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Mitochondria-Associated Molecular Mechanisms in Endometriosis - A Mini Review

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Abstract

Endometriosis is a multifaceted disorder, with a variety of factors and processes at play. Research is currently investigating the influence of genetics, epigenetics, signaling pathways, and oxidative stress in its etiology. It is clear that these elements have an effect on the mitochondria in different cells, which are responsible for regulating ROS production, energy metabolism, and signal transduction in endometriosis. An assessment of mitochondrial-related molecular mechanisms in endometriosis is in progress.

Keywords: Mitochondrial; Endometriosis

Abbreviations: ROS: Reactive Oxygen Species; TEM: Transmission Electron Microscopy; ESCs: Endometrial Stromal Cells; OCR: Oxygen Consumption Rate; ECAR: Extracellular Acidification Rate; OXPHOS: Oxidative Phosphorylation; ERK: Extracellular Regulated Protein Kinases; MAPK: Mitogen-Activated Protein Kinase; AKT: Protein Kinase B; NF-κB: Nuclear Factor kappa-B; PDK: Pyruvate Dehydrogenase; LDHA: Lactate Dehydrogenase A; Drp1: Dynamin-related Protein 1; PHB: Prohibitin; Mst1: Mammalian Sterile 20-like kinase 1; NLRP: Nucleotide-binding Oligomerization Domain.

Introduction

Endometriosis is a common gynecological condition in which endometrial tissue, composed of glands and stroma, is found outside the uterus [1]. It is a benign disease, yet its symptoms may resemble those of a malignant tumor, including implantation, invasion, and distant metastasis. Endometriosis affects an estimated 10-15% of women of reproductive age [2] and is found in 40-50% of women with fertility issues [3]. Endometriosis is a complex disorder that has yet to be fully elucidated, with genetic, epigenetic, and environmental factors likely influencing its etiology [4]. At the start of the 20th century, Sampson's menstrual flow retrograde planting theory was the classic explanation for the condition, although it failed to account for the fact that menstrual flow retrograde is common in 90% of women of childbearing age, yet only 15% of these women experience endometriosis. Alternative hypotheses for its origin include genetic disease, inflammation, immune dysfunction, hemorrhagic disease, hormone-dependent disease, organ-dependent disease,

and tumor-related disorders. Recent data suggest that a low body mass index and impaired adipogenesis might indicate an early development of the condition [5], while metabolic dysfunction, chronic inflammation, immune system disruption, and oxidative stress appear to be important factors in the pathology of endometriosis [6]. A review of the pathoetiology and pathophysiology of endometriosis found that alterations in mitochondrial function are key in the numerous cell types and body systems associated with its pathogenesis [5]. As such, this article examines the role of mitochondria in the pathogenesis of endometriosis, as well as potential therapeutic approaches targeting mitochondria.

Mitochondria in Endometriosis

Structure of Mitochondria in Endometriosis

Mitochondrial structure is accompanied by oxygen partial pressure, mitochondrial respiration, and energy requirements [7]. Furthermore, it has been reported that mitochondria alter their morphology and cristae in response to oxidative stress [8]. When exposed to oxidative damage, mitochondria adapt by switching to an elongated shape [7]. The longer shape with expanded cristae is used for more metabolic bioenergetics, glycolysis and ROS production. Mitochondrial ultrastructure in patients with endometriosis was compared with that in non-patients using transmission electron microscopy (TEM).Mitochondria in ESCs are located near the nucleus or near the plasma membrane, and the mitochondria are more elongated, with more rounded cristae and a higher electron matrix density. Mitochondria of ectopic ESCs exhibited 60% class I morphology, rarely showed class II morphology, and some were labeled as class III morphology due to the unique morphological appearance of cristae. Mitochondria in situ ESCs and controls belonged to class I morphology. They are oval in shape with parallel cristae and distinct intracristal spaces [9].

Metabolic Activity of Mitochondria in Endometriosis

Measurements of the oxygen consumption rate (OCR) of mitochondrial oxidative phosphorylation, glycolysis, and extracellular acidification rate (ECAR) were used to determine the level of mitochondrial metabolic activity in endometriosis. Ectopic ESCs' basal OCR increased by 95% when compared to eutopic ESCs and by 51% when compared to controls. In comparison to situ ESCs and controls, ectopic ESCs had a greater rate of proton leakage. Ectopic ESCs had glycolysis levels that were 132% greater than controls and 14% higher than eutopic ESCs [10]. These findings show that the levels of glycolysis and oxidative phosphorylation in ectopic endometrial stromal cells differ depending on the energy needs. In addition, a glycolysis rate assay revealed that the basal glycolysis rates of ectopic ESCs were 64% and 168% higher than those of eutopic ESCs and controls, respectively. In comparison to eutopic ESCs and controls, ectopic ESCs' compensatory glycolysis rates were 21% and 139% higher, respectively. Ectopic ESCs experience more severe hypoxia, causing the mitochondria to switch from OXPHOS to glycolysis. In a recent investigation, it was discovered that endometriosis-affected women had higher amounts of the indicators lactate and ethanol in their peritoneal fluid [11]. Increased energy supply and lactate production encouraged the proliferation of ectopic ESCs, which eventually led to the formation of ectopic lesions. Additionally, this mechanism promotes local fibrosis and an inflammatory response, aggravating endometriosis symptoms [12].

EMT is Induced by Mitochondrial Oxidative Stress

The mitochondrial electron transport chain is the main site of reactive oxygen species generation, mainly in respiratory chain complex I (NADH-Q reductase) and complex III (panthenol cytochrome C reductase). Glucose metabolism intermediates (citrate and succinate) are increased in EMT patients, and it is hypothesized that increased glucose metabolism in EMT patients can lead to increased reactive oxygen species production [13]. There are several high-frequency mutations in the mitochondria of EMT patients with specific genotypes, and these mutations alter the normal electron transport chain structure and increase the rate of electron leakage, leading to increased reactive oxygen species [14]. By detecting 36 biomarkers related to oxidative stress, 23 of them were found to be significantly more expressed in EMT patients, suggesting a peroxidative state in EMT patients [15]. Reactive oxygen can act as a second messenger for cell proliferation, activating intracellular signaling pathways such as ERK1/2, MAPK, and promoting cell proliferation and invasion [16]. It can also activate protein kinase B (AKT), NF-κB and other pathways to promote EMT formation [17].

Molecular Mechanisms Associated with Mitochondria in EMT

IF1

The IF1 protein, encoded by the ATPIF1 gene, was first identified by Pullman and Monroy in 1963 [18] and is highly conserved evolutionarily. When glycolytic metabolism is productive, the metabolites acidify the cytoplasm and intra-mitochondrial matrix and lower the pH, causing IF1 to form dimers and bind two units of FI-ATPase, promoting FI-ATPase formation of dimers and thus inhibiting ATP hydrolysis [19]. It was shown that the expression of IF1 and hypoxia-responsive factor were higher in ectopic lesions than in normal in situ

endothelium and in the in situ endothelium of patients with endothelial. The key enzymes of glycolysis, PDK1, and LDHA, were also highly expressed in ectopic lesions, suggesting that ectopic lesions grow similarly to tumor cells, using glycolysis to provide energy, while mRNA expression did not differ significantly between groups, suggesting post-transcriptional regulation of IF1 expression. Previous studies have shown that overexpression of IF1 in tumor cells inhibits oxidative phosphorylation of mitochondria and promotes glycolytic metabolism [20], and overexpression of IF1 also protects the structure of the inner mitochondrial membrane, inhibits the clustering of the proapoptotic proteins Bax and Drp1 in the outer mitochondrial membrane, and prevents the release of Cytc from the inner mitochondrial membrane, thus resisting apoptosis [21]. In addition, IF1 promotes cell proliferation, invasion, and survival by initiating ROX-mediated changes in cellular adaptation dependent on the NFrB system [22]. Thus, high endometrial expression of IF1, on the one hand, facilitates endometrial proliferation and repair, while on the other hand, it may become a trigger for endometriosis formation in response to hypoxic stress stimulation [23].

PHB

Prohibitin (PHB) is a highly conserved protein found in bacteria, plants, yeast, and mammals, and is part of the Stomatin/Prohibitin/Flotillin/HflK/C (SPFH) family. Studies have shown that PHB1 and the high-molecular-weight ring complex formed by PHB2 are mainly located in the inner membrane of mitochondria, and serve as a molecular chaperone to preserve mitochondrial shape and function, as well as influencing cellular energy metabolism, proliferation, apoptosis, and nuclear transcription [24]. Abnormal expressions of PHB have been linked to mitochondrial dysfunction, oxidative stress injury, and various diseases, including ovarian epithelial tumors, prostate cancer, breast cancer, inflammatory bowel disease [25], insulin resistance/type 2 diabetes, and obesity. Moreover, PHB is highly expressed in the eutopic endometrium of endometriosis patients and is located in the nuclei and cytoplasm of endometriotic stromal cells (ESCs). It has been suggested that PHB can alter the energy metabolism of ESCs, modulate their proliferation and cell cycle, and affect the development of endometriosis [26].

Mst1

Studies have demonstrated that the expression of Mst1 in endometriosis endometrium is significantly lower than that of normal endometrium. Mechanistically, it has been revealed that restoring Mst1 through p53 can significantly increase the post-transcriptional phosphorylation of Drpl at Ser616, inhibit the transcriptional activity of Parkin, promote mitochondrial fission, and simultaneously inhibit mitophagy. Drpl-related mitochondrial fission can initiate caspase9-mediated mitochondrial apoptosis and inhibit F-actin-dependent pseudopodia formation through the HtrA2/Omi-related pathway [27]. Additionally, Parkin-mediated mitophagy can induce energy metabolism disorders, leading to cellular oxidative stress and cytoplasmic calcium iron overload. Ultimately, Mst1 induces apoptosis of ESCs and inhibits their migration by triggering excessive mitochondrial apoptosis and abnormal mitophagy. It has been confirmed that NR4A/miR-181c is the upstream signal of Mst1 inactivation in endometriotic endometrial cells. These findings demonstrate that the Mst1 gene in the Hippo signaling pathway is closely associated with the regulation of tissue regeneration, the proliferation of adult stem cells, and the occurrence of cancer [28,29].

NLRP3

NLRs, a family of pattern recognition intracellular receptors [30], have a fundamental role in innate immunity and the inflammatory response of organisms [31]. Reactive oxygen species (ROS) have been identified as a key factor in the formation and activation of NLRP3 inflammatory vesicles, which are composed of NLRP3, ASC, and pro-caspase-1 [32]. Elliott, et al. found that mouse NLRP3 and caspase-1 interact with mitochondrial lipid cardiolipin, which is externalized to the outer mitochondrial membrane in response to ROS stimulation. This leads to the assembly and activation of the vesicles, with mitochondria playing an essential role [33]. It has been observed that NLRP3 inflammatory vesicle activation is significantly increased in peritoneal fluid macrophages from patients with endometriosis, resulting in a notable increase in the secretion of IL-1β. This can activate the AKT-mTOR pathway in endometrial mesenchymal cells, thereby promoting their proliferation and migration [34].

Discussion

Treatment options for endometriosis currently available are able to suppress ovarian function, yet there is no cure. This form of treatment is not suitable for women attempting to become pregnant, thus research into new drugs that do not suppress ovarian function have been initiated [35]. Scientists have focused on genes and proteins that may affect metabolic pathways to promote the survival and growth of endometriosis cells. Estrogen is not only involved in hormone action, but also in various functions such as mitochondrial biosynthesis and energy metabolism. Estrogen can also regulate the expression of mitochondrial genes, thus influencing ATP production, energy conversion, ROS production, and antioxidant defense [36]. Genes downstream of estrogen involved in mitochondrial metabolic biosynthesis, such as peroxisome proliferator-activated receptor-gamma coactivator 1α, may be potential targets

for non-hormonal therapy of endometriosis. Pain associated with endometriosis may be caused by superoxide anion from methemoglobin, and compounds and natural substances that can inhibit superoxide anion/ROS are being explored as potential therapeutic candidates [37].

Conclusion

The pathological etiology and pathophysiology of endometriosis are very complex, and many factors and processes are involved in its occurrence and development. Current research mainly addresses the role of genetic susceptibility, epigenetic regulation, altered signaling pathways, and oxidative stress. Most of the factors and processes associated with endometriosis affect mitochondrial function in many different cells, so mitochondrial function can be altered to improve cellular energy homeostasis, balance oxidative stress, inhibit proliferation of endometriotic lesions. Since the extracellular environment has several aberrant signaling pathways, this may mean that there are multiple opportunities for the extracellular environment to mediate endometrial growth, and the targeting of specific kinases can trigger hyperactivation of compensatory pathways.

Therefore, to successfully treat endometriosis by inhibiting these pathways, more information is needed on kinase activation, the extracellular environment of endometriosis, and the effects of altering this interaction.

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