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REVIEW

Unveiling the Network regulatory mechanism of ncRNAs on the Ferroptosis Pathway: Implications for Preeclampsia

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Abstract: Non-coding RNAs (ncRNAs) are transcripts originating from the genome that do not serve as templates for protein synthesis. They function as epigenetic and translational regulators in various pathophysiological mechanisms, including cell proliferation and apoptosis. The ferroptosis signaling pathway, a novel mode of cell death, participates in numerous pathophysiological processes. Its signaling transmission is both complex and precise, featuring interconnected and interdependent pathways. Recent studies suggest that ncRNAs can finely regulate key genes in the ferroptosis pathway, thus modulating cellular functions, reducing oxidative stress, and maintaining maternal-fetal interface homeostasis. Future strategies targeting the ncRNA/ferroptosis axis may provide new perspectives and potential intervention points for treating preeclampsia. This article clarifies how the ncRNA/ferroptosis axis impacts preeclampsia, revealing how ncRNAs interact with ferroptosis, and pinpointing new molecular targets for the treatment of preeclampsia, thereby providing theoretical support for clinical strategies.

Keywords: preeclampsia, non-coding RNAs, ferroptosis, network regulation, treatment strategies

Introduction

Preeclampsia (PE), a frequent and serious hypertensive condition in pregnancy, generally manifests beyond the 20th week of gestation. It presents with newly developed hypertension and proteinuria, and frequently involves dysfunction in various maternal end-organs.[1] Risk factors for PE include age, obesity, diabetes, and a history of hypertension.[2] It is worth mentioning that paternal inheritance also participates in and affects the implantation and vasculogenesis of the fetal placenta, thereby mediating the occurrence and development of PE.[3] PE is the leading cause of death among pregnant women and fetuses, impacting around 2-5% of global pregnancies. Annually, over 70,000 women and 500,000 infants die following a diagnosis of PE.[4,5] Despite extensive international research, the precise mechanisms of PE onset remain elusive. Given the complex pathophysiology of the disease, current preventative measures include using low-dose aspirin to reduce the incidence of PE. Once diagnosed, the definitive treatment for PE involves the delivery of the dysfunctional placenta.[6,7] With advancements in epigenetics, many researchers have discovered that manipulating the ncRNA/ferroptosis axis can regulate the progression of PE.

Non-coding RNAs (NcRNAs) are RNA molecules transcribed from the genome and exist in various forms, primarily grouped into two kinds: structural ncRNAs and regulatory ncRNAs.[8] Regulatory ncRNAs, which vary in nucleotide length, are classified into small ncRNAs (sncRNA, 18-200 nt), long ncRNAs (lncRNA, >200 nt), and circular RNAs (circRNA). Additionally, several subclasses of sncRNAs, including microRNA (miRNA), piwi-interacting RNA

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(piRNA), and tRNA-derived small RNA (tsRNA), exist along with other varieties.[9] Once deemed "junk" transcription products, these RNA molecules are now recognized for their substantial impact on various physiological processes, such as RNA maturation, processing, signal transduction, gene expression, protein functionality, and cellular metabolism.[10] Key ncRNAs, including miRNA, lncRNA, and circRNA, are involved in the development of the placental vascular system and in the invasion, migration, proliferation, and apoptosis of trophoblasts.[11] Furthermore, studies indicate that ncRNAs influence the development and progression of PE by targeting essential signaling molecules in the ferroptosis pathway.[12,13]

In recent years, ferroptosis, as a novel form of cell death, has gradually emerged as a research hotspot in scientific inquiry. Ferroptosis represents a programmed cell death process mediated by iron-dependent lipid peroxidation, characterized by the accumulation of intracellular iron ions and a surge in lipid peroxide production, ultimately leading to cell membrane rupture and cell death.[14] This particular mode of cell death differs from traditional apoptosis, necrosis, or autophagy and it assumes a pivotal position in a wide array of physiological and pathological processes, including cancer-related pathologies.[15] Notably, ferroptosis signaling pathways have been identified as one of the potential underlying mechanisms for various reproductive disorders and pregnancy complications characterized by dysregulated iron homeostasis.[16] In placental tissues from patients with PE, abnormal ferroptosis activation may damage and disrupt trophoblast cells, thus impairing normal placental development and the stability of the maternal-fetal interface.[17] This underscores the significant regulatory role of the ferroptosis signaling pathway in PE.

This review posits that the advancement of PE is governed by the interactions between key target molecules within ncRNAs and the ferroptosis signaling pathway, thus providing new insights into understanding PE. It systematically explores the molecular mechanisms and functions of ncRNAs in PE, particularly those associated with the ferroptosis pathway. Having integrated and analyzed recent research findings, it seeks to uncover potential links between ncRNAs and the ferroptosis pathway, thereby identifying new molecular targets and theoretical foundations for preventing and treating PE.

Expression and Function of ncRNA in Preeclampsia

Proteins, the primary functional products of genetic information, are encoded by less than 2% of the transcribed genes in the human genome,[18] while the remaining approximately 98% of transcriptional output comprises ncRNAs.[19] Recent advancements in sequencing technologies and molecular biology have led to the discovery of many previously unknown ncRNAs. Research has shown that gene expression is extensively regulated not only by proteins but also by ncRNAs. NcRNAs have garnered heightened recognition for their pivotal regulatory functions in diverse physiological processes, encompassing cell proliferation, differentiation, and apoptosis.[20,21] Their expression patterns are intimately intertwined with a broad spectrum of human disease states, thereby exerting profound influences on health outcomes and disease progression.[22–24] Consequently, researching the expression and function of ncRNAs in the context of PE is crucial for developing treatments for this condition.

MiRNAs in Preeclampsia

MiRNAs, small non-coding single-stranded transcripts 18-25 nucleotides long, bind specifically to target transcripts to induce degradation. They regulate various metabolic pathways at transcriptional and translational levels, maintaining cellular and tissue homeostasis. The canonical gene regulation by miRNAs involves post-transcriptional mechanisms, binding to the 3' UTR of target mRNAs to suppress expression.[25] MiRNAs are known to inhibit thousands of target genes and coordinate normal physiological processes. However, studies have shown that in patients with PE, miRNA levels are disrupted, particularly in human chorionic villous trophoblast cells under pregnancy-related oxidative stress (OS), indicating altered expression levels that diverge from their normal regulatory roles.[26] Notably, several cutting-edge studies have indicated that miRNAs also possess the potential to predict the occurrence of PE as early as the first trimester of pregnancy.[27] This groundbreaking discovery offers a novel vantage point and instrumentality that significantly enhances the capability for early identification of high-risk pregnancy cohorts, thereby facilitating the prompt implementation of targeted interventions. Furthermore, it underscores the immense potential of miRNA biomarkers in facilitating the early diagnosis of preeclampsia. As pivotal regulatory molecules in the intricate pathogenesis of

preeclampsia, miRNA biomarkers merit our utmost attention, as they hold the promise of unlocking more efficacious management and treatment paradigms.

The placenta plays a critical role in maintaining pregnancy equilibrium, and dysfunctional placentas are linked to the onset of PE. Chu and others, noted that reduced miR-126-3p expression in trophoblast cells from preeclamptic placentas promotes increased IL-6 and TNFα production, diminishing the anti-inflammatory and antioxidant activities in PE.[28] Thus, boosting miR-126-3p levels might effectively constitute a powerful therapeutic strategy for managing PE. Additionally, studies have found that overexpressed miR-210 can promote the progression of PE by suppressing anti-inflammatory Th2 cytokines.[29] Numerous researchers have shown that miR-155 serves as a marker and determinant of PE severity. For instance, the miR-155-CYR61-VEGF pathway disrupts trophoblast migration, hindering placental angiogenesis and potentially suppressing trophoblast proliferation and invasion by downregulating cyclin D1, exacerbating dysfunctional placenta formation and leading to PE.[30,31] In summary, miRNAs are involved in multiple processes leading to PE. Fully elucidating the impact of miRNAs on this complex condition is crucial for improving its diagnosis and treatment. Thus, further exploration of miRNA roles in PE is imperative.

LncRNAs in Preeclampsia

Recently, research into lncRNA in PE has emerged as a significant area of study. LncRNAs, a class of non-coding RNAs longer than 200 nucleotides that do not encode proteins, regulate interactions between proteins and nucleic acids in both the nucleus and cytoplasm, establishing robust, flexible, and specific transcriptional and post-transcriptional controls.[32] As such, lncRNAs play crucial roles in many physiological processes, including cellular development, proliferation, differentiation, and apoptosis.[33] Recent high-throughput analyses of epigenetics in developing placentas have shown that in PE, lncRNA DIAPH2-AS1 is upregulated. This upregulation recruits lysine-specific demethylase 1 and DNA methyl-transferase 1 to the PAX3 promoter, leading to increased methylation of the PAX3 promoter region and suppression of PAX3 gene expression, ultimately affecting trophoblast cell proliferation, migration, and invasion involved in the evolution of PE.[34,35] Additionally, Jiang and others found that lncRNAs block the transcription factor CENPB from attaching to the promoter of tumor necrosis factor receptor-associated factor 1, thereby inhibiting trophoblast cell invasion and migration during placental development.[36] Liu and others[37] confirmed that lncRNA MEG3 acts as a sponge for miR-21, regulating the expression of BMPR2 and promoting trophoblast cell proliferation and invasion, thus preventing the development of PE.

Based on the aforementioned research, it becomes clear that lncRNAs have a critical impact on the onset and advancement of PE. They may interact with other genes or proteins to co-regulate the physiological functions of the placenta. These interactions could involve mechanisms such as epigenetic regulation, transcriptional control, or post-transcriptional modulation. Additionally, lncRNAs can function as signaling molecules or act as "sponges" for miRNAs, binding to them and preventing their interaction with target mRNAs, thus regulating gene expression.[38–41] These mechanisms are not mutually exclusive; they can intertwine and collectively influence the pathogenesis of PE. The specific mechanisms of lncRNA action in PE are not yet fully understood, necessitating further in-depth research. Moreover, the therapeutic potential of lncRNAs and their clinical value should not be underestimated.

CircRNAs in Preeclampsia

CircRNAs are a group of closed-loop single-stranded RNA molecules that interact with proteins in unique ways and play significant roles in various diseases.[42,43] Compared to other types of RNA, circRNAs are more abundant and highly structured, showing potential as biomarkers for detecting the heterogeneous manifestations of PE. Researchers, after analyzing a circRNA microarray and assessing the circRNA expression profiles of normal pregnant women and PE patients, found significant abnormalities in the expressions of circRNA-0004904, circRNA-0001855, and circPAPP-A, thus confirming circRNAs as novel biomarkers for the early diagnosis and treatment of PE.[44] Furthermore, several studies analyzing samples from PE patients revealed a significant upregulation of circ_0055724 and a downregulation of circFURIN, with various other circRNAs also involved in the pathogenesis of PE.[45,46] These studies indicate that circRNA expression levels are closely associated with the severity and stage of the disease. Additionally, circRNAs influence the development of PE by regulating gene expression, signaling pathways, and cellular functions.[47] For example, circ_0008726 regulates RYBP expression by sponging miR-345-3p, contributing further to the pathogenesis

of PE.[48] Additionally, circVRK1 serves as a ceRNA for miR-221-3p, controlling PTEN expression and consequently attenuating PI3K/Akt pathway activation. This action effectively restricts the migration, invasion, and epithelial-mesenchymal transition of trophoblast cells.[49] It is evident that circRNAs act as molecular sponges for miRNAs, specifically absorbing miRNAs to regulate downstream protein expression and thus modulate the expression of genes and protein transport related to PE.[50]

CircRNAs play a significant regulatory role in PE, not only as potential biomarkers but also in conjunction with other ncRNAs through complex regulatory networks affecting the disease's development. However, current research on the individual mechanisms of action of circRNAs is limited. Future studies should delve further into this aspect to deepen our understanding of the pathogenesis and biological functions of PE and provide new insights for disease diagnosis and treatment.

In conclusion, ncRNAs are inextricably linked with PE. Research into their expression and function in PE remains an active and challenging field, requiring further exploration.

Key Molecular Mechanisms of ncRNA Regulation in the Ferroptosis Pathway

Regulation of Key Ferroptosis Genes by ncRNA

In recent studies, ncRNAs are recognized to exert essential regulatory functions across a range of cellular biological processes.[18] Increasingly, ncRNAs have been shown to regulate the biological processes of ferroptosis, thereby influencing the onset, progression, and prognosis of PE.[13,51] Therefore, exploring the role of ncRNAs in regulating key ferroptosis genes is crucial for understanding the pathological mechanisms of PE. Ferroptosis represents a unique form of regulated cell death, different from both apoptosis and autophagy, characterized by iron-driven phospholipid peroxidation.[14,52] Polyunsaturated fatty acids are essential factors that undergo iron-catalyzed lipid peroxidation to produce lipid-Reactive Oxygen Species(ROS).[53] When intracellular lipid-ROS levels exceed the antioxidant activity of Glutathione Peroxidase 4(GPX4), an imbalance between OS and the antioxidant system leads to ferroptosis.[54,55] Ferroptosis is involved in numerous pathophysiological processes and is characterized by iron dependence, accumulation of ROS and lipid peroxidation, and loss of antioxidant generation and transformation.[56] Moreover, researchers have found that ferroptosis contributes to OS and lipotoxicity in placental trophoblasts, leading to excessive death of trophoblast cells and disruption of normal cell turnover.[57,58] Trophoblast cell ferroptosis can induce the failure of uterine spiral artery remodeling, thereby contributing to the onset of PE.[59] Overall, the ferroptosis pathway participates in the onset and progression of PE, featuring a complex and extensive mechanism of action (see Figure 1). In the process of ferroptosis, ncRNAs have been demonstrated to finely meticulously control the expression of crucial genes, both directly and indirectly. Research has shown that specific ncRNAs can bind directly to the mRNA of key ferroptosis genes, thereby directly affecting intracellular iron concentrations, accumulation of lipid peroxides, and antioxidant system activity.[12,60] For example, lncRNA RP11-89 acts as a "sponge", absorbing miR-129-5p and upregulating PROM, which further activates iron efflux pathways to inhibit ferroptosis.[61] Lu and others[62] proposed that a positive feedback cycle is present in the lncRNA PVT1/miR-214/p53 pathway. In this system, lncRNA PVT1 influences ferroptosis by controlling the expression of TFR1 and TP53 via miR-214. Furthermore, miRNAs have been demonstrated to participate in the biological processes of ferroptosis.[63] Experiments indicate that miR-25-3p can directly target the downstream effector P53, thereby further regulating the SLC7A11/GPX4 pathway to counteract ferroptosis.[64] Researchers, in recent experiments through bioinformatics analysis, identified ferroptosis-related miRNAs and mRNAs. Subsequent functional rescue experiments verified that miR-144-3p can regulate Zinc Finger E-box Binding Homeobox 1, indirectly disrupting redox homeostasis and iron metabolism, thereby triggering or exacerbating ferroptosis.[65]

In summary, ncRNAs finely regulate key genes involved in ferroptosis, both directly and indirectly. This regulatory role not only unveils new functions of ncRNAs in the process of cell death but also provides new perspectives and potential intervention targets for therapeutic strategies targeting ferroptosis.

Regulation of Key Proteins in the Ferroptosis Pathway by ncRNA

In the process of ferroptosis, the regulatory role of ncRNAs on key proteins is particularly important, as they modulate the ferroptosis pathway by influencing post-translational modifications, protein stability, and protein interaction networks.

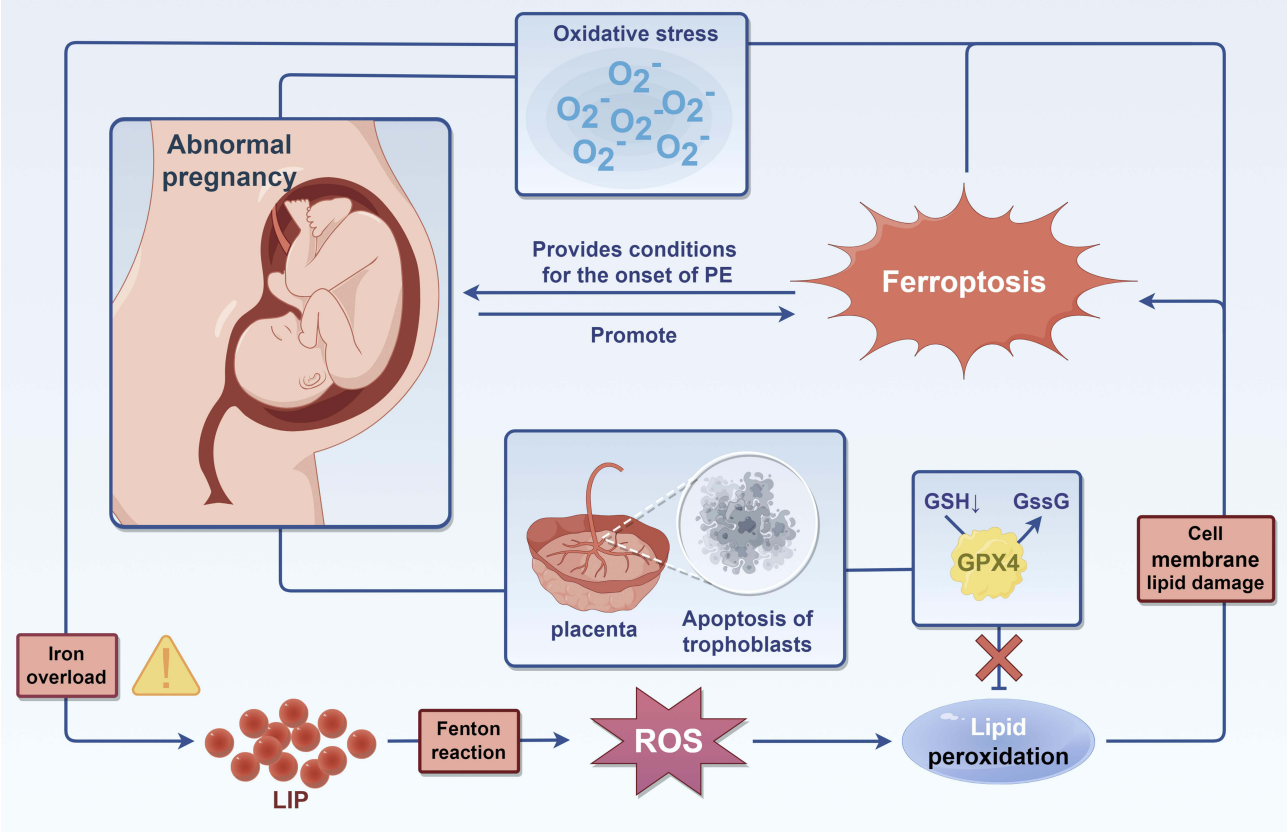

Figure 1 Regulatory Mechanisms of the Ferroptosis Signaling Pathway in Preeclampsia. Ferroptosis triggers extensive apoptosis in placental trophoblast cells, leading to a significant oxidative stress response and creating an environment conducive to the development of PE. Furthermore, in PE, the downregulation of glutathione (GSH) due to ferroptosis exacerbates the progression of the disease. GSSG: GPX4 converts GSH into oxidized glutathione. By Figdraw.

Researchers showed that lncRNA HEPFAL promotes ferroptosis by reducing the expression of SLC7A11, a key cystine transporter and upstream regulator of ferroptosis that influences cellular GSH levels and ferroptosis sensitivity, while simultaneously increasing lipid ROS and iron levels.[66,67] Investigations indicate that miR-137 suppresses both the initiation and progression of ferroptosis by specifically binding to the glutamine transporter SLC1A5, which in turn diminishes glutamine absorption and lowers malondialdehyde levels.[68] Additionally, GPX4, a crucial protein in the ferroptosis pathway, is regulated by ncRNA. Researchers have observed that ischemia/reperfusion -induced overexpression of MIR-182-5P and MIR-378A-3P results in the downregulation of GPX4 and SLC7A11.[69] Thus, suppressing mir-182-5P and mir-378A-3P expression may inhibit ferroptosis development. Targeting the VDAC family, including VDAC1, VDAC2, and VDAC3, has been linked to mitochondrial dysfunction, which promotes ROS release and subsequent cell ferroptosis.[70] Stabilizing VDACs can protect mitochondria, whereas miR-7 reduces VDAC1 and VDAC3 expression, promoting ferroptosis progression.[71,72] It is proposed that miR-7 may serve effectively as a therapeutic target in managing conditions associated with ferroptosis.

ncRNA-Mediated Transmission of Ferroptosis Signals

Ferroptosis signal transmission is a complex and intricate biochemical process involving interconnected and mutually influential signaling pathways. NcRNAs are recognized as major regulatory factors in various cellular processes, with numerous ncRNAs confirmed to participate in ferroptosis signal transmission mechanisms.[73] Research confirms that ncRNAs can act as structural bases for protein complexes, interacting with specific proteins to modulate signaling pathways in signal transmission.[74] For example, miR-210 targets key molecules in the ferroptosis pathway, including the Iron-Sulfur Cluster Assembly Enzyme and Transferrin Receptor (TfR). Transfection of miR-210 reduces transferrin uptake by inhibiting TfR expression, while anti-miR-210 inhibition upregulates Iron-Sulfur Cluster Assembly Enzyme

expression.[75,76] This ultimately influences the ferroptosis process through effects on the iron metabolism pathway. In addition, various signaling pathways are involved, including PI3K-AKT-mTORC1, KEAP1-NRF2-ARE, and NAD(P)H/FSP1/CoQ10 pathways.[77,78] Furthermore, ferroptosis signal transmission involves multiple cellular structures, especially mitochondria and cell membranes. Mitochondria are crucial in iron utilization, catabolic and anabolic metabolism pathways, significantly influencing both iron metabolism and material and energy metabolism in the ferroptosis process.[79] Studies show that lncRNA HOXA11os, found in mitochondria under baseline conditions, interacts with the core subunit of the Electron Transport Chain Complex I to maintain its activity. HOXA11os deficiency results in Complex I deficiency, oxidative phosphorylation dysfunction, and increased mitochondrial reactive oxygen species production.[80] Ling and others discovered that γ-Tocotrienol modifies ncRNA, inhibiting mitochondrial complexes and oxidative phosphorylation.[81] Consequently, it is hypothesized that mitochondrial dysfunction and ROS production mutually enhance each other, exacerbating cellular OS and ferroptosis. Additionally, lipid peroxidation on the cell membrane, a significant marker of ferroptosis, leads to cell membrane damage and cell death. Research indicates that miR-210-5p regulates lipid peroxidation levels and enhances mitochondrial function by inhibiting JAK1/STAT3 signaling.[82] Wu and others[83] used overexpression and silencing experiments with lncRNA NEAT1 to explore its role in cell death and lipid peroxidation. Studies suggest that NEAT1 regulates ACSL4 and protein levels associated with ferroptosis and the classical apoptosis pathway. Silencing NEAT1 decreases ACSL4, SLC7A11, and GPX4 levels, implying that NEAT1 affects the lipid peroxidation process and enhances ferroptosis sensitivity. Furthermore, studies indicate that ncRNAs can mediate ferroptosis through activation of inflammation-related signaling pathways; notably, miR-125b-5p mitigates inflammation-induced ferroptosis in PMVECs by regulating Keap1/Nrf2/GPX4 expression.[84,85]

In summary, ncRNA-mediated ferroptosis signal transmission is crucial for maintaining cellular homeostasis and preventing cell damage, thereby supporting tissue health and balance. This process involves multiple key pathways and cellular structures, forming a complex network. The combined effects of these factors ultimately dictate whether cells undergo ferroptosis. Changes in the ferroptosis regulatory network may lead to various diseases, although research in this field is still nascent. Therefore, a thorough investigation of ncRNA-mediated ferroptosis signal transmission mechanisms is crucial for understanding the pathogenesis of these diseases and developing novel therapeutic strategies.

Regulation of ncRNA Networks in PE

Increasing evidence suggests that abnormal ncRNA expression can lead to various diseases, playing a crucial role in the pathophysiological processes of PE. Throughout the progression of this disease, ncRNAs are extensively involved at various stages of PE pathogenesis.[11,86] The interaction among ncRNA molecules constitutes a highly active research area, as each ncRNA node is integral to a sophisticated regulatory framework. This intricate system effectively regulates various molecular targets, thereby eliciting particular physiological or pathological responses that consequently lead to diverse clinical results.

Further analysis has shown that most lncRNAs possess miRNA binding sites, with some associated with PE.[87] Additionally, Hu and others performed microarray studies on ceRNAs within placentas of women experiencing acute PE compared to those with typical pregnancies, uncovering that mRNAs, lncRNAs, and circRNAs can influence one another by vying for access to identical miRNA pools.[88] LncRNAs and circRNAs are significant in influencing miRNA-mediated gene regulation. They can act as "sponges" within a ceRNA network, effectively diminishing miRNA targeting of mRNAs and thereby regulating gene expression.[89] Reports indicate that in PE patients, Lnc-T-cell leukemia/lymphoma 6 (TCL6) is overexpressed and miR-21 is downregulated. Overexpression of Lnc-TCL6, by targeting miR-21, has been shown to regulate apoptosis and contribute to PE pathogenesis.[90] Inadequate remodeling of uterine spiral arteries is a key pathogenic mechanism of PE. Research indicates that lncRNA AGAP2-AS1 facilitates the remodeling of uterine spiral arteries by downregulating miR-574, potentially reducing the incidence of PE.[91,92] In PE patients, lncRNA ZEB2-AS1 is downregulated in the placenta compared to normal pregnancies. LncRNA ZEB2-AS1 functions as a molecular sponge for miR-149, affecting the miR-149/PGF axis, which is linked to the cell biology behaviors of HTR-8/SVneo cells, potentially exacerbating PE.[93] Notably, overexpression of Linc00261 has been shown to inhibit the activity of HTR-8/SVneo cells. Studies show that Linc00261 is upregulated in the placental tissues of women with PE and serves as a ceRNA for miR-558, suppressing its expression. Results indicate that Linc00261 inhibits trophoblast cell invasion and

migration via the miR-558/TIMP4 axis, potentially playing a role in PE pathogenesis.[94] Additionally, research demonstrates that miR-210 significantly affects the biological behavior of HTR8/SVneo cells by suppressing the expression of lncRNA MEG3.[95] PE is closely associated with placental dysfunction and insufficient trophoblast invasion. Studies have shown that hsa_circ_0111277 is upregulated in the placentas of PE cases compared to those of normal pregnancies. This RNA regulates trophoblast cell migration and invasion via the hsa_circ_0111277/miR-494-3p/HTRA1/Notch-1 axis, offering new insights into PE treatment.[96] CircTNRC18 enhances the protein levels of Grhl2, a transcription factor associated with epithelial-mesenchymal transition. Researchers confirmed that in PE placentas, underexpression of miR-762 and overexpression of circ-TNRC18 promote trophoblast cell migration and epithelial-mesenchymal transition, contributing to PE.[97] Additionally, in placental tissues of PE, both circ_0001438 and NLRP3 expressions are elevated. Low miR-942 expression inhibits the biological behavior of HTR-8/Svneo cells while promoting apoptosis and inflammation, effects that are reversed when NLRP3 is overexpressed and binds with miR-942. Research has demonstrated that Circ_0001438, by sponging miR-942, regulates NLRP3 expression and exacerbates dysfunction in human chorionic villous trophoblasts via the miR-942/NLRP3 axis.[98]

In summary, ceRNA activity constitutes a large-scale regulatory network within the transcriptome, significantly enriching the functional genetic information in the human genome and playing a pivotal role in pathological conditions like PE. Therefore, it is crucial to explore how lncRNAs and circRNAs use microRNA response elements to "communicate" with each other. Currently, a significant research gap exists regarding the role of small interfering RNA and Piwi-interacting RNA (piRNA) in PE pathogenesis. Research has shown that small interfering RNA-mediated knockdown of the NCAM1 gene inhibits the p38MAPK signaling pathway, reduces OS, and enhances the migration and invasion of human umbilical vein endothelial cells.[99] In another study, researchers initially demonstrated the unique role of piRNA and PIWIL proteins in the placental tissue of PE. They discovered that PIWIL1, crucial for trophoblast cell proliferation, is significantly downregulated in PE, likely due to indirect piRNA-mediated downregulation of PIWIL1 gene expression in placental trophoblast cells.[100] Consequently, the PIWIL1/piRNA axis is hypothesized to be a potential therapeutic target for PE. Recent research indicates that non-coding RNAs play a pivotal part in PE, affecting both its onset and progression, and are promising for clinical diagnosis and therapeutic application. However, the precise molecular mechanisms through which non-coding RNAs influence PE and the interactions involved in this regulatory process remain largely unexplored. Non-coding RNAs are poised to become a focal point for future PE treatment research. The effects and mechanisms of non-coding RNAs on PE are itemized in Table 1.

Role of the ncRNA/Ferroptosis Axis in PE

In both research and clinical care, PE is widely recognized as a multisystemic syndrome. Our ongoing research into its pathophysiology has underscored the roles of inflammation, OS, endoplasmic reticulum stress, and vascular developmental dysfunction in its pathogenesis.[101] Recent evidence indicates that PE associated with ncRNAs displays diverse clinical characteristics linked to the ferroptosis signaling pathway. A pathologically elevated iron environment underlies hypertensive disorders of pregnancy, including PE, with ncRNAs directly targeting proteins involved in ferroptosis or indirectly affecting downstream targets or pathways that regulate cellular iron levels.[16] Moreover, the ncRNA/ferroptosis axis is known to impact the progression of PE by modulating hypoxia and has been demonstrated to be involved in regulating cancer initiation and progression. In this section, we delve into the expression patterns of the ncRNA/ferroptosis axis in PE, alongside its associated clinical features, functions, and operational mechanisms, as outlined in Table 2. Furthermore, drawing upon existing research on cancer, we speculate that the cancer-related ncRNA/Ferroptosis axis may potentially play a role in the treatment of PE.

Role of the miRNA/Ferroptosis Axis in PE

MiRNAs target genes across various pathophysiological processes, controlling the expression of more than 60% of all protein-coding genes, including those involved in iron metabolism within ferroptosis mechanisms.[116,117] Consequently, miRNAs and the ferroptosis signaling pathway significantly influence the development and progression of PE. For example, the upregulation of miR-155, identified as a marker for PE, disrupts trophoblast cell migration and impedes placental angiogenesis, thereby promoting PE development.[30] Furthermore, researchers observed that inhibiting miR-155

Table 1 Role and Mechanism of ncRNA in PE

MiRNA	MiR-126-3P	Reduce the antioxidant activity and anti-inflammatory of placental trophoblast cells	Aggravation	↓	IL-6, TNFα	[28]
	MiR-210	Promote the occurrence of inflammatory response	Aggravation	↑	Th2	[29]
	MiR-155	Interfere with the biological behavior of trophoblast cells and hinder placental angiogenesis	Aggravation	↑	CYR61-VEGF, cyclin D1	[30,31]
LncRNA	LncRNA DIAPH2-AS1	Inhibit the invasion and proliferation of trophoblast cells	Aggravation	↑	PAX3	[34,35]
CircRNA	Circ_0055724	–	Aggravation	↑	–	[45]
	Circ\u FURIN	–	Aggravation	↑	–	[46]
Crosstalk regulation	LncRNA MEG3 /miR-21	Inhibit the proliferation and invasion of trophoblast cells	Aggravation	↓	BMPR2	[37]
	Lnc TCL6/miR-21	Promote trophoblast cell apoptosis	Aggravation	↑	–	[90]
	LncRNA AGAP2-AS1/miR-574	Promote uterine spiral artery remodeling	Mitigation	↑	–	[91,92]
	LncRNA ZEB2-AS1/miR-149	Inhibit the proliferation and invasion of trophoblast cells	Aggravation	↓	PGF	[93]
	Lnc00261/miR-558	Inhibit the migration, invasion of trophoblast cells	Aggravation	↑	TIMP4	[94]
	Circ 0008726 /miR-345-3p	Inhibit the migration, invasion of trophoblast cells	Aggravation	↑	RYBP	[48]
	CircVRK1/miR-221-3p	Reduce the migratory and invasive capabilities of trophoblast cells	Aggravation	↑	PI3K/Akt	[49]
	Circ_0111277/miR-494-3p	Inhibit the proliferation and invasion of trophoblast cells	Aggravation	↑	HTRA1/Notch-1	[96]
	CircTNRC18/miR-762	Promote trophoblast migration and epithelial-mesenchymal transition	Aggravation	↑	Grhl2	[97]
	Circ_0001438/miR-942	Promote dysfunction of human chorionic trophoblast	Aggravation	↑	NLRP3	[98]

Table 2 Role and Mechanism of ncRNA/Ferroptosis in PE

	NcRNA/ferroptosis	Function	Effects on PE	Expression	Key molecule	Refs.
MiRNA	MiR-155/ferroptosis	Enhance the expression level of TNF and promote inflammatory response	Aggravation	↑	TNF	[30,102]
	MiR-30b-5p/ferroptosis	Promote the death of trophoblast cells	Aggravation	↑	SLC7A11, Pax3	[12]
	MiR-30/ferroptosis	Inhibit apoptosis and promote proliferation of trophoblast cells	Mitigation	↑	MAPK/ERK	[103]
	MiR-2115-3p/ferroptosis	Promote proliferation of trophoblast cells	Mitigation	↓	GOT1	[104]
	MiR-214-3p/ferroptosis	Inhibit GPX4 levels and promote cell apoptosis	Aggravation	↑	GPX4	[105,106]
LncRNA	LncRNA TUG1/ferroptosis	Disrupt uterine spiral artery remodeling and promote inflammatory response	Aggravation	↓	ACSL4	[51,107]
CircRNA	Circ-ITCH/ferroptosis	Restore trophoblast vitality	Mitigation	↑	NRF2	[108]
	circRNA_0004904/ferroptosis	–	Aggravation	↑	–	[109]
	circRNA_0001855/ferroptosis	–	Aggravation	↑	–	[109]
	circ-DMNT1/ferroptosis	Promote trophoblast cell proliferation and invasion	Mitigation	↓	p53	[110]
Crosstalk regulation	LncRNA MALAT1/ miR-145-5p/ferroptosis	Inhibit the migration, invasion of trophoblast cells	Aggravation	↓	MUC1	[111]
	LncRNA SNHG14/miR-206/ ferroptosis	–	Aggravation	↓	–	[112]
	LncRNA TCL6/miR-485-5p/ ferroptosis	Promote trophoblast cell proliferation and inhibit inflammatory response	Mitigation	↓	TFRC	[13,113]
	LncRNA HOTAIR/miR-106/ ferroptosis	Reduce trophoblast viability	Aggravation	↑	UPF1/ACSL4	[114,115]
	circ_FURIN/miR-34a-5p/ ferroptosis	Reduce the biological activity of trophoblast cells and promote inflammatory responses.	Aggravation	↓	TFAP2A	[46]
	circRNA_0111277/miR-494-3p/ ferroptosis	Inhibit the migration and invasion of trophoblast cells	Aggravation	↑	Notch-1	[96]

Notes: ↓ represents down-regulated expression; ↑ represents up-regulated expression.

Abbreviations: PE, preeclampsia; ROS, Reactive Oxygen Species; NcRNA, Non-coding RNA; OS, oxidative stress; ROS, Reactive Oxygen Species; GPX4, Glutathione Peroxidase 4; TFR/TFRC, Transferrin Receptor; MAPK, mitogen-activated protein kinase; p-ERK, phosphorylated extracellular signal-regulated kinase; GOT1, Glutamic-oxaloacetic transaminase 1; IRI, ischemia-reperfusion injury; TFAP2A, transcription factor AP-2 alpha.

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in HOXA11-AS-silenced and scratch-injured B4G12 cells alleviated ferroptosis, reduced intracellular and lipid ROS levels, upregulated GPX4 and SLC7A11, and downregulated ACSL4.[118] Excessive M1 macrophages can induce an inflammatory state, precipitating PE onset. The ferroptosis pathway enhances the M1 macrophage phenotype accumulation by increasing TNF expression through iron accumulation.[119] MiR-155 actively targets and enhances macrophage polarization towards the M1 phenotype, which leads to the significant production of pro-inflammatory cytokines including TNF-a, IL6, and MCP1.[102] Notably, TNF-a also plays a role in further inducing miR-155. It is hypothesized that activation of the miR-155/ferroptosis pathway increases TNF expression and M1 macrophage accumulation, thereby inducing an inflammatory state that contributes to PE manifestation. This provides a new perspective on potential therapeutic targets for PE. In another study, researchers employed microarray analysis, bioinformatics, and luciferase reporter assays to demonstrate the critical role of miR-30b-5p upregulation in the ferroptosis pathway within a PE model. Aberrant upregulation of miR-30b-5p led to the downregulation of SLC7A11 and Pax3, affecting trophoblast cell ferroptosis via the GPX4 pathway. Subsequent experiments revealed that inhibiting miR-30b-5p expression and employing a ferroptosis inhibitor alleviated PE-related symptoms in the same rat model.[12] Consequently, miR-30b-5p may represent a potential therapeutic target for PE. Moreover, it has been determined that distinctive characteristics of ferroptosis, such as heightened levels of intracellular iron and enhanced lipid peroxidation, impact the functionality of the mitogen-activated protein kinase (MAPK) pathway.[84] MiR-30 activates the MAPK/ERK signaling pathway, increasing proliferating cell nuclear antigen expression by elevating phosphorylated extracellular signal-regulated kinase (p-ERK) levels and the p-ERK/ERK ratio, thereby suppressing apoptosis while enhancing the proliferation of trophoblast cells.[103] By upregulating miR-30 and targeting the ferroptosis/MAPK signaling pathway, trophoblast cell activity is enhanced, ultimately influencing the occurrence and development of PE. Reports suggest that miR-2115-3p is a ferroptosis-related gene, with the miR-2115-3p/Glutamic-oxaloacetic transaminase 1 (GOT1) axis playing a role in regulation in PE patients.[104] MiR-2115-3p enhances the degradation of ferritin via its interaction with GOT1, facilitating the release of iron from ferritin for Fenton reactions and thus contributing to ferroptosis-mediated PE pathogenesis.[120,121] GPX4 is a known target of miR-214-3p; inhibition of miR-214-3p enhances GPX4 and SLC7A11 expression, while reducing ACSL4 levels.[122] MiR-214-3p is overexpressed in patients with PE, and this overexpression increases ferroptosis sensitivity by inhibiting GPX4 levels.[105,106] Thus, the miR-214-3p/ferroptosis axis provides new insights into the regulatory mechanisms of PE. Notably, miR-34a levels are markedly elevated in the placentas of patients with PE than normal ones, with miR-34a confirmed to participate in three metabolic pathways that regulate ferroptosis, impacting all key mechanisms.[123] This suggests that targeting the miR-34a/ferroptosis axis might represent a viable approach for developing treatments for PE. To conclude, the functional impact of the miRNA/ferroptosis axis in PE primarily involves regulating trophoblast cell behavior and inflammatory responses, thereby influencing the development and severity of PE through the control of trophoblast cell activities and OS states (see Figure 2). Identifying effective target molecules in the miRNA/ferroptosis axis during the development of PE lays a more comprehensive foundation for the design of targeted molecular treatments.

Role of the lncRNA/Ferroptosis Axis in PE

Increasing evidence shows that abnormal lncRNAs have both positive and negative regulatory effects on the development of PE. LncRNAs mediate ferroptosis through multiple pathways, including iron metabolism, GSH metabolism, and System Xc-, and by various methods, such as regulating cell survival signaling pathways, binding to miRNAs, and modulating other OS reactants.[124] Research by Liang and others shows that the downregulation of lncRNA MALAT1 promotes erastin-induced ferroptosis through the miR-145-5p/MUC1 signaling pathway, with MALAT1 being continuously downregulated during this process.[111] Mechanistically, MALAT1 functions as a competitive endogenous RNA for miR-145-5p, regulating the expression of MUC1, a ferroptosis inhibitor. Studies have demonstrated that MALAT1 is downregulated in PE patients and influences PE during epithelial-mesenchymal transition by affecting the behavior of extra-villous trophoblasts.[125] These findings underscore the significant potential of the MALAT1/ferroptosis axis as a therapeutic target for PE. Numerous studies have shown that lncRNA SNHG14 is significantly suppressed in PE patients, promoting ferroptosis by upregulating miR-206 and thereby exacerbating PE progression.[112] Sun and others[107] found that in a mouse model of ischemia-reperfusion injury (IRI) induced ferroptosis, upregulation of lncRNA TUG1

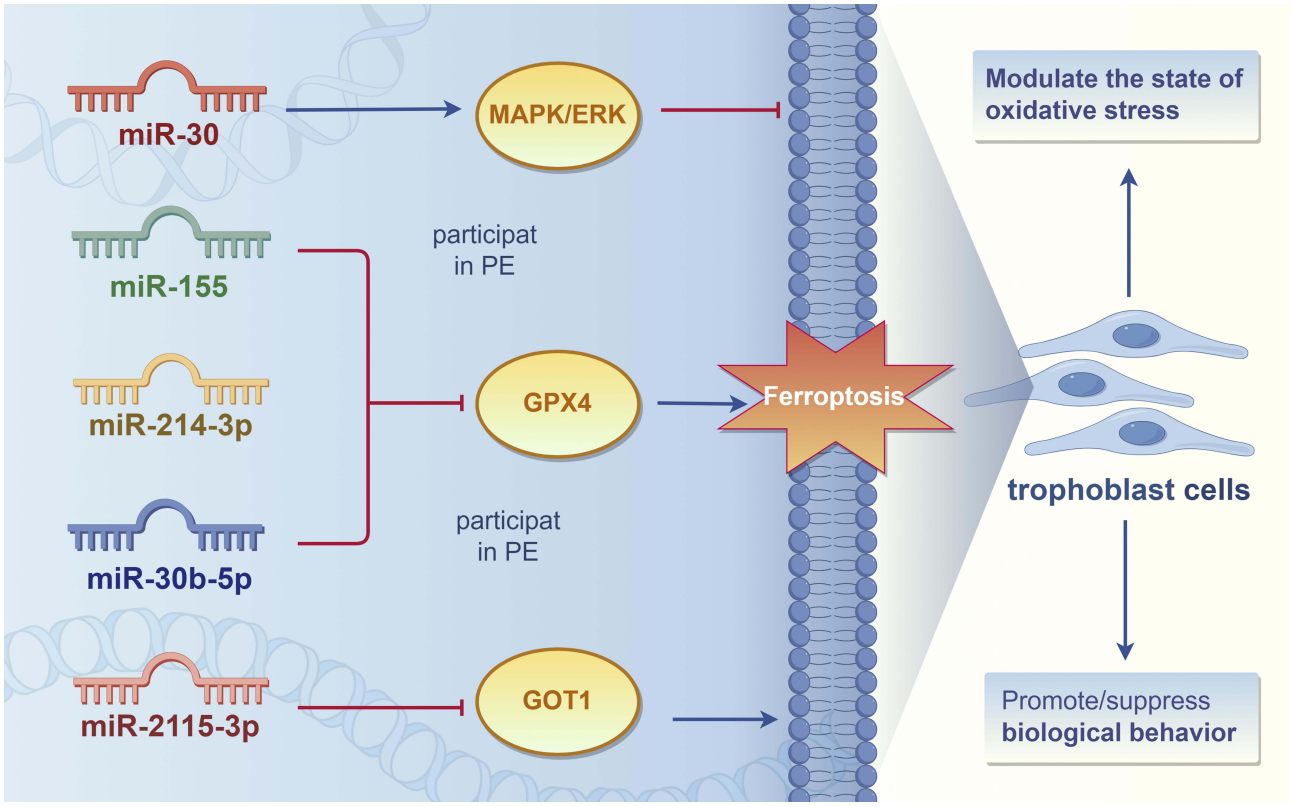

Figure 2 Regulatory Mechanisms of the MiRNA/Ferroptosis Axis in Preeclampsia. MiR-30 activates the MAPK/ERK signaling pathway, thereby inhibiting the ferroptosis pathway; miR-155, miR-214-3p, and miR-30b-5p inhibit GPX4 expression, thereby activating the ferroptosis pathway; miR-2115-3p targets and inhibits GOT1, subsequently activating the ferroptosis pathway. By Figdraw.

inhibited ACSL4-mediated cellular ferroptosis and ameliorated IRI-induced kidney damage. IRI and impairments in uterine spiral artery remodeling are considered crucial in the pathogenesis of PE. In another experiment, the down-regulation of TUG1 was found to disrupt the spiral artery remodeling process, implicating it in PE.[126] Therefore, it is hypothesized that the TUG1/ferroptosis axis may play a role in regulating PE. Further research indicates that alterations in ferroptosis activity may precede PE development, with reduced leukocyte lncRNA TUG1/mRNA in PE potentially regulating OS and iron toxicity. Downregulation of lncRNA TUG1 via the ferroptosis pathway reduces the cell's anti-inflammatory capabilities, increases circulating ferritin, disrupts iron homeostasis, and promotes PE development.[51] These findings offer new insights into TUG1's role in the ferroptosis mechanisms of PE, though additional in vivo studies are required to confirm these results. Researchers have identified high expression levels of TCL6 in PE patients. Through the mediation of the miR-485-5p/(transferrin receptor) TFRC axis, upregulation of TCL6 inhibits trophoblast cell proliferation and promotes apoptosis and inflammatory responses, thereby inducing ferroptosis.[13,113] In 2017, Song and others[127] discovered that levels of lncRNA HOTAIR are elevated in cases of PE, inhibiting trophoblast cell activity, although the specific target genes and molecular mechanisms were not identified. In the past three years, overexpressed HOTAIR has been shown to target miR-106, reducing trophoblast cell vitality and mediating the UPF1/ACSL4 axis to induce ferroptosis.[114,115] As more molecular mechanisms and target genes associated with lncRNA are identified, the significance of the lncRNA/ferroptosis axis in PE increases, influencing the expression of related proteins and genes through cytokine modulation, thereby affecting PE's pathophysiological processes (see Figure 3).

Role of the circRNA/Ferroptosis Axis in PE

It is particularly noteworthy that circRNAs involved in the ferroptosis pathway play a crucial role in PE. Circ-ITCH is widely recognized as a tumor suppressor-related gene. Recent studies have shown that upregulation of circ-ITCH restores the vitality of human umbilical vein endothelial cells and angiogenesis, and activates the NRF2 signaling pathway to

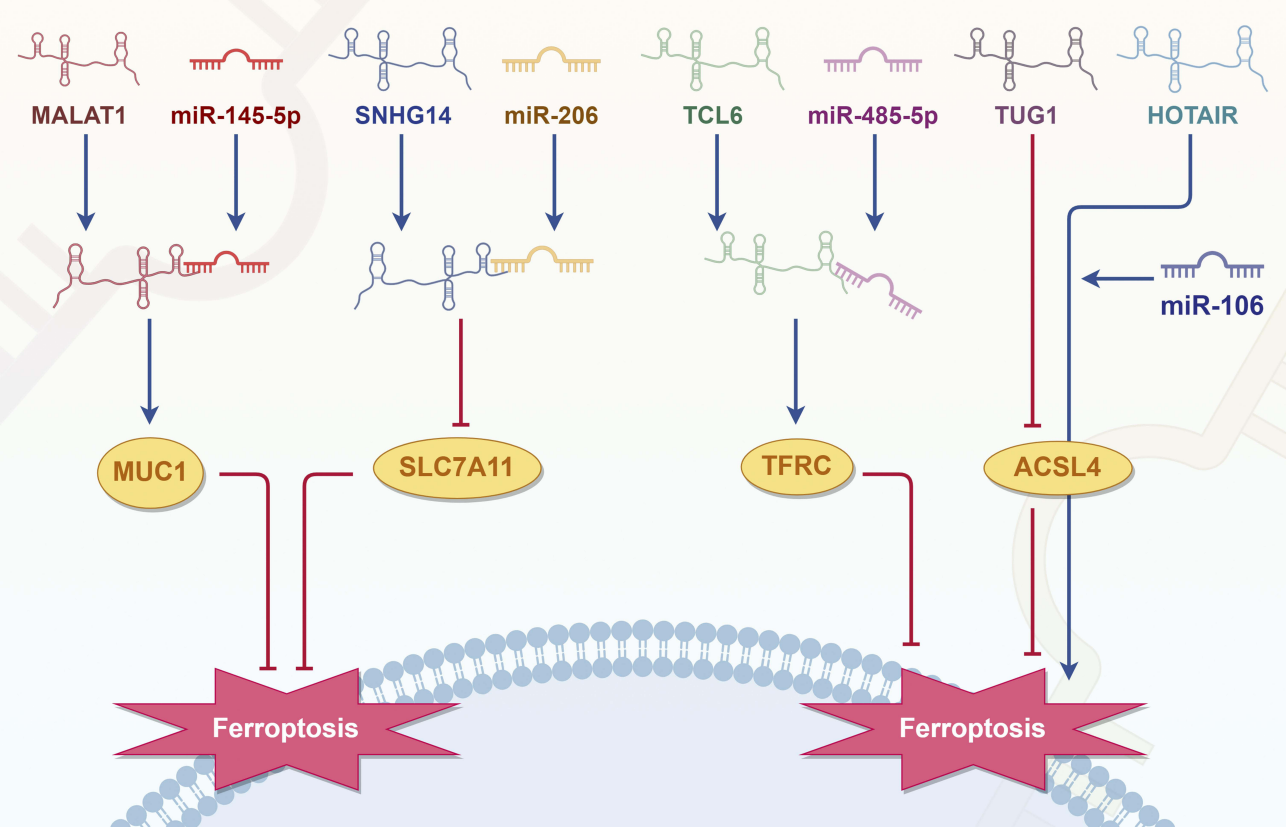

Figure 3 Regulatory Mechanisms of the LncRNA/Ferroptosis Axis in Preeclampsia. LncRNA MALAT1 promotes MUC1 expression by sponging miR-145-5p, thereby inhibiting the ferroptosis pathway. LncRNA SNHG14 regulates the ferroptosis pathway by sponging miR-206 and subsequently inhibiting SLC7A11 expression. LncRNA TCL6 regulates the ferroptosis pathway by sponging miR-485-5p and modulating TFRC. LncRNA TUG1 inhibits the ferroptosis pathway by suppressing ACSL4, while LncRNA HOTAIR promotes the ferroptosis pathway by enhancing ACSL4 expression after sponging miR-106. By Figdraw.

inhibit ferroptosis.[108] NRF2, which plays a crucial role in regulating cellular antioxidant activities, has been shown to inhibit two key ferroptosis targets, SLC7A11 and GPX4. Research suggests that NRF2 holds significant potential in diseases characterized by lipid peroxidation and ferroptosis.[128] Liao and others[129] discovered that trophoblast cells are highly sensitive to ferroptosis, and the activated NRF2/GPX4 signaling pathway promotes trophoblast cell proliferation and invasiveness, while reducing OS and apoptosis, offering positive implications for PE treatment. Conversely, ongoing ferroptosis could reverse this process and exacerbate PE development. Studies have also shown that circ_FURIN is downregulated in PE-related tissues. Circ_FURIN enhances trophoblast cell activity by inducing the expression of the transcription factor AP-2 alpha (TFAP2A), targeting miR-34a-5p.[46] Notably, TFAP2A plays a key role in ferroptosis; its downregulation increases intracellular Fe2+ and malondialdehyde accumulation, thus intervening in the ferroptosis process.[130,131] Therefore, we hypothesize that circ_FURIN is closely linked to the pathophysiological mechanisms of PE through its regulation of the key ferroptosis pathway factor TFAP2A. Additionally, circRNA_0004904 and circRNA_0001855 are significantly upregulated in PE, and their miRNA sponge target, Pregnancy-associated plasma protein-A (PAPP-A), is overexpressed in vivo.[109] The levels of PAPP-A are linked to iron ions, inflammation, and OS in the body. Moreover, circRNA_0111277, upregulated in PE placentas, influences the PE process by regulating trophoblast cell migration and invasion via the miR-494-3p/Notch-1 axis.[96] Similarly, in PE, highly expressed circ-DMNT1 collaborates with elevated p53 (a classic ferroptosis regulatory pathway) to inhibit trophoblast cell proliferation and invasion, thereby promoting the onset of PE.[110] Compared to the miRNA/ferroptosis and lncRNA/ferroptosis axes, research on the circRNA/ferroptosis axis in PE is still nascent, with most circRNA molecules yet unstudied and their functions unknown. Future research should validate the connections between circRNAs and the ferroptosis pathway and further explore their potential roles in PE.

In summary, ncRNAs constitute a distinct group of biomolecules with potent and extensive capabilities to regulate gene expression. Although research on PE still has some gaps, the role of ncRNAs as regulators of the ferroptosis pathway in PE is undeniable. Additionally, ncRNAs hold promise as non-invasive diagnostic markers for PE, and compounds targeting ncRNAs could represent promising therapeutic strategies for controlling disease-related gene expression.

Cancer Insights Illuminating the Therapeutic Potential of ncRNA/Ferroptosis Axis in PE

In recent years, there has been a growing trend towards inducing ferroptosis in cancer cells as a means of eliminating tumorous cells, as well as exploiting the ncRNA/ferroptosis axis as novel drug targets for cancer therapy. Extensive research has revealed that a diverse array of ncRNAs, including specific examples such as lncRNA NEAT1, can either directly or indirectly regulate the expression of key ferroptosis-related genes, thereby playing a pivotal role in cancer progression. The upregulation of lncRNA NEAT1 in response to ferroptosis inducers, notably erastin and RSL3, leads to decreased intracellular levels of NADPH and GSH, ultimately enhancing ferroptosis. Importantly, NEAT1 overexpression significantly augments the antitumor efficacy of these ferroptosis inducers, erastin and RSL3, through potentiation of ferroptosis in both experimental and preclinical settings.[132] This pivotal discovery underscores a promising therapeutic avenue for individuals afflicted with Hepatocellular Carcinoma. Furthermore, the modulation of ferroptosis sensitivity in cancer cells embedded within the tumor microenvironment (TME) by ncRNAs has garnered considerable attention. For instance, in lung squamous cell carcinoma (LUSC), a prevalent malignancy of the respiratory tract, the development and progression of LUSC are intimately linked to the lncRNA/ferroptosis axis.[133] This intricate interplay facilitates antitumor immune responses by modulating the infiltration patterns of pertinent immune cells within the TME, thereby establishing it as a promising therapeutic target for LUSC management.

Despite being distinct diseases, cancer and PE exhibit commonalities in cell death regulation, hypoxia, and inflammatory responses, which hint at potential translational applications of cancer research findings to PE therapies. Drawing from the regulatory mechanisms of the ncRNA/ferroptosis axis in cancer research reveals that ncRNAs are capable of modulating the expression of ferroptosis-related genes, either directly or indirectly, contributing to disease progression. Specifically, lncFASA, in the context of breast cancer, has been shown to regulate ferroptosis by interacting with specific domains of PRDX1 and modulating its activity, thereby exerting a tumor suppressive effect. This process involves inhibiting PRDX1's peroxidase activity, which leads to lipid peroxidation accumulation, disruption of intracellular ROS homeostasis, and, ultimately, inhibition of tumor growth.[134] Given these insights, it is intriguing to speculate whether the lncRNA/ferroptosis axis could similarly impact placental trophoblast cell fate in PE by regulating PRDX1. Notably, researchers have observed significant associations between altered PRDX1 expression, oxidative stress levels, and neonatal birth weight in PE.[135] Furthermore, investigations have clarified PRDX1's role in trophoblast cells during PE, influencing migration, invasion, and angiogenesis through modulation of autophagy and ROS levels.[136] Consequently, it is plausible to hypothesize that, analogous to lncFASA's impact on cell fate through PRDX1 regulation in cancer, ncRNAs/ferroptosis axes with similar functions could also influence the pathological processes of PE, characterized by similar redox imbalances and alterations in PRDX1 activity. Nevertheless, this hypothesis awaits further experimental validation to confirm its validity.

In conclusion, considering the intricate disease mechanisms and interindividual variability among pregnant women, it is premature to definitively assert that the ncRNA/ferroptosis axis, previously implicated in cancer biology, will undoubtedly find application in PE therapy. However, based on the current data, a plausible inference emerges, suggesting the existence of such a potential. Future research endeavors will further clarify the potential roles and therapeutic avenues of these ncRNA/ferroptosis axes in PE, thereby advancing our understanding of this complex disorder.

Conclusion and Prospects

To our knowledge, this review is the first to focus on the significance of the ncRNAs/ferroptosis axis in PE. Undoubtedly, a close relationship exists between ferroptosis and PE, with increasing experimental evidence demonstrating that ncRNAs regulate PE development through the ferroptosis pathway and that targeting these ncRNAs may inhibit or promote disease progression. Abnormal expression of ncRNAs in PE acts as a crucial regulatory switch in its pathophysiology, with ncRNAs, especially miRNAs and lncRNAs, extensively participating in various stages of PE

pathogenesis.[11,86] Furthermore, the ferroptosis signaling pathway, engaged in multiple cellular functions, is critical for the advancement of disease processes. Ferritin, a key component of this pathway, responds significantly to OS, with changes in its expression indicating shifts in disease progression.[137] Yang and others[59] proposed that ferritin light chains could serve as potential biomarkers for PE. They identified a linear relationship between PE severity and ferroptosis, closely linked to ferritin light chains levels in patient serum. As previously mentioned, the upregulation of miR-30b-5p can trigger ferroptosis in trophoblast cells, while blocking miR-30b-5p directly inhibits ferroptosis, thereby reversing PE onset.[12] Therefore, it is speculated that the ncRNA/ferroptosis axis regulates various trophoblast cell activities, influencing PE progression. Additionally, the ncRNA/ferroptosis axis participates in disease pathogenesis by regulating inflammatory responses and the expression of PE-related proteins. Therefore, exploring the role of the ncRNA network within ferroptosis is essential.

We have identified ncRNAs as critical therapeutic targets for PE, as they regulate trophoblast cell activity or disrupt iron homeostasis through the ferroptosis pathway, thereby inducing PE. However, the mechanisms of action for many ncRNAs remain unclear, as only a small portion has been studied in the context of ferroptosis and PE. The limited sample sizes in related experiments and the complexity of the involved pathways and biological networks make understanding ncRNAs related to PE challenging. Here, we outline several potential issues. First, iron, a crucial element in the human body, increases during pregnancy to support fetal placental development. However, excessive iron-induced ferroptosis negatively affects the biological behavior of trophoblast cells. Addressing how to use this "double-edged sword" to treat PE is an urgent issue. Secondly, ncRNAs intersect with diseases influenced by ferroptosis, and there is cross-regulation between other types of programmed cell death and ferroptosis.[138] NcRNAs can target multiple genes and may be regulated simultaneously. For example, different ncRNAs may regulate the same target. The GOT1 pathway, which induces ferroptosis, is co-inhibited by miR-9 and miR-2115-3p. In PE patients, both the miR-2115-3p-GOT1 and miR-9-GOT1 axes are involved in regulation, while the overexpressed NEAT1 regulates the miR-9-GOT1 axis to promote ferroptosis.[104,139,140] The development and advancement of PE are influenced by multiple intricate factors, which underscore the need for creating novel therapeutic strategies and more potent medications to prevent and manage this condition. However, effective targeted treatment strategies are currently inadequate. In the future, ncRNA therapies leveraging the ferroptosis pathway could offer potential innovative treatments for PE. Additionally, key proteins and molecules within the ncRNAs/ferroptosis signaling pathways play a role in regulating PE and could serve as targets for drug action. The dysregulation of ncRNAs in bodily fluids and extracellular vesicles makes them potential non-invasive diagnostic biomarkers. NcRNAs have the capability to act as powerful, versatile regulators across all biological processes. NcRNAs, particularly miRNA and lncRNA, play a role in interacting with the ferroptosis pathway, influencing early diagnosis, progression, and treatment outcomes of PE. Notably, nanoparticles loaded with ncRNAs that target key ferroptosis genes are actively tested in vitro and in vivo, and preparing ncRNA therapies chemically is straightforward.[141]

In our review of the impact of the ncRNA/ferroptosis axis on PE, we found that ncRNAs are vital in controlling iron homeostasis and affecting the biological behavior of trophoblast cells. Besides being essential targets for the creation of new drugs, they also lay the groundwork for discovering novel therapeutic targets to treat PE. Thus, this paper explores the potential of ncRNAs as novel regulators through the ferroptosis pathway in controlling PE, including their potential clinical application, although still in nascent stages. Therefore, more clinical trials are needed to deepen our understanding of ncRNAs related to the ferroptosis signaling pathway during the critical stages of PE development. In summary, the application of the ncRNA/ferroptosis axis in the prevention, early treatment, and prognosis of PE shows significant preclinical promise.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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