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Research Progress on the Clinical Application of Endoplasmic Reticulum Stress in Polycystic Ovary Syndrome

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Abstract: Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder in reproductive-aged women. It is characterized by infrequent or absent ovulation, hyperandrogenemia, and polycystic-like changes in the ovaries, among other clinical features, which affect the reproductive and metabolic health of patients. Increasing studies have shown that endoplasmic reticulum stress (ERS) plays a crucial role in multiple pathological and physiological processes of PCOS, providing a new research direction for the precise diagnosis and treatment of this disease. This article comprehensively reviews the potential value of endoplasmic reticulum stress-related markers in the diagnosis and prognosis assessment of PCOS, as well as the clinical progress and challenges of targeted ERS treatment, with the aim of providing new ideas for the clinical management of PCOS.

Keywords: Polycystic Ovary Syndrome; Endoplasmic Reticulum Stress; Biomarkers; Targeted Therapy; Precision Diagnosis and Treatment.

1. Introduction

Polycystic Ovary Syndrome (PCOS) affects approximately 5% to 20% of women of childbearing age worldwide, being the most common chronic reproductive and metabolic endocrine disorder [1]. Its main characteristics include chronic anovulation, hyperandrogenemia (HA), insulin resistance (IR), and ovarian polycystic-like changes, etc. [2]. It is not only closely related to infertility but also significantly increases the risk of patients developing various metabolic complications such as cardiovascular and cerebrovascular events, type 2 diabetes, etc., as well as the occurrence probability of long-term adverse outcomes such as venous thromboembolism and endometrial cancer, seriously affecting the reproductive health and long-term prognosis of patients [3]. Studies have shown that endoplasmic reticulum stress occurring in follicles is a key component of the pathophysiology of polycystic ovary syndrome (PCOS) [4]. Endoplasmic reticulum stress (ERS) is a situation where the demand for protein folding and the protein folding capacity of the endoplasmic reticulum are unbalanced, and unfolded or misfolded proteins accumulate in the endoplasmic reticulum, which is a disruption of endoplasmic reticulum homeostasis [5]. ERS regulates key aspects such as ovarian granulosa cell apoptosis, insulin secretion function, and lipid metabolism homeostasis [6], providing a core target for clinical translation. Currently, the core direction of clinical translation application is focused on the clinical validation of ERS-related diagnostic markers, the clinical efficacy of targeted ERS treatment, and the challenges of clinical translation. This article will integrate traditional Chinese and Western treatment strategies and multiple research evidence to provide practical references for the precise diagnosis and treatment of PCOS.

2. Clinical Translation of ERS-related Diagnostic and Prognostic Markers

The diagnosis of polycystic ovary syndrome (PCOS) currently follows the internationally recognized Rotterdam criteria [7]: oligoovulation or anovulation; clinical manifestations of hyperandrogenism and/or hyperandrogenemia; polycystic ovary morphology (PCOM); two out of the three criteria must be met and other diseases that may cause hyperandrogenism and abnormal ovulation must be excluded. The early symptoms of PCOS are not typical and the clinical manifestations are diverse. Approximately one-third or more of the patients have the problem of delayed diagnosis [8]. Relevant studies have shown that endoplasmic reticulum stress is closely related to multiple pathological and physiological processes of female PCOS [9]. ER-related markers can provide guidance value for the early clinical diagnosis and prognosis of PCOS.

2.1. Clinical Value of a Single ERS Marker

The main pathways of endoplasmic reticulum stress are as follows: the PERK pathway involving eIF2α and ATF4, the IRE1 pathway involving IRE1α and XBP1, and the ATF6 pathway [10]. When endoplasmic reticulum stress occurs, PERK, IRE1, and ATF6 are activated and separated from GRP78, thereby inducing the transcription of C/EBP homologous protein (CHOP) and glucose-regulated protein 78 (GRP78). GRP78, CHOP, ATF4, and XBP1 are often used as markers of endoplasmic reticulum stress activation [11]. GRP78 belongs to the heat shock protein 70 (HSP70) family, which can correct misfolded and assembled proteins and prevent the transport of misfolded proteins or protein subunits [12]. It is the central molecule of endoplasmic reticulum stress and studies have shown that GRP78 is significantly elevated in the serum, granulosa cells, and follicular fluid of PCOS patients, reflecting local stress in the ovary and the degree of

insulin resistance [13]. Its decrease after treatment can reflect the therapeutic effect, and its continuous high expression indicates an increased risk of metabolic complications [14]. CHOP is a pro-apoptotic marker. In polycystic ovary syndrome (PCOS), high androgen levels activate endoplasmic reticulum stress in granulosa cells, which upregulates the expression of death receptor 5 (DR5) and CHOP, thereby inducing granulosa cell apoptosis and triggering follicular closure [15]. It is positively correlated with ovarian stromal fibrosis and ovulation disorders [16]. In addition, endoplasmic reticulum stress upregulates CHOP expression, induces ovarian granulosa cell apoptosis, and is also related to the reduction in the number of blastocysts [17]. Its level has certain reference significance for predicting the embryo quality of ovulation induction treatment. ATF4 participates in the regulation of energy homeostasis and glucose metabolism. Di et al. [18] revealed that ATF4 is highly expressed in granulosa cells (hGCs) of PCOS patients with obesity and insulin resistance, confirming that the increase in ATF4 is an important factor for lipid accumulation and abnormal transduction of insulin signaling in PCOS patients, and can be used as an auxiliary diagnostic tool and for metabolic risk stratification. XBP1 is highly expressed in PCOS granulosa cells, reflecting the activation of the IRE1 pathway, and is associated with insulin resistance and hyperandrogenemia [19, 20]. It can be used as a combined diagnostic marker for metabolic-reproductive damage. Although a single ER stress marker cannot directly diagnose PCOS, it can serve as an early sensitive indicator of endoplasmic reticulum stress activation, distinguishing PCOS patients from healthy individuals, especially for adolescent PCOS patients, whose puberty development is often similar to the characteristics of PCOS symptoms. Combined metabolic indicators can improve diagnostic efficacy and can also be used as indicators of disease progression risk and prognosis stratification.

2.2. Development and Validation of a Multi-Index Combined Diagnostic Model

Constructing a multi-index combined diagnostic model for the ERS gene can significantly improve the sensitivity and specificity of PCOS diagnosis. Based on bioinformatics, Niu et al. [21] integrated the differentially expressed genes (DEGs) between the PCOS group and the control group with the ERS gene list in the database, screened out 14 differentially expressed ERS genes related to PCOS (DE-ERS genes), and then selected 8 key molecules as diagnostic indicators to construct a diagnostic model. This model showed good diagnostic efficacy in the training set (AUC = 0.983) and the validation set (AUC = 0.802), accurately predicting the risk of PCOS onset, providing quantitative references for clinical decision-making, and providing objective molecular diagnostic evidence for PCOS without obvious anovulation and hyperandrogenism. In addition, A study by Zhang et al.[22] discovered two low-expression genes NQO1 and NPY, as well as three high-expression genes TFEB, JUP, and ATF4 in PCOS cases. Based on these 5 key genes, a diagnostic model was constructed, and the areas under the ROC curves of NQO1, TFEB, JUP, NPY, and ATF4 in the validation set were 0.629, 0.600, 0.629, 0.543, and 0.743, respectively. This indicates that the PCOS diagnostic model constructed based on these 5 key genes has high reliability, enriching the exploration of the role of endoplasmic reticulum stress in polycystic ovary syndrome and potential therapeutic targets, and providing new insights for the early diagnosis of PCOS. In summary, the multi-index combined diagnostic model has both high sensitivity and specificity, not only filling the research gap of ERS-related diagnostic markers in PCOS, but also providing important experimental evidence and theoretical support for analyzing the disease pathogenesis and developing targeted treatment plans.

3. Clinical Translation Study of Therapeutic Strategies Targeting ERS

The imbalance of endoplasmic reticulum stress-mediated apoptosis, metabolic disorders and inflammatory responses of ovarian granulosa cells is one of the core pathological mechanisms of PCOS. Targeted regulation of the ERS pathway has become a new direction for the treatment of PCOS. The key to targeted therapy lies in precisely regulating the three branches of the pathway [23] (PERK-eIF2α-ATF4, IRE1α-XBP1, ATF6), correcting excessive activation of ERS and restoring endoplasmic reticulum homeostasis.

3.1. The ERS Regulatory Mechanism of Traditional Medicines and Their Clinical Applications

Metformin is a common hypoglycemic drug that is often used to treat polycystic ovary syndrome patients to improve insulin resistance. Studies have shown that metformin inhibits p38 MAPK phosphorylation, alleviates ERS induced by testosterone, reduces the expression of GRP78, CHOP and XBP1-s, significantly improves insulin resistance, increases ovulation rate by more than 30%, and reduces abnormal COC expansion induced by androgens [11]. Metformin can improve insulin resistance, menstrual regularity and androgen levels, and is particularly suitable for obese or insulin-resistant patients with polycystic ovary syndrome. Combined with other treatments, it may enhance fertility [24]. Metformin has been recommended as a treatment option for patients with PCOS with abnormal glucose regulation, insulin resistance or diabetes, and its efficacy is proven.

3.2. Exploration of ERS Inhibitors

Endoplasmic reticulum stress plays a crucial role in the occurrence and development of PCOS. The exploration of endoplasmic reticulum stress inhibitors can provide new directions for the treatment of PCOS. TUDCA (taurine deoxycholic acid) is a specific ER stress inhibitor. Azhary et al. [25] found that in PCOS patients and granulosa cells induced by dehydroepiandrosterone, the accumulation of advanced glycation end products (AGE) and the expression of AGEs (RAGE) in granulosa cells were upregulated. Injecting RAGE inhibitors FPS-ZM1 or TUDCA into PCOS mice could reduce the expression of RAGE and the accumulation of AGEs in granulosa cells, improve their estrous cycle, and reduce the number of closed antral follicles. In addition, Zhang et al. [26] found that the ER stress inhibitor 4-PBA (4-phenylbutyric acid) reduces iron apoptosis induced by palmitic acid (PA) in PCOS ovaries by inhibiting ER stress, thereby improving the symptoms of PCOS-like conditions induced by PA. The application of ER stress inhibitors still requires further clinical research and experimental verification to provide guidance for the precise treatment of PCOS.

3.3. The Clinical Translational Potential of Natural Compounds

The treatment of polycystic ovary syndrome involves not only medication but also dietary and dietary factors, which play a significant role in disease management. Some natural compounds also contribute to the treatment of PCOS. Jabarpour et al. [27] demonstrated that astaxanthin (ASX), through its antioxidant activity as a natural supplement, modifies the molecular pathways of endoplasmic reticulum stress, down-regulates the expression of GRP78 and CHOP, up-regulates the activity of ATF4, enhances antioxidant capacity, and significantly increases the rates of high-quality oocytes, high-quality embryos, and oocyte maturation ($P<0.05$). ASX is a natural carotenoid compound found in various seafood and microorganisms. It can be extracted for the treatment of PCOS, but the optimal supplementation dose and treatment course of ASX still require further research.

3.4. The ERS-mediated Mechanism of Traditional Chinese Medicine's Unique Therapeutic Methods

The traditional Chinese medicine (TCM) characteristic therapies also have certain effects in the treatment of PCOS. Herbal compound prescriptions: The core of PCOS treatment lies in balancing spleen and kidney, tonifying the kidney and strengthening the spleen, and mutual support between spleen and kidney [28]. The Liver-Daoyu Tonifying Kidney Decoction inhibits ferroptosis through the PERK pathway and ERS, and improves the damage of mouse ovarian tissue [29]; the Tonifying Kidney and Nourishing Essence Decoction may increase the number and function of oocytes by inhibiting ERS [30]; it has been found that the Tonifying Kidney and Regulating Menstruation Formula promotes ERα expression and inhibits endometrial endoplasmic reticulum stress-related in COH mice, improving the endometrial receptivity of COH mice [31]; the Tonifying Kidney and Regulating Menstruation Formula can activate the ERK pathway, inhibit GRP78 expression and ERS, promote endometrial angiogenesis, and improve endometrial receptivity [32]; Studies by PAN et al.[33] have shown that the "tonifying the kidney, resolving depression, regulating the flow" formula can further delay the apoptosis of ovarian granulosa cells mediated by endoplasmic reticulum stress (ERS) by inhibiting the PERK-ATF4-CHOP signaling pathway and down-regulating the expression of GRP78. the Qi-Boosting and Diabetes-Relieving Formula can inhibit the activity of PERK, eIF2α, and CHOP through the PERK-eIF2α-CHOP signaling pathway, improve endoplasmic reticulum stress to protect min6 cells [34]. Acupuncture treatment: Selecting acupoints such as Sanyinjiao, Guanyuan, uterus, and Fenglong [35], acupuncture on the Sanyinjiao and Zusanli acupoints of rats, the expression of the classic product of ERS, phosphorylated protein kinase-like endoplasmic reticulum kinase antibody (p-PERK), is down-regulated, while the expressions of apoptosis-related proteins C/Enhancer Binding Homologous Protein (CHOP), B-cell lymphoma-2 gene (Bcl-2), and Caspase-12 are reduced, suggesting that acupuncture treatment can effectively inhibit ERS in fat cells during obesity [36]. In conclusion, the research on the ERS-mediated mechanism in TCM treatment has laid a theoretical foundation for the TCM treatment of PCOS, and individualized application based on the patient's condition in clinical practice is the key to treatment.

4. Clinical Transformation Challenges and Solutions

At present, studies on ERS-related markers in PCOS have achieved certain results, but there are still challenges in clinical translation. Most of the existing studies are small-scale, lacking unified detection standards, and require large-scale multi-center research to verify the specificity and sensitivity of the markers. Some markers (such as granulosa cell genes) have invasive sampling methods. Whether non-invasive detection techniques in serum/urine can be developed to improve clinical applicability is also an issue. In the future, an integrated model of ERS markers - clinical phenotypes - prognosis can be constructed to achieve precise diagnosis, individualized treatment, and risk prediction throughout the entire process of PCOS management.

5. Summary and Outlook

In conclusion, the ER-related diagnostic markers have the potential to enhance the accuracy of PCOS diagnosis and can also serve as monitoring indicators after PCOS treatment. Targeted ER therapy (including traditional drugs, ER inhibitors, and integrated traditional Chinese and Western medicine regimens) can effectively improve metabolic and reproductive outcomes, and possess significant clinical translational value. In the future, the development of ovarian tissue-specific ER regulatory agents, the construction of a multi-omics (genomics + proteomics + metabolomics) combined diagnostic model, the conduct of real-world studies to accumulate long-term efficacy and safety data, and the deepening of the association mechanism research between TCM syndrome differentiation and the ER pathway will promote the optimization of individualized treatment plans for PCOS.

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