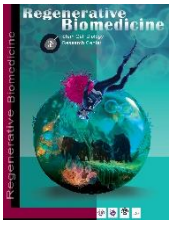

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Mini-Review Article

Exosomes, a Promising Future for Endometriosis

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Abstract

Endometriosis is characterized as the development of endometrial organs and stromal cells in a heterotopic area with immune dysregulation. Considering endometriosis is a chronic progressive disease primarily affecting young reproductive ages, early interventions to prevent disease progression is mandatory. Medical treatment may be effective to alleviate the symptoms, but recurrence after the cessation of medicine is frequent. In addition, there is a potential for decrease endometrial receptivity, an increase in free radicals, excessive production of prostaglandins, estrogen, as well as an imbalance in the level of cytokines, interleukins and various growth factors in this disease. Exosomes (Exos) are extracellular nanovesicles that are released from almost all cell, so Exos are one of the strategies for cellular cross-talk. Recent studies have shown that during implantation, Exos can participate in the complex dialogue between the embryo and maternal tissues. Here, we review how endometriosis develops as a heterogeneous disease, and introduce the Exos and its potential as a new strategy in improving symptoms and fertility in these patients.

Keywords: Endometriosis, Exosomes, stem cell, Herbal products, Endometriosis animal model

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Introduction

Endometriosis, which is the presence of extrauterine endometrial-like lesions, occurs in 5–10% of females who are in their reproductive years, but rare premenarcheal and postmenopausal forms have also been reported (1). Severe menstrual and non-menstrual pain in the lower abdomen, pelvis, or lumbosacral region is common in women with endometriosis, and in 30%–50% of cases, it is associated with deep dyspareunia, dyschezia, and dysuria. (1, 2). To date, the etiology of endometriosis is not fully understood. Although Sampson's theory of retrograde menstruation (3) is considered the strongest theory, it does not explain why only some women develop endometriosis because retrograde menstruation is physiological. Recent studies have also shown A combination of factors such as aberrant cytokine expression, impaired immune surveillance, and the intrinsic nature of endometrial physiology that confers a survival advantage, such as gene mutations, are thought to contribute to the inability to clear aberrant endometrium from the pelvic cavity leading to The creation of endometriosis lesions and the development of the disease (2). According to the latest ESHRE guidelines on this disease, it no longer recommends diagnostic laparoscopy as the gold standard diagnostic tool, but instead reserves it for women with negative MRI or ultrasound imaging, and/or in cases where empiric therapy has failed (4). Currently, medical treatments are based on suppressing estrogen or treating symptoms rather than curing the disease (5, 6). In addition, the recurrence rate after current medical and surgical treatments for endometriosis is high (4, 5). In recent years, medicinal plants and other herbal products have become popular due to their anti-proliferative, antioxidant, analgesic and anti-inflammatory to relieve the symptoms of many gynecological disorders such as endometriosis (6). Kiani et al. (2019) investigated the anti-angiogenic activity of Calligonum comosum ethyl acetate fraction (CCEAF) in different in vitro angiogenesis assays (5). Moreover, they surgically induced endometriotic lesions in BALB/c mice, which received 50 mg/kg Calligonum comosum total extract (CCTE) or vehicle (control) over 4 weeks (5). The growth, cyst formation, vascularization and immune cell infiltration of the lesions were assessed with high-resolution ultrasound imaging, caliper measurements, histology and immunohistochemistry (5). CCTE significantly inhibited the growth and cyst formation of developing murine endometriotic lesions when compared to vehicle-treated controls (5). Here, we discuss the role of exosome as a new and alternative cell therapy tool for endometriosis. Exosomes (Exos) are extracellular nanovesicles that are released from almost all cells. Events such as disposal of waste proteins, antigen supply, immune response, angiogenesis, inflammation, metastasis, spread of pathogens and many other activities, including the roles of these vesicles, depend on their content in the body (7). According to the definition of international society for extracellular vesicle (ISEV), Exos are small vesicles with a phospholipid bilayer membrane, size of 40 to 150 nm, which are present in almost all body fluids such as:

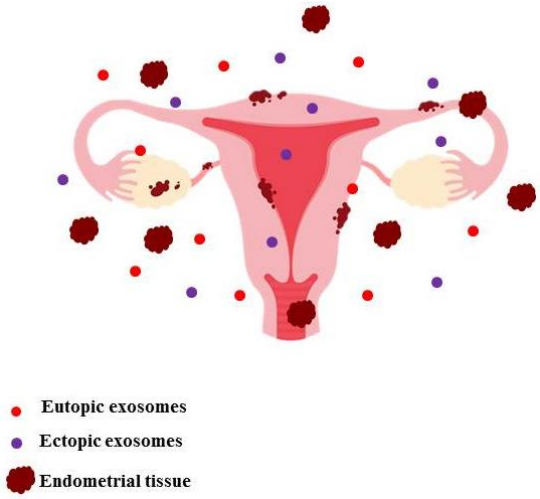

Figure 1: Endometriotic lesions and Exos

blood, urine, serum, saliva, semen, ... (5). The cargos of EVs are heterogeneous, such as: nucleic acids (DNA, mRNA, microRNAs and long non-coding RNAs), lipids, a variety of proteins membrane and binding transporters (Annexin, GTPase) , tetraspanins (CD6, CD9, CD63, CD81, CD82) and heat shock proteins (Hsp90, Hsp70) (6). Among the nucleic acids, microRNAs are present with a higher proportion in Exos. The growth and function of multicellular tissue requires intercellular communication, so Exos are one of the strategies for cellular cross-talk. Potential cell therapies for endometriosis may be based on aspects of disease pathogenesis such as inhibition of estrogen receptor activity, angiogenesis, fibrosis, and reduction of stem cell content in endometriosis foci (7). isolation and use of Exos compared to cell therapy has significant advantages such as: increased stability, reduced contamination of the culture medium, non-rejection of cells due to surface markers participating in the immune system, non-tumorigenesis and reduced problems in maintenance and their displacement has been noticed in recent years (8, 9). Early studies of extracellular vesicles in endometriosis focused on their potential use as disease biomarkers (3). As several studies have shown promising diagnostic potential for using Exos as a non-invasive diagnostic biomarker, the validity of these studies in large populations is important (2). So far, three studies have investigated the therapeutic potential of Exos miRNAs in vivo In mice, two studies investigated the role of Exos hsa miR 214 3p in reducing fibrosis, and one study investigated Exos hsa miR 30c 5p in inhibiting the invasive and migratory potential of the endometrium (Figure 1) (3). Due to the heterogeneous nature of endometriosis, the diagnosis and treatment of this disease remains a major clinical challenge (2). Exos contribute to cell migration, implantation and immunomodulation in endometriosis; this can likely be a promising tool to better understand the pathophysiology of endometriosis or a potential diagnostic and therapeutic tool (2, 3).

References

1. Chen L-H, Lo W-C, Huang H-Y, Wu H-M. A lifelong impact on endometriosis: pathophysiology and pharmacological treatment. International Journal of Molecular Sciences. 2023;24(8):7503.

2. Scheck S, Paterson ES, Henry CE. A promising future for endometriosis diagnosis and therapy: extracellular vesicles-a systematic review. Reproductive Biology and Endocrinology. 2022;20(1):174.

3. Nazri HM, Greaves E, Quenby S, Dragovic R, Tapmeier TT, Becker CM. The role of small extracellular vesicle-miRNAs in endometriosis. Human Reproduction. 2023;38(12):2296-311.

4. Bonavina G, Taylor HS. Endometriosis-associated infertility: From pathophysiology to tailored treatment. Frontiers in endocrinology. 2022;13:1020827.

5. Kiani K, Rudzitis-Auth J, Scheuer C, Movahedin M, Lamardi SNS, Ardakani HM, et al. Calligonum comosum (Escanbil) extract exerts anti-angiogenic, anti-proliferative and anti-

inflammatory effects on endometriotic lesions. Journal of ethnopharmacology. 2019;239:111918.

6. Kiani K, Sadati Lamardi SN, Laschke MW, Malekafzali Ardakani H, Movahedin M, Ostad SN, et al. Medicinal plants and natural compounds in the treatment of experimental endometriosis: A systematic review protocol. Evidence-based Preclinical Medicine. 2016;3(2):1-6.

7. Kowalczyk A, Wrzecińska M, Czerniawska-Piątkowska E, Kupczyński R. Exosomes–Spectacular role in reproduction. Biomedicine & Pharmacotherapy. 2022;148:112752.

8. Artemova D, Vishnyakova P, Gantsova E, Elchaninov A, Fatkhudinov T, Sukhikh G. The prospects of cell therapy for endometriosis. Journal of Assisted Reproduction and Genetics. 2023;40(5):955-67.

9. Izadi M, Rezvani ME, Aliabadi A, Karimi M, Aflatoonian B. Mesenchymal stem cells-derived exosomes as a promising new approach for the treatment of infertility caused by polycystic ovary syndrome. Frontiers in pharmacology. 2022;13:1021581.