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Research Progress on Ferroptosis Mechanism in Endometrial Cancer

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Abstract

Endometrial cancer is one of the most common gynecological malignancies in the female reproductive system. Its incidence has been increasing year by year and it is gradually affecting younger women, posing a serious threat to women's health. In recent years, ferroptosis has become a hot topic in cancer research. Ferroptosis is an iron-ion-dependent programmed regulatory mode that participates in a series of pathophysiological processes under the regulation of mechanisms such as iron metabolism, amino acid metabolism, lipid metabolism, oxidative stress, and glutathione redox. Studies have shown that ferroptosis plays a certain role in the occurrence, development, and treatment of endometrial cancer. This article will review the basic mechanisms of ferroptosis and its research progress in endometrial cancer.

Keywords

Ferroptosis, Endometrial Cancer, Pathogenesis, Treatment

1. Introduction

Endometrial Cancer (EC) is an epithelial malignant tumor originating from the endometrium. It is one of the three most common malignant reproductive system tumors in gynecology. The lifetime risk of a woman developing endometrial cancer is 3% [1]. According to the data from the Global Cancer Center, there were 420,242 new cases and 97,704 deaths of endometrial cancer [2]. Statistics from the National Cancer Center of China show that the number of newly diagnosed endometrial cancer cases is approximately 77,000, with 13,500 deaths. The incidence rate is 7.03 per 100,000 people, and the mortality rate is 1.06 per 100,000 people. It accounts for about 20% - 30% of gynecological tumors [3]. With the delay of

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child-bearing age, the improvement of living standards, the increasing prevalence of obesity, hypertension, diabetes, and infertility, the incidence of endometrial cancer affected by estrogen has been increasing year by year in post-menopausal women, and the global incidence shows a continuous upward trend [4]. Most endometrial cancers have no significant symptoms in the early stage, resulting in patients being diagnosed at the middle or advanced stage, with poor prognosis and high mortality. Due to the lack of effective treatment methods for recurrence, drug resistance, and even metastasis of advanced endometrial cancer, the treatment of EC still faces great challenges.

The concept of ferroptosis was first proposed by Dixon *et al.* in 2012 [5]. It is a new type of cell death different from necrosis, apoptosis, and autophagy. Its core mechanism is the iron-dependent lipid peroxidation reaction, which is characterized by the regulation of the iron metabolism pathway and the glutamate metabolism pathway [6]. In recent years, studies have shown that ferroptosis plays an important role in various cancers, including colorectal cancer, lung cancer, breast cancer, ovarian cancer, and cervical cancer [7]. However, research on ferroptosis in endometrial cancer is still in its infancy. In this paper, we analyze the relationship between ferroptosis and EC from the perspective of the mechanism of ferroptosis, aiming to provide a reference for the clinical treatment of EC.

2. Overview of Ferroptosis

2.1. Definition and Essence of Ferroptosis

Ferroptosis is a unique form of cell death. Its essence lies in the disorder of intracellular lipid oxide metabolism. Under the catalysis of iron ions, a large number of reactive oxygen species (ROS) are produced, which disrupts the cellular redox balance and attacks biological macromolecules [8]. Its typical manifestations include the inactivation of glutathione peroxidase 4 (GPX4) and the accumulation of ROS. The morphological characteristics mainly include cell membrane shrinkage, nuclear pyknosis, reduction in cell volume, increased mitochondrial membrane density, chromatin condensation, and reduction or absence of cristae [9].

2.2. Mechanism of Ferroptosis

Ferroptosis mainly causes disorders in the oxidative metabolism of cell-membrane phospholipids through iron metabolism, lipid metabolism, amino acid metabolism, and glutathione redox. Iron ions catalyze the oxidation of polyunsaturated fatty acid phospholipids through the Fenton reaction, generating a large amount of reactive oxygen species that accumulate in cells, leading to cell-membrane rupture and ultimately cell death [10]-[12]. This process depends on the free divalent Fe^{2+} in the intracellular labile iron pool, the level of which is determined by the dynamic balance of iron import, transport, storage, and export.

2.2.1. Iron Metabolism

Iron is one of the key factors in the occurrence of ferroptosis. Extracellular iron

ions exist in the form of iron-transferrin, which binds to the transferrin receptor (TFRC) on the cell membrane and is transported to the endosome. Then, it is stored in the ferritin complex formed by the ferritin heavy chain (FTH) and light chain (FTL) in the form of heme, iron-sulfur clusters, etc., and the rest remains in the cytoplasm to form the labile iron pool [13]. The driving factor for ferroptosis in cells is the level of iron accumulation. Under normal circumstances, iron metabolism in the body is in a balanced state, but "iron overload" is the core link in the occurrence of ferroptosis and is harmful to the human body. For example, the study by Ahmed *et al.* [14] showed that patients with thalassemia who receive regular blood transfusions experience iron overload and back pain, and their blood glucose levels are higher than normal. Tang *et al.* [15] found that ubiquitin-specific protease 7 (USP7) promotes cardiac death in rats with ischemia/reperfusion by activating the p53/TFR1 pathway to increase iron absorption. The study by Chen *et al.* [16] showed that increasing cellular iron uptake and reducing iron efflux can increase the amount of intracellular free iron, and ferroptosis inducers can also be regulated in this way. Therefore, intracellular ferroptosis and iron metabolism are controlled by iron uptake, iron accumulation, and iron-efflux-induced ferroptosis. It can be seen that iron homeostasis is an important factor in maintaining normal human life activities, and when iron homeostasis is disrupted, diseases progress.

2.2.2. Lipid Metabolism

Lipid metabolism also plays an important role in ferroptosis. It is due to the intensification of the imbalance between oxidation and anti-oxidation in the body, which triggers ROS to oxidize biological membranes, causing the peroxidation of phospholipid membranes rich in polyunsaturated fatty acids (PUFAs). During ferroptosis, the peroxidation of polyunsaturated fatty acids (PUFA) in the plasma membrane disrupts the lipid bilayer, thereby changing the membrane function. The large-scale accumulation of lipid peroxides enhances oxidative stress and ferroptosis [17] [18]. Lipoxygenase (LOX) and phosphorylase kinase G2 (PHKG2) are two key drivers of lipid oxidation. PHKG2 regulates the availability of iron for LOX, while LOX drives ferroptosis through the peroxidation of PUFAs at the bis-allylic position [19] [20]. In addition, some lipid-metabolism-related enzymes, such as acyl-CoA synthetase long-chain family member 4 (ACSL4), can promote the esterification of PUFAs, thereby increasing the content of PUFAs in membrane phospholipids and enhancing the cell's sensitivity to ferroptosis [21]-[23]. In summary, studying the mechanism of lipid metabolism helps to gain a deeper understanding of ferroptosis.

2.2.3. Amino Acid Metabolism

The cystine/glutamate antiporter system (system Xc^-) is an important amino-acid transporter. System Xc^- is located on the cell membrane and consists of two functional subunits, recombinant solute carrier family 3 member 2 (SLC3A2) and recombinant solute carrier family 7 member 11 (SLC7A11). It can effectively main-

tain amino-acid metabolism, is responsible for the exchange of intracellular glutamate and extracellular cystine and the conversion of cystine to cysteine, participates in the production of the endogenous antioxidant glutathione (GSH), and is also a regulatory protein in the ferroptosis pathway [24] [25]. Therefore, abnormal amino-acid metabolism is closely related to ferroptosis, as changes in cystine and glutamate metabolism are associated with reduced GSH synthesis, decreased GPX4 activity, failed cell self-repair, and an increased risk of ferroptosis [26] [27].

2.2.4. Oxidative Stress

Oxidative stress is an important driving force for the occurrence of ferroptosis. The production and increase of intracellular ROS and the decline in the function of the antioxidant defense system lead to the accumulation of lipid peroxidation, which in turn triggers ferroptosis. GPX4 is an important antioxidant enzyme in cells, which can catalyze the reaction between GSH and ROS, thereby scavenging ROS and inhibiting lipid peroxidation [28]. When the activity of GPX4 is inhibited, the level of intracellular ROS increases, lipid peroxidation intensifies, and ultimately, ferroptosis occurs.

2.2.5. Signaling Pathway Regulation

In recent years, studies have found that common tumor-related signaling pathways such as P53, RAS, nuclear factor E2-related factor 2 (Nrf2), and hypoxia-inducible factor (HIF) can also regulate ferroptosis and participate in the occurrence and development of tumors. For example, P53 is an important tumor-suppressor protein that can regulate cell growth and senescence, promote cell apoptosis and DNA repair under stress conditions, and inhibit ferroptosis through multiple pathways [29]. Nrf2 is an endogenous transcription factor that participates in various cellular processes such as ferroptosis, regulation of inflammation, and autophagy. Nrf2 mainly inhibits ferroptosis by activating genes related to iron metabolism, GSH metabolism, and anti-peroxide genes [16].

3. Ferroptosis and Endometrial Cancer

3.1. The Occurrence of Ferroptosis in Endometrial Cancer

An important cause of ferroptosis is the abnormal accumulation of iron in cells, which is associated with many endometrial diseases, such as endometrial hyperplasia, endometriosis, and endometrial cancer [30]. In addition, endometrial hyperplasia caused by overweight, obesity, and high estrogen levels is also an inducing factor for endometrial cancer. Studies have shown that in women with a body mass index (BMI) $\geq 25\ kg/m^2$ or post-menopausal women, the incidence of endometrial cancer is positively correlated with dietary iron intake. The destruction of endometrial cancer cells by ferroptosis is limited, which promotes the occurrence and development of endometrial cancer. There are abnormalities in biological processes such as iron metabolism, lipid metabolism, and oxidative stress in endometrial cancer tissues. These abnormalities may lead to the inhibition of ferroptosis, thereby promoting the survival and proliferation of tumor cells.

3.2. The Relationship between Ferroptosis and the Development of Endometrial Cancer

Many signaling pathways are considered to be involved in the occurrence and development of endometrial cancer, such as the DNA repair process, the PI3K-Akt pathway, the HCAR1/MCT1-SREBP1-SCD1 pathway, and the ferroptosis pathway. Among them, targeting the ferroptosis signaling pathway has been regarded as a new therapeutic strategy for the treatment of endometrial cancer (EC). Studies have found that iron-induced apoptosis is related to autophagy changes. AMP-activated protein kinase (AMPK) mediates the phosphorylation of the autophagy-regulating protein (BECN1) and forms a BECN1-SLC7A11 complex, which inhibits System Xc^- and thereby induces iron-induced apoptosis [31]. The Nrf2-mediated oxidative stress pathway also plays an important role in ferroptosis. In many cancers, Nrf2 mainly inhibits ferroptosis by activating iron-metabolism-related genes (SLC40A1 and MT1G), anti-peroxide genes (AKR1C1 and NQO1), and GSH-metabolism-related genes (SLC7A11 and GCLM). In vitro cell studies have found that the p62-Keap1-Nrf2 signaling pathway inhibits ferroptosis and promotes estrogen-induced endometrial malignant hyperplasia. On the one hand, Nrf2 directly and indirectly regulates the expression of the GPX4 gene, and the GPX4 gene inhibits iron degradation; on the other hand, overexpression of Nrf2 can promote the expression of SLC7A11, thereby increasing the intracellular GSH level and preventing ferroptosis [32]. PTPN18 (also known as BDP1) is a member of the protein tyrosine phosphatase (PTP) family and is related to the occurrence and development of various human cancers. PTPN18 is up-regulated in endometrial cancer tissues, promoting the proliferation and metastasis of EC cells. Studies have shown that knockdown of PTPN18 can increase the intracellular ROS level, inhibit the expression of GPX4 and SLC7A11 by up-regulating the expression of P-P38, and induce ferroptosis in EC cells. GPX4 is a key inhibitor of the ferroptosis pathway. Multiple proteomic analyses have shown that compared with normal endometrial tissues, the expression levels of GPX4 and ferroptosis suppressor protein 1 (FSP1) are higher in early-stage endometrial cancer tissues.

4. Application of Ferroptosis Mechanism in the Treatment of Endometrial Cancer

4.1. Inducing Ferroptosis to Treat Endometrial Cancer

Since ferroptosis occurs commonly in endometrial cancer cells, and endometrial cancer cells are highly sensitive to ferroptosis induction, regulating iron metabolism and oxidative stress in endometrial cancer cells can promote ferroptosis in cancer cells and inhibit tumor cell proliferation. At present, some natural compounds and drugs have been found to be able to induce ferroptosis in endometrial cancer cells. For example, apigenin, a natural flavonoid, can increase iron ions, decrease the content of GSH, increase the content of MDA, increase the protein expression of P62, HMOX1, and ferritin in Ishikawa cells, decrease the protein expression of SLC7A11 and GPX4, and induce ferroptosis in Ishikawa cells [33].

Quinone compounds have good anti-tumor and anti-inflammatory effects. After treating EC cells with juglone, the expression level of the gene GPX4 involved in ferroptosis decreases, and the expression level of HO-1 increases significantly, resulting in ROS accumulation and lipid peroxidation, thereby triggering ferroptosis in cells and achieving anti-cancer effects.

In addition, using ferroptosis inducers to treat endometrial cancer has become a potential therapeutic strategy. For example, juglone is a new type of ferroptosis inducer [34]. FIN56 can induce ferroptosis by regulating intracellular iron metabolism. RSL3 can induce ferroptosis by inhibiting the activity of GPX4. Although these ferroptosis inducers have shown good anti-tumor effects in in vitro experiments and animal models, their clinical application still faces many challenges, such as the toxic side effects of drugs, the stability, and bioavailability of drugs, which still need to be further addressed.

4.2. Ferroptosis Escape Mechanism in Chemotherapy Resistance

Chemotherapy is the main treatment for advanced and recurrent endometrial cancer, but the emergence of drug resistance severely limits its efficacy. Increasing evidence shows that ferroptosis escape is an important mechanism of chemotherapy resistance [35]. Studies have found that cisplatin-resistant cell lines show upregulation of GPX4 expression and a decrease in lipid peroxide levels, and can induce the expression of ferritin and GSH synthase by activating the Nrf2 antioxidant pathway. In addition, drug-resistant cells also upregulate the expression of ferroportin 1 (FPN1), reducing intracellular iron accumulation. The expression of ferroptosis suppressor protein 1 (FSP1) is significantly increased in paclitaxel-resistant cells. FSP1 scavenges lipid free radicals by reducing ubiquinone (CoQ10) and plays an anti-ferroptosis role independently of the GPX4 pathway. Targeted inhibition of FSP1 can restore the toxicity of paclitaxel to drug-resistant cells [36]. Wang *et al.* conducted cluster analysis on endometrial cancer patients by analyzing the differential expression of ferroptosis-related genes and found that when the expression of ferroptosis-related genes in patients was lower, the half-inhibitory concentrations of temsirolimus, erlotinib, and rapamycin were higher, while when the expression of ferroptosis-related genes was higher, the half-inhibitory concentrations of paclitaxel and cisplatin were lower [37].

5. Challenges and Prospects in the Study of Ferroptosis in Endometrial Cancer

5.1. Challenges

Although certain progress has been made in the study of ferroptosis in endometrial cancer, there are still some challenges. Firstly, the specific molecular mechanism of ferroptosis is still not fully understood, especially the regulatory mechanism in endometrial cancer needs to be further studied in depth. Secondly, although existing studies have shown that endometrial cancer cells are highly sensitive to ferroptosis induction, individual differences among different patients and

the heterogeneity of tumor cells may lead to differences in treatment effects. Therefore, how to accurately predict which patients are more sensitive to ferroptosis-inducing treatment is an urgent problem to be solved. Thirdly, how to accurately evaluate the efficacy and safety of ferroptosis in the treatment of endometrial cancer also needs to be addressed. In addition, most current studies still remain at the animal model and in vitro experimental stages, and their clinical application effects still need to be further verified.

5.2. Prospects

In response to the above challenges, future research can be carried out in the following aspects: First, conduct large-scale clinical studies and strengthen the combination of basic research and clinical research to verify the effectiveness and safety of the ferroptosis mechanism in the treatment strategy of endometrial cancer; second, deeply study the specific mechanism of ferroptosis in endometrial cancer, especially its role in gene expression regulation, cell signal transduction, and the interaction with the tumor microenvironment; third, strengthen the exploration of the relationship between ferroptosis and other cell death modes and their common mechanism in the occurrence and development of endometrial cancer; fourth, combine bioinformatics analysis and multi-omics technologies to deeply understand the molecular network and signaling pathways of ferroptosis in endometrial cancer and provide a basis for personalized treatment; fifth, use gene-editing technology and high-throughput screening technology to discover more key molecules involved in ferroptosis regulation and provide targets for the development of new therapeutic drugs.

6. Conclusion

As a new type of cell death mode, ferroptosis has important research value in the occurrence, development, and treatment of endometrial cancer. An in-depth study of the ferroptosis mechanism can not only enrich the theoretical basis of tumor biology but also provide new ideas for overcoming clinical treatment difficulties. Although there are still some challenges at present, with the continuous in-depth research and technological development, the treatment strategy of ferroptosis in endometrial cancer is expected to be realized in the next 5 - 10 years. Achieving this goal requires close cooperation among basic research, clinical medicine, and drug development fields, so as to ultimately benefit patients with endometrial cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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