller, F. Zandkarimi, J. Merl-Pham, X. Bao, N. Anastasov, J. Kossl, S. Brandner, J.D. Daniels, P. Schmitt-Kopplin, S.M. Hauck, B.R. Stockwell, K. Hadian, J.A. Schick, GTP Cyclohydrolase 1/Tetrahydrobiopterin Counteract Ferroptosis through Lipid Remodeling, ACS Cent Sci 6 (1) (2020) 41–53.
[103] M.C. Jaramillo, D.D. Zhang, The emerging role of the Nrf2-Keap1 signaling pathway in cancer, Genes Dev 27 (20) (2013) 2179–2191.

[104] T. Suzuki, H. Motohashi, M. Yamamoto, Toward clinical application of the Keap1-Nrf2 pathway, Trends Pharmacol Sci 34 (6) (2013) 340–346.
[105] H.W. Leung, E.Y.T. Lau, C.O.N. Leung, M.M.L. Lei, E.H.K. Mok, V.W.S. Ma, W.C. S. Cho, I.O.L. Ng, J.P. Yun, S.H. Cai, H.J. Yu, S. Ma, T.K.W. Lee, NRF2/SHH signaling cascade promotes tumor-initiating cell lineage and drug resistance in hepatocellular carcinoma, Cancer Lett 476 (2020) 48–56.
[106] C. Gourzones, C. Bellanger, S. Lamure, O.K. Gadacha, E.G. De Paco, L. Vincent, G. Cartron, B. Klein, J. Moreaux, Antioxidant Defenses Confer Resistance to High Dose Melphalan in Multiple Myeloma Cells, Cancers (Basel) 11 (4) (2019).
[107] C.R. Rocha, G.S. Kajitani, A. Quinet, R.S. Fortunato, C.F. Menck, NRF2 and glutathione are key resistance mediators to temozolomide in glioma and melanoma cells, Oncotarget 7 (30) (2016) 48081–48092.
[108] Z.H. Wan, T.Y. Jiang, Y.Y. Shi, Y.F. Pan, Y.K. Lin, Y.H. Ma, C. Yang, X.F. Feng, L. F. Huang, X.N. Kong, Z.W. Ding, Y.X. Tan, L.W. Dong, H.Y. Wang, RPB5-Mediating Protein Promotes Cholangiocarcinoma Tumorigenesis and Drug Resistance by Competing With NRF2 for KEAP1 Binding, Hepatology 71 (6) (2020) 2005–2022.
[109] T. Xun, Z. Lin, X. Zhan, S. Song, L. Mo, H. Feng, Q. Yang, D. Guo, X. Yang, Advanced oxidation protein products upregulate efflux transporter expression and activity through activation of the Nrf-2-mediated signaling pathway in vitro and in vivo, Eur J Pharm Sci 149 (2020), 105342.
[110] X. Sun, X. Niu, R. Chen, W. He, D. Chen, R. Kang, D. Tang, Metallothionein-1G facilitates sorafenib resistance through inhibition of ferroptosis, Hepatology 64 (2) (2016) 488–500.
[111] A. Houessinon, C. Francois, C. Sauzay, C. Louandre, G. Mongelard, C. Godin, S. Bodeau, S. Takahashi, Z. Saidak, L. Gutierrez, J.M. Regimbeau, N. Barget, J. C. Barbare, N. Ganne, B. Chauffert, R. Coriat, A. Galmiche, Metallothionein-1 as a biomarker of altered redox metabolism in hepatocellular carcinoma cells exposed to sorafenib, Mol Cancer 15 (1) (2016) 38.
[112] V. Gambardella, F. Gimeno-Valiente, N. Tarazona, C. Martinez-Ciarpaglini, D. Roda, T. Fleitas, P. Tolosa, J.M. Cejalvo, M. Huerta, S. Rosello, J. Castillo, A. Cervantes, NRF2 through RPS6 Activation Is Related to Anti-HER2 Drug Resistance in HER2-Amplified Gastric Cancer, Clin Cancer Res 25 (5) (2019) 1639–1649.
[113] B.S. Moses, W.L. Slone, P. Thomas, R. Evans, D. Piktel, P.M. Angel, C.M. Walsh, P. S. Cantrell, S.L. Rellick, K.H. Martin, J.W. Simpkins, L.F. Gibson, Bone marrow microenvironment modulation of acute lymphoblastic leukemia phenotype, Exp Hematol 44 (1) (2016), 50-9 e1-2.
[114] J.C. Crack, N.E. Le Brun, Redox-Sensing Iron-Sulfur Cluster Regulators, Antioxid Redox Signal 29 (18) (2018) 1809–1829.
[115] S. Patra, D.P. Barondeau, Mechanism of activation of the human cysteine desulfurase complex by frataxin, Proc Natl Acad Sci U S A 116 (39) (2019) 19421–19430.
[116] Y. Chen, Z. Fan, Y. Yang, C. Gu, Iron metabolism and its contribution to cancer (Review), Int J Oncol 54 (4) (2019) 1143–1154.
[117] S.W. Alvarez, V.O. Sviderskiy, E.M. Terzi, T. Papagiannakopoulos, A.L. Moreira, S. Adams, D.M. Sabatini, K. Birsoy, R. Possemato, NFS1 undergoes positive selection in lung tumours and protects cells from ferroptosis, Nature 551 (7682) (2017) 639–643.
[118] S.W. Alvarez, R. Possemato, Leveraging the iron-starvation response to promote ferroptosis, Oncotarget 9 (13) (2018) 10830–10831.
[119] J. Du, Y. Zhou, Y. Li, J. Xia, Y. Chen, S. Chen, X. Wang, W. Sun, T. Wang, X. Ren, X. Wang, Y. An, K. Lu, W. Hu, S. Huang, J. Li, X. Tong, Y. Wang, Identification of Frataxin as a regulator of ferroptosis, Redox Biol 32 (2020) 101483.
[120] J. Du, T. Wang, Y. Li, Y. Zhou, X. Wang, X. Yu, X. Ren, Y. An, Y. Wu, W. Sun, W. Fan, Q. Zhu, Y. Wang, X. Tong, DHA inhibits proliferation and induces ferroptosis of leukemia cells through autophagy dependent degradation of ferritin, Free Radic Biol Med 131 (2019) 356–369.
[121] R. Mittler, M. Darash-Yahana, Y.S. Sohn, F. Bai, L. Song, I.Z. Cabantchik, P. A. Jennings, J.N. Onuchic, R. Nechushtai, NEET Proteins: A New Link Between Iron Metabolism, Reactive Oxygen Species, and Cancer, Antioxid Redox Signal 30 (8) (2019) 1083–1095.
[122] I. Ferecatu, S. Goncalves, M.P. Golinelli-Cohen, M. Clemancey, A. Martelli, S. Riquier, E. Guittet, J.M. Latour, H. Puccio, J.C. Drapier, E. Lescop, C. Bouton, The diabetes drug target MitoNEET governs a novel trafficking pathway to rebuild an Fe-S cluster into cytosolic aconitase/iron regulatory protein 1, J Biol Chem 289 (41) (2014) 28070–28086.
[123] C.H. Lipper, M.L. Paddock, J.N. Onuchic, R. Mittler, R. Nechushtai, P.A. Jennings, Cancer-Related NEET Proteins Transfer 2Fe-2S Clusters to Anamorsin, a Protein Required for Cytosolic Iron-Sulfur Cluster Biogenesis, PLoS One 10 (10) (2015), e0139699.
[124] Y.S. Sohn, S. Tamir, L. Song, D. Michaeli, I. Matouk, A.R. Conlan, Y. Harir, S. H. Holt, V. Shulaev, M.L. Paddock, A. Hochberg, I.Z. Cabanchick, J.N. Onuchic, P. A. Jennings, R. Nechushtai, R. Mittler, NAF-1 and mitoNEET are central to human breast cancer proliferation by maintaining mitochondrial homeostasis and promoting tumor growth, Proc Natl Acad Sci U S A 110 (36) (2013) 14676–14681.
[125] W.J. Geldenhuys, R.R. Nair, D. Piktel, K.H. Martin, L.F. Gibson, The MitoNEET Ligand NL-1 Mediates Antileukemic Activity in Drug-Resistant B-Cell Acute Lymphoblastic Leukemia, J Pharmacol Exp Ther 370 (1) (2019) 25–34.
[126] E.H. Kim, D. Shin, J. Lee, A.R. Jung, J.L. Roh, CISD2 inhibition overcomes resistance to sulfasalazine-induced ferroptotic cell death in head and neck cancer, Cancer Lett 432 (2018) 180–190.
[127] S. Toyokuni, F. Ito, K. Yamashita, Y. Okazaki, S. Akatsuka, Iron and thiol redox signaling in cancer: An exquisite balance to escape ferroptosis, Free Radic Biol Med 108 (2017) 610–626.
[128] J. Lu, A. Holmgren, The thioredoxin antioxidant system, Free Radic Biol Med 66 (2014) 75–87.
[129] Z. Du, X. Liu, T. Chen, W. Gao, Z. Wu, Z. Hu, D. Wei, C. Gao, Q. Li, Targeting a Sirt5-Positive Subpopulation Overcomes Multidrug Resistance in Wild-Type Kras Colorectal Carcinomas, Cell Rep 22 (10) (2018) 2677–2689.
[130] W. Jeong, H.W. Yoon, S.R. Lee, S.G. Rhee, Identification and characterization of TRP14, a thioredoxin-related protein of 14 kDa. New insights into the specificity of thioredoxin function, J Biol Chem 279 (5) (2004) 3142–3150.
[131] S.F. Zhang, X.Y. Wang, Z.Q. Fu, Q.H. Peng, J.Y. Zhang, F. Ye, Y.F. Fu, C.Y. Zhou, W.G. Lu, X.D. Cheng, X. Xie, TXNDC17 promotes paclitaxel resistance via inducing autophagy in ovarian cancer, Autophagy 11 (2) (2015) 225–238.
[132] W. Zhou, C. Fang, L. Zhang, Q. Wang, D. Li, D. Zhu, Thioredoxin domain-containing protein 9 (TXNDC9) contributes to oxaliplatin resistance through regulation of autophagy-apoptosis in colorectal adenocarcinoma, Biochem Biophys Res Commun 524 (3) (2020) 582–588.
[133] W.X. Tan, T.M. Xu, Z.L. Zhou, X.J. Lv, J. Liu, W.J. Zhang, M.H. Cui, TRP14 promotes resistance to cisplatin by inducing autophagy in ovarian cancer, Oncol Rep (2019).
[134] E. Llabani, R.W. Hicklin, H.Y. Lee, S.E. Motika, L.A. Crawford, E. Weerapana, P. J. Hergenrother, Diverse compounds from pleuromutilin lead to a thioredoxin inhibitor and inducer of ferroptosis, Nat Chem 11 (6) (2019) 521–532.
[135] A. Kyani, S. Tamura, S. Yang, A. Shergalis, S. Samanta, Y. Kuang, M. Ljungman, N. Neamati, Discovery and Mechanistic Elucidation of a Class of Protein Disulfide Isomerase Inhibitors for the Treatment of Glioblastoma, ChemMedChem 13 (2) (2018) 164–177.
[136] T.M. Penning, Aldo-Keto Reductase Regulation by the Nrf2 System: Implications for Stress Response, Chemotherapy Drug Resistance, and Carcinogenesis, Chem Res Toxicol 30 (1) (2017) 162–176.
[137] J. Chen, C. Solomides, F. Simpkins, H. Simpkins, The role of Nrf2 and ATF2 in resistance to platinum-based chemotherapy, Cancer Chemother Pharmacol 79 (2) (2017) 369–380.
[138] E. Novotna, N. Bukum, J. Hofman, M. Flaxova, E. Kouklikova, D. Louvarova, V. Wsol, Roscovitine and purvalanol A effectively reverse anthracycline resistance mediated by the activity of aldo-keto reductase 1C3 (AKR1C3): A promising therapeutic target for cancer treatment, Biochem Pharmacol 156 (2018) 22–31.
[139] M. Gagliardi, D. Cotella, C. Santoro, D. Cora, N.A. Barlev, M. Piacentini, M. Corazzari, Aldo-keto reductases protect metastatic melanoma from ER stress-independent ferroptosis, Cell Death Dis 10 (12) (2019) 902.
[140] H.M. Lei, K.R. Zhang, C.H. Wang, Y. Wang, G.L. Zhuang, L.M. Lu, J. Zhang, Y. Shen, H.Z. Chen, L. Zhu, Aldehyde dehydrogenase 1A1 confers erlotinib resistance via facilitating the reactive oxygen species-reactive carbonyl species metabolic pathway in lung adenocarcinomas, Theranostics 9 (24) (2019) 7122–7139.
[141] Y. Otsuki, J. Yamasaki, K. Suina, S. Okazaki, N. Koike, H. Saya, O. Nagano, Vasodilator oxyfedrine inhibits aldehyde metabolism and thereby sensitizes cancer cells to xCT-targeted therapy, Cancer Sci 111 (1) (2020) 127–136.
[142] S. Okazaki, S. Shintani, Y. Hirata, K. Suina, T. Semba, J. Yamasaki, K. Umene, M. Ishikawa, H. Saya, O. Nagano, Synthetic lethality of the ALDH3A1 inhibitor dyclonine and xCT inhibitors in glutathione deficiency-resistant cancer cells, Oncotarget 9 (73) (2018) 33832–33843.
[143] Z. Fan, A.K. Wirth, D. Chen, C.J. Wruck, M. Rauh, M. Buchfelder, N. Savaskan, Nrf2-Keap1 pathway promotes cell proliferation and diminishes ferroptosis, Oncogenesis 6 (8) (2017) e371.
[144] N. Liu, X. Lin, C. Huang, Activation of the reverse transsulfuration pathway through NRF2/CBS confers erastin-induced ferroptosis resistance, Br J Cancer 122 (2) (2020) 279–292.
[145] D. Chen, Z. Fan, M. Rauh, M. Buchfelder, I.Y. Eyupoglu, N. Savaskan, ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner, Oncogene 36 (40) (2017) 5593–5608.
[146] D. Chen, M. Rauh, M. Buchfelder, I.Y. Eyupoglu, N. Savaskan, The oxido-metabolic driver ATF4 enhances temozolamide chemo-resistance in human gliomas, Oncotarget 8 (31) (2017) 51164–51176.
[147] C. Sarcinelli, H. Dragic, M. Piecyk, V. Barbet, C. Duret, A. Barthelaix, C. Ferraro-Peyret, J. Fauvre, T. Renno, C. Chaveroux, S.N. Manie, ATF4-Dependent NRF2 Transcriptional Regulation Promotes Antioxidant Protection during Endoplasmic Reticulum Stress, Cancers (Basel) 12 (3) (2020).
[148] P.K. Mandal, A. Seiler, T. Perisic, P. Kolle, A. Banjac Canak, H. Forster, N. Weiss, E. Kremmer, M.W. Lieberman, S. Bannai, P. Kuhlencordt, H. Sato, G. W. Bornkamm, M. Conrad, System x(c)- and thioredoxin reductase 1 cooperatively rescue glutathione deficiency, J Biol Chem 285 (29) (2010) 22244–22253.
[149] S. Nishizawa, H. Araki, Y. Ishikawa, S. Kitazawa, A. Hata, T. Soga, T. Hara, Low tumor glutathione level as a sensitivity marker for glutamate-cysteine ligase inhibitors, Oncol Lett 15 (6) (2018) 8735–8743.
[150] D. Basuli, L. Tesfay, Z. Deng, B. Paul, Y. Yamamoto, G. Ning, W. Xian, F. McKeon, M. Lynch, C.P. Crum, P. Hegde, M. Brewer, X. Wang, L.D. Miller, N. Dyment, F. M. Torti, S.V. Torti, Iron addiction: a novel therapeutic target in ovarian cancer, Oncogene 36 (29) (2017) 4089–4099.
[151] J. Dachert, V. Ehrenfeld, K. Habermann, N. Dolgikh, S. Fulda, Targeting ferroptosis in rhabdomyosarcoma cells, Int J Cancer 146 (2) (2020) 510–520.
[152] J.L. Roh, E.H. Kim, H. Jang, D. Shin, Nrf2 inhibition reverses the resistance of cisplatin-resistant head and neck cancer cells to artesunate-induced ferroptosis, Redox Biol 11 (2017) 254–262.
[153] N. Wang, G.Z. Zeng, J.L. Yin, Z.X. Bian, Artesunate activates the ATF4-CHOP-CHAC1 pathway and affects ferroptosis in Burkitt's Lymphoma, Biochem Biophys Res Commun 519 (3) (2019) 533–539.

[154] C. Ishikawa, M. Senba, N. Mori, Evaluation of artesunate for the treatment of adult T-cell leukemia/lymphoma, Eur J Pharmacol 872 (2020), 172953.
[155] C. Louandre, Z. Ezzoukhry, C. Godin, J.C. Barbare, J.C. Maziere, B. Chauffert, A. Galmiche, Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib, Int J Cancer 133 (7) (2013) 1732–1742.
[156] M.H. Larraufie, W.S. Yang, E. Jiang, A.G. Thomas, B.S. Slusher, B.R. Stockwell, Incorporation of metabolically stable ketones into a small molecule probe to increase potency and water solubility, Bioorg Med Chem Lett 25 (21) (2015) 4787–4792.
[157] Y. Zhang, H. Tan, J.D. Daniels, F. Zandkarimi, H. Liu, L.M. Brown, K. Uchida, O. A. O'Connor, B.R. Stockwell, Imidazole Ketone Erastin Induces Ferroptosis and Slows Tumor Growth in a Mouse Lymphoma Model, Cell Chem Biol 26 (5) (2019) 623–633, e9.
[158] L. Schockel, A. Glasauer, F. Basit, K. Bitschar, H. Truong, G. Erdmann, C. Algire, A. Hagebarth, P.H. Willems, C. Kopitz, W.J. Koopman, M. Heroult, Targeting mitochondrial complex I using BAY 87-2243 reduces melanoma tumor growth, Cancer Metab 3 (2015) 11.
[159] F. Basit, L.M. van Oppen, L. Schockel, H.M. Bossenbroek, S.E. van Emst-de Vries, J.C. Hermeling, S. Grefte, C. Kopitz, M. Heroult, P. Hgm Willems, W.J. Koopman, Mitochondrial complex I inhibition triggers a mitophagy-dependent ROS increase leading to necroptosis and ferroptosis in melanoma cells, Cell Death Dis 8 (3) (2017) e2716.
[160] S.L. Cramer, A. Saha, J. Liu, S. Tadi, S. Tiziani, W. Yan, K. Triplett, C. Lamb, S. E. Alters, S. Rowlinson, Y.J. Zhang, M.J. Keating, P. Huang, J. DiGiovanni, G. Georgiou, E. Stone, Systemic depletion of L-cyst(e)ine with cyst(e)inase increases reactive oxygen species and suppresses tumor growth, Nat Med 23 (1) (2017) 120–127.
[161] L. Zhang, W. Liu, F. Liu, Q. Wang, M. Song, Q. Yu, K. Tang, T. Teng, D. Wu, X. Wang, W. Han, Y. Li, IMCA Induces Ferroptosis Mediated by SLC7A11 through the AMPK/mTOR Pathway in Colorectal Cancer, Oxid Med Cell Longev 2020 (2020), 1675613.
[162] Z. Gao, G. Deng, Y. Li, H. Huang, X. Sun, H. Shi, X. Yao, L. Gao, Y. Ju, M. Luo, Actinidia chinensis Planch prevents proliferation and migration of gastric cancer associated with apoptosis, ferroptosis activation and mesenchymal phenotype suppression, Biomed Pharmacother 126 (2020), 110092.
[163] L. Probst, J. Dachert, B. Schenk, S. Fulda, Lipoxygenase inhibitors protect acute lymphoblastic leukemia cells from ferroptotic cell death, Biochem Pharmacol 140 (2017) 41–52.
[164] X. Sui, R. Zhang, S. Liu, T. Duan, L. Zhai, M. Zhang, X. Han, Y. Xiang, X. Huang, H. Lin, T. Xie, RSL3 Drives Ferroptosis Through GPX4 Inactivation and ROS Production in Colorectal Cancer, Front Pharmacol 9 (2018) 1371.
[165] X. Wang, S. Lu, C. He, C. Wang, L. Wang, M. Piao, G. Chi, Y. Luo, P. Ge, RSL3 induced autophagic death in glioma cells via causing glycolysis dysfunction, Biochem Biophys Res Commun 518 (3) (2019) 590–597.
[166] M. Weiwer, J.A. Bittker, T.A. Lewis, K. Shimada, W.S. Yang, L. MacPherson, S. Dandapani, M. Palmer, B.R. Stockwell, S.L. Schreiber, B. Munoz, Development of small-molecule probes that selectively kill cells induced to express mutant RAS, Bioorg Med Chem Lett 22 (4) (2012) 1822–1826.
[167] J.H. Woo, Y. Shimoni, W.S. Yang, P. Subramaniam, A. Iyer, P. Nicoletti, M. Rodriguez Martinez, G. Lopez, M. Mattioli, R. Realubit, C. Karan, B. R. Stockwell, M. Bansal, A. Califano, Elucidating Compound Mechanism of Action by Network Perturbation Analysis, Cell 162 (2) (2015) 441–451.
[168] M.M. Gaschler, A.A. Andia, H. Liu, J.M. Csuka, B. Hurlocker, C.A. Vaiana, D. W. Heindel, D.S. Zuckerman, P.H. Bos, E. Reznik, L.F. Ye, Y.Y. Tyurina, A.J. Lin, M.S. Shchepinov, A.Y. Chan, E. Peguero-Pereira, M.A. Fomich, J.D. Daniels, A. V. Bekish, V.V. Shmanai, V.E. Kagan, L.K. Mahal, K.A. Woerpel, B.R. Stockwell, FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation, Nat Chem Biol 14 (5) (2018) 507–515.
[169] R. Lin, Z. Zhang, L. Chen, Y. Zhou, P. Zou, C. Feng, L. Wang, G. Liang, Dihydroartemisinin (DHA) induces ferroptosis and causes cell cycle arrest in head and neck carcinoma cells, Cancer Lett 381 (1) (2016) 165–175.
[170] G.Q. Chen, F.A. Benthani, J. Wu, D. Liang, Z.X. Bian, X. Jiang, Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis, Cell Death Differ 27 (1) (2020) 242–254.
[171] L. Shi, F. Ito, Y. Wang, Y. Okazaki, H. Tanaka, M. Mizuno, M. Hori, T. Hirayama, H. Nagasawa, D.R. Richardson, S. Toyokuni, Non-thermal plasma induces a stress response in mesothelioma cells resulting in increased endocytosis, lysosome biogenesis and autophagy, Free Radic Biol Med 108 (2017) 904–917.
[172] T. Furuta, L. Shi, S. Toyokuni, Non-thermal plasma as a simple ferroptosis inducer in cancer cells: A possible role of ferritin, Pathol Int 68 (7) (2018) 442–443.
[173] T.T. Mai, A. Hamai, A. Hienzsch, T. Caneque, S. Muller, J. Wicinski, O. Cabaud, C. Leroy, A. David, V. Acevedo, A. Ryo, C. Ginestier, D. Birnbaum, E. Charafe-Jauffret, P. Codogno, M. Mehrpour, R. Rodriguez, Salinomycin kills cancer stem cells by sequestering iron in lysosomes, Nat Chem 9 (10) (2017) 1025–1033.
[174] L.C. Chang, S.K. Chiang, S.E. Chen, Y.L. Yu, R.H. Chou, W.C. Chang, Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis, Cancer Lett 416 (2018) 124–137.
[175] A.T. Shaw, M.M. Winslow, M. Magendantz, C. Ouyang, J. Dowdle, A. Subramanian, T.A. Lewis, R.L. Maglathin, N. Tolliday, T. Jacks, Selective killing of K-ras mutant cancer cells by small molecule inducers of oxidative stress, Proc Natl Acad Sci U S A 108 (21) (2011) 8773–8778.
[176] E. Ooko, M.E. Saeed, O. Kadioglu, S. Sarvi, M. Colak, K. Elmasaoudi, R. Janah, H. J. Greten, T. Efferth, Artemisinin derivatives induce iron-dependent cell death (ferroptosis) in tumor cells, Phytomedicine 22 (11) (2015) 1045–1054.
[177] J. Dachert, H. Schoeneberger, K. Rohde, S. Fulda, RSL3 and Erastin differentially regulate redox signaling to promote Smac mimetic-induced cell death, Oncotarget 7 (39) (2016) 63779–63792.
[178] T. Bai, S. Wang, Y. Zhao, R. Zhu, W. Wang, Y. Sun, Haloperidol, a sigma receptor 1 antagonist, promotes ferroptosis in hepatocellular carcinoma cells, Biochem Biophys Res Commun 491 (4) (2017) 919–925.
[179] D. Shin, E.H. Kim, J. Lee, J.L. Roh, Nrf2 inhibition reverses resistance to GPX4 inhibitor-induced ferroptosis in head and neck cancer, Free Radic Biol Med 129 (2018) 454–462.
[180] A.T. Mbaveng, G.T.M. Bitchagno, V. Kuete, P. Tane, T. Efferth, Cytotoxicity of ungeremine towards multi-factorial drug resistant cancer cells and induction of apoptosis, ferroptosis, necroptosis and autophagy, Phytomedicine 60 (2019), 152832.
[181] X. Gao, N. Guo, H. Xu, T. Pan, H. Lei, A. Yan, Y. Mi, L. Xu, Ibuprofen induces ferroptosis of glioblastoma cells via downregulation of nuclear factor erythroid 2-related factor 2 signaling pathway, Anticancer Drugs 31 (1) (2020) 27–34.
[182] Y. Li, F. Chen, J. Chen, S. Chan, Y. He, W. Liu, G. Zhang, Disulfiram/Copper Induces Antitumor Activity against Both Nasopharyngeal Cancer Cells and Cancer-Associated Fibroblasts through ROS/MAPK and Ferroptosis Pathways, Cancers (Basel) 12 (1) (2020).
[183] S.G. Kathman, J. Boshart, H. Jing, B.F. Cravatt, Blockade of the Lysophosphatidylserine Lipase ABHD12 Potentiates Ferroptosis in Cancer Cells, ACS Chem Biol 15 (4) (2020) 871–877.
[184] C.P. Anderson, C.P. Reynolds, Synergistic cytotoxicity of buthionine sulfoximine (BSO) and intensive melphalan (L-PAM) for neuroblastoma cell lines established at relapse after myeloablative therapy, Bone Marrow Transplant 30 (3) (2002) 135–140.
[185] A. Ongaro, A. Pellati, M. De Mattei, F. De Terlizzi, C.R. Rossi, L.G. Campana, Enhancement of melphalan activity by buthionine sulfoximine and electroporation in melanoma cells, Anticancer Drugs 26 (3) (2015) 284–292.
[186] A. Yoshida, H. Takemura, H. Inoue, T. Miyashita, T. Ueda, Inhibition of glutathione synthesis overcomes Bcl-2-mediated topoisomerase inhibitor resistance and induces nonapoptotic cell death via mitochondrial-independent pathway, Cancer Res 66 (11) (2006) 5772–5780.
[187] H. Konig, N. Hartel, B. Schultheis, M. Schatz, C. Lorentz, J.V. Melo, R. Hehlmann, A. Hochhaus, P. La Rosee, Enhanced Bcr-Abl-specific antileukemic activity of arsenic trioxide (Trisenox) through glutathione-depletion in imatinib-resistant cells, Haematologica 92 (6) (2007) 838–841.
[188] F. Cilurzo, M.C. Cristiano, M. Da Pian, E. Cianflone, L. Quintieri, D. Paolino, G. Pasut, Overcoming Cancer Cell Drug Resistance by a Folic Acid Targeted Polymeric Conjugate of Buthionine Sulfoximine, Anticancer Agents Med Chem 19 (12) (2019) 1513–1522.
[189] J.D. Whitt, A.B. Keeton, B.D. Gary, L.A. Sklar, K. Sodani, Z.S. Chen, G.A. Piazza, Sulindac sulfide selectively increases sensitivity of ABCC1 expressing tumor cells to doxorubicin and glutathione depletion, J Biomed Res 30 (2) (2016) 120–133.
[190] C.R. Rocha, C.C. Garcia, D.B. Vieira, A. Quinet, L.C. de Andrade-Lima, V. Munford, J.E. Belizario, C.F. Menck, Glutathione depletion sensitizes cisplatin- and temozolomide-resistant glioma cells in vitro and in vivo, Cell Death Dis 6 (2015) e1727.
[191] W.B. Zhou, X.X. Zhang, Y. Cai, W. Sun, H. Li, Osthole prevents tamoxifen-induced liver injury in mice, Acta Pharmacol Sin 40 (5) (2019) 608–619.
[192] A.H. Ringwood, D.E. Conners, The effects of glutathione depletion on reproductive success in oysters, Crassostrea virginica, Mar Environ Res 50 (1-5) (2000) 207–211.
[193] L. Chen, X. Li, L. Liu, B. Yu, Y. Xue, Y. Liu, Erastin sensitizes glioblastoma cells to temozolomide by restraining xCT and cystathionine-gamma-lyase function, Oncol Rep 33 (3) (2015) 1465–1474.
[194] Y. Yu, Y. Xie, L. Cao, L. Yang, M. Yang, M.T. Lotze, H.J. Zeh, R. Kang, D. Tang, The ferroptosis inducer erastin enhances sensitivity of acute myeloid leukemia cells to chemotherapeutic agents, Mol Cell Oncol 2 (4) (2015), e1054549.
[195] H.H. Zhou, X. Chen, L.Y. Cai, X.W. Nan, J.H. Chen, X.X. Chen, Y. Yang, Z.H. Xing, M.N. Wei, Y. Li, S.T. Wang, K. Liu, Z. Shi, X.J. Yan, Erastin Reverses ABCB1-Mediated Docetaxel Resistance in Ovarian Cancer, Front Oncol 9 (2019) 1398.
[196] J.L. Roh, E.H. Kim, H.J. Jang, J.Y. Park, D. Shin, Induction of ferroptotic cell death for overcoming cisplatin resistance of head and neck cancer, Cancer Lett 381 (1) (2016) 96–103.
[197] Y. Li, H. Yan, X. Xu, H. Liu, C. Wu, L. Zhao, Erastin/sorafenib induces cisplatin-resistant non-small cell lung cancer cell ferroptosis through inhibition of the Nrf2/xCT pathway, Oncol Lett 19 (1) (2020) 323–333.
[198] P.W. Gout, A.R. Buckley, C.R. Simms, N. Bruchovsky, Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x(c)- cystine transporter: a new action for an old drug, Leukemia 15 (10) (2001) 1633–1640.
[199] J. Guan, M. Lo, P. Dockery, S. Mahon, C.M. Karp, A.R. Buckley, S. Lam, P.W. Gout, Y.Z. Wang, The xc- cystine/glutamate antiporter as a potential therapeutic target for small-cell lung cancer: use of sulfasalazine, Cancer Chemother Pharmacol 64 (3) (2009) 463–472.
[200] M. Lo, V. Ling, C. Low, Y.Z. Wang, P.W. Gout, Potential use of the anti-inflammatory drug, sulfasalazine, for targeted therapy of pancreatic cancer, Curr Oncol 17 (3) (2010) 9–16.
[201] A. Arlt, A. Gehrz, S. Muerkoster, J. Vorndamm, M.L. Kruse, U.R. Folsch, H. Schafer, Role of NF-kappaB and Akt/PI3K in the resistance of pancreatic carcinoma cell lines against gemcitabine-induced cell death, Oncogene 22 (21) (2003) 3243–3251.
[202] M.Z. Ma, G. Chen, P. Wang, W.H. Lu, C.F. Zhu, M. Song, J. Yang, S. Wen, R.H. Xu, Y. Hu, P. Huang, Xc- inhibitor sulfasalazine sensitizes colorectal cancer to cisplatin by a GSH-dependent mechanism, Cancer Lett 368 (1) (2015) 88–96.

[203] F. Wada, H. Koga, J. Akiba, T. Niizeki, H. Iwamoto, Y. Ikezono, T. Nakamura, M. Abe, A. Masuda, T. Sakaue, T. Tanaka, T. Kakuma, H. Yano, T. Torimura, High expression of CD44v9 and xCT in chemoresistant hepatocellular carcinoma: Potential targets by sulfasalazine, Cancer Sci 109 (9) (2018) 2801–2810.
[204] R.M. Drayton, E. Dudziec, S. Peter, S. Bertz, A. Hartmann, H.E. Bryant, J.W. Catto, Reduced expression of miRNA-27a modulates cisplatin resistance in bladder cancer by targeting the cystine/glutamate exchanger SLC7A11, Clin Cancer Res 20 (7) (2014) 1990–2000.
[205] L. Wagmann, H.H. Maurer, M.R. Meyer, Inhibition and stimulation of the human breast cancer resistance protein as in vitro predictor of drug-drug interactions of drugs of abuse, Arch Toxicol 92 (9) (2018) 2875–2884.
[206] N. Hwang, S.W. Chung, Sulfasalazine attenuates tamoxifen-induced toxicity in human retinal pigment epithelial cells, BMB Rep 53 (5) (2020) 284–289.
[207] A. Hamacher-Brady, H.A. Stein, S. Turschner, I. Toegel, R. Mora, N. Jennewein, T. Efferth, R. Eils, N.R. Brady, Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalyzed lysosomal reactive oxygen species production, J Biol Chem 286 (8) (2011) 6587–6601.
[208] N. Eling, L. Reuter, J. Hazin, A. Hamacher-Brady, N.R. Brady, Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells, Oncoscience 2 (5) (2015) 517–532.
[209] X. Papanikolaou, S. Johnson, T. Garg, E. Tian, R. Tytarenko, Q. Zhang, C. Stein, B. Barlogie, J. Epstein, C. Heuck, Artesunate overcomes drug resistance in multiple myeloma by inducing mitochondrial stress and non-caspase apoptosis, Oncotarget 5 (12) (2014) 4118–4128.
[210] Z. Wang, Q. Wang, T. He, W. Li, Y. Liu, Y. Fan, Y. Wang, Q. Wang, J. Chen, The combination of artesunate and carboplatin exerts a synergistic anti-tumour effect on non-small cell lung cancer, Clin Exp Pharmacol Physiol 47 (6) (2020) 1083–1091.
[211] Z. Li, Y.T. Zhu, M. Xiang, J.L. Qiu, S.Q. Luo, F. Lin, Enhanced lysosomal function is critical for paclitaxel resistance in cancer cells: reversed by artesunate, Acta Pharmacol Sin (2020).
[212] S. Codenotti, M. Poli, M. Asperti, D. Zizioli, F. Marampon, A. Fanzani, Cell growth potential drives ferroptosis susceptibility in rhabdomyosarcoma and myoblast cell lines, J Cancer Res Clin Oncol 144 (9) (2018) 1717–1730.
[213] J. Ye, X. Jiang, Z. Dong, S. Hu, M. Xiao, Low-Concentration PTX And RSL3 Inhibits Tumor Cell Growth Synergistically By Inducing Ferroptosis In Mutant p53 Hypopharyngeal Squamous Carcinoma, Cancer Manag Res 11 (2019) 9783–9792.
[214] Z. Ye, Q. Hu, Q. Zhuo, Y. Zhu, G. Fan, M. Liu, Q. Sun, Z. Zhang, W. Liu, W. Xu, S. Ji, X. Yu, X. Xu, Y. Qin, Abrogation of ARF6 promotes RSL3-induced ferroptosis and mitigates gemcitabine resistance in pancreatic cancer cells, Am J Cancer Res 10 (4) (2020) 1182–1193.
[215] Q. Liu, K. Wang, The induction of ferroptosis by impairing STAT3/Nrf2/GPx4 signaling enhances the sensitivity of osteosarcoma cells to cisplatin, Cell Biol Int 43 (11) (2019) 1245–1256.
[216] B. Hassannia, E. Logie, P. Vandenabeele, T. Vanden Berghe, W. Vanden Berghe, Withaferin A: From ayurvedic folk medicine to preclinical anti-cancer drug, Biochem Pharmacol 173 (2020), 113602.
[217] A.M. Alnuqaydan, B. Rah, A.G. Almutary, S.S. Chauhan, Synergistic antitumor effect of 5-fluorouracil and withaferin-A induces endoplasmic reticulum stress-mediated autophagy and apoptosis in colorectal cancer cells, Am J Cancer Res 10 (3) (2020) 799–815.
[218] J.H. Hsu, P.M. Chang, T.S. Cheng, Y.L. Kuo, A.T. Wu, T.H. Tran, Y.H. Yang, J. M. Chen, Y.C. Tsai, Y.S. Chu, T.H. Huang, C.F. Huang, J.M. Lai, Identification of Withaferin A as a Potential Candidate for Anti-Cancer Therapy in Non-Small Cell Lung Cancer, Cancers (Basel) 11 (7) (2019).
[219] X. Li, F. Zhu, J. Jiang, C. Sun, X. Wang, M. Shen, R. Tian, C. Shi, M. Xu, F. Peng, X. Guo, M. Wang, R. Qin, Synergistic antitumor activity of withaferin A combined with oxaliplatin triggers reactive oxygen species-mediated inactivation of the PI3K/AKT pathway in human pancreatic cancer cells, Cancer Lett 357 (1) (2015) 219–230.
[220] R.F. Dielschneider, H. Eisenstat, S. Mi, J.M. Curtis, W. Xiao, J.B. Johnston, S. B. Gibson, Lysosomotropic agents selectively target chronic lymphocytic leukemia cells due to altered sphingolipid metabolism, Leukemia 30 (6) (2016) 1290–1300.
[221] A. Fassl, C. Brain, M. Abu-Remaileh, I. Stukan, D. Butter, P. Stepien, A.S. Feit, J. Bergholz, W. Michowski, T. Otto, Q. Sheng, A. Loo, W. Michael, R. Tiedt, C. DeAngelis, R. Schiff, B. Jiang, B. Jovanovic, K. Nowak, M. Ericsson, M. Cameron, N. Gray, D. Dillon, J.J. Zhao, D.M. Sabatini, R. Jeselsohn, M. Brown, K. Polyak, P. Sicinski, Increased lysosomal biomass is responsible for the resistance of triple-negative breast cancers to CDK4/6 inhibition, Sci Adv 6 (25) (2020) eabb2210.
[222] N.H. Petersen, O.D. Olsen, L. Groth-Pedersen, A.M. Ellegaard, M. Bilgin, S. Redmer, M.S. Ostenfeld, D. Ulanet, T.H. Dovmark, A. Lonborg, S.D. Vindelov, D. Hanahan, C. Arenz, C.S. Ejsing, T. Kirkegaard, M. Rohde, J. Nylandsted, M. Jaattela, Transformation-associated changes in sphingolipid metabolism sensitize cells to lysosomal cell death induced by inhibitors of acid sphingomyelinase, Cancer Cell 24 (3) (2013) 379–393.
[223] P.B. Gupta, T.T. Onder, G. Jiang, K. Tao, C. Kuperwasser, R.A. Weinberg, E. S. Lander, Identification of selective inhibitors of cancer stem cells by high-throughput screening, Cell 138 (4) (2009) 645–659.
[224] A. Versini, L. Colombeau, A. Hienzsch, C. Gaillet, P. Retailleau, S. Debieu, S. Muller, T. Caneque, R. Rodriguez, Salinomycin Derivatives Kill Breast Cancer Stem Cells by Lysosomal Iron Targeting, Chemistry 26 (33) (2020) 7416–7424.
[225] S. Schmidtova, L.C.J. Dorssers, K. Kalavska, A.J.M. Gillis, J.W. Oosterhuis, H. Stoop, S. Miklikova, Z. Kozovska, M. Burikova, K. Gercakova, E. Durinikova, M. Chovanec, M. Mego, L. Kucerova, L.H.J. Looijenga, Napabucasin overcomes cisplatin resistance in ovarian germ cell tumor-derived cell line by inhibiting cancer stemness, Cancer Cell Int 20 (2020) 364.
[226] M. Michalak, M.S. Lach, M. Antoszczak, A. Huczynski, W.M. Suchorska, Overcoming Resistance to Platinum-Based Drugs in Ovarian Cancer by Salinomycin and Its Derivatives-An In Vitro Study, Molecules 25 (3) (2020).
[227] M. Gruber, F. Handle, Z. Culig, The stem cell inhibitor salinomycin decreases colony formation potential and tumor-initiating population in docetaxel-sensitive and docetaxel-resistant prostate cancer cells, Prostate 80 (3) (2020) 267–273.
[228] P. Januszyk, K. Januszyk, M. Wierzbik-Stronska, D. Boron, B. Grabarek, Analysis of the differences in the Expression of mRNAs and miRNAs Asso-ciated with Drug Resistance in Endometrial Cancer Cells Treated with Salinomycin, Curr Pharm Biotechnol (2020).
[229] W. Boehmerle, H. Muenzfeld, A. Springer, P. Huehnchen, M. Endres, Specific targeting of neurotoxic side effects and pharmacological profile of the novel cancer stem cell drug salinomycin in mice, J Mol Med (Berl) 92 (8) (2014) 889–900.
[230] Y. Chen, R. Li, Y. Zhu, S. Zhong, J. Qian, D. Yang, A. Jurczyszyn, M. Beksac, C. Gu, Y. Yang, Dihydroartemisinin Induces Growth Arrest and Overcomes Dexamethasone Resistance in Multiple Myeloma, Front Oncol 10 (2020) 767.
[231] Z. Yao, A. Bhandari, Y. Wang, Y. Pan, F. Yang, R. Chen, E. Xia, O. Wang, Dihydroartemisinin potentiates antitumor activity of 5-fluorouracil against a resistant colorectal cancer cell line, Biochem Biophys Res Commun 501 (3) (2018) 636–642.
[232] Y. Wang, Y. Li, D. Shang, T. Efferth, Interactions between artemisinin derivatives and P-glycoprotein, Phytomedicine 60 (2019), 152998.
[233] D.H. Lee, M. Hasanuzzaman, D. Kwon, H.Y. Choi, S.M. Kim, D.J. Kim, D.J. Kang, T.H. Hwang, H.H. Kim, H.J. Shin, J.G. Shin, S. Oh, S. Lee, S.W. Kim, 10-Phenyltriazoyl Artemisinin is a Novel P-glycoprotein Inhibitor that Suppresses the Overexpression and Function of P-glycoprotein, Curr Pharm Des 24 (46) (2018) 5590–5597.
[234] C. Gai, M. Yu, Z. Li, Y. Wang, D. Ding, J. Zheng, S. Lv, W. Zhang, W. Li, Acetaminophen sensitizing erastin-induced ferroptosis via modulation of Nrf2/heme oxygenase-1 signaling pathway in non-small-cell lung cancer, J Cell Physiol 235 (4) (2020) 3329–3339.
[235] J.L. Roh, E.H. Kim, H. Jang, D. Shin, Aspirin plus sorafenib potentiates cisplatin cytotoxicity in resistant head and neck cancer cells through xCT inhibition, Free Radic Biol Med 104 (2017) 1–9.
[236] T. Sehm, Z. Fan, A. Ghoochani, M. Rauh, T. Engelhorn, G. Minakaki, A. Dorfler, J. Klucken, M. Buchfelder, I.Y. Eyupoglu, N. Savaskan, Sulfasalazine impacts on ferroptotic cell death and alleviates the tumor microenvironment and glioma-induced brain edema, Oncotarget 7 (24) (2016) 36021–36033.
[237] W.H. Yang, Z. Huang, J. Wu, C.C. Ding, S.K. Murphy, J.T. Chi, A TAZ-ANGPTL4-NOX2 Axis Regulates Ferroptotic Cell Death and Chemoresistance in Epithelial Ovarian Cancer, Mol Cancer Res 18 (1) (2020) 79–90.
[238] C. Wu, M.Q. Gong, B.Y. Liu, R.X. Zhuo, S.X. Cheng, Co-delivery of multiple drug resistance inhibitors by polymer/inorganic hybrid nanoparticles to effectively reverse cancer drug resistance, Colloids Surf B Biointerfaces 149 (2017) 250–259.
[239] M.Q. Gong, C. Wu, X.Y. He, J.Y. Zong, J.L. Wu, R.X. Zhuo, S.X. Cheng, Tumor Targeting Synergistic Drug Delivery by Self-Assembled Hybrid Nanovesicles to Overcome Drug Resistance, Pharm Res 34 (1) (2017) 148–160.
[240] M. Gao, J. Deng, F. Liu, A. Fan, Y. Wang, H. Wu, D. Ding, D. Kong, Z. Wang, D. Peer, Y. Zhao, Triggered ferroptotic polymer micelles for reversing multidrug resistance to chemotherapy, Biomaterials 223 (2019), 119486.
[241] K.J. Huang, Y.H. Wei, Y.C. Chiu, S.R. Wu, D.B. Shieh, Assessment of zero-valent iron-based nanotherapeutics for ferroptosis induction and resensitization strategy in cancer cells, Biomater Sci 7 (4) (2019) 1311–1322.
[242] H. Xiong, C. Wang, Z. Wang, Z. Jiang, J. Zhou, J. Yao, Intracellular cascade activated nanosystem for improving ER+ breast cancer therapy through attacking GSH-mediated metabolic vulnerability, J Control Release 309 (2019) 145–157.