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Review Paper: Mesenchymal Stem Cells as a Resource for Male Infertility Treatment

Hamed Fereidooni[1*], Mohamad Reza Sadraei[2]

1. Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

2. Department of biology, Collage of Science, Shiraz branch Islamic Azad University, Shiraz, Iran

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ABSTRACT

Male infertility due to decreased semen quality is a growing global problem. Commonly used strategies for treating infertility include medication, intrauterine insemination, and in vitro fertilization. In recent years, mesenchymal stem cells (MSCs) have created new opportunities to treat a variety of disorders, including infertility and new expectations for managing reproductive disabilities. Stem cells (SCs) are undifferentiated cells that are able to regenerate and proliferate and are also able to produce specialized cells under appropriate conditions. They are present in all stages of the fetus, embryo and adult and can multiply in different cells. While many questions remain about SCs, SCs have undoubtedly opened up new avenues for infertility treatment. In this review, we discuss and summarize different stem cell approaches to the treatment of male infertility to provide updates on SCs therapy research.

Corresponding Author:
Hamed Fereidooni, PhD
Address: *Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran*
Tel: *+987132305488*
E-mail: *fereidooni_hamed@yahoo.com*

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1. Background

Male infertility means the inability of a man to conceive a woman with the ability to have children(1). Male infertility accounts for between 40-50% of all infertility problems (2). Infertility in men is usually caused by defects in semen(3).male infertility is usually caused by defects sperm production. This is often due to a number of reasons, including low sperm production, defective or immobilized sperm, or obstruction that prevents sperm release(4). Diseases, injuries, chronic heart problems, lifestyle and other factors can affect infertility(5).

Today, infertility and its individual and social problems are considered as one of the most important issues in social life. In Europe, 14% of couples of childbearing age suffer from this problem(6). Among Iranian couples, this infertility rate is higher than international standards and is about 20.2%(7). A variety of disorders, including genetic, hormonal, and physical and mental problems can contribute to infertility(8).

Infertility has a major negative effect on quality of life in cancer survivors(9). Patients receiving immunosuppression for non-cancer illnesses are also at risk of reduced fertility and would also benefit from another option for fertility preservation(10). The most common cause of infertility in men is a lack of sperm count, which occurs due to unknown factors(11). Due to the importance of the issue and the side effects of this defect, many efforts have been made to treat this complication. To solve this problem is considered. In the current decade, the emerging field of stem cell therapy has quickly become a new era of regenerative medicine. The diverse potential of stem cells is a focus of research of many scientists in molecular biology, genetic engineering, and even general medicine for developing new approaches in the treatment of a number of diseases, which have always been a challenge for clinicians.

2. Stem Cells (SCs)

In recent years, significant advances have been made in stem cell therapy. The diverse potential of stem cells has led to new approaches to treating diseases. One of these diseases is male infertility. SCs are those cells of the body that are not yet differentiated and have the power to proliferate and have the ability to differentiate and transform into other types of cells in the body(figure1)(12). The term SCs, first used in 1908 by A Russian histologist named Alexander Maksimov emerged(13). The origin of this designation was the observation of the reproduction of blood cells in the human body by another group of cells, and since some cells were considered as the source of other cells in the body, they were called SCs (14). SCs are classified by origin into the following categories: Embryonic SCs (ESCs), Embryonic germ cells, multipotent germ line SCs, Embryonic carcinoma cells, adult SCs(ASCs) and induced pluripotent SCs (IPSCs) (15). IPSCs, discovered in 2007, indicated the reprogramming of cells and their induction into pluripotent stem cells(8). These cells have a bright future for tissue repair and the treatment of infertility(16). The causes of male infertility can be divided into two categories of dysfunctional functions before and after the testicles. In male infertility, testicular function occurs before the release of pituitary and hypothalamic hormones entering the testis, while post-testicular function occurs due to physical reasons such as obstruction(17)

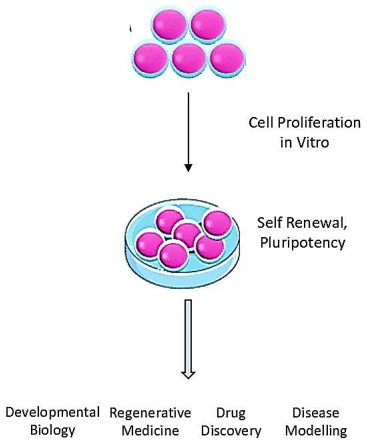

Figure 1. The Promise of the Pluripotent Stem Cells

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(MSCs) Extraction Sources: Mesenchymal stem cells (MSCs), which are a group of adult, stem cells. They have two main properties, which are the ability to proliferate and produce cells like themselves and differentiate into different types of functional cells, also because they do not cause an immune response, they are suitable for repair and because of this feature, they are suitable candidates for infertility treatment. These benefits in both autograft and allograft transplants, as well as being far from ethical issues, have led to interest in using these cells in therapy(18, 19).

The most important source for MSCs isolation is the bone marrow, first identified by Among these, umbilical cord MSCs due to easy access, non-invasive detachment during childbirth, lack of moral and spiritual barriers to separation(20), large volume extraction, rapid growth with high proliferation rate, spread to Colony form, having embryonic-like properties, being negative for CD34 and CD45 and being positive for CD44, CD105, CD29 and CD59, self-renewing capacity for adult SCs and also preventing immunological rejection have been considered(21-23). Human umbilical cord Warton-derived MSCs have unlimited proliferative properties that can, under suitable conditions, be derived from all three embryonic layers such as neurons, chondrocytes, cardiomyocytes, adipocytes, and cells. Bone cells, skeletal muscle cells, and more recently germ-like cells are differentiated (24).

Adipose Derived Stem Cell (ADSc): In recent years, adipose tissue has been considered as an available source for stem cell extraction. Separating stem cells from adipose tissue is easy and has few side effects. This population consists of adipocytes, stromal cells, which are composed of immature adipocytes (progenitor cells), fibroblasts, smooth myofibroblasts, endothelial cells as well as immune cells, and blood cells (25). Injection of adipose-derived MSCs (ADSc) has been reported as an effective method in improving sperm parameters including movement and reducing DNA failure and repairing sperm damage (26). ADSc-derived proteins, due to their similarity to factors in seminal fluid, can have many positive effects on sperm disorders and help treat infertility, as well as improve sperm parameter (27).

Bone marrow Derived Stem Cell (BM-SCs): Bone marrow is the main source of adult SCs. There are two types of SCs in bone marrow.

A. Bone marrow hematopoietic SCs

These SCs are the primary progenitor cells, and all myeloid and lymphoid blood cells are differentiated and can even form bone marrow after radiotherapy (28).

B. Bone marrow mesenchymal cells

These cells are different from hematopoietic cells. Mature BM-SCs are a mixed cell population and have the ability to differentiate into hematopoitic as well as non-hematopoietic cells such as endothelial cells, bone, muscle and nerve (29). BM-SCs, as hypoimmune cells have immunomodulatory properties, therefore they could be a good option for transplantation.(30) Studies have shown the effects of BM-SC immune modulation on the production of anti-sperm antibodies in mice after testicular rupture. Because Sertoli cells are immune-resistant cells, this ensures the survival of the injected cells after transplantation (20, 31)

Umbilical cord Derived Stem Cell (UCSCs): Cord blood is blood that is present in the umbilical cord and placenta after birth. This blood is one of the most important sources of non-embryonic stem cells and has hematopoietic SCs and MSCs. Umbilical cord hematopoietic SCs are able to differentiate into red blood cells and immune cells (32). These cells have advantages over embryonic and adult SCs (33). Their use has no particular moral problems and is also less immunogenic and less stimulates lymphocytes (34). There is also the possibility of rejection of these cells and infection after transplantation Other resources are less(35). UcMSC may be a candidate to provide an in vitro model to assist the study of germ cell growth. UcMSCs can be differentiated from male germ cells in vitro, but germ-like cells derived from UcMSC express only some of the germ cell markers. (36). cell-to-cell interaction between UcMSC and SC plays an essential role in differentiating male germ cells from UcMSC (37).

3. Spermatogenesis

Spermatogenesis is a complex and highly organized process of proliferation and differentiation of spermatogonia SCs that, during successive divisions of mitosis and meiosis, eventually differentiate into countless spermatozoa(38). The formation of the

sperm from a germ cell precursor, its maturation, transport, viability, and the final steps of fertilization are all complicated and sensitive processes. The production and formation of sperm occurs in the seminiferous tubules of the testis. Seminiferous tubules contain germ cells at various stages of development as well as the somatic cells known as Sertoli cells (24).

Germ cells during meiosis may have chromatin decondensed; therefore they are particularly susceptible to nuclear damage. During mitotic and meiotic divisions, several major types of cell can be distinguished in mammalian seminiferous tubules. These are the diploid stem germ cells (spermatogonia); germ cells after the first and second meiotic division (primary and secondary spermatocyte); developing haploid germ cells (spermatids) and testicular sperm (39).

4. The Role of Stem Cells in Sperm Production

Spermatogonia SCs are found in all species that maintain spermatogenesis throughout a man's lifetime and are constantly being produced inside the testicles, producing more than 100 million of these cells daily are the bases of sperm production(38). Spermatogonia SCs, with their ability to regenerate and differentiate into daughter cells, play an important role in the production of the next generation and the transfer of genetic material to it, so they are unique among different SCs in the body. The self spermatogonia stem (SPG) cell theory suggests that the volume of de novo mutations vary among sperm. Karyotyping is important for selection SPG (40). Preserving SPG for differentiation in the future could help address the 30% of men with unsuccessful surgical sperm retrieval (41).

5. Stem Cells Transplantation and Cryopreservation for Male Infertility

Transplanting SSCs into a member of the same species or returning to the original host is a useful way to keep SSCs and sperm out of the donor. Increasing the level of seminiferous tubules before transplantation decreased the number of tubes per unit area in azoospermia (42). Using autologous sperm stem cell transplantation may be a practical and useful method in young men who are about to undergo treatments such as chemotherapy or radiotherapy (43). If the microenvironment is supported, different haploid cells can be transplanted into the donor testis, or the differentiation into functional sperm can continue (44).

Several studies have been performed to evaluate the effect of bone marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs) on azoospermia in animal's model which have been chemically or surgically created(45). Testes treated with MSCs appear to be morphologically normal. Spermatogenesis has been detected in some tubes of cell-treated testes, and changes in the differentiation of MSCs into spermatogenic cells have been shown in some studies. MSC therapy improves the expression of germ cell markers in the testes (46). In addition, MSCs can reduce the factors contributing to infertility by reducing apoptosis and suppressing anti-sperm antibodies, indicating an impressive effect of MSCs in the treatment of infertility. BM-MSCs significantly reduce testicular oxidative stress by increasing antioxidant capacity and decreasing great levels of malondialdehyde (47). In addition, they increase sperm concentration and improve sperm quality. Due to the irreversible nature of spermatogenesis damage in patients with azoospermia, testicular biopsy and assisted reproductive technologies are the only ways to achieve fertility. However, due to the fact that the use of these technologies has limited success in the treatment of azoospermia and due to its unlimited source and high differentiation potential, MSCs have been considered as a potential new therapeutic agent for infertility treatment (48, 49).

MSCs transplantation was evaluated to improve spermatogenesis in later generations. For this purpose, growth factor proteins GFP that represent bone marrow MSCs were examined at the desired level, in addition to morphogenetic proteins (BMPs) and beta growth factor (TGF-β), which are male germ cells and have the ability to regenerateand improve cell function (42, 50). Testosterone as sexual hormone is secreted by Leydig cells, which is involved in the maturation of spermatids and the elevated of FSH and LH secrete by the anterior pituitary gland. MSc increase secretion of testosterone, it also produces stem cell factors in the damaged testicle(51, 52)

Numerous studies showed the BM-MSC-transplanted in mice can generation of germ cells in vivo and differentiate into sperm, In addition, BM-MSC transplantation in testicular torsion and azoospermia in a rat model showed improve fertility(53).

Table 1. overview of application of different SCs in animal studies used for infertility treatment

Author	Year	Stem cell type	Method Of Use	Outcome
Abd Allah et al. (55)	2017	Human Umbilical cord blood stem cells	The injection of these cells into testis	The injection of these cells into busulfan-induced azoospermia mice restored the spermatogenic Ability
Cakici et al. (42)	2014	Adipose derived MSCs	Transplantation of ADMSCs into testes of busulfan-treated mice	Transplantation of MSCs derived from adipose tissue could be used for recovery of spermatogenesis and treatment of infertility
Hassan et al. (61)	2014	Bone marrow MSCs	Treatment of rats with BM-MSCs after injection of lead nitrate	Treatment with MSCs can decrease the toxic effects induced by lead nitrate and it can be used as an effective way for treatment of infertility
Sabbaghi et al. (49)	2012	Bone marrow MSCs	Transplantation into torsion azoospermia testes	the differentiation of the MSCs into germ cells showed no regeneration of mature sperm after 95 days post-transplantation
Ghasemzadeh et al. (50)	2016	Bone marrow MSCs	Transplantation into the testes of infertile rats	BM-MSCs had the capacity to differentiate into spermatogonia in the testes
Vahdati et al. (62)	2017	Bone marrow MSCs	Bone marrow MSCs transplantation to busulfan induced azoospermia hamster model	BM-MSCs transplantation improved spermatogenesis in busulfan-induced azoospermia model
Mehrabani et al. (46)	2015	ADMSCs	The injection of ADMSC into the efferent duct of right testes	The histological examination demonstrated the presence of spermatogenesis in treated seminiferous tubules
Karimaghai et al. (59)	2018	ADMSCs	Injection ASCs or PBS into efferent ducts of busulfan-sterilized hamsters	Presence of spermatozoa in Seminiforous tubules of mice from the ASC-transplanted group
Kadam et al. (63)	2017	bone marrow or hematopoietic SCs	Injection of 1×105 MSCs enriched by bone Marrow into the rete testis of busulfan-treated mice	Higher percentage of spermatogenesis in MSC-injected group; detection of cells coexpressing Leydig and Sertoli

Adipose tissue MSCs and umbilical cord MSCs were also used to treat azoospermia as well as to induce spermatogenesis, injecting them into the seminiferous tubules to improve fertility in mice and rat models also human umbilical cord MSCs (UC-MSCs) showed the ability to differentiate into germ cells in the seminiferous tubules (Table1)

In adult patients with cancer undergoing treatments that may interfere with fertility, sperm cryopreservation is a viable option(54). Immature recipients in

infertility treatment applying cryopreservation SCs are an encouraging technique in the male infertility therapies(Table1)(55). Slow freezing protocols are accessible to preserve human testicular tissue over the lasting term, and challenging protocols such as vitrification have also been extended(56). Studies have shown that induced pluripotent stem cells have the ability to transform and differentiate into germ cells at all stages of spermatogenesis, such as spermatozoa, primary spermatocyte, and secondary spermatocyte and round spermatid, indicating their ability to treat infertility (57, 58).
Another study showed that histopathologically, injection of MSCs in azoospermia increases seminiferous tubules, increases tube diameter, reduces interstitial space and improves tube structure, indicating the restorative effect of stem cells in improving the mechanism of spermatogenesis(59, 60). Therapeutic studies of MSCs in animal models have shown the possibility of using these cells in the treatment of azoospermia in humans and have been proposed as a new treatment for inducing spermatogenesis and infertility treatment in men.

6. Conclusion and Future Prospects

Advancement in medical knowledge and practice is linked to SCs research especially in reproductive medicine. MSCs have demonstrated great potential and availability for treating female infertility in animal and human studies. Although clinical trials have been planned for the effect of MSCs transplantation in the treatment of
, the outcome is currently unknown. Different sources of MSC in different studies and evaluation methods make it difficult to compare the results with each other, but due to this, more favorable isolation and fewer side effects should be considered to achieve the desired cell follow-up to achieve more and more suitable cells. In summary, most studies have shown that MSCs can be used as a viable option for the treatment of azoospermia in men. However, there is a need for further evaluation of the effectiveness of these cells in treating infertility.

7. Abbreviations

MSCs: mesenchymal stem cells, SCs: Stem cells, ESCs: Embryonic SCs, ASCs: adult SCs, IPSCs: induced pluripotent SCs, ADSc: Adipose Derived Stem Cell, UCSCs: Umbilical cord Derived Stem Cell.

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Authors' contributions

I confirm that all authors had access to the data and participated in the writing of the manuscript and have seen and approved the submitted version. H Fereidooni designed the study. MR Sadraie and H Fereidooni wrote the manuscript.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not applicable for this section

Competing interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the research reported

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