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The Present State of Research on Ferroptosis in Women's Reproductive System Disorders

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Abstract: ***Ferroptosis is considered a new autophagy-dependent form of cell death, characterized chiefly by the buildup of reactive oxygen species and over-oxidation of lipids that culminate in cellular demise. The process is finely tuned by cellular iron, lipid, and amino-acid metabolic pathways, which engage in numerous pathophysiological mechanisms; these can both drive disease initiation and impede its progression. Gynecologic and obstetric disorders constitute female reproductive system diseases; factors such as lifestyle, environmental exposures, and stress jeopardize women's quality of life and overall health. Scientific studies indicate that iron deficiency exerts a crucial impact on the onset, progression, and therapeutic management of female reproductive disorders. The present review comprehensively examines studies on ferroptosis mechanisms, outlines its involvement in clinical gynecologic and obstetric diseases, and deliberates on the current research landscape, outstanding challenges, and prospective directions, aiming to deepen insight into ferroptosis and propose novel therapeutic strategies for female reproductive disorders.***

Keywords: Ferroptosis, Lipid peroxidation, Ovarian carcinoma, Premature ovarian insufficiency, Polycystic ovarian syndrome, Endometrial carcinoma, Cervical cancer, Preeclampsia**.**

1. Introduction

Ferroptosis represents a novel, iron-dependent form of programmed cell death that differs from apoptosis and autophagy. In 2012, Dixon and his team first coined the term "ferroptosis," (Dixon et al., 2012) [1] describing it as a new form of cell death dependent on autophagy [2]. Ferroptosis is characterized by cell death driven by the accumulation of reactive oxygen species (ROS) and lipid peroxidation, and it is finely regulated by intracellular iron, lipid, and amino acid metabolic pathways. Research demonstrates [3] that ferroptosis is a process in which iron-dependent lipid peroxidation reaches lethal thresholds, thereby regulating iron homeostasis to induce cell death. Emerging evidence [4] suggests that ferroptosis arises from the infiltration of polyunsaturated fatty acids into the cell membrane, resulting in a persistent susceptibility that evolves into a complex system capable of both exploiting and defending against this vulnerability (lipid peroxidation) across diverse environments. The underlying mechanisms of ferroptosis not only drive disease pathogenesis but also potentially confer tumor-suppressive properties, offering promising strategies for cancer therapy, and are involved in a wide array of physiological and pathological processes. This paper will comprehensively outline the regulatory mechanisms of ferroptosis and its current research landscape in female reproductive system diseases, striving to provide innovative perspectives for clinical interventions.

2. Regulatory Mechanisms of Ferroptosis

Since its initial characterization in 2012 as an iron-dependent, novel autophagy-associated form of programmed cell death, investigations into the mechanisms and functions of ferroptosis have expanded considerably. Ferroptosis arises from an oxidative-reductive imbalance generated by oxidants and antioxidants, driven by dysregulated expression and activity of multiple redox-active enzymes that produce or scavenge free radicals and lipid peroxidation products, and is tightly controlled at genetic, transcriptional, and translational levels. Central to this cascade is the point at which lipid peroxidation attains a threshold, triggering iron-mediated Fenton chemistry that catalyzes the formation of lipid-derived free radicals, which then accumulate intracellularly to lethal concentrations. Cellular susceptibility to ferroptosis is dictated by the import, export, storage, and intercellular transport of iron ions, processes that are modulated by a suite of pivotal proteins. Ferroptosis proceeds via two principal routes: an exogenous, transporter-dependent axis (e.g., SLC7A11, SLC38A1, NOXs, TFRC) and an endogenous, enzyme-regulated axis (e.g., ACSL4, ALOXs, GPX4, POR, GCH1, NOS, AIFM2). The crux of the pathway lies in the iron-catalyzed Fenton reaction that, once lipid peroxidation surpasses a critical threshold, expedites cellular demise [5].

3. Iron metabolism and Ferroptosis

Iron metabolism encompasses the transport, distribution, utilization, conversion, storage, and elimination of iron within the body following its entry in diverse forms. Iron's propensity to readily donate and accept electrons makes it a crucial participant for numerous proteins and cofactors in oxygen and energy metabolism, as well as an auxiliary factor in other fundamental metabolic pathways. It partakes in numerous physiological processes, including the synthesis of hemoglobin and myoglobin, the formation of cytochrome enzymes and DNA, and the maintenance of mitochondrial function. Iron is a vital trace element for life, and both iron excess and deficiency can lead to physiological disturbances and disease. Humans acquire iron through dietary intake, with food containing iron in the forms of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions. For absorption, dietary ferric iron (Fe^{3+}) must be reduced to ferrous iron (Fe^{2+}), which is then transported into epithelial cells via the divalent metal transporter 1 (DMT1). Heme iron (heme IX) can be directly absorbed by intestinal epithelial cells, stored as ferritin, while excess iron enters the bloodstream via the membrane transporter protein (FPN). Ferrous iron is oxidized to ferric iron with the assistance of

auxiliary proteins, after which it binds to transferrin (TF) and is transported to various organs to perform its functions [6]. The primary transcriptional regulators of intracellular iron metabolism are Iron Regulatory Protein 1 (IRP1) and Iron Regulatory Protein 2 (IRP2). Research has shown [7] that IRP2 can enhance cellular sensitivity to ferroptosis by suppressing the synthesis of ferritin heavy chain (FTH) and ferritin light chain (FTL). Ferroptosis suppressor protein 1 (FSP1) is a redox enzyme that converts coenzyme Q10 (CoQ10) to its reduced form, thereby preventing the buildup of lipid peroxidation products and alleviating their inhibitory effect on ferroptosis [8]. Consequently, various iron metabolism regulators are involved in maintaining the body's iron balance. The cellular susceptibility to ferroptosis varies with fluctuations in systemic iron levels; increased iron intake, decreased excretion, or reduced storage may lead to iron overload, culminating in ferroptosis.

4. Lipid Metabolism and Ferroptosis

Research suggests [9] that small molecule inhibitors of glutathione peroxidase 4 (GPX4) may promote lipid peroxide accumulation, consequently triggering ferroptotic cell death. The mechanism through which iron elicits cell death within biological systems encompasses lipid oxidation pathways. Phosphorylase kinase G2 (PHKG2) modulates iron-mediated effects on lipoxygenases in this pathway, and lipoxygenases drive lipid peroxidation by extracting bis-allylic hydrogen atoms from polyunsaturated fatty acids (PUFAs); this cascade of reactions results in augmented intracellular lipid oxidation and culminates in ferroptosis. Subsequent investigations indicate that lipid peroxidation requires lipoxygenase (LOX) and phosphorylase kinase G2 (PHKG2) as essential factors. PHKG2 modulates how LOX exploits iron [10], whereas LOX advances ferroptosis by catalyzing peroxidation reactions of polyunsaturated fatty acids (PUFAs). In a landmark study [11], Dixon et al. employed large-scale insertional mutagenesis in haploid KBM7 cells and identified genes participating in small molecule-induced non-apoptotic cell death, including key enzymes such as acyl-CoA synthetase long-chain family member 4 (ACSL4) in fatty acid metabolism and lysophosphatidylcholine acyltransferase 3 (LPCAT3) in lipid reactions; studies demonstrate that ACSL4 and LPCAT3, which participate in PUFA synthesis, play critical functions in ferroptotic mechanisms. ACSL4 acylates PUFAs with coenzyme A, and subsequent to LPCAT action, catalyzes esterification and phosphatidylethanolamine reactions to generate phospholipids enriched with polyunsaturated fatty acids (PUFA-PE); these PUFA-PE serve both as substrates for lipid peroxidation and as critical phospholipids driving ferroptotic cell death.

5. Ferroptosis Regulated by Amino Acid and Glutathione Metabolism

The cystine/glutamate antiporter, termed system Xc-, resides in the plasma membrane and primarily consists of solute carrier family 3 member 2 (SLC3A2) and SLC7A11. System Xc- mediates the import of extracellular cystine into cells and the export of intracellular glutamate to the extracellular space; cystine is then conjugated with glutathione (GSH) following enzymatic catalysis. GSH is a fundamental antioxidant within the body that facilitates the removal of free radicals. Decreasing cystine uptake via system Xc- inhibits glutathione synthesis, subsequently causing peroxide accumulation and triggering ferroptosis; thus, system Xc- is considered a negative regulator of ferroptosis. Metabolomic investigation results [12] demonstrate that AMPKK regulates Beclin-1 (BECN1) function, directly suppressing system Xc- activity and thereby promoting ferroptosis; this mechanism is accomplished through binding to the core component SLC7A11 (solute carrier family 7 member 11). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a critical antioxidant transcription factor in the human body; Nrf2 knockout significantly downregulates the expression of SLC7A11 and heme oxygenase 1 (HO-1). Under the OGD/R model, suppression of SLC7A11 substantially enhances Nrf2-HO-1 expression and concurrently reduces apoptosis; these findings indicate [13] that Nrf2 plays a role in downregulating ferroptosis through regulation of SLC7A11 and HO-1. Glutathione peroxidase 4 (GPX4) is an intracellular lipid peroxidase that facilitates GSH-mediated efficient scavenging of intracellular peroxidized lipid products, preventing iron-induced cell death and maintaining normal cellular physiological functions [14]. Research indicates [15] that GPX4 in biological organisms depends on selenocysteine (Sec); Sec aids in maintaining GPX4 function, and GPX4 employs selenocysteine to resist irreversible oxidation, making it highly susceptible to peroxide-induced ferroptosis. Consequently, selenium deficiency suppresses GPX4 activity, thereby inducing ferroptosis.

6. Research Progress on Ferroptosis in Female Reproductive System Diseases

(1) Ovarian Carcinoma: Ovarian cancer (OC) is among the prevalent malignant neoplasms affecting the female reproductive system. Early-stage OC presents with high occultness and is challenging to detect; it readily develops drug resistance with poor prognosis, and over 70% of patients experience relapse within 2-3 years following treatment [16]. Research indicates that ferroptosis plays a significant role in the pathogenesis and progression of ovarian cancer [17]. The p53 gene represents one of the most extensively investigated tumor suppressor genes. p53 modulates ferroptosis via transcriptional or post-transcriptional mechanisms; first, p53 promotes ferroptosis by suppressing SLC7A11 expression or by upregulating SAT1 (spermidine/spermine N1-acetyltransferase 1) and GLS2 (glutaminase 2) expression. Second, p53 can directly suppress DPP4 (dipeptidyl peptidase 4) activity or inhibit ferroptosis by inducing the expression of CDKN1A/p21 (cyclin-dependent kinase inhibitor) [18]. Wang and colleagues [19] discovered that the combination of Apatinib and Olaparib decreases GPX4 expression via a p53-mediated Nrf2 pathway, thereby inducing ferroptotic damage in ovarian cancer cells. P14ARF represents a widely accepted tumor suppressor that triggers ferroptosis by suppressing Nrf2-mediated SLC7A11 transcription. The CRL2-KLHDC3 ubiquitin ligase complex significantly contributes to the induction of P14ARF ubiquitination and subsequent degradation [20]. This research demonstrates that P14ARF protein stability and its pro-ferroptotic function are regulated by the CRL2 E3 ubiquitin ligase complex, and indicates that KLHDC3 overexpression-mediated suppression of the p14ARF-Nrf2-SLC regulatory pathway may advance cancer therapeutic strategies. In conclusion, the induction of

ferroptosis represents a potential novel therapeutic strategy for ovarian cancer.

(2) Primary Ovarian Insufficiency: Premature ovarian insufficiency (POI) represents a clinical syndrome of ovarian dysfunction manifesting as diverse impairments in female reproductive capacity. Presently, the pathogenesis of POI remains unclear in clinical settings; prior to widespread acceptance of the POI concept, this clinical manifestation was uniformly termed premature ovarian failure (POF). With advancing research into POF etiology and accumulating clinical case data, it has become apparent that ovarian failure follows a progressive trajectory; upon POF diagnosis, ovarian function is typically irreversible, rendering comprehensive POI investigation urgently necessary. POI typically results from oocyte apoptosis or granulosa cell dysfunction, resulting in impaired formation of the primordial follicle pool, follicular recruitment and maturation defects, follicular atresia, and ovarian stromal fibrosis, ultimately progressing to premature follicular depletion and irreversible decline in ovarian reserve. Genetic-level studies [21] have revealed that deletion of Basic Nuclear Protein 1 (BNC1) diminishes BMP15 and p-AKT levels while suppressing oocyte meiotic progression. In female mouse models harboring BNC1 frameshift mutations, serum follicle-stimulating hormone levels were markedly elevated, ovarian size was diminished, follicle counts were reduced, and infertility was manifested, consistent with human POI. Wang and colleagues reported [22] that BNC1 deficiency results in premature follicular activation and aberrant follicular atresia. Mechanistically, BNC1 deletion induces oocyte ferroptosis via the NF2-YAP pathway; NF2 transcript levels in oocytes are significantly downregulated, while YAP and downstream targets including Transferrin Receptor (TFRC) and ACSL4 are upregulated, thereby triggering oocyte ferroptosis. It has been observed that doxorubicin and cisplatin can induce excessive reactive oxygen species (ROS) production in ovarian-injured granulosa cells, triggering lipid peroxidation and ferroptosis, resulting in follicular developmental abnormalities and ovarian stromal fibrosis that compromise ovarian function [23]. These studies suggest that targeting relevant genes may modulate the positive and negative regulation of ferroptosis, enabling early intervention and therapeutic strategies to preserve ovarian reproductive function.

(3) Polycystic Ovary Syndrome: Polycystic ovary syndrome (PCOS) represents a multifactorial reproductive endocrine disorder manifesting with heterogeneous clinical presentations, primarily characterized by menstrual irregularity, chronic anovulation, hyperandrogenemia, and insulin resistance, accompanied by pathological polycystic ovarian morphology, affecting 6%-20% of the global population [24]. Serum examinations in the majority of PCOS patients reveal elevated serum ferritin concentrations, indicating that iron homeostasis and iron metabolism may contribute to PCOS pathogenesis. Among these, the antioxidant N-acetylcysteine (NAC) plays a pivotal role in preserving the redox balance in PCOS; thus, through modulation of lipid peroxidation processes, NAC can attenuate cellular susceptibility to ferroptosis [25]. Additional research has demonstrated [26]that receptors for 1,25-dihydroxyvitamin D3 are predominantly localized within granulosa cell nuclei; this localization contributes to oxidative stress suppression and improvement of hyperandrogen-induced ferroptosis in KGN cells, offering novel perspectives on PCOS pathophysiology and therapeutic strategies. Numerous studies indicate that ferroptosis plays a critical role in modulating endocrine metabolism and female reproductive function in PCOS. Approaching from the ferroptosis perspective and investigating its triggering mechanisms and molecular mechanisms that affect PCOS can provide novel therapeutic directions for PCOS, requiring active exploration and investigation on our part.

(4) Endometriosis: Endometriosis (EM) is defined as the abnormal proliferation and invasion of eutopic endometrial tissue at extra-uterine sites, affecting approximately 10% of the population [27]. EM lesions demonstrate extensive involvement, morphological heterogeneity, marked invasiveness, high recurrence rates, and exhibit hormone-dependent growth characteristics. The principal clinical manifestations of EM encompass dysmenorrhea, infertility, and chronic pelvic pain, significantly impacting women's quality of life. It is hypothesized [28] that ectopic endometrium undergoes cyclic hemorrhage under ovarian hormone regulation, resulting in macrophage-mediated degradation of erythrocytes within ectopic lesions, leading to substantial release of free intracellular iron, iron overload, oxidative injury, and subsequent chronic inflammation. Erythrocyte fragmentation releases pro-oxidative and pro-inflammatory mediators including hemoglobin and its toxic byproducts—heme and free iron. Unchelated heme and free iron are critical contributors to reactive oxygen species (ROS) generation [29]. The hallmark of EM lesions is resistance to iron-mediated programmed cell death, specifically ferroptosis resistance; interactions between ferroptotic signaling pathways and the mevalonate pathway may confer survival advantage to EM cells under ferroptotic stress conditions [30]. Enhanced comprehension of these molecular and cellular mechanisms will deepen our understanding of endometriosis pathogenesis and open avenues for novel diagnostic and therapeutic strategies.

(5) Endometrial Carcinoma: Endometrial carcinoma (EC) encompasses a spectrum of epithelial malignancies originating in the endometrium, wherein adenocarcinoma derived from endometrial glands represents the predominant histological subtype. The histological subtype of lesions confirmed postoperatively exerts a critical influence on survival outcomes and prognosis in EC patients. Moreover, the 5-year survival rate is merely 25%-30% [31]. The etiology of EC remains incompletely elucidated; prior investigations have demonstrated a strong association between early-stage endometrial carcinoma and iron homeostasis dysregulation. GPX4 serves as a favorable prognostic indicator in endometrial carcinoma patients; research indicates [32] that in early-stage EC specimens, GPX4 is bound by heat shock protein 70-kDa, which suppresses its degradation, thereby facilitating EC progression. Notably, GPX4 functions as a pivotal suppressor within the ferroptosis pathway. Furthermore, SLC7A11, serving as an additional ferroptosis suppressor, demonstrates aberrant expression that warrants significant attention. Research has indicated [33] that elevated SLC7A11 expression correlates significantly with adverse prognosis in patients with endometrial carcinoma. Moreover, numerous investigations have identified that an array of

ferroptosis-associated genes contribute to EC metastasis and recurrence, including cyclin-dependent kinase inhibitor 1A (CDKN1A) and fanconi anemia complementation group D2 (FANCD2). Notably, CDKN1A demonstrates strong associations with recurrence and metastasis of type II EC; furthermore, as an activator of ferroptosis, it correlates significantly with favorable prognosis in endometrial carcinoma. FANCD2 functions as a ferroptosis suppressor involved in DNA damage repair mechanisms [34]. Collectively, these studies underscore ferroptosis as a novel form of programmed cell death, offering fresh perspectives for investigating EC pathophysiological mechanisms and therapeutic interventions.

(6) Cervical Cancer: Cervical cancer constitutes a malignant neoplasm originating in the cervix that significantly impacts women's health. The principal pathological subtypes comprise cervical squamous cell carcinoma (CSCC) and cervical adenocarcinoma (CAC). The incidence and mortality rates of cervical cancer in China have demonstrated a progressive upward trend year by year. Extensive investigations have elucidated that ferroptosis is associated with the initiation and progression of cervical cancer. In the study conducted by Wu and colleagues [35], circEPSTI1 exhibited significant upregulation in cervical cancer. The circEPSTI1-miR-375/409-3P/515-5p-SLC7A11 axis modulated cervical cancer proliferation via the competing endogenous RNA (ceRNA) mechanism and was implicated in ferroptosis, wherein circEPSTI1 attenuated SLC7A11-mediated ferritin function. Consequently, knockdown of circEPSTI1 facilitates SLC7A11-mediated ferroptosis in cervical cancer cells. Based on data from The Cancer Genome Atlas (TCGA) database, Qi and colleagues identified [36] 15 differentially expressed ferroptosis-related genes (FRGs). They discovered that elevated expression of TFRC, ACACA, and SQLE, coupled with reduced PHKG2 expression, demonstrated strong correlation with adverse prognosis in cervical cancer patients. Notably, TFR1 encoded by TFRC serves as an essential transporter for cellular iron uptake.

(7) Preeclampsia: Preeclampsia (PE) is a multisystem disorder characterized by the onset of new-onset hypertension following 20 weeks of gestation, accompanied by dysfunction in multiple organ systems including cardiovascular, coagulation, hepatic, and renal functions. The pathogenesis of PE is associated with inadequate trophoblast cell invasion and impaired remodeling of spiral arterioles,In PE, dysregulation of arterial vascular remodeling results in compromised oxygen perfusion, thereby promoting the generation of reactive oxygen species (ROS) and toxic lipid peroxides [37], which exacerbate oxidative stress. Iron overload mediates ferroptosis of trophoblast cells involved in PE pathogenesis. Notably, iron overload not only significantly upregulates SLC7A11 expression but also triggers ferroptosis in SLC7A11-/- cells. Genetic ablation of SLC7A11 promotes ferroptosis under conditions of elevated iron concentrations [38]. Mechanistic studies indicate [39] that SIRT3 deficiency suppresses activation of the AMPK-mTOR pathway, thereby elevating glutathione peroxidase 4 (GPX4) levels, which consequently inhibits both autophagy and ferroptosis. Conversely, upregulation of SIRT3 activates the AMPK-mTOR pathway and reduces GPX4 levels, thereby enhancing autophagy activation and inducing ferroptosis in trophoblast cells. In conclusion, further investigation into the role of ferroptosis in PE pathogenesis holds promise for developing protective interventions for both mothers and fetuses.

7. Summarization and Prospect

Ferroptosis represents a novel form of regulated cell death that is autophagy-dependent, characterized by the accumulation of reactive oxygen species (ROS) and lipid peroxidation, which is subject to precise regulation through multifaceted intracellular metabolic pathways. With the multifaceted impacts of contemporary lifestyle factors, the incidence of disorders affecting the female reproductive system has demonstrated a progressive upward trend. Collectively, the aforementioned investigations elucidating the relationship between ferroptosis and diverse female reproductive disorders have yielded novel insights into disease pathogenesis. These findings suggest that elucidating pathogenic mechanisms through the ferroptosis lens, coupled with exploration at molecular and genetic levels, holds promise for implementing positive and negative regulatory interventions targeting ferroptosis. Such approaches may offer novel therapeutic avenues and directions for clinical management of these diseases.

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