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Research Progress of TGF-B Signaling Pathway Involved in Intrauterine Adhesion

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Abstract: Intrauterine adhesion (IUA) is one of the main causes of secondary infertility, and its pathogenesis is mainly related to abnormal repair, fibrosis and scar formation after endometrial basal layer injury. In recent years, studies have shown that transforming growth factor-β signaling pathway plays a key role in the occurrence, development and treatment of IUA. In particular, TGF-β1 plays an important role in the process of endometrial fibrosis by inducing excessive deposition of extracellular matrix (ECM) and promoting epithelial-mesenchymal transition (EMT). In addition, TGF-β signaling pathway interacts with other signaling pathways (such as Wnt and Hippo) to further affect the pathological process of IUA. This article discusses the potential application of TGF-β signaling pathway in IUA, and the intervention of TGF-β signaling pathway by cells, exosomes, drugs and other molecular targets provides new ideas for the occurrence, improvement and prevention of IUA.

1. Introduction

Intrauterine adhesion (IUA) seriously affects women's fertility and overall reproductive health. At present, intrauterine adhesion is mainly treated by hysteroscopic adhesion separation, but the postoperative recurrence rate is high, and some patients have a poor response to treatment, with many limitations. Therefore, it is of great significance to further study the pathogenesis of IUA and find new effective treatment methods. In recent years, more and more studies have shown that Transforming growth factor β (TGF-β) signaling pathway plays a key role in the occurrence, development and treatment of IUA. Tgf-β1 is the main cytokine in this pathway. It plays an important role in the process of endometrial fibrosis by inducing excessive deposition of Extracellular matrix (ECM) and promoting Epithelial-mesenchymal transition (EMT). In addition, TGF-β signaling pathway interacts with other signaling pathways (such as Wnt and Hippo signaling pathways) to further affect the pathological process of IUA. In-depth exploration of the mechanism of this pathway is expected to provide theoretical basis for the development of new therapeutic strategies.

2. Definition and pathogenesis of intrauterine adhesions

IUA refers to a disease in which the uterine cavity is partially or completely closed due to adhesions

or fibrosis of the endometrium caused by basal layer damage caused by uterine surgery (e.g., induced abortion or postpartum curettage) or infection (e.g., endometrial tuberculosis) [1].Its clinical manifestations mainly include infertility, stillbirth, abortion, dysmenorrhea, abnormal menstrual volume or amenorrhea, which seriously affect female fertility and overall reproductive health [2].The pathogenesis of IUA mainly involves abnormalities in the repair process of endometrial injury, leading to fibrosis and scar formation. Intrauterine surgery is the key cause of most cases of IUA. Damage to the basal layer of the endometrium during the operation will trigger local inflammatory response and activate a variety of cytokines and growth factors, such as TGF-β1, which will induce EMT of endometrial stromal cells, promote excessive deposition of ECM, and eventually lead to fibrosis and scar formation [3].In addition, individual genetic factors and immune status may also affect the pathogenesis of IUA. For example, the polymorphism of some genes may make individuals more susceptible to IUA, and the abnormal activation of the immune system may lead to the attack of their own endometrial tissue, aggravating the degree of damage and fibrosis [4].

3. Overview of the TGF-β signaling pathway

TGF-β signaling is a stable dimeric domain that contains a cysteine structure linked by disulfide bonds. It is composed of extracellular ligands, cell membrane surface receptors, and intracellular SMAD proteins. The TGF-β family ligands are divided into the TGF-β/Nodal/Activin subfamily and the BMP subfamily, which initiate signaling by binding to specific receptors [5].The TGF-β1/Smads signaling pathway is a classical fibrosis signaling pathway, which is composed of TGF-β1, TGF-β1 receptor (TGF-βR), Smads protein family and regulatory genes. TGF-β1 activates signal transduction to the downstream Smads family by binding to its receptors. TGF-β1 is the most powerful fibrogenic factor discovered so far, and plays a central role in the pathogenesis of fibrotic diseases. Tgf-β1 can bind to specific receptors in fibroblasts to activate multiple signaling pathways [6].At the same time, it can promote fibroblasts to synthesize α-smooth Muscle Actin (α-SMA) and induce cells to produce a variety of extracellular matrix components, as well as enzymes and molecular chaperones involved in the process of collagen assembly and cross-linking. In addition, activated fibroblasts are able to secrete a variety of cytokines, which interact with epithelial cells, immune cells, and endothelial cells through paracrine effects [7].As a member of the TGF-β family, Tgf-β1 plays a crucial role in inducing and promoting the differentiation and proliferation of mesenchymal cells, secreting extracellular matrix-related components, and as a major cytokine in the initiation and termination of tissue repair downstream of the TGF-β/Smad signaling pathway [8].TGF-β signaling pathway plays an important role in the occurrence, development and treatment of intrauterine adhesions. In-depth study of the mechanism of action of these signaling pathways is of great significance for the development of new therapeutic strategies and improvement of therapeutic effects.

4. TGF-β signaling pathway is involved in IUA

4.1 Cellular pathways regulate TGF-β signaling

To study the repair effect of Human umbilical cord blood mesenchymal stem cells (hUCB-MSC) on IUA by establishing an animal model. The results suggest that hUCB-MSC may repair the damaged endometrium in rabbit intrauterine adhesion model by increasing the number of endometrial glands and improving the level of fibrosis by regulating the expression of TGF-β1 [9].Human Wharton's jelly mesenchymal stem cells (hWJ-MSCs) derived from umbilical cord have strong self-renewal and proliferation ability. Some studies have found that hWJ-MSCs transplantation may repair endometrial injury and reduce epithelial fibrosis in IUA rats through TGF-β1-mediated inhibition of RhoA/ROCKI signaling [10].M2 macrophages may inhibit TGF-β1-induced fibrosis of human

endometrial stromal cells by negatively regulating the expression of COL1A1 and α-SMA. Targeting macrophage phenotype and promoting macrophage polarization to M2 may become a new strategy for the clinical treatment of IUA [11].Although the TGF-β1 pathway is considered a key driver of IUA pathogenesis, uterine cellular heterogeneity and different expression profiles between different cell types highlight the importance of single-cell studies [12].These studies provide new insights into potential therapeutic targets for IUA by regulating the TGF-β signaling pathway, but further in vitro and in vivo studies are needed to verify the clinical application potential of these targets, especially through long-term follow-up and multi-factor mechanism studies to promote the clinical transformation of IUA treatment.

4.2 Exosomes regulate the TGF-β pathway

Exosomes are nanoscale vesicles secreted by mesenchymal stem cells, containing a variety of bioactive molecules, such as miRNA and proteins, which can regulate intercellular signal transduction,promote tissue repair and regeneration, and play an important role in the treatment of IUA [13].derived exosomes were found to be enriched in specific mirnas that inhibit TGF-β signaling by targeting key molecules of the Tgf-β signaling pathway, such as Smad2 and Smad3. Thus, it downregulates TGF-β signaling pathway and reduces endometrial fibrosis [14].For example, miR-122 is a key regulator in the repair of endometrial fibrosis. miR-122 inhibits fibrosis by directly targeting the 3' untranslated region of Smad family member 3 and down-regulating the TGF-β/Smad pathway to inhibit its expression, which provides a new idea for the clinical treatment of IUA [15].Bone Marrow Mesenchymal Stem Cell-Derived Exosomes (BMSC-Exo) containing miR-340 could down-regulate the expression of TGF-β1. It can inhibit the expression of fibrosis genes induced by TGF-β1 in endometrial stromal cells and play an anti-fibrosis role [16].As a cell-free therapy, exosomes have the advantages of low immunogenicity and reusability. Exosomes can improve IUA by regulating the TGF-β/Snad signaling pathway, which is considered to be a potential treatment strategy for IUA. However, the current research on exosomes in IUA is still in its infancy, and there are certain limitations in the treatment strategy and application scope. Moreover, its safety and long-term effect in humans still need to be further verified.

4.3 Drugs regulate the TGF-β signaling pathway

Experimental studies have confirmed that dulaglutide can reduce inflammatory response by inhibiting M1 macrophage polarization and inflammatory factor release, and may improve endometrial fibrosis by inhibiting EMT through TGF-β/Smad2 signaling [17].Another study used transgenic silkworm cocoon to extract silk fibroin and FGF1, and formed FGF1-SS hydrogel after removing urea and salt by dialysis. Fgf1-ss hydrogel can stably release FGF1 and inhibit the formation of fibrosis in the endometrial stromal cell injury model through the TGF-β/Smad pathway, which has a long-term therapeutic effect on endometrial injury [18].Through animal experiments, adiponectin may inhibit the activation of NLRP3 inflammasome and TGF-β1/Smad2 signaling pathway to reduce endometrial inflammation and inhibit the progression of fibrosis in rats with intrauterine adhesions [19].Bushen Huayu Decoction can reduce the expression of fibrosis markers TGF-β1, Smad2 and Smad3, increase the expression of Smad7 in the uterine tissue of IUA rats, improve the degree of fibrosis injury through TGF-β1/Smads signaling pathway, and promote the repair of endometrium. This study provides a new direction for the subsequent application of integrated traditional Chinese medicine in the treatment of IUA [20].In general, these drugs have some potential in the treatment of endometrial fibrosis by regulating TGF-β signaling pathway, but there are also challenges such as limitations of mechanism of action, problems of drug characteristics, insufficient efficacy and safety. In the future, further optimization of drug design and treatment

strategies are needed to improve its clinical application value.

4.4 Other

Overexpression of Glycine N-methyltransferase (GNMT) reduces the degree of IUA fibrosis by inhibiting the TGF-β1/Smad3 signaling pathway and reducing the phosphorylation level of its downstream Smad3 protein [21].The efficacy of Eupatilin on TGF-β-induced endometrial fibrosis was assessed by examining morphological changes and expression levels of fibrosis markers using immunofluorescence staining and quantitative real-time reverse transcription-polymerase chain reaction. It provides a new idea for the treatment of endometrial fibers [22].Acupuncture can reduce the expression of TGF-β1 signaling pathway, inhibit the excessive accumulation of ECM, improve endometrial fibrosis in IUA rats, reduce the inflammatory response of uterine tissue, enhance endometrial receptivity, and promote endometrial repair[23].Stranded non-coding Rnas can promote endometrial fibrosis by activating the TGF-β1/Smad signaling pathway, suggesting that inhibition of long non-coding Rnas may represent a promising therapeutic option for inhibiting endometrial fibrosis[24].Candida albicans (C.albicans) infection may promote the development of IUA by activating the TGF-β/Smad signaling pathway, leading to more severe endometrial fibrosis. The regulatory relationship of C.albicans-TGF-β/Smad-IL-6 axis can be further verified. To find new ideas and potential targets for the prevention and treatment of IUA [25].These studies suggest that TGF-β/Smad signaling plays a key role in the pathogenesis of endometrial fibrosis and IUA. It provides a potential therapeutic strategy for the treatment of endometrial fibrosis.

5. Discussion

As a common gynecological disease, IUA seriously affects women's fertility and reproductive health. In recent years, with the in-depth study of the pathogenesis of IUA, the key role of TGF-β signaling pathway has been gradually revealed. This article mainly describes the effects of cells, exosomes, drugs and other molecular targets on the generation, development and treatment of intrauterine adhesions through the intervention of TGF-β signaling pathway. However, despite the progress made in basic research, the clinical management of IUA still faces many challenges. The limitations of existing treatment methods, the efficacy and safety of drugs, and the long-term effect of emerging technologies such as exosomes in humans still need to be further verified. Future research needs to further explore the interaction mechanism between TGF-β signaling pathway and other signaling pathways, develop more effective animal models, and strengthen the translation research from basic research to clinical application. In addition, with the development of single-cell sequencing technology, in-depth study of endometrial cell heterogeneity and its role in IUA will help to further reveal the pathogenesis of IUA and provide the possibility of precision treatment. In conclusion, TGF-β signaling plays a central role in the occurrence, development, and treatment of IUA. Future research should focus on in-depth analysis of the complex regulatory mechanism of this pathway, explore the synergistic mechanism of multiple factors, and promote the clinical transformation of more innovative treatment strategies, in order to provide more effective and safer treatment options for IUA patients and improve their prognosis and quality of life.

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