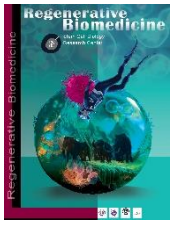

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Mini-Review Article

Mesenchymal Stem/Stromal Cells Derived Exosomes-based Therapy and Polycystic Ovary Syndrome

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Abstract

Infertility is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. It has involved various communities worldwide and brought social outcomes for infertile women. However, in societies in which cultural norms value being a woman more than being a mother, these outcomes are intensified and lead to complications such as married life instability, violence and isolation. The infertility rate in Iran is estimated to be about 20%, which is above the global average (12-15%). Infertility can be caused by various factors, one of the most common reasons of which is polycystic ovary syndrome (PCOS). Women with PCOS show higher levels of circulating free testosterone (CFT), postprandial glucose, fasting insulin and triglycerides as well as lower levels of sex hormone binding globulin (SHBG). Several treatment methods have been proposed to treat this syndrome, but nowadays researchers used cell therapy as the best treatment method, looking for a better way to treat it. Cell therapy is a treatment based on stem cells and mesenchymal stem/stromal cells (MSCs) are known as promising candidates for it. The secretome of these cells contains growth factors, cytokines and extracellular vesicles (exosomes, microvesicles and apoptotic bodies), which can act as a potential therapeutic tool for the treatment of female infertility.

Keywords: Exosome, Infertility, Infertile women, Mesenchymal stem/stromal cell, Polycystic ovary syndrome

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Introduction

Infertility is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse (1). Infertility has different causes, one of the most common causes of which is PCOS (2). Several treatment methods (such as lifestyle changes, surgery, drug use and etc.) have been proposed to treat this syndrome, but nowadays researchers used cell therapy as the best treatment method, looking for a better way to treat it. Cell therapy is a treatment based on stem cells and MSCs are known as promising candidates for it (3). The secretome of these cells includes growth factors, cytokines, and extracellular vesicles, which exhibit immunosuppressive, anti-apoptotic, anti-inflammatory and anti-fibrotic properties. These elements may serve as potential therapeutic agents for addressing female infertility (4). Extracellular vesicles can be categorized into exosomes, microvesicles and apoptotic vesicles based on their characteristics and functions. Exosomes are tiny vesicles (diameter 30–150 nm) secreted by cells in culture and found in all body fluids. These tiny vesicles, loaded with unique RNA and protein cargos, have many biological functions, of which only a small fraction is currently understood (5)

Infertility

Infertility affects different societies all over the world and its psychological and social consequences plague infertile women. But in societies where cultural norms value women more than the role of being a mother, these consequences are intensified and complications such as instability of joint life, violence and isolation will follow (6). Infertility has different causes, one of the most common causes of which is PCOS (2).

PCOS

PCOS is among the most prevalent endocrine disorders in women and is the leading cause of infertility linked to anovulation. The definition of this syndrome is controversial and still unknown due to its heterogeneous nature and its naming is due to the presence of large ovaries containing many small cysts (in most of the affected women, but not in all). This syndrome was first defined by Stein and Leventhal in 1935, These scientists examined 7 patients who suffered from amenorrhea, hirsutism and ovarian enlargement with many follicles. Since then, there have been regular reports of this disorder until at the 2003 Notre Dame meeting, PCOS specialists from all over the world came together and adopted a universal diagnostic criteria for the disease. The diagnosis of this disease is based on the presence of two out of the following three conditions:

1. Biochemical hyperandrogenism accompanied by clinical symptoms such as alopecia (localized hair loss on the scalp), acne and hirsutism.

2. Irregular menstruation, oligomenorrhea and amenorrhea or lack of ovulation.

3. The presence of polycystic ovaries in ultrasound is more than 12 follicles in small size of 2 to 9 mm. Ultrasound diagnosis of PCOS varies among sonographers. The most accepted ultrasound definition of PCOS was expressed by Adams et al., which includes the presence of multiple cysts of 10 or more with a diameter of 2-8 mm that are

located in the ovarian environment. On the other hand, the presence of numerous follicles and the increase of the ovarian stroma causes the ovaries to become large and bulky, although the size of the ovaries may remain within the normal range in some patients despite the symptoms of PCOS. About 20-33% of women with this syndrome show the mentioned symptoms in ultrasound, and about three quarters of them have the clinical features of the syndrome. Since anti Müllerian hormone (AMH) indicates various aspects of ovarian function and PCOS is frequently marked by a higher number of antral follicles, AMH could be beneficial for diagnosing PCOS. Women diagnosed with PCOS typically exhibit elevated levels of circulating free testosterone (CFT), postprandial glucose, fasting insulin and triglycerides alongside lower levels of sex hormone-binding globulin (SHBG) and an increased ratio of luteinizing hormone (LH) to follicle stimulating hormone(FSH) (7) (Fig.1).

Mesenchymal stem/stromal cells and their exosomes

MSCs are a population of mature multipotent cells that reside in the bone marrow and most connective tissues of the body and can differentiate into cells and tissues related to the mesenchymal lineage, such as fat, bone, cartilage, muscle and tendon. These cells were first isolated from the bone marrow and until now they have been isolated from various tissues such as fetal tissues, bone marrow, fat tissue, amniotic fluid, amniotic membrane, dental pulp, endometrium, menstrual blood, peripheral blood, salivary glands, skin, foreskin, subamniotic membrane of the umbilical cord, synovial fluid and Wharton's jelly have also been reported (3). Various researches demonstrate that MSCs derived exosomes have functions similar to those of MSCs, such as suppressing inflammatory responses, repairing tissue damage and modulating the immune system. However, the mechanisms are still not fully understood and the results remain controversial. Compared with cells, exosomes are more stable and reservable, have no risk of aneuploidy, a lower possibility of immune rejection following in vivo allogeneic administration and may provide an alternative therapy for various diseases(8). A recent study explored the use of Endometrial Stem Cells (EnSCs) encapsulated in an alginate/gelatin hydrogel (SC-H) as a potential treatment for PCOS. In a rat model of PCOS, this novel approach improved symptoms such as increased body and ovarian weights, hormone imbalances and ovarian histology. The encapsulated stem cells showed strong anti-inflammatory effects, suggesting that biomaterials like SC-H could enhance the therapeutic potential of EnSCs for PCOS, paving the way for future clinical applications (9).

Conclusion

Considering the increasing trend of PCOS in the world and the adverse effects of this syndrome on social relationships and being under the influence of family relationships on the one hand and its side effects in the development and development of additional conditions such as cardiovascular diseases, Type 2 diabetes, hypertension and others which causes a lot of treatment costs, it is necessary to try to find new and cost-effective treatment methods such as cell therapy to

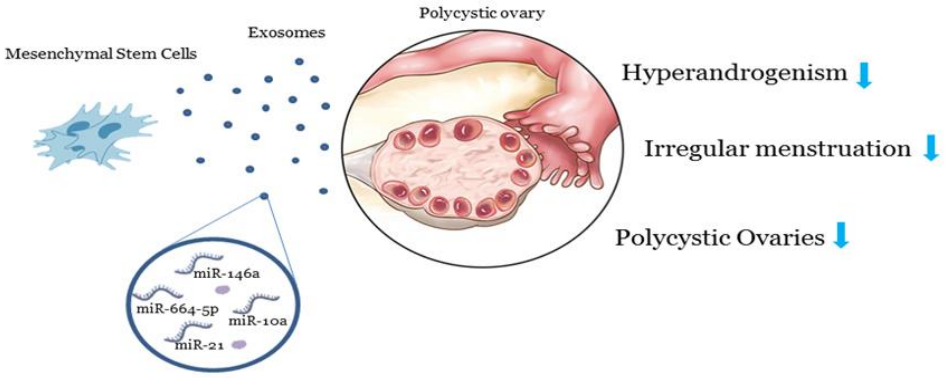

Figure1. Exosome therapy in PCOS using MSCs

reduce the adverse effects of this syndrome and its associated disorders and have an effective role on the quality The lives of women are affected.

Conflict of interest

The authors have no conflict of interest to declare.

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