Review Article
Epigenetic modifications in ferroptosis regulation of breast cancer

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Abstract: Breast cancer (BC) is the most frequently diagnosed type of cancer worldwide and has become the primary cause of cancer deaths in women, presenting many difficulties for treatment due to its molecular heterogeneity, dynamic tumor microenvironment and frequent development of resistance to traditional drugs and targeted therapies. Ferroptosis is a type of genetically regulated, iron-dependent cell death that occurs due to the extensive accumulation of phospholipid hydroperoxides, and it has been identified as an essential tumor-suppressive mechanism with significant implications for the pathogenesis, progression and treatment response of BC. Recent evidence shows that epigenetic mechanisms, including DNA methylation, histone post-translational modifications, and non-coding RNA-mediated regulation (microRNA, long non-coding RNA, circular RNA), precisely control the core ferroptosis machinery system Xc-, GPX4, ACSL4, and FSP1 in a context-dependent manner. This review introduces the systematic and mechanistic integration of the current knowledge base on the modulation of BC cells' ferroptosis susceptibility by epigenetic reprogramming across molecular subtypes. We critically assess the preclinical and translational evidence linking specific epigenetic regulators to ferroptosis evasion, identify emerging biomarkers predictive of ferroptosis vulnerability, and discuss the therapeutic potential of epigenetic-ferroptosis co-targeting strategies to restore ferroptosis sensitivity, circumvent drug resistance, and enhance survival outcomes in patients with refractory or metastatic BC.

Keywords: Breast cancer, ferroptosis, epigenetic modification

Introduction

Breast cancer (BC) is a common type of cancer that poses the second highest risk to women globally and is one of the main culprits in deaths from cancer, making it an intractable problem for public health today [1]. Recently, estimates from the International Agency for Research on Cancer (IARC) showed that approximately 2.3 million new cases and 670,000 deaths occurred in 2022 [1]. If the current situation continues, it is expected that by 2050, about 3.2 million new cases of BC and about 1.1 million deaths from BC will occur each year [2]. The clinical management of BC is essentially determined by the accurate determination of its molecular subtypes, which directly guides subsequent treatment plans. BC can be classified according to various systems, and one of them

is a typical classification based on molecular and histological evidence. Therefore, BC is usually classified into the following three major categories of treatment: hormone receptor-positive BC (expressing estrogen receptor (ER+) or progesterone receptor (PR+)), human epidermal growth factor receptor 2 (HER2)-positive BC, and triple-negative BC (TNBC, ER-, PR-, HER2-) [3]. These distinct subtypes exhibit unique molecular profiles, which in turn necessitate different treatment approaches. With the development of technology, our diagnosis, examinations and treatments of BC have all been continuously enhancing. However, there are still many unknowns and complex causes related to this disease [4]. TNBC is often regarded as a typical refractory disease, due to the different degrees of sensitivity of each subtype to treatment and the lack of clear molecular targets

[5]. In addition, some kinds of drug-resistant BC are also difficult to handle. As a result, the high incidence, molecular heterogeneity and development of therapeutic resistance in BC have all urged us to find new ways as soon as possible that can help treat BC and develop more effective treatment plans.

In recent years, ferroptosis has received widespread attention in the research community due to its involvement in pathogenesis such as organ fibrosis [6] and tumor progression. Because it involves a special form of cell death, it has also gained attention as a potential therapy for BC [7]. In 2012, "ferroptosis" was introduced to denote a type of regulated cell death that primarily involves excessive accumulation of lipid reactive oxygen species (ROS) and is significantly reliant on iron [8]. Specifically, during ferroptosis, polyunsaturated fatty acids (PUFAs), primarily derived from arachidonic acid (AA) and eicosanoids, are sequentially catalyzed by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) into PUFA-containing phospholipids (PUFA-PLs) [9]. The oxidation of PUFA-PLs primarily occurs via two pathways. One is an enzyme-catalyzed, iron-dependent reaction in which lipoxygenases (LOXs) oxidize PUFA-PLs in the presence of iron to produce lipid peroxides. The other is the iron-catalyzed Fenton reaction, where free divalent iron in cells readily catalyzes the generation of ROS to cause lipid peroxidation. Lipid peroxides gradually accumulate and decompose into various lipid ROS, causing membranes damage, loss of self-repair ability of cells, and eventually leading to ferroptosis [10]. Both mechanisms involve iron.

Defense mechanisms of the cellular level that alleviate ferroptosis are mainly responsible for lipid peroxidation scavenging. SLC7A11-GSH-GPX4 axis that makes up the core components of the antioxidant defense signal transduction pathway. This path begins with System-Xc⁻, which is a cystine/glutamate antiporter comprising two subunits (SLC7A11 and SLC3A2). System Xc⁻ facilitates the import of one molecule of cystine in exchange for the export of one molecule of glutamate [11]. Intracellularly, cystine is reduced to cysteine, and then further synthesized into glutathione (GSH), the most abundant cellular antioxidant and reducing ag-

ent [12]. Utilizing GSH as the reducing agent, glutathione peroxidase 4 (GPX4) can convert lipid peroxides into non-toxic lipid alcohols, thereby detoxifying lipid peroxides [13]. Beyond the SLC7A11-GSH-GPX4 axis, several GPX4-independent antioxidant systems have been identified, such as FSP1-CoQ10-NAD(P)H axis [14, 15], and GCH1-BH4 system [16, 17], which provide additional protective mechanisms, and jointly resist ferroptosis (**Figure 1**).

Ferroptosis has emerged as a natural tumor-suppressive mechanism. Various tumor suppressor genes in cells can prevent the occurrence of tumors by influencing the ferroptosis mechanism [18]. Conversely, BC cells can acquire a growth and metastatic advantage by evading or suppressing ferroptosis. Studies have shown that the frequency of p53 gene mutations in BC is extremely high. Mutant p53 often loses its function and inhibits the expression of SLC7A11, making the cells more sensitive to ferroptosis [19]. Furthermore, BC cells can activate alternative pathways to confer ferroptosis resistance, such as through the expression of α6β4 integrin [20] or hepatocellular leukemia factor (HLF) [21], which promote the proliferation and metastasis of TNBC cells. As more and more ferroptosis-related factors have been found in BC, the therapeutic potential of targeting this cell death pathway for treating cancer by killing cancer cells has also emerged (**Figure 2**). Many studies have explored the potential of ferroptosis in tumors to activate anti-tumor immune response [22]. In addition, some pharmacological agents, such as metformin [23] and ketamine [24], have been identified to modulate ferroptosis susceptibility through epigenetic mechanisms. These epigenetic modifications can change the expression or activity of key ferroptosis regulators at the transcriptional and post-transcriptional levels, thereby precisely regulating the ferroptosis response [25].

Therefore, regulating the epigenetic modification of ferroptosis is expected to be able to inhibit tumorigenesis and proliferation. As the development and evolution of ferroptosis are crucial factors determining whether BC can develop, progress or develop resistance to treatment; therefore, the epigenetic modifications regulating the occurrence and development process of this phenomenon have begun
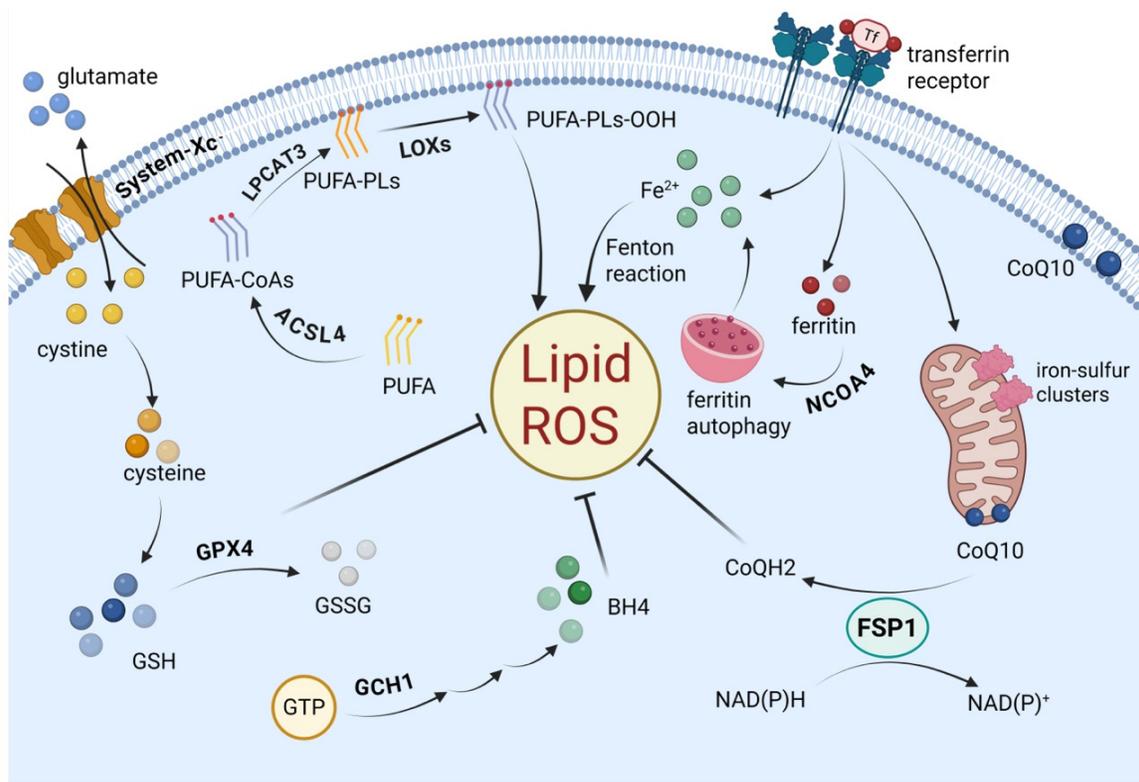
Figure 1. Schematic diagram of ferroptosis. Ferroptosis is mainly caused by the excessive accumulation of lipid reactive oxygen species (Lipid ROS), which triggers a series of reactions: first, it causes lipid peroxidation; then it leads to cell membrane rupture; and finally, the cell dies. Lipid peroxidation during ferroptosis mainly occurs through two types of pathways: the enzymatic reaction pathway and the iron-dependent Fenton reaction pathway. The former is catalysed by the ACSL4-LPCAT3-LOXs axis to promote the peroxidation of polyunsaturated fatty acids (PUFAs), and the iron-dependent Fenton reaction pathway is associated with some key regulatory proteins, such as transferrin (Tf) and NCOA4. The antioxidant defence system is a primary mechanism for resisting ferroptosis, and its primary functional axes are as follows: the SLC7A11-GSH-GPX4 axis, the FSP1-CoQ10-NAD(P)H axis, and the GCH1-BH4 axis.

to attract widespread attention. In this review, based on summarizing the mechanism by which epigenetic modification, covering DNA methylation, histone modifications and non-coding RNA network, regulates ferroptosis as well as its effects on BC progression and response to treatment. A more profound exploration of this epigenetic-ferroptosis axis is expected to reveal new therapeutic targets and biomarkers, provide references for the development of new treatments, and ultimately improve the clinical outcome of BC patients.

The regulatory role of epigenetic modifications in ferroptosis in BC progression

Epigenetics refers to heritable in an organism that do not alter to the DNA sequence. Epigenetic modification mainly includes DNA methylation, histone modifications, chromatin

remodeling, and the regulation by non-coding RNAs (ncRNAs) [26]. Although chromatin remodeling is an essential epigenetic mechanism, there has been a lack of specific research linking it to ferroptosis in BC up to now. Therefore, this review will focus on the roles of DNA methylation, histone modifications, and ncRNA-mediated regulation in modulating ferroptosis under the context of BC. DNA methylation typically occurs at cytosine residues in CpG dinucleotides and generally results in transcriptional repression and stable gene silencing. Histone modifications, such as methylation, acetylation, and phosphorylation, belong to post-translational changes of histones that alter the structure of chromatin and dynamically regulate gene expression. NcRNAs regulate genes primarily at the post-transcriptional level, for example, by affecting the stability of mRNA and the degradation process, but it is
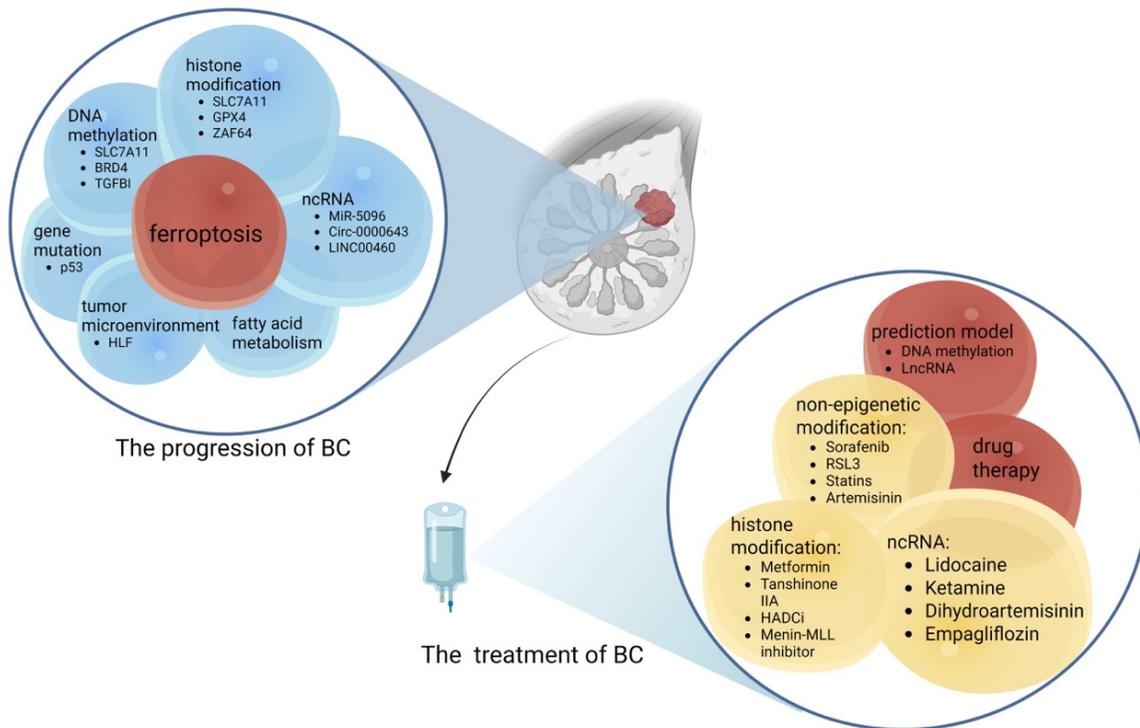
Figure 2. The development of BC is closely related to ferroptosis regulation. During the progression of breast cancer, mutations in many driver genes occur simultaneously, and at the same time, the tumor microenvironment undergoes significant reorganisation and fatty acid metabolism is disrupted. Moreover, numerous epigenetic modifications have been found in ferroptosis-related genes, including abnormal DNA methylation, histone post-translational modifications, and the disturbance of non-coding RNA (ncRNA)-mediated regulatory network. Given these mechanistic links, ferroptosis is expected to become a new additional treatment approach for BC. Translation Applications include the development of diagnostic and prognostic models based on DNA methylation and long non-coding RNA (lncRNA) signatures. In addition, there is a continuous expansion of pharmacological agents that target histone modification, ncRNA expression and other non-epigenetic modifiers of ferroptosis in preclinical and clinical research, with potential applications in BC treatment.

possible that they participate in some degree in regulating transcription and the state of epigenetics, adding a complex layer of regulation to gene expression [27, 28].

The role of epigenetic regulation in elucidating the molecular link between tumorigenesis and ferroptosis is also receiving more and more attention. Especially these epigenetic regulation mechanisms are not independent of each other; instead, through a complex information network, they jointly affect ferroptosis [29, 30].

DNA methylation in ferroptosis regulation

DNA methylation is a typical form of epigenetic modifications, it primarily involves methylation at the cytosine residue of DNA, facilitated by DNA methyltransferases (DNMT3a, DNMT3b, and DNMT1). DNMTs catalyze the transfer of a

methyl group to the cytosine residue in CpG dinucleotides, these nucleotides often occur in clusters known as CpG islands, which are located in gene promoters and enhancers [31]. DNA methylation changes are often associated with many biological processes and diseases [32].

SLC7A11 is a key component of the cellular antioxidant defense system. Overexpression of SLC7A11 confers resistance to ferroptosis and promotes the progression of caner [33]. Trastuzumab is already recognized as an essential medicine in the treatment of HER2-positive breast cancer and has achieved satisfying results clinically [34]. For HER2-positive BC with trastuzumab resistance, studies have shown that the global DNA 5-methylcytosine (5mC) content is lower than that of sensitive patients. The CpG methylation in the SLC7A11 promoter region is reduced in the resistant cell

lines, which improves the expression of SLC-7A11 and enhances the antioxidant defense capability of cancer cells [35]. Hypermethylation of the TGFBI gene is significantly related to trastuzumab resistance [36]. Moreover, the MUC1-C transmembrane oncoprotein is related to GSH levels and redox status. The overexpression is mainly due to the activity of xCT (SLC7A11). Specifically, xCT function is to inhibit the formation of repressive epigenetic modifications, such as histone H3K9 methylation and DNA methylation, on the MUC1 gene promoter. Epigenetic modification causes an increase in MUC1 expression, inhibits iron-related cell death (ferroptosis), and therefore promotes tumorigenesis in triple-negative breast cancer (TNBC) [37].

SLC7A11 is one of the axes around which DNA methylation regulates key ferroptosis regulators, besides it, bromodomain and extraterminal domain (BET) family protein BRD4 is an epigenetic regulator of tumor progression that regulates fatty acid metabolism to promote the expression of oncogenes [38, 39]. Pharmacological inhibition of BRD4 down-regulates FSP1 expression and sensitizes cells to ferroptosis [40]. The methylation level of the BRD4 gene in TNBC is lower than that in normal tissues, which may be associated with the high expression of the BRD4 gene, and eventually promotes the development of TNBC [41]. Therefore, targeting BRD4 to induce ferroptosis is a potential therapeutic approach for BC.

There are also some correlations between the methylation status of certain genes and ferroptosis in BC. The endoplasmic reticulum membrane protein complex (EMC) subunit EMC2 is implicated in ferroptosis regulation. Database mining and analysis revealed that EMC2 promoter hypomethylation in BC correlates with increased expression, and this is related to a poor overall survival rate of BC [42]. Similarly, the long non-coding RNA NORAD is also highly expressed in BC. Up-regulation of NORAD is positively associated with promoter DNA hypomethylation and high level of histone acetylation, representing an epigenetic condition conducive to the inhibition of ferroptosis [43]. Some studies have also found that the methylation level of centrosome and spindle pole-associated protein (CSPP1) gene is lower in BC, this alteration disrupts the process of ferroptosis in the development of BC [44].

In summary, DNA methylation is a critical regulatory level that controls the sensitivity of BC to ferroptosis. SLC7A11 and several central genes of the antioxidant defense system, as well as various ferroptosis-related proteins including MUC1, BRD4, EMC2, this regulation will lead to changes in their expression levels. A uniform pattern of promoter hypomethylation leading to the upregulation of ferroptosis-inhibitory genes indicates that a typical epigenetic mechanism is deployed by cancer cells to avoid ferroptosis. Finally, targeting the epigenetic changes or the genes they regulate can promote iron-overload cell death (ferroptosis) therapy for BC.

Histone modification in ferroptosis regulation

Histone modifications, such as methylation, acetylation, and phosphorylation, also belong to the content of epigenetic regulation in ferroptosis and have certain impacts on BC research. Through these variations in chromatin state, gene expression is regulated to influence key cellular activities such as the cell cycle, DNA damage response and repair, oncogene signal transduction pathways that promoting carcinogenesis [45]. In the regulation of these histone modifications, the related proteins are generally divided into three categories: writers that add the corresponding groups to the histones; erasers that remove these groups from the histones; readers that recognize the modifications on the histones and regulate DNA transcription [46]. The coordinated activity of writers, erasers, and readers has a decisive effect on modulating ferroptosis sensitivity in BC cells.

Histone methylation is a common form of histone modification that can regulate ferroptosis. HEPH is a multi-copper ferroxidase that plays a vital role in iron transport from the intestine to the blood [47]. The H3K9 methyltransferase G9a mediates hypermethylation of the HEPH gene promoter, thereby suppressing HEPH expression and promoting BC development. Further research found that the histone deacetylase HDAC1 cooperates with G9a to intensify this suppression [48]. SETDB1 is another histone methyltransferase that promotes the accumulation of histone H3 lysine 9 trimethylation (H3K9me3) at the SLC7A11 promoter, thereby interfering with SLC7A11 expression and inhibiting ferroptosis [49].

Unlike methylation, lysine-specific demethylase 1A (KDM1A) is an enzyme that participates in histone demethylation. Studies have found that the expression of KDM1A is increased in BC cells, and its high expression is closely related to a poor prognosis [50]. The BC cells increase KDM1A expression and then remove the upregulated SUMOylation of SLC7A11 mediated by PIAS4, thereby stabilizing the SLC7A11 protein and preventing ferroptosis [51].

At present, research on histone acetylation and deacetylation is relatively abundant and has provided clearer regulatory roles of these modifications in the ferroptosis process of BC. Lysine acetyltransferase 5 (KAT5) is an upstream regulatory factor of GPX4. Downregulation of KAT5 can inhibit the expression of GPX4, leading to ferroptosis and inhibiting BC cell proliferation [24]. In addition, the hepatocyte nuclear factor 4 alpha (HNF4α) is able to recruit the histone acetyltransferase p300/CBP to enhance SLC-7A11 expression; it thereby inhibits ferroptosis and promotes tumor development. Therefore, HNF4α is necessary for ferroptosis in BC [52].

Histone deacetylase (HDAC), as an essential enzyme complex involved in histone modification. As shown in studies, HDAC may utilize its catalytic function to enhance the combination of DNA with histone, then it reduces the expression levels of m6A erasers FTO and ALKBH5. The HDAC inhibitor HADCi promotes HDAC-mediated demethylation of FSP1 mRNA, thereby reducing its expression and inhibiting the antioxidant effect of the FSP1-CoQ10-NAD(P)H axis [53]. Combining omics-based drug-HIFU therapy with HDAC inhibition can effectively promote ferroptosis and activate the anti-tumor immune response [54]. However, there are also reports indicating that BC may acquire resistance to HADCi through regulation of HDAC and other ways; As a result, treatment effectiveness has decreased [55]. HDAC is still a promising predictive biomarker that may help determine the neoadjuvant chemotherapy regimen [56, 57].

In addition to the more commonly occurring histone modifications, other modifications such as histone lactylation are also involved in tumorigenesis [58]. The zinc finger protein ZAF64 that is highly expressed in BC can promote the transcription of ferroptosis-related genes GCH1 and FTH1. Cancer-associated fibroblasts have been found to secrete lactate that can up-regulate histone lactylation in TNBC cells, thereby promoting the expression of ZAF64 and conferring resistance to doxorubicin (DOX) and inhibiting ferroptosis [59].

Although the functions of specific histone-modifying proteins in BC ferroptosis have not yet been fully clarified, they have emerged as key therapeutic targets with significant clinical potential. For instance, p53 gain-of-function (GOF) mutants bind to and upregulate the histone methyltransferase MLL1, which results in genome-wide increases in histone methylation. The menin-MLL inhibitors can induce the ferroptosis and inhibit tumor development [60]. The inhibitor AZD1775 can compensate for the reduction of SLC7A11 expression by inhibiting the expression of SETDB1 and other pathways, thereby enhancing the cellular resistance to ferroptosis. This inhibitor shows efficacy in suppressing lung cancer growth and has also demonstrated inhibitory effects in BC [49]. Ketamine can also act as an inhibitor of KAT, suppresses ferroptosis and is expected to become a potential strategy for treating BC [24]. These histone-modifying inhibitors are all expected to undergo further research and become part of the clinical treatment regimens.

ncRNA in ferroptosis

Most genes in the entire genome transcribe non-coding RNAs. These non-coding RNAs mainly include long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs). According to current research, these non-coding RNAs are involved in all stages of BC development and metastasis (**Figure 3**).

miRNAs in ferroptosis: MiRNAs play significant regulatory roles in ferroptosis during BC, thereby attracting extensive attention [61]. These miRNAs mainly enhance or inhibit ferroptosis by influencing the expression of important proteins such as GPX4, SLC7A11, and ACSL4, thereby influencing BC development. Summarizing the mechanisms by which miRNAs regulate ferroptosis can enhance our understanding of their significance and aid in developing optimized treatment strategies for clinical application.
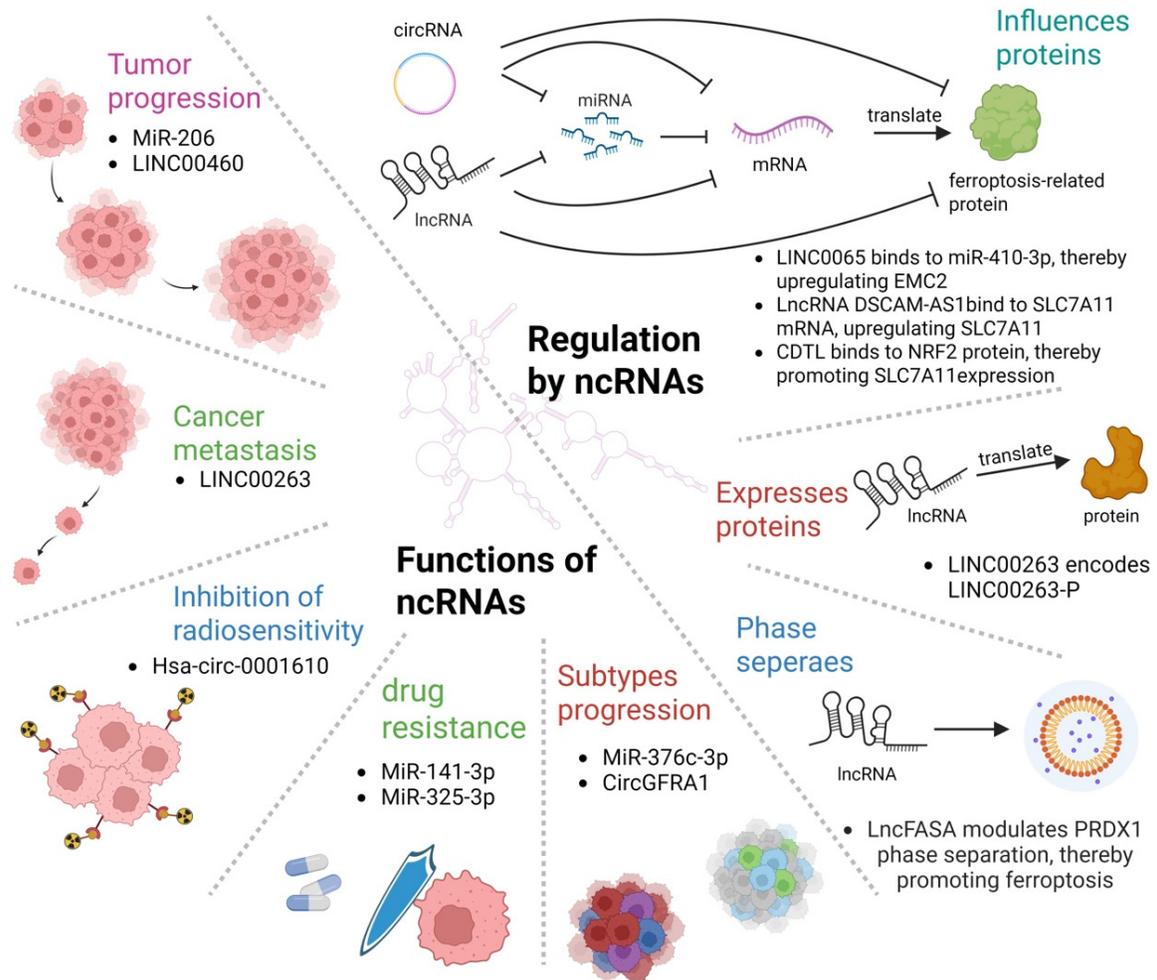
Figure 3. The regulation of ncRNAs in ferroptosis. Non-coding RNA (ncRNA), by regulating the expression of iron overload-induced cell death through positive feedback mechanisms and thereby interfering with protein expression associated with this type of regulated necrosis; in addition, it can also achieve such effects indirectly by affecting related transcription factors. Some long non-coding RNAs (lncRNAs) can not only encode functional peptides directly but also regulate the assembly of phase-separated biomolecular condensates containing ferroptosis-related proteins, thereby exerting a regulatory effect on the initiation and development of ferroptosis. The ferroptosis-modulating functions of ncRNAs collectively regulate tumorigenesis, tumor invasion, the modulation of radio-sensitivity, the development of drug resistance, and the specification of tumor subtypes in cancer.

The regulation of the transporter SLC7A11 by miRNAs has been extensively studied. SLC7A11 is crucial for glutathione synthesis and antioxidant defense. Its expression is regulated by multiple upstream miRNAs. The miR-153 is an upstream regulator of SLC7A11. By binding to the 3'-UTR of SLC7A11 mRNA, miR-153 can induce a reduction in the expression of SLC7A11, further interfering with the cell's antioxidant defense mechanism and thereby inducing ferroptosis due to oxidative stress [62]. Similarly, miR-5096 and miR-376c-3p can also respectively bind to SLC7A11 mRNA to inhibit its expression thereby inducing ferropto-

sis [63, 64]. Collectively, these miRNAs modulate cellular oxidative stress responses through their regulation of SLC7A11.

Apart from the well-studied SLC7A11, other proteins like GPX4 and ACSL4 are also important targets of miRNAs. Some miRNAs can directly regulate the expression of these proteins. MiR-324-3p directly targets GPX4, binding to its mRNA to downregulate expression, thereby inducing ferroptosis in BC cells by disrupting cellular antioxidant defense [65]. In BC tissues, the expression of miR-454-3p was significantly increased, which negatively regulated

Table 1. MiRNAs regulate ferroptosis in BC

Category	MiRNA	Role in BC	Impact on ferroptosis	References
SLC7A11	MiR-382-5p	Inhibits	Promotes	[88]
SLC7A11	MiR-153	Inhibits	Promotes	[62]
SLC7A11	MiR-376c-3p	Inhibits TNBC	Promotes	[64]
SLC7A11	MiR-5096	Inhibits	Promotes	[63]
SLC7A11	MiR-139-5p	Enhances the radiosensitivity of BC cells	Promotes	[72]
GPX4	MiR-324-3p	Inhibits	Promotes	[65]
ACSL4	MiR-454-3p	Inhibits lipid metabolism in BC	Inhibits	[66]
TMEM189	MiR-499a-5p	Inhibits	Promotes	[94]
STAT3	MiR-106a-5p	Inhibits the malignant progression of the BC	Promotes	[95]
MTOR	MiR-144-3p	Promotes	Inhibits	[43]
MAL2	MiR-320a	Inhibits	Promotes	[96]
Keap1	MiR-141-3p	Promotes paclitaxel resistance	Inhibits	[97]
Sp1/CD98hc	MiR-128-3p	Inhibits	Promotes	[98]
Sp1/	MiR-335-5p	Inhibits	Promotes	[67]
AIFM2	MiR-1228	Attenuates HER-2-positive BC progression	Promotes	[73]
EMC2	MiR-410-3p	Correlates with poor prognosis and tumor immune infiltration in BC	Promotes	[42]
CERS2	MiR-206	Inhibits	Promotes	[99]
GSTP1	MiR-325-3p	Enhances chemosensitivity and restores paclitaxel sensitivity in resistant TNBC cells	Promotes	[100]

the expression of ACSL4, thereby inhibiting lipid metabolism and ferroptosis, and promoting tumor development [66]. There are also some miRNAs that exert their effects on these proteins by acting on their regulatory factors. For example, miR-335-5p is a tumor suppressor in various cancers, including BC. It can negatively regulate Sp1, which is an important transcription factor for GPX4, thereby promoting ferroptosis in cells and inhibiting the development of BC [67].

In addition to the general miRNAs that directly affect the antioxidant system, there are also some miRNAs that mainly affect cell autophagy and oxidative stress and thereby influence ferroptosis. For instance, miR-144-3p can inhibit ferroptosis in tumors by suppressing mTOR, a key inhibitor of autophagy [43]. MiR-106a-5p can inhibit the expression of STAT3. This downregulation promotes ferroptosis, potentially through mechanisms involving lysosomal membrane permeabilization [68]. By targeting STAT3, miR-106a-5p can induce ferroptosis in BC.

MiRNAs themselves serve as important targets within epigenetic regulatory networks. Adenosine deaminases acting on RNA 1 (ADAR1) can regulate miR-335-5p thus affecting the ferroptosis in BC [67]. The lncRNA SNHG8 can also promote BC cell migration via miR-335-5p/PYGO2 axis [69]. Circular RNA circ-0000643 can induce the upregulation of SLC7A11 expression by sequestering miR-153 [62]. Collectively, these examples show that miRNAs are regulated by upstream factors, including various other ncRNAs and proteins. These regulatory networks of epigenetic modifications are interwoven, highlighting the complexity of the regulatory landscape. **Table 1** summarizes the impact of representative miRNAs on BC development via the ferroptosis pathway.

The function of circRNAs in ferroptosis: Apart from miRNAs, circRNAs are also important epigenetic regulatory factors that significantly contribute to initiating and promoting ferroptosis in BC. These circRNAs modulate the expression or activity of downstream ferroptosis-related proteins by interacting with other miRNAs or proteins, thereby indirectly influencing the development of BC [70, 71]. Understanding the mechanism by which these circRNAs affect ferroptosis in BC will help us gain new insights into BC and facilitate the development of a new round of highly effective targeted drugs.

Table 2. CircRNAs regulate ferroptosis in BC

Category	CircRNA	Role in BC	Impact on ferroptosis	References
MiR-153/SLC7A11	Circ-0000643	Promote	Inhibit	[62]
MiR-139-5p/SLC7A11	Hsa-circ-0001610	Inhibits the radiosensitivity of BC cells.	Inhibits	[72]
MiR-106a-5p/STAT3	CircRHOT1	Promotes progression of BC	Inhibits	[95]
MiR-1228/FSP1	CircGFRA1	Facilitates the malignant progression of HER-2-positive BC	Inhibits	[73]
OTUB1/SLC7A11	Circ-BGN	Resistance in HER2-positive BC	Inhibits	[101]
OTUB1/SCD1	Hsa-circ-0019512	Promotes BC cell growth	Inhibits	[74]
NRF2/SLC7A11	CDTL	Promotes	Inhibits	[75]
HSPB1	CrVDAC3	Resistance in HER2-low BC	Inhibits	[102]
GCH1	CircSEPT9	Attenuates the DDP chemosensitivity of TNBC cells	Inhibits	[103]

The primary mechanism by which circRNAs exert their effects is through binding to miR-NAs, thereby relieving the inhibitory effect of miRNAs on downstream proteins. These downstream proteins mainly include SLC7A11, AIFM2 and STAT3. Apart from the circ-0000643 influencing miR-153/SLC7A11 axis mentioned above, hsa-circ-0001610 also participates the ferroptosis. The research found that its expression is elevated in irradiated BC cells. Further research indicated that hsa-circ-0001610 can inhibit the effect of miR-139-5p, thereby increasing the SLC7A11 expression, helping cancer cells resist ferroptosis and reduce radiosensitivity [72]. CircGFRA1 functions through a similar miRNA-dependent mechanism. Specifically, it sequesters miR-1228 to relieve its inhibition of FSP1, thereby inhibiting ferroptosis via the FSP1-CoQ10-NAD(P)H axis and promoting the malignant progression of HER2-positive BC [73].

In addition, some circRNAs also exert their functions by acting on other proteasomes, such as the deubiquitinase OTUB1 and transcription factor NRF2. Stearoyl-CoA desaturase 1 (SCD1) plays a crucial role in fatty acid metabolism by primarily facilitating the transformation of saturated fatty acids into monounsaturated fatty acids. Therefore, SCD1 can regulate the lipid peroxidation and reduce cellular sensitivity to ferroptosis. Research has identified an upstream circular RNA, circSCD1 (hsa-circ-0019512). The high expression of this circRNA can weaken SCD1 ubiquitination through the circSCD1/OTUB1/SCD1 axis, stabilizing the SCD1 protein, thereby inhibiting ferroptosis and promoting BC development [74]. Similarly, the cDTL (a circular RNA derived from DTL gene) can directly bind to the NRF2 protein, thereby increasing SLC7A11 expression, inhibiting ferroptosis, and then promoting BC development [75].

Although research on circRNAs is not as extensive than that on other ncRNAs, their role in the ferroptosis process of BC development has been explored. These circRNAs can bind to other miRNAs and proteins, making the mechanism much more complicated, but a clearly defined path is also very useful for drug screening (**Table 2**).

LncRNAs in ferroptosis: Long non-coding RNAs (lncRNAs) are defined as RNA molecules over 200 nucleotides in length that do not encode proteins [76]. LncRNAs act as epigenetic regulators of ferroptosis in tumors, and they are involved in the progression of BC. By activating or inhibiting different pathways to promote or prevent the occurrence of ferroptosis, it also affects the development of BC and determines whether there is drug resistance [77].

As mentioned before, lncRNA can regulate cellular ferroptosis by interacting with miRNA. LncRNA PTPRG-AS1 can target miR-376c-3p to upregulate the expression of SLC7A11, thereby inhibiting ferroptosis and promoting the development of BC [64]. Similarly, LINC0065 can upregulate the expression of EMC2 by regulating the miR-410-3p/EMC2 axis, and elevated EMC2 is associated with poor prognosis of BC and tumor immune infiltration [42].

Table 3. LncRNAs regulate ferroptosis in BC

Category	LncRNA	Role in BC	Impact on ferroptosis	References
MiR-376c-3p/SLC7A11	LncRNA PTPRG-AS1	Promotes TNBC	Inhibits	[64]
MiR-320a/MAL2	LINC00460	Promotes	Inhibits	[96]
MiR-206/CERS2	HOTAIR	Promotes	Inhibits	[99]
GPX4/SLC7A11	LncRNA OTUD6B-AS1	Promotes	Inhibits	[104]
FUS/NR3C1/SLC7A11	LncRNA NORAD	Promotes	Inhibits	[105]
IGF2BP1/GPX4	LncRNA RUNX1-IT1	Promotes	Inhibits	[106]
SLC7A11	LncRNA DSCAM-AS1	Promotes	Inhibits	[79]
PDE4D/cAMP/Ca2$^+$	LINC00152	Tamoxifen resistance in ER$^+$ BC	Inhibits	[107]
P53	LncRNA P53RRA	Inhibits	Promotes	[108]
PRDX1	LncFASA	Inhibits TNBC	Promotes	[78]
HCP5-132aa	LncRNA-HCP5	Promotes the Progression of TNBC	Inhibits	[82]
LINC00263-P	LINC00263	Promotes BC osteolytic bone metastasis	Inhibits osteoclast ferroptosis	[83]
Unknown	LncRNA-H19	Promotes autophagy	Inhibits	[109]

Beyond miRNA sponging, lncRNAs can also function by interacting with proteins or mRNA, thereby indirectly regulating ferroptosis-related proteins such as GPX4 and SLC7A11. LncFASA can bind to the peroxidase PRDX1 and further disrupt the cellular ROS homeostasis through the SLC7A11/GPX4 axis, thereby promoting the ferroptosis. Studies have shown that lncFASA expression is highly correlated with the overall survival rate of BC patients, highlighting its potential as a therapeutic target in BC [78]. Another example is lncRNA DSCAM-AS1, which can bind to m6A sites on SLC7A11 mRNA, then enhancing its stability and consequently upregulating the expression of SLC7A11 to inhibit ferroptosis [79].

LncRNAs can also modulate ferroptosis through distinct mechanisms. One such mechanism involves modulating biomolecular condensate formation via liquid-liquid phase separation (LLPS), thereby regulating downstream protein expression. Researchers found that RUNX1 intronic transcript 1 (RUNX1-IT1) can promote the formation of insulin like growth factor 2 mRNA binding protein 1 (IGF2BP1) liquid-liquid phase separation (LLPS) biomolecular condensates. Furthermore, through the action of IGF2BP1, the stability of GPX4 mRNA is enhanced, which in turn increases the inhibition of ferroptosis by GPX4 and promotes the occurrence of BC tumors [80].

Notably, although most lncRNAs do not encode proteins, some studies still found that a small subset can translate proteins [81]. In TNBC, the oncogenic lncRNA HLA complex P5 (HCP5) encodes a protein, HCP5-132aa. This protein regulates GPX4 expression and cellular ROS levels, thereby inhibiting ferroptosis and promoting TNBC progression [82]. The protein LINC00263-P encoded by LINC00263 can also reduce ferroptosis in osteoclasts through a series of complex mechanisms, induce osteoclastogenesis, thereby promoting the osteolytic bone metastasis in BC [83].

Beyond serving as promising drug targets, lncRNAs also hold potential for constructing prognostic prediction models in various cancers [84, 85]. For instance, in BC, some researchers selected 8 ferroptosis-related lncRNAs (AC108474.1, AL133467.1, LINC01235, AC072039.2, TDRKH-AS1, USP30-AS1, MAPT-AS1, and LIPE-AS1) to construct a predictive model. The risk score derived from this model significantly predicts distinct immune cell infiltration landscapes between high- and low-risk groups, as well as prognostic outcomes under different drug treatments. Notably, its predictive value remains consistent across major BC subtypes, including HR-Her2+, luminal, and TNBC [80]. In another study, a prognostic model was established based on seven lncRNAs with differential expression linked to both ferroptosis and immunity. This model can effectively serve as prognostic and diagnostic biomarker for breast infiltrating duct and lobular carcinoma [86]. These predictive models are expected to serve as auxiliary tools for prognostic assessment in the clinical management of BC patients. In summary, **Table 3** outlines

the roles of key lncRNAs in modulating ferroptosis during BC.

Conclusion

In recent years, research on ferroptosis provided a considerable number of mechanisms and translation for breast cancer (BC). The epigenetic regulation of ferroptosis has become an essential axis for BC initiation, progression, and treatment response. This review offers a systematic and in-depth summary of the current evidence for the mechanism by which DNA methylation, histone modifications, and non-coding RNAs (especially miRNAs and lncRNAs) regulate the key components of ferroptosis machinery and iron metabolism regulators. Based on context-specific epigenetic pathways that sensitize or inhibit ferroptosis among molecular BC subtypes, with an emphasis on the influence of such mechanisms on redox equilibrium, mitochondrial function and altered membrane phospholipid composition. Additionally, the new prospects of epigenetic-ferroptotic crosstalk as a basis for rational combinatorial strategies, such as using epigenetic modulators in combination with ferroptosis inducers, to overcome drug resistance and enhance therapeutic specificity. Considering the diverse heterogeneity of intra- and inter-tumor heterogeneity in BC, such as different genetic backgrounds, transcriptional patterns, and micro-environmental interactions, accurate molecular subtyping and early biomarker identification of ferroptosis are likely to bring high value to risk stratification, treatment direction indication, and dynamic treatment effect observation under individualized oncology scenarios [87]. Numerous studies have shown that epigenetic modifications, including DNA hypomethylation in the promoter regions of ferroptosis-regulatory genes and abnormal expression of non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs), are dynamically altered during the initiation, progression and treatment response of breast cancer (BC) [42]. Emerging evidence strongly supports that some lncRNAs are robust independent prognostic biomarkers of BC, and there is a validated correlation between them and recurrence-free survival, overall survival, and resistance to treatment [80, 86]. These collectively indicate that epigenetic dysregulation in the ferroptosis pathway, mainly transcriptional silencing or activa-

tion mediated by DNA methylation, histone modification, and lncRNA-mRNA or lncRNA-miRNA interactions, is a biologically coherent and clinically practicable axis. Such modifications are expected to become novel mechanistically informed diagnostic and prognostic biomarkers, potentially enabling early detection, molecular subtyping, risk stratification, and real-time monitoring of therapeutic ferroptosis induction in clinical oncology practice. In BC therapy, the epigenetic regulation of key genes associated with ferroptosis, such as SLC7A11 [88], GPX4 [66] and ACSL4 [67], may be necessary directions for research owing to their essential functions in disease development. Under the premise that selective regulators which have been therapeutic targets can be killed more efficiently by cancer cells, it is likely to enhance the effect of treatment. In addition, for drug-resistant BC, it was found that combining two traditional ways with a new ferroptosis inducer can significantly enhance the anti-tumor effect [54].

Little attention has been paid to it in scholarly work. There is a lack of research on the molecular mechanism of ferroptosis in BC. In addition, the roles of key intrinsic and extrinsic factors, such as autophagy and components of the tumor microenvironment, in regulating ferroptosis in BC are not yet fully understood. The complex interactions between these elements and their effects on ferroptosis cell death need to be studied systematically in more detail [89]. In addition, although many potential therapeutic targets have been found, most evidence remains confined to preclinical studies, and in vitro or animal experiments are primarily used; there is a severe shortage of clinical trials. An incomplete mechanistic understanding also fails to enable precise prediction of potential interference of targeting ferroptosis in normal cells, thereby increasing the probability of unexpected and adverse clinical outcomes.

Although some previous studies have investigated the connection between epigenetics and ferroptosis dynamically, there is currently limited research on this issue. Research has shown that ferroptosis can influence epigenetic modifications through metabolic reprogramming. Recently, a report has shown that ferroptosis strongly induces the accumulation of lactic acid (LA) and this process leads to protein lacty-

lation, ultimately conferring resistance to lung adenocarcinoma (LUAD) cells against ferroptosis. In addition, a previously uncharacterized lactylation modification-SUMO2-K11 lactylation (SUMO2-K11la), which is significantly upregulated upon ferroptosis induction and functions as a key regulatory determinant. This modification can inhibit the SUMOylation of ACSL4 and promote its degradation to inhibit ferroptosis [90]. N6-methyladenosine (m6A) is a highly common modification that occurs after mRNA transcription. Duan *et al.* discovered that m6A methylation modification is linked to ferroptosis triggered by cigarette smoke in human bronchial epithelium [91].

Ferroptosis often occurs in the presence of severe redox and metabolic perturbations. The rapid increase of ROS can cause oxidative damage to the cell, which is then reflected by changing its relevant enzymatic activity DNMTs, HDACs and other substances' subsequent triggering of epigenetic modification [92, 93] will also increase the generation of peroxides. Based on this, it is suspected that in BC, ferroptosis-driven epigenetic modifications may induce a maladaptive positive feedback loop. This loop may be related to the silencing of tumor suppressor genes, the entrenchment of pro-tumorigenic metabolic programmers, and the alteration of cellular ferroptosis sensitivity, thereby shaping disease progression and therapeutic responses. Therefore, the potential mechanisms mentioned above may collectively provide a possible explanation for the close relationship between ferroptosis and epigenetics in BC. There is a deficiency in research on the effects of ferroptosis on the epigenome, and studies have been lacking. In addition, there may be a more profound connection among all aspects of the two-way influence in the future; this will require further exploration.

Despite the dynamic nature of epigenetic alterations in cancer cells, utilizing these changes to construct precise predictive models and develop individualized treatment strategies holds great promise. In this case, the induction of ferroptosis is likely to become an alternative approach for co-treatment. We expect that this review will provide valuable references and stimuli for follow-up studies on the optimization of therapies for BC.

Disclosure of conflict of interest

None.

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