Xiang *et al.*
Cellular & Molecular Biology Letters (2024) 29:40
https://doi.org/10.1186/s11658-024-00560-2

Cellular & Molecular Biology Letters

MINI REVIEW Open Access

Role of ferroptosis and ferroptosis-related long non'coding RNA in breast cancer

Shasha Xiang[1,2†], Wen Yan[1†], Xing Ren[2], Jianbo Feng[1*] and Xuyu Zu[1*]

†Shasha Xiang and Wen Yan have contributed equally to this work.

*Correspondence: fengjianbobody@126.com; zuxuyu0108@hotmail.com

[1] Cancer Research Institute, The First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China
[2] Department of Clinical Laboratory Medicine, The First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China

Abstract

Ferroptosis, a therapeutic strategy for tumours, is a regulated cell death characterised by the increased accumulation of iron-dependent lipid peroxides (LPO). Tumour-associated long non-coding RNAs (lncRNAs), when combined with traditional anti-cancer medicines or radiotherapy, can improve efficacy and decrease mortality in cancer. Investigating the role of ferroptosis-related lncRNAs may help strategise new therapeutic options for breast cancer (BC). Herein, we briefly discuss the genes and pathways of ferroptosis involved in iron and reactive oxygen species (ROS) metabolism, including the X_C^-/GSH/GPX4 system, ACSL4/LPCAT3/15-LOX and FSP1/CoQ10/NAD(P)H pathways, and investigate the correlation between ferroptosis and LncRNA in BC to determine possible biomarkers related to ferroptosis.

Keywords: LncRNA, Breast cancer, Ferroptosis, Ferroptosis-related lncRNA, Biomarker

Introduction

The GLOBOCAN 2020 Global Cancer Burden report states that the risk of breast cancer (BC) is higher in women, which is the fourth leading cause of cancer-related deaths worldwide [1]. BC, which can be classified as either invasive or non-invasive [2], is a condition in which various carcinogens act on the breast epithelial cells, resulting in abnormal or uncontrolled proliferation [3]. BC is typically characterised by the presence of breast lumps, nipple discharge and increased/enlarged lymph nodes in the axilla. In advanced stages, cancer cells can metastasise to distant locations, resulting in multi-organ damage and increasing the risk of mortality [4, 5].

Programmed cell death and accidental cell death (ACD) are the two main types of cell death. Accidental attacks and injuries can trigger ACD, outweighing any control mechanism, and are regulated by precise signalling cascades triggered by specific effector molecules with distinct biochemical, functional and immunological effects [6]. The different forms of regulated cell death include apoptosis, necrosis, autophagy and ferroptosis. This study explored ferroptosis as a novel regulatory mode of cell death dependent on iron and lipotoxicity [6, 7], and several genes and pathways are involved in the modulation of iron and reactive oxygen species (ROS) metabolism, including the X_C^-/GSH/GPX4 system and ACSL4/LPCAT3/15-LOX and FSP1/CoQ10/NAD(P)H pathways

© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

[8–10]. Dysregulation of iron metabolism, one of the risk factors for tumours, and the overdependence of cancer cells on iron proliferation promote the growth of tumour cells [11]. Activating ferroptosis in cancer cells is a novel approach to mitigating cancer risk, particularly for those resistant to conventional chemotherapy [12, 13]. Cilamethicin and lapatinib can trigger ferroptosis in BC cells, suggesting that they could serve as viable treatments for BC patients [14]. Nevertheless, studies analysing the relationship between BC and ferroptosis are lacking, and the influence of ferroptosis on the prognosis of patients with BC remains uncertain.

Long non-coding RNAs (lncRNAs) are RNA molecules that are longer than 200 nucleotides and lack the ability to encode proteins [15, 16]. Because of their unique involvement in cancer, lncRNAs have gained considerable attention [17]. Peptides or proteins encoded by tumour-associated lncRNAs increase efficacy and reduce mortality in combination with conventional cancer drugs and radiotherapy [18]. LncRNA-encoded ASRPS contributes to the progression of triple-negative breast cancer (TNBC), whereas the lncRNA HOXB cluster anti-sense RNA 3 (HOXB-AS3) peptide inhibits the growth of colorectal cancer (CRC) [19, 20]. Moreover, lncRNAs regulate ferroptosis in BC [21]. However, existing studies on lncRNAs related to ferroptosis in BC are scarce, and only a few lncRNAs involved in regulating ferroptosis have been identified. However, the recognition of the repetitive molecular mechanisms of lncRNAs has been made possible by emerging technologies that have enhanced the ability of researchers to functionally annotate cancer-related lncRNAs, such as the identification of potential ferroptosis-associated lncRNAs, which can be achieved using high-speed sequencing technologies [22].

This review discusses lncRNAs associated with the activation or inhibition of cellular ferroptosis, which exert anti-cancer effects, thereby providing potential insights for strategising new cancer treatment regimens. However, studies on ferroptosis-related lncRNAs in BC remain limited. Therefore, we briefly discuss the role of ferroptosis in BC, the association between BC and lncRNAs,and identify potential ferroptosis-related lncRNAs in BC.

Ferroptosis: a brief overview

Ferroptosis was first discovered in 2003 and involved the use of erastin to selectively induce cell death in genetically engineered cells with oncogenic RAS mutations, but not in normal cells [23]. Brent Stockwell, in 2012, coined the term ferroptosis for the iron-dependent cell death mode of non-apoptotic RCD induced by erastin [24]. Ferroptosis is a distinct type of regulated cell death mediated by iron and lipotoxicity that has been recently identified. Ferroptosis inhibits the activity of the lipid repair enzyme glutathione peroxidase 4 (GPX4), leading to the accumulation of lipid ROS, particularly lipid hydroperoxides [7]. In terms of genetics, multiple genes regulate ferroptosis. In contrast to other morphological changes associated with cell death, ferroptosis occurs primarily within the cell. This results in smaller mitochondria, increased membrane density, decreased and disappeared cristae, fragmentation of the outer membrane without disruption of the cell membrane and minimal transformation in the morphology of the nucleus without chromatin concentration [24–26]. Biochemically, the phospholipid peroxidase GPX4 primarily contributes to the deficiency in peroxidation repair capacity,

acquisition of reactive iron and oxidation of polyunsaturated fatty acids (PUFA)-containing phospholipids that induce ferroptosis [27]. The intracellular antioxidant capacity decreases and lipid ROS accumulates, ultimately leading to cellular ferroptosis. Glutathione peroxidase is affected by various pathways, such as the X_C^-/GSH/GPX4 system, and the ACSL4/LPCAT3/15-LOX and FSP1/CoQ10/NAD(P)H pathways [8–10] (Fig. 1).

System X_C^-/GSH/GPX4 and ferroptosis

Both impaired elimination and overproduction of lipid peroxide (LPO) during ferroptosis can lead to its accumulation to lethal levels. Cystine availability, glutathione (GSH) biosynthesis and GPX4 function are required to maintain redox homeostasis and protect cells from ferroptosis [24, 28, 29].

System X_C^-/GSH/GPX4 is the antioxidant system that is crucial for ferroptosis [30]. System X_C^- functions as a glutamate–cysteine reverse transporter at the plasma membrane, importing cysteine into the cytosol to facilitate GSH biosynthesis [31]. The inhibition of system X_C^- results in a reduction in the intracellular cysteine pool, which is a precursor for glutathione synthesis [32]. GPX4 is the primary enzyme involved in the reduction and detoxification of phospholipid hydroperoxides (PLOOHs) in mammalian cells [33]; therefore, a general mechanism for the induction of ferroptosis by erastin/RSL3 has been identified. GSH peroxidase 4 inhibitor (RSL3) directly inactivates GPX4, whereas erastin indirectly inactivates it by inhibiting cysteine input, thereby depriving the cells of cysteine, an essential cellular component of GSH. Therefore, the accumulation of PLOOHs may cause rapid and irreversible damage to cell membranes, resulting in cell death.

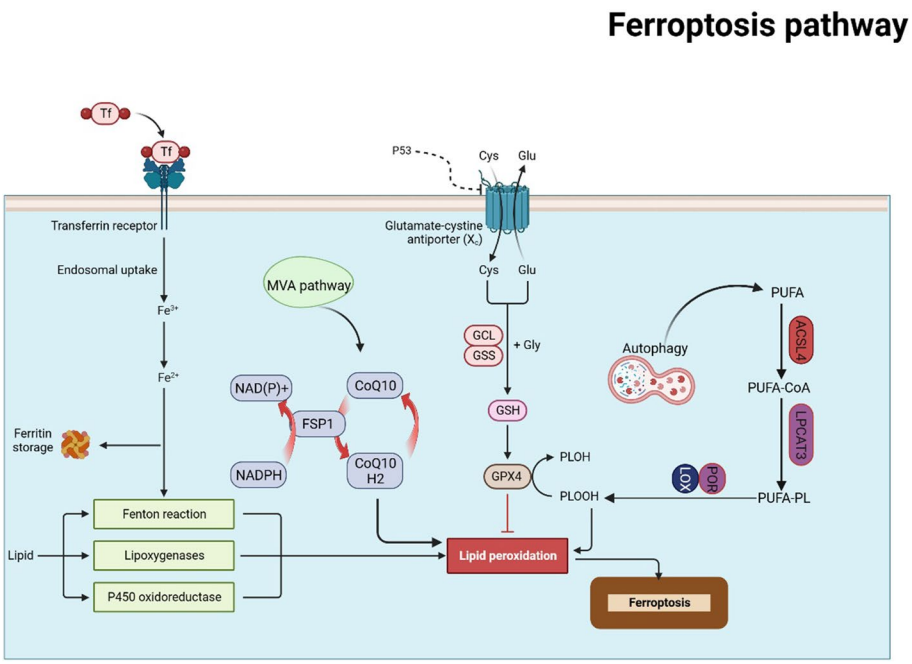

Fig. 1 Ferroptosis pathways. Genes and pathways of ferroptosis involved in the regulation of iron and ROS metabolism, including the system X_C^-/GSH/GPX4, and ACSL4/LPCAT3/15-LOX and FSP1/CoQ10/NAD(P)H pathways. Created with https://www.biorender.com/

GPX4 converts GSH to oxidised glutathione disulphide (GSSG), reduces LPO and maintains cell redox homeostasis [28]. Moreover, GPX4 is the only enzyme that directly reduces hydrogen peroxide from biofilm lipids [34]. Suppressing the system X_C^-/GSH/GPX4 axis results in the accumulation of LPO, thereby leading to ferroptosis; for example, system X_C^- activity is directly inhibited by the ferroptosis inducer erastin, which disrupts redox homeostasis and increases LPO accumulation, leading to ferroptosis [24]. Intracellular and extracellular cysteine are needed to maintain glutathione biosynthesis and inhibit mammalian cell death, which can also be treated with iron sequestrants or hydrophilic antioxidants [35].

ACSL4/LPCAT3/15-LOX with ferroptosis

Clustered regularly interspaced palindromic repeats (CRISPR)–Cas9 and genome-wide haploid-based screening analyses have identified two membrane turnover enzymes: lysophosphatidylcholine acyltransferase 3 (LPCAT3) and acyl-coenzyme A synthase long chain family member 4 (ACSL4) [36, 37] as key drivers of ferroptosis. These enzymes are essential for endogenous iron chain activation through metabolic lipid reprogramming [38]. ACSL4 is a prominent isoenzyme involved in the biometabolism of PUFAs and determines their susceptibility to ferroptosis [39]. Lipid synthesis-mediated production of PUFAs increases the susceptibility to ferroptosis [40]. The entry of PUFAs into phospholipids, a crucial step in ferroptosis, requires ACSL4 [40], which links coenzyme A to long-chain PUFAs, which are then transesterified into phospholipids by several LPCATases, increasing the integration of long-chain PUFAs into lipids and membranes [7].

Elevated ACSL4 expression increases the sensitivity of cells to ferroptosis by optimising the catalysis of several PUFAs, with a strong affinity for arachidonic acid (AA) and adrenaline (AdA). ACSL4 catalyses the conversion of AA and AdA into AACoA and AdA-CoA, respectively, resulting in LPO production. The derivatives were first esterified with LPCAT3 to form phosphatidylethanolamines (AA-PE and AdA-PE), followed by the direct oxidation of their lipid hydrogen peroxide by 15-LOX (ALOX15), which acts as a signal for ferric ions and, ultimately, promotes ferroptosis [31, 36, 41, 42]. Additionally, this process affects the cellular lipid composition [8, 36]. Therefore, ACSL4/LPCAT3/15-LOX may play an important role in the generation of lethal LPOs during ferroptosis.

ACSL4 determines the susceptibility to ferroptosis by modifying cellular lipid composition [36, 43]. The lipoxygenase enzyme, which contains iron, promotes cell death by producing LPO via lipid biosynthesis in ACSL4 [40]. ACSL4, a target of miR-424-5P, is upregulated in ovarian cancer (OC) and inhibits OC cell ferroptosis [44]. The inhibition of ACSL4 expression may be the primary mechanism that renders cells insensitive to iron leaps.

FSP1/CoQ10/NAD(P)H with ferroptosis

Apoptosis-inducing factor mitochondria-associated 2 (AIFM2), a member of the apoptosis-inducing factor (AIF) family, is involved in oxidoreductase function and can induce programmed cell death [45]. Recently, AIFM2 was recognised as an anti-iron porphyrin gene and was later renamed ferrocyte apoptosis suppressor protein 1 (FSP1). FSP1

inhibits iron through ubiquitin ketone (CoQ10), a reductant that scavenges the lipid peroxyl radicals responsible for lipid peroxidation. The use of FSP1 as a pharmacological target in combination with GPX4 inhibitors induces ferroptosis in various tumour types [46].

CoQ10 plays key roles in the mevalonate (MVA) pathway; regulating the MVA pathway could be a possible strategy for controlling the course of ferroptosis [47]. Following cardamoylation, FSP1 is recruited to the plasma membrane, where it acts as an oxidoreductase to catalyse the generation of ubiquitin from CoQ10 via NADPH. As a lipophilic anti-radical catcher, NADPH decreases LPO levels [46, 48]. Therefore, FSP1/CoQ10/NAD(P)H acts synergistically with GPX4 and GSH to protect against phospholipid peroxidation and ferroptosis [46].

Other genes and pathways for ferroptosis

P53 mediates cell cycle pausing, senescence and apoptosis, and its inactivation is a key factor in the formation of most tumours; therefore, the p53 gene is considered a potential tumour suppressor gene. Additionally, P53 is involved in various metabolic activities [49]. P53 downregulates the expression of solute carrier family 7 member 11 (SLC7A11) and inhibits the systemic uptake of cystine through GPX4 activity. This leads to reduced cellular antioxidant capacity and the accumulation of lipid ROS, resulting in ferroptosis [49, 50].

In addition, autophagy contributes to ferroptosis. Although ferroptosis can lead to the lipid peroxidation of plasma membranes, the major membrane modulator proteins remain unclear [51, 52]. Autophagy removes a wide range of components by forming dynamic membrane structures, such as phagosomes, autophagic vesicles and autophagosomes [53]. However, excessive autophagic activity mediates ferroptosis [54]. Autophagy facilitates swift, non-apoptotic, non-necrotic cell death during amino acid starvation. This condition triggers potent autophagy, but only if sufficient serum is provided in the culture medium, as it requires iron-supporting transferrin and the amino acid glutamine in saline. Death is triggered by cysteine deficiency in the cell growth media, which could be attributed to ferroptosis [55]. Autophagy is implicated in cysteine deprivation and is sensitised to ferroptosis through the autophagic degradation of ferritin, which is also termed ferritin autophagy, leading to increased levels of unstable iron in cells [56, 57]. For instance, HPCAL1 (hippocampalin-like protein 1) is a novel autophagic receptor that selectively degrades CDH2 (calbindin 2) during ferroptosis. HPCAL1 facilitates ferroptosis through its non-canonical role in autophagy. The CDH2/*N*-calbindin protein is a straightforward substrate for HPCAL1-dependent autophagic degradation and triggers ferroptosis by compromising membrane tension [52, 58].

In addition, methods for inducing or inhibiting ferroptosis have been extensively studied. For instance, glucose starvation inhibits ferroptosis [59, 60], whereas arachidonic acid enhances RSL3-mediated ferroptosis in mouse foetal fibroblasts[38]. Other signalling pathways that regulate cellular ferroptosis, such as Keleh-like ECH-associated protein 1 (Keap1), nuclear factor red lineage-associated factor 2 (Nrf2) and lymphoid tissue-specific deconjugating enzyme (LSH), have also been identified. Furthermore, EgI nine homologue 1 (EGLN1)/cellular myeloid cell tumour proto-oncogene (c-Myc),

sulphur transfer, mucin 1C-terminal (MUC1-C)/ systemic X_C^- (xCT) and heat-shock factor-1 (HSF1)/heat-shock protein beta 1 (HSPB1) pathways mediate ferroptosis [61].

Association between ferroptosis and BC

Ferroptosis has been implicated in the pathological processes of several disorders, such as neurological disorders, blood disorders, kidney damage, ischaemia–reperfusion injury and tumours. However, the natural mechanisms underlying the induction of ferroptosis under these conditions remain unclear. Ferroptosis is an oxidative stress-induced cell death process that is closely associated with cellular metabolism. Cancer cells, which have a more active metabolism and a higher ROS load, may have a stronger tendency towards ferroptosis. Because cellular ferroptosis inhibits tumour growth, targeting ferroptosis pathways could be a promising anti-cancer strategy [27]. In addition, ferroptosis occurs during cancer treatment. For example, low-density lipoprotein (LDL)–docosahexaenoic acid (DHA) nanoparticles and sorafenib induce ferroptosis in hepatocellular carcinoma cells [9, 62]. Cysteine dioxygenase 1 (CDO1) modulates erastin in vitro in gastric cancer cells [63], whereas cisplatin and dipeptidyl peptidase-4 (DPP4) regulate erastin-induced ferroptosis in colorectal cancer [64, 65]. Piperonylamine (PL), cyclophosphamide (CNA), liuzasulfapyridine combination, cottonin A (CN-A), phenethyl isothiocyanate (PEITC) and artesunate (ART) induce ROS generation, activation and ferroptosis in pancreatic cancer cell lines to inhibit proliferation [66, 67]. Erastin upregulates and activates P53, inhibits the activity of SLC7A11 and induces ferroptosis in lung cancer cells [68].

Cellular ferroptosis is recognised as a key mechanism by which certain chemotherapeutic agents induce cell death in cancer cells [65, 69]. BC is a diverse tumour; based on the hormone receptors (ER and PR) and HER2 (ERBB2) signatures, BC is clinically classified into three main subtypes: TNBC, tubular ER^+ and PR^+, and $HER2^+$ [3, 70, 71]. The National Comprehensive Cancer Network (NCCN) recommendations recommends endocrine therapy for ER^+ BC and anti-HER2-targeted therapy for $HER2^+$ BC. Targeted therapies for TNBC are currently lacking [72]. Although the potential benefits of inducing ferroptosis in tumour therapy have been suggested, the genes related to ferroptosis have not been extensively studied in BC patients [73].

Treatment of TNBC remains challenging, and identifying the coordinated role of pathways in regulating ferroptosis will provide a fresh impetus for a therapeutic strategy for TNBC. TNBC was more sensitive to ferroptosis than ER^+ BC [36]. TNBC can be divided into four categories: mesenchymal-like subtype (MES), luminal androgen receptor (LAR) subtype, immunomodulatory subtype (IM) and basal-like immunosuppressive subtype (BLIS) subtypes. The LAR subtype can induce ferroptosis using GPX4 inhibitors. This subtype is characterised by the upregulation of the oxidised phosphatidylethanolamine and glutathione metabolism (in particular, GPX4). Furthermore, inhibition of GPX4 not only leads to tumour ferroptosis but also enhances anti-tumour immune function [74]. By signalling epithelial-to-mesenchymal transition, MES cells can promote the activity of iron-connected molecules (as transferrin receptor 1, ferritin) and enhance iron uptake, storage and utilisation [10, 75]. Notably, this process is not limited to cancer cells but can also occur in non-cancerous cells. MES is characterised by an MES state enriched in iron metabolic pathways but lacking fatty acid (FA) metabolism

and ROS pathway activity, indicating that, compared with LAR, MES subtypes are more susceptible to ferroptosis [76, 77]. Both IM and BLIS are characterised by typical stromal-like tumours in the presence of ferroptotic area [74].

One finding demonstrated that GPX4 expression was lower in BC MCF7 and MDA-MB-231 cell lines than in non-BC MCF10A cell lines [78], and that GPX4 expression was positively correlated with ER and PR labelling [79]. GPX4 may exert anti-tumour activity and reflect an improved differentiation phenotype in BC [73]. Erastin targets MDA-MB-231 cells selectively and effectively induces ferroptosis in TNBC cells [80].

Notably, ACSL4 expression levels in a subpopulation of TNBC cell lines were correlated with their sensitivity to ferroptosis reagents. This correlation appears to be similar to that observed in the treatment of refractory mesenchymal carcinoma cells and clear cell renal carcinoma cells [7]. ACSL4 is elevated in BC tissues compared with in healthy tissues adjacent to the cancer, and ACSL4 expression is negatively correlated with ER [81, 82]. Clinically, radiotherapy upregulates the expression of ACSL4, resulting in increased lipid synthesis and, consequently, oxidative injury, leading to ferroptosis [83]. High expression of ACSL4 promotes BC aggressiveness, is a potential prognostic indicator and therapeutic target [82], and plays a substantial role in radiation resistance in BC by modulating the expression of transporter proteins implicated in cancer resistance via the mTOR pathway and regulating forkhead box protein M1 (FOXM1) [84].

These findings indicate that ferroptosis may be an essential adaptation process for eradicating cancer cells [85].

Role of lncRNAs in BC

LncRNAs are RNA molecules that are ˃ 200 nucleotides long and lack the ability to encode proteins [86]. They are widely present in humans and are critical in regulating human gene expression and physiological and pathological processes [87]. LncRNAs can be broadly classified into the following three types: direct linking to DNA or transcription factors at the transcription level; binding of mRNAs, miRNAs or proteins to modulate their activity and steady state in a post-transcriptional manner; and interference with the chromatin complex to activate or suppress gene expression in an epigenetic manner [86, 88–90].

The mammalian genome contains numerous lncRNAs. A small but increasing number of these lncRNAs have functional profiles in various processes and diseases, such as infection, innate immunity and acquired immunity [91–96]. Cancer is a genetic disease that involves an alteration in the flow of information within the cell to alter cellular homeostasis and promote growth [22]. Non-coding RNAs regulate inter- and intracellular signalling in BC [97]. LncRNA-encoded peptides affect BC cells [98]. For instance, the micropeptide CIP2A-binding peptide (CIP2A-BP) encoded by LINC0665 is highly correlated with the survival of BC recipients. Poor CIP2A-BP expression is associated with low survival in BC patients. In addition, CIP2A-BP levels in patients with metastatic BC were markedly lower than in those without metastasis. Both the introduction of the CIP2A-BP gene and direct infusion of the CIP2A-BP micropeptide markedly attenuated lung metastasis and improved overall survival, suggesting that the micropeptide CIP2A-BP suppressed the migration and invasion of TNBC cells [99]. LINC00908

encodes ASRPS, a potential anti-cancer micropeptide that is endogenously expressed and downregulated in TNBC and inhibits tumour angiogenesis in BC [19].

Several lncRNAs that promote BC development have been identified and their functions have been investigated. This information can aid in the diagnosis, prognostic judgement, pathogenesis prediction and therapeutic intervention for BC (Table 1).

LncRNAs that inhibit BC development

NKILA, NEF,GAS5, MT1JP, LET, LncKLHDC7B and TFAP2A-AS1 prevent BC cell invasion and migration; NLIPMT, XIXT, MALAT1 and MEG3 inhibit distant metastasis in BC cells [100].

LINC02273 knockdown inhibits BC metastasis [101]. LncRNA GAS5 is frequently downregulated in several cancers. In BC, GAS5 activates several proteins, including DKK2, PTEN, SUFU, PDCD4 and FOXO1, via various miRNA-mediated competing endogenouse RNA (ceRNA) mechanisms. These mechanisms involve miR-196a-5p, miR-21, miR-221-3p, miR-222 and miR-378a-5p, which bind to multiple microRNA response elements (MREs) in GAS5 to upregulate the expression of BC suppressor proteins. Furthermore, through epigenetic and other mechanisms, GAS5 may enhance the sensitivity to several drugs and improve prognosis [102].

LncRNAs that promote BC development

Several lncRNAs that affect the invasiveness, proliferation and apoptosis of BC cells have been identified. For instance, LINC00461, DANCR, H19, HOX transcriptional anti-toxic intergenic RNAs (HOTAIR), LINC00152, LINC01857 and NEAT1 facilitate BC cell invasion and migration; and HOTAIR, H19, MALAT1, RP1 and HIF1A-AS2 promote BC cell long-distant metastasis. LncRNAs, including H19 [103], PRNCR1, HOTAIR [104], LSINCT5 [105], SRA [106], Smad7 [107], NEAT1 [108], LINC01296 [109] AFAP1-AS1 [110], GHET1 [111], BRAF [112] and SNHG12 [113] promote cell proliferation and inhibit apoptosis in BC. Some lncRNAs can promote BC cell resistance, such as UCA1 [114], CRALA [115], lnc-ATB [116], LINC00518 [117] and DSCAM-AS1 [118].

H19 is located in the human genome downstream of IGF2, and its levels are elevated in a variety of cancers, notably BC, promoting BC cell proliferation [103, 119]. H19 expression is significantly upregulated in tamoxifen-refractory BC cell lines and tissues, and silencing of H19 in MCF7/TAMR cells is sensitive to tamoxifen therapy in vivo and in vitro [120]. Metformin may cause ferroptosis in BC by blocking autophagy in H19 [121]. UCA1 inhibits p27, which partially contributes to its oncogenic role in BC. Overexpression of UCA1 is overexpressed causes hnRNP I in the cytoplasm to be recruited to UCA1, reducing the access of p27 to hnRNP I, inducing a cell cycle pause in the G1 stage; therefore, UCA1 could be a potential biomarker for BC diagnosis [122].

HOTAIR, a new type of lncRNAs belonging to a subclass of intergenic lncRNAs tightly regulates genes related to mammalian embryonic development [123]. HOTAIR expression is highly upregulated in BC, and silencing HOTAIR induces apoptosis and prevents cell proliferation. The mechanism of action involves linking miRNA and post-transcriptional networks to promote BC development [123, 124]. For instance, HOTAIR acts as a mediator between frizzled homologue 7 (FZD7) and miR-129-5p, and promotes epithelial–mesenchymal transition and metastasis,

Table 1 Role of various lncRNAs in breast cancer

LncRNA	Regulation	Work	References
HOTAIR	–	Potential metastatic, drug-resistant and prognostic regulators of BC; highly predictive of metastatic disease progression and overall survival	[123, 127]
	miR-206	Enhances BC cell proliferation	[129]
	Chondroitin sulfate	Enhances BC cell invasion	[130]
	miR-203/CAV1 axis	Influences BC cell migration, proliferation and invasion	[104]
	miR-20a-5p/HMGA2 axis	Influences BC cell apoptosis, growth, migration and invasion	[131]
	miR-129-5p/FZD7 axis	Promotes BC	[125]
UCA1	miR-375	Inhibits BC progression	[132]
RP11-19E11	E2F1	Proliferation and survival of basal BC	[133]
LINC00963	miR-324-3p/ ACK1	Promotes tumourigenesis and radiation resistance in BC	[134]
LINC00899	miR-425	Inhibits BC cell migration, proliferation and invasion	[135]
LINC01787	niR-125b	Promotes BC cell growth, proliferation and migration of BC xenografts	[136]
NKILA	IκB	Inhibits BC metastasis	[137]
Gas5	–	Sensitizes BC cells to ionising radiation by inhibiting DNA repair	[138]
NORAD	PUM1/Eif2 axis	Inhibits BC progression	[139]
	TGFβ	High expression is indicative of poor prognosis	[140]
	YAP pathway	Inhibits BC metastasis	[141]
BCRT1	miR-1303/PTBP3 axis	Promotes BC progression	[142]
SEMA3B-AS1	miR-3940/KLLN axis	Inhibits BC progression	[143]
NR2F1-AS1	IGF-1/IGF-1R/ERK pathway	Promotes angiogenesis in BC	[144]
BC069792	KCNQ4	Inhibits tumour progression in BC	[145]
SNHG1	macrophage M2-like polarization	Promotes BC growth and metastasis	[146]
GHET1	EMT	Promotes BC cell proliferation, invasion and migration	[111]
PRNCR1	microRNA-377/CCND2/MEK/MAPK axis	Promotes BC proliferation and inhibit apoptosis	[147]
NEAT1	miR-133b	Promotes migration and invasion of BC cells	[148]
NEF	–	Downregulated expression is suggestive of poor prognosis	[149]
TPA	TGFβ	Promotes BC invasion and metastasis	[150]
ERINA	E2F1/RB1 pathway	Inhibits cell-cycle progression and tumour cell proliferation	[151]
LCPAT1	MFAP2	Promotes BC progression	[152]
PlncRNA-1	TGFβ1, PHGDH	Inhibits the growth of BC	[153]
ITGB2-AS1	ITGB2	Promotes BC migration and invasion	[154]
RP1-5O6.5	KLF5	Promotes growth and metastasis of BC	[155]
LSINCT5	–	Promotes BC cell proliferation	[105]
LncRNA-CDC6	microRNA-251	Promotes BC progression and function as ceRNA	[156]
MALAT1	miR-497-5p/SHOC2 axis	Regulates the paclitaxel resistance of BC	[157]
	–	Overexpression inhibits BC metastasis in transgenic, xenograft and homologous models	[158]

Table 1 (continued)

LncRNA	Regulation	Work	References
Uc003xsl.1	NFκB/IL8 axis	Promotes progression of TNBC, growth and metastasis	[159]
CARMN	miR143-3p	Promotes prognosis and chemosensitivity of TNBC	[160, 161]
BREA2	Notch signalling	Drivers of metastasis in BC	[162]
DIO3OS	PTBP1, LDHA	Correlated with a worse prognosis in BC patients on AI therapies	[163]
KB-1980E6.3	lncRNA KB-1980E6.3/IGF2BP1/c-Myc axis	Maintain the stemness of BC stem cells	[164]
BORG	TRIM28, BORG	Drives BC metastasis and disease recurrence; elicits the metastatic outgrowth of latent BC cells	[165]
EPB41L4A-AS1	–	Regulates cell metastasis, proliferation and apoptosis in BC	[166]
FOXD3-AS1	miR-127-3p	Affects BC cell proliferation, migration, invasion and growth	[167]
LGALS8-AS1	miR-125b-5p/SOX12	Promotes BC metastasis	[168]
CASC15	miR-654-5p/MEF2D axis	Regulates BC cell stemness	[169]
GHET1	–	Knockdown suppresses BC activity	[170]
DUXAP8	PI3K/AKT/mTOR pathway, EZH2-E-cadherin/ RHOB axis	Promotes radiation resistance in BC	[171]
RP11-214F16.8	SENP3	Drives BC tumourigenesis	[172]
MIR17HG	miR-454-3p	Suppresses BC cell proliferation and migration	[173]
EGOT	Hedgehog pathway	Decreases BC cell viability and migration	[174]
SNHG6	miR-26a/VASP axis	Silencing suppresses proliferation and invasion of BC cells	[175]
SNHG8	miR-634/ZBTB20 axis	Serves as an oncogene in BC	[176]
PVT1	miR-145-5p	Influences glycolysis in BC cells	[177]
APOC1P1-3	miRNA-188-3p	Promotes metastasis in BC	[178]
FGD5-AS1	has-miR-195-5p/NUAK2 axis	Promotes BC progression	[179]
FBXL19-AS1	miR-718	Promotes proliferation and invasion of BC cells	[180]
PTCSC3	lncRNA H19	Inhibits TNBC cell proliferation	[181]

leading to BC progression. HOTAIR knockdown inhibited tumour growth in a xenograft mode, whereas killing of miR-129-5p reversed the silencing function of HOTAIR and FZD7 restored the suppressive function of miR-129-5p, suggesting that HOTAIR controls the miR-129-5p/FZD7 axis [125]. HOTAIR further facilitates BC metabolism by targeting miR-601 via a sponge mechanism to control AKT signalling, which is dependent on zinc finger E-box binding homology box 1 (ZEB1) [126]. HOTAIR overexpression in surgically resected early stage BC is a strong predictor of metastatic disease progression and overall survival [127].

The significance of cell signalling pathways in tumourigenesis, tumour progression and metastasis cannot be overlooked. LncRNAs affect aspects of tumourigenesis by participating in or interfering with these pathways and, consequently, they exhibit either an oncogenic or a tumour-suppressive role [128].

Ferroptosis-associated lncRNAs in BC

Diverse physiological conditions and pathological stressors trigger ferroptosis in humans and animals [24]. Ferroptosis has been increasingly recognised as an adaptive feature in the elimination of malignant tumours. The immune system plays a crucial role in the suppression of tumourigenesis, by removing cells that have been damaged by infection, environmental stress or a lack of key nutrients [182]. The classical oxidative stress pathway is an important therapeutic element that may contribute to ferroptosis. Despite the delicate balance between thiols and catalytic iron in cancer cells under sustained oxidative stress, this process occurs infrequently during cancer progression. However, the underlying molecular mechanisms remain unclear [13].

Abnormally expressed lncRNAs typically affect disease progression by regulating transcription and translation and can also influence cancer progression through the regulation of ferroptosis. The cytoplasmic lncRNA P53RRA in lung adenocarcinoma cancer cells binds to the structural portion of the Ras GTPase-activating protein-binding protein 1 (G3BP1) RNA recognition motif (RRM), leading to nuclear segregation of P53 and retained P53 in the nucleus and accumulation of lipid ROS in the nucleus, subsequently leading to cellular ferroptosis [21]. LncRNA LINC00618-induced ferroptosis increases lipid ROS and iron levels, and lowers SLC7A11 expression [183]. LncRNA GABPB1-AS1 modulates erastin-induced GABPB1 ferroptosis in HepG2 hepatoma cells [184]. Similarly, the GSK3β/Nrf2 signalling pathway is implicated in BC, which increases Nrf2 expression to counteract ferroptosis [185]. In addition, prominence protein 2 (PROM2) could reduce ferroptosis in BC cells and facilitate tumour progression by encouraging iron transport [186]. Because only specific lncRNAs are associated with ferroptosis, existing studies on ferroptosis-associated lncRNAs in BC are scarce.

RNA-sequencing data and one-way COX regression analyses in BC patients have led to the identification of 231 lncRNAs which affects the prognosis; 293 genes associated with ferroptosis were also downloaded from the Ferroptosis Database [187]. Furthermore, 11 lncRNAs (AC092916.1, L133467.1, USP30-AS1, AC108474.1, LINC01235, AL365356.1, AC072039.2, AC012213.3, LIPE-AS1, MAPT-AS1 and TDRKHAS1) that were significantly different were identified. Among them, lncRNA USP30-AS1 was co-expressed with nine ferroptosis-linked genes (SOCS1, CAPG, IFNG, PML, TNFAIP3, NCF2, SLC2A6, GCH1 and CYBB), suggesting that overexpression of USP30-AS1 in BC is associated with prolonged overall survival. LncRNA LIPE-AS1 interacts with five ferroptosis genes (GPX4, PHKG2, EGLN2, MAPK14 and HRAS), and improves the prognosis of BC patients. AC108474.1 interacts with five ferroptosis-related genes (HIC1, ISCU, PLIN4, CAV1 and TAZ), suggesting that AC108474.1 is also a protective factor for BC patients [188].

LncRNA HCP5 regulates baculoviral IAP repeat-containing 3 (BIRC3) by sponging miR-219a-5p as a ceRNA and promotes TNBC progression [189]. Moreover, the amino acid encoded by HCP5, HCP5-132aa promotes the malignant progression of TNBC through its dependence on GPX4 and lipid ROS levels. RNA sequencing results showed that silencing of the HCP5-132 amino acid (aa) open reading frame (ORF) resulted in an enrichment of differentially expressed genes (DEGS) associated with the ferroptosis pathway (which had a positive impact on intracellular Fe homeostasis, progesterone metabolic processes and cell proliferation), suggesting that disturbances in ferroptosis,

progesterone metabolism and cell proliferation may affect BC development [190]. This resulted in an increase in the mitochondrial membrane density and a reduction in the mitochondrial cristae, with effects similar to those of erastin. In contrast, overexpression of HCP5-132aa ORF inhibited erastin-induced changes in mitochondrial morphology. Moreover, silencing of HCP5-132aa, along with the elevation of ROS levels when cells were primed with the ferroptosis enhancers RSL3 and erastin, was also counteracted by ferroptosis inhibitors and upregulation of HCP5-132aa. Furthermore, excessive expression of HCP5-132aa was associated with a worse patient prognosis, suggesting that HCP5-132aa might be a prognostic factor in TNBC [191] (see Fig. 2).

Knockdown of RUNX1 intronic transcript 1 (RUNX1-IT1), a newly identified lncRNA that plays a key role in breast carcinogenesis, was significantly overexpressed in human BC tissues, inhibited BC cell survival and invasion, and suppressed tumour growth in an in situ transplantation model. Furthermore, RUNX1-IT1 inhibited ferroptosis by increasing GPX4 expression. RUNXI-IT1 specifically binds directly to the *N*6-methyladenosine M6A reader, IGF2BP1, and promotes the assembly of the IGF2BP1 liquid–liquid phase (LLP) biomolecule condensate site, resulting in IGF2BP1 greater occupancy of GPX4 mRNA and increased GPX4 mRNA stability. The elevated GPX4 expression prevent lipid peroxidation and ferroptosis, thereby promoting BC development, which indicates that the abnormal regulation of RUNX1-IT1/IGF2BP1/GPX4 is associated with BC development [192].

Ferroptosis-associated lncRNAs can serve as prognostic indicators for constructing a prognostic map of BC based on early warning signs, treatment goals and the anti-tumour immune microenvironment of BC to guide clinical therapy. A previous study screened 11 lncRNAs associated with ferroptosis from the TCGA dataset and built a prognostic map. Based on differences in the expression levels of ferroptosis-associated lncRNAs in tissues from BC patients and healthy tissues, patients were grouped into high- and low-risk clusters. In this study, three genes, lncRNAs YTHDF3-AS1, AC079298.3 and AC012213.3, which are overexpressed in at-risk populations, were screened, indicating

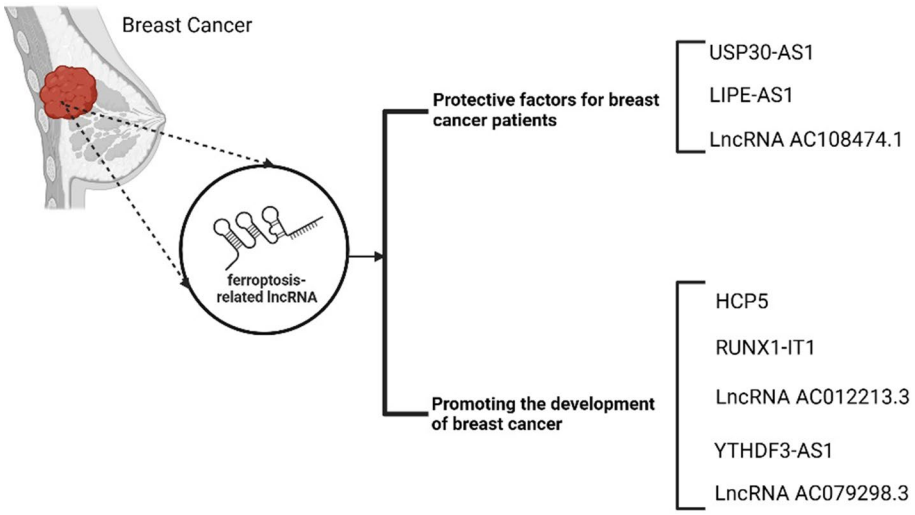

Fig. 2 Ferroptosis-related lncRNAs in breast cancer. Created with https://www.biorender.com/

that they may be at-risk oncogenes for BC. In addition, lncRNA NC012213.3, a downstream molecule of AC012213.3, and overexpressed LncRNA AC012213.3 promotes BC multiplication, invasion and invasiveness through the RAD54B/PI3K/AKT axis and is associated with poor patient outcomes [193]. However, studies on YTHDF3-AS1 and AC079298.3 are limited and require further investigation. To date, lncRNA-associated ferroptosis particularly its association with BC has not been documented, warranting further research to identify new therapeutic targets for BC [190].

Conclusions

Our study has comprehensively elucidated the underlying mechanism of ferroptosis in relation to BC, providing potential insights for strategising new approaches for antitumour therapy. Ferroptosis occurs when there is an imbalance between the detoxification and accumulation of lipid hydroperoxides [194]. A stressful environment can cause an imbalance in lipid ROS accumulation, which contributes to ferroptosis [195]. Cancer cells typically promote survival and metastasis by resisting ferroptosis. Certain drugs used in BC treatment [196], such as cyclophosphamide, tamoxifen, paclitaxel and anthracycline, may induce excessive ROS generation, resulting in cell death [197–200]. LncRNAs are common transcription products in human and mammalian genomes. The roles of certain lncRNAs in tumourigenesis and tumour development have gained considerable attention, with established functions elucidated in primary studies. The disclosure of the universal genetic code has enabled researchers to identify defects in functional proteins; however, understanding the impact of lncRNA biology on cellular function remains challenging using existing predictive frameworks [22]. Owing to their enhanced efficiency, tissue specificity and stability, lncRNAs have the potential to be initial diagnostic and therapeutic targets [190].

Therefore, understanding the relationship between lncRNAs and ferroptosis, as well as their regulatory mechanisms in BC, can be beneficial for the development and therapy of this disease. Our findings demonstrated that lncRNA HCP5 encodes a novel protein, HCP5-132aa, and promotes TNBC growth by controlling GPX4 and inhibiting ROS levels, ultimately inhibiting ferroptosis. Patients with TNBC who overexpress HCP5-132aa typically have worse disease characteristics and prognoses [191]. Ferroptosis-associated lncRNAs may play a prognostic role in BC, enabling the construction of a prognostic model for screening markers, therapeutic targets, evaluating the anti-tumour immune microenvironment and guiding clinical therapy [190]. Nevertheless, future studies investigating the correlation between lncRNAs and ferroptosis and their underlying mechanisms in BC are warranted.

Abbreviations

AA	Arachidonic acid
ACD	Accidental cell death
ACSL4	Acyl-Coenzyme A synthase long chain family member 4
AdA	Adrenaline
AIF	Apoptosis-inducing factor
AIFM2	Apoptosis-inducing factor mitochondria-associated 2
ALOX15	AdA-PE to lipid hydroperoxides by 15-LOX
ART	Artesunate
BC	Breast cancer
BIRC3	Baculoviral IAP repeat containing 3
BLIS	Basal-like immunosuppressive subtype

CAN	Cyclophosphamide
CCTs	Circulating tumor cells
CDH2	Calbindin 2
CDO1	Cysteine dioxygenase 1
CRC	Colorectal cancer
CIP2A-BP	CIP2A-binding peptide
c-Myc	Cellular myeloid cell tumor proto-oncogene
CNA	Combination of cottonin A
CoQ10	Ubiquitin ketone
DHA	Docosahexaenoic acid
DPP4	Dipeptidyl peptidase-4
EGLN1	Egl nine homologue 1
FA	Fatty acid
FINs	Ferroptosis inducers
FOXM1	Forkhead box protein M1
FSP1	Ferrocyte apoptosis suppressor protein 1
FZD7	Frizzled homolog 7
Gas5	Growth inhibitory specific 5
GPX4	Glutathione peroxidase 4
GSH	Glutathione
GSSG	Glutathione disulphide
G3BP1	Ras GTPase-activating protein-binding protein 1
HOTAIR	HOX transcriptional anti-sense intergenic RNAs
HPCAL1	Hippocampalin-like protein 1
HSF-1	Heat-shock factor-1
HSPB1	Heat-shock protein beta 1
IM	Immunomodulatory subtype
Keap1	Keleh-like ECH-associated protein 1
LAR	Luminal androgen receptor subtype
LDHA	Lactate dehydrogenase a
LDL	Low-density lipoprotein
LncRNA	Long non-coding RNA
LLP	Liquid–liquid phase
LOXs	Lipoxygenases
LPO	Lipid peroxide
LPCAT3	Lysophosphatidylcholine acyltransferase 3
LSH	Lymphoid tissue-specific deconjugating enzyme
MES	Mesenchymal-like subtype
MEG3	Maternal expression 3
MUC1-C	Mucin 1C-terminal
MVA	Mevalonate
NCCN	National Comprehensive Cancer Network
Nrf2	Nuclear factor red lineage-associated factor 2
OC	Ovarian cancer
PEITC	Phenethyl isothiocyanate
PL	Piperonylamine
PLOOH	Phospholipid hydroperoxides
PROM2	Prominence protein 2
PTBP1	Polypyrimidine tract-binding protein 1
PUFA	Polyunsaturated fatty acids
RCD	Programmed cell death
ROS	Reactive oxygen species
RRM	RNA recognition motif
RUNX1-IT1	RUNX1 intronic transcript 1
RSL3	GSH peroxidase 4 inhibitor
SLC7A11	Solute carrier family 7 member 11
TGF	Transforming growth factor
TNBC	Triple-negative breast cancer
xCT	Systemic X_C^-
ZEB1	Zinc finger E box-binding homology box 1

Acknowledgements
Not applicable.

Author contributions
SX and WY collected relevant literature and received and drafted the manuscript. XR summarized the figures and tables. XZ and JF reviewed the manuscript and revised it. All authors contributed to the manuscript and approved its submission.

Funding
This study was supported by grants from Postgraduate Scientific Research Innovation Project of Hunan Province (CX20230955), the National Natural Science Foundation of China (no. 82103171, Jianbo Feng) and the Natural Science

Foundation of Hunan Province (no. 2022JJ70121, Xing Ren) and the Clinical Medical Research "4310" Program of the University of South China (20224310NHYCG07).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 18 December 2023 Accepted: 15 March 2024
Published online: 26 March 2024

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
2. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017;50:33.
3. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet (London, England). 2021;397:1750–69.
4. Alkabban FM, Ferguson T. Breast Cancer, StatPearls, StatPearls Publishing Copyright © 2023. Treasure Island: StatPearls Publishing LLC.; 2023.
5. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J, Cardoso F. Breast cancer. Nat Rev Dis Primers. 2019;5:66.
6. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019;29:347–64.
7. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22:266–82.
8. Li D, Li Y. The interaction between ferroptosis and lipid metabolism in cancer. Signal Transduct Target Ther. 2020;5:108.
9. Louandre C, Marcq I, Bouhlal H, Lachaier E, Godin C, Saidak Z, François C, Chatelain D, Debuysscher V, Barbare JC, Chauffert B, Galmiche A. The retinoblastoma (Rb) protein regulates ferroptosis induced by sorafenib in human hepatocellular carcinoma cells. Cancer Lett. 2015;356:971–7.
10. Wu J, Minikes AM, Gao M, Bian H, Li Y, Stockwell BR, Chen ZN, Jiang X. Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling. Nature. 2019;572:402–6.
11. Manz DH, Blanchette NL, Paul BT, Torti FM, Torti SV. Iron and cancer: recent insights. Ann NY Acad Sci. 2016;1368:149–61.
12. Hassannia B, Vandenabeele P, Vanden Berghe T. Targeting ferroptosis to iron out cancer. Cancer Cell. 2019;35:830–49.
13. Mou Y, Wang J, Wu J, He D, Zhang C, Duan C, Li B. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol. 2019;12:34.
14. Ma S, Henson ES, Chen Y, Gibson SB. Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells. Cell Death Dis. 2016;7: e2307.
15. Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. Nature. 2012;482:339–46.
16. Safi A, Saberiyan M, Sanaei MJ, Adelian S, Davarani Asl F, Zeinaly M, Shamsi M, Ahmadi R. The role of noncoding RNAs in metabolic reprogramming of cancer cells. Cell Mol Biol Lett. 2023;28:37.
17. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL, Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458:223–7.
18. Wu P, Mo Y, Peng M, Tang T, Zhong Y, Deng X, Xiong F, Guo C, Wu X, Li Y, Li X, Li G, Zeng Z, Xiong W. Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. Mol Cancer. 2020;19:22.
19. Wang Y, Wu S, Zhu X, Zhang L, Deng J, Li F, Guo B, Zhang S, Wu R, Zhang Z, Wang K, Lu J, Zhou Y. LncRNA-encoded polypeptide ASRPS inhibits triple-negative breast cancer angiogenesis. J Exp Med. 2020;217:e20190950.
20. Huang JZ, Chen M, Chen D, Gao XC, Zhu S, Huang H, Hu M, Zhu H, Yan GR. A peptide encoded by a putative lncRNA HOXB-AS3 suppresses colon cancer growth. Mol Cell. 2017;68:171-184.e176.
21. Mao C, Wang X, Liu Y, Wang M, Yan B, Jiang Y, Shi Y, Shen Y, Liu X, Lai W, Yang R, Xiao D, Cheng Y, Liu S, Zhou H, Cao Y, Yu W, Muegge K, Yu H, Tao Y. A G3BP1-interacting lncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53. Can Res. 2018;78:3484–96.
22. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell. 2016;29:452–63.
23. Dolma S, Lessnick SL, Hahn WC, Stockwell BR. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. Cancer Cell. 2003;3:285–96.

24. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B 3rd, Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72.
25. Abrams RP, Carroll WL, Woerpel KA. Five-membered ring peroxide selectively initiates ferroptosis in cancer cells. ACS Chem Biol. 2016;11:1305–12.
26. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, Sun B, Wang G. Ferroptosis: past, present and future. Cell Death Dis. 2020;11:88.
27. Li Z, Chen L, Chen C, Zhou Y, Hu D, Yang J, Chen Y, Zhuo W, Mao M, Zhang X, Xu L, Wang L, Zhou J. Targeting ferroptosis in breast cancer. Biomark Res. 2020;8:58.
28. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, Brown LM, Girotti AW, Cornish VW, Schreiber SL, Stockwell BR. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014;156:317–31.
29. Seiler A, Schneider M, Förster H, Roth S, Wirth EK, Culmsee C, Plesnila N, Kremmer E, Rådmark O, Wurst W, Bornkamm GW, Schweizer U, Conrad M. Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. Cell Metab. 2008;8:237–48.
30. Li FJ, Long HZ, Zhou ZW, Luo HY, Xu SG, Gao LC. System X(c) (-)/GSH/GPX4 axis: an important antioxidant system for the ferroptosis in drug-resistant solid tumor therapy. Front Pharmacol. 2022;13: 910292.
31. Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, Kapralov AA, Amoscato AA, Jiang J, Anthonymuthu T, Mohammadyani D, Yang Q, Proneth B, Klein-Seetharaman J, Watkins S, Bahar I, Greenberger J, Mallampalli RK, Stockwell BR, Tyurina YY, Conrad M, Bayır H. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017;13:81–90.
32. Yang WS, Stockwell BR. Ferroptosis: death by lipid peroxidation. Trends Cell Biol. 2016;26:165–76.
33. Ursini F, Maiorino M, Valente M, Ferri L, Gregolin C. Purification from pig liver of a protein which protects liposomes and biomembranes from peroxidative degradation and exhibits glutathione peroxidase activity on phosphatidylcholine hydroperoxides. Biochim Biophys Acta. 1982;710:197–211.
34. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta. 1830;2013:3289–303.
35. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascon S, Hatzios SK, Kagan VE, Noel K, Jiang X, Linkermann A, Murphy ME, Overholtzer M, Oyagi A, Pagnussat GC, Park J, Ran Q, Rosenfeld CS, Salnikow K, Tang D, Torti FM, Torti SV, Toyokuni S, Woerpel KA, Zhang DD. Ferroptosis: a regulated cell death nexus linking metabolism. Redox Biol Dis Cell. 2017;171:273–85.
36. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, Prokisch H, Trümbach D, Mao G, Qu F, Bayir H, Füllekrug J, Scheel CH, Wurst W, Schick JA, Kagan VE, Angeli JP, Conrad M. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017;13:91–8.
37. Zou Y, Palte MJ, Deik AA, Li H, Eaton JK, Wang W, Tseng YY, Deasy R, Kost-Alimova M, Dančík V, Leshchiner ES, Viswanathan VS, Signoretti S, Choueiri TK, Boehm JS, Wagner BK, Doench JG, Clish CB, Clemons PA, Schreiber SL. A GPX4-dependent cancer cell state underlies the clear-cell morphology and confers sensitivity to ferroptosis. Nat Commun. 2019;10:1617.
38. Liao P, Wang W, Wang W, Kryczek I, Li X, Bian Y, Sell A, Wei S, Grove S, Johnson JK, Kennedy PD, Gijón M, Shah YM, Zou W. CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. Cancer Cell. 2022;40:365-378.e366.
39. Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z. ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. Brain Behav Immun. 2021;93:312–21.
40. Chen X, Li J, Kang R, Klionsky DJ, Tang D. Ferroptosis: machinery and regulation. Autophagy. 2021;17:2054–81.
41. Küch EM, Vellaramkalayil R, Zhang I, Lehnen D, Brügger B, Sreemmel W, Ehehalt R, Poppelreuther M, Füllekrug J. Differentially localized acyl-CoA synthetase 4 isoenzymes mediate the metabolic channeling of fatty acids towards phosphatidylinositol. Biochim Biophys Acta. 1841;2014:227–39.
42. Soupene E, Kuypers FA. Mammalian long-chain acyl-CoA synthetases. Exp Biol Med (Maywood). 2008;233:507–21.
43. Yuan H, Li X, Zhang X, Kang R, Tang D. Identification of ACSL4 as a biomarker and contributor of ferroptosis. Biochem Biophys Res Commun. 2016;478:1338–43.
44. Ma LL, Liang L, Zhou D, Wang SW. Tumor suppressor miR-424-5p abrogates ferroptosis in ovarian cancer through targeting ACSL4. Neoplasma. 2021;68:165–73.
45. Novo N, Ferreira P, Medina M. The apoptosis-inducing factor family: Moonlighting proteins in the crosstalk between mitochondria and nuclei. IUBMB Life. 2021;73:568–81.
46. Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, Goya Grocin A, Xavier da Silva TN, Panzilius E, Scheel CH, Mourão A, Buday K, Sato M, Wanninger J, Vignane T, Mohana V, Rehberg M, Flatley A, Schepers A, Kurz A, White D, Sauer M, Sattler M, Tate EW, Schmitz W, Schulze A, O'Donnell V, Proneth B, Popowicz GM, Pratt DA, Angeli JPF, Conrad M. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019;575:693–8.
47. Warner GJ, Berry MJ, Moustafa ME, Carlson BA, Hatfield DL, Faust JR. Inhibition of selenoprotein synthesis by selenocysteine tRNA[Ser]Sec lacking isopentenyladenosine. J Biol Chem. 2000;275:28110–9.
48. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, Roberts MA, Tong B, Maimone TJ, Zoncu R, Bassik MC, Nomura DK, Dixon SJ, Olzmann JA. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019;575:688–92.
49. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520:57–62.
50. Jiang L, Hickman JH, Wang SJ, Gu W. Dynamic roles of p53-mediated metabolic activities in ROS-induced stress responses. Cell Cycle. 2015;14:2881–5.
51. Lin Z, Liu J, Kang R, Yang M, Tang D. Lipid metabolism in ferroptosis. Adv Biol. 2021;5: e2100396.
52. Chen X, Song X, Li J, Zhang R, Yu C, Zhou Z, Liu J, Liao S, Klionsky DJ, Kroemer G, Liu J, Tang D, Kang R. Identification of HPCAL1 as a specific autophagy receptor involved in ferroptosis. Autophagy. 2023;19:54–74.
53. Dikic I, Elazar Z. Mechanism and medical implications of mammalian autophagy. Nat Rev Mol Cell Biol. 2018;19:349–64.

54. Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D. Autophagy-dependent ferroptosis: machinery and regulation, cell. Chem Biol. 2020;27:420–35.
55. Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and transferrin regulate ferroptosis. Mol Cell. 2015;59:298–308.
56. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ 3rd, Kang R, Tang D. Autophagy promotes ferroptosis by degradation of ferritin. Autophagy. 2016;12:1425–8.
57. Gao M, Monian P, Pan Q, Zhang W, Xiang J, Jiang X. Ferroptosis is an autophagic cell death process. Cell Res. 2016;26:1021–32.
58. Rebaud S, Wang CK, Sarkis J, Mason L, Simon A, Blum LJ, Hofmann A, Girard-Egrot AP. Specific interaction to PIP2 increases the kinetic rate of membrane binding of VILIPs, a subfamily of neuronal calcium sensors (NCS) proteins. Biochim Biophys Acta. 1838;2014:2698–707.
59. Lee H, Zandkarimi F, Zhang Y, Meena JK, Kim J, Zhuang L, Tyagi S, Ma L, Westbrook TF, Steinberg GR, Nakada D, Stockwell BR, Gan B. Energy-stress-mediated AMPK activation inhibits ferroptosis. Nat Cell Biol. 2020;22:225–34.
60. Li C, Dong X, Du W, Shi X, Chen K, Zhang W, Gao M. LKB1-AMPK axis negatively regulates ferroptosis by inhibiting fatty acid synthesis. Signal Transduct Target Ther. 2020;5:187.
61. Cao JY, Dixon SJ. Mechanisms of ferroptosis. Cell Mol Life Sci. 2016;73:2195–209.
62. Ou W, Mulik RS, Anwar A, McDonald JG, He X, Corbin IR. Low-density lipoprotein docosahexaenoic acid nanoparticles induce ferroptotic cell death in hepatocellular carcinoma. Free Radic Biol Med. 2017;112:597–607.
63. Hao S, Yu J, He W, Huang Q, Zhao Y, Liang B, Zhang S, Wen Z, Dong S, Rao J, Liao W, Shi M. Cysteine dioxygenase 1 mediates erastin-induced ferroptosis in human gastric cancer cells. Neoplasia. 2017;19:1022–32.
64. Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, Zhong M, Yuan H, Zhang L, Billiar TR, Lotze MT, Zeh HJ 3rd, Kang R, Kroemer G, Tang D. The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. Cell Rep. 2017;20:1692–704.
65. Guo J, Xu B, Han Q, Zhou H, Xia Y, Gong C, Dai X, Li Z, Wu G. Ferroptosis: a novel anti-tumor action for cisplatin. Cancer Res Treat. 2018;50:445–60.
66. Eling N, Reuter L, Hazin J, Hamacher-Brady A, Brady NR. Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells. Oncoscience. 2015;2:517–32.
67. Yamaguchi Y, Kasukabe T, Kumakura S. Piperlongumine rapidly induces the death of human pancreatic cancer cells mainly through the induction of ferroptosis. Int J Oncol. 2018;52:1011–22.
68. Alvarez SW, Sviderskiy VO, Terzi EM, Papagiannakopoulos T, Moreira AL, Adams S, Sabatini DM, Birsoy K, Possemato R. NFS1 undergoes positive selection in lung tumours and protects cells from ferroptosis. Nature. 2017;551:639–43.
69. Zhang X, Sui S, Wang L, Li H, Zhang L, Xu S, Zheng X. Inhibition of tumor propellant glutathione peroxidase 4 induces ferroptosis in cancer cells and enhances anticancer effect of cisplatin. J Cell Physiol. 2020;235:3425–37.
70. Yeo SK, Guan JL. Breast cancer: multiple subtypes within a tumor? Trends Cancer. 2017;3:753–60.
71. Denkert C, Liedtke C, Tutt A, von Minckwitz G. Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. Lancet (London, England). 2017;389:2430–42.
72. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Blair SL, Burstein HJ, Dang C, Elias AD, Giordano SH, Goetz MP, Goldstein LJ, Hurvitz SA, Isakoff SJ, Jankowitz RC, Javid SH, Krishnamurthy J, Leitch M, Lyons J, Matro J, Mayer IA, Mortimer J, O'Regan RM, Patel SA, Pierce LJ, Rugo HS, Sitapati A, Smith KL, Smith ML, Soliman H, Stringer-Reasor EM, Telli ML, Ward JH, Wisinski KB, Young JS, Burns JL, Kumar R. NCCN guidelines® insights: breast cancer, version 4.2021. J Natl Compr Canc Netw. 2021;19:484–93.
73. Sha R, Xu Y, Yuan C, Sheng X, Wu Z, Peng J, Wang Y, Lin Y, Zhou L, Xu S, Zhang J, Yin W, Lu J. Predictive and prognostic impact of ferroptosis-related genes ACSL4 and GPX4 on breast cancer treated with neoadjuvant chemotherapy. EBioMedicine. 2021;71: 103560.
74. Yang F, Xiao Y, Ding JH, Jin X, Ma D, Li DQ, Shi JX, Huang W, Wang YP, Jiang YZ, Shao ZM. Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy. Cell Metab. 2023;35:84-100.e108.
75. Müller S, Sindikubwabo F, Cañeque T, Lafon A, Versini A, Lombard B, Loew D, Wu TD, Ginestier C, Charafe-Jauffret E, Durand A, Vallot C, Baulande S, Servant N, Rodriguez R. CD44 regulates epigenetic plasticity by mediating iron endocytosis. Nat Chem. 2020;12:929–38.
76. Gong Y, Ji P, Yang YS, Xie S, Yu TJ, Xiao Y, Jin ML, Ma D, Guo LW, Pei YC, Chai WJ, Li DQ, Bai F, Bertucci F, Hu X, Jiang YZ, Shao ZM. Metabolic-pathway-based subtyping of triple-negative breast cancer reveals potential therapeutic targets. Cell Metab. 2021;33:51-64.e59.
77. Xiao Y, Ma D, Yang YS, Yang F, Ding JH, Gong Y, Jiang L, Ge LP, Wu SY, Yu Q, Zhang Q, Bertucci F, Sun Q, Hu X, Li DQ, Shao ZM, Jiang YZ. Comprehensive metabolomics expands precision medicine for triple-negative breast cancer. Cell Res. 2022;32:477–90.
78. Rusolo F, Capone F, Pasquale R, Angiolillo A, Colonna G, Castello G, Costantini M, Costantini S. Comparison of the seleno-transcriptome expression between human non-cancerous mammary epithelial cells and two human breast cancer cell lines. Oncol Lett. 2017;13:2411–7.
79. Cejas P, García-Cabezas MA, Casado E, Belda-Iniesta C, De Castro J, Fresno JA, Sereno M, Barriuso J, Espinosa E, Zamora P, Feliu J, Redondo A, Hardisson DA, Renart J, González-Barón M. Phospholipid hydroperoxide glutathione peroxidase (PHGPx) expression is downregulated in poorly differentiated breast invasive ductal carcinoma. Free Radic Res. 2007;41:681–7.
80. Yu M, Gai C, Li Z, Ding D, Zheng J, Zhang W, Lv S, Li W. Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells. Cancer Sci. 2019;110:3173–82.
81. Monaco ME, Creighton CJ, Lee P, Zou X, Topham MK, Stafforini DM. Expression of long-chain fatty acyl-coA synthetase 4 in breast and prostate cancers is associated with sex steroid hormone receptor negativity. Transl Oncol. 2010;3:91–8.
82. Dinarvand N, Khanahmad H, Hakimian SM, Sheikhi A, Rashidi B, Pourfarzam M. Evaluation of long-chain acyl-coenzyme A synthetase 4 (ACSL4) expression in human breast cancer. Res Pharm Sci. 2020;15:48–56.

83. Lei G, Zhang Y, Koppula P, Liu X, Zhang J, Lin SH, Ajani JA, Xiao Q, Liao Z, Wang H, Gan B. The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression. Cell Res. 2020;30:146–62.
84. Kwon YS, Lee MG, Baek J, Kim NY, Jang H, Kim S. Acyl-CoA synthetase-4 mediates radioresistance of breast cancer cells by regulating FOXM1. Biochem Pharmacol. 2021;192: 114718.
85. Dixon SJ. Ferroptosis: bug or feature? Immunol Rev. 2017;277:150–7.
86. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22:96–118.
87. Mei J, Hao L, Wang H, Xu R, Liu Y, Zhu Y, Liu C. Systematic characterization of non-coding RNAs in triple-negative breast cancer. Cell Prolif. 2020;53: e12801.
88. Marchese FP, Raimondi I, Huarte M. The multidimensional mechanisms of long noncoding RNA function. Genome Biol. 2017;18:206.
89. Salviano-Silva A, Lobo-Alves SC, Almeida RC, Malheiros D, Petzl-Erler ML. Besides pathology: long non-coding RNA in cell and tissue homeostasis. Noncoding RNA. 2018;4:3.
90. Fernandes JCR, Acuña SM, Aoki JI, Floeter-Winter LM, Muxel SM. Long non-coding RNAs in the regulation of gene expression: physiology and disease. Noncoding RNA. 2019;5:17.
91. Wang P, Xu J, Wang Y, Cao X. An interferon-independent lncRNA promotes viral replication by modulating cellular metabolism. Science (New York, NY). 2017;358:1051–5.
92. Gomez JA, Wapinski OL, Yang YW, Bureau JF, Gopinath S, Monack DM, Chang HY, Brahic M, Kirkegaard K. The NeST long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-γ locus. Cell. 2013;152:743–54.
93. Fortes P, Morris KV. Long noncoding RNAs in viral infections. Virus Res. 2016;212:1–11.
94. Castellanos-Rubio A, Fernandez-Jimenez N, Kratchmarov R, Luo X, Bhagat G, Green PH, Schneider R, Kiledjian M, Bilbao JR, Ghosh S. A long noncoding RNA associated with susceptibility to celiac disease. Science (New York, NY). 2016;352:91–5.
95. Atianand MK, Hu W, Satpathy AT, Shen Y, Ricci EP, Alvarez-Dominguez JR, Bhatta A, Schattgen SA, McGowan JD, Blin J, Braun JE, Gandhi P, Moore MJ, Chang HY, Lodish HF, Caffrey DR, Fitzgerald KA. A long noncoding RNA lincRNA-EPS acts as a transcriptional brake to restrain inflammation. Cell. 2016;165:1672–85.
96. Ranzani V, Rossetti G, Panzeri I, Arrigoni A, Bonnal RJ, Curti S, Gruarin P, Provasi E, Sugliano E, Marconi M, De Francesco R, Geginat J, Bodega B, Abrignani S, Pagani M. The long intergenic noncoding RNA landscape of human lymphocytes highlights the regulation of T cell differentiation by linc-MAF-4. Nat Immunol. 2015;16:318–25.
97. Klinge CM. Non-Coding RNAs in breast cancer: intracellular and intercellular communication. Noncoding RNA. 2018;4:40.
98. Jin H, Du W, Huang W, Yan J, Tang Q, Chen Y, Zou Z. lncRNA and breast cancer: progress from identifying mechanisms to challenges and opportunities of clinical treatment. Mol Ther Nucleic Acids. 2021;25:613–37.
99. Guo B, Wu S, Zhu X, Zhang L, Deng J, Li F, Wang Y, Zhang S, Wu R, Lu J, Zhou Y. Micropeptide CIP2A-BP encoded by LINC00665 inhibits triple-negative breast cancer progression. EMBO J. 2020;39: e102190.
100. Huang QY, Liu GF, Qian XL, Tang LB, Huang QY, Xiong LX. Long non-coding RNA: dual effects on breast cancer metastasis and clinical applications. Cancers. 2019;11:1802.
101. Xiu B, Chi Y, Liu L, Chi W, Zhang Q, Chen J, Guo R, Si J, Li L, Xue J, Shao ZM, Wu ZH, Huang S, Wu J. LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription. Mol Cancer. 2019;18:187.
102. Zhang Z, Zhu Z, Watabe K, Zhang X, Bai C, Xu M, Wu F, Mo YY. Negative regulation of lncRNA GAS5 by miR-21. Cell Death Differ. 2013;20:1558–68.
103. Berteaux N, Lottin S, Monté D, Pinte S, Quatannens B, Coll J, Hondermarck H, Curgy JJ, Dugimont T, Adriaenssens E. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. J Biol Chem. 2005;280:29625–36.
104. Shi F, Chen X, Wang Y, Xie Y, Zhong J, Su K, Li M, Li Y, Lin Q, Zhou Y, Wang J, Xiong L. HOTAIR/miR-203/CAV1 crosstalk influences proliferation, migration, and invasion in the breast cancer cell. Int J Mol Sci. 2022;23:11755.
105. Silva JM, Boczek NJ, Berres MW, Ma X, Smith DI. LSINCT5 is over expressed in breast and ovarian cancer and affects cellular proliferation. RNA Biol. 2011;8:496–505.
106. Lanz RB, Chua SS, Barron N, Söder BM, DeMayo F, O'Malley BW. Steroid receptor RNA activator stimulates proliferation as well as apoptosis in vivo. Mol Cell Biol. 2003;23:7163–76.
107. Arase M, Horiguchi K, Ehata S, Morikawa M, Tsutsumi S, Aburatani H, Miyazono K, Koinuma D. Transforming growth factor-β-induced lncRNA-Smad7 inhibits apoptosis of mouse breast cancer JygMC(A) cells. Cancer Sci. 2014;105:974–82.
108. Lo PK, Zhang Y, Wolfson B, Gernapudi R, Yao Y, Duru N, Zhou Q. Dysregulation of the BRCA1/long non-coding RNA NEAT1 signaling axis contributes to breast tumorigenesis. Oncotarget. 2016;7:65067–89.
109. Jiang M, Xiao Y, Liu D, Luo N, Gao Q, Guan Y. Overexpression of long noncoding RNA LINC01296 indicates an unfavorable prognosis and promotes tumorigenesis in breast cancer. Gene. 2018;675:217–24.
110. Ma D, Chen C, Wu J, Wang H, Wu D. Up-regulated lncRNA AFAP1-AS1 indicates a poor prognosis and promotes carcinogenesis of breast cancer. Breast Cancer. 2019;26:74–83.
111. Song R, Zhang J, Huang J, Hai T. Long non-coding RNA GHET1 promotes human breast cancer cell proliferation, invasion and migration via affecting epithelial mesenchymal transition. Cancer Biomark. 2018;22:565–73.
112. Jiang J, Shi SH, Li XJ, Sun L, Ge QD, Li C, Zhang W. Long non-coding RNA BRAF-regulated lncRNA 1 promotes lymph node invasion, metastasis and proliferation, and predicts poor prognosis in breast cancer. Oncol Lett. 2018;15:9543–52.
113. Wang O, Yang F, Liu Y, Lv L, Ma R, Chen C, Wang J, Tan Q, Cheng Y, Xia E, Chen Y, Zhang X. C-MYC-induced upregulation of lncRNA SNHG12 regulates cell proliferation, apoptosis and migration in triple-negative breast cancer. Am J Transl Res. 2017;9:533–45.
114. Li X, Wu Y, Liu A, Tang X. Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1α feedback regulatory loop. Tumour Biol. 2016;37:14733–43.

115. Li Y, Wang B, Lai H, Li S, You Q, Fang Y, Li Q, Liu Y. Long non-coding RNA CRALA is associated with poor response to chemotherapy in primary breast cancer. Thorac Cancer. 2017;8:582–91.
116. Shi SJ, Wang LJ, Yu B, Li YH, Jin Y, Bai XZ. LncRNA-ATB promotes trastuzumab resistance and invasion-metastasis cascade in breast cancer. Oncotarget. 2015;6:11652–63.
117. Chang L, Hu Z, Zhou Z, Zhang H. Linc00518 contributes to multidrug resistance through regulating the MiR-199a/MRP1 axis in breast cancer. Cell Physiol Biochem. 2018;48:16–28.
118. Ma Y, Bu D, Long J, Chai W, Dong J. LncRNA DSCAM-AS1 acts as a sponge of miR-137 to enhance Tamoxifen resistance in breast cancer. J Cell Physiol. 2019;234:2880–94.
119. Xu X, Ji S, Li W, Yi B, Li H, Zhang H, Ma W. LncRNA H19 promotes the differentiation of bovine skeletal muscle satellite cells by suppressing Sirt1/FoxO1. Cell Mol Biol Lett. 2017;22:10.
120. Wang J, Xie S, Yang J, Xiong H, Jia Y, Zhou Y, Chen Y, Ying X, Chen C, Ye C, Wang L, Zhou J. The long noncoding RNA H19 promotes tamoxifen resistance in breast cancer via autophagy. J Hematol Oncol. 2019;12:81.
121. Chen J, Qin C, Zhou Y, Chen Y, Mao M, Yang J. Metformin may induce ferroptosis by inhibiting autophagy via lncRNA H19 in breast cancer. FEBS Open Bio. 2022;12:146–53.
122. Huang J, Zhou N, Watabe K, Lu Z, Wu F, Xu M, Mo YY. Long non-coding RNA UCA1 promotes breast tumor growth by suppression of p27 (Kip1). Cell Death Dis. 2014;5: e1008.
123. Raju GSR, Pavitra E, Bandaru SS, Varaprasad GL, Nagaraju GP, Malla RR, Huh YS, Han YK. HOTAIR: a potential metastatic, drug-resistant and prognostic regulator of breast cancer. Mol Cancer. 2023;22:65.
124. Müller V, Oliveira-Ferrer L, Steinbach B, Pantel K, Schwarzenbach H. Interplay of lncRNA H19/miR-675 and lncRNA NEAT1/miR-204 in breast cancer. Mol Oncol. 2019;13:1137–49.
125. Wu D, Zhu J, Fu Y, Li C, Wu B. LncRNA HOTAIR promotes breast cancer progression through regulating the miR-129-5p/FZD7 axis. Cancer Biomark. 2021;30:203–12.
126. Wang Y, Gong G, Xu J, Zhang Y, Wu S, Wang S. Long noncoding RNA HOTAIR promotes breast cancer development by targeting ZEB1 via sponging miR-601. Cancer Cell Int. 2020;20:320.
127. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464:1071–6.
128. Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017;36:5661–7.
129. Ding W, Ren J, Ren H, Wang D. Long noncoding RNA HOTAIR modulates MiR-206-mediated Bcl-w signaling to facilitate cell proliferation in breast cancer. Sci Rep. 2017;7:17261.
130. Liu LC, Wang YL, Lin PL, Zhang X, Cheng WC, Liu SH, Chen CJ, Hung Y, Jan CI, Chang LC, Qi X, Hsieh-Wilson LC, Wang SC. Long noncoding RNA HOTAIR promotes invasion of breast cancer cells through chondroitin sulfotransferase CHST15. Int J Cancer. 2019;145:2478–87.
131. Zhao W, Geng D, Li S, Chen Z, Sun M. LncRNA HOTAIR influences cell growth, migration, invasion, and apoptosis via the miR-20a-5p/HMGA2 axis in breast cancer. Cancer Med. 2018;7:842–55.
132. Zhao C, Ling X, Xia Y, Yan B, Guan Q. LncRNA UCA1 promotes SOX12 expression in breast cancer by regulating m(6)A modification of miR-375 by METTL14 through DNA methylation. Cancer Gene Ther. 2022;29:1043–55.
133. Giro-Perafita A, Luo L, Khodadadi-Jamayran A, Thompson M, Akgol Oksuz B, Tsirigos A, Dynlacht BD, Sánchez I, Esteva FJ. LncRNA RP11–19E11 is an E2F1 target required for proliferation and survival of basal breast cancer. NPJ Breast Cancer. 2020;6:1.
134. Zhang N, Zeng X, Sun C, Guo H, Wang T, Wei L, Zhang Y, Zhao J, Ma X. LncRNA LINC00963 promotes tumorigenesis and radioresistance in breast cancer by sponging miR-324-3p and inducing ACK1 expression. Mol Ther Nucleic Acids. 2019;18:871–81.
135. Mondal P, Meeran SM. Long non-coding RNAs in breast cancer metastasis. Noncoding RNA Res. 2020;5:208–18.
136. Li Y, Song Y, Wang Z, Zhang Z, Lu M, Wang Y. Long non-coding RNA LINC01787 drives breast cancer progression via disrupting miR-125b generation. Front Oncol. 2019;9:1140.
137. Liu B, Sun L, Liu Q, Gong C, Yao Y, Lv X, Lin L, Yao H, Su F, Li D, Zeng M, Song E. A cytoplasmic NF-κB interacting long noncoding RNA blocks IκB phosphorylation and suppresses breast cancer metastasis. Cancer Cell. 2015;27:370–81.
138. Ma Y, Yu L, Yan W, Qiu L, Zhang J, Jia X. lncRNA GAS5 sensitizes breast cancer cells to ionizing radiation by inhibiting DNA repair. Biomed Res Int. 2022;2022:1987519.
139. Shi P, Zhang J, Li X, Li W, Li H, Fu P. Long non-coding RNA NORAD inhibition upregulates microRNA-323a-3p to suppress tumorigenesis and development of breast cancer through the PUM1/eIF2 axis. Cell Cycle. 2021;20:1295–307.
140. Zhou K, Ou Q, Wang G, Zhang W, Hao Y, Li W. High long non-coding RNA NORAD expression predicts poor prognosis and promotes breast cancer progression by regulating TGF-β pathway. Cancer Cell Int. 2019;19:63.
141. Tan BS, Yang MC, Singh S, Chou YC, Chen HY, Wang MY, Wang YC, Chen RH. LncRNA NORAD is repressed by the YAP pathway and suppresses lung and breast cancer metastasis by sequestering S100P. Oncogene. 2019;38:5612–26.
142. Liang Y, Song X, Li Y, Chen B, Zhao W, Wang L, Zhang H, Liu Y, Han D, Zhang N, Ma T, Wang Y, Ye F, Luo D, Li X, Yang Q. LncRNA BCRT1 promotes breast cancer progression by targeting miR-1303/PTBP3 axis. Mol Cancer. 2020;19:85.
143. Hu J, Huang H, Xi Z, Ma S, Ming J, Dong F, Guo H, Zhang H, Zhao E, Yao G, Yang L, Zhang F, Zheng W, Chen H, Huang T, Li L. LncRNA SEMA3B-AS1 inhibits breast cancer progression by targeting miR-3940/KLLN axis. Cell Death Dis. 2022;13:800.
144. Zhang Q, Li T, Wang Z, Kuang X, Shao N, Lin Y. lncRNA NR2F1-AS1 promotes breast cancer angiogenesis through activating IGF-1/IGF-1R/ERK pathway. J Cell Mol Med. 2020;24:8236–47.
145. Zhang Y, Dong X, Guo X, Li C, Fan Y, Liu P, Yuan D, Ma X, Wang J, Zheng J, Li H, Gao P. LncRNA-BC069792 suppresses tumor progression by targeting KCNQ4 in breast cancer. Mol Cancer. 2023;22:41.
146. Zong S, Dai W, Guo X, Wang K. LncRNA-SNHG1 promotes macrophage M2-like polarization and contributes to breast cancer growth and metastasis. Aging. 2021;13:23169–81.

147. Ouyang J, Liu Z, Yuan X, Long C, Chen X, Wang Y, Liu L, Liu S, Liang H. LncRNA PRNCR1 promotes breast cancer proliferation and inhibits apoptosis by modulating microRNA-377/CCND2/MEK/MAPK axis. Arch Med Res. 2021;52:471–82.
148. Li X, Deng S, Pang X, Song Y, Luo S, Jin L, Pan Y. LncRNA NEAT1 silenced miR-133b promotes migration and invasion of breast cancer cells. Int J Mol Sci. 2019;20:3616.
149. Song X, Liu Z, Yu Z. LncRNA NEF is downregulated in triple negative breast cancer and correlated with poor prognosis. Acta Biochim Biophys Sin (Shanghai). 2019;51:386–92.
150. Li Q, Mo W, Ding Y, Ding X. Study of lncRNA TPA in promoting invasion and metastasis of breast cancer mediated by TGF-β signaling pathway. Front Cell Dev Biol. 2021;9: 688751.
151. Fang Z, Wang Y, Wang Z, Xu M, Ren S, Yang D, Hong M, Xie W. ERINA is an estrogen-responsive LncRNA that drives breast cancer through the E2F1/RB1 pathway. Can Res. 2020;80:4399–413.
152. Gong X, Dong T, Niu M, Liang X, Sun S, Zhang Y, Li Y, Li D. lncRNA LCPAT1 upregulation promotes breast cancer progression via enhancing MFAP2 transcription. Mol Ther Nucleic Acids. 2020;21:804–13.
153. Li Q, Gao H, Zhou S, Liao Y. LncRNA PlncRNA-1 overexpression inhibits the growth of breast cancer by upregulating TGF-β1 and downregulating PHGDH. Breast Cancer. 2018;25:619–25.
154. Liu M, Gou L, Xia J, Wan Q, Jiang Y, Sun S, Tang M, He T, Zhang Y. LncRNA ITGB2-AS1 could promote the migration and invasion of breast cancer cells through up-regulating ITGB2. Int J Mol Sci. 2018;19:1866.
155. Jia X, Shi L, Wang X, Luo L, Ling L, Yin J, Song Y, Zhang Z, Qiu N, Liu H, Deng M, He Z, Li H, Zheng G. KLF5 regulated lncRNA RP1 promotes the growth and metastasis of breast cancer via repressing p27kip1 translation. Cell Death Dis. 2019;10:373.
156. Kong X, Duan Y, Sang Y, Li Y, Zhang H, Liang Y, Liu Y, Zhang N, Yang Q. LncRNA-CDC6 promotes breast cancer progression and function as ceRNA to target CDC6 by sponging microRNA-215. J Cell Physiol. 2019;234:9105–17.
157. Shi C, Ren S, Zhao X, Li Q. lncRNA MALAT1 regulates the resistance of breast cancer cells to paclitaxel via the miR-497-5p/SHOC2 axis. Pharmacogenomics. 2022;23:973–85.
158. Kim J, Piao HL, Kim BJ, Yao F, Han Z, Wang Y, Xiao Z, Siverly AN, Lawhon SE, Ton BN, Lee H, Zhou Z, Gan B, Nakagawa S, Ellis MJ, Liang H, Hung MC, You MJ, Sun Y, Ma L. Long noncoding RNA MALAT1 suppresses breast cancer metastasis. Nat Genet. 2018;50:1705–15.
159. Xu Y, Ren W, Li Q, Duan C, Lin X, Bi Z, You K, Hu Q, Xie N, Yu Y, Xu X, Hu H, Yao H. LncRNA Uc003xsl.1-mediated activation of the NFκB/IL8 axis promotes progression of triple-negative breast cancer. Cancer Res. 2022;82:556–70.
160. Sheng X, Dai H, Du Y, Peng J, Sha R, Yang F, Zhou L, Lin Y, Xu S, Wu Y, Yin W, Lu J. LncRNA CARMN overexpression promotes prognosis and chemosensitivity of triple negative breast cancer via acting as miR143-3p host gene and inhibiting DNA replication. J Exp Clin Cancer Res. 2021;40:205.
161. Liu P, Feng Y, Li H, Chen X, Wang G, Xu S, Li Y, Zhao L. Ferrostatin-1 alleviates lipopolysaccharide-induced acute lung injury via inhibiting ferroptosis. Cell Mol Biol Lett. 2020;25:10.
162. Zhang Z, Lu YX, Liu F, Sang L, Shi C, Xie S, Bian W, Yang JC, Yang Z, Qu L, Chen SY, Li J, Yang L, Yan Q, Wang W, Fu P, Shao J, Li X, Lin A. lncRNA BREA2 promotes metastasis by disrupting the WWP2-mediated ubiquitination of Notch1. Proc Natl Acad Sci USA. 2023;120: e2206694120.
163. Chen X, Luo R, Zhang Y, Ye S, Zeng X, Liu J, Huang D, Liu Y, Liu Q, Luo ML, Song E. Long noncoding RNA DlO3OS induces glycolytic-dominant metabolic reprogramming to promote aromatase inhibitor resistance in breast cancer. Nat Commun. 2022;13:7160.
164. Zhu P, He F, Hou Y, Tu G, Li Q, Jin T, Zeng H, Qin Y, Wan X, Qiao Y, Qiu Y, Teng Y, Liu M. A novel hypoxic long noncoding RNA KB-1980E6.3 maintains breast cancer stem cell stemness via interacting with IGF2BP1 to facilitate c-Myc mRNA stability. Oncogene. 2021;40:1609–27.
165. Gooding AJ, Zhang B, Jahanbani FK, Gilmore HL, Chang JC, Valadkhan S, Schiemann WP. The lncRNA BORG drives breast cancer metastasis and disease recurrence. Sci Rep. 2017;7:12698.
166. Yang F, Lv S. LncRNA EPB41L4A-AS1 regulates cell proliferation, apoptosis and metastasis in breast cancer. Ann Clin Lab Sci. 2022;52:3–11.
167. Zhang X, Zhao X, Chang L, Liu F, Li C, Ge P. LncRNA FOXD3-AS1 promotes breast cancer progression by mediating ARF6. Breast Cancer. 2022;29:908–20.
168. Zhai D, Li T, Ye R, Bi J, Kuang X, Shi Y, Shao N, Lin Y. LncRNA LGALS8-AS1 promotes breast cancer metastasis through miR-125b-5p/SOX12 feedback regulatory network. Front Oncol. 2021;11: 711684.
169. Shen P, Yu Y, Yan Y, Yu B, You W. LncRNA CASC15 regulates breast cancer cell stemness via the miR-654-5p/MEF2D axis. J Biochem Mol Toxicol. 2022;36: e23023.
170. Han M, Wang Y, Gu Y, Ge X, Seng J, Guo G, Zhang X, Zhao Y, Dou D. lncRNA GHET1 knockdown suppresses breast cancer activity in vitro and in vivo. Am J Transl Res. 2019;11:31–44.
171. Lei C, Li S, Fan Y, Hua L, Pan Q, Li Y, Long Z, Yang R. LncRNA DUXAP8 induces breast cancer radioresistance by modulating the PI3K/AKT/mTOR pathway and the EZH2-E-cadherin/RHOB pathway. Cancer Biol Ther. 2022;23:1–13.
172. Lv X, Zhang Q. LncRNA RP11–214F16.8 drives breast cancer tumorigenesis via a post-translational repression on NISCH expression. Cell Signal. 2022;92:110271.
173. Xu J, Hu M, Gao Y, Wang Y, Yuan X, Yang Y, Song W, Yin W, Gong P, Wei L, Zhang J. LncRNA MIR17HG suppresses breast cancer proliferation and migration as ceRNA to target FAM135A by sponging miR-454–3p. Mol Biotechnol. 2023. https://doi.org/10.1007/s12033-023-00706-1.
174. Qiu S, Chen G, Peng J, Liu J, Chen J, Wang J, Li L, Yang K. LncRNA EGOT decreases breast cancer cell viability and migration via inactivation of the Hedgehog pathway. FEBS Open Bio. 2020;10:817–26.
175. Li K, Ma YB, Tian YH, Xu XL, Gao Y, He YQ, Pan WT, Zhang JW, He CJ, Wei L. Silencing lncRNA SNHG6 suppresses proliferation and invasion of breast cancer cells through miR-26a/VASP axis. Pathol Res Pract. 2019;215: 152575.
176. Xu X, Xie Q, Xie M, Zeng Y, Liu Q. LncRNA SNHG8 serves as an oncogene in breast cancer through miR-634/ZBTB20 axis. Cancer Manag Res. 2021;13:3017–28.
177. Qu H, Li X, Chen F, Zhang M, Lu X, Gu Y, Lv M, Lu C. LncRNA PVT1 influences breast cancer cells glycolysis through sponging miR-145-5p, Genes. Genomics. 2023;45:581–92.

178. Lu Q, Wang L, Gao Y, Zhu P, Li L, Wang X, Jin Y, Zhi X, Yu J, Li X, Qin X, Zhou P. lncRNA APOC1P1-3 promoting anoikis-resistance of breast cancer cells. Cancer Cell Int. 2021;21:232.
179. Fang K, Xu ZJ, Jiang SX, Tang DS, Yan CS, Deng YY, Zhao FY. lncRNA FGD5-AS1 promotes breast cancer progression by regulating the hsa-miR-195-5p/NUAK2 axis. Mol Med Rep. 2021;23:1.
180. Ding Z, Ye P, Yang X, Cai H. LncRNA FBXL19-AS1 promotes breast cancer cells proliferation and invasion via acting as a molecular sponge to miR-718. Biosci Rep. 2019;39:BSR20182018.
181. Wang N, Hou M, Zhan Y, Sheng X. LncRNA PTCSC3 inhibits triple-negative breast cancer cell proliferation by downregulating lncRNA H19. J Cell Biochem. 2019;120:15083–8.
182. Fearnhead HO, Vandenabeele P, Vanden Berghe T. How do we fit ferroptosis in the family of regulated cell death. Cell Death Differ. 2017;24:1991–8.
183. Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, Tam S, Xiao D, Liu S, Wen F, Tao Y. A nuclear long non-coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis. Mol Ther. 2021;29:263–74.
184. Qi W, Li Z, Xia L, Dai J, Zhang Q, Wu C, Xu S. LncRNA GABPB1-AS1 and GABPB1 regulate oxidative stress during erastin-induced ferroptosis in HepG2 hepatocellular carcinoma cells. Sci Rep. 2019;9:16185.
185. Wu X, Liu C, Li Z, Gai C, Ding D, Chen W, Hao F, Li W. Regulation of GSK3β/Nrf2 signaling pathway modulated erastin-induced ferroptosis in breast cancer. Mol Cell Biochem. 2020;473:217–28.
186. Brown CW, Amante JJ, Chhoy P, Elaimy AL, Liu H, Zhu LJ, Baer CE, Dixon SJ, Mercurio AM. Prominin2 drives ferroptosis resistance by stimulating iron export. Dev Cell. 2019;51:575-586.e574.
187. Zhou N, Bao J. FerrDb: a manually curated resource for regulators and markers of ferroptosis and ferroptosis-disease associations. Database (Oxford). 2020;2020:baaa021.
188. Zhang K, Ping L, Du T, Liang G, Huang Y, Li Z, Deng R, Tang J. A ferroptosis-related lncRNAs signature predicts prognosis and immune microenvironment for breast cancer. Front Mol Biosci. 2021;8: 678877.
189. Wang L, Luan T, Zhou S, Lin J, Yang Y, Liu W, Tong X, Jiang W. LncRNA HCP5 promotes triple negative breast cancer progression as a ceRNA to regulate BIRC3 by sponging miR-219a-5p. Cancer Med. 2019;8:4389–403.
190. Jia CL, Yang F, Li R. Prognostic model construction and immune microenvironment analysis of breast cancer based on ferroptosis-related lncRNAs. Int J Gen Med. 2021;14:9817–31.
191. Tong X, Yu Z, Xing J, Liu H, Zhou S, Huang Y, Lin J, Jiang W, Wang L. LncRNA HCP5-encoded protein regulates ferroptosis to promote the progression of triple-negative breast cancer. Cancers. 2023;15:1880.
192. Wang S, Wang Y, Li Q, Zeng K, Li X, Feng X. RUNX1-IT1 favors breast cancer carcinogenesis through regulation of IGF2BP1/GPX4 axis. Discov Oncol. 2023;14:42.
193. Zhong H, Zeng G, He L. Overexpression of the lncRNA AC012213.3 promotes proliferation, migration and invasion of breast cancer via RAD54B/PI3K/AKT axis and is associated with worse patient prognosis. Cancer Manag Res. 2021;13:7213–23.
194. Dixon SJ, Stockwell BR. The hallmarks of ferroptosis. Ann Rev Cancer Biol. 2019;3:35–54.
195. Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, Liao P, Lang X, Kryczek I, Sell A, Xia H, Zhou J, Li G, Li J, Li W, Wei S, Vatan L, Zhang H, Szeliga W, Gu W, Liu R, Lawrence TS, Lamb C, Tanno Y, Cieslik M, Stone E, Georgiou G, Chan TA, Chinnaiyan A, Zou W. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;569:270–4.
196. Lu B, Chen XB, Ying MD, He QJ, Cao J, Yang B. The role of ferroptosis in cancer development and treatment response. Front Pharmacol. 2017;8:992.
197. Stěrba M, Popelová O, Vávrová A, Jirkovský E, Kovaříková P, Geršl V, Simůnek T. Oxidative stress, redox signaling, and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. Antioxid Redox Signal. 2013;18:899–929.
198. Roy SS, Chakraborty P, Bhattacharya S. Intervention in cyclophosphamide induced oxidative stress and DNA damage by a flavonyl-thiazolidinedione based organoselenocyanate and evaluation of its efficacy during adjuvant therapy in tumor bearing mice. Eur J Med Chem. 2014;73:195–209.
199. Jiang H, Zhang XW, Liao QL, Wu WT, Liu YL, Huang WH. Electrochemical monitoring of paclitaxel-induced ROS release from mitochondria inside single cells. Small. 2019;15: e1901787.
200. Vernier M, Dufour CR, McGuirk S, Scholtes C, Li X, Bourmeau G, Kuasne H, Park M, St-Pierre J, Audet-Walsh E, Giguère V. Estrogen-related receptors are targetable ROS sensors. Genes Dev. 2020;34:544–59.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.