Chapter 7
Bladder Dysfunction

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Abstract The studies focusing on the use of stem cells in treatment of different medical condition is growing over the time. But yet a few studies conducted to evaluate efficacy and safety of stem cell therapy in different types of bladder dysfunction. In addition, these studies are mainly focuse on experimental models rather than tissue engineering and bladder regeneration. There are some defined models of bladder dysfunction in literature: bladder outlet obstruction, cryoinjured, diabetes, ischemia, and spinal cord injury models. Among the different subgroups of stem cells, adipose derived stem cells (ADSCs), skeletal muscle derived stem cells (SkMSCs) and bone marrow stem cells (BMSCs) are used more commonly in favor of bladder dysfunction treatment. These stem cells with unique characteristics and multiple mechanisms of action (migration, differentiation and their paracrine effect) are so suitable for using in different clinical approaches to treat bladder dysfunction including bladder bioengineering and bioprinting.

This chapter is aimed at providing the current status of using stem cells for bladder dysfunction treatment as well as exploring future prospects on this topic.

Keywords Bladder dysfunction · Treatment · Stem cell

7.1 Introduction

While various therapies have been developed for different types of bladder dysfunction, such as detrusor overactivity or underactivity, but little progress has been made in reduction of voiding dysfunction using stem cells. Recently, growing attractions are toward stem cell therapy in the field of bladder dysfunction and investigators are willing to document promising results in this area.

Stem cells (SCs) or Mesenchymal stem cells (MSCs) have ability of self-renewal and differentiation to create different lines of mature cells [1]. Because of their distinc-

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tive characteristics, unique plasticity of migration, and capacity for tissue repair or regeneration, stem cells are use to perform injury repair in different injured organs. Among bladder dysfunction models, bladder outlet obstruction (BOO) is the well-defined one. The other forms of bladder dysfunction template are yet in an incomplete state. There are current clinical efforts to both prevent and cure BOO. There are studies conducted to provide better understanding of the cellular-level consequences and specific mechanisms responsible for developing BOO. Although abundant reports have demonstrated the MSCs capability to engrave different tissues like brain, heart, liver, and lung, data on bladder dysfunction repair is still scarce [2–4].

7.2 Stem Cells Sources and Their Mechanism of Action in Bladder Dysfunction Recovery

MSCs have self-renewing ability and can differentiate into a range of different cell types, such as chondrocytes, osteoblasts, and adipocytes. While all MSCs including bone marrow stem cells (BM-MSCs), skeletal muscle stem cells (SkMSCs), and adipose tissue stem cells (ADSCs) have similar properties, their availability vary very much based on therapeutic goals [5]. For instance, although SkMSCs need a long expansion with a difficult isolation procedure, it is possible to prepare ADSCs within a few hours. ADSCs are some kinds of mesenchymal cells which are found in the perivascular areas of the adipose tissue [6]. The advantage of ADSCs is that plenty of them are easily accessible in comparison to other types of stem cells. In experimental studies ADSCs showed efficacy on urological diseases [7, 8]. SkMSCs are primarily used in injury models [9, 10]. As a stem cell source for autologous transplantation, SkMSCs have several benefits because the skeletal muscle can be reached quite easy and safe and during surgery SkMSCs can easily be harvested. Cells in the $CD3^{-}/CD45^{-}$ fraction (Sk-DN cells) and $CD34^{+}/CD45^{-}$ fraction (Sk-34 cells) can reconstitute nerve-muscle units of the blood vessel synchronously after transplantation. SkMSC transplantation results in significant functional regeneration of skeletal muscle cells, vascular cells and peripheral nerve cells through cell differentiation [11, 12]. So, different human tissues can be used as the source of stem cells and selection is based on the goal of their therapeutic use.

Stem cell migration, differentiation and their paracrine effect are discussed here for better understanding of these cells mechanism of action for treating bladder dysfunction.

SCs migration into the bladder tends to be associated with improvements in histopathological and functional parameters [13]. MSCs can migrate into the damaged, ischemic or inflamed tissues. This migration is contributed to expression and secretion of specific chemokines by such tissues [14]. There is a wide range of studies on the stem cells migration into many different organs [15–18].

Differentiation is the novel mechanism for stem cell therapy, and bladder regeneration via differentiation has been recurrently shown in models of nonpathogenic bladder. Many studies conducted focusing on non-pathogenic tissue regeneration

models have documented the differentiation of stem cells into detrusor smooth muscles that can finally lead to bladder repair or even replacement [19, 20].

Although differentiation is an important mechanism, it seems rational to assume the effects of paracrine cytokines and growth factors released by transplantated MSCs or adjacent cells. That is called "paracrine effect". SCs secretory factors are shown to induce therapeutic effects by regulating local and systemic immune responses and promoting regeneration of local tissue, as well as recruiting host cells. MSCs replace damaged cells, by secreting growth factor via their paracrine effect [21]. BM-MSCs or ADSCs may secrete multiple growth factors, such as insulin-like growth factor (IGF), hepatic growth factor (HGF) and endothelial vascular growth factor (VEGF) [22]. They play an important role in an antifibrosis pathway in the damaged tissue, which indicates that the reduction of fibrosis is rather contributed to paracrine processes than cell incorporation [15, 23, 24]. HGF as a strong mitogen of hepatocytes has an important role in tissue regeneration [21, 25]. Besides antifibrotic functions, BM-MSCs or ADSCs can also secrete free radical scavengers and antioxidants into ischemic tissues [26].

These three interesting charachteristics of stem cells make them capable for using in treatment of various pathologic conditions and that's why stem cell therapy attracts attentions for treating bladder dysfunction.

7.3 Stem Cell Therapy and Pathogenic Models of Bladder Dysfunction

Kim et al. in a comprehensive review explain deferent models of bladder dysfunction such as bladder outlet model, bladder ischemia model, diabetes model, etc. [27]. The BOO model is the only well-described model of bladder dysfunction and the other pathological models are yet in a challenging condition.

7.3.1 Bladder Outlet Model

Bladder outlet obstruction (BOO) as a result of collagen accumulation is a common condition involving elderly males. Deposition of collagen in the bladder is seen in various pathological processes and ultimately ends in bladder fibrosis and makes the bladder flaccid. The bladder fibrosis impairs function of detrusor smooth muscles and bladder compliance [28]. Bladder dysfunction was observed when the bladder outlet was obstructed [29].

Lee et al. stated that in a rat BOO model, transplantation of human MSCs marked with nanoparticles (superparamagnetic iron oxide) into the bladder, prevented fibrosis and improved bladder dysfunction [16]. Growth factors also have an important role in bladder wall remodeling following an outlet obstruction [30]. This finding

that human MSCs over-expressing HGF inhibite collagen deposition and improved cystometric parameters in rat BOO, was also reported by Song et al. [17].

Fibrosis and hypertrophy are believed to cause vessel compression that lead to reduction of bladder blood flow. So, as a result, severe tissue ischemia can be a possible explanation of bladder dysfunction [31, 32].

Differentiation of MSCs into the detrusor smooth muscles is not only make them suitable to treat detrusor overactivity but also make them useful in underactive detrusors. Nishijima et al. [33] showed that transplanted BMCs would cause an improvement in detrusor muscles contractility after differentiation into smooth muscle-like cells in an underactive BOO bladder.

7.3.2 Bladder Ischemia Model

Using bilateral ligation of the iliac artery [34] or hyperlipidemia [35], The ischemia prototype for the bladder is found. Several research [36] have shown that ischemia can lead to major structural and functional changes in the bladder. The bladder dysfunction mechanism caused by ischemia is complex, and ischemic denervation may be involved. This makes the M-cholinergic receptors hypersensitive to acetylcholine [37] which results in bladder overactivity. Since the ischemia is a high probable process in the elderly, ischemia rat model can be a proper model for investigating detrusor changes caused by aging [34]. Huang et al. [35] indicated that bladder instillation or intravenous administration of ADSCs can improve both tissue and urodynamics parameters in rats with overactive bladder.

7.3.3 Diabetes Model

Diabetic bladder dysfunction (DBD) usually causes gradual and progressive impairment in both storage and voiding phase. In early phase, DBD causes detrusor overactivity. Over the time, detrusor muscle will be decompensated, resulting in an underactive or atonic bladder.

In rats treated with ADSCs, Zhang et al. [38] reported voiding function improvement compared to saline rats treated with phosphate buffer. The DBD trend in their experimental model was hypocontractile bladders. Although some ADSCs have been transformed into detrusor smooth muscles, their paracrine antiapoptotic effects can not be ignored in this process. These data will offer an opportunity for clinical use of stem cell therapy for difficult-treating underactive bladder conditions.

7.3.4 Spinal Cord Injured Model

spinal cord injury (SCI) causes so many lower urinary tract problems such as recurrent infections, impaired bladder compliance and voiding dysfunction [39]. In a study, it was shown that spinal cord injured rats had a higher thickness of bladder wall and a higher collagen to smooth muscle ratio [40].

The main goals of urinary tract care in spinal cord injured patients is to reduce the episodes of urinary infections, maintain function of kidneys, and enhance patients' quality of life. In an animal model study, neural stem cell transplantation into the damaged spinal cord caused an improvement in behavior of the bladder [41].

The functional recovery of the bladder after SCI is limited because new neurons or glial cells are not generated after maturation of central nervous system.

Nonetheless, recent studies have shown that transplanted neural progenitor cells make it easier to restore bladder function by regenerating the damaged tissues [41–44]. Stem cells are directly inserted with a needle into the affected lesion in most of these trials. In an study it was shown that intravenously administered BMSCs resided in L3-4 which cause bladder function improvement in rats following spinal cord injury [45]. So, both intravesical and intravascular administration of the stem cells can be used in treating bladder dysfunction in spinal cord injured patients. Although, more strong studies are required to assess the safety, efficacy and durability of stem cell therapy and studies to make comparison between different rout of stem cell administration.

7.3.5 Cryo-Injured Model

In cyro-injured model, bladder hypertrophy exists but with an inappropriate collagene to smooth muscle ratio just like what happens in BOO models [46]. The main result of stem cell transplantation into cryo-injured model is to decrease surviving smooth muscle cells' size and differentiation of stem cells into the smooth muscle cells. This compensatory smooth muscle cells hypertrophy play a key role in remodeling of the injured bladder.

Huard et al. [47] showed that injected muscle-derived cells (MDCs) could nest in the bladder and enhance the bladder contractility in the cryo-injured model.

Sakuma et al. [48] have shown that fat cells that were dedifferentiated could differentiate into smooth muscle cell lines and contribute to bladder smooth muscle regeneration.

Thus, interestingly not only stem cells but also dedifferentiated cells can be used for treatment of bladder dysfunction.

7.3.6 Other Bladder Dysfunction Models

Based on Nitta et al. [9], transplantation of multipotent stem cells originating from the skeletal muscle in the bladder branch of pelvic plexus (BBBP) causes a drastically higher bladder functional improvement in injured model. Kwon et al. [10] achieved similar results in rats with unilateral transected pelvic plexus.

7.4 Regeneration of the Bladder

As far as bladder tissue engineering is concerned, there are few revolutionary studies which have shown that stem cells or BMSCs derived from embryoid bodies seeded on small intestinal submucosa (SIS) promote regeneration in partially cystectomized model [49–51]. Recently, many other types of stem cells which are seeded on bladder acellular matrix (BAM) demonstrate potential for bladder regeneration like hair stem cells and ADSCs [52, 53]. In studies on the use of synthetic scaffolds instead of using BAM and SIS results showed that BMSCs seeded on thin film of 1,8-octanediol-co-citrate can lead to bladder regeneration [54]. In addition, Tian et al. demonstrated the potential for bladder engineering of BMSCs with myogenic differentiation which are seeded on polylactic acid scaffolds [9, 55]. Similarly, polylactic glycolic acid seeded with human ADSCs with myogenically differentiation preserved both bladder compliance and capacity when transplanted into partially cystectomized rats [19]. In comparison to use of differentiated cells, bladder tissue engineering by the use of MSCs could produce better results. MSCs can differentiate into SMC after migration to the bladder's grafts and [56] such cells will replace the grafts rapidly with a good neural function and also low fibrosis formation [48].

During the past two decades researchers have eagerly waited to see the regenerated bladders full success, while over the last 80 years the intestine was effectively used to replace the bladder. So, one of the organs that can be a target of stem cell researches is the human bladder. Nonetheless, these studies are very limited; there are no systematic reports of dysfunction of the bladder. Only trials focusing on the urethral sphincter and neobladder could be found in literature. Urologists need a suitable replacement for traditional conduits and neobladders due to their adhesion problems, mucus development, emptying difficulties, and metabolic conditions and transformations into malignancies. Autotransplantation was used in innovative work to build artificially engineered bladder tissues [57]. Both urothelial and detrusor smooth muscle cells retrieved by bladder biopsy and cultured for 7 weeks and transplanted into a bladder-shaped biodegradable scaffold mainly consists of polyglycolic acid and collagen.

Many other approaches for reconstructing the bladder [58–60] were investigated in attempt to find safe and usable bowel replacement material and to prevent the complications. Nonetheless, only modest success is yet achieved. Although both

robotic and open route is available for radical cystectomy, open surgery is usually performed in most patients with urinary diversion. Costs of this method vary in different countries. Involvement of an intestinal segment is responsible for the main proportion of the costs.

Hospital readmission rates are high after cystectomy and urinary diversion; thus, the readmission cost is important, too.

Thus, new alternative solutions are looked-for to lessen the significant economic burden of cystectomy and post urinary diversion complications. So, a great deal of the latest research focuses on bioengineering methods for the reconstruction of urinary bladder including tissue engineering, bioreactors and bioprinting.

7.4.1 Tissue Engineering

So far, tissue engineering has focused on the reconstruction of bladder tissue, and significant progress is made. A multidisciplinary approach to bioengineering is mainly based on the human body's potential of natural regeneration and involves the use of a polymers matrix or cell-seeded scaffolds to promote more regeneration [61]. Such complex technologies of regeneration are being studied to create an efficiently designed bladder.

Tissue engineering for bladder reconstruction has significant benefits. It is time-saving in the operating room, helps to prevent digestive problems and increases patient quality of life. Also, this technique is a very promising approach and develops new treatments for other pathologies of the lower urinary tract that do not essentially require a total replacement of the bladder [57]. To date, different animal models were used to ensure the effectiveness of different scaffolds for cell-seeding [62, 63]. The concept of using tissue engineering for urinary bladder regeneration actually goes back to the 1950s.

Type and charachteristics of the scaffolds has a key role to support the complex chemical and mechanical bladder function during both filling and emptying. The matrix microenvironment can influences the stem cells migration, proliferation and differentiation into the regenerating cells [62].

The biomaterials used in bladder tissue engineering should have acceptable mechanical and chemical properties as well as appropriate biocompatibility [64] to provide a good support for structure of several separate layers of cells.

An ideal biomaterial should offer an adequate plane for attachment of urothelial cells at its lumen, and its visceral side should be capable of nesting the muscle cells, which are necessary to form a unidirectional muscle layers and suitable for quick vascularization and innervation [65].

Another main objectives is to prevent the regenerative bladder from rising the host immune response that leads to compromised efficiency and durability of the bladder [66].

As a result, most biomaterials and issues, including acellular tissues, natural or artificial polymers, and composites, were used as substitutes for urinary bladder tissue and matrix scaffolds.

7.4.2 Bioreactors

Bioreactors are advanced modeling biosystems capable for controlling environment by influencing factors such as pH, oxygen concentration and temperature. Simulating the normal physiological functions (both filling and emptying) by bioreactor in vitro can improve the functional results after implantation [67, 68] and can strengthen the stability of the matures tissues. Another promising approach in the field of bladder regeneration is in vivo bioreactors which are used in target scaffold before the main implantation. This preconditioning can further enhance the bioengineered tissue growth, improve tissue vascularization and inhibit fibrosis and consequently prevent contractility loss [65]. Although discovery and use of different types of bioreactors and preconditioning before stem cell implantation in aim of enhancing the outcomes are so interesting, but to date few studies have been conducted focusing on this specific field and more studies are yet required.

7.4.3 Bioprinting

Bioprinting technology is a powerful computer-controlled method for generating cell-based living functional tissues and organs [69]. It needs stem cells for seeding into a biodegradable scaffolds as primary structure and different bioreactors such as growth factors for inducing tissue formation [70]. The great clinical benefit of transplanting such tissues is that they will not raise the host immune response, an issue that cause so many complications in other types of transplantation including allograft tissue transplant.

In this technique a bio-printer first produce a three dimensional (3 D) structure which will be then use as a scaffold for stem cell seeding. Different material can be used as the scaffolds. The most known material is hydrogels. Hydrogels are both biocompatible and biodegradable. In addition, they have specific sites that help cell adhesion that is needed for further cell growth and differentiation [71].

Bioprinting techniques were tested in many kinds of tissues, but some more specific human organs like trachea, bronchi [72], blood vessels [73], and bladder [74] have achieved clinical success in this area of bioengineering, so far. Therefore, we are hopeful that bioprinting will potentially offer an actual solution for shortage of organ donors and complications related to allograft transplantation, soon in future [69].

7.5 Conclusion

Stem cell therapy for treatment of bladder dysfunction is an interesting approach which seems work through the ability of stem cells including self renewal, differentiation and also their paracrine effect. Inhibiting the bladder tissue fibrosis and restoring the detrusor muscle contractility seem to be the main stem cells' mechanisms of action in recovery of bladder dysfunction. Furthermore, this fact that stem cells potentially can differentiate into detrusor smooth muscle cells, offers new approaches for treatment of bladder dysfunction such as bladder regeneration and bladder bioprinting.

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