Stem Cells for the Treatment of Urinary Incontinence

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Abstract Stress urinary incontinence (SUI) is highly prevalent. As of now, there is no minimally invasive long-term treatment available. Adult stem cells are nonimmunogenic and have the ability to self-renew and to differentiate into multiple cell types. Over the past decade, in vivo studies have described periurethral injections of adult-derived stem cells for the treatment of SUI. The ultimate goal has been to achieve a permanent cure for SUI by restoration of the intrinsic and extrinsic urethral sphincter and the surrounding connective tissue, including peripheral nerves and blood vessels. For this purpose, future studies need to focus on delivery systems, cell survival, and functional improvement of the urethral closure mechanism, including improvement of innervation and vascularization.

Keywords Stress urinary incontinence · Adult stem cell therapy · Mesenchymal-derived stem cells · Adipose-derived stem cells · Bone marrow-derived stem cells · Muscular-derived stem cells · Periurethral injection

Introduction

Urinary incontinence affects about 17 million people in the United States with an estimated annual cost of $32 billion [1]. Stress urinary incontinence (SUI), a common form of urinary incontinence, also is highly prevalent, especially in women [2]. SUI is associated with significant impairment in quality of life and has a significant socioeconomic impact, with costs steadily increasing as the population ages [3]. The female urethra consists of a proximal, a midurethral, and a distal segment. The elongation of detrusor muscle fibers at the bladder neck characterizes the proximal urethral segment. The midurethra consists of the inner smooth and outer striated muscles, which mainly build the urethral sphincteric complex [4]. The smooth muscle consists of a longitudinal and circumferential layer and is encircled by the striated rhabdosphincter muscle. Urinary continence depends on the integrity of the intrinsic sphincter and the extrinsic sphincter. The intrinsic sphincter consists of the mucosa, the submucosa, an estrogen-dependent vascular plexus, and smooth muscle layers. It achieves urethral coaptation passively and involuntarily. The extrinsic sphincter consists of the striated urethral rhabdosphincter and compresses the urethra voluntarily supported by the compressor urethrae muscle, the pubococcygeus, and the urethrovaginal sphincter muscle [4]. The pathophysiology of SUI is multifactorial, including atrophy of the smooth muscle and the rhabdosphincter, changes in connective tissue, changes in blood perfusion of the periurethral vasculature and submucosal tissue, and loss of neuronal mass. Those changes are seen after vaginal delivery [5] and as part of the aging process [6], which contributes to the development of this condition.

A number of surgical procedures are available to treat SUI. Injectable bulking agents are minimally invasive but have poor long-term efficacy. More invasive approaches, such as sling procedures and bladder neck suspensions, are more efficacious, but have a higher morbidity [7]. These limitations have motivated investigations into therapies that may provide safer and longer-lasting outcomes in the treatment of SUI by repairing the damaged continence mechanism. Given stem cells’ ability to induce tissue
regeneration, investigators have turned to the use of stem cells for the treatment of SUI. Stem cells represent a self-renewing population of cells derived from healthy tissue that can be differentiated into a variety of cells. The ideal strategy for curing SUI would allow for the regeneration of functional periurethral tissue to provide adequate mucosal coaptation and to restore resting urethral closure pressures.

Multiple animal models have been used to study the effect of stem cells in tissue regeneration of the urethra. A number of experimental models that simulate some of the components of the human pathophysiology of SUI due to trauma of vaginal delivery, such as vaginal balloon dilation [8] and pudendal crush injuries [9], have been described. Other more durable models, such as pudendal or spinal cord transection [10, 11] and urethrolysis [12], also have been validated.

Use of Adult Stem Cells for Restoration of the Urethral Sphincteric Mechanism

Embryonic stem cells are pluripotent cells obtained from the inner cell cluster of blastocysts. They have the potential to differentiate in vitro into cells from all three embryonic germ layers. To avoid ethical and political considerations limiting the use of embryonic stem cells, research into therapies for SUI has focused on the use of autologous adult-derived stem cells. These are a self-renewing population of cells, are present in niches in multiple organs, and hold the plasticity to transdifferentiate into cell types from different germ layers. In contrast to embryonic stem cells, adult stem cells tend not to be immortal and have more limited differentiation potential. These limitations also may make them safer, because they do not tend to form teratomas.

Investigations of the use of stem cells for the treatment of SUI have focused on mesenchymal-derived stem cells. Mesenchyme is connective tissue derived from the embryonic mesoderm. Many of these cells are easily expanded in vitro, can differentiate into cells derived from mesoderm as well as other germ layers, and are capable of releasing paracrine factors to stimulate the regeneration of surrounding tissue [13]. These cells can be isolated from different adult tissue sources, such as adipose tissue, liver tissue, muscle, amniotic fluid, placenta, umbilical cord, dental pulp, and bone marrow [14], and share similar surface immunophenotype and multilineage differentiation capacity [15]. Multiple adult-derived stem cells have been studied for the treatment of SUI. Table 1 provides a chronological overview of the literature of animal and human studies that have been conducted since the year 2000.

Preclinical Animal Studies

Bone Marrow-Derived Stem Cells

Of all mesenchymal stem cells, bone marrow-derived stem cells (BMSCs) have been most widely studied. They have been used for the regeneration of cardiac muscle [16], bladder detrusor muscle [17], anal sphincter muscle [18], and many other structures [19]. In a pilot study, Droste et al. [20] transplanted BMSCs into the bladder neck of athymic rats and pretreated them with the differentiation agent 5-azacitidine to induce myogenic differentiation. BMSCs expressed smooth and striated muscle antigens. Autologous BMSCs also have been transplanted into injured urethral sphincters of Sprague-Dawley rats [21•]. Urethral sphincters were injured with urethrolysis and cardiotoxin injection. One week after the urethral injury, the cultured BMSCs were injected periurethrally. Abdominal leak point pressure (ALPP) was measured preoperatively and 13 weeks after cell injection. Histological and immunohistochemistry evaluation verified that transplanted BMSCs survived and differentiated into striated muscle cells and peripheral nerve cells to a significantly greater degree than the cell-free group. Nevertheless, no significant difference was seen in ALPP among the groups [21•].

Muscle-Derived Stem Cells

Postnatal regeneration of skeletal muscle has been thought to emerge from local progenitors, such as skeletal muscle satellite cells. Muscle-derived progenitor or stem cells (MDSCs) can naturally differentiate to multinucleated muscle fibers and display stem cell characteristics [22]. MDSCs have the ability to undergo long-term proliferation, multipotent differentiation, and self-renewal. MDSCs are quiescent satellite cells found in myofibers that can proliferate to form myoblasts and, eventually, form myotubes and new muscle tissue. Chancellor et al. [23] conducted the first experiments using MDSCs harvested from striated muscle. In vitro expanded skeletal myoblasts obtained from mice were injected into the urinary tract of Sprague-Dawley rats. Contractile myoblasts and myotubes were verified by positive desmin expression [23]. Longer survival times of up to 28 days for autologous MDSCs transplanted into the bladder and urethral wall of rats have been demonstrated by Yokoyama et al. [24] and Yiou et al. [25]. Studies have shown that MDSCs are capable of restoring muscular contraction of the urethral sphincter 2 weeks after injection [26] and contribute to the functional recovery of damaged pelvic nerves [27]. It has been suggested that the formation of myotubes may activate intrinsic nerve regeneration and formation of
The potential to reconstitute peripheral nerves also has been seen after transplantation into severely damaged skeletal muscle [29]. The same group has shown that MDSCs contribute to the synchronized reconstitution of blood vessels, muscle fibers, and peripheral nerves [29].

In animal models, MDSCs also may improve neurogenic bladder dysfunction by reconstitution of damaged peripheral neuromuscular junctions [28].
nerve cells (e.g., Schwann cells, perineum) and vascular cells (e.g., vascular smooth muscle cells, pericytes, endothelial cells) [30••]. Preclinical trials for the application of this technology also have been conducted in larger animals. Myoblasts have been used for the treatment of SUI in a pig model and injected to the striated urinary sphincter. The animals have shown an increase in urethral pressure profile and muscular myofibrils [31].

Adipose-Derived Stem Cells

Fat tissue contains pluripotent cells, termed as adipose-derived stem cells (ADSCs), which have the ability to differentiate into cells of the same and of another germ layer, such as adipogenic, chondrogenic, myogenic, osteogenic, and neurogenic cells [32]. For the treatment of urinary incontinence, ADSCs are of special interest for mesodermal and neuronal regeneration and to promote revascularization. ADSCs are easily obtained from minimally invasive liposuction [33]. ADSCs can differentiate into fibroblasts [34], myoblasts [35], smooth muscle cells [36], endothelial cells [37], or skeletal muscle [38]. They can express specific striated muscle markers (e.g., desmin, myod1, myogenin, myosin heavy chain), form multinucleated cells characteristic of myotubes, and have been shown to regenerate the functional capacity of damaged skeletal muscle [38]. ADSCs express nerve growth factor at the time of neural differentiation. Neural-differentiated ADSCs present glial characteristics and promote nerve regeneration, as observed 7 days after transplantation in a rat model in vivo [39]. Rodriguez et al. [36] have described conditions necessary to differentiate ADSCs into functional smooth muscle cells, which express early and late smooth muscle markers, such as α-smooth muscle actin, caldesmon, SM22, smoothelin, and myosin heavy chain. Smooth-muscle differentiated ADSCs have the ability in vitro to contract and relax in response to pharmacologic stimuli [36]. In an immune-competent, incontinent rat model of SUI, periurethrally injected ADSCs exhibited in vivo differentiation into smooth muscle cells and improved urethral resistance [40]. Fu et al. [35] predifferentiated ADSCs with 5-azacitidine into myoblasts and injected these cells periurethrally into incontinent rats. After 3 months, a significant difference in bladder capacity and leak point pressure was observed between the control group and the pretreated group. An increased number of myoblasts under the mucosa and α-smooth muscle actin expression was observed 3 months after implantation [35]. Human ADSCs also have been delivered periurethrally in an athymic rat model [41]. ADSCs, which expressed smooth muscle markers, were viable in the lower urinary tract for up to 12 weeks. Other studies demonstrated improved urethral function after periurethral injection of ADSCs [42].

Human Studies

Few human trials have been conducted using autologous derived stem cells in the treatment of urinary incontinence, which all involved the use of MDSCs. Strasser et al. [43, 44] conducted the first clinical experiments in women and men with SUI. Myoblasts and fibroblasts were obtained from muscular biopsies of each patient. Autologous myoblasts were injected under transurethral ultrasound guidance into the rhabdosphincter of the midurethra. Separate injections of a suspension of autologous fibroblasts and collagen, which functioned as carrier material, were additionally performed into the submucosa cranial and caudal to the injection side of the myoblasts with good outcomes at 1 year [44]. Unfortunately, these published study results have been retracted due to deficiencies in obtaining patients’ consents, protocol irregularities, and a missing ethical committee approval [45]. Carr et al. [46] presented therapeutic efficacy in a clinical trial after transurethral injection of autologous MDCSs in eight women diagnosed with SUI. The study end point was at 12 months. Five out of eight women reported improvement, as demonstrated by a voiding diary and pad weight test, with the onset between 3 to 8 months postinjection. One patient achieved complete continence up to the study end point at 12 months. Two patients achieved reduction of 50% from their baseline incontinence episodes and received a reinjection after their initial injection between 4 and 8 months later with minor improvement [46]. The same group demonstrated a treatment effect of SUI in a blinded randomized study enrolling 29 female patients with SUI. In this study, patients received cystoscopic-assisted transurethral injections of autologous MDCSs at different cell concentrations with a second injection after 3 months. The follow-up end point was 1 year. Almost half of the patient population, who received two injections, reported no leakage at 12 months [47]. These promising early clinical results warrant further evaluation to validate results, determine durability and focus on safety and possible adverse reactions.

Conclusions

Future Directions

Although promising preclinical and clinical studies have demonstrated the potential for the use of adult-derived stem cells in the treatment of SUI, a lot is yet to be known. We have little understanding of how these cells are mediating their effects on the continence mechanism, how long they survive, or if they induce other local mediators, which may improve continence. There also are concerns regarding the
tendency for stem cells to migrate to other organs [48, 49]. Studies need to be conducted to increase the survival and retention of these cells in the target tissues. Future studies need to evaluate not only the mechanism of action of these cells but also the long-term safety. Lastly, myogenic defects are just one of the multiple components likely leading to SUI. Little has been done to evaluate how regeneration of neuronal mass or vascular components may contribute to the treatment of SUI and regeneration of functional urethral tissue.

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