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Ferroptosis contributes to the progression of female-specific neoplasms, from breast cancer to gynecological malignancies in a manner regulated by non-coding RNAs: Mechanistic implications

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ABSTRACT

Ferroptosis, a recently identified type of non-apoptotic cell death, triggers the elimination of cells in the presence of lipid peroxidation and in an iron-dependent manner. Indeed, ferroptosis-stimulating factors have the ability of suppressing antioxidant capacity, leading to the accumulation of reactive oxygen species (ROS) and the subsequent oxidative death of the cells. Ferroptosis is involved in the pathophysiological basis of different maladies, such as multiple cancers, among which female-oriented malignancies have attracted much attention in recent years. In this context, it has also been unveiled that non-coding RNA transcripts, including microRNAs, long non-coding RNAs, and circular RNAs have regulatory interconnections with the ferroptotic flux, which controls the pathogenic development of diseases. Furthermore, the potential of employing these RNA transcripts as therapeutic targets during the onset of female-specific neoplasms to modulate ferroptosis has become a research hotspot; however, the molecular mechanisms and functional alterations of ferroptosis still require further investigation. The current review comprehensively highlights ferroptosis and its association with non-coding RNAs with a focus on how this crosstalk affects the pathogenesis of female-oriented malignancies, from breast cancer to ovarian, cervical, and endometrial neoplasms, suggesting novel therapeutic targets to decelerate and even block the expansion and development of these tumors.

1. Introduction

Female-oriented neoplasms, including breast and gynecological malignancies, are considered one of the leading causes of death in the global female population. Genetics, age, lifestyle and eating habits, menopause state, and history of being exposed to carcinogens are the principal determinants of the onset and frequency of these types of malignancies. Treatment of female-specific cancers, similar to other cancers, is considered a huge challenge, and eliminating tumor cells without hurting non-cancerous cells is a key concept of cancer therapy. Following the discovery of regulated cell death (RCD) researchers found that the cell death process can potentially be controlled [1–3]. For a long time, apoptosis was considered the only type of RCD, and a broad range of anti-tumor medications were designed to stimulate apoptosis in cancer cells; however, it became clear that tumor cells exhibit, and develop, various degrees of resistance to these drugs and, thus, apoptosis [4]. Accordingly, recent studies have attempted to target non-apoptotic cell death pathways for possible reduction of cancer cell resistance against apoptosis-inducing drugs.

In the context of non-apoptotic RCDs, ferroptosis as an iron-dependent type of RCD, was first characterized in 2012 [5].

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Abbreviations

BC	breast cancer
ceRNA	competing endogenous RNA
circRNA	circular RNA
DDP	cisplatin
DEFerlncRNA	differentially expressed lncRNAs
EC	endometrial cancer
ecEM	ectopic endometrium cells
ESC	endometrial stromal cell
euEM	normal endometrium cells
FerroScore	ferroptosis score
FIRLs	ferroptosis and iron-metabolism related lncRNAs
GC	gynecological cancer
GSH	glutathione
HCC	hepatocellular carcinoma
lncRNA	long non-coding RNA
MDA	malondialdehyde
miRNA	microRNA
ncRNA	non-coding RNA
OC	ovarian cancer
ORFs	open reading frames
OS	overall survival
PI3K	phosphoinositide 3-kinase
RCD	regulated cell death
ROS	reactive oxygen species
TNBC	triple-negative breast cancer
UTR	untranslated region

Ferroptosis is responsible for the inhibition of RAS mutant tumor cells and it was subsequently shown that this process is strongly related to tumor cell death [5,6]. This RCD pathway is modulated by the canonical *TP53/p53* tumor suppressor gene through blocking the cystine/glutamate antiporter/xCT/system xc^- [7,8]. Interestingly, many tumor cells, although resistant to common therapeutic interventions, are sensitive to ferroptosis. Thus, induction of this cell death mechanism might help eradicate those cells [9]. Moreover, ferroptosis is also associated with immunotherapeutic interventions, as it can be triggered in tumor cells by T cells and IFNG/IFNγ (interferon gamma) [10].

According to recent evidence, the ferroptotic flux can be regulated by non-coding RNA (ncRNA) transcripts, among which microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) play the most important roles [11,12]. In association with ferroptosis, the corresponding ncRNA molecules participate in iron metabolism, as well as ferroptosis-related amino acid metabolism to regulate the ferroptotic flux [13]. Furthermore, reactive oxygen species (ROS) metabolism is also regulated by ncRNAs, and it is accepted that intracellular lipid ROS accumulation is a major stimulant for ferroptosis [14]. Moderate elevation of ROS levels inside cells triggers cell proliferation, survival, and malignant transformation; however, ncRNAs have the ability to modulate ROS levels to maintain redox dynamics and the decrease in ROS blocks ferroptosis [11]. In conclusion, ferroptosis, as a critical process in cancer development, can be controlled by ncRNAs, leading to either the progression or suppression of malignant conditions. In the current review, the modulatory mechanisms related to ferroptosis are first summarized, and then the involvement of this non-apoptotic RCD in female-oriented malignancies, from breast cancer to endometrial neoplasm, under the regulation of ncRNAs is discussed. Current application status and opportunities of targeting ferroptosis in female cancer therapies are then considered.

2. Female-specific neoplasms: from breast cancer to common gynecological malignancies

Breast cancer (BC) is the most common type of female malignancy with more than 2 million cases each year [15]. Breast tumors are often formed and expanded due to ductal hyperproliferation and can represent either a benign or malignant phenotype as the result of the existing relationship between continuous induction and varied tumorigenic parameters. Stromal cells and macrophages residing in the tumor microenvironment significantly affect the progression of this neoplasm [16,17]. In detail, macrophages provoke the angiogenic processes and also increase the immune resistance of tumor cells through producing a mutagenic inflammatory microenvironment [18]. Moreover, DNA methylation, as well as other epigenic modifications developed in the tumor microenvironment, elevates the risk of BC tumorigenesis. Consistent with this finding, cancer stem cells also have a role in BC carcinogenesis, immune evasion, recurrence, and therapeutic resistance (Fig. 1) [19].

In the case of other female-oriented neoplasms, gynecological cancers (GCs) are of great importance among women worldwide. Ovarian cancer (OC), as one of the well-studied GC subtypes, is not as common as other female malignancies but unfortunately has the highest rate of cancer mortality. It been estimated that OCs have an incidence of 11.7–12.1 per 100,000 in European countries and the U.S, with a lower rate among the Middle East and Asian nations [20,21]. Regarding the pathology of OC, a non-homogenous cluster of malignancies are formed and expanded in the germ cells, as well as epithelial cells, fallopian tube, and mesenchyme with different patterns of etiology and molecular biology. Nonetheless, the majority of OCs have been detected with an epithelial origin [22]. Most OC patients are diagnosed when the disease has entered its advanced progression levels, terminating with high mortality rates. Therefore, it is crucial to improve preventive measures and allow a timely diagnosis, as early detection of OC provides a higher survival rate up to 93% [19,23].

Cervical cancer is the other GC in this field, which is categorized as the fourth most common type of malignancy and the fourth prime cause of cancer deaths among the female population (BC, colorectal cancer, and lung neoplasm are the first three leading causes). The Lancet Global Health has reported that approximately 570,000 women experienced CC in 2018, among which 311,000 died [24]. It has been elucidated that human papillomavirus/HPV infections, especially those being developed by carcinogenic species, are the major leading cause of CC onset. Therefore, human papillomavirus screening, along with vaccination against these viral species can improve the preventive approaches [25,26]. CCs are histologically divided into two principal subtypes, including adenocarcinoma (25% of cases) and squamous cell carcinoma (70% of cases) [27,28]. The conventional Pap smear test can help detect early alterations in the cervical epithelium and thus the early stage of invasive CC [29]. Beyond the ovary and uterine cervix, the endometrium can also be affected by malignancy. In this context, endometrial cancer (EC) is considered as the most common GC with more than 61,000 cases detected yearly in the U.S [30,31]. EC primarily affects the glandular epithelium, lining the uterus, which is typically responsible for releasing substances required for menstruation or even embryonic development [32]. The onset of EC is principally affected by obesity, along with hormonal deregulation, reproductive parameters, and being genetically vulnerable. This GC has a heterogenous genetic pattern except for a subgroup of patients with a cancer predisposition syndrome, Lynch syndrome, stimulated by the germline changes of DNA mismatch repair genes such as *MLH1*, *PMS2*, *MSH2*, and *MSH6*. Furthermore, ECs are represented through a high degree of many other germline mutations in malignancy predisposition genes (Fig. 1) [19,33,34].

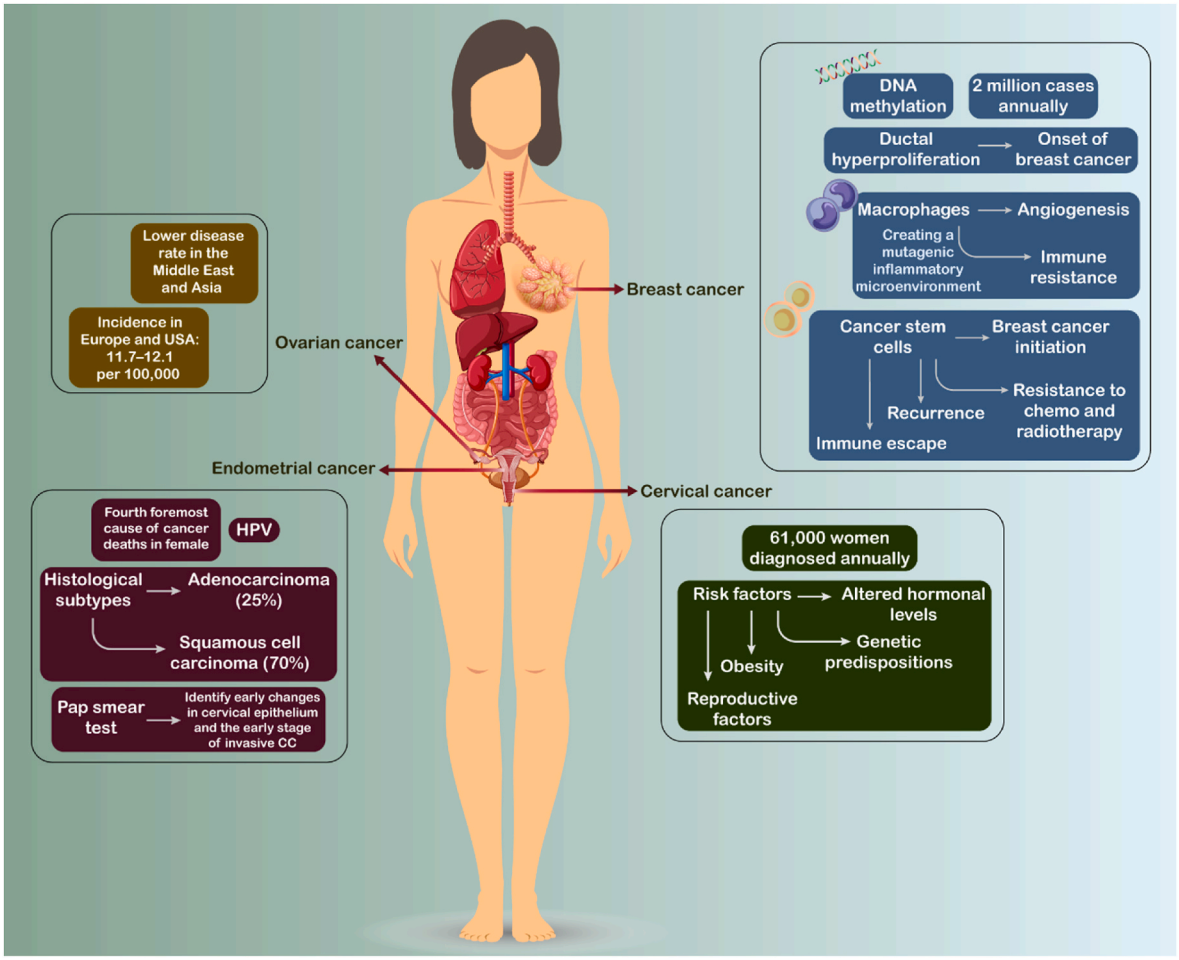

Fig. 1. Female-specific cancers: Breast, ovarian, cervical, and endometrial cancers. (A) Breast cancer: The most common female malignancy (although also occurring in males), BC arises from ductal hyperproliferation and is influenced by the tumor microenvironment. Macrophages and epigenetic modifications in this environment contribute to BC progression. Cancer stem cells also play a role in BC development, immune evasion, recurrence, and resistance to treatment. (B) Ovarian cancer: Though less frequent than other GCs, OC has the highest mortality rate. OC encompasses various types of malignancies with diverse origins. Most cases are of epithelial origin, and early detection is crucial due to high mortality rates in advanced stages; (C) Cervical cancer: The fourth most common female malignancy, CC is primarily caused by human papillomavirus (HPV) infections, particularly carcinogenic strains. Vaccination and screening programs are crucial for prevention. Histologically, CC is divided into adenocarcinoma and squamous cell carcinoma subtypes. (D) Endometrial cancer: The most common GC of the uterus, EC affects the glandular epithelium and is influenced by factors such as obesity, hormonal imbalances, and genetics. Most cases of EC exhibit a heterogeneous genetic pattern, except for those with Lynch syndrome.

3. Ferroptosis: A non-apoptotic type of regulated cell death

Iron (Fe), with a vast array of biological roles in the human body, is critical for cell survival, due to its role in oxygen transport, DNA biosynthesis, and ATP production [35,36]. Moreover, iron is strongly correlated with the onset and expansion of tumors, and thus iron metabolism defects might result in tumor growth [37,38]. Once iron-dependent oxidative phosphorylation has progressed in mitochondria, cells generate ROS and ATP. Increasing ROS levels result in oxidative stress responses, leading to cell injury or death [39]. In this context, ferroptosis primarily results from the aggregation of iron--dependent lipid peroxide (Fig. 2) [40,41].

Although the term ferroptosis was first used in 2012, the inducers of this non-apoptotic RCD were discovered before it was named. During a large-scale analysis conducted in 2003, Stockwell et al., noticed that a newly discovered compound called erastin could provoke death of RAS-mutated tumor cells in a non-apoptotic manner [12]. Later, other chemicals, such as sorafenib, artemisinins, and 1, 2-dioxolane (FINO2), as a cyclic peroxide, were affirmed to stimulate ferroptosis [40,42,43]. Mechanistically, ferroptosis differs from other RCDs and is biochemically identified by intracellular iron and ROS accumulation, lipid peroxidation, and depletion of glutathione and lipid repair enzymes [44]. Moreover, autophagy, which is a highly conserved eukaryotic cellular recycling process [45–47], has a strong correlation with ferroptosis, as it triggers the removal of proteins related to ferroptosis through ferritinophagy and chaperone-mediated autophagy [48].

In comparison to the other types of regulated cell death processes, it is known that PCD is a critical physiological process in all living organisms, with roles spanning embryonic development, organ function maintenance, aging, and immune response regulation. Phagocytic processes efficiently remove dead cells under normal conditions. Apoptosis, necroptosis, and pyroptosis are the most well-characterized forms of PCD. Apoptosis is a highly conserved cell death pathway across different animal species that has been extensively studied for decades [49]. Initially considered the sole regulated PCD mechanism, apoptosis involves the controlled release of CYCS (cytochrome *c*, somatic) from mitochondria. A delicate balance between pro-apoptotic (BCL2 family) and anti-apoptotic proteins regulates this process. Additionally, initiator caspases (CASP8, CASP9 and CASP10) together with effector caspases (CASP3, CASP6 and CASP7) play crucial roles during apoptosis activation. Apoptosis culminates in a series of distinctive events: nuclear membrane breakdown by CASP6, cleavage of intracellular proteins (e.

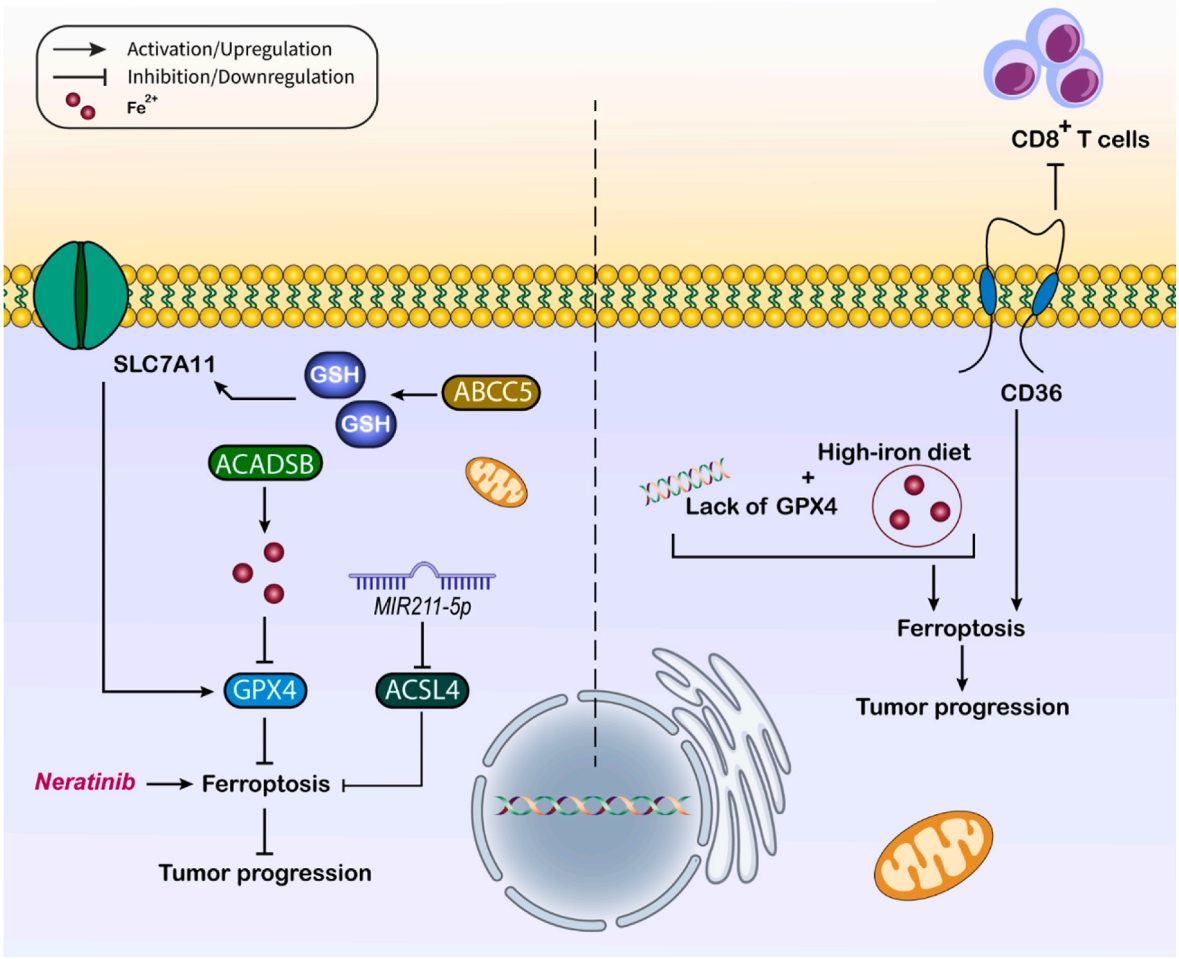

Fig. 2. Ferroptosis: a tumor-suppressor or an oncogenic process? With regard to the tumor suppressive effects of ferroptosis, it disrupts cell proliferation, migration, and invasion in various cancers, including blood malignancies and solid tumors. Studies suggest a negative correlation between ferroptosis and metastasis, with ferroptosis-silenced tumors exhibiting increased metastatic potential. Ferroptosis inducers such as neratinib may block brain metastasis in breast cancer models. Lower expression of ferroptosis inhibitors, including SLC7A11 and ABCC5, and higher expression of ferroptosis modulators such as ACSL4 and GPX4, are associated with better prognosis in some cancers. Conversely, in KRAS-driven pancreatic cancer models, ferroptosis induction via GPX4 knockdown or high-iron diet accelerate tumor progression. CD36 may suppress anti-tumor $CD8^+$ T cells by triggering ferroptosis, suggesting a context-dependent role.

g., PARP, lamin, etc.), membrane blebbing, and fragmentation of genomic DNA into nucleosomes [3,50,51]. These hallmarks are employed to identify the specific PCD pathway engaged [3,52].

Previously, apoptosis was contrasted with necrosis, a supposedly uncontrolled process leading to membrane rupture and leakage; however, recent research has identified necroptosis, a non-apoptotic regulated PCD pathway promoting tissue repair and pathogen detection [53,54]. Triggered by TNF/TNF-α (tumor necrosis factor) or other stimuli such as FAS-FASLG/FasL, TLRs (toll like receptors), and cytosolic nucleic acid sensors, necroptosis relies on TNFRSF1A/TNFR1 (TNF receptor superfamily member 1A) activation [53,55–58]. Whereas these pathways often activate proinflammatory and prosurvival NFKB/NF-κB (nuclear factor kappa B) signals, necroptosis is specifically induced when CASP8 is inhibited by microbes or drugs [59].

Furthermore, pyroptosis, as a PCD pathway triggered by inflammasome sensors (NLR family, AIM2 [absent in melanoma 2], MEFV [MEFV innate immunity regulator, pyrin]), culminates in membrane leakage. Inflammasomes detect pathogen-associated molecular patterns/PAMPs and danger/damage-associated molecular patterns/DAMPs, acting as a defense mechanism against pathogens and cellular stress [60]. This lytic cell death prevents microbial spread and alerts the immune system but can lead to pathological inflammation if dysregulated. Initially thought to be CASP3-dependent apoptosis, pyroptosis was distinguished due to its reliance on CASP1 [60,61]. Parenthetically, the term "pyroptosis" reflects the inflammatory nature ("pyro" meaning fire) and programmed cell death aspect ("ptosis" meaning falling) [62].

Interestingly, cells that experience ferroptosis present different morphological characteristics compared to apoptosis and/or autophagy; for instance, the cell membrane is ruptured during ferroptosis, whereas it is not impaired through apoptotic or autophagic fluxes. In ferroptosis, mitochondrial atrophy, along with the disappearance of the mitochondrial ridge, without any change in nucleus size except for chromatin condensation are considered as the specific characteristics [63]. Recently, ferroptosis has been found to play crucial roles in the pathogenesis of multiple diseases, including a vast array of malignancies. Once the ferroptosis-related regulatory molecular mechanism(s) is deeply explored, the interaction between ferroptosis and cancer development will be better elucidated. As mentioned above, the modulation of ferroptosis is controlled by particular signaling pathways through iron accumulation, lipid peroxidation, and cellular membrane impairments, and thus ferroptosis can be regulated by specific drugs or genetic interventions. Within this context, regulation of homeostasis between oxidative and antioxidant systems is considered the prime mechanism in ferroptosis [64–67]. Thereby, it is expected that cancerous conditions can be ameliorated or even cured by exerting specific interventions into the ferroptotic flux.

4. Ferroptosis plays a dual role in cancer

According to the existing evidence, ferroptosis can serve as a tumor suppressive flux in many blood malignancies, as well as solid tumors to affect multiple steps from the cell cycle and proliferation to tumor expansion [68]. In this context, cytosolic GOT1 (glutamic-oxaloacetic transaminase 1), which is necessary for oxidant/antioxidant balance, blocks cell proliferation and increases cytotoxicity, especially when used in combination with the ferroptosis-inducing agent RSL3 [69,70]. Other than cell proliferation, ferroptosis also blocks the migration of tumor cells, and thus suppresses tumor invasion. As an example, KLF2/Krüppel-like factor 2 (KLF transcription factor 2) can repress tumor cell migration and invasion in clear cell renal carcinoma through GPX4 (glutathione peroxidase 4)-mediated regulation of ferroptosis [71]. ACSL4 (acyl-CoA synthetase long chain family member 4) is another ferroptosis modulator in this regard that can act at downstream of the miRNA *MIR211-5p*, which suppresses cell proliferation, as well as migration and invasion in hepatocellular carcinoma (HCC) [72].

Ferroptosis is also correlated with metastasis in a negative manner, as it has been revealed that metastatic trait is more common in ferroptosis-silenced tumors compared to those with activated ferroptosis [73,74]. Additionally, in HCC, ferroptosis inhibition is closely related to worse tumor expansion, high degrees of metastasis, and poor prognosis [75]. In line with this fact, Liu et al. indicated that resistance against ferroptosis may enhance the probability of metastasis, which can be reversed by ferroptosis inhibitors, such as the aforementioned GPX4 [76]. Consistent with this observation, ferroptosis inducers, such as neratinib as a pan-tyrosine kinase inhibitor, potentially block brain metastasis in a synergistic model of human $EGFR^{+}$ BC metastasis [63,77].

In clinical settings, ferroptosis has also been proposed to be in negative association with prognosis and overall survival (OS). Within this context, the overexpression of SLC7A11 provides a poor prognosis, specifically due to ferroptosis inhibition [78]. In clinical specimens collected from HCC patients, ABCC5 (ATP binding cassette subfamily C member 5) exhibits an overexpressed pattern with a negative interconnection with ferroptosis through stabilizing SLC7A11 and enhancing reduced glutathione (GSH) levels inside the cells. Sorafenib-resistant HCC cells also exhibit an increase in ABCC5 expression levels, indicating poor prognosis [79,80]. As indicated above, ACSL4 and GPX4 are ferroptosis modulators, and their expression can be utilized as a prognostic factor for disease-free survival. In detail, ACSL4 overexpression results in a better OS, whereas patients with GPX4 overexpression exhibit better metastasis-free survival [81]. Together, these findings propose that ferroptosis can be considered a tumor suppressive process by regulating varied molecular and cellular mechanisms [63].

In contrast, some recent evaluations have suggested that under particular circumstances ferroptosis may act as a tumor activator. This hypothesis can be exemplified by the enhancement of pancreas weight and mortality in KRAS4-driven animals with pancreatic malignancy due to GPX4 knockdown or receiving a high-iron diet. Thus, the absence of GPX4 or the administration of a high-iron diet accelerates the progression of KRAS-induced pancreatic ductal adenocarcinoma [82,83]. CD36 decreases the antitumor activity of $CD8^{+}$ T cells by triggering ferroptosis and lipid peroxidation. Nonetheless, the basic modulatory mechanisms and pathways supporting the carcinogenic role of ferroptosis are still ambiguous [63,84].

5. The interconnection between non-coding RNAs and ferroptosis

As we know, ncRNAs, including miRNAs, lncRNAs, and circRNAs contribute to a vast array of genetic modulatory mechanisms [85,86]. In this era, researchers have tried to elucidate these regulatory pathways that are related to ferroptosis and fortunately have discovered valuable information. Based on their research, they noticed that specific ncRNA transcripts can control the ferroptosis flux by direct modulation of key factors or indirect regulation of molecular targets located upstream of this process [87–89]. The following sections provide more detailed information on the existing network between ncRNAs and the process of ferroptosis.

5.1. MiRNAs and ferroptosis: regulatory mechanisms

MiRNAs, which are a subclass of the ncRNA superfamily that are 20–25 nucleotides in length [90–92], have recently been shown to control ferroptosis through multiple pathways (Fig. 3) (Table 1) [93]. With a mechanistic view, miRNAs can affect lipid metabolism in tumor cells to regulate ferroptosis. In this regard, MFN2 (mitofusin 2) that is central to the process of mitochondrial fusion, is responsible for the regulation of ROS generation in cellular lipid metabolism [94].

ALOX15 (arachidonate 15-lipoxygenase), which belongs to the LOX family, has the ability of converting arachidonic acid, along with other unsaturated fatty acids residing on the cell membrane, into lipid peroxides, and thus oxidative stress-mediated cell death and inflammation can specifically be regulated by ALOX15 [95]. In gastric neoplasms, exosomal *MIR522* targets ALOX15 further decreasing ROS levels, which in turn blocks ferroptosis and stimulates chemo-resistance in these malignancies [96].

The serine-threonine kinase AURKA (aurora kinase A), as another defined regulator for ferroptosis, aids in controlling mitosis-related spindle formation. Several types of cancer exhibit AURKA overexpression in this context. By siRNA-mediated silencing of AURKA translation, GPX4 expression can be downregulated, implying that GPX4's upstream factors are controlled by AURKA. Upon the conducted bioanalysis, a binding site was found for *MIR4715-3p* in the 3′-untranslated region (3′-UTR) of *AURKA* mRNA. Once *MIR4715-3p* is turned on, AURKA expression declines and a reduction is observed in GPX4 expression in pancreatic cancer cells. Accordingly, the AURKA-GPX4 axis is a prime route by which *MIR4715-3p* may trigger ferroptosis [97,98].

Other than interfering with lipid metabolism, miRNAs can also control ferroptosis through regulating the metabolism of amino acids. For example, the pathway responsible for the breakdown of glutamine is a crucial regulator of intracellular glutamate levels. GLS2 (glutaminase 2) and SLC1A5 (solute carrier family 1 member 5) are significant regulatory factors for the uptake and breakdown of glutamine in this framework. Reduced intracellular glutamate content can decrease ROS accumulation and block ferroptosis, as occurs with lower expression of SLC1A5 or GLS2. Notably, by binding SLC1A5 at the 3′-UTR, *MIR137* overexpression can adversely control ferroptosis in melanoma cells. Niu et al. also suggested that by targeting GLS2 and mitigating intracellular glutamate levels, *MIR103A-3p* can cause ferroptosis resistance in gastric cancer cells. Similarly, it was affirmed that patients suffering from gastric carcinoma have a poor prognosis when *MIR103A-3p* is overexpressed [99–102].

In acute kidney injury, cell damage resulting from ferroptosis is considered a critical mechanism. To enhance the function of the cystine/glutamate antiporter/xCT and raise the intracellular GSH level, ATF4 (activating transcription factor 4) can upregulate the expression of transmembrane transporter SLC7A11 [67]. Moreover, HSPA5 (heat shock protein family A (Hsp70) member 5) is also activated by ATF4 to increase GPX4 expression and activity, thereby shielding cells from ferroptosis. Ferroptosis in HCC cells may be promoted by the overexpression of *MIR214*, which implies that *MIR214* can inhibit *ATF4* transcription and, in turn, the ATF4-HSPA5-GPX4 pathway, leading to the stimulation of ferroptosis [103–105].

Tumor cell ferroptosis can be controlled by miRNAs through interfering with intracellular iron metabolism. Maintaining the balance of Fe^{2+} within the cytoplasm and mediating its entry into mitochondria are the primary functions of TF (transferrin). By controlling TF to lower intracellular Fe^{2+} levels and prevent ferroptosis, *MIR7-5p* causes

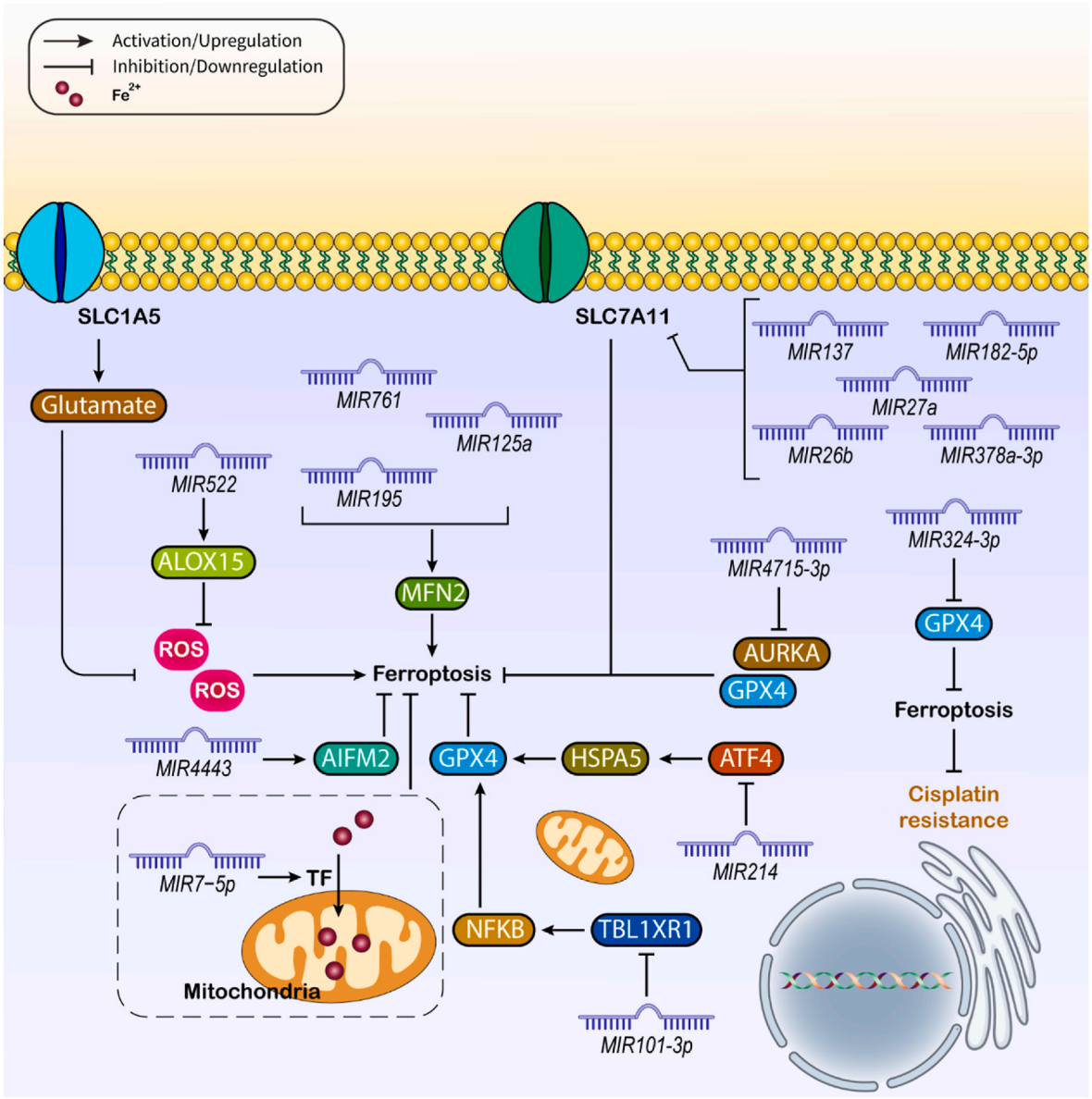

Fig. 3. MiRNAs and ferroptosis. MiRNAs can influence ferroptosis through various pathways, including lipid and amino acid metabolism, as well as iron homeostasis as illustrated in this figure. *MIR522* in gastric cancer targets ALOX15, as an enzyme involved in lipid peroxidation, reducing ROS levels and blocks ferroptosis. *MIR4715-3p* targets AURKA in pancreatic cancer, leading to GPX4 (a ferroptosis inhibitor) downregulation and increased ferroptosis. *MIR137* overexpression in melanoma inhibits SLC1A5, reducing glutamate uptake and ferroptosis. *MIR103A-3p* targets *GLS2* in gastric cancer, decreasing glutamate levels and promoting ferroptosis resistance. *MIR214* in HCC inhibits ATF4, inducing a decreased GPX4 expression and promoting ferroptosis. *MIR7-5p* reduces iron uptake by targeting TF, preventing ferroptosis and promoting radiation resistance. *MIR335* targets FTH1 in Parkinson disease, increasing iron levels and promoting ferroptosis. Several miRNAs (including *MIR124*, *MIR30B-5p*, *MIR20A*, and *MIR485-3p*) have the ability of targeting iron exporters or regulators, influencing ferroptosis susceptibility. Other miRNAs such as *MIR7*, *MIR200A*, *MIR101*, and *MIR455* target negative regulators of NFE2L2 (a ferroptosis inhibitor), promoting ferroptosis. *MIR28*, *MIR153-3p*, etc. also target NFE2L2 directly or indirectly, again promoting ferroptosis.

radiation resistance. Besides, in the context of Parkinson disease, *MIR335* targets *FTH1* (ferritin heavy chain 1) to promote ferroptosis by elevating intracellular Fe^{2+} content [106,107]. Mammals have only one cellular iron exporter, SLC40A1/ferroportin 1, which is essential for maintaining the cellular iron homeostasis. Underexpression of this iron exporter, achieved by *MIR124*, provokes neuronal death in murine models of intracerebral hemorrhage through increasing ferroptosis [108]. Along these lines, ferroptosis-induced oxidative stress, which has been identified as a major leading cause of pre-eclampsia-related adverse outcomes, is correlated with *MIR30B-5p* that is responsible for downregulation of SLC40A1/ferroportin 1 to provoke ferroptosis in trophoblasts [109]. In a similar manner, *MIR20A*, along with *MIR485-3p* can also decrease the generation of Fe^{2+} ions through targeting ferroptosis, which indeed stimulates resistance against ferroptotic flux [36,110].

The KEAP1 (kelch like ECH associated protein 1)-NFE2L2 (NFE2 like bZIP transcription factor 2) regulatory pathway, a key axis that suppresses ferroptosis through blocking ROS generation and decreasing iron load, can be substantially targeted by miRNAs to control ferroptosis. In this regard, overexpressed *MIR7* and *MIR200A* target *KEAP1* to degrade its mRNA and activate NFE2L2. In addition, *MIR101* and *MIR455* have the ability to target *CUL3* (cullin 3) to induce NFE2L2. In contrast, a vast array of miRNAs, including *MIR28*, *MIR153-3p*, *MIR142-5p*, *MIR27A*, *MIR144*, and *MIR155*, along with others repress NFE2L2 either directly or indirectly. Thereby, all these miRNAs can be considered as potential molecules in modulating cellular ferroptosis [94,111,112].

Table 1
MiRNAs implicated in ferroptosis regulation during gynecological and breast cancers.

miRNA	Cancer type	Role in ferroptosis	Target	Reference
MIR1-3p	Ovarian	Enhances the sensitivity of ovarian cancer cells to ferroptosis	*FZD7*	[156]
MIR424-5p	Ovarian	Negatively regulates ferroptosis	*ACSL4*	[159]
MIRNA660-5p	Cervical	Inhibits cancer cell ferroptosis	*ALOX15*	[161]
MIR382-5p	Breast/ ovarian	Promotes ferroptosis	SLC7A11 axis	[168]
MIR5096	Breast	Promotes ferroptosis	*SLC7A11*/ xCT	[169]
MIR499A-5p	Breast	Promotes ferroptosis	*PEDS1*/ *TMEM189*	[178]
MIR324-3p	Breast	Metformin induces ferroptosis by upregulating *MIR324-3p*	GPX4 axis	[173]

5.2. LncRNAs and ferroptosis

The other subgroup of ncRNAs, i.e., lncRNAs, which are 200 nucleotides or more in length, significantly interfere with gene expression modulation at transcriptional, translational, and post-translational levels by connecting to DNA, mRNA, proteins, or even miRNA transcripts [113,114]. Traditionally, lncRNAs have been defined by the absence of protein-coding capacity. However, recent bioinformatic analyses have identified open reading frames (ORFs) within lncRNA sequences, suggesting potential coding ability [115]. Furthermore, studies have shown a significant correlation between some lncRNAs and ribosomes, hinting at the possibility of lncRNAs harboring coding regions for short peptides [116].

Supporting this notion, analyses of ribosome profiling data revealed that 40% of lncRNAs and pseudogene RNAs in human cells undergo translation. Mass spectrometry data further confirmed the translation of lncRNAs into small peptides [117,118]. For instance, the lncRNA *HOXB-AS3* (HOXB cluster antisense RNA 3) encodes a functional 53-amino acid peptide that can suppress colon cancer cell growth [119]. Notably, translated lncRNAs exhibit preferential cytoplasmic localization, whereas untranslated lncRNAs are predominantly nuclear [117]. The translational efficiency of cytoplasmic lncRNAs is similar to that of mRNAs, suggesting active ribosomal engagement. However, the functionality of most lncRNA-derived peptides remains unclear, as they might be unstable byproducts [118]. The evaluation of lncRNA coding potential is inherently challenging due to their structural similarities to mRNAs. Additionally, coding sequences can reside within introns or overlapping exons of other genes, further complicating the analysis. With only a small fraction of lncRNA-encoded products functionally characterized, a vast landscape of potential lncRNA-derived peptides awaits exploration [120]. Ferroptosis is one of the key cellular processes regulated by lncRNAs within cancer cells (Fig. 4) (Table 2). For example, CBS (cystathionine beta-synthase), a potential target for ferroptosis modulation, is regulated by the lncRNA LINC00336 (long intergenic non-protein coding RNA 336) in a positive manner, which in turn triggers cysteine production through trans-sulfuration flux and blocks ferroptosis in lung tumor cells. By binding to MIR6852, LINC00336 can also increase the suppressive effects of the CBS axis on ferroptosis [121, 122].

TP53 is a well-known tumor suppressor gene, being responsible for cell cycle arrest induction to repair DNA damage; different TP53 target genes have interestingly been shown to contribute to ferroptosis modulation. Mao and colleagues noticed that the lncRNA *LINC00472/p53*RRA had the ability of interacting with G3BP1 (G3BP stress granule assembly factor 1) to generate a new complex, i.e., *LINC00472/p53*RRA-G3BP1. In consequence, this newly-formed complex enhances the intranuclear *TP53* gene transcriptome content by disrupting the attachment of TP53 to G3BP1 [123,124]. Likewise, *PVT1*, another lncRNA, can also target TP53 in conjunction with *MIR214*; the targeted TP53 triggers ferroptosis through repressing the transcription of *SLC7A11*, as well as decreasing the cysteine levels within the cell [125].

LINC00618 is a lncRNA with the potential of increasing ROS and iron accumulation in leukemic patients, thus making cells susceptible to ferroptosis and its inducers. This lncRNA transcript induces ferroptosis in a manner depending on apoptosis [126]. Furthermore, LINC00618 can downregulate HELLS/LSH (helicase, lymphoid specific), which otherwise promotes expression of SLC7A11 and blocks ferroptosis. As a newly recognized lncRNA, *ZFAS1* (ZNFX1 antisense RNA 1; located on chromosome 20q13.13) has been associated with varied modulatory roles in an array of diseases [127]. For instance, *ZFAS1* underexpression abolishes pharmacological lipid peroxidation during pneumonic conditions [128]. In detail, *ZFAS1* can serve as a competing endogenous RNA (ceRNA) to potentiate cell susceptibility against ferroptosis through sponging *MIR150-5p* to suppress SLC38A1 expression; SLC38A1 is considered a principal mediator of glutamine uptake and lipid peroxidation metabolism [129].

Multiple processes can result in a ferroptosis blockade including exosome-mediated export of iron from the cells. PROM1 (prominin 1) and PROM2 are glycoproteins with five transmembrane domains. PROM1 regulates autophagy through inhibition of MTOR (mechanistic target of rapamycin kinase) complex 1 (MTORC1), whereas PROM2 promotes the formation of ferritin-containing exosomes. Recently, it was found that PROM2 expression in bladder cancer can be induced by the lncRNA *LINC01833/RP11-89* through sponging *MIR129-5p*, resulting in ferroptosis inhibition [130].

5.3. CircRNAs and ferroptosis

CircRNAs, which are well-known for their specific closed loop structure, are synthesized from pre-mRNAs through back splicing or lariat-driven processes [131,132]. This closed ring structure makes circRNAs resistant to exonuclease-mediated degradation, and thus these ncRNA transcripts are expressed in a stable manner [133–135]. Due to their structural stability, multiple binding sites for miRNAs, and the ability to regulate cellular processes, circRNAs have attracted much attention in biological studies and cancer research [136–138].

Within this context, circRNAs are proposed to be involved in the modulation ferroptosis by sponging different miRNAs inside tumor cells (Fig. 4) (Table 3). *CircTTBK2* (tau tubulin kinase 2) is one of these tumor-associated circRNAs that is markedly expressed in gliomas and is responsible for regulating tumor cell proliferation, migration, and invasion [139]. This circRNA also controls cell metabolism by sponging *MIR1283*, *MIR520B*, *MIR217*, and *MIR761*, among which *MIR761* can potentially modulate the ferroptotic flux in HCC via targeting MFN2 [140–142]. *ITGB8* (integrin subunit beta 8) is a specific target for *circTTBK2* that triggers the suppression of ferroptosis in glioma cells by sponging *MIR761* [143].

According to recently published evidence, ferroptosis can also be considered an autophagy-dependent cell death mode. For example, ALKBH5 (alkB homolog 5, RNA demethylase) is a major N6-methyladenosine (m6A) demethylase and is a principal autophagy blocker [144,145]. Once ALKBH5's function in autophagy regulation is inhibited by the circRNA *has_circ_0008367*, ferroptosis is triggered in an autophagy-dependent manner [146]. *Circ_0008035* is another ferroptosis-related circRNA that is overexpressed in gastric cancer. Mechanistically, *circ_0008035* underexpression results in the suppression of gastric cancer cell proliferation, which in turn causes an increase in apoptosis, as well as ferroptosis. Li et al. suggest that the inhibition of ferroptosis in gastric cancer is due to direct targeting of *MIR599* by overexpressed *circ_0008035* through the *MIR599*-EIF4A1 (eukaryotic translation initiation factor 4A1) regulatory axis [147].

The mutual interaction between different circRNAs and miRNAs in

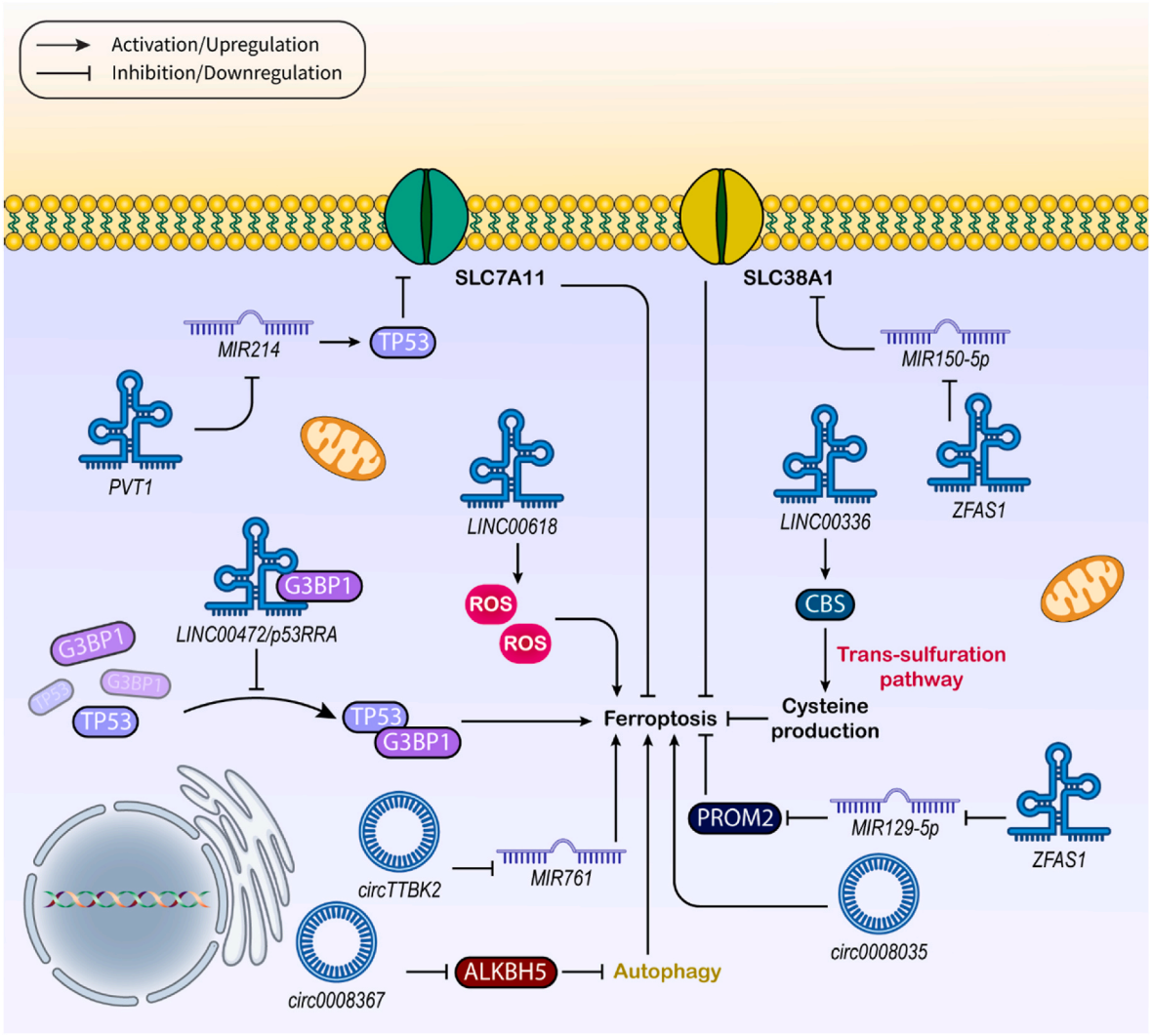

Fig. 4. LncRNAs and circRNAs in association with ferroptosis. lncRNAs and circRNAs have emerged as important regulators of ferroptosis pathways in cancer cells; understanding their specific roles may open doors for novel therapeutic strategies. In the case of lncRNAs, LINC00336 promotes ferroptosis resistance in lung cancer by increasing cysteine production through the CBS axis and suppressing ferroptosis-promoting miRNAs, such as *MIR6852*. *LINC00472/p53*RRA enhances TP53 gene expression, promoting ferroptosis. *PVT1* targets *TP53* in conjunction with *MIR214*, leading to ferroptosis by repressing SLC7A11 and lowering cysteine levels. LINC00618 sensitizes leukemic cells to ferroptosis by increasing ROS and iron accumulation and suppressing SLC7A11 expression. *ZFAS1* acts as a competing endogenous RNA (ceRNA), sponging *MIR150-5p* to increase ferroptosis susceptibility by suppressing SLC38A1, which is a key player in glutamine uptake and lipid metabolism. *LINC01833/RP11-89* promotes ferroptosis inhibition in bladder cancer by sponging *MIR129-5p* and inducing PROM2 expression, which facilitates iron export through ferritin-containing exosomes. Regarding the role of circRNAs, *circTTBK2*, as a glioma-associated circRNA, regulates ferroptosis by sponging multiple miRNAs, including *MIR761*, which can target *MFN2*. *CircTTBK2* sponges *MIR761*, leading to ITGB8 upregulation and ferroptosis suppression in glioma cells. *Circ_0008367* triggers ferroptosis in an autophagy-dependent manner by inhibiting the autophagy-promoting function of ALKBH5. *Circ_0008035* inhibits ferroptosis in gastric cancer by directly targeting *MIR599* and affecting the *MIR599*-EIF4A1 regulatory axis. *CircIL4R* and *circEPSTI1* regulate ferroptosis through the *MIR541-3p*-GPX4 and *MIR375-MIR409-3p-MIR515-5p*-SLC7A11 axes, respectively. Eventually, *circSNX12* interacts with *MIR224-5p* to target *FTH1*, encoding a regulator of iron homeostasis and ferroptosis susceptibility.

ferroptosis modulation has been demonstrated by several lines of investigation. One recent study shows that *circIL4R* and *circEPSTI1* can mediate ferroptosis regulation via the *MIR541-3p*-GPX4 and *MIR375-MIR409-3p-MIR515-5p*-SLC7A11 axes, respectively [148,149]. Another example is seen with *circSNX12* that can interact with *MIR224-5p* to target *FTH1* (ferritin heavy chain 1); FTH1 is a subunit of the ferritin complex, which negatively correlates with ferroptosis by trapping and then oxidizing Fe^{2+} ions inside cells, as well as decreasing ROS formation. It has been reported that FTH1 is significantly underexpressed in heart failure conditions; however, there is no evidence for the expression of *circSNX12* in heart tissues, and its function needs to be better elucidated [150,151].

6. The existing crosstalk between ferroptosis and non-coding RNAs regulates the onset and progression of female-oriented cancers: A focus on miRNAs, lncRNAs, and circRNAs

6.1. The regulatory network between microRNAs and ferroptosis in gynecological neoplasms, as well as breast cancer

FZD7 (frizzled class receptor 7) is activated in a wide range of malignancies and was recently found to be overexpressed in OC, which in turn leads to a decrease in platinum-resistant OC cells' sensitivity to the ferroptotic flux, and subsequent tumor cell survival (Fig. 5) [152]. FZD7 has the ability to regulate both canonical and non-canonical WNT signaling mechanisms [153]. When FZD7 is overexpressed the WNT-CTNNB1/β-catenin pathway is overactivated and a group of

Table 2
LncRNAs in association with ferroptosis regulation, having roles in gynecological and breast neoplasms.

LncRNA	Cancer type	Role in ferroptosis	Target	Reference
ADAMTS9-AS1	Epithelial ovarian cancer	Attenuates ferroptosis	*MIR587*-SLC7A11 axis	[184]
CACNA1G-AS1	Ovarian	Inhibits ferroptosis	*FTH1*	[183]
ADAMTS9-AS1	Endometriosis	Represses ferroptosis	*MIR6516-5p*-GPX4 axis	[211]
H19	Breast	Inhibits ferroptosis	Downregulation of *H19* can inhibit autophagy to induce an increase in ferroptosis	
RUNX1-IT1	Breast	Inhibits ferroptosis	IGF2BP1-GPX4 axis; *RUNX1-IT1* promotes breast cancer carcinogenesis through blocking ferroptosis via elevating GPX4	[213]
HCP5	Triple-negative breast cancer	Inhibits ferroptosis	Regulating GPX4 expression and lipid ROS level	[214]
LINC00460	Breast	Inhibits ferroptosis	*MIR320A*-MAL2 axis	[217]
LncFASA	Triple-negative breast cancer	Promotes cancer ferroptosis	Binds to PRDX1 and inhibits its peroxidase activity	[232]

cancers, such as gastric neoplasm, will be triggered. The upregulated FZD7 can also provoke the onset and progression of OC depending on the regulation of WNT signaling [154,155].

The above-stated findings are also supported by in vitro analyses, as FZD7 overexpression enhances cell viability and survival of HO8910 or SKOV3 human OC cell lines that are treated with erastin or RSL3 [156]. Mechanistically, *MIR1-3p*, by binding to the *FZD7* 3′-UTR, directly targets *FZD7* to block its expression. Conversely, the mimics of this miRNA transcript reduce cell viability of the corresponding OC cell lines and elevate the malondialdehyde (MDA; a product of polyunsaturated fatty acid peroxidation) levels inside the erastin- or RSL3-treated cells; *MIR1-3p* blockers exert the opposite effects, as they enhance cell viability and mitigate MDA levels. Thus, erastin or RSL3 induce ferroptosis, and *MIR1-3p* mimics these effects on ferroptosis, and being activated by these treatments, can be suppressed by FZD7 upregulation. Indeed, *MIR1-3p* increases the sensitivity of OC cells to ferroptosis through targeting *FZD7* [156].

MIR424-5p is another miRNA in association with OC, which is a key player in suppressing ferroptosis [157,158]. *MIR424-5p* achieves this effect by silencing ACSL4, a molecule that promotes ferroptosis. When *MIR424-5p* levels decrease, ACSL4 expression increases, making ovarian cancer cells more susceptible to ferroptosis. This finding suggests that targeting ACSL4 could be an effective strategy for treating ovarian cancer. ACSL4 is also involved in other cancers and may be a promising target for broader cancer therapies [159].

Tumor cells and macrophages interact through exosomes. In the case of CC, tumor-associated macrophages may transport miRNAs to cancer cells, reducing their sensitivity to ferroptosis inducers [160]. A macrophage-secreted miRNA, *MIR660-5p*, suppresses ferroptosis by downregulating the lipoxygenase ALOX15, an enzyme involved in lipid metabolism [161]. *MIR660* expression varies across cancer types, with low levels observed in CC and high levels in hepatocellular carcinoma and breast cancer [162,163]. Blocking the transcription factor STAT6 (signal transducer and activator of transcription 6) suppresses *MIR660-5p* levels in tumor-associated macrophages, suggesting its involvement in regulating *MIR660* expression. Further research is needed to fully understand the role of exosomes, miRNAs, and STAT6 in CC [161].

Studies suggest that targeting ferroptosis may be a promising approach for treating BC, as well. Triple-negative breast cancer (TNBC) patients, who are less responsive to traditional therapies, may be particularly sensitive to ferroptosis-inducing agents [164,165]. Lidocaine, a commonly used local anesthetic, affects the development of various cancers, including ovarian and breast cancer. Lidocaine can inhibit the cellular resistance against cytotoxicity, increase apoptosis, and decrease cell proliferation in different types of tumor cells [166, 167]. In one study, researchers found that lidocaine induces ferroptosis in both ovarian and breast cancer cells. They also demonstrated that lidocaine augments the expression of *MIR382-5p*, which downregulates *SLC7A11* expression. The inhibition of *MIR382-5p* blocks lidocaine-mediated ferroptosis. These findings suggest that lidocaine may inhibit the malignant progression of ovarian and breast neoplasms by stimulating ferroptosis and that *MIR382-5p* plays a role in this process. However, further research is needed to validate the clinical value of lidocaine in the treatment of these cancers [168]. Additionally in relation to SLC7A11, researchers explored how *MIR5096*, a miRNA that is expressed at a low level in human BC cells, affects BC development and spread [169]. They discovered that *MIR5096* lowers the levels of SLC7A11; this lowering of SLC7A11 causes more cell death and less cell growth in BC cells. These researchers also observed that *MIR5096* causes ferroptosis to be more severe in TNBC cells than in other types of BC. Moreover, the study showed that *MIR5096* prevents tumor metastasis from occurring in zebrafish models with transplanted tumors [169]. These results indicate that *MIR5*096 might be a useful target for BC therapy, especially TNBC, by causing ferroptosis and stopping tumor development and expansion. More studies are required to fully comprehend how *MIR5096* works and its potential in the clinic [169].

Metformin, a commonly used diabetes medication, also possesses anti-tumor properties; this drug inhibits the proliferation and metastasis of various cancers, including BC [170]. Studies suggest that metformin induces ferroptosis under cancer-forming circumstances. This process

Table 3
CircRNAs that are involved in ferroptosis regulation through the progression of gynecological and breast neoplasms.

CircRNAs	Cancer type	Role in ferroptosis	Target	Reference
circSNX12	Ovarian cancer	Inhibiting ferroptosis	*MIR194-5p*-SLC7A11 axis	[234]
hsa_circ_0007615	Ovarian cancer	Knockdown of *hsa_circ_0007615* in EOC cells leads to the blocking of cell proliferation, migration and invasion, but an increase of cell death presenting as ferroptosis	Sponging *MIR874-3p* and moderating TUBB3.	[237]
circACAP2	Cervical cancer	Suppresses ferroptosis	*MIR193A-5p*-GPX4	[239]
circLMO1	Cervical cancer	Promotes cervical cancer cell ferroptosis	Sponging *MIR4192-ACSL4*	[243]
circEPSTI1	Cervical cancer	Silencing of *circEPSTI1* induces ferroptosis	*MIR375-MIR409-3p-MIR515-5p*-SLC7A11 axis	[242]
CircRAPGEF5	Endometrial cancer	*circRAPGEF5* promotes the formation of TFRC with exon 4 skipping and confers ferroptosis resistance in EC cells	Interaction with RBFOX2	[244]
circ_0000643	Breast cancer	Reduced cell ferroptosis	*MIR153*-SLC7A11 axis	[250]
RHOT1	Breast cancer	Inhibits ferroptosis	*MIR106A-5p*-STAT3 axis	[253]
CircGFRA1	Breast cancer	Downregulation of *circGFRA1* promotes ferroptosis	Sponging of *MIR1228* and enhancing AIFM2 expression	

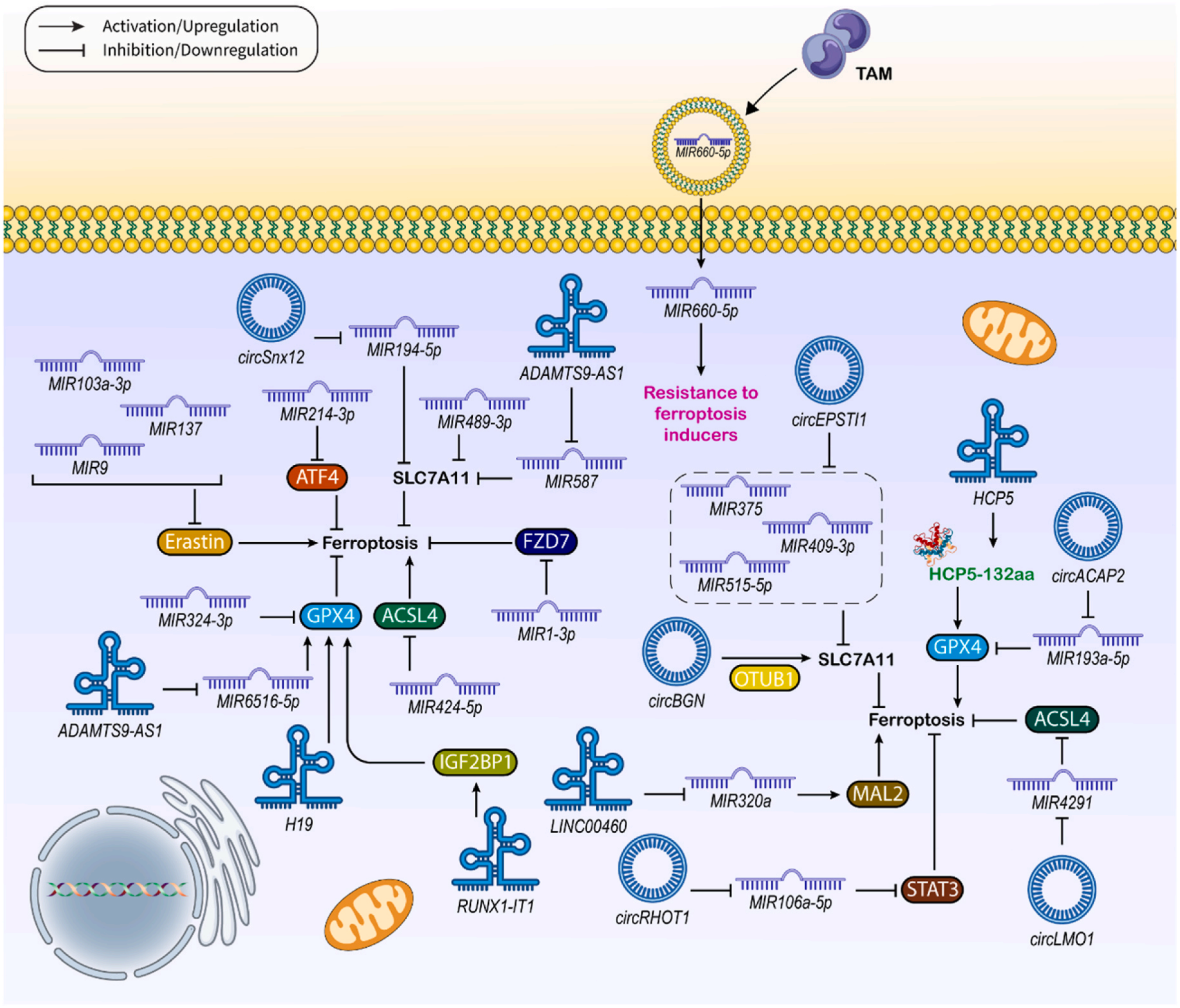

Fig. 5. The interplay between ferroptosis and miRNAs, lncRNAs, and circRNAs relative to the pathogenesis and progression of female-specific neoplasms. TAM, tumor-associated macrophage. See Tables 1–3 for further information.

involves the accumulation of Fe^{2+} and ROS, leading to the downregulation of the antioxidant enzyme GPX4 [171,172]. Metformin also increases the expression of *MIR324-3p*, a miRNA that negatively regulates *GPX4* expression. Based on a luciferase reporter assay, expression of GPX4 is blocked by a *MIR324-3p* mimic (promoting Fe^{2+} aggregation), whereas a *MIR324-3p* inhibitor enhances the expression of GPX4 (suppressing Fe^{2+} accumulation) [173]. Both the *MIR324-3p* mimic and the *MIR324-3p* inhibitor have minimal effects on the expression of a GPX4 mutant with an altered 3′-UTR. These findings highlight the potential of metformin and *MIR324-3p* as novel therapeutic agents for cancer treatment [173].

On another front of investigation, *MIR499A-5p* has been demonstrated to play a dual role in cancer. *MIR499A-5p* is significantly underexpressed in several cancer tissues, including EC, CC, and NSCLC [174–176]. In this regard, once *MIR499A-5p* is downmodulated, tumor growth and metastasis are provoked. However, *MIR499A-5p* also has tumor-suppressing effects by targeting *EIF4E* and *VAV3* (vav guanine nucleotide exchange factor 3) [174,176]. In BC, *MIR499A-5p* is associated with a significant decrease in cancer risk. PEDS1/TMEM189 (plasmanylethanolamine desaturase 1) is involved in the synthesis of ether lipids, which are important for the regulation of ferroptosis [177,178]. PEDS1/TMEM189 underexpression sensitizes cells to ferroptosis, and its overexpression contrarily blocks ferroptosis [179,180]. PEDS1/TMEM189 is highly expressed in various human cancers, and its expression is correlated with the expression of GPX4 [179]. In BC cells, *MIR499A-5p* directly targets *PEDS1/TMEM189* to decrease its expression, promoting ferroptosis. This finding suggests that *MIR499A-5p* could be a potential therapeutic target for BC by inducing ferroptosis and inhibiting tumor growth [178].

6.2. *Long non-coding RNAs and other ncRNAs associated with ferroptosis in gynecological cancers and breast neoplasm*

As mentioned above, the growth and spread of OC is influenced by several molecular factors. One of them is IGF2BP1 (insulin like growth factor 2 mRNA binding protein 1), a protein that attaches to mRNA and controls its stability and translation, affecting how tumor cells grow and invade [181,182]. Another factor is *CACNA1G-AS1*, a long RNA molecule that does not code for proteins but interacts with IGF2BP1 and increases the expression of FTH1, an enzyme that regulates iron levels. m6A methylation of FTH1, which correlates with a poor cancer prognosis, is linked with *CACNA1G-AS1*. High FTH1 expression makes cells more resistant to ferroptosis, which implies that interfering with the methylation of FTH1, especially the *CACNA1G-AS1*-IGF2BP1 pathway, could be a potential treatment for OC patients [183]. In addition, researchers also explored if the lncRNA *ADAMTS9-AS1*, can control the expression of SLC7A11 and prevent ferroptosis in OC cells by competing with *MIR587* [184]. Their in vitro experiments showed that *ADAMTS9-AS1* indeed prevents ferroptosis in OC cells by affecting the *MIR587*-SLC7A11 pathway. It was also discovered that *ADAMTS9-AS1* is overexpressed in OC cells, especially in the OVCAR3 and CAOV-3 cell lines. Moreover, reducing *ADAMTS9-AS1* in OC cells stops their growth

and movement by increasing ferroptosis. This result agrees with findings in other cancers, implying that *ADAMTS9-AS1* may have a wider role in controlling cancer cell behavior. The study's findings are backed up by the idea of ceRNAs [185,186]. Fang et al. showed that *ADAMTS9-AS1* can reduce the invasive behavior of BC cells by competing with *MIR513A-5p* and controlling ZFP36 (ZFP36 ring finger protein) expression, which correlates with an improved OS [187]. This finding supports the idea that *ADAMTS9-AS1* can change cellular processes by interfering with small RNA regulation [184].

In OCs, ferroptosis is also enhanced by the interaction of lncRNA *LINC00472/P5*3RRA and G3BP1, which prevents the tumor suppressor protein TP53 from exiting the nucleus. In lung cancer, the lncRNA LINC00336 prevents the formation of ferritin [188]. We know that the HIF1A (hypoxia inducible factor 1 subunit alpha) signaling pathway stimulates tumor growth and spread by controlling various signaling molecules. The response of OC cells that are resistant to cisplatin can be improved by reducing HIF1A [189,190]. The lncRNAs *TLR8-AS1* and *LBX2-AS1* are linked to OC spread and resistance to chemotherapy drugs, and they could be used as targets for therapy or diagnosis [191–193]. A relevant study found 11 lncRNAs related to ferroptosis that are increased in OC tissues, indicating their role in OC growth and expansion. These lncRNAs could be potential targets for OV therapy [194].

In order to help patients with OC make treatment decisions and predict their prognosis, a research team discovered a signature consisting of eight ferroptosis and iron-metabolism related lncRNAs (FIRLs) [195]. Included in the signature are the following FIRLs: *AC083880*.1, LINC01558, AL023583.1, AP005205.2, AC007114.1, LINC00665, and AC138904.1. To visualize the FIRLs and make their interpretation easier, the researchers created two nomograms in addition to the signature [195]. The potential of a multi-label fusion collaborative matrix factorization/MLFCMF approach with an area under the curve/AUC value of 0.8612 has been shown in previous research for predicting lncRNA-disease associations [196]. Furthermore, studies on OC cell lines have looked into the function of a number of FIRLs, including *TONSL-AS1* [197], *SNHG20* (small nucleolar RNA host gene 20) [198], and *MSC-AS1* [199]. Still, not much research has been done on the function of FIRLs in the creation of OC risk signatures. This study lays the groundwork for upcoming in vivo and in vitro assays and offers a significant step toward comprehending the prognostic significance of FIRLs in OC [195].

Beyond the OC, CCs are often diagnosed at an advanced stage, making it difficult to treat effectively [200]. Ferroptosis-related lncRNAs have been studied in other cancers, but their role in CC prognosis is poorly understood. Researchers constructed a co-expression network of ferroptosis-related genes and lncRNAs, identifying 1393 lncRNAs with ferroptosis-related functions. Using these lncRNAs, they developed a prognostic model for CC [201]. The model showed that AC099568.2 was the most consistently associated lncRNA with CC prognosis across different stages of the disease. This suggests that AC099568.2 may be a valuable prognostic biomarker and may play a role in CC development. The CC prognostic model developed in this study also shows superior predictive accuracy compared to other prognostic models [202,203], highlighting its potential as a valuable tool for improving CC patient outcomes [201].

Classifying ferroptosis-related gene expression in CC patients was essential due to the importance of ferroptosis in CC immune modulation and the heterogeneity of ferroptosis phenotype in individual CC cells. The low-ferroptosis score (FerroScore) group shows significantly higher expression of immune checkpoints CTLA4 (cytotoxic T-lymphocyte associated protein 4) and PDCD1 (programmed cell death 1) compared to the high-FerroScore group [204]. This observation suggests that low-FerroScore patients may benefit more from checkpoint blockade therapy, which is consistent with the predictions of the submap algorithm. It has been proposed that combining immune checkpoint inhibitors with ferroptosis inducers could be a promising therapeutic strategy, leading to the development of novel combination therapies and immunotherapeutic agents [205].

Three other ferroptosis-associated lncRNAs were also affirmed to be expressed in CC samples [206–208]. Of these lncRNAs, AC026790.1 underwent additional validation in multiple ferroptosis-related experiments. Ferroptosis-related markers such as MDA, Fe^{2+}, and ROS levels are found to increase in cells overexpressing AC026790.1 in comparison to the control group, indicating that AC026790.1 promotes erastin-induced ferroptosis [205]. The results show that AC026790.1 may be an important molecule in controlling ferroptosis in CC and may represent a viable target for CC treatment. For CC patients, combining lncRNA analysis with FerroScore may enhance patient prognosis and enable individualized treatment [205].

In the case of EC, the levels of *ADAMTS9-AS1*, as a subtype of lncRNA family, are much higher in EC than in normal endometrium cells [209]. *ADAMTS9-AS1* not only prevents ferroptosis and enhances endometrial stromal cell (ESC) movement and growth, but also acts as a ceRNA that absorbs *MIR6516-5p* [210,211]. By doing so, *ADAMTS9-AS1* boosts the production of GPX4, an essential enzyme that protects cells from ferroptosis. These findings highlight the significance of the *ADAMTS9-AS1-MIR6516-5p*-GPX4-ferroptosis pathway in regulating the survival and migration of embryonic stem cells [211]. This pathway could also be a potential therapeutic target for ectopic endometrium treatment. The pathophysiology of ectopic pregnancy has been demonstrated to involve the lncRNA *ADAMTS9-AS1*. In contrast to normal endometrium cells (euEM), ectopic endometrium cells (ecEM) exhibit significantly higher expression of *ADAMTS9-AS1* [209]. Functional studies were carried out in both human and mouse models to examine the biological role of *ADAMTS9-AS1* in ectopic pregnancy. The researchers discovered that whereas overexpressing *ADAMTS9-AS1* enhances cell viability and migration, inhibiting its expression in endometrial stem cells decreases these properties. *ADAMTS9-AS1* may activate ecEMs, according to these results [211]. Also, by sponging *MIR6516-5p*, *ADAMTS9-AS1* functions as a ceRNA. Furthermore, GPX4 is negatively regulated by the miRNA *MIR6516-5p*. *ADAMTS9-AS1* protects ecEMs from ferroptosis by sponging *MIR6516-5p*, which delays the degradation of GPX4, resulting in elevated GPX4 expression. According to these results, the miRNA-GPX4 axis is the mechanism by which *ADAMTS9-AS1* controls ferroptosis resistance [211]. Through the regulation of *MIR6516-5p*-GPX4-dependent ferroptosis, *ADAMTS9-AS1* also expedites the proliferation and migration of ESCs. The development of novel treatment approaches for ectopic pregnancy may result from these findings, which offer fresh perspectives on the function of *ADAMTS9-AS1* [211].

Researchers found that in ecEM cells as opposed to euEM cells, nine differentially expressed lncRNAs (DEFerlncRNAs) are present. They then employed Cox regression analysis to create a prognostic model for ectopic pregnancy based on these nine DEFerlncRNAs. Based on the analysis, it was found that the DEFerlncRNA prognostic model is a more effective, sensitive, and specific prognostic index in EC [212]. Furthermore, the researchers employed Gene Set Enrichment Analysis/GSEA to detect differentially expressed genes between the two groups (ecEM and euEM). They discovered that these differentially expressed genes are functionally enriched in a set of pathways, such as the Hedgehog signaling pathway, apoptotic flux, extracellular matrix receptor interaction, and natural killer cell-mediated cytotoxicity, along with others. For the purpose of predicting the prognosis of EC and immune-infiltrating conditions, the researchers also discovered a 9-lncRNA model, which includes *CFAP58-DT* (CFAP58 divergent transcript) [212]. The lncRNA in the model with the highest coefficient is *CFAP58-DT*, and poor EC outcomes are associated with high *CFAP58-DT* expression. Researchers knocked down *CFAP58-DT* expression in HEC-1A and Ishikawa cells to further explore the function of *CFAP58-DT* in EC. They discovered that this significantly decreases cell viability, invasion, and migration abilities. These results imply that *CFAP58-DT* might contribute to EC carcinogenesis. Nonetheless, to clarify the

mechanisms behind this lncRNA's effects on EC cells and to confirm its role in EC, more clinical research is necessary [212].

For another female-oriented malignancy, i.e. BC, the GEO, TCGA, and related cohorts reveal that *RUNX1-IT1* (RUNX1 intronic transcript 1) is overexpressed in BC tissues [213]. It was also discovered that *RUNX1-IT1* inhibition blocks tumor growth in vivo, as well as BC cell invasion and proliferation in vitro. Further research shows that *RUNX1-IT1* directly binds to IGF2BP1 and promotes the formation of ribonucleoprotein condensates. Because of this binding, IGF2BP1 is able to bind to *GPX4* mRNA with greater tenacity, preventing *GPX4* mRNA degradation. Consequently, the elevated GPX4 protein promotes BC tumorigenesis by obstructing ferroptosis and lipid peroxidation. These results point to *RUNX1-IT1* as a novel oncogenic lncRNA [213]. In addition, the research suggests that the development and progression of breast cancer are caused by dysregulation of the *RUNX1-IT1*-IGF2BP1-GPX4 axis. Furthermore, it was demonstrated that by controlling the IGF2BP1-GPX4 axis, *RUNX1-IT1* inhibits ferroptosis and thus promotes BC tumorigenesis. This discovery offers a possible therapeutic target and prognostic marker for BC [213].

According to the findings of a relevant study, the 132-amino acid protein HCP5-132aa, which is encoded by the lncRNA *HCP5*, regulates the ferroptosis pathway and contributes to the advancement of TNBC [214,215]. Scientists discovered that GPX4 is expressed at a lower level when the HCP5-132aa ORF is knocked down. Elevated levels of ROS, a characteristic of ferroptosis, are caused by this decrease in GPX4 activity [214]. They also discovered that when the HCP5-132aa ORF is knocked down, the effects are akin to those of the drug erastin, which causes ferroptosis, by increasing mitochondrial membrane density and decreasing mitochondrial crest. Moreover, they demonstrated that the ferroptosis activators RSL3 and erastin stimulate cells, which results in the highest ROS levels that are directly elevated by knocking down the HCP5-132aa ORF. Using ferroptosis inhibitors and overexpressing HCP5-132aa can counteract this effect. The results of their research point to HCP5-132aa as a potential therapeutic target for TNBC, as well as a novel prognostic factor for the disease [214].

In BC tissues, the lncRNA LINC00460 has a higher expression level than in normal breast tissues [216]. This lncRNA enhances the growth and survival of BC cells by preventing ferroptosis. LINC00460 increases the expression of MAL2 (mal, T cell differentiation protein 2), a protein that belongs to the MAL family and is associated with cancer development, by binding to *MIR320A* [217]. The effects of LINC00460 inhibition on BC cell proliferation and ferroptosis are reversed by MAL2 overexpression. These results indicate that the *LINC00460*-MAL2 pathway could be a new indicator and treatment option for BC [217].

Another group of researchers revealed that four lncRNAs LINC01152, AC004585.1, MAPT-IT1, and AC026401.3 have a significant relation to BC prognosis [218]. Low expression of LINC01152 is linked to poor OS in patients. The study also showed that MAPT-IT1 has a significant association with BC OS. BC has a higher expression of AC026401.3, which suggests that AC026401.3 could be a prognostic marker for BC [216,219,220]. These results imply that these four lncRNAs could be potential indicators of BC prognosis [218].

Largely found in the cytoplasm, the lncRNA *H19* (H19 imprinted maternally expressed transcript) is responsible for regulating a number of different biological functions. For example, *H19* is necessary for embryonic development and growth and is involved in controlling the expression of other genes via a variety of processes [221]. Many human cancers have been related to elevated *H19* expression, indicating that *H19* may be a promising target for treatment. *H19* can boost ferroptosis by preventing autophagy [222]. This revelation emphasizes the function of *H19* in controlling cellular fate and clarifies the intricate relationship between autophagy and ferroptosis. In human tissues and plasma, *H19* also shows stability, which makes it a viable biomarker and therapeutic target for the treatment of cancer. Taken together, these data offer a theoretical framework for comprehending the function of *H19* in the genesis of cancer and the medicinal possibilities of metformin, a medication that that causes ferroptosis [223].

A specific evaluation performed by Fan et al. identified the lncRNA *LncFASA* as a tumor suppressor in triple-negative breast cancer (TNBC) [224]. They reported that *LncFASA* increases TNBC susceptibility to ferroptosis. Mechanistically, *LncFASA* directly binds to the Ahpc-TSA domain of PRDX1 (peroxiredoxin 1), a peroxidase enzyme. This binding drives the formation of PRDX1-containing droplets and disrupts its peroxidase activity through liquid-liquid phase separation. Consequently, *LncFASA* disrupts intracellular ROS homeostasis, leading to lipid peroxidation accumulation via the SLC7A11-GPX4 axis. Notably, high *LncFASA* expression correlates with improved overall survival in breast cancer patients. Furthermore, *LncFASA* impedes the growth of breast xenograft tumors by promoting ferroptosis, highlighting its potential as a therapeutic target [224].

Twenty-one ferroptosis-related lncRNAs were found to be correlated with recurrence-free survival (RFS) in BC patients. To predict the recurrence of BC, these lncRNAs may combine to form a new signature. Among the 21 lncRNAs, *LINC01235* is particularly significant because aggressive BC cells express a high level of this gene [225]. Another lncRNA in the signature, *LINC02166*, is also implicated in autophagy and has the potential to enhance the prognostic significance of BC [84]. It is still unclear what other lncRNAs do in BC. In a different study, researchers looked at the TCGA-BRCA cohort's expression of ferroptosis-related lncRNAs and selected lncRNAs linked to OS in BC patients [226]. *CYTOR* (cytoskeleton regulator RNA) is overexpressed in colorectal cancer samples and is linked to a poorer prognosis. This suggests that *CYTOR* may have an impact on proliferation and metastasis [227]. Another lncRNA that was studied, *USP30-AS1*, is also linked to a longer overall survival in patients with cervical cancer. The study's findings add to our understanding of lncRNA involvement in BC [228]. A notable upsurge is observed in *LINC01235* and *LINC02166* in breast cancer cell lines [229,230]. More investigation is required to elucidate the precise biological roles of these lncRNAs, which may play a significant role in the development of tumors. Ferroptosis-related lncRNA models developed in this work also provide hints regarding the molecular mechanisms underlying ferroptosis. The lack of stratification analysis based on BC molecular subtypes and the limited validation using external databases, however, could introduce biases into the results and therefore call for more research [225].

Together, it is possible to determine the prognosis of BC and possibly uncover the underlying mechanisms of lncRNAs in ferroptosis by examining the ferroptosis-associated lncRNAs found in different studies. With respect to accurately predicting how BC patients will react to immunotherapy, the developed predictive model shows great promise. To verify the model using separate datasets and determine whether it applies to various BC molecular subtypes, more research is necessary [231].

6.3. Circular RNAs also interfere with ferroptosis to control the onset and progression of female-oriented cancers

As substantial regulators of chemosensitivity in a variety of cancers, circRNAs have come to light [233]. Researchers examined whether the ferroptosis-regulating circRNA *circSNX12* aids in cisplatin resistance in OC in light of the increasing significance of ferroptosis in cancer treatment [234]. It was observed that OC tissues and cisplatin (DDP)-resistant cells have considerably higher levels of *circSNX12*. Ferroptosis is improved and DDP sensitivity is regained in DDP-resistant OC cells by reducing *circSNX12* expression [234]. Additionally, DDP's anti-tumor efficacy in vivo is improved by pharmacologically suppressing *circSNX12* via viral shRNA delivery. These results show that chemoresistance in OC can be effectively prevented in vitro and in vivo by downregulating *circSNX12*. Researchers determined that *MIR194-5p* might be *circSNX12's* target by using bioinformatic analysis [234]. Several malignancies have been linked to *MIR194-5p* as a mechanism of chemo-resistance. The researchers found that *MIR194-5p* regulates ZEB1

(zinc finger E-box binding homeobox 1) and MDM2 (MDM2 proto-oncogene) expression in OC cells, which supports earlier findings [235,236]. Additionally, they noticed that through sequestering *MIR194-5p*, *circSNX12* increases the expression of SLC7A11 in OC. *MIR194-5p*'*s* exact function in OC DDP resistance is still unknown. The researchers did note, however, that in DDP-resistant OC tissues, *MIR194-5p* expression is repressed. To fully understand the mechanisms by which circRNA-miRNA interactions affect cancer will require additional research [234].

To determine which circRNAs are overexpressed in OC, researchers looked at the publicly accessible dataset GSE192410. Using 113 OC tissues, along with the corresponding normal tissues as a patient cohort, they assessed the expression levels of a particular circRNA, *hsa_circ_0007615*. They verified that *hsa_circ_0007615* has a prognostic value for predicting the overall survival and recurrence of OC patients by examining clinical parameters, Kaplan-Meier curves, and Cox proportional hazards models [237]. With OC cell lines, the researchers performed cell-based experiments to evaluate the functional implications of *hsa_circ_0007615*. Assays for cell proliferation, transwell migration, and cell death were used to examine the consequences of *hsa_circ 0007615* knockdown [237]. Based on their research, they discovered that *hsa_circ_0007615* knockdown promotes ferroptosis while suppressing invasion, migration, and proliferation of cells. Notably, blocking the regulatory microRNA *MIR874-3p* can counteract the tumor-suppressive effect of *hsa_circ_0007615* knockdown. *MIR874-3p* targets *TUBB3* (tubulin beta 3 class III), a gene involved in cell proliferation and microtubule stability. All things considered, *hsa_circ_0007615* may be a useful biomarker for OC prognosis, and its suppression can halt the growth of tumors. By controlling *TUBB3* and sponging *MIR874-3p*, *hsa_circ_0007615* may mechanistically aid in the advancement of OC. *Hsa_circ_0007615* may thus prove to be the basis for a useful treatment [237].

In the development of some cancers, the circRNA *circACAP2* is essential. Research has demonstrated that *MIR143-3p* regulates HK2 (hexokinase 2) expression, thereby promoting invasion and migration of neuroblastoma cells [238]. Through its interaction with *MIR193A-5p* and impact on GPX4 expression, *circACAP2* modulates cancer cell ferroptosis. Scavenging ROS is a key function of GPX4, which helps shield cells from ferroptosis [239]. Reduction of cell viability and elevation of ROS, Fe^{2+}, and iron levels are observed in CC cells upon downregulating *circACAP2* with siRNAs. By inhibiting ferroptosis, these results imply that *circACAP2* aids in the advancement of CC. Additionally, *circACAP2* functions as a *MIR193A-5p* ceRNA, targeting and downregulating GPX4 expression. *circACAP2* indirectly promotes GPX4 expression and shields cells from ferroptosis by sequestering *MIR193A-5p* [239]. *CircaCAP2* knockdown-induced inhibition of cell viability may be mitigated by overexpressing GPX4 or inhibiting *MIR193A-5p*. GPX4 and *circACAP2* have elevated expression in CC tissues, whereas the expression of *MIR193A-5p* is downregulated. These data imply that a potential therapeutic target for CC treatment may be the *circACAP2-MIR193-A-5p*-GPX4 axis [239].

Prior studies have demonstrated that *circEPSTI1* stimulates the growth of CC cells by controlling the ferroptosis mediated by SLC7A11. Additionally, *circEPSTI1* is essential for the invasion and metastasis of cancer [240]. Research has shown that *circEPSTI1* controls the expression of *EPSTI1* and influences the progression of OC through *MIR942*, and it also modulates the apoptosis and proliferation of BC through the ceRNA mechanism of *MIR6809-MIR4753* [241]. Nevertheless, the precise function of circEPSTI1 in CC remains incompletely understood. A recent study looked into *circEPSTI1*'*s* function in CC. In comparison to normal cells, the researchers observed that CC cell lines have higher levels of *circEPSTI1* expression. They also showed that the growth of CC cell lines is markedly repressed by *circEPSTI1* knockdown using siRNAs [242]. Furthermore, in mouse xenograft models of HeLa cell lines, *circEPSTI1* silencing inhibits the growth of tumors. According to these results, *circEPSTI1* functions as an oncogene and may present a therapeutic target worth pursuing in the management of CC. The mechanism by which *circEPSTI1* works was further examined. It was discovered that *MIR375*, *MIR409-3p*, and *MIR515-5p* are sequestered by *circEPSTI1*, which functions as a ceRNA [242]. These microRNAs target and suppress the expression of the ferroptosis-related gene *SLC7A11*. Through the sequestration of these miRNAs, *circEPSTI1* suppresses ferroptosis and indirectly increases the expression of SLC7A11, both of which are involved in CC cell proliferation [242].

Subsequent research revealed that ferrostatin-1/Fer-1 significantly blocks *circLMO1*-induced cell death, suggesting that *circLMO1* causes ferroptosis to trigger cell death in CC cells [243]. It was discovered that *circLMO1* does not control SLC7A11 expression, in contrast to an earlier study. Rather, *circLMO1* sequesters *MIR4291* to cause ferroptosis, which in turn causes CC cells to express ACSL4 more abundantly. As anticipated, the promotion of ferroptosis by *circLMO1* is effectively countered by overexpressing *MIR4291* or downregulating ACSL4 [243]. The results indicate that *circLMO1* is downregulated in cancerous cells, and its overexpression suppresses the growth and metastasis of CC by encouraging ferroptosis mediated by *MIR4291*-ACSL4. For the purpose of creating therapeutic approaches for the treatment of CC, this mechanism offers a fresh target [243].

With regard to the gynecological malignancy endometrial cancer, tumor cells have significantly higher levels of the circRNA *circRAPGEF5*, which is primarily concentrated in the nucleus [244]. Researchers found that *circRAPGEF5* increases EC cell proliferation and resistance to ferroptosis through gain-of-function and loss-of-function experiments. By controlling the RNA binding protein RBFOX2 (RNA binding fox-1 homolog 2) splicing activity toward the *TFRC* (transferrin receptor) pre-mRNA, *circRAPGEF5* exhibits its pro-tumor effects. *circRAPGEF5* can directly bind to the RBFOX2 protein's Fox-1 C-terminal domain, significantly lowering RBFOX2's binding to downstream genes' pre-mRNAs [244]. Prior work conducted by Hilmar and colleagues showed that MALT1 (MALT1 paracaspase), a protease involved in the BCR (BCR activator of RhoGEF and GTPase)-NFKB signaling pathway, has its splicing regulation controlled by RBFOX2. This discovery was expanded upon in this study by demonstrating that RBFOX2 is also essential for the splicing of the transcripts of multiple other genes, such as *TFRC*, *ANXA2*, *EIF5A*, *ITGAE*, *SIKE1*, and *TSPO*, in EC cells. Furthermore, it was found that RBFOX2's ability to splice these target genes is diminished by a direct binding of the circular RNA *circRAPGEF5*. The formation of alternative splicing isoforms that facilitate tumor progression is a result of *circRAPGEF5* binding to RBFOX2. More research is necessary to determine the exact molecular mechanism by which *circRAPGEF5* blocks RBFOX2 splicing activity [244].

Furthermore, the phosphoinositide 3-kinase (PI3K) signaling pathway and the inactivation of the PTEN (phosphatase and tensin homolog) tumor suppressor gene, which are common characteristics of many cancers, have been demonstrated to make human cancer cells resistant to ferroptosis [245]. Furthermore, when the PI3K-AKT (AKT serine/threonine kinase)-MTOR signaling pathway is inhibited, cancer cells are generally more vulnerable to ferroptosis [245]. According to these findings, endometrial cancer often exhibits dysregulation of the PI3K-AKT-MTOR pathway, and the majority of ECs have *PTEN* gene inactivating mutations, which are present in up to 83% of endometrioid tumors [246]. These data lead us to hypothesize that *circRAPGEF5* could sequester RBFOX2 and thereby desensitize EC cells to ferroptosis. This novel mechanism may contribute to the resistance of EC cells to ferroptosis, suggesting that *circRAPGEF5* may be a viable therapeutic target for the treatment of this disease [244].

Other than the genital tract malignancies, to find better ways for treating ERBB2/HER2-positive BC patients, it is crucial to understand why some of them become resistant to trastuzumab, a drug that is often used for this type of cancer [247]. Researchers found that a circular RNA molecule called *circBGN* is very abundant in trastuzumab-resistant breast cancer tissues and is associated with poor prognosis [248]. *CircBGN* promotes ferroptosis by increasing the interaction between

OTUB1 (OTU deubiquitinase, ubiquitin aldehyde binding 1) and SLC7A11 and the level of SLC7A11 protein. This ferroptosis is not affected by inhibitors of other cell death pathways, such as apoptosis, necroptosis, or autophagy, suggesting that it is specifically related to trastuzumab resistance. Moreover, the ferroptosis inducer erastin can make breast cancer cells more sensitive to trastuzumab, and this effect is enhanced when *circBGN* is knocked down. These findings suggest that a new strategy to overcome trastuzumab resistance in ERBB2/HER2-positive breast cancer patients could be to target the *circBGN*-OTUB1-SLC7A11 pathway and use ferroptosis inducers together with trastuzumab [248].

One transcription factor involved in the development of BC is FOXQ1 (forkhead box Q1) [249]. Prior research has demonstrated that FOXQ1 can accelerate the growth of tumors by upregulating the expression of ferroptosis-inhibiting genes *SLC7A11* and *GPX4*. Nevertheless, it is still unknown how FOXQ1 controls SLC7A11. The authors of this study examined the function of FOXQ1 in controlling SLC7A11 and discovered that FOXQ1 can upregulate the expression of *circ_0000643*, a circular RNA that interacts with *MIR153*, to control the expression of SLC7A11 [250]. Additionally, the authors demonstrated that FOXQ1 can directly bind to the *circ_0000643* host gene's promoter to boost transcription of that gene. The development of novel therapeutic approaches for breast cancer may aim to target this mechanism [250].

BC progression has also been demonstrated to be influenced by *circ0052112*, *circ0001982*, and *circ0072309*. The targets of these circular RNAs increase invasion and migration of BC cells, inhibit *MIR143* to enhance carcinogenesis, and regulate *MIR492* to suppress invasion and proliferation, respectively, in BC cells [104,251,252]. Not only does *circRHOT1* suppress apoptosis and ferroptosis in BC cells, but it also stimulates the invasion, migration, and multiplication of these cells by controlling SLC7A11. Thus, *circRHOT1* may be a target for breast cancer treatment [253]. Mechanistically, by enclosing *MIR106A-5p*, *circRHOT1* suppresses ferroptosis in BC cells. In these cells, *MIR106A-5p* induces ferroptosis by targeting *STAT3* (signal transducer and activator of transcription 3). The inhibition of proliferation and enhancement of apoptosis caused by *circRHOT1* depletion in BC cells are reversed by overexpression of STAT3 and inhibition of *MIR106A-5p*. These results provide new evidence that the *circRHOT1*-*MIR106A-5p*-STAT3 signaling pathway is important in controlling the progression of BC and uncover a correlation between *circRHOT1*, *MIR106A-5p*, and STAT3 [253].

In order to help BC cells withstand the cell death brought on by ferroptosis, researchers have identified a new system against ferroptosis involving AIFM2/FSP1 (apoptosis inducing factor mitochondria associated 2). Due to its sponging of *MIR1228*, *circGFRA1* can control the expression of AIFM2. The increase in AIFM2 levels prevents ERBB2/HER2-positive BC cells from undergoing ferroptosis [254]. Through the reduction of CoQ10 (coenzyme Q10), an endogenous antioxidant that inhibits ferroptosis, by NAD(P)H, AIFM2 has an anti-ferroptosis effect [255,256]. Another route that keeps cells safe from ferroptosis is the GSH-GPX4 system. Researchers discovered that ERBB2/HER2-positive BC cells have higher expression of GPX4, AIFM2, and the glutathione-level indicator GSH:GSSG ratio. ERBB2/HER2-positive breast cancer treatment may benefit from targeting these pathways as a therapeutic approach [254].

7. Ferroptosis and ncRNAs: exploring therapeutic strategies, limitations, and directions of improvement that could be further investigated

Ferroptosis has been implicated in various pathologies including neurodegeneration, organ fibrosis, and ischemia-reperfusion injuries [65,257,258]. Notably, cancer cells are particularly susceptibility to ferroptosis [259,260]. Mesenchymal and dedifferentiated cancer cells, often resistant to traditional therapies and apoptosis, are highly susceptible to ferroptosis inducers, suggesting its potential to overcome therapeutic resistance.

Several strategies are being explored to exploit ferroptosis for cancer therapy. Targeting key ferroptosis enzymes in cancer cells is one approach. Pharmacological and genetic inhibition of the cystine/glutamate antiporter/xCT, achieved by blocking SLC3A2 and SLC7A11, has yielded promising results in preclinical models with minimal toxicity [14,261,262]. Similarly, targeting AIFM2/FSP1 is a promising avenue due to its dispensability in normal development, suggesting a potentially broad therapeutic window [263,264].

However, GPX4, another ferroptosis target, is crucial for healthy tissues including renal cells and neurons [265–267]. Clearly, GPX4 inhibitors (e.g., RSL3) require specific delivery to cancer cells to minimize side effects. Indirect ferroptosis inducers such as erastin may suffer from low solubility and rapid metabolic breakdown [268]. Encapsulation of ferroptosis inducers within protective delivery systems, such as nanoparticles, is being explored to address this issue.

Nanoparticle-based delivery of iron, peroxides, and ncRNAs targeting inhibitors of ferroptosis are actively being investigated in vitro and in vivo. NcRNAs, in particular, offer several advantages. They are naturally occurring cellular molecules, potentially leveraging existing metabolic pathways. Additionally, ncRNAs often target multiple genes across interconnected pathways, leading to a broader yet specific anticancer response — exemplified by the *MIR15-MIR16* cluster, which regulates multiple anti-apoptotic and cell cycle proteins [269]. Eventually, ncRNA therapeutics hold promise for cost-effective production through chemical synthesis.

Despite these advantages, ncRNA-based ferroptosis therapies face potential limitations. First, the regulation of tumorigenesis through ncRNA-mediated ferroptosis may have restricted efficacy. Second, individual variations in ncRNA expression and response to therapeutic interventions pose a challenge for predictability. Third, achieving a balance between promoting ferroptosis for tumor suppression and preventing chemoresistance using ncRNAs requires further investigation. Consequently, further research is necessary to explore the clinical potential of targeting ferroptosis-related ncRNAs.

Our understanding of ferroptosis remains incomplete, with several key questions unanswered. The precise relationship between ferroptosis and other regulated cell death pathways, such as TP53-mediated apoptosis, with share some upstream mechanisms, requires further elucidation. While iron is a key player in ferroptosis, the possibility of redox-independent roles for iron and the involvement of other metals such as copper necessitate further investigation. Additionally, a comprehensive understanding of the molecular events leading to ferroptosis execution is lacking. This knowledge gap is particularly pronounced concerning the downstream events following lipid peroxidation, especially the critical point(s) beyond which ferroptosis becomes irreversible.

Furthermore, the lack of specific markers for identifying ferroptosis in live cells and intact tissues presents a significant challenge. NcRNAs, a diverse group of non-coding transcripts with remarkable regulatory and biomarker potential, remain largely unexplored in the context of ferroptosis and cancer. While current evidence suggests that dysregulation of tightly controlled ncRNA networks in cancer frequently suppresses ferroptosis, which promotes tumor cell survival and progression, further research is necessary. Nonetheless, the ability to artificially induce ferroptosis holds significant therapeutic promise for cancer treatment.

8. Conclusion

Ferroptosis is known as a newly identified regulated cell death mechanism, involving iron-dependent lipid peroxidation and oxidative stress. This type of regulated cell death has been implicated in various diseases, particularly cancers. This review explores the role of ferroptosis in the progression of female-specific cancers, such as breast cancer and gynecological malignancies, and how it is regulated by ncRNAs. The review summarizes the current understanding of the molecular mechanisms, biomarker potential, and therapeutic implications of ferroptosis

and ncRNAs in these cancers. Additionally, it highlights the challenges and promising directions for future research in this area. The authors conclude that ferroptosis and ncRNAs hold promise as targets for the diagnosis and treatment of female-specific cancers, and that further studies are essential to fully comprehend their intricate interactions and functions.

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