Current Perspectives on Stem Cell Therapy for Erectile Dysfunction

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ABSTRACT

Introduction: Erectile dysfunction (ED) is a common sexual disorder that affects the lives of millions of male patients and their partners. Various medical and surgical therapies exist, with the most common being oral intake of phosphodiesterase 5 inhibitors. One therapeutic strategy in preclinical development to treat ED is stem cell transplantation.

Aim: To examine the studies that have investigated stem cells for the treatment of ED.

Methods: A literature review was performed through PubMed focusing on stem cells and ED.

Main Outcome Measures: An assessment of different types of stem cells and how they may be applied therapeutically in the treatment of ED.

Results: The stem cell types that have been investigated for the treatment of ED include bone marrow–derived mesenchymal, adipose–derived, muscle–derived, testes, urine–derived, neural crest, and endothelial progenitor. Depending on the cell type, research has demonstrated that with transplantation, stem cells exert a paracrine effect on penile tissue, and can differentiate into smooth muscle, endothelium, and neurons.

Conclusion: Multiple stem cell lines are currently being studied for their potential to treat ED. To date, stem cells have proven safe and effective in both animal and human models of ED. More research is needed to understand their full therapeutic potential.

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Key Words: Stem Cell Therapy; Erectile Dysfunction; Penile Tissue

INTRODUCTION

Erectile dysfunction (ED) is a sexual disorder defined as the inability to initiate or maintain an erection that is satisfactory for sexual intercourse, impacting the lives of male patients and their partners.[1] It is estimated that at least 30 million men in the United States suffer from ED.[2] The Massachusetts Male Aging Study found that 52% of men between the ages of 40 and 70 have reported some degree of ED.[3] After the age of 70, that percentage grows.

A penile erection is a complex event that requires vascular, neural, endocrine, and psychological inputs. It requires the integration of signals from nerves, endothelium, and smooth muscle; and when this signaling pathway fails, the result is ED.[4] A broad arsenal of medical therapies has been developed for the treatment of ED, with phosphodiesterase 5 inhibitors (PDE5i) being the most commonly prescribed medications due to their overall efficacy and few contraindications.[5] However, there are patients who do not respond to PDE5i, and still others who do not respond to any form of medical therapy, thus making the penile prosthesis the only viable option.

ED that is refractory to medical therapy is often observed in post-prostatectomy patients, diabetics, and those with veno-occlusive dysfunction due to severe Peyronie's disease. Nerve-sparing radical prostatectomy (RP) can lead to ED in up to 50% of patients, and is the result of damage to the neurovascular bundle or an indirect neuropraxia, all of which leads to hypoxia, fibrosis, and apoptosis of cavernosal nerve cells.[6,7] ED resulting from diabetes mellitus is caused by decreased nerve signaling, endothelial dysfunction, and increased oxidative stress.[8] In Peyronie's disease, an abnormal accumulation of fibrous plaques in the tunica albuginea often leads to penile malformations associated with veno-occlusive ED.[9] To explore the mechanisms and future treatments of these conditions, animal models have been developed to reproduce post-RP, diabetic, age-related and Peyronie's-related ED. One therapeutic strategy in preclinical and early clinical development is stem cell transplantation.

With the advent of stem cell use for the treatment of ED, researchers have evaluated a number of adult stem cells in experimental rat models. These stem cell types include bone

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marrow—derived mesenchymal stem cells (BM-MSCs), adipose—derived stem cells (ADSCs), muscle—derived stem cells (MDSCs), testes—derived stem cells (TDSCs), urine—derived stem cells (UDSCs), neural crest stem cells (NCSCs), and endothelial progenitor stem cells (EPCs).[10] A review of each lineage follows, along with the preclinical studies that have evaluated their use in treating ED. It is important to recognize that the mechanism through which these stem cells exert their effects may differ based on the particular cell lineage and the disease model being used. As such, examining the preclinical studies within the context of the cell type will serve to highlight the differing mechanisms that researchers have utilized to design effective therapies suitable for human trial.

Bone Marrow—Derived Mesenchymal Stem Cells

BM-MSCs have served as the model cell type in the study of stem cell therapy for ED. This cell line, originally isolated and cultured in vitro by Friedenstein, differentiates into a wide range of cell types including osteocytes, chondrocytes, myocytes, adipocytes, and pancreatic islets cells.[11–13] To obtain this stem cell line, the bone marrow must be aspirated. Then the BM-MSCs can be isolated from the hematopoietic stem cells by way of their selective adherence in tissue culture flasks. This cell line in particular has received greater therapeutic interest because of its low immunogenicity. Chamberlain et al demonstrated that BM-MSCs lack costimulatory molecules required for T-cell activation.[11] Another attribute of BM-MSCs is their ability to secrete proteins that promote cellular differentiation and proliferation, as well as modify inflammatory responses through modulation of cytokine production and immune cell suppression.[12]

Fall et al evaluated the effects of intracavernous BM-MSC injection in the bilateral nerve crush (BCNI) rat model for post-prostatectomy ED.[14] They found that treatment decreased the number of cells undergoing apoptosis, increased the speed at which neuronal (nNOS) and endothelial (eNOS) nitric oxide synthase normalized, and partially increased intracavernosal pressures (ICPs) as compared to control. However, despite nNOS recovery, erectile responses remained impaired, most likely because full erectile recovery is dependent not only on nerve regeneration, but also the preservation of cavernosal tissue. There have been other studies that observed similar efficacy of BM-MSC in treating the nerve crush injury rat model.[15–17]

The diabetic rat model also has been used to evaluate BM-MSC therapies for ED. Qui et al transplanted BM-MSCs into the corpora cavernosa of streptozocin-induced diabetic rats. This demonstrated an increase in erectile function, as well as increases in smooth muscle and endothelium cell concentrations, as compared to diabetic control rats.[18] Furthermore, they found that 4 weeks after treatment, only a few stem cells remained, suggesting that a paracrine mechanism was at work. Instead of differentiating and incorporating into the tissue after transplantation, these stem cells acted through the release of signaling molecules, resulting in immunomodulation and inhibition of fibrosis and apoptosis. In addition to their antiapoptotic effect within the corpora, Sun et al subsequently showed that BM-MSCs are capable of promoting neuroregeneration through the secretion of neurotrophins, specifically brain—derived neurotrophic factor (BDNF), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF).[19]

Adipose—Derived Stem Cells

ADSCs have similarly shown considerable therapeutic potential in the treatment of ED. In 2001, Zuk et al performed suction-assisted lipectomy (liposuction) of human adipose tissue to isolate ADSCs.[20] These cells could then be induced to further differentiate in vitro into adipogenic, chondrogenic, myogenic, and osteogenic cells. ADSCs also can be harvested from bone marrow, but this is an extremely painful procedure and results in a much smaller yield. Studies have shown that adipose tissue may have up to 500 times more ADSCs than bone marrow, making subcutaneous and visceral fat the most efficient location for ADSC extraction.[21] Studies regarding the exact location of ADSCs within the adipose tissue have led most researchers to believe that the cells reside in a stromal stem cell niche, which can be found within the adipose vasculature.[22] Depending on the cells' environment, differentiating potential includes vascular smooth muscle, endothelial cells, adipose tissue, and a variety of mesenchymal cell lines.[23] Once the adipose tissue is obtained, it must be further digested using a collagenase to isolate the stem cells, resulting in the adipose—derived stromal-vascular fraction (AD-SVF).[24] Specific cellular markers then sort the stem cells.

The cavernosal nerve injury model has allowed researchers to gain insight into how ADSCs may be used to treat post-RP neuropraxia.This model has since been used to better understand the mechanism of action of ADSCs.[25] One month after BCNI and simultaneous treatment with ADSCs, lysed ADSCs (lysate), or control, erectile function and penile tissue were evaluated. Results showed that both ADSCs and lysate led to a significant recovery of erectile function when compared to controls, along with a significantly higher expression of nNOS, increased preservation of smooth muscle, and reduced fibrosis. Since both the ADSCs and the lysed ADSCs exerted similar effects on surrounding tissue, the authors concluded that the mechanism of action was not the previously held notion of cell-cell induction, but rather the release of growth factors and cytokines in a paracrine fashion, similar to that of BM-MSC. In support of this hypothesis, one study showed that after ADSC injection, only a small proportion of stem cells was detectable at 5 weeks, yet improvement in erectile function was observed.[26]

To further clarify the mechanism-driving improvement in erectile function with ADSC, a study using EdU-labeled ADSC tracked cells at different time points after injection in a cavernosal nerve injury model.[27] It was found that stromal cell—derived factor-1 (SDF-1), which acts as a signal for recruitment for ADSCs, was upregulated in the major pelvic ganglion. This showed that cavernosal nerve injury leads to