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Chapter

Mesenchymal Stem Cell Therapy of Male Infertility

Amin Tamadon, Ulanbek Zhan-byrbekuly, Ilyas Kairgaliyev and Arezoo Khoradmehr

Abstract

Nowadays mesenchymal stem cell (MSC) therapy offers a broad spectrum of treatment of different conditions, including male infertility. Lots of studies suggest that injection of MSC promotes differentiation of germ cells and/or stimulates gonadal tissue development. Currently, there are plenty of MSC therapies of azoospermia which have been studied on animal models and demonstrated good results. Most of the studies were conducted using MSC derived from adipose tissue, the bone marrow, and umbilical cord. Despite the fact that this type of treatment in humans is not established as a first choice option, the use of these techniques gives us hope for a gradual introduction into our daily practice.

Keywords: infertility, azoospermia, stem cell therapy, mesenchymal stem cell

1. Introduction

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. This disorder affects one in six couples [2]. Different factors including genetics, environmental factors, and anatomical defects have been illustrated to play a role in the fertility ability of individuals [3, 4].

After identifying the high capability of stem cells to produce different cell types, a number of scientists have proposed the use of stem cells and cell-based therapies as a possible new therapeutic choice for male infertility [5]. Stem cells are undifferentiated cell types that have two main characteristics, self-renewal with the production of identical daughter cells, and the ability to differentiate into more specialized cell types. The two main non-manipulated stem cell classes are embryonic (ESCs) and adult stem cells (ASCs) [5]. The next type of stem cells is induced pluripotent stem cells (iPSCs) which are genetically manipulated somatic cells [6]. The experimental platform for understanding the development of germ cells could be provided by the *in vitro* generation of male germ cells from stem cells [7, 8].

The ESCs, iPSCs, and spermatogonial stem cells (SSCs) are among the most investigated stem cells for the production of male germ cells in *in vitro* conditions [9, 10]. Application of these cell types has some limitations. ESCs present with some ethical problems and their sources are limited. iPSCs have both oncological and genetic instabilities. SSCs have low content in the testis, and their isolation, identification, and culturing are difficult *in vitro*.

On the other hand, mesenchymal stem cells (MSCs) do not have such problems in applications. MSCs are a group of ASCs which are available in most tissues. These cells were separated from the bone marrow [11], adipose tissue [12–14], hair follicle [15], endometrium [16, 17], dental pulp [18], nose [19], umbilical cord [20], and menstrual blood [21]. The MSCs in bone marrow stromal comprise a restricted area; but it can be easily proliferated [22]. These cells have the potential to proliferate and differentiate into other cells such as osteoblast [23, 24], adipocyte [25], chondroblasts [26], and neuron-like cells [27, 28] which can be a good candidate for treatment of male infertility. MSCs contains heterogeneous population of cells and contain pluripotent stem cells, namely multilineage-differentiating stress-enduring cells, which is the same as ESCs, which has the ability to differentiate into all cells from three germ layers spontaneously [29, 30].

2. Treatment of male infertility by MSC transplantation

Several animal studies have been conducted to investigate the effect of MSC transplantation on azoospermia. The effect of bone marrow-derived MSCs (BM-MSCs) and adipose tissue-derived MSCs (AD-MSCs) in induced azoospermia rodents was explored [11, 12, 24, 26, 31, 32]. After busulfan injection for azoospermia induction [33], the rats were injected with the MSCs into rete testes. After 2 months, testes treated with MSCs appeared morphologically normal. Spermatogenesis was detected, not in every but in some tubules of cell-treated testes. The trans-differentiation of MSCs into spermatogenetic cells in the appropriate microenvironment has been shown in some studies [32]. To demonstrate the entire recovery of spermatogenesis, rats, which were under cell treatment, were mated, and consequently next generations were obtained. The GFP expression was identified in the MSCs derived from the bone marrow and adipose tissue and in the sperm of offsprings as well [32].

Numerous *in vivo* research surveys have been conducted to assess the spermatogenesis induction potential of mesenchymal stem cells in mouse and rat animal models. In the mentioned study groups, bone marrow-derived mesenchymal stem cells have been used for the induction of spermatogenesis. There are some disputes, in mice model, regarding advisability of bone marrow-derived mesenchymal stem cell transplantation in azoospermic mice, for example, there was a report that bone marrow-derived mesenchymal stem cells could not differentiate into sperm [34], but other studies confirmed the generation of germ cells *in vivo* in BM-MSC-transplanted mice [35, 36]. At the same time, in azoospermic rat model, BM-MSC allotransplantation amplified endogenous fertility recovery in both testicular torsion model and busulfan-induced model of azoospermia induction [26, 37–40]. The potential of BM-MSCs to differentiate or trans-differentiate into multi-lineage cells, secrete paracrine factors to recruit the resident stem cells to participate in tissue regeneration, or fuse with the local cells in the affected region has been demonstrated [39].

The next group used AT-MSCs for induction of spermatogenesis. Intra-tubal injection of AT-MSCs in rat model of busulfan-treated azoospermia led to recovery of fertility [12, 32]. The last group of studies induces spermatogenesis using xenotransplantation of human umbilical cord MSCs in immunodeficient mice seminiferous tubule [41] or a combination of *in vitro* differentiation of induced pluripotent stem cells from mice and humans into germ cells, and also their transplantation was performed to obtain advanced differentiated spermatozoa [42]. Interestingly, the capability of human umbilical cord MSCs (UC-MSCs) for differentiation into germ cells in the lumen of seminiferous tubules of immunocompetent mice has been shown [41, 43]. Furthermore, the therapeutic effects of BM-MSCs against toxic effects of lead (Pb) in the male gonads of rats have been shown [44].

MSC transplantation may induce reconstitution of the tubular microenvironment in azoospermic hamster which helps the remaining inactivated germinal cells to proliferate in the host seminiferous tubules. Sertoli cells play a major role in cooperation with seminiferous tubules, providing cyclic and dynamic regulation of spermatogenesis. In recent time, it has been demonstrated that in *in vitro* co-culture system, there is an availability of Sertoli cells to mediate differentiation of male germ cell-like cells, which were derived from human umbilical cord mesenchymal stem cells [45]. Moreover, Sertoli cells are considered as immune tolerant cells [46], and they can cause protection and survival of the allotransplanted donor AT-MSCs against inflammatory or immune reaction. In contrast, the hypoimmunogenic character of mesenchymal stem cells makes them appropriate for allogenic transplantation [47]. Nevertheless, mesenchymal stem cells generate immunosuppression or immunosurveillance upon transplantation [48]. It is interesting to mention that, related to the treatment of azoospermia, IV allogenic bone marrow-derived mesenchymal stem cell transfusion encourages the production of antisperm antibody modulated by immune system, after testis rupture in mice [49], which illustrates the other therapeutic potential of mesenchymal stem cells in the treatment of infertility. In fact, the possible mechanisms of azoospermia healing by mesenchymal stem cells are unclear; three main mechanisms could be responsible for the recovering of testicular function during the tissue regeneration process period by mesenchymal stem cells. The first option of mesenchymal stem cells differentiation into the spermatozoa via appropriate induction conditions as it has been demonstrated in rats models [32]. Another mechanism which is not confirmed yet is that secretion of growth factors by mesenchymal stem cells stimulates the restoration of spermatogenesis in the inactivated spermatogonia stem cells or Sertoli cells. And the last one is that mesenchymal stem cells merged with the endogenous spermatogonia stem cells recover the spermatogenesis, which is also needed to be further studied deeply.

The necessity for consideration of another point in cell therapy of azoospermia was illustrated by histomorphometric analysis of the treated seminiferous tubules [31]. The increase of the area of the seminiferous tubules before transplantation caused the decline of the number of tubes per unit area in azoospermia. This pathological condition may be created due to decrease of cellular layers which caused the reduction of the tubal structure and collapsing of several tubules under the pressure of intratubular hydrostatic pressure of hamster seminiferous tubules. The growth of the amount of the spaces in testis may result in rise of the other tubes' diameter and also decrease in intratubular hydrostatic pressure. It is necessary to mention that the role of this pressure in the mechanism of spermatogenesis has not been clarified, but it could be the one reason for the increase of diameter of cellular layer in mesenchymal stem cell-treated tubes. Next, histomorphometric analysis with the increase of the number of tubules per unit area in mesenchymal stem cells treated tubes has been obtained [31]. This alteration may be caused by the decline of the volumes of intertubular spaces or by the busulfan therapy complications. Moreover, the increase of the whole area of tubes during azoospermia induction could reduce the ability of contraction of contractile myofibroblast cells, in which the decrease of intratubular hydrostatic pressure in peritubular layer probably resulted in the reduction of spermatozoa concentration in epididymis after mesenchymal stem cell therapy.

3. Conclusion

The obtained results of performed research trials on animal models provide a better and deeper overview of MSC therapy in male infertility conditions. The

demonstrated results of used options in the treatment of these conditions revealed that methods using the MSCs derived from umbilical cord, adipose tissue, and the bone marrow appear more appropriate to recover the fertility due to better results. Although a case report is available for treatment of azoospermia in man [50], applying those methods into the human practice seems to be investigated before introducing this method into clinic.

Conflict of interest

The authors declare no conflict of interest.

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