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Advances in stem cell therapy for intrauterine adhesions

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Abstract: Intrauterine adhesions are an important problem in the field of obstetrics and gynecology, which seriously affects female fertility and reproductive health. In recent years, stem cells have gradually attracted attention in the treatment of intrauterine adhesions due to their unique biological characteristics and potential therapeutic value. In this paper, the research progress of stem cells in this field is systematically described, including its mechanism of action, clinical research results, challenges and prospects, in order to provide reference for further research and clinical application in this field.

Intrauterine adhesions (IUA) as one of the most common reproductive diseases in women, its prevalence has increased widely in the past decade, and the current big data shows that the main factor leading to the occurrence of IUA is the increase in the use of intrauterine surgery, such as: hysterectomy, dilation and curettage. Current studies have shown that the main cause of IUA is the serious damage to endometrial integrity caused by uterine manipulation [1]. To date, hysteroscopic adhesion-release surgery is considered the treatment of choice for patients with IUA. Other postoperative adjuvant treatments, including hormones, IUD, hyaluronic acid gel and intrauterine balloon, also achieved a certain effect. However, in severe intrauterine adhesives, pregnancy rates remain unsatisfactory due to failure of functional endometrial regeneration, which is associated with poor pregnancy outcomes and high recurrence adhesion rates. Therefore, it is critical to find appropriate treatment strategies to overcome existing problems[2].

1. Pathogenesis of intrauterine adhesions

1.1. Theory of active fibrocyte proliferation

1.1.1. TGF-β

Studies have shown that TGF-β superfamily mainly includes TGF-β (TGF), inhibitin, Nodal (Nodal), bone morphogenetic proteins (BMPs), growth differentiation factors (BMPs) and anti-Muller (Mol). Among them, TGF-β protein (TGF) is an important regulatory gene, which plays an important role in cell proliferation and differentiation. TGF-β plays an important role in a variety of diseases. TGF-β1 has three different isomers, namely TGF-β1, β2,3[3].

TGF-β1 is widely present in human beings and a variety of biological tissues, and is a key factor in fibrosis of multiple organs such as lung, kidney, liver and heart [4-7]. LiNa L et al. [8] constructed a rat model of IUA using curettage, and the results showed that the level of TGF-β1 and TGF-β1 in the tissue of rats in the curettage group was significantly increased after curettage, suggesting that TGF-β1 may be involved in intrauterine fibrosis. Honglei Z et al. [9] found that the expression of TGF-β1 was significantly increased in endometrial tissues of IUA patients. Some studies [10] found that the expression of TGF-β1 gene and protein was significantly increased in endometrial tissues of patients with severe IUA, and the abnormal increase was closely related to the disease of IUA. To explore the molecular mechanism of TGF-β1 regulation of endometrial hyperplasia, and to use this as a target for intervention, is the focus of current research in the field of endometriosis.

1.1.2. TGF-β/Smad pathway

A large number of studies have shown that TGF-β/Smad signaling pathway is involved in the occurrence and development of endometriosis. Some research teams believe that TGF-β/Smad is an important regulatory factor. TGF-β1 may activate TGF-β1/Smad signaling by interacting with its downstream downstream molecule (TGF-βRII). In this process, TGF-β1 promotes the phosphorylation of TGF-βRII by recruiting TGF-βRII (TGF-βRII), which in turn promotes the activation of its downstream signaling pathway. They found that R-Smad protein interacts with Smad4 (co-Smad) in the nucleus to regulate downstream target gene expression and promote liver fibrosis. Eickelberg et al. confirmed that by preparing β-sugar chains in vitro, the generation of TGF-β1 and the receptor complex on its membrane can be blocked, and the expression of TGF-β1/Smad can be blocked, thus promoting the expression of TGF-β1. At the same time, it was found that the administration of Smad3 inhibitor (SIS3) could reduce the phosphorylation of Smad3, block the binding of Smad3 and Smad4, up-regulate the expression of Smad7, and reduce the regulation of TGF-β1 on ECM [11-14]. Other studies [15] found that the expression of Smad6 in rat endometrial tissue was significantly reduced, suggesting that Smad6 and Smad7 may play a negative regulatory effect by down-regulating the TGF-β family pathway. In general, the TGF-β/Smad signaling pathway can bind to nuclear DNA via Smad2,3,4,6,7 and other pathways, thereby regulating phases. On this basis, a hypothesis was proposed: by regulating TGF-β signaling pathway, the transcription and expression of downstream target proteins were regulated, and then endometrial fibrosis was regulated, leading to uterine adhesion.

1.1.3. T cell growth factor-β (TGF-β) and connective tissue growth factor (CTGF)/CCN2 (CCN2)

In addition, TGF-β1 also promotes its pro-fibrosis through the CTGF/CCN2 pathway. CTGF/CCN2 is an important extracellular secretory factor. Literature has shown that compared with healthy people, the expression of TGF-β1 and CTGF in endometrial tissues of patients with adhesion disorder is significantly increased [8]. Further studies have shown that TGFβ1 can promote the secretion of collagen by fibroblasts through the CTGF/CCN2 pathway, thus affecting uterine adhesion [16]. However, the role of TGF-β1/CTGF in the pathogenesis of IUA is unclear.

1.1.4. Transforming growth factor-β and matrix metalloproteinase-9 (MMP-9)

MMPs are important anti-fibrocyte injury factors. It can effectively decompose ECM, including type IV collagen and collagen V, and reduce the precipitation of ECM [17]. It has been reported in the literature that the expression of MMP-9 in the endometrium of IUA patients is significantly reduced. Further studies found that the expression level of MMP9 gene in endometrial stroma after endometriosis surgery was lower than that of the control group, and the expression level of TGF-β1

was increased [18,19]. Therefore, it is speculated that TGF-β1 can affect the synthesis and decomposition of ECM and promote the occurrence of IUA by down-regulating the expression and activity of MMP-9. However, it was also found that the expressions of TGF-β1 and MMP-9 in endometrial tissues of IUA patients and IUA rats were significantly increased [20]. These differences may be due to the different pathophysiological periods and sample sizes of the subjects. Studies have found that MMP-9 and TGF-β1 have different biological functions in the occurrence and development of IUA, but the molecular mechanism of their regulation is not completely clear. It is possible to achieve the prevention and treatment of IUA by regulating the expression of MMP-9 gene, but further research is needed.

1.1.5. Other regulatory pathways

It is currently known that TGF-β can not only activate Smad in uterine endothelial cells, but also participate in the pathogenesis of uterine adhesion through various signaling pathways such as MAPK, RHO, PI3K, serine/threonine kinase (AKT), ERK and NF-CAMb [21]. ZN W et al. [22] confirmed that Junn-terminal kinase (JNK) can negatively regulate TGF-β1 by down-regulating TGF-β1 by giving JNK signaling pathway. In addition, it was found that Hippo/TAZ/Yap dissociated in the cytoplasm, which blocked its binding with the nucleus, thereby reducing the activation of TGF-β/Smad, thereby blocking the activation of TGF/Smad pathway, and thereby interfering with the pathogenesis of IUA. Overall, TGF-β-induced endometrial interstitial fibrosis is a very complex process, involving both the joint regulation of TGF-β/Smad and non-classical pathways as well as other signal transduction pathways [23]. Recent studies have shown that IL-11 plays a key regulatory role in the fibrosis process of lung, kidney, heart and other organs, and TGF-β1 has been found to promote tissue fibrosis by up-regulating the transcription and expression of IL-11. IL-11 is also a potential target gene for many fibrotic molecules. IL-11 overexpression in mice can cause multiple organ fibrosis. TGF-β (TGF-β) is currently an ideal target for the treatment of organ fibrosis, but it has a great impact on the body, and its specific blocking will lead to a variety of adverse effects, therefore, the key to its prevention and treatment is to block TGF-β1 and its downstream inflammatory factors that promote fibrosis [24]. Therefore, IL-11 may be a new therapeutic target for organ fibrosis. The role of IL11 in IUA development needs further study.

2. Overview of stem cells

Stem cells have the ability of self-renewal and multidirectional differentiation in a specific environment. At present, more and more attention has been paid to its role in the medical field. stem cells can be divided into embryonic stem cells (ESC), induced pluripotent stem cells (iPSCs) and adult stem cells (ASCs). iPSCs are a new type of stem cells that acquire stem-like characteristics from adult stem cells regulated by transcription factors, but their own genetic structure is unstable, which limits their clinical application. Adipocytes (ASCs) are a class of tissue-derived stem cells with the ability to differentiate. During the proliferation of stem cells, there are two different patterns of division, namely asymmetric division and symmetrical division. The former is often seen in the expansion of the number of stem cells themselves, while the latter produces differentiated cells in addition to self-renewal [25].

2.1. Study on the use of MSCs in endometrial injury

ASCs has high proliferative ability and multi-potential, which has become the focus of clinical research. Bone marrow mesenchymal stem cells (MSCs) are the most studied type in clinical practice. They have abundant sources and can migrate to damaged areas and chronic inflammatory

areas, and have advantages such as low immunogenicity and easy cultivation in vitro [26]. Studies [27] have found that in the treatment of endometrial injury, the sources of MSCs include bone marrow mesenchymal stem cells (BMSCs), umbilical cord blood (BMSCs), umbilical cord blood (ADSCs), and endometrium-mesenchymal stem cells (MSCs). For the identification of bone marrow mesenchymal stem cells, the minimum criteria recommended by IARC are: adhesion ability; There are specific marker molecules on the surface of cells, such as CD73 and CD90, but lack CD14, CD45 and HLA-DR, showing certain immune function. It can differentiate into adipocytes, chondrocytes and bone cells in vitro. In addition, CD29, CD44, CD140b+, CD146+ can also be used as markers of MSCs. Previous studies [28,29] have shown that CD90 exhibits adhesion, migration and other properties in a variety of tumor cells. Major pharmaceutical companies now have commercially available surface marker testing tools for MSCs.

2.2. Clinical research and application of MSCs

2.2.1. Bone marrow stromal stem Cells (BMSCs)

Autologous BMSC can be used to repair the damaged endometrium and promote the physiological cycle. There have been reports of successful conception, but due to its limited source, only 10-20m1 is taken at one time, which has disadvantages such as large trauma and pain, so it cannot be used clinically. Recent studies [15,16] used the traditional smooth muscle embolization method to migrate bone marrow mesenchymal stem cells (BMSC) in vitro, and then transplanted into the endometrium through peripheral blood mononuclear cell collection (BMSC) and blood tube intubation (BMSC), and found that it could significantly increase the endometrium thickness and promote pregnancy in some patients [30,31].

2.2.2. UC-MSCs

Umbilical cord blood MSCs are rich in sources and easy to collect. They are the link between embryo and placenta. It is surrounded by an amniotic membrane and has one umbilical vein and two umbilical arteries in the center, which are surrounded by a kind of colloidal fetal connective tissue called Huatong gum. At present, researchers at home and abroad have obtained UC-MSCs from umbilical cord blood, amniotic membrane, umbilical vein endothelial cells, Huatong gel and other methods. Previous studies have found that UC-MSCs can survive and colonize damaged endometrium, and significantly reduce inflammatory response [32].

At present, UC-MSCs have been gradually applied in the clinical treatment of severe uterine adhesions and IVF-embryo transfer assisted pregnancy. At present, in order to avoid the excretion of stem cells from outside the uterine cavity in a single lavage of 2*10-7, some studies [33] compound cord blood stem cells with collagen and remove them after 3 days of placement. After 2 months of continuous perfusion, it was found that the distribution of blood vessels, estrogen receptors and progesterone receptors in the endometrium increased significantly. Endometrial thickness increased from 4.08 mm to 5.87 mm, and 15 women became pregnant after transplantation, 2 aborted at 25 weeks gestation, and 2 became pregnant naturally after embryo transfer due to repeated thinning. However, the role of UC-MSCs in improving endometrial thickness, pregnancy outcome and long-term safety needs further study.

2.2.3 Endometrial mesenchymal stem cells (eMSCs)

Some scholars isolated 1000 endometrium from the rat endometrium and injected it after 3 generations of purification, and found that the thickness of the endometrium increased, the number of endometrial glands increased, and the number of blood vessels increased. Human endometrial

mesenchymal stem cells (eMSCs) were isolated from the intact endometrial layer of endometrial, and after enzymatic hydrolysis and mechanical treatment, the number of the source mesenchymal stem cells was significantly higher than that of the epithelium, and the number of eMSCs in the membrane during proliferation was significantly higher than that in the secretory stage, but the specific mechanism remained unclear. Bone marrow mesenchymal stem cells (MSCs) are centered on blood vessels, mainly in functional layer and basal layer. Menstrual blood-derived endometrial stem cells (MenSCs) refer to the increase of stem/precursor cells on the surface of the endometrium, between the intima - muscle layers, and between the base and the base during the menstrual cycle. Repair of the endometrium is determined by many types of stem/precursor cells. Bone marrow mesenchymal stem cells (BMSCS) have the properties of promoting regeneration and inflammatory response. Menstrual blood contains functional membrane cells, which have the function of promoting endometrial regeneration in the late menstrual period. In addition, the function of MET in a mouse menstrual-like animal model was examined. The stromal cells closest to the uterine epithelial repair site also have both epithelial and stromal cell markers. In addition, during vascular intimal repair, marker proteins in stromal cells decreased while marker proteins in epithelial cells increased, suggesting a possible mechanism of MET occurrence [34,35].

Hematopoietic stem cells in the blood source is simple, easy to isolate and culture, but easy to be infected in the blood. Studies have found that bone marrow mesenchymal stem cells (MSCs) grow slowly within 3 days in vitro, then prolifize rapidly within 7 to 14 days, and reach logarithmic growth within 7 to 14 days, and continue to be cryotherapy after subgeneration [36]. Patients with endometrial adhesion have scarce menstruation, and the proliferation and differentiation of MSCs are decreased, which is still a problem to be further studied. In addition, how to ensure the non-toxicity and low toxicity of MSCs is the focus of further research in the future.

3. Challenges of stem cell therapy

3.1. Security Issues

Because of its high cost, its use in clinic is restricted to some extent. In the process of applying stem cell therapy, how to ensure that the endometrial can be effectively repaired under normal conditions without causing excessive hyperplasia of the endometrial is an urgent problem in clinical practice. In addition, long-term safety and potential adverse effects require ongoing attention and evaluation.

3.2. Standardization of cell source and preparation

At present, the source of stem cells may vary, and the stem cell preparation process is not uniform. To ensure the stability and high quality of stem cells is the key to clinical application

3.3. Optimization of treatment plan

The key parameters, such as cell dose, transplantation pathway and transplantation timing, have not been unified and need to be further studied.

4. Summary and prospect

Stem cells play a key role in the regeneration and repair of uterine adhesion endometrium, and provide a new potential treatment method and idea for refractory uterine adhesion endometrium. In addition, in the process of stem cell therapy, how to ensure that the endometrium can be efficiently

repaired under normal conditions without causing excessive hyperplasia of the endometrium is an urgent problem to be solved clinically. Although stem cells face many challenges in the treatment of intrauterine adhesions, with the continuous deepening of research and technological progress, it is expected to overcome these difficulties and bring new hope for patients with intrauterine adhesions. Future research should further focus on the in-depth study of the mechanism of action of stem cells, the optimization of treatment regimens, and the comprehensive evaluation of clinical efficacy and safety.

References

[1] Wicks IP, Roberts AW.Targeting GM-CSF in inflammatory diseases.Nat Rev Rheumatol 2016:12:37–48.

[2] Li C, Hu Y. Extracellular Vesicles Derived from Mesenchymal Stem Cells as Cell-Free Therapy for Intrauterine Adhesion. Int J Stem Cells. 2023 Aug 30; 16(3):260-268.

[3] Business Research, Wu Nana. Effect of estrogen on endometrial epithelialization, endometrial duct density and ovarian blood supply function after uterine adhesion [J]. Modern Medicine and Hygiene, 2019, 39(20): 3486-3489+3494. (in Chinese)

[4] LI Yingying, Zhang Lindong, Zhang Qinshan et al. Effect of growth hormone and expression of growth hormone receptor and estrogen alpha receptor in endometrial of patients with moderate to severe intrauterine adhesions after operation [J]. Journal of Practical Obstetrics and Gynecology, 2019, 39(10):775-779.(in Chinese)

[5] Zhao Suxia, Fu Xiuhong. Incidence and influencing factors of intrauterine adhesion in patients with endometrial polyps after surgery [J]. Journal of Henan Medical Research, 2019, 32(19):3548-3551. (in Chinese)

[6] Liping Z ,Jin H ,Qiaoling Z , et al.The humanin analogue (HNG) alleviates intrauterine adhesions by inhibiting endometrial epithelial cells ferroptosis: a rat model-based study.[J].Human reproduction (Oxford, England),2023.

[7] CHENG G Z. The clinical expression and significance of HMGA2 in endometrial tissues of patients with uterine adhesions [J]. Chinese Journal of Eugenics and Genetics, 2019, 31(09):1843-1847. (in Chinese)

[8] LiNa L ,XiaoDan L ,Juan D .The effect of aspirin on uterine arterial blood flow and endometrium in moderate and severe intrauterine adhesion after transcervical resection of adhesion: a systematic review and meta-analysis.[J].The journal of maternal-fetal neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 2023, 36(1): 2209818.

[9] Honglei Z ,Huayan L ,Kunjie G , et al.Chorionic villi-derived nanofibers enhanced mesenchymal stem cell extracellular vesicle secretion and bioactivity for endometrium regeneration toward intrauterine adhesion treatment[J]. Nano Today, 2023, 52.

[10] Qiu Ling, Zhu Mohao, Yan Tianya et al. Effect of sequential acupuncture and moxibustion therapy combined with Youshi Tiaomembrane-prevention prescription on endometrium volume tolerance after uterine adhesions [J]. Hubei Journal of Traditional Chinese Medicine, 2023, 45(09):3-7.(in Chinese)

[11] Weili Q ,Jiawei W ,Qianwen H , et al.Melatonin-pretreated HucMSCs improved endometrium regeneration and fertility recovery through macrophage immunomodulation in rats with intrauterine adhesions.[J].Biology of reproduction, 2023,109(6):918-937.

[12] Zhu Jiajuan, Di Chunguang, Yao Qiuping et al. Macrophage polarization regulates the expression of CD68, CD163 and VEGF in endometrial adhesion and its clinical significance [J]. Zhejiang Trauma Surgery, 2023, 28(07): 1207-1210.(in Chinese)

[13] Simin Y ,Zhenhua Z ,Limin W , et al.Targeting endometrial inflammation in intrauterine adhesion ameliorates endometrial fibrosis by priming MSCs to secrete C1INH[J].iScience, 2023, 26(7):107201.

[14] Liu Jia, Wu Dandan, Yu Liji et al. Effect of different dose and administration frequency of estradiol valerate in the postoperative treatment of moderate intrauterine adhesions by laparoscopy [J]. Clinical Rational Use of drugs, 2019, 16(20):20-23.(in Chinese)

[15] Qiu Daner, Zhang Wanlin, Xiao Xifeng et al. Research progress of intrauterine infusion of platelet-rich plasma for adjuvant therapy after intrauterine adhesion separation [J]. Journal of PLA Medical College, 2019, 44(07): 812-816.(in Chinese)

[16] Yan P , Jin X ,JingYu L , et al.[Observation on the effect of electroacupuncture on the regeneration of endometrium in rats with intrauterine adhesion].[J].Acupuncture research, 2023, 48(6):550-556.

[17] Zhang Mingwei, Liu Qian, Xie Qingzhen. Effect of chronic endometritis on the outcome of uterine adhesions treatment [J]. Journal of Reproductive Medicine, 2019,32(06):823-828. (in Chinese)

[18] He Junxia, Yang Xiaomin, Ma Ruifen. Effect of high dose estrogen combined with low molecular weight heparin on endometrial receptivities in patients with repregnancy after hysteroscopic adhesion separation [J]. China Maternal and

Child Health Care,2023,38(12):2210-2213.(in Chinese)
[19] Qi Z, Simin Y, Ziying Y , et al.Ferroptosis contributes to endometrial fibrosis in intrauterine adhesions.[J].Free radical biology medicine, 2023, 205: 151-162.
[20] Chang Yanan, Duan Hua. The effect of endometrial adhesion on endometrial susceptibility and treatment progress [J]. Chinese Journal of Family Planning and Obstetrics and Gynecology, 2019,15(05):27-31. (in Chinese)
[21] Pan Yan, Xi Jin, Liu Jingyu, et al. Effect of electroacupuncture on endometrial repair in rats with uterine adhesion [J]. Acupuncture Research, 2019,48(06):550-556.(in Chinese)
[22] ZN W, MS W, X X .Clinical evidence of positive correlation between intrauterine adhesions and chronic endometritis: a retrospective study.[J].European review for medical and pharmacological sciences, 2023, 27(10): 4601-4607.
[23] Zhang Siwen, Wang Houmei, Xing Mingyue et al. Research progress of mesenchymal stem cells combined with estrogen in the treatment of uterine adhesions [J]. Guangxi Med, 2023,45(07):837-842. (in Chinese)
[24] Feng Dan, Li Yang, Wang Ying et al. Infiltration of M2-type macrophages in endometrial of patients with uterine adhesion and its correlation with endometrial fibrosis [J]. Journal of Reproductive Medicine, 2019,32(03):398-403.(in Chinese)
[25] Yanhua M ,Yuan Y ,Congcong S , et al.Human amniotic mesenchymal stem cells promote endometrium regeneration in a rat model of intrauterine adhesion.[J].Cell biology international,2022,47(1):75-85.
[26] Wen H ,Xuejing Z ,Aijie X , et al.Long-term maintenance of human endometrial epithelial stem cells and their therapeutic effects on intrauterine adhesion[J].Cell Bioscience,2022,12(1):175.
[27] Qiu Shuang, Zhang Xuan, Wang Xiaoqing. Expression of serum TGF-β1, VEGF and HIF-1α in patients with endometrial polyps and their relationship with intrauterine adhesion after polyp resection [J]. Chinese Journal of Obstetrics and Gynecology, 2019,23(05):486-488.(in Chinese)
[28] Peng Yanzhen, Duan Hua. Clinical application of uterine adhesion evaluation index in endometrial injury [J]. Chinese Journal of Applied Gynecology and Obstetrics,2022,38(09):873-877. (in Chinese)
[29] Rui X ,Manchao L ,Zhongjia G , et al.Chronic endometritis positively correlates with the aggravation of intrauterine adhesions but has limited effects on reproductive prognosis with antibiotic application.[J].International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 2022, 160(3):986-992.
[30] Liu Lei, Yan Siqing, QIU Meigui et al. Study of endometrial metabolomics in patients with uterine adhesion [J]. Advances in Modern Obstetrics and Gynecology,2022,31(07):521-525+529. (in Chinese)
[31] HeYu L ,ZhengYan Z ,XueMei C,et al.A review of the effects of estrogen and epithelial-mesenchymal transformation on intrauterine adhesion and endometriosis.[J].Transplant immunology,2022,79:101679.
[32] Qing H ,Yong Z ,Hongjuan L , et al.Human umbilical cord blood-derived MSCs trans-differentiate into endometrial cells and regulate Th17/Treg balance through NF-κB signaling in rabbit intrauterine adhesions endometrium. [J].Stem cell research therapy,2022,13(1):301.
[33] Feng Wenjuan. Estrogens vaginal drug delivery to improve the receptivity of endometrium thin research [D]. Shandong university, 2022. The DOI: 10.27272 /, dc nki. Gshdu. 2022.000865.(in Chinese)
[34] Zhang Xiaole, Wang Minyan, Liang Chengcheng et al. Effect of Bushen Huoxue Recipe on endometrial morphology and pinocytosis in rats with uterine adhesion [J]. Journal of Reproductive Medicine, 2019, 30(12):1634-1640. (in Chinese)
[35] LI Jiao, Lin Jie, Yi Xingxing et al. Study on the effect and mechanism of Bushen Huayu formula on endometrial fibrosis in rats with uterine adhesion based on TGF-β1/Smad pathway [J]. Review of Chinese Medicine, 2021, 27(11): 7-11+17. (in Chinese)
[36] Liu Xiaodan, Feng Jieling, Wang Jiamin et al. Evaluation of the effect of pelvic floor neuromuscular electrical stimulation on endometrial repair after moderate to severe uterine adhesions [J]. Journal of Sun Yat-sen University (Medical Sciences Edition), 2012,43(01):140-145.(in Chinese)