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Review

Exploring Ferroptosis and Epigenetic Regulation in Gynecological Cancers: Implications for Treatment Strategies

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Abstract

Gynecological malignancies, particularly cervical, ovarian, and endometrial cancers, provide considerable worldwide health challenges due to the increasing incidence of new cases and mortality. Iron-dependent lipid peroxidation, a regulated process of cell death, has emerged as a highly promising focus for cancer clinical treatment. This article presents a thorough analysis of the many processes involved in ferroptosis, focusing specifically on the influence of epigenetic control, which includes histone modification, DNA methylation, non-coding RNAs (ncRNAs), and RNA modifications such as N6-methylcytosine (m6C). Recent findings clarify the complex interactions between epigenetic variables and the expression of genes associated with ferroptosis, which in turn affect the survival, proliferation, and response to treatment of gynecological cancers. Ferroptosis is strongly influenced by epigenetic control, which may lead to better management of gynecological malignancies. More effective treatments for endometrial, ovarian, and cervical malignancies may result from focusing on processes including histone modification, DNA methylation, and non-coding RNAs. Applying these discoveries to improve clinical outcomes and lower mortality should be the main goal of future initiatives.

1. Introduction

Female gynecological malignancies, including cervical, ovarian, and endometrial cancers, constitute a significant worldwide health concern. In 2020, research findings showed that approximately 1.34 million women received diagnoses for these malignancies, leading to approximately 650,000 deaths [1,2]. Significantly, the death incidence for endometrial cancer has increased by an average of 1% per year. Despite the doubling of ovarian cancer incidence in industrialized countries, the overall mortality risk is similar in industrialized and developing regions [3]. The main therapeutic approaches for malignant malignancies currently include surgical procedures, chemotherapy, radiation, and targeted or immunobiological therapies. Nevertheless, the ongoing existence of medication resistance is a huge challenge, reducing the effectiveness of treatment, increasing the possibility of recurrence, and placing substantial financial burdens on healthcare systems [4,5]. As a result, it is critical to investigate molecular mechanisms and therapeutic targets relevant to gynecological malignancies.

In 2012, scientists identified ferroptosis as a distinct form of programmed cell death that diverges from necrosis, apoptosis, and autophagy by depending on iron and substantial lipid peroxidation [6]. In 2012, scientists found that ferroptosis is a unique type of programmed cell death that is different from necrosis, apoptosis, and autophagy because it relies on iron and a lot of lipid peroxidation [7,8]. Current studies frequently demonstrate a correlation between tumor development and the suppression of ferroptosis, suggesting the involvement of many proto-oncogenes and tumor suppressor pathways in its regulation [6,9]. Studies have shown that ferroptosis plays a pivotal role in gynecological cancers by influencing tumor growth, chemotherapy resistance, and overall patient prognosis. For example, the suppression of ferroptosis has been directly linked to enhanced tumor aggressiveness and reduced sensitivity to conventional therapies in cervical, ovarian, and endometrial cancers [10-14].

Epigenetic regulation, which influences gene expression or activity without altering the DNA sequence, plays a significant role in gene expression through transcriptional and posttranscriptional processes [15]. Key processes like histone changes, DNA methylation,

specific noncoding RNAs (ncRNAs), and posttranscriptional regulation by miRNAs mediate transcriptional regulation [16]. Four distinct categories of regulators enable the dynamic and reversible characteristics of epigenetic alterations: "writers," "erasers," "readers," and "remodelers." These regulators play a crucial role in the addition, removal, recognition, and moderation of chromatin states, respectively [17]. Emerging research shows that both conventional signaling pathways and epigenetic processes regulate the expression of ferroptosis-related genes (FRGs) [18].

This article provides an overview of the recent advancements in studying ferroptosis in gynecological cancers. Changing histone proteins, DNA methylation, ncRNAs, and RNA m6A modification are some of the epigenetic control mechanisms that are being looked at in detail. Furthermore, it emphasizes the significance of these epigenetic regulators in biological processes and their possible impact on the treatment of ferroptosis-related diseases. The review's objective is to identify novel therapy targets and improve gynecological cancer management by elucidating these mechanisms. The present investigation aims to explore the association between epigenetic regulation and ferroptosis. This has the potential to offer novel strategies for combating cervical, ovarian, and endometrial malignancies. Given the critical role of ferroptosis in modulating tumor dynamics and therapy resistance in gynecological cancers, further exploration of its regulatory mechanisms could unveil novel therapeutic opportunities, offering more effective and personalized treatment strategies for patients.

2. Ferroptosis: An Overview

Regulated cell death (RCD) encompasses diverse processes essential for preserving cellular equilibrium, supporting development, and responding to infections. Among these, apoptosis is a widely recognized non-lytic form of cell death characterized by intact membrane integrity, cellular shrinkage, and the activation of specific caspase proteins [19]. In contrast, lytic forms of RCD, such as pyroptosis, necroptosis, and ferroptosis, involve cellular disintegration that leads to the release of inflammatory molecules. Pyroptosis is mediated by inflammasomes and gasdermin proteins, playing a key role in immune activation [20]. Necroptosis, in turn, is regulated by receptor-interacting protein kinases (RIPK1 and RIPK3) and mixed-lineage kinase domain-like protein (MLKL), while ferroptosis is uniquely defined by its dependence on lipid peroxidation driven by iron accumulation and oxidative stress [21,22].

Additionally, emerging forms of RCD, including cuproptosis and PANoptosis, have expanded our understanding of these mechanisms. Cuproptosis is triggered by the accumulation of copper that causes mitochondrial protein aggregation, resulting in cell death. Meanwhile, PANoptosis integrates features from pyroptosis, apoptosis, and necroptosis under specific stimuli [23]. These pathways collectively illustrate the complexity of cell death mechanisms, especially in cancer biology, where disruptions in RCD processes often contribute to resistance against therapies and tumor progression.

Iron dependence and lipotoxicity are distinguishing features of ferroptosis, a specific form of controlled cell death that has been discovered in recent years [24]. This mechanism impedes the function of the lipid repair enzyme glutathione peroxidase 4 (GPX4), resulting in the accumulation of lipid reactive oxygen species (ROS), which are lipid hydroperoxides [25]. At the genetic level, several genes are involved in the control of ferroptosis [26]. In contrast to other forms of cell death that cause noticeable changes in the physical structure of cells, ferroptosis mostly affects the internal composition of cells. This includes a reduction in mitochondrial size, an increase in membrane density, the absence of cristae, and the fragmentation of the outer mitochondrial membrane. Meanwhile, the cell membrane remains intact, and there are minimal changes in the nuclear structure without chromatin condensation [25].

The main contributing factors to ferroptosis are the enzyme GPX4's inability to repair peroxidation, the accumulation of reactive iron, and the oxidation of phospholipids containing polyunsaturated fatty acids (PUFAs) [27]. As a result, the cells experience a decrease in their antioxidant capacity and an increase in the accumulation of lipid ROS, ultimately leading to cell death [28]. Several pathways modulate the activity of glutathione peroxidase, including the XC-/GSH/GPX4 system, the ACSL4/LPCAT3/15-LOX pathway, and the FSP1/CoQ10/NAD(P)H pathway [29]. These pathways' overall contribution to ferroptosis regulation highlights their complex molecular features.

2.1 Ferroptosis: An Investigation of the Function of the System XC−/GSH/GPX4 Axis

The System XC-/GSH/GPX4 axis is critical in regulating ferroptosis as an essential antioxidant system. The plasma membrane-bound system XC- acts as a reverse transporter, facilitating the importation of cysteine into the cytosol to assist in the synthesis of glutathione (GSH) [30]. System XC- inhibition leads to a decrease in intracellular cysteine levels, which is essential for GSH synthesis [31]. Enzyme GPX4 is the primary catalyst for reducing and detoxifying phospholipid hydroperoxides (PLOOHs) in the cells of mammal [32]. Erastin and RSL3 both increase ferroptosis, but they do so in different ways. RSL3 stops GPX4 from working directly, while erastin stops it indirectly by lowering the import of cysteine. This lowers the amount of cysteine in cells, which is needed to make GSH [33]. Aggregation of PLOOHs causes rapid and irreversible damage to the cell membrane, eventually leading to cell death [34].

The mechanism of action of GPX4 involves the conversion of reduced GSH into its oxidized state, recognized as glutathione disulfide (GSSG) [35]. This mechanism facilitates the reduction of lipid peroxide (LPO) levels and the preservation of cellular redox equilibrium. This enzyme is the only one that directly catalyzes the reduction of hydrogen peroxide generated by biofilm lipids [36]. The suppression of the System XC-/GSH/GPX4 pathway leads to the accumulation of

lipid peroxidation (LPO) and the subsequent initiation of ferroptosis [37]. The molecule erastin functions as a ferroptosis inducer through effectively blocking System XC-, therefore disturbing the equilibrium of redox processes and causing an elevation in the buildup of lipid peroxidation [38]. In mammalian cells, the preservation of GSH synthesis and the prevention of cell death are dependent on the presence of both intracellular and extracellular cysteine [39]. Iron sequestrants or hydrophilic antioxidants can help to mitigate this process by maintaining cysteine levels in equilibrium and decreasing ferroptosis [29].

2.2 The Function of the ACSL4/LPCAT3/15-LOX Axis in Ferroptosis

Lipopolyphosphatidylcholine acyltransferase 3 (LPCAT3) and acyl-coenzyme A synthase long chain family member 4 (ACSL4) are recognized as crucial catalysts for ferroptosis [40]. These enzymes play a vital role in activating internally located iron chains by reprogramming metabolic lipids. ACSL4 is a key isoenzyme in the metabolism of PUFAs, and it plays a major role in determining how susceptible cells are to ferroptosis [41]. It accomplishes this by facilitating the incorporation of PUFAs into phospholipids, an essential step in ferroptosis [42]. By binding to coenzyme A, ACSL4 acts as a catalyst for activating long-chain PUFAs. LPCAT3 then transforms these activated PUFAs into phospholipids through transesterification, thereby improving PUFA integration into cellular membranes [43].

Higher levels of ACSL4 make cells more sensitive to ferroptosis [40]. ACSL4 improves the metabolism of PUFAs, particularly arachidonic acid (AA) and adrenic acid (AdA), to achieve this. ACSL4 facilitates the conversion of AA and AdA into their CoA derivatives, which LPCAT3 then esterifies to form phosphatidylethanolamines (AA-PE and AdA-PE) [44]. he enzyme 15-LOX (ALOX15) oxidizes these derivatives, leading to the formation of lipid hydroperoxides [45]. In turn, these hydroperoxides function as signals for ferric ions, thereby promoting ferroptosis. The ACSL4/LPCAT3/15-LOX axis greatly influences the cellular lipid composition and plays a vital role in the generation of lethal lipid peroxides during ferroptosis [29].

The altered cellular lipid content by ACSL4 is instrumental in determining susceptibility to ferroptosis. By making lipid peroxides through ACSL4-mediated lipid biosynthesis [46], the lipoxygenase enzyme, which contains iron, helps cells die. In ovarian cancer, miR-424-5P specifically targets ACSL4 expression, leading to the inhibition of ferroptosis in cancer cells. Because of this, stopping the expression of ACSL4 may be a key way that cells become resistant to ferroptosis (Figure 1) [47].

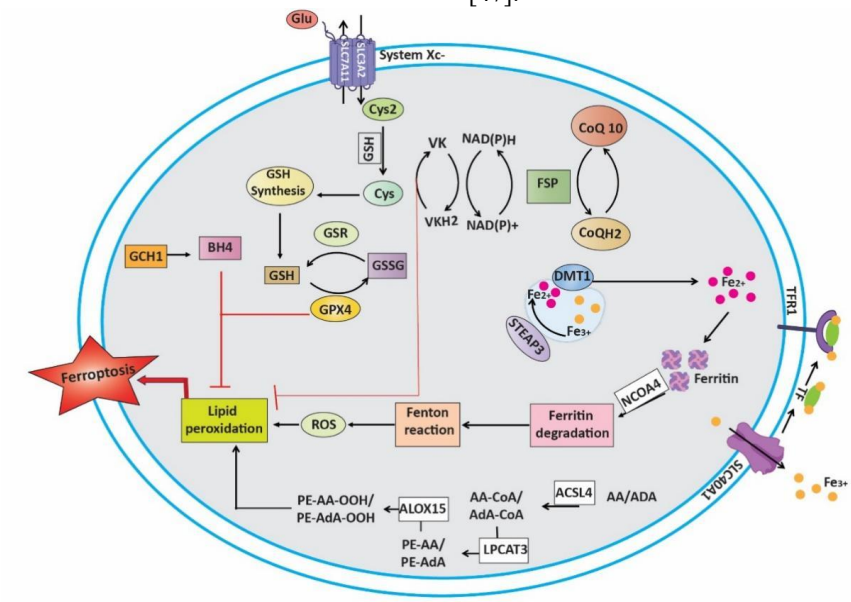

Figure 1. Overview of Ferroptosis Mechanisms and Lipid Peroxidation Defense Pathways. This illustration details the process of ferroptosis, driven by the oxidation of lipids dependent on polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) and adrenic acid (AdA), alongside ROS and iron. Transferrin and its receptor (TFR1) are essential for Fe^{3+} transport, while STEAP3 and DMT1 facilitate the reduction and transport of Fe^{2+}, leading to lipid peroxidation. Enzymes like ACSL4 and LPCAT3 are key in forming AA-PE/AdA-PE, with PKCβII detecting lipid peroxidation and enhancing it by phosphorylating ACSL4. GPX4 uses GSH to convert toxic lipid peroxides (PL-OOH) into non-toxic forms (PL-OH), supported by the cystine/glutamate antiporter xCT. FSP1 mitigates lipid peroxidation by reducing oxidized CoQ to CoQH2 independently of GSH and activates a vitamin K cycle to inhibit ferroptosis. Additionally, BH4 provides antioxidant protection independent of GPX4 and FSP1, while NRF2, a key regulator of antioxidant responses, inhibits lipid peroxidation by upregulating multiple ferroptosis inhibitors.

2.3 Investigation of the FSP1/CoQ10/NAD(P)H axis in Ferroptosis

AIFM2, a constituent of the apoptosis-inducing factor (AIF) family, participates in the activity of oxidoreductases and has the ability to trigger predetermined cell death Following its recognition as an anti-iron porphyrin gene, AIFM2 has been dubbed ferrocyte apoptosis suppressor protein 1 (FSP1) [29]. FSP1 functions to prevent iron-induced lipid

peroxidation by interacting with ubiquinone (CoQ10), a reductant that neutralizes lipid peroxyl radicals. Researchers have demonstrated that combining pharmacological targeting of FSP1 with GPX4 inhibitors stimulates ferroptosis in various tumor types [48].

The activation of CoQ10 is essential in the mevalonate (MVA) pathway, and modifying this pathway presents a promising approach for controlling ferroptosis [49]. Cardamoylation transports FSP1 to the plasma membrane, where it acts as an oxidoreductase, enabling the synthesis of ubiquinone from CoQ10 via NADPH [50,51]. NADPH reduces lipid peroxide levels by acting as a lipophilic anti-radical agent. When working together with GPX4 and GSH, the FSP1/CoQ10/NAD(P)H axis protects against phospholipid peroxidation and stops ferroptosis [50].

3. The Mechanisms Underlying Ferroptosis in Cancer

Multiple forms of regulated cell death, including apoptosis, autophagy, necrosis, and ferroptosis, can occur in cancer cells as tumors progress [52-54]. Ferroptosis, an iron- and lipid-peroxidation-dependent type of cell death, has garnered significant attention due to its dual impact on tumor biology, functioning as both a potent tumor suppressor in many contexts and, under certain conditions, contributing to tumorigenesis or progression [55]. Below, we integrate evidence for ferroptosis as a tumor-suppressive mechanism and discuss how cancer cells can adapt or exploit this pathway, thereby promoting tumor advancement.

3.1 Induction of Ferroptosis for Tumor Suppression

Ferroptosis serves as a powerful tumor-suppressive mechanism by inducing cell death through oxidative damage. This process disrupts critical cellular functions in cancer cells, curtailing their growth, migration, and resistance to therapies. Silencing GPX4, an essential regulator of ferroptosis, using small interfering siRNAs, significantly depletes GPX4 protein levels and leads to an accumulation of lipid ROS, resulting in ferroptotic death in renal cell carcinoma cells. This effect can be reversed by antioxidants or iron chelators, demonstrating the pivotal role of GPX4 in maintaining redox balance [56]. Inhibiting the cystine/glutamate transporter SLC7A11 (System Xc−), either pharmacologically or genetically, impairs cystine uptake and GSH synthesis, triggering oxidative stress and ferroptotic death across various cancer models [57,58]. Elevated levels of SLC7A11 or GPX4 in tumors act as protective mechanisms against ferroptosis, and their inhibition significantly suppresses tumor cell proliferation and metastatic potential [56,59].

Additional studies highlight the role of other molecular players in enhancing ferroptosis. GOT1 inhibition increases GSSG and NADP+ levels, rendering cancer cells more susceptible to ferroptosis, especially when combined with butionine sulfoximine (BSO). This synergy can be reversed by ferrostatin-1, demonstrating the ferroptosis-specific nature of this cytotoxicity [60]. In clear cell renal cell carcinoma, KLF2 downregulates GPX4, reducing cancer cell invasiveness [61].

Similarly, in hepatocellular carcinoma, miR-211-5p suppresses ACSL4, a key ferroptosis regulator, leading to decreased tumor proliferation, migration, and invasion [62].

Ferroptosis also mitigates metastatic potential. Increased expression of SLC7A11 correlates with higher rates of lymph node metastases in esophageal squamous cell carcinoma [63], while elevated GPX4 levels facilitate renal cancer cell motility [64,65]. Combining ferroptosis inducers with radiotherapy amplifies lipid ROS and ACSL4 expression, significantly improving the radiosensitivity of cervical cancer cells [66].

The tumor-suppressive function of ferroptosis is supported by several key genes. TP53, for instance, represses SLC7A11 in an ALOX12-dependent manner, promoting ferroptosis and inhibiting tumor growth [67,68]. Mutations in TP53 that abolish its ability to regulate ferroptosis also compromise its tumor-suppressive role [69,70]. BAP1, a tumor suppressor, reduces histone H2A ubiquitination at the SLC7A11 promoter, enhancing ferroptosis and restricting tumor progression [71,72]. Additional tumor suppressors, including FH, KEAP1, and MLL4, contribute to ferroptosis-mediated cancer suppression by regulating oxidative stress pathways and lipid metabolism [73-75].

3.2 Tumors Activating Role of Ferroptosis

Although ferroptosis is a well-documented tumor-suppressive mechanism, under specific conditions, it may paradoxically promote tumor progression. This dual nature depends on the context, such as the tumor microenvironment or the adaptive capabilities of cancer and immune cells.

In a pancreatic ductal adenocarcinoma (PDAC) model, reduced GPX4 expression or an iron-rich diet accelerated the progression of pancreatic intraepithelial neoplasia, heightened stromal activation, and worsened survival outcomes. Mice with KrasG12D/+ and Gpx4 alterations also exhibited increased rates of liver and lung metastases. These findings suggest that partial ferroptotic stress or iron overload can inadvertently support malignancy by creating a microenvironment conducive to tumor growth [76].

Immune evasion is another avenue through which ferroptosis may facilitate tumor progression. CD36-mediated fatty acid uptake induces ferroptosis in tumor-infiltrating CD8+ T cells, weakening their antitumor function. Blocking CD36 or ferroptosis in these immune cells restores their cytotoxic capacity and limits tumor expansion [77].

Tumors frequently evade ferroptosis by upregulating antioxidant defenses and iron-regulatory systems. Overexpression of SLC7A11, GPX4, and FSP1, along with elevated GSH levels, equips cancer cells to withstand oxidative damage [78-81]. Genetic and metabolic adaptations further reinforce this resistance; for instance, NFS1, Frataxin, CISD2, and prominin 2

reduce the labile iron pool, limiting lipid peroxidation and ferroptosis [82,83].

The tumor microenvironment also plays a crucial role in ferroptosis evasion. Lymphatic tissues rich in oleic acid promote MUFA-phospholipid synthesis via ACSL3, stabilizing membranes against oxidative damage [84]. Hormonal factors, including estrogen and androgen, regulate enzymes such as MBOAT1 and MBOAT2, further protecting hormone-sensitive tumors from ferroptosis [85]. These adaptations illustrate how tumors can co-opt ferroptosis-related pathways to ensure survival and progression.

The dual nature of ferroptosis highlights its context-dependent role in cancer biology (Table 1). While robust induction of ferroptosis effectively suppresses tumor growth, metastasis, and therapy resistance, partial ferroptotic stress can reshape the tumor microenvironment, enabling cancer cells or immune cells to adapt and thrive. Understanding the genetic, metabolic, and environmental factors influencing these outcomes is essential for developing therapeutic strategies that maximize the anti-tumor potential of ferroptosis while minimizing unintended consequences.

Table 1. Strategies for Ferroptosis Induction and Inhibition in Cancer

Category	Strategy	Mechanism	Perspective	References
Induction of Ferroptosis for Tumor Suppression	Targeting GPX4	Inhibits the key enzyme reducing lipid peroxides, leading to ferroptotic death in cancer cells.	A pivotal approach for directly inducing ferroptosis, offering a potent mechanism to eliminate tumor cells resistant to conventional therapies. Requires precise delivery systems to avoid collateral damage to healthy tissues.	[57]
	Inhibition of SLC7A11/System Xc−	Blocks cystine import, depleting GSH and inducing oxidative stress.	A widely applicable strategy in ferroptosis induction, particularly effective in tumors overexpressing SLC7A11. Optimal outcomes may depend on combinatorial regimens with chemotherapy or radiotherapy.	[58,59]
	Enhancing Radiation Sensitivity	Combines ferroptosis inducers with radiotherapy to amplify lipid ROS and tumor cell death.	A synergistic approach that leverages ferroptosis to potentiate the cytotoxic effects of radiotherapy, particularly in radioresistant cancers. Promises enhanced treatment efficacy while reducing the required radiation dose.	[67]
	Inducing Oxidative Stress Through GOT1	Increases GSSG and NADP+, enhancing ferroptosis sensitivity.	Targets metabolic vulnerabilities specific to cancer cells, offering a precise method to enhance ferroptosis induction. Particularly beneficial in combination with ferroptosis-inducing agents for maximizing therapeutic effects.	[61]
	Activating Tumor-Suppressive Pathways	Promotes ferroptosis by regulating genes like TP53, BAP1, and KEAP1.	Exploits natural tumor-suppressive mechanisms to induce ferroptosis, providing a targeted approach for therapy. Clinical applications may require strategies to selectively activate these pathways in tumor cells.	[68-75]
Tumors Activating Role of Ferroptosis	Partial Ferroptosis from Iron Overload	Creates a pro-tumor microenvironment through ferroptotic stress and iron accumulation.	Highlights the dual role of ferroptosis in cancer, where partial activation can inadvertently promote tumor progression. Requires careful modulation to avoid such outcomes.	[76]
	Immune Cell Ferroptosis via CD36	CD36-mediated fatty acid uptake induces ferroptosis in CD8+ T cells, weakening immune defenses.	A critical challenge in immunotherapy, where ferroptosis induction in immune cells compromises antitumor immunity. Targeting CD36 may restore immune function and enhance therapeutic outcomes.	[77]
	Antioxidant and Iron-Regulatory Adaptations	Tumors upregulate SLC7A11, GPX4, and other pathways to evade ferroptosis.	Represents a significant barrier to ferroptosis-based therapies. Inhibiting these adaptive mechanisms could improve treatment efficacy and counteract therapy resistance.	[78-81]
	Microenvironmental Lipid Modulation	Tumor microenvironment stabilizes membranes via MUFA synthesis, reducing lipid peroxidation.	Underscores the role of the tumor microenvironment in ferroptosis evasion. Targeting lipid metabolic pathways may enhance ferroptosis susceptibility in resistant tumors.	[82-85]

3.3 Ferroptosis as a Therapeutic Strategy for Drug-Resistant Cancers and Its Broader Clinical Potential

Ferroptosis has emerged as a promising approach to address the challenge of drug resistance in cancer therapy. In hepatocellular carcinoma (HCC), for example, YAP/TAZ co-regulates the expression of SLC7A11 with ATF4, enabling tumor cells to evade sorafenib-induced ferroptosis and thereby fostering drug resistance [86]. Resistance mechanisms also involve NRF2, which modulates genes such as GPX4 and SLC7A11 along the SLC7A11-GPX4-GSH pathway [87,88]. Similarly, ZEB1 has been shown to increase in chemotherapy-resistant stromal cells, yet this upregulation renders them

more vulnerable to ferroptosis triggered by statins or GPX4 inhibitors [89]. Intriguingly, drug-resistant neuroblastomas can also be targeted by ferritin A-induced ferroptosis, suppressing cell proliferation in high-risk cases [90].

One major part of ferroptosis induction is through inhibition of System Xc-, which regulates cystine uptake. Erastin exemplifies this strategy by depleting intracellular GSH, triggering ferroptosis, particularly in RAS-mutated cancers [91-93]. Despite erastin's promise in enhancing the efficacy of cisplatin and doxorubicin, its poor solubility and stability have spurred the development of variants such as Piperazine erastin (PE) and ketone erastin [94]. Sulfasalazine (SAS), traditionally an anti-inflammatory agent, also induces ferroptosis via System Xc- blockade, albeit with lower potency [95].

Sorafenib, a multikinase inhibitor frequently used against advanced cancers, presents a unique paradox: although it can induce ferroptosis in some settings, it may also inhibit ferroptosis in HCC through NRF2 and Rb activation [96]. Resistance to sorafenib has been tied to MT-1G signaling, prompting efforts to block MT-1G and enhance drug efficacy [97]. Additionally, certain cancer cells can bypass System Xc- inhibition by activating the transsulfuration pathway and synthesizing cysteine from methionine, thus evading ferroptosis [30]. Beyond System Xc-, targeting GPX4-a critical enzyme preventing lipid peroxidation-can directly induce ferroptosis. Compounds like RSL3 inactivate GPX4 by modifying its functional residues [98], while FIN56 both degrades GPX4 and depletes CoQ10 [99]. Other agents, including withaferin A and BAY 87-2243, promote iron accumulation or GPX4 inactivation, further sensitizing cells to ferroptosis [100,101].

Recent advances extend to nanotechnology-based ferroptosis inducers, such as αMSH-PEG-C' dots, which increase intracellular iron and ROS while depleting GSH [101]. Iron-containing nanoparticles similarly release reactive iron in acidic tumor microenvironments, promoting ferroptosis [102,103]. For instance, SRF@FeIIIITA (SFT) nanoparticles inhibit GPX4 under lysosomal conditions, and arginine-rich manganese silicate nanobubbles effectively scavenge GSH, enhancing ferroptotic cell death [104,105].

Complementary to these findings, mounting evidence shows how ferroptosis-inducing compounds can reverse cancer therapy resistance in a variety of malignancies. Baicalin, for example, destabilizes NRF2 through ubiquitin-mediated degradation, curbing NRF2 targets such as GPX4 and xCT, and thereby eliciting ferroptosis [106]. Wogonin increases iron levels, lipid peroxidation, and superoxide production while reducing ferroptosis suppressor proteins, effectively targeting pancreatic cancers [107]. Another agent, ponicidin, blocks pancreatic cancer cell proliferation by inhibiting the gamma-glutamyl cycle and regulating polyunsaturated fatty acid metabolism [108].

Lung cancer, a persistently prevalent malignancy, has likewise been shown to respond to ferroptosis inducers. Bufotalin (BT), a GPX4 inhibitor, triggers ferroptosis via GPX4 ubiquitination and degradation in non-small cell lung cancer [109]. Similarly, Timosaponin AIII (Tim-AIII) binds to heat shock protein 90 (HSP90), boosting GPX4 ubiquitination and degradation [110]. In renal cell carcinoma, salinomycin-induced ferroptosis is mediated by the Disulfide Isomerase Family A Member 4 (PDIA4), whose autophagic degradation enhances tumor cell sensitivity to ferroptosis [111].

Notably, sorafenib continues to demonstrate potent antitumor effects as a ferroptosis inducer across multiple cancers [112]. An important study reported that sorafenib upregulates activating transcription factor 2 (ATF2), which in turn targets HSPH1. This protein interacts with SLC7A11, stabilizing it and influencing ferroptosis [113]. These diverse pro-ferroptotic agents-including wogonin, ponicidin, sorafenib, and salinomycin-underscore the broad potential of ferroptosis in cancer therapy [114,115].

Targeted interventions, including small molecules, natural compounds, and nanotechnology-based agents, offer significant translational potential. By integrating ferroptosis-based therapies with established and emerging treatments, the oncology community may unlock novel strategies to overcome resistance, enhance patient survival, and usher in a new era of cancer care.

4. Epigenetic Regulation in Ferroptosis

Epigenetics is the study of heritable alterations in gene function that result in phenotypic phenomena without any modifications in the DNA sequence. Accumulating data suggests that epigenetic control influences ferroptosis through gene transcription, posttranscription, or post-translation processes. Therefore, focusing on epigenetic mechanisms in ferroptosis is anticipated to offer a novel approach for treating disorders associated with ferroptosis. The present study will concentrate on the epigenetic control mechanisms encompassing histone modifications, DNA methylation, ncRNAs, and RNA modifications in the context of ferroptosis (Figure 2).

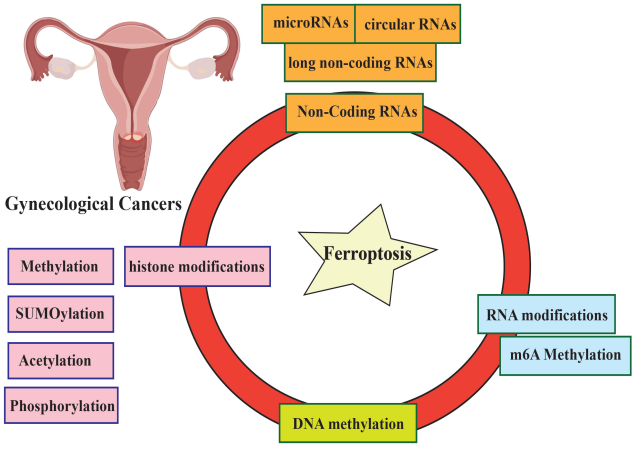

Figure 2. Epigenetic control mechanisms involved in the context of ferroptosis in gynecological cancers.

4.1 DNA Methylation

Recent studies have shown how important epigenetic inheritance is for keeping iron balance. This is done by methylating DNA in CpG islands (CGIs), which are key for controlling gene expression [116,117]. Approximately 80% of CpG dinucleotides in vertebrates are methylated, with 5-methylcytosine (5mC) being a hallmark of gene silence. However, CGIs commonly stay hypomethylated [118]. However, CGIs commonly stay hypomethylated. The distinctive characteristics of CGIs, such as their abundant CpG and GC content and binding sites for transcription factors, promote gene activation. Alterations in DNA methylation can have a substantial effect on gene expression since higher levels of methylation result in gene suppression, whereas lower levels are associated with gene activation [119]. Increased quantities of free iron can impede the function of DNA methyltransferase, as observed in HFE mutant mice [120]. Iron chelators such as deferoxamine can be administered to restore this function, indicating a clear correlation between iron levels and epigenetic alterations [121]. Furthermore, enzymes like 3-hydroxybutyrate dehydrogenase 2 play a crucial role in regulating iron equilibrium. Blocking these enzymes can lead to excessive iron accumulation, particularly affecting the growth of cancer cells and the translation of genes related to iron metabolism [122].

In cancer biology, the process of methylation of certain genes has become a crucial determinant of cell survival and the advancement of the illness. Significantly, in cervical squamous cell carcinoma (CESC), researchers have linked the cancer cells' ability to avoid ferroptosis, a type of iron-dependent cell death, to the reduction in methylation of FRGs like AQP3, MGST1, and TFRC. Researchers have shown that methylation alterations in specific genes like AQP3, MGST1, and TFRC confer resistance to ferroptosis. This resistance is linked to the disease's behavior, which impedes immune responses and patient outcomes. The results show that methylation is important for keeping cervical cancer cells alive by stopping ferroptosis. This shows how important it is for both the progression of cancer and new ways to treat it [123]. In endometrial cancer (EC), FAM83H-AS1 activates DNMT1-mediated hypermethylation of the CDO1 promoter, hence enhancing resistance to ferroptosis. Epigenetic silencing reduces CDO1 expression, indicating that FAM83H-AS1 may be a promising candidate for addressing ferroptosis resistance in EC [124].

Simultaneously, the field of therapy has witnessed impressive advancements with the advent of DNA hypomethylating drugs such as NTX-301. This chemical effectively targets ovarian cancer cells by downregulating DNA methyltransferases, leading to a significant reprogramming of gene expression that affects 15,000 genes. The reprogramming process changes lipid metabolism by lowering unsaturated fatty acids and raising oxidized lipids. This causes ferroptosis, a type of cell death. Both *in vitro* and *in vivo* studies have demonstrated the capacity of NTX-301 to cause ferroptosis, resulting in a substantial inhibition of tumor development. What they found shows that NTX-301 is a new way to treat ovarian cancer because it changes epigenetics to cause ferroptosis [125].

4.2 Histone Modifications in Ferroptosis

A recent investigation has shown that chemical alterations of the tails of the four main histone proteins, namely H2A, H2B, H3, and H4, have a substantial impact on the interactions between histones and other nuclear proteins. Modifications of this nature are essential for controlling target gene expression. For instance, studies have demonstrated that histone changes in non-Hodgkin lymphoma control genes related to ferroptosis, such as GPX4 and SLC7A11 [126,127]. hus, histone changes intricately control ferroptosis, highlighting the significance of epigenetic mechanisms in managing cellular processes related to this specific type of controlled cell death. These modifications encompass acetylation, methylation, phosphorylation, adenylation, ubiquitination, and SUMOylation [128].

The hypoxic tumor microenvironment in cervical cancer facilitates epigenetic remodeling, which is a key factor in the development of ferroptosis resistance. Integral to this mechanism is the increase in expression of KDM4A, which enhances HIF1 transcription by altering the H3K9me3 marker in the promoter region of HIF1α. This increase in expression results in higher levels of ferroptosis resistance indicators, including TfR1 and DMT1, as well as increased iron concentration and MDA levels. KDM4A and HIF1α exhibit significant expression and a strong positive correlation in cervical cancer tissues. Suppressing KDM4A lowers HIF1α expression, raises H3K9me3 expression, and makes cells more vulnerable to ferroptosis. This shows how important epigenetic control is for protecting cells from ferroptosis in low-oxygen environments [129]. An investigation has revealed that the SUMOylation of KDM4A at the K471 locus is a crucial element in determining resistance to ferroptosis in cervical cancer cells, particularly under hypoxia-like conditions. The aforementioned conditions enhance the protein levels of KDM4A, SUMO1, and Ubc9 while decreasing the levels of SENP1. The enhanced interaction between KDM4A and SUMO1 results in reduced H3K9me3 concentrations in the promoter region of SLC7A11, thereby facilitating the production of SLC7A11 and GPX4. Silencing KDM4A or altering its K471 locus reduces SUMOylation levels, increases H3K9me3, decreases SLC7A11 expression, and reduces ferroptosis resistance in cervical cancer cells [130].

Researchers have extensively explored the therapeutic implications of histone alterations, particularly focusing on the effect of histone deacetylase (HDAC) inhibitors. Experimental demonstrations have demonstrated the epigenically driven mechanism by which sodium butyrate (NaBu), a well-characterized HDAC inhibitor, induces ferroptosis in endometrial cancer cells. NaBu triggers epigenetic modifications that increase RBM3 expression by inhibiting HDACs. Consequently, the decreased expression of SLC7A11, a crucial gene implicated in resistance to ferroptosis, results in

heightened ferroptosis in cancer cells. This study suggests that NaBu exerts its anti-cancer effects by modifying the RBM3/SLC7A11 axis at the epigenetic level. This presents a new treatment strategy for specifically targeting endometrial cancer through epigenetic processes [131].

Furthermore, new research has revealed that the Cdc25A/PKM2/ErbB2 axis plays a role in providing resistance to ferroptosis in cervical cancer. Previous studies have demonstrated that Cdc25A suppresses ferroptosis in cervical cancer cells by removing phosphate groups from PKM2, resulting in elevated ErbB2 levels and decreased autophagy. This mechanism contributes to the development of resistance against the cancer medication sorafenib. Evidence indicates that focusing on the Cdc25A/PKM2/ErbB2 pathway may be a promising approach to augment ferroptosis and boost therapy results in cervical cancer [132].

4.3 RNA Modifications in Ferroptosis

RNA methylation, which accounts for more than 60% of all RNA modifications, has garnered considerable interest in the field of epigenetics over the last decade. Within this group, N6-methyladenosine (m6A) is the most prevalent post-transcriptional alteration observed in messenger RNAs [133]. The enzymes METTL3, METTL14, WTAP, and KIAA1429 are responsible for facilitating the incorporation of methyl groups into RNA, hence establishing the m6A modification. In contrast, "erasers" such as ALKBH5 and FTO play a vital role in eliminating these methyl marks through demethylation [134]. Some well-known "readers" are the YTH domain protein family and the heterogeneous nuclear ribonucleoprotein (HNRNP) family, which are RNA-binding proteins that only find m6A-modified mRNAs [135]. These components collectively have a crucial function in controlling the stability, splicing, translation, and degradation of RNA, therefore exerting influence on various cellular processes and biological parameters.

Studies have demonstrated that METTL14 enhances sorafenib-induced ferroptosis in cervical cancer by decreasing the stability of FTH1 mRNA through m6A methylation. There is a negative correlation between decreased expression of METTL14 and m6A methylation and the prognosis of cervical cancer patients. Researchers have found that overexpressing METTL14 increases FTH1 mRNA methylation, which decreases FTH1 stability and expression. However, knocking down METTL14 lowers ferroptosis. Inhibition of the PI3K/Akt pathway or overexpression of FTH1 counteracts METTL14's increase in sorafenib-induced ferroptosis, indicating that METTL14 may be a promising target for improving sorafenib's anticancer effectiveness [136].

Analysis of endometrial cancer reveals that PRMT3 plays a crucial role in enhancing resistance to therapy by methylating METTL14. This, in turn, promotes m6A methylation through a mechanism that depends on m6A-YTHDF2. This mechanism stabilizes GPX4 mRNA, thereby decreasing ferroptosis. PRMT3 inhibition disrupts this process, leading to increased ferroptosis and enhancing the effectiveness of treatments like anti-PD-1, cisplatin, and radiation. Targeting PRMT3 may improve treatment outcomes in endometrial cancer by making cancer cells more likely to undergo ferroptosis [137]. Further emphasizing the role of RNA methylation in cancer, miR-30c-5p induce the m6A modification of KRAS to decrease the growth and movement of cervical cancer cells. This implies the existence of a wider regulatory network in which non-coding RNAs impact gene expression mediated by m6A transcription [138].

Additionally, m6A methylation mediated by HNRNPA2B1 has been shown to enhance FOXM1 expression in endometrial cancer, which in turn promotes tumor progression and resistance to ferroptosis. The stabilization of FOXM1 mRNA by HNRNPA2B1 through m6A alteration leads to higher expression of LCN2, which helps cells become resistant to ferroptosis. In cisplatin-resistant endometrial cancer cells, decreasing FOXM1 levels enhances ferroptosis. Overexpression of LCN2, on the other hand, can reverse this effect. This suggests that targeting the HNRNPA2B1/FOXM1/LCN2 axis may help overcome drug resistance [139].

The study demonstrates that HNRNPA2B1 methylation of m6A promotes FOXM1 expression in endometrial cancer, thereby facilitating tumor advancement and increasing its resistance to ferroptosis. The stabilization of FOXM1 mRNA by HNRNPA2B1 via m6A alteration results in enhanced expression of LCN2, thus contributing to the development of ferroptosis resistance. Lowering the amount of FOXM1 in cisplatin-resistant EC cells caused more ferroptosis, but increasing the amount of LCN2 had the opposite effect. These findings indicate that focusing on the HNRNPA2B1/FOXM1/LCN2 pathway may be effective in overcoming medication resistance in endometrial cancer [140]. Furthermore, ovarian cancer recognizes IGF2BP3 as a crucial regulator that specifically targets CACNA1A via m6A RNA modification, suppressing ferroptosis and stimulating tumor development. CACNA1A inhibition disrupts calcium equilibrium, leading to elevated levels of ROS and ferroptosis. This suggests that targeting the IGF2BP3-CACNA1A axis may be a potentially effective therapeutic approach for the treatment of ovarian cancer (Figure 3) [141].

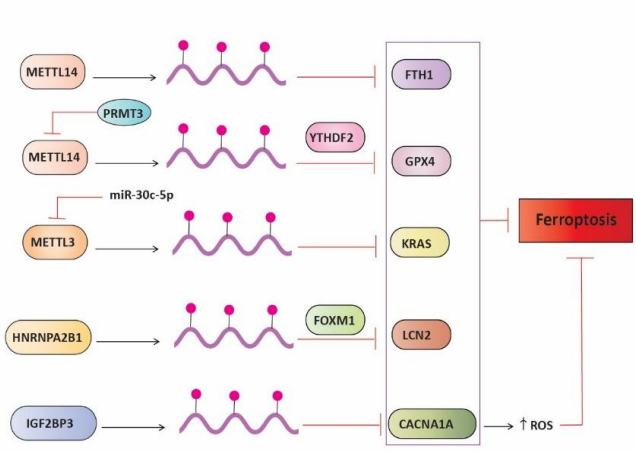

Figure 3. RNA modifications affect ferroptosis in gynecological cancers.

4.4 Non-Coding RNAs in Ferroptosis: Implications for Gynecological Cancers

RNA, an essential macromolecule in cells, plays an important role in gene control and information transmission. From a functional perspective, it can be classified into two distinct types: coding RNA and non-coding RNA [142]. Although coding RNAs are primarily responsible for creating proteins, non-coding RNAs (ncRNAs) can have crucial functions in disease processes, such as encoding peptides or proteins associated with tumors. This part looks at how non-coding RNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), work in the ferroptosis process that is connected to gynecological cancers [143-146].

4.4.1 MiRNAs Related to Gynecological Cancers in Ferroptosis

Among the most intensively researched non-coding RNAs in tumor biology are microRNAs. These short, single-stranded RNA molecules, which are usually 20–24 nucleotides long and are made by endogenous genes, play key roles in controlling both translational and transcriptional activity [147,148]. The involvement of miRNAs in several biological processes encompasses the regulation of metabolic pathways, facilitation of tumor growth, modulation of cell migration and invasion, and contribution to resistance against chemotherapeutic regimens [149]. When target mRNAs are processed after transcription, microRNAs bind to the 3′ untranslated region of those mRNAs. This effectively controls gene expression. This interaction has the ability to impede protein translation by either repressing the translation process or diminishing the ceRNA's stability [150,151]. Investigating microRNAs linked to ferroptosis as a treatment approach shows enormous potential in the therapeutic domain of cancer [152]. Only a small portion of identified miRNAs, with either pro- or anti-ferroptosis properties, have found direct therapeutic applications. These findings emphasize the urgent requirement for additional research to fully exploit their promise in the field of cancer therapy. The intricate relationship among miRNAs, ferroptosis, and cancer advancement makes it highly promising to target these molecules for treatment, especially in gynecological malignancies like cervical and ovarian cancer.

MicroRNAs play a crucial role in cancer biology by directly influencing the expression of genes essential for ferroptosis, a type of programmed cell death. In ovarian cancer, miR-424-5p assumes this function by specifically targeting ACSL4, a crucial enzyme involved in lipid metabolism, therefore diminishing the susceptibility to ferroptosis inducers such as erastin and RSL3. Amplification of ACSL4 expression can counteract miR-424-5p-induced ferroptosis suppression. The suppression of ACSL4 by miR-424-5p not only enhances the survival of cancer cells but also is associated with a negative prognosis, underscoring its potential as a viable target for improving ferroptosis-based treatments [47].

Similarly, in ovarian cancer, miR-93-5p exerts a substantial effect by suppressing SLC7A11, an essential constituent of the cystine/glutamate antiporter. Lowering the levels of SLC7A11 through miR-93-5p leads to better ferroptosis and slower tumor growth. Erastin, a selective inhibitor of SLC7A11, stimulates ferroptosis and can mitigate the consequences of miR-93-5p suppression. This study indicates that miR-93-5p may serve as a promising therapeutic target for ovarian cancer by controlling the process of SLC7A11-mediated ferroptosis. Highlighting the potential of directed treatment of this miRNA to impede the progression of malignancy [153]. The involvement of miR-1-3p in ovarian cancer serves to further demonstrate the influence of miRNAs on the ferroptosis process. The biological activity of miR-1-3p inhibitors is the opposite of that of miR-1-3p mimics, which increase ferroptosis and decrease cell survival. Inhibition of FZD7 by miR-1-3p can counterbalance the reduced sensitivity to ferroptosis inducers caused by overexpression of FZD7. These results indicate that miR-1-3p may be a promising therapeutic target for stimulating ferroptosis in ovarian cancer [154].

The regulation of ferroptosis is also evident in cervical cancer, where miR-660-5p plays a crucial role. Disseminated by tumor-associated macrophages (TAMs), miR-660-5p reduces the expression of ALOX15, a crucial gene involved in lipid peroxidation, hence preventing ferroptosis. The STAT6 pathway, which is activated by IL4/IL13, slows down this process. This shows how the tumor microenvironment and miRNA control cell death are connected in a complex way [155]. Similarly, in ovarian cancer, the release of IL-6 from M2 macrophages further strengthens the mechanism by enhancing GPX4 expression, which in turn augments ferroptosis resistance. Bioinformatics analysis revealed a dramatic upregulation of miR-1228-3p in ovarian cancer patients. The upregulation of miR-1228-3p expression by IL-6 leads to the subsequent stimulation of IL-6 production by M2 macrophages, thereby establishing a feedback loop that amplifies the expression of GPX4 and resistance to ferroptosis. *In vivo* studies demonstrated that upregulation of GPX4 and miR-1228-3p leads to an increase in tumor growth, whereas suppression effectively decreases it. The results emphasize the miR-1228-3p/GPX4 pathway as a promising therapeutic focus for ovarian cancer [156]. Furthermore, researchers have identified EPAS1, a gene strongly associated with hypoxia and ferroptosis, as a crucial factor in promoting malignant behavior in cervical cancer. When EPAS1 is overproduced in cervical cancer tissues, it increases cell proliferation, invasion, and migration while decreasing apoptosis. The regulation in question pertains to the MALAT1/miR-182-5p axis and super-enhancers, namely elements E1 and E3. This observation implies that EPAS1 has the potential to be a target for both the diagnosis and therapy of cervical cancer [157].

A cervical cancer prognostic model, incorporating gene expressions linked to ferroptosis, showcases the predictive role of miRNAs in cancer progression. This model revealed a substantial upregulation of CA9 mRNA in cancer lesions, controlling a competitive endogenous RNA (ceRNA) pair, CA9/ULBP2. The participation of

hsa-miR-34a in this regulatory network provides a novel understanding of cervical cancer development and presents opportunities for possible therapeutic approaches aimed at this axis [158].

Studies that show medicines like lidocaine and zinc oxide nanoparticles (ZON) can activate ferroptosis through miRNA pathways highlight the therapeutic potential of miRNA regulation even more. Lidocaine stimulates ferroptosis in ovarian and breast malignancies by increasing the expression of miR-382-5p, which in turn reduces the expression of SLC7A11. This results in a higher generation of ROS and increased iron buildup. These effects not only increase cellular apoptosis but also establish lidocaine as a highly promising therapeutic choice [159,160]. Similarly, ZON exerts its anti-cancer effects on cervical cancer by enhancing the expression of miR-506-3p, thereby reducing the expression of CD164, a protein associated with cancer cell proliferation and resistance to ferroptosis. The utilization of nanoparticles in this research presents a new and promising therapeutic strategy, which may also be relevant to other forms of cancer [161]. A comprehensive analysis of miRNA studies in ferroptosis reveals the complex regulatory functions these molecules have in cancer, providing valuable understanding of novel therapeutic approaches that utilize miRNA modification to overcome resistance and induce cell death.

4.4.2 LncRNAs Associated with Gynecological Cancers in Ferroptosis

Long non-coding RNAs are RNA molecules that exceed 200 nucleotides in length. These molecules have considerable importance in regulating gene expression at several levels, such as transcription and post-transcriptional control. [162]. Research indicates that numerous biological processes, including cellular differentiation, cell cycle control, and the preservation of stem cell pluripotency, are dependent on lncRNAs [162]. By downregulating membrane receptors and inhibiting proteins linked with necroptosis, the overexpression of specific long non-coding RNAs (lncRNAs) can impede the extrinsic apoptotic pathway in cancer cells. Long non-coding RNAs (lncRNAs) have also become important regulators of ferroptosis, which changes how cancer cells react to this type of controlled cell death [163].

LncRNAs often change ferroptosis by attaching to certain miRNAs. This changes the expression of important genes connected to ferroptosis. In epithelial ovarian cancer (EOC), ADAMTS9-AS1 controls ferroptosis by specifically targeting the miR-587/SLC7A11 axis. Increasing miR-587 and decreasing SLC7A11 to lower ADAMTS9-AS1 improves ferroptosis. This suggests that targeting this long non-coding RNA (lncRNA) could be a new way to treat essential oily cyst (EOC) [164]. EGFR-AS1 modulates ferroptosis in cervical cancer by upregulating miR-133b, which in turn downregulates EGFR. Therefore, the increase in autophagy-mediated ferroptosis suggests that targeting EGFR-AS1 has the potential to improve treatment outcomes [165]. In endoplasmic reticulum, LINC02936 inhibits ferroptosis by targeting SIX1 to the promoter of the CP gene, resulting in elevated CP production. Given its function in promoter control, this lncRNA is a crucial target for improving ferroptosis and slowing down tumor development [166].

By suppressing ferroptosis, these long non-coding RNAs (lncRNAs) directly contribute to the promotion of tumor development and malignancy, making them promising targets for cancer treatment. The FTH1/IGF2BP1 pathway mediates the action of CACNA1G-AS1 in ovarian cancer, suppressing ferroptosis and promoting cell proliferation and migration. Downregulation of this long non-coding RNA reduces tumor proliferation, establishing CACNA1G-AS1 as a major factor in ovarian cancer development [167]. In cervical cancer, the TMPO-AS1 protein interacts with lipocalin 2 (LCN2), which lowers the levels of iron and lipid ROS inside cells. This, in turn, increases resistance to ferroptosis and promotes the development of tumors. Directly targeting TMPO-AS1 may offer therapeutic advantages in situations characterized by elevated TMPO-AS1 expression [168]. In ovarian cancer, TPT1-AS1 controls ferroptosis by modulating GPX4 expression through the transcription factor CREB1. By inhibiting ferroptosis, TPT1-AS1 promotes cancer cell survival and proliferation, making it a crucial therapeutic target [169].

Long non-coding RNAs exhibit involvement in both tumor advancement and resistance to therapy. Additionally, they serve as significant indicators for predicting outcomes, thus informing treatment approaches and patient care. A prognostic model based on ferroptosis-related long non-coding RNAs has established the carcinogenic nature of CFAP58-DT in endometrial cancer. The present model categorizes patients into distinct risk groups, whereas CFAP58-DT shows promise as a prognostic indicator and a reference for the administration of immunotherapy and chemotherapy [170]. RNA sequencing analysis has revealed that LINC01833 and LINC02321 are genes associated with cuproptosis (copper-induced cell death) in cervical cancer. Their elevated expression is associated with increased cell proliferation and migration, indicating that they may serve as targets for treatment in cervical cancer [171].

4.4.3 Circular RNAs and Gynecological Cancers in Ferroptosis

Circular RNAs (circRNAs) are chiefly categorized into three groups based on their structural features: exonic, circular intronic, and exonic-intronic circRNAs [172,173]. These molecules perform critical functions in their roles as miRNA sponges and protein scaffolds. Compared to miRNAs, circRNAs are more common, stay the same over time, and are specific to tissues. This makes them very appealing as biomarkers for a wide range of diseases. A notable example is the discovery of aberrant expression of circRNA-002178 in lung cancer, which greatly facilitates its identification. The majority of circular RNAs (circRNAs) exhibit exceptional stability and specificity [174]. In cancer cells, aberrant expression levels of circular RNAs are associated with

cellular activities such as cell proliferation, autophagy, and apoptosis, so they play a role in defined cell death pathways [174]. Furthermore, circular RNAs exert an impact on the stability of microRNAs (miRNAs) after transcription by adjusting the expression of their target genes. In cancer cells, circRNAs function as sponges to control the process of ferroptosis [175].

Some circular RNAs promote cancer development by suppressing ferroptosis, therefore enabling cancer cells to avoid this type of cell death. In cervical cancer, the expression of circEPSTI1 is increased, and it is involved in the regulation of cell ferroptosis via the miR-375/409-3P/515-5p-SLC7A11 pathway. CircumEPSTI1 inhibits ferroptosis and enhances cancer cell growth. Both *in vivo* and *in vitro* research, including studies using mice xenografts, validate its substantial contribution to cancer progression and support its potential as a biomarker and therapeutic target [176]. circACAP2 is another circRNA upregulated in cervical cancer, where it suppresses ferroptosis via the miR-193a-5p/GPX4 axis. Acting as a ceRNA, circACAP2 sponges miR-193a-5p, leading to enhanced GPX4 expression, which is crucial for cancer cell survival. Knockdown of circACAP2 reduces cell viability and increases ferroptosis, indicating its role in malignant progression and as a potential target for therapy [177]. The expression of hsa_circ_0007615 is increased in epithelial ovarian cancer and is linked to a negative prognostic outcome. Specifically targeting miR-874-3p and the TUBB3 gene, it changes ferroptosis to help cancer cells grow, migrate, and invade. Inhibiting hsa_circ_0007615 increases ferroptosis, suggesting its potential as a prognostic indicator and a therapeutic target in early EOC [178].

Certain circRNAs contribute to chemoresistance by suppressing ferroptosis, which allows therapy-resistant cancer cells to persist. CircSnx12 enhances ovarian cancer's resistance to cisplatin by inhibiting ferroptosis through the miR-194-5p/SLC7A11 pathway. This circular RNA inhibits ferroptosis by acting as a molecular sponge for miR-194-5p, enabling cancer cells to withstand cisplatin therapy. To address cisplatin resistance in ovarian cancer, an effective therapeutic approach may involve targeting circSnx12 [179].

Some circRNAs establish interactions with splicing regulators, resulting in alternative splicing events that enhance resistance to ferroptosis. In endometrial cancer, circRAPGEF5 enhances ferroptosis resistance through its interaction with the splicing regulator RBFOX2, resulting in alternative splicing of the TFRC gene. During this splicing event, exon-4 is omitted, leading to a decrease in iron availability and lipid peroxide generation. Consequently, cancer cells become more resistant to ferroptosis. The circRAPGEF5/RBFOX2 axis offers a promising therapeutic avenue for addressing ferroptosis resistance in endometrial cancer (Figure 4) [180].

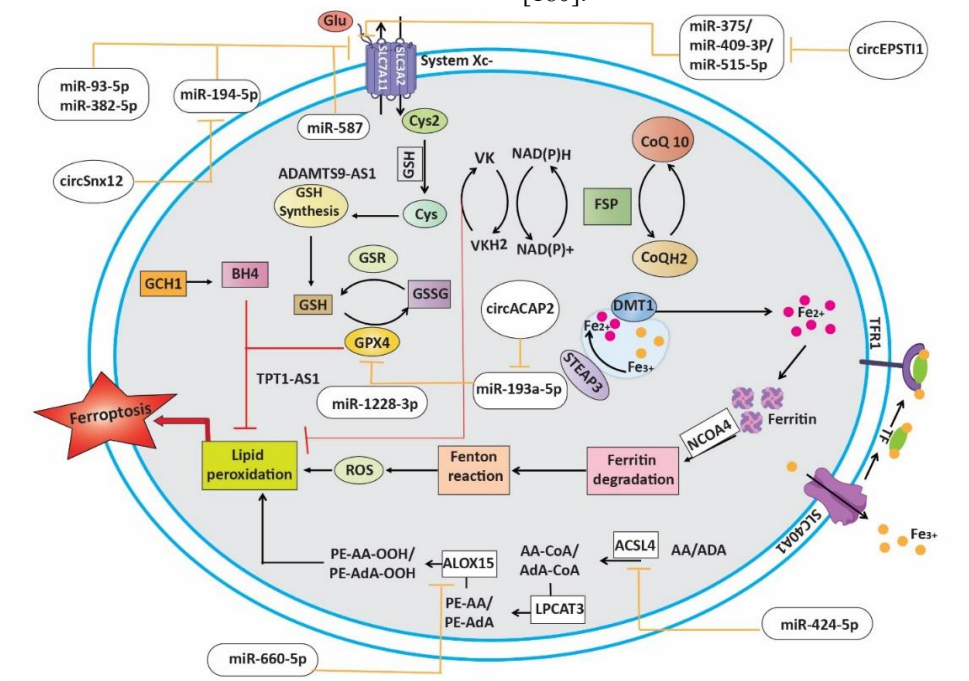

Figure 4. The role of non-coding RNA and their direct targets in ferroptosis.

5. Conclusion

An exploration of ferroptosis and its complex control by epigenetic processes offers a potential new area of research in the management of gynecological malignancies. It is possible to target these pathways for therapeutic advantage due to the intricate interaction between the expression of ferroptosis-related genes and numerous epigenetic modifications, including DNA methylation, histone alterations, RNA modifications including m6C, and the involvement of ncRNAs. These approaches have the potential to alleviate the difficulties presented by medication resistance, thereby enhancing the therapeutic results for patients suffering from cervical, ovarian, and endometrial cancers. Therefore, future studies should give priority to translating these findings into practical clinical applications, promoting a fundamental change in the treatment of gynecological malignancies and improving the effectiveness of current therapeutic approaches.

Abbreviations

GPX4: Glutathione Peroxidase 4

ROS: Reactive Oxygen Species

ncRNAs: Non-coding RNAs

m6C: N6-methylcytosine

GSH: Glutathione

PLOOHs: Phospholipid Hydroperoxides

PUFA: Polyunsaturated Fatty Acids

SLC7A11: Solute Carrier Family 7 Member 11

ACSL4: Acyl-CoA Synthetase Long Chain Family Member 4

LPCAT3: Lysophosphatidylcholine Acyltransferase 3

15-LOX: 15-Lipoxygenase

FSP1: Ferroptosis Suppressor Protein 1

CoQ10: Coenzyme Q10

NADPH: Nicotinamide Adenine Dinucleotide Phosphate

AIFM2: Apoptosis-Inducing Factor Mitochondria-Associated 2

FTH1: Ferritin Heavy Chain 1

GSSG: Glutathione Disulfide

DFO: Deferoxamine

HDAC: Histone Deacetylase

KDM4A: Lysine Demethylase 4A

HIF1: Hypoxia-Inducible Factor 1

MVA: Mevalonate

miRNAs: MicroRNAs

siRNAs: Small Interfering RNAs

lncRNAs: Long Non-Coding RNAs

circRNAs: Circular RNAs

RBM3: RNA Binding Motif Protein 3

TMPO-AS1: Thymopoietin Antisense RNA 1

TPT1-AS1: Tumor Protein Translationally-Controlled 1 Antisense RNA 1

TFRC: Transferrin Receptor

CACNA1G-AS1: CACNA1G Antisense RNA 1

LCN2: Lipocalin 2

GOT1: Glutamate Oxaloacetate Transaminase 1

SLC1A5: Solute Carrier Family 1 Member 5

ACADSB: Acyl-CoA Dehydrogenase Short/Branched Chain

RBFOX2: RNA Binding Fox-1 Homolog 2

EPAS1: Endothelial PAS Domain Protein 1

m6A: N6-Methyladenosine

FZD7: Frizzled Class Receptor 7

IL-6: Interleukin 6

Cdc25A: Cell Division Cycle 25A

PKM2: Pyruvate Kinase M2

ErbB2: Erb-B2 Receptor Tyrosine Kinase 2

SENP1: SUMO1/Sentrin Specific Peptidase 1

SUMO1: Small Ubiquitin-Like Modifier 1

ALOX15: Arachidonate 15-Lipoxygenase

FOXM1: Forkhead Box M1

IGF2BP3: Insulin Like Growth Factor 2 MRNA Binding Protein 3

CACNA1A: Calcium Voltage-Gated Channel Subunit Alpha1 A

CD164: CD164 Molecule Scaffold Attachment Factor 1

KRAS: KRAS Proto-Oncogene, GTPase

LC3: Microtubule Associated Protein 1 Light Chain 3

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

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The authors declare no competing interests.

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References

[1] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: a Cancer Journal for Clinicians. 2023, 73(1), 17-48. DOI: 10.3322/caac.21763

[2] Vakili-Ojarood M, Naseri A, Shirinzadeh-Dastgiri A, Saberi A, HaghighiKian SM, et al. Ethical Considerations and Equipoise in Cancer Surgery. Indian Journal of Surgical Oncology. 2024, 15(3), 363-373. DOI: 10.1007/s13193-024-02023-8

[3] Zhang YT, Luo GF, Li MJ, Guo P, Xiao YJ, et al. Global patterns and trends in ovarian cancer incidence: age, period and birth cohort analysis. BMC Cancer. 2019, 19(1), 984. DOI: 10.1186/s12885-019-6139-6

[4] Guy H, Walder L, Fisher M. Cost-effectiveness of niraparib versus routine surveillance, olaparib and

rucaparib for the maintenance treatment of patients with ovarian cancer in the United States. Pharmacoeconomics. 2019, 37(3), 391-405. DOI: 10.1007/s40273-018-0745-z

[5] Nie J, Wu HN, Sun L, Ding YJ, Luan YP, et al. Cost-effectiveness of fuzuloparib compared to routine surveillance, niraparib and olaparib for maintenance treatment of patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian carcinoma in China. Frontiers in Pharmacology. 2023, 13, 987337. DOI: 10.3389/fphar.2022.987337

[6] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012, 149(5), 1060-1072. DOI: 10.1016/j.cell.2012.03.042

[7] Jiang L, Kon N, Li T, Wang SJ, Su T, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015, 520(7545), 57-62. DOI: 10.1038/nature14344

[8] Chen DL, Tavana O, Chu B, Erber L, Chen Y, et al. NRF2 is a major target of ARF in p53-independent tumor suppression. Molecular Cell. 2017, 68(1), 224-232. DOI: 10.1016/j.molcel.2017.09.009

[9] Yang ML, Luo HS, Yi X, Wei X, Jiang DS. The epigenetic regulatory mechanisms of ferroptosis and its implications for biological processes and diseases. MedComm. 2023, 4(3), e267. DOI: 10.1002/mco2.267

[10] Wang WW, Cai J, Wen JY, Li XY, Yu YJ, et al. Boosting ferroptosis via abplatin (iv) for treatment of platinum-resistant recurrent ovarian cancer. Nano Today. 2022, 44, 101459. DOI: 10.1016/j.nantod.2022.101459

[11] Yang X, Yu YJ, Huang X, Chen QX, Wu H, et al. Delivery of platinum (II) drugs with bulky ligands in trans-geometry for overcoming cisplatin drug resistance. Materials Science and Engineering: C. 2019, 96, 96-104. DOI: 10.1016/j.msec.2018.10.092

[12] Yu BZ, Wang YS, Bing TJ, Tang YJ, Huang J, et al. Platinum prodrug nanoparticles with COX-2 inhibition amplify pyroptosis for enhanced chemotherapy and immune activation of pancreatic cancer. Advanced Materials. 2024, 36(11), e2310456. DOI: 10.1002/adma.202310456

[13] Tang SL, Chen L. The recent advancements of ferroptosis of gynecological cancer. Cancer Cell International. 2024, 24(1), 351. DOI: 10.1186/s12935-024-03537-5

[14] Xu J, Zheng BH, Wang W, Zhou ST. Ferroptosis: a novel strategy to overcome chemoresistance in gynecological malignancies. Frontiers in Cell and Developmental Biology. 2024, 12, 1417750. DOI: 10.3389/fcell.2024.1417750

[15] Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. Nature. 2019, 571(7766), 489-499. DOI: 10.1038/s41586-019-1411-0

[16] Deans C, Maggert KA. What do you mean,“epigenetic”? Genetics. 2015, 199(4), 887-896. DOI: 10.1534/genetics.114.173492

[17] Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. Cell. 2012, 150(1), 12-27. DOI: 10.1016/j.cell.2012.06.013

[18] Cao J, Yan Q. Cancer epigenetics, tumor immunity, and immunotherapy. Trends in Cancer. 2020, 6(7), 580-592. DOI: 10.1016/j.trecan.2020.02.003

[19] Twiddy D, Cohen GM, Macfarlane M, Cain K. Caspase-7 is directly activated by the similar to 700-kDa apoptosome complex and is released as a stable XIAP-caspase-7 similar to 200-kDa complex. The Journal of Biological Chemistry. 2006, 281(7), 3876-3888. DOI: 10.1074/jbc.M507393200

[20] Shi JJ, Zhao Y, Wang K, Shi XY, Wang Y, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 2015, 526(7575), 660-665. DOI: 10.1038/nature15514

[21] Sun LM, Wang HY, Wang ZG, He SD, Chen S, et al. Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell. 2012, 148(1), 213-227. DOI: 10.1016/j.cell.2011.11.031

[22] Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell. 2022, 185(14), 2401-2421. DOI: 10.1016/j.cell.2022.06.003

[23] Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, et al. Synergism of TNF-α and IFN-γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. Cell. 2021, 184(1), 149-168. DOI: 10.1016/j.cell.2020.11.025

[24] Zhou BR, Liu J, Kang R, Klionsky DJ, Kroemer G, et al., Ferroptosis is a type of autophagy-dependent cell death. Seminars in Cancer Biology. 2020, 68, 89-100. DOI: 10.1016/j.semcancer.2019.03.002

[25] Wu J, Wang Y, Jiang RT, Xue R, Yin XH, et al. Ferroptosis in liver disease: new insights into disease mechanisms. Cell Death Discovery. 2021, 7(1), 276. DOI: 10.1038/s41420-021-00660-4

[26] Le YF, Zhang ZJ, Wang C, Lu DZ. Ferroptotic cell death: new regulatory mechanisms for metabolic diseases. Endocrine, Metabolic & Immune Disorders-Drug Targets. 2021, 21(5), 785-800. DOI: 10.2174/1871530320666200731175328

[27] Forcina GC, Dixon SJ. Dixon. GPX4 at the crossroads of lipid homeostasis and ferroptosis. Proteomics. 2019, 19(18), e1800311. DOI: 10.1002/PMIc.201800311

[28] Rochette L, Dogon G, Rigal E, Zeller M, Cottin Y, et al. Lipid peroxidation and iron metabolism: two corner stones in the homeostasis control of ferroptosis. International Journal of Molecular Sciences. 2022, 24(1), 449. DOI: 10.3390/ijms24010449

[29] Xiang SS, Yan W, Ren X, Feng JB, Zu XY. Role of ferroptosis and ferroptosis-related long non'coding RNA in breast cancer. Cellular & Molecular Biology Letters. 2024, 29(1), 40. DOI: 10.1186/s11658-024-00560-2

[30] Daher B, Vučetić M, Pouysségur J. Cysteine depletion, a key action to challenge cancer cells to ferroptotic cell death. Frontiers in Oncology. 2020, 10, 723. DOI: 10.3389/fonc.2020.00723

[31] Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, et al. The cystine/glutamate antiporter system xc− in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxidants & Redox Signaling. 2013, 18(5), 522-555. DOI: 10.1089/ars.2011.4391

[32] Maiorino M, Conrad M, Ursini F. GPx4, lipid peroxidation, and cell death: discoveries, rediscoveries, and open issues. Antioxidants & Redox Signaling. 2018, 29(1), 61-74. DOI: 10.1089/ars.2017.7115

[33] Nguyen THP, Mahalakshmi B, Velmurugan BK. Functional role of ferroptosis on cancers, activation and deactivation by various therapeutic candidates-an update. Chemico-Biological Interactions. 2020, 317, 108930. DOI: 10.1016/j.cbi.2019.108930

[34] Girotti AW. Photosensitized oxidation of membrane lipids: reaction pathways, cytotoxic effects, and cytoprotective mechanisms. Journal of Photochemistry and Photobiology B: Biology. 2001, 63(1-3), 103-113. DOI: 10.1016/s1011-1344(01)00207-x

[35] Ursini F, Maiorino M. Lipid peroxidation and ferroptosis: The role of GSH and GPx4. Free Radical Biology and Medicine. 2020, 152, 175-185. DOI: 10.1016/j.freeradbiomed.2020.02.027

[36] Niki E. Lipid peroxidation: physiological levels and dual biological effects. Free Radical Biology and Medicine. 2009, 47(5), 469-484. DOI: 10.1016/j.freeradbiomed.2009.05.032

[37] Zhao SN, Guo Y, Yin XZ. Lipid peroxidation in ferroptosis and association with nonalcoholic fatty liver disease. Frontiers in Bioscience-Landmark. 2023, 28(12), 332. DOI: 10.31083/j.fbl2812332

[38] Zhao YC, Li YQ, Zhang RF, Wang F, Wang TJ, et al. The role of erastin in ferroptosis and its prospects in cancer therapy. OncoTargets and Therapy. 2020, 13, 5429-5441. DOI: 10.2147/OTT.S254995

[39] Circu ML, Aw TY. Glutathione and modulation of cell apoptosis. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2012, 1823(10), 1767-1777. DOI: 10.1016/j.bbamcr.2012.06.019

[40] Ding KY, Liu CB, Li L, Yang M, Jiang N, et al. Acyl-CoA synthase ACSL4: an essential target in ferroptosis and fatty acid metabolism. Chinese Medical Journal. 2023, 136(21), 2521-2537. DOI: 10.1097/CM9.0000000000002533

[41] Chen FQ, Kang R, Liu J, Tang DL. The ACSL4 network regulates cell death and autophagy in diseases. Biology. 2023, 12(6), 864. DOI: 10.3390/biology12060864

[42] Luo MH, Yan JJ, Hu XY, Li HL, Li HS, et al. Targeting lipid metabolism for ferroptotic cancer therapy. Apoptosis: an International Journal on Programmed Cell Death. 2023, 28(1-2), 81-107. DOI: 10.1007/s10495-022-01795-0

[43] Lu LX, Jifu CL, Xia J, Wang JT. E3 ligases and DUBs target ferroptosis: A potential therapeutic strategy for neurodegenerative diseases. Biomedicine & Pharmacotherapy. 2024, 175, 116753. DOI: 10.1016/j.biopha.2024.116753

[44] Cheng H, Wang M, Su JJ, Li YY, Long J, et al. Lipid metabolism and cancer. Life. 2022, 12(6), 784. DOI: 10.3390/life12060784

[45] Singh NK, Rao GN. Emerging role of 12/15-Lipoxygenase (ALOX15) in human pathologies. Progress in Lipid Research. 2019, 73, 28-45. DOI: 10.1016/j.plipres.2018.11.001

[46] Lin Z, Liu J, Kang R, Yang MH, Tang DL. Lipid metabolism in ferroptosis. Advanced Biology. 2021, 5(8), 2100396. DOI: 10.1002/ADBI.202100396

[47] Ma LL, Liang L, Zhou D, Wang SW. Tumor suppressor miR-424-5p abrogates ferroptosis in ovarian cancer through targeting ACSL4. Neoplasma. 2021, 68(1), 165-173. DOI: 10.4149/neo_2020_200707N705

[48] Cheng JM, Yu QL, Li JX, Xu ZY, Li JH, et al. Intrinsic tumor-targeted murine Ferritin nanocage co-delivers GPX4 and FSP1 inhibitors for synergistic ferroptosis-immunotherapy. Nano Today. 2024, 58, 102411. DOI: 10.1016/j.nantod.2024.102411

[49] Liu M, Kong XY, Yao Y, Wang XA, Yang W, et al. The critical role and molecular mechanisms of ferroptosis in antioxidant systems: a narrative review. Annals of Translational Medicine. 2022, 10(6), 368. DOI: 10.21037/atm-21-6942

[50] Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019, 575(7784), 693-698. DOI: 10.1038/s41586-019-1707-0

[51] Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019, 575(7784), 688-692. DOI: 10.1038/s41586-019-1705-2

[52] Kerr JF, Winterford CM, Harmon BV. Apoptosis. Its significance in cancer and cancer therapy. Cancer. 1994, 73(8), 2013-2026. DOI: 10.1002/1097-0142(19940415)73:8<2013::aid-cncr2820730802>3.0.co;2-j

[53] Kondo Y, Kanzawa T, Sawaya R, Kondo S. The role of autophagy in cancer development and response to therapy. Nature Reviews Cancer. 2005, 5(9), 726-734. DOI: 10.1038/nrc1692

[54] Amaravadi RK, Thompson CB. The roles of therapy-induced autophagy and necrosis in cancer treatment. Clinical Cancer Research. 2007, 13(24), 7271-7279. DOI: 10.1158/1078-0432

[55] Bano I, Horky P, Abbas SQ, Majid M, Bilal AHM, et al. Ferroptosis: a new road towards cancer management. Molecules. 2022, 27(7), 2129. DOI: 10.3390/molecules27072129

[56] Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, et al. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014, 156(1-2), 317-331. DOI: 10.1016/j.cell.2013.12.010

[57] Huang Y, Dai Z, Barbacioru C, Sadée W. Cystine-glutamate transporter SLC7A11 in cancer chemosensitivity and chemoresistance. Cancer Research. 2005, 65(16), 7446-7454. DOI: 10.1158/0008-5472.CAN-04-4267

[58] Liu XX, Li XJ, Zhang B, Liang YJ, Zhou CX, et al. MicroRNA-26b is underexpressed in human breast cancer and induces cell apoptosis by targeting SLC7A11. FEBS Letters. 2011, 585(9), 1363-1367. DOI: 10.1016/j.febslet.2011.04.018

[59] Wang YF, Yang L, Zhang XJ, Cui W, Liu YP, et al. Epigenetic regulation of ferroptosis by H2B monoubiquitination and p53. EMBO Reports. 2019, 20(7), e47563. DOI: 10.15252/embr.201847563

[60] Kremer DM, Nelson BS, Lin L, Yarosz EL, Halbrook CJ, et al. GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis. Nature Communications. 2021, 12(1), 4860. DOI: 10.1038/s41467-021-24859-2

[61] Lu YQ, Qin HX, Jiang B, Lu WF, Hao J, et al. KLF2 inhibits cancer cell migration and invasion by regulating ferroptosis through GPX4 in clear cell renal cell carcinoma. Cancer Letters. 2021, 522, 1-13. DOI: 10.1016/J.CANlet.2021.09.014

[62] Qin X, Zhang J, Lin Y, Sun XM, Zhang JN, et al. Identification of MiR-211-5p as a tumor suppressor by targeting ACSL4 in Hepatocellular Carcinoma. Journal of Translational Medicine. 2020, 18, 1-13. DOI: 10.1186/s12967-020-02494-7

[63] Feng L, Zhao KK, Sun LC, Yin XY, Zhang JP, et al. SLC7A11 regulated by NRF2 modulates esophageal squamous cell carcinoma radiosensitivity by inhibiting ferroptosis. Journal of Translational Medicine. 2021, 19(1), 376. DOI: 10.1186/s12967-021-03042-7

[64] Xu FS, Guan YB, Xue L, Zhang P, Li MR, et al. The roles of ferroptosis regulatory gene SLC7A11 in renal cell carcinoma: A multi-omics study. Cancer Medicine. 2021, 10(24), 9078-9096. DOI: 10.1002/cam4.4395

[65] Lu D, Yang ZY, Xia QY, Gao SJ, Sun SF, et al. ACADSB regulates ferroptosis and affects the migration, invasion, and proliferation of colorectal cancer cells. Cell Biology International. 2020, 44(11), 2334-2343. DOI: 10.1002/cbin.11443

[66] Lei G, Zhang YL, Koppula P, Liu XG, Zhang J, et al. The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression. Cell Research. 2020, 30(2), 146-162. DOI: 10.1038/S41422-019-0263-3

[67] Chu B, Kon N, Chen DL, Li TY, Liu T, et al. ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. Nature Cell Biology. 2019, 21(5), 579-591. DOI: 10.1038/S41556-019-0305-6

[68] Jennis M, Kung CP, Basu S, Budina-Kolomets A, Leu JI, et al. An African-specific polymorphism in the TP53 gene impairs p53 tumor suppressor function in a mouse model.

Genes & Development. 2016, 30(8), 918-930. DOI: 10.1101/Gad.275891.115

[69] Leu JI, Murphy ME, George DL. Mechanistic basis for impaired ferroptosis in cells expressing the African-centric S47 variant of p53. Proceedings of the National Academy of Sciences. 2019, 116(17), 8390-8396. DOI: 10.1073/pnas.1821277116

[70] Wang SJ, Li DW, Ou Y, Jiang L, Chen Y, et al. Acetylation is crucial for p53-mediated ferroptosis and tumor suppression. Cell Reports. 2016, 17(2), 366-373. DOI: 10.1016/j.celrep.2016.09.022

[71] Zhang YL, Shi JJ, Liu XG, Feng L, Gong ZH, et al. BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nature Cell Biology. 2018, 20(10), 1181-1192. DOI: 10.1038/s41556-018-0178-0

[72] Ranjbaran J, Safarpour H, Nomiri S, Tavakoli T, Rezaei Z, et al. Experimental validation of in silico analysis estimated the reverse effect of upregulated hsa-miR-106a-5p and hsa-miR-223-3p on gene expression in Iranian patients with colorectal adenocarcinoma by RT-qPCR. Cancer Medicine. 2023, 12(6), 7005-7018. DOI: 10.1002/cam4.5499

[73] Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nature Genetics. 2002, 30(4), 406-10. DOI: 10.1038/ng849

[74] Lee JE, Wang CC, Xu SY, Cho YW, Wang LF, et al. H3K4 mono- and di-methyltransferase MLL4 is required for enhancer activation during cell differentiation. Elife. 2013, 2, e01503. DOI: 10.7554/eLife.01503

[75] Scalera S, Mazzotta M, Cortile C, Krasniqi E, De Maria R, et al. KEAP1-Mutant NSCLC: The Catastrophic Failure of a Cell-Protecting Hub. Journal of Thoracic Oncology. 2022, 17(6), 751-757. DOI: 10.1016/j.jtho.2022.03.011

[76] Dai E, Han L, Liu J, Xie YC, Zeh HJ, et al. Ferroptotic damage promotes pancreatic tumorigenesis through a TMEM173/STING-dependent DNA sensor pathway. Nature Communications. 2020, 11(1), 6339. DOI: 10.1038/s41467-020-20154-8

[77] Ma XZ, Xiao LL, Liu LT, Ye LQ, Su P, et al. CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. Cell Metabolism. 2021, 33(5), 1001-1012. DOI: 10.1016/j.cmet.2021.02.015

[78] Harris IS, Treloar AE, Inoue S, Sasaki M, Gorrini C, et al. Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Cancer Cell. 2015, 27(2), 211-22. DOI: 10.1016/j.ccell.2014.11.019

[79] Anasagasti MJ, Martin JJ, Mendoza L, Obrador E, Estrela JM, et al. Glutathione protects metastatic melanoma cells against oxidative stress in the murine hepatic microvasculature. Hepatology (Baltimore, Md.). 1998, 27(5), 1249-56. DOI: 10.1002/hep.510270510

[80] Estrela JM, Ortega A, Mena S, Sirerol JA, Obrador E. Glutathione in metastases: From mechanisms to clinical applications. Critical Reviews In Clinical Laboratory Sciences. 2016, 53(4), 253-67. DOI: 10.3109/10408363.2015.1136259

[81] Yang C, Chen Z, Wei M, Hu S, Cai MY, et al. A self-amplified ferroptosis nanoagent that inhibits the tumor upstream glutathione synthesis to reverse cancer chemoresistance. Journal of Controlled Release. 2023, 357, 20-30. DOI: 10.1016/j.jconrel.2023.03.030

[82] Du J, Zhou Y, Li YC, Xia J, Chen YJ, et al. Identification of Frataxin as a regulator of ferroptosis. Redox Biology. 2020, 32, 101483. DOI: 10.1016/j.redox.2020.101483

[83] Brown CW, Amante JJ, Chhoy P, Elaimy AL, Liu H, et al. Prominin2 Drives Ferroptosis Resistance by Stimulating Iron Export. Developmental Cell. 2019, 51(5), 575-586. DOI: 10.1016/j.devcel.2019.10.007

[84] Xie YZ, Wang BY, Zhao YN, Tao ZH, Wang Y, et al. Mammary adipocytes protect triple-negative breast cancer cells from ferroptosis. Journal Of Hematology & Oncology. 2022, 15(1), 72. DOI: 10.1186/s13045-022-01297-1

[85] Belavgeni A, Tonnus W, Linkermann A. Cancer cells evade ferroptosis: sex hormone-driven membrane-bound O-acyltransferase domain-containing 1 and 2 (MBOAT1/2) expression. Signal Transduction and Targeted Therapy. 2023, 8(1), 336. DOI: 10.1038/s41392-023-01593-3

[86] Gao R, Kalathur RKR, Coto-Llerena M, Ercan C, Buechel D, et al. YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by preventing ferroptosis. EMBO Molecular Medicine. 2021, 13(12), e14351. DOI: 10.15252/emmm.202114351

[87] Chen D, Fan Z, Rauh M, Buchfelder M, Eyupoglu IY, et al. ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner. Oncogene. 2017, 36(40), 5593-5608. DOI: 10.1038/onc.2017.146

[88] Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. Redox Biology. 2019, 23, 101107. DOI: 10.1016/j.redox.2019.101107

[89] Singh MK, Han S, Kim S, Kang I. Targeting Lipid Metabolism in Cancer Stem Cells for Anticancer Treatment. International Journal of Molecular Sciences. 2024, 25(20), 11185. DOI: 10.3390/ijms252011185

[90] Guo ZW, Wang S, Hao HF, Deng XX, Fu JL, et al. Targeting Ferroptosis in Cancer by Natural Products: An Updated Review. The American Journal of Chinese Medicine. 2023, 51(3), 547-574. DOI: 10.1142/S0192415X23500271

[91] Yamaguchi H, Hsu JL, Chen CT, Wang YN, Hsu MC, et al. Caspase-independent cell death is involved in the negative effect of egf receptor inhibitors on cisplatin in non–small cell lung cancer cells. Clinical Cancer Research. 2013, 19(4), 845-854. DOI: 10.1158/1078-0432.CCR-12-2621

[92] Chen LY, Li XX, Liu LB, Yu B, Xue YX, et al. Erastin sensitizes glioblastoma cells to temozolomide by restraining xCT and cystathionine-γ-lyase function. Oncology Reports. 2015, 33(3), 1465-1474. DOI: 10.3892/or.2015.3712

[93] Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife. 2014, 3, e02523. DOI: 10.7554/eLife.02523

[94] Magri J, Gasparetto A, Conti L, Calautti E, Cossu C, et al. Tumor-associated antigen xCT and mutant-p53 as molecular targets for new combinatorial antitumor strategies. Cells. 2021, 10(1), 108. DOI: 10.3390/cells10010108

[95] Li FJ, Long HZ, Zhou ZW, Luo HY, Xu SG, et al. System Xc-/GSH/GPX4 axis: An important antioxidant system for the ferroptosis in drug-resistant solid tumor therapy. Frontiers in Pharmacology. 2022, 13, 910292. DOI: 10.3389/fphar.2022.910292

[96] Louandre C, Marcq I, Bouhlal H, Lachaier E, Godin C, et al. The retinoblastoma (Rb) protein regulates ferroptosis induced by sorafenib in human hepatocellular carcinoma cells. Cancer Letters. 2015, 356(2 Pt B), 971-977. DOI: 10.1016/j.canlet.2014.11.014

[97] Fu R, Zhao BR, Chen M, Fu XL, Zhang Q, et al. Moving beyond cisplatin resistance: Mechanisms, challenges, and prospects for overcoming recurrence in clinical cancer therapy. Medical Oncology. 2023, 41(1), 9. DOI: 10.1007/s12032-023-02237-w

[98] Wei YP, Lv HH, Shaikh AB, Han W, Hou H, et al. Directly targeting glutathione peroxidase 4 may be more effective than disrupting glutathione on ferroptosis-based cancer therapy. Biochimica et Biophysica Acta (BBA)-General Subjects. 2020, 1864(4), 129539. DOI: 10.1016/j.bbagen.2020.129539

[99] Nengroo MA, Sinha A, Datta D, Iron Vulnerability of Cancer Stem Cells: Role of ROS and Beyond. Handbook of Oxidative Stress in Cancer: Therapeutic Aspects. 2022, 2509-2537. DOI:10.1007/978-981-16-5422-0_235

[100] Chang LC, Chiang SK, Chen SE, Yu YL, Chou RH, et al. Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis. Cancer Letters. 2018, 416, 124-137. DOI: 10.1016/j.canlet.2017.12.025

[101] Gaschler MM, Andia AA, Liu H, Csuka JM, Hurlocker B, et al. FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation. Nature Chemical Biology. 2018, 14(5), 507-515. DOI: 10.1038/s41589-018-0031-6

[102] Yue LD, Dai ZC, Chen X, Liu CM, Hu ZF, et al. Development of a novel FePt-based multifunctional ferroptosis agent for high-efficiency anticancer therapy. Nanoscale. 2018, 10(37), 17858-17864. DOI: 10.1039/c8nr05150j

[103] Ma PA, Xiao HH, Yu C, Liu JH, Cheng ZY, et al. Enhanced cisplatin chemotherapy by iron oxide nanocarrier-mediated generation of highly toxic reactive oxygen species. Nano Letters. 2017, 17(2), 928-937. DOI: 10.1021/acs.nanolett.6b04269

[104] Liu T, Liu WL, Zhang MK, Yu WY, Gao F, et al. Ferrous-supply-regeneration nanoengineering for cancer-cell-specific ferroptosis in combination with imaging-guided photodynamic therapy. ACS Nano. 2018, 12(12), 12181-12192. DOI: 10.1021/acsnano.8b05860

[105] Wang SF, Li FY, Qiao RR, Hu X, Liao HW, et al. Arginine-rich manganese silicate nanobubbles as a ferroptosis-inducing agent for tumor-targeted theranostics. ACS Nano. 2018, 12(12), 12380-12392. DOI: 10.1021/acsnano.8b06399

[106] Wen RJ, Dong X, Zhuang HW, Pang FX, Ding SC, et al. Baicalin induces ferroptosis in osteosarcomas through a novel Nrf2/xCT/GPX4 regulatory axis. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2023, 116, 154881. DOI: 10.1016/j.phymed.2023.154881

[107] Liu X, Peng XH, Cen S, Yang CT, Ma ZJ, et al. Wogonin induces ferroptosis in pancreatic cancer cells by inhibiting the Nrf2/GPX4 axis. Frontiers in Pharmacology. 2023, 14, 1129662. DOI: 10.3389/fphar.2023.1129662

[108] Cui WQ, Zhang JW, Wu DQ, Zhang JX, Zhou H, et al. Ponicidin suppresses pancreatic cancer growth by inducing ferroptosis: Insight gained by mass spectrometry-based metabolomics. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2022, 98, 153943. DOI: 10.1016/j.phymed.2022.153943

[109] Zhang W, Jiang BP, Liu YX, Xu L, Wan M. Bufotalin induces ferroptosis in non-small cell lung cancer cells by facilitating the ubiquitination and degradation of GPX4. Free Radical Biology and Medicine. 2022, 180, 75-84. DOI: 10.1016/j.freeradbiomed.2022.01.009

[110] Zhou C, Yu T, Zhu R, Lu J, Ouyang X, et al. Timosaponin AIII promotes non-small-cell lung cancer ferroptosis through targeting and facilitating HSP90 mediated GPX4 ubiquitination and degradation. International Journal of Biological Sciences. 2023, 19(5), 1471-1489. DOI: 10.7150/ijbs.77979

[111] Kang LC, Wang DK, Shen TY, Liu X, Dai B, et al. PDIA4 confers resistance to ferroptosis via induction of ATF4/SLC7A11 in renal cell carcinoma. Cell Death & Disease. 2023, 14(3), 193. DOI: 10.1038/s41419-023-05719-x

[112] Fan GH, Wei XY, Xu X. Is the era of sorafenib over? A review of the literature. Therapeutic Advances in Medical Oncology. 2020, 12, 1758835920927602. DOI: 10.1177/1758835920927602

[113] Xu X, Li YX, Wu YL, Wang ML, Lu YD, et al. Increased ATF2 expression predicts poor prognosis and inhibits sorafenib-induced ferroptosis in gastric cancer. Redox Biology. 2023, 59, 102564. DOI: 10.1016/j.redox.2022.102564

[114] Feng SJ, Tang D, Wang YC, Li X, Bao H, et al. The mechanism of ferroptosis and its related diseases. Molecular Biomedicine. 2023, 4(1), 33. DOI: 10.1186/s43556-023-00142-2

[115] Li X, Wu LL, Tian X, Zheng WP, Yuan MS, et al. miR-29a-3p in Exosomes from Heme Oxygenase-1 Modified Bone Marrow Mesenchymal Stem Cells Alleviates Steatotic Liver Ischemia-Reperfusion Injury in Rats by Suppressing Ferroptosis via Iron Responsive Element Binding Protein 2. Oxidative Medicine and Cellular Longevity. 2022, 2022, 6520789. DOI: 10.1155/2022/6520789

[116] Patnaik MM, Tefferi A. Myelodysplastic syndromes with ring sideroblasts (MDS-RS) and MDS/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T)-"2021 update on diagnosis, risk-stratification, and management". American Journal of Hematology. 2021, 96(3), 379-394. DOI: 10.1002/ajh.26090

[117] Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomedicine & Pharmacotherapy. 2021, 139, 111708. DOI: 10.1016/j.biopha.2021.111708

[118] Blackledge NP, Klose R. CpG island chromatin: a platform for gene regulation. Epigenetics. 2011, 6(2), 147-152. DOI: 10.4161/epi.6.2.13640

[119] Illingworth RS, Gruenewald-Schneider U, Webb S, Kerr AR, James KD, et al. Orphan CpG islands identify numerous conserved promoters in the mammalian genome. PLoS Genetics. 2010, 6(9), e1001134. DOI: 10.1371/journal.pgen.1001134

[120] Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nature Reviews. Genetics. 2018, 19(6), 371-384. DOI: 10.1038/s41576-018-0004-3

[121] Macková E, Hrušková K, Bendová P, Vávrová A, Jansová H, et al. Methyl and ethyl ketone analogs of salicylaldehyde isonicotinoyl hydrazone: novel iron chelators with selective antiproliferative action. Chemico-Biological Interactions. 2012, 197(2-3), 69-79. DOI: 10.1016/j.cbi.2012.03.010

[122] Yang WC, Lin SF, Wang SC, Tsai WC, Wu CC, et al. The effects of human BDH2 on the cell cycle, differentiation, and apoptosis and associations with leukemia transformation in myelodysplastic syndrome. International Journal of Molecular Sciences. 2020, 21(9), 3033. DOI: 10.3390/ijms21093033

[123] Yu LJ, Gao ZW, Li ZY, Liu P, Gao Y, et al. Identification of ferroptosis-related molecular subtypes and a methylation-related ferroptosis gene prognostic signature in cervical squamous cell carcinoma. Journal of Cancer Research and Clinical Oncology. 2023, 149(16), 14673-14689. DOI: 10.1007/s00432-023-05267-z

[124] Wang RY, Yu XZ, Ye H, Ao MY, Xi MR, et al. LncRNA FAM83H-AS1 inhibits ferroptosis of endometrial cancer by promoting DNMT1-mediated CDO1 promoter hypermethylation. Journal of Biological Chemistry. 2024, 300(9) 107680. DOI: 10.1016/j.jbc.2024.107680
[125] Wang Y, Situ X, Cardenas H, Siu E, Alhunayan SA, et al. Preclinical Evaluation of NTX-301, a Novel DNA Hypomethylating Agent in Ovarian Cancer. Clinical Cancer Research. 2024, 30(6), 1175-1188. DOI: 10.1158/1078-0432.CCR-23-2368
[126] Wang XH, Liu K, Gong HM, Li DZ, Chu WF, et al. Death by histone deacetylase inhibitor quisinostat in tongue squamous cell carcinoma via apoptosis, pyroptosis, and ferroptosis. Toxicology and Applied Pharmacology. 2021, 410, 115363. DOI: 10.1016/j.taap.2020.115363
[127] He CY, Wang CZ, Liu HS, Shan BE. Kayadiol exerted anticancer effects through p53-mediated ferroptosis in NKTCL cells. BMC Cancer. 2022, 22(1), 724. DOI: 10.1186/s12885-022-09825-5
[128] Wang Y, Yan D, Liu JB, Tang DL, Chen X. Protein modification and degradation in ferroptosis. Redox Biology. 2024, 103259. DOI: 10.1016/j.redox.2024.103259
[129] Xiong J, Nie MF, Fu C, Chai XS, Zhang YJ, et al. Hypoxia Enhances HIF1α Transcription Activity by Upregulating KDM4A and Mediating H3K9me3, Thus Inducing Ferroptosis Resistance in Cervical Cancer Cells. Stem Cells International. 2022, 2022(1), 1608806. DOI: 10.1155/2022/1608806
[130] Xiong J, Chen PX, He L, Chai XS, Zhang YJ, et al. Functional mechanism of hypoxia-like conditions mediating resistance to ferroptosis in cervical cancer cells by regulating KDM4A SUMOylation and the SLC7A11/GPX4 pathway. Environmental Toxicology. 2024, 39(8), 4207-4220. DOI: 10.1002/tox.24304
[131] Wang Z, Shu W, Zhao R, Liu Y, Wang H. Sodium butyrate induces ferroptosis in endometrial cancer cells via the RBM3/SLC7A11 axis. Apoptosis. 2023, 28(7-8), 1168-1183. DOI: 10.1007/s10495-023-01850-4
[132] Wang C, Zeng J, Li LJ, Xue M, He SL. Cdc25A inhibits autophagy-mediated ferroptosis by upregulating ErbB2 through PKM2 dephosphorylation in cervical cancer cells. Cell Death & Disease. 2021, 12(11), 1055. DOI: 10.1038/s41419-021-04342-y
[133] Xu ZJ, Peng B, Cai Y, Wu GT, Huang JZ, et al. N6-methyladenosine RNA modification in cancer therapeutic resistance: current status and perspectives. Biochemical Pharmacology. 2020, 182, 114258. DOI: 10.1016/j.bcp.2020.114258
[134] Wilkinson E, Cui YH, He YY. Roles of RNA modifications in diverse cellular functions. Frontiers in Cell and Developmental Biology. 2022, 10, 828683. DOI: 10.3389/fcell.2022.828683
[135] Chen JX, Fang X, Zhong PC, Song ZF, Hu XT. N6-methyladenosine modifications: interactions with novel RNA-binding proteins and roles in signal transduction. RNA Biology. 2019, 16(8), 991-1000. DOI: 10.1080/15476286.2019.1620060
[136] Li LJ, Zeng J, He SL, Yang YF, Wang C. METTL14 decreases FTH1 mRNA stability via m6A methylation to promote sorafenib-induced ferroptosis of cervical cancer. Cancer Biology & Therapy. 2024, 25(1), 2349429. DOI: 10.1080/15384047.2024.2349429
[137] Wang YR, Wang C, Guan X, Ma Y, Zhang SJ, et al. PRMT3-Mediated Arginine Methylation of METTL14 Promotes Malignant Progression and Treatment Resistance in Endometrial Carcinoma. Advanced Science. 2023, 10(36), 2303812. DOI: 10.1002/advs.202303812
[138] Gong YM, Luo GF, Zhang SF, Chen YJ, Hu Y. Transcriptome sequencing analysis reveals miR-30c-5p promotes ferroptosis in cervical cancer and inhibits growth and metastasis of cervical cancer xenografts by targeting the METTL3/KRAS axis. Cellular Signalling. 2024, 117, 111068. DOI: 10.1016/j.cellsig.2024.111068
[139] Chen SJ, Zhang J, Zhou T, Rao SS, Li Q, et al. Epigenetically upregulated NSUN2 confers ferroptosis resistance in endometrial cancer via m5C modification of SLC7A11 mRNA. Redox Biology. 2024, 69, 102975. DOI: 10.1016/j.redox.2023.102975
[140] Jiang J, Zhu JM, Qiu P, Ni J, Zhu W, et al. HNRNPA2B1-mediated m6A modification of FOXM1 promotes drug resistance and inhibits ferroptosis in endometrial cancer via regulation of LCN2. Functional & Integrative Genomics. 2023, 24(1), 3. DOI: 10.1007/s10142-023-01279-7
[141] Gong XY, Jiang AL, Shao CX, Jiang Y, Du XX, et al. IGF2BP3 regulates CACNA1A-Mediated Ferroptosis in Ovarian Cancer Through m6A Modification. Available at SSRN 4517182. 2023. DOI: 10.2139/ssrn.4517182
[142] Hombach S, Kretz M. Non-coding RNAs: classification, biology and functioning. Advances in Experimental Medicine and Biology. 2016, 937, 3-17. DOI: 10.1007/978-3-319-42059-2_1
[143] Wang K, Mei S, Cai M, Zhai D, Zhang D, et al. Ferroptosis-related long noncoding RNAs as prognostic biomarkers for ovarian cancer. Frontiers in Oncology. 2022, 12, 888699. DOI: 10.3389/fonc.2022.888699
[144] Yang SY, Ji J, Wang M, Nie JF, Wang SJ. Construction of ovarian cancer prognostic model based on the investigation of ferroptosis-related lncRNA. Biomolecules. 2023, 13(2), 306. DOI: 10.3390/biom13020306
[145] Sadri F, Hosseini SF, Aghayei A, Fereidouni M, Rezaei Z. The Tumor Suppressor Roles and Mechanisms of MiR-491 in Human Cancers. DNA and Cell Biology. 2022, 41(9), 810-823. DOI: 10.1089/dna.2022.0274
[146] Hazari V, Samali SA, Izadpanahi P, Mollaei H, Sadri F, et al. MicroRNA-98: the multifaceted regulator in human cancer progression and therapy. Cancer Cell International. 2024, 24(1), 209. DOI: 10.1186/s12935-024-03386-2
[147] Rezaei Z, Sadri F. MicroRNAs involved in inflammatory breast cancer: oncogene and tumor suppressors with possible targets. DNA and cell biology. 2021, 40(3), 499-512. DOI: 10.1089/dna.2020.6320
[148] Hosseini SF, Javanshir-Giv S, Soleimani H, Mollaei H, Sadri F, et al. The importance of hsa-miR-28 in human malignancies. Biomedicine & Pharmacotherapy. 2023, 161, 114453. DOI: 10.1016/j.biopha.2023.114453
[149] He BX, Zhao ZY, Cai QD, Zhang YQ, Zhang PF, et al. miRNA-based biomarkers, therapies, and resistance in Cancer. International Journal of Biological Sciences. 2020, 16(14), 2628. DOI: 10.7150/ijbs.47203
[150] Brümmer A, Hausser J. MicroRNA binding sites in the coding region of mRNAs: extending the repertoire of post-transcriptional gene regulation. Bioessays. 2014, 36(6), 617-626. DOI: 10.1002/bies.201300104
[151] Noorian M, Chamani E, Salmani F, Rezaei Z, Khorsandi K. Effects of doxorubicin and apigenin on chronic myeloid leukemia cells (K562) in vitro: anti-proliferative and apoptosis induction assessments. Natural Product Research. 2023, 37(19), 3335-3343. DOI: 10.1080/14786419.2022.2069765
[152] Shan C, Liang Y, Wang K, Li P. Noncoding RNAs in cancer ferroptosis: from biology to clinical opportunity. Biomedicine & Pharmacotherapy. 2023, 165, 115053. DOI: 10.1016/j.biopha.2023.115053
[153] Li CX, Wang ZT, Wang YQ, Liu H, Cheng YX. Cheng. MiR-93-5p Inhibits Ovarian Cancer Through SLC7A11-Mediated-Ferroptosis. Heliyon. 2024, 10(15), e35457. DOI: 10.1016/j.heliyon.2024.e35457

[154] Zhang D, Qu B, Hu B, Cao KX, Shen HM. MiR-1-3p enhances the sensitivity of ovarian cancer cells to ferroptosis by targeting FZD7. Journal of Central South University. Medical Sciences. 2022, 47(11), 1512-1521. DOI: 10.11817/j.issn.1672-7347.2022.210800

[155] Luo YL, Chen YB, Jin H, Hou BX, Li HS, et al. The suppression of cervical cancer ferroptosis by macrophages: The attenuation of ALOX15 in cancer cells by macrophages-derived exosomes. Acta Pharmaceutica Sinica B. 2023, 13(6), 2645-2662. DOI: 10.1016/j.apsb.2023.03.025

[156] Wang Y, Wu N, Luo X, Liao QL, Wang J. M2 Macrophages Crosstalk with Ovarian Cancer Cells by Regulating Cell Ferroptosis via the miR-1228-3p/GPX4 Pathway. 2022. DOI: https://doi.org/10.21203/rs.3.rs-1379507/v1

[157] Lu XQ, Zhang WY, Zhang JY, Ren D, Zhao PP, et al. EPAS1, a hypoxia- and ferroptosis-related gene, promotes malignant behaviour of cervical cancer by ceRNA and super-enhancer. Journal of Cellular and Molecular Medicine. 2024, 28(9), e18361. DOI: 10.1111/jcmm.18361

[158] Du HJ, Tang YM, Ren YX, Zhang F, Yang W, et al. A prognostic model for cervical cancer based on ferroptosis-related genes. Frontiers in Endocrinology. 2022, 13, 991178. DOI: 10.3389/fendo.2022.991178

[159] Sun D, Li YC, Zhang XY. Zhang. Lidocaine promoted ferroptosis by targeting miR-382-5p/SLC7A11 axis in ovarian and breast cancer. Frontiers in Pharmacology. 2021, 12, 681223. DOI: 10.3389/fphar.2021.681223

[160] Parsa H, Saravani H, Sameei-Rad F, Nasiri M, Farahaninik Z, et al. Comparing Lavage of the Peritoneal Cavity with Lidocaine, Bupivacaine and Normal Saline to Reduce the Formation of Abdominal Adhesion Bands in Rats. The Malaysian Journal of Medical Sciences: MJMS. 2017, 24(3), 26-32. DOI: 10.21315/mjms2017.24.3.4

[161] Lei JY, Li SX, Li F, Li H, Lei YS. Zinc oxide nanoparticle regulates the ferroptosis, proliferation, invasion and steaminess of cervical cancer by miR-506-3p/CD164 signaling. Cancer Nanotechnology. 2022, 13(1), 33. DOI:10.1186/s12645-022-00134-x

[162] Bridges MC, Daulagala AC, Kourtidis A. Kourtidis. LNCcation: lncRNA localization and function. The Journal of Cell Biology. 2021, 220(2), e202009045. DOI: 10.1083/jcb.202009045

[163] Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017, 36(41), 5661-5667. DOI: 10.1038/onc.2017.184

[164] Cai L, Hu XQ, Ye L, Bai PJ, Jie YK, et al. Long non-coding RNA ADAMTS9-AS1 attenuates ferroptosis by Targeting microRNA-587/solute carrier family 7 member 11 axis in epithelial ovarian cancer. Bioengineered. 2022, 13(4), 8226-8239. DOI: 10.1080/21655979.2022.2049470

[165] Dong CL, Dong RF, Song J, Yu CQ, Zhuang YJ, et al. Knockdown of lncRNA EGFR-AS1 promotes autophagy-mediated ferroptosis in cervical cancer via regulating EGFR expression through miR-133b. Molecular & Cellular Toxicology. 2024, 20(1), 139-147. DOI:10.1007/s13273-023-00332-7

[166] Zhang ZH, Li BS, Wang Z, Yang L, Peng JX, et al. Novel LncRNA LINC02936 Suppresses Ferroptosis and Promotes Tumor Progression by Interacting with SIX1/CP Axis in Endometrial Cancer. International Journal of Biological Sciences. 2024, 20(4), 1356-1374. DOI: 10.7150/ijbs.86256

[167] Jin YP, Qiu JP, Lu XF, Ma Y, Li GW. LncRNA CACNA1G-AS1 up-regulates FTH1 to inhibit ferroptosis and promote malignant phenotypes in ovarian cancer cells. Oncol Res. 2023, 31(2), 169-179. DOI: 10.32604/or.2023.027815

[168] Ju Y, Liu X, Na JT, He J, Wu LL, et al. LncRNA TMPO-AS1 Facilitates Cervical Cancer Cell Tumorigenesis and Ferroptosis Resistance via Interaction with LCN2. 2024. DOI:10.21203/rs.3.rs-4441640/v1

[169] Cao L, Wang Y, Liu JN, Bai XY, Chi XH. Long non-coding RNA TPT1-AS1 inhibits ferroptosis in ovarian cancer by regulating GPX4 via CREB1 regulation. American Journal of Reproductive Immunology. 2024, 92(2), e13864. DOI: 10.1111/aji.13864

[170] Qin AJ, Qian QX, Cui XP, Bai WL. Ferroptosis-related lncRNA model based on CFAP58-DT for predicting prognosis and immunocytes infiltration in endometrial cancer. Annals of Translational Medicine. 2023, 11(3), 151. DOI: 10.21037/atm-22-6659

[171] Huang YT, Pan CX, Wu SN, Ye F, Yang LH. A combination of cuproptosis and lncRNAs predicts the prognosis and tumor immune microenvironment in cervical cancer. Discover Oncology. 2024, 15(1), 116. DOI: 10.1007/s12672-024-00964-8

[172] Chen L, Wang CL, Sun HY, Wang JX, Liang YC, et al. The bioinformatics toolbox for circRNA discovery and analysis. Briefings in Bioinformatics. 2021, 22(2), 1706-1728. DOI: 10.1093/bib/bbaa001

[173] Seyedi D, Espandar N, Hojatizadeh M, Mohammadi Y, Sadri F, et al. Noncoding RNAs in rheumatoid arthritis: modulators of the NF-κB signaling pathway and therapeutic implications. Frontiers in Immunology. 2024, 15, 1486476. DOI: 10.3389/fimmu.2024.1486476

[174] Wang JF, Zhao XH, Wang YB, Ren FH, Sun DW, et al. circRNA-002178 act as a ceRNA to promote PDL1/PD1 expression in lung adenocarcinoma. Cell Death & Disease. 2020, 11(1), 32. DOI: 10.1038/s41419-020-2230-9

[175] Liu ZQ, Wang Q, Wang X, Xu ZZ, Wei XQ, et al. Circular RNA cIARS regulates ferroptosis in HCC cells through interacting with RNA binding protein ALKBH5. Cell Death Discovery. 2020, 6(1), 72. DOI: 10.1038/s41420-020-00306-x

[176] Wu P, Li CX, Ye DM, Yu KN, Li YX, et al. Circular RNA circEPSTI1 accelerates cervical cancer progression via miR-375/409-3P/515-5p-SLC7A11 axis. Aging (Albany NY). 2021, 13(3), 4663-4673. DOI: 10.18632/aging.202518

[177] Liu YC, Li L, Yang Z, Wen D, Hu ZY. Circular RNA circACAP2 Suppresses Ferroptosis of Cervical Cancer during Malignant Progression by miR-193a-5p/GPX4. Journal of Oncology. 2022, 2022, 5228874. DOI: 10.1155/2022/5228874

[178] Wei W, Wang N, Lin L. Prognostic Value of hsa_circ_0007615 in Epithelial Ovarian Cancer and its Regulatory Effect on Tumor Progression. Hormone and Metabolic Research. 2023, 55(11), 801-808. DOI: 10.1055/a-2119-3229

[179] Qin KY, Zhang FH, Wang HX, Wang N, Qiu HB, et al. circRNA circSnx12 confers Cisplatin chemoresistance to ovarian cancer by inhibiting ferroptosis through a miR-194-5p/SLC7A11 axis. BMB Reports. 2023, 56(2), 184-189. DOI: 10.5483/BMBRep.2022-0175

[180] Zhang J, Chen SJ, Wei ST, Cheng SS, Shi R, et al. CircRAPGEF5 interacts with RBFOX2 to confer ferroptosis resistance by modulating alternative splicing of TFRC in endometrial cancer. Redox Biology. 2022, 57, 102493. DOI: 10.1016/j.redox.2022.102493