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Human Adipose Derived Stem Cells in Female Infertility Treatment

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Abstract

Population issue has always been a major topic in national development. Female infertility is one of the factors leading to demographic problems. Literature review was done in order to realize how far researchers have reached among area of human adipose derived stem cells'(ADSC) usage in female infertility treatment. It seems that not all diseases are fit to ADSC therapy. In terms of polycystic ovary syndrome, endometriosis, intrauterine adhesion and premature ovarian failure, existed researches have shown the promising prospect of ADSC treatment. Further researches should be carried out in the future in order to clarify how ADSC can treat infertility-related diseases and eventually apply ADSC to clinical practice.

Keywords: ADSC; Female infertility; Polycystic ovary syndrome; Endometriosis; Intrauterine adhesion; Premature ovarian failure.

Introduction

Population issue has always been a major topic in national development. The sustained and steady growth of the population is of great significance to the steady development of the country. However, there are over 30 countries/districts suffering decrease of population worldwide. Infertility is one of the factors leading to the current population problems.

Infertility is defined as failure to achieve pregnancy after 12 months of regular sexual intercourse without contraception [1]. The incidence of female infertility around the world is about 8%-12% [2]. How to ameliorate the patients' fecundity has become a major task for reproductive doctors. According to different pathogenesis, female infertility can be roughly divided into two categories: pelvic factors and ovulation disorders. Pelvic factors mainly refer to: congenital reproductive system malformations, cervical insufficiency, endometriosis, adenomyosis, endometrial polyps, intrauterine adhesion, fallopian tubal obstruction, and gynecological tumors. Ovulation disorders are mainly caused by diseases of the hypothalamus-pituitary gland-ovary axis, such as eating disorder amenorrhea, pituitary adenoma, Sheehan syndrome, premature ovarian failure, polycystic ovary syndrome, Turner syndrome and other diseases. In addition, other endocrine disorders, such as Cushing's syndrome and hypothyroidism, may also lead to female infertility.

For different diseases, doctors have different treatments such as drugs or surgery in order to improve the patient's fertility function. However, existing treatments cannot meet the full range of clinical needs. Therefore, the search for new treatment options is constantly on the way. Stem cell therapy has always been a hot direction in scientific research. In recent years, various types of stem cells have been used to study their efficacy on female infertility. Human adipose derived stem cells (ADSC) are favored by researchers for their wide distribution, easy access, strong expansion ability, and low immunity

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[3,4]. Therefore, a literature research was conducted on the therapeutic application of ADSC in female infertility-related area and finally four diseases that are relatively common seen and well studied were reviewed: polycystic ovary syndrome, endometriosis, intrauterine adhesion and premature ovarian failure.

Isolation, Cultivation and Identification of ADSCs

Since Zuk [4] et al. first reported ADSC, the laboratory acquisition method of this line of cells has been gradually fixed. The process is briefly described as follow: the adipose tissue is washed by PBS and digested with collagenase. Until the large fatty tissue is invisible to the naked eye, complete medium (DMEM medium + 10% fetal bovine serum + 1% penicillin/streptomycin bi-antibody) is added to terminate digestion. After centrifuge, the supernatant is discarded. The sediment is adipose derived stromal vascular fraction containing ADSC. Resuspend the fraction with complete medium and plant the cells into a Petri dish. ADSC is found to be spindle-shaped and wall-adherent growth. Serial subcultivation can be performed when the cell confluency reaches about 80%. A purer ADSC cell line can be obtained using low-density planting methods. ADSC is a type of mesenchymal stem cell, so they have the relevant characteristics of mesenchymal stem cells, namely: wall-adherent growth, cell surface markers (identification of CD29+, CD44+, CD73+, CD90+, CD105+; CD31-, CD45-,via flow cytometry) and multidirectional differentiation potential. This allows for identification of ADSC [5].

ADSC in Treating Polycystic Ovary Syndrome

Polycystic Ovarian Syndrome (PCOS) is a common reproductive endocrine metabolic disease that seriously affects the reproductive health of patients. It is characterized by hyperandrogenism, anovulation, and polycystic ovarian morphology [6]. Due to high androgen level, insulin resistance and other factors, patients with PCOS mostly exhibit oligo-ovulation or anovulation, making PCOS the most common cause of ovulation disorders in infertility [1].

Infertile patients with PCOS can get pregnant through lifestyle modification and controlled ovulation induction [6]. However, some patients cannot obtain a live birth or achieve clinical pregnancy even with the help of assisted reproductive technology. Therefore, the exploration of other potential treatments is still needed.

Zhao et al [7] used ADSC and their exosomes as mediator to carry MiR-323-3p and treat PCOS. Cumulus cells showed promoted cell growth and inhibited apoptosis after treatment. Further experiments confirmed that PDCD4 was the targeted gene of MiR-323-3p, revealing a possible therapy for PCOS patients and the possible underlying mechanism.

Cao et al. [8] found that both ADSC and their exosomes can reverse the metabolic disorders of PCOS rats. More importantly, the estrus disorder and infertility were also ameliorated. Experiments both in vitro and in vivo showed that MiR-21-5p in ADSC exosomes, targeting Btg2, may play an important role in activating insulin signaling pathway. The role shown by ADSCs and their exosomes in alleviating symptoms in rat models of PCOS demonstrates their potential for development as a new therapeutic strategy for human PCOS.

ADSC in treating Endometriosis

Endometriosis refers to the ectopic endometrial glands and stroma, resulting in pain, infertility or other symptoms. It affects 5%-10% female of reproductive age globally. About 50% of females suffering infertility have endometriosis [9].

In vitro fertilization-embryo transfer (IVF-ET) remains a core treatment for infertile endometriosis patients [9]. Yet the presence of ovarian endometriosis may affect the process of controlled ovarian stimulation during IVF-ET [10]. Meantime routine surgery before IVF-ET is no longer recommended [11]. Hence loads of researches for new therapies have been carried out. ADSC treatment is one of the attempts.

Endometriosis has been believed to be a chronic inflammatory disease. This was confirmed by Falomo et al in 2015 [12]. However, this research did not identify the exact effect of ADSC in the treatment of endometriosis, for both anti-and pro-inflammatory cytokines were found to be increased after intervention. Meligy et al [13] and Toyofumi Hirakawa et al [14]both found morphological improvement after ADSC treatment, less ectopic endometrial glands and thinner fibrosis respectively. Both teams confirmed the decrease in pro-inflammatory cytokines like interleukine-6 while less alteration in anti-inflammatory factors like interleukine-10 among ADSC-treated endometriosis lesions. Huang et al [15] used ADSC conditioned medium(ADSC-CM) to treat endometriosis model mice. They concluded that ADSC-CM can effectively reduce the development of endometriosis and improve pregnancy outcomes, by decreasing secretion of intracellular adhesion molecule-1 and vascular endothelial growth factor. This provides a promising tool to curing infertile endometriosis patients.

ADSC in treating Intrauterine Adhesion

Intrauterine adhesion (IUA), also known as Asherman syndrome, refers to fibrous tissue formation inside uterine cavity because of injury to the basal layer of the endometrium [16]. The incidence of IUA among infertile females is about 6%-7% [17]. Hyteroscopic surgery is the only clinical acknowledged effective method that can be used for treating IUA [18]. Recurrence after repeat hysteroscopic surgery can be up to 10.9% [19]. Consequently new therapies like ADSC treatment have been studied. Zhao et al [20] used ADSC derived exosomes in the IUA rat model. The endometrium thickness got thicker and the fibrotic area got smaller after

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delivering ADSC-exosomes into the rats' uteri. Pregnancy test also showed promising results. Pregnancy rate and number of embryos went increased by using ADSC-exosomes.

Yet the complicated environment of IUA uteri makes it difficult for ADSC and ADSC-exosomes to survive. Thus researchers try combining ADSC or their exosomes with biological/chemical materials to see if this can improve the efficacy. Han's team [21] combined ADSC with acellular human amniotic membrane (AHAM). Zhao et al [22] mixed ADSC with ShakeGel™3D. Both teams found thicker endometrium, less fibrosis and more endometrial glands after treatment. The latter team also discovered that the cell-gel complex may ameliorate IUA through BMP7-Smad5 signaling pathway. All these researches provide evidence for ADSC serving as a new therapy for IUA treatment.

ADSC in treating Premature Ovarian Failure

Premature ovarian failure(POF) is the terminal stage of premature ovarian insufficiency(POI), referring to amenorrhea, lack of mature follicles and infertility due to ovarian function impairment before the age of 40. Blood tests show elevated gonadotropin levels (FSH＞40U/L), and fluctuating decreased estrogen levels [23,24]. The incidence of POF is approximately 1.1% globally [25].

Due to the fluctuation of hormone levels, POF increases the risk of osteoporosis and cardiovascular disease, which not only endangers the physical and mental health of patients, but also threats their family happiness and even social stability [26]. Therefore, patients with POF should be given adequate attention and treatment should be initiated as early as possible.

However, there still lacks understanding on the etiology of POF. Studies have shown that genetic factors, autoimmune factors, infectious factors, iatrogenic factors and psychosocial factors are possibly involved in the onset of POF, yet more than half of POF patients are idiopathic [24]. This brings difficulty to POF treatment. At present, the treatment for POF includes hormone supplementation therapy, assisted reproductive technology and fertility preservation technology. These approaches are efficient to POF patients in only one aspect, either hormone insufficiency or infertility. Along with their corresponding limitations, more efficient therapies are called by clinical practice [27,28].

Up till now, corresponding studies have confirmed the safety and efficacy of adipose stem cells in the treatment of POF. Several studies have found that ADSC treatment in POF rat or mouse models can increase the number of all levels of healthy follicles, restore reproductive hormone levels, and improve fertility [29,30,31]. Halicioglu et al [30] further proved that ADSC may repress apoptosis through the connexin43 and pannexin1, both of which are critical to female fertility, with the former serving as a molecule among gap junction while the latter in releasing ATP.

Huang et al [32] used ADSC-exsosomes to treat POF mice induced by cyclophosphamide. It was found that ADSC-exosomes could increase the number of all levels of healthy follicles and ameliorate the hormone levels in mice. Further studies discovered that these exosomes may function via SMAD pathway.

Su et al [33] attached ADSC to a collagen-made scaffold and injected it into the ovaries of POF mice. It was found that ADSC could exist stably with the scaffold. After ADSC-scaffold treatment, the number of ovarian follicles at all levels increased. Estrogen level got recovered. The pregnancy rate and litter size got increased. All results were better than those in the group treated by ADSC alone, suggesting that the combination of material media can improve the therapeutic effect of ADSC on POF.

In particular, Mashayekhi et al [34] studied the efficacy of ADSC in POF patients via ovarian transplantation. The results showed that ADSC can ameliorate menstruation and restore ovulation to a certain extent in patients with POF. The level of AMH hormone was also increased after treatment.

These promising studies provide a possible new therapy for the large number of POF patients.

Summary and Outlook

Female infertility is one of the factors leading to demographic problems. Because of the complex etiology of infertility and its difficulties to be cured, the search for new treatment is always ongoing. As a major research field that has become increasingly popular since the 21st century, stem cells are favored by researchers for their low immunogenicity, multi-directional differentiation and paracrine characteristics. As one sort of the stem cells, ADSC have broad application prospects because of their wide distribution in organisms and easiness to harvest. Through literature search and study of ADSC in the treatment of reproductive medicine area, mainly focusing on female infertility, the author found that not all diseases are suitable for the pursuit of stem cell therapy. For example, Turner syndrome is a chromosomal disease, pluripotent stem cell therapy is ineffective, so there are no relevant studies. PCOS and endometriosis have formed relatively fixed therapies. From endocrine disorders to ovulation disorders, there are corresponding effective drug and surgery to ameliorate syndromes, so ADSC relevant studies are not abundant. Yet existing researches proved the effectiveness of ADSC in both diseases. In contrast, intrauterine adhesions and premature ovarian failure, as two diseases that lack efficient treatments, are studied along with ADSC quite thoroughly. The feasibility and effectiveness of ADSC in both diseases have been proved. The trials that have been carried out so far have shown the therapeutic potential of ADSC in related diseases. It is worth conducting further researches in the future in order to clarify how ADSC can

treat infertility-related diseases and eventually apply ADSC to clinical practice.

Conflicts of Interest

All authors declare no conflicts of interest.

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