Published in final edited form as:
J Urol. 2011 March ; 185(3): 779–780. doi:10.1016/j.juro.2010.12.014.

Stem Cell Therapy for the Bladder: Where Do We Stand?

Ching-Shwun Lin
Knuppe Molecular Urology Laboratory, Department of Urology, School of Medicine, University of California, San Francisco, CA 94143, USA Phone: 415-476-3800 Fax: 415-476-3803 clin@urology.ucsf.edu

Stem cell therapy for the bladder has thus far been conducted on an experimental basis in two areas: bladder dysfunction and tissue engineering. For bladder dysfunction, Nishijima et al [1] showed that intra-bladder injection of bone marrow cells (not sorted or tested for stem cell properties) restored bladder contraction in rats with underactive bladder due to bladder outlet obstruction (BOO). More recently, Huang et al [2] showed that intra-bladder or intravenous injection of adipose-derived stem cells (ADSCs) improved urodynamics and tissue parameters in a rat model of hyperlipidemia-associated overactive bladder (OAB). In the current issue of this Journal Woo et al [3] report that intravenous injection of bone marrow stem cells (BMSCs) in a mouse model of BOO resulted in the recruitment of the transplanted cells to the bladder with concomitant improvements in histological and functional parameters. Importantly, while Nishijima et al found evidence of smooth muscle differentiation from the transplanted cells, Huang et al and Woo et al found little or no such evidence.

Stem cells' therapeutic efficacy was originally thought to derive from their ability to differentiate into various cell types. In this regard several studies have shown that stem cells isolated from the embryo, bone marrow, amniotic fluid, and adipose tissue could differentiate into "bladder" smooth muscle cells. More recent studies have also shown that ADSCs and BMSCs could differentiate into the more complex urothelial cells [4, 5]. However, it should be pointed out that evidence presented in most of these studies was based on detection of smooth muscle or urothelial markers in cultured stem cells that were maintained in certain conditioned media or co-cultured with native bladder cells. The few "in vivo" studies that presented evidence of smooth muscle differentiation in the bladder also need to be interpreted with caution. Perhaps the most provocative is a recent study on the reconstitution of neurogenic bladder dysfunction with skeletal muscle-derived stem cells (SkMSC) - several different cell types including Schwann cells, perineurial cells, and pericytes were suggested to have been differentiated from the transplanted cells [6]. Further studies are needed to verify such claims.

While cellular differentiation has long been considered the main mechanism underlying stem cells' regenerative capacity, it is increasingly clear that stem cell secretion of trophic and immunomodulatory factors is just as important if not more so. In this regard stem cell secretory factors have been shown to exert therapeutic effects by (1) modulation of local and systematic inflammatory responses, (2) stimulation of local tissue regeneration, and/or (3) recruitment of host cells such as BMSCs as repair cells. In bladder research, prevention of tissue injury and stimulation of tissue regeneration following stem cell transplantation have been reported in the above-mentioned studies by Huang et al and Woo et al. In addition, earlier study by De Coppe et al [7] showed that paracrine mechanism might regulate post-injury bladder remodeling following intra-bladder transplantation of amniotic fluid or bone marrow stem cells. In regard to stem cell recruitment, Tanaka et al [8] (coauthors in Woo's paper) reported that BOO induced migration of bone marrow-derived cells to the bladder.

Furthermore, we have found that transplantation of ADSCs induced recruitment of label-retaining cells (host stem cell?) to injured bladder and urethra (Lin et al, unpublished).

For bladder tissue engineering, three pioneering studies have shown that embryoid body-derived stem cells or BMSCs seeded on small intestinal submucosa (SIS) facilitated the regeneration of partially cystectomized bladder [9–11]. Recently, hair stem cells and ADSCs seeded on bladder acellular matrix (BAM) have also demonstrated bladder regeneration potential [12, 13]. In studies that explored the use of synthetic scaffolds instead of SIS and BAM, Sharma et al [14] reported that BMSCs seeded on poly(1,8-octanediol-co-citrate) thin film supported partial bladder regeneration, and Tian et al [5, 15] showed that myogenic-differentiated BMSCs seeded on poly-l-lactic acid scaffold exhibited bladder engineering potential. Likewise, poly-lactic-glycolic acid seeded with myogenically differentiated human ADSCs was found to maintain bladder capacity and compliance when grafted in hemicystectomized rats [16].

One of the most exciting developments in stem cell research is the successful demonstration of therapeutic efficacy with SkMSCs or ADSCs in the treatment of stress urinary incontinence (SUI) in human patients. While SUI is admittedly a simpler target, lessons learned from these clinical trials can nevertheless provide guidance for future research in stem cell therapy for the bladder. One of such lessons is the importance of choosing the most promising stem cell types. While all mesenchymal stem cells, including BMSCs, SkMSCs, and ADSCs, exhibit very similar biological properties and therapeutic potentials, their availability and scalability differ greatly. For example, while SkMSCs require complicated isolation procedure and long expansion time, ADSCs can be prepared in hours. In fact, several machines are now on the market that can process a patient's lipoaspirates into a cell preparation suitable for autologous injection on the same day. Undoubtedly, while cells prepared this way are sufficient for treating patients with SUI, OAB, or BOO, they will have to be expanded in order to meet the demand of recreating the whole or part of the bladder. Indeed, bladder augmentation or replacement also requires the selection of an ideal scaffold and an appropriate regeneration environment. While detailed discussion on these issues is beyond this editorial comment, recent studies have indicated the excellent prospect of fabricating adipose tissue into acellular matrices. Thus, medical wastes such are lipoaspirates can be turned into therapeutic treasures such are stem cells and tissue engineering scaffolds.

Regardless of their tissue origin, all stem cell types are being scrutinized for their possible association with tumorigeness – whether they themselves become tumors or they encourage the growth/metastasis of existing tumors. While several studies on the former aspect have turned out to be due to tumor cell line contamination, an ever-increasing number of publications are sounding the alarm on the latter issue. However, these studies all relied on the use of animal models transplanted with tumor cell lines – an approach whose clinical relevance has long been questioned. Thus, the promise of stem cell therapy for diseases such as bladder dysfunction appears to outweigh the risk of tumorigenesis.

References

1. Nishijima S, Sugaya K, Miyazato M, Kadekawa K, Oshiro Y, Uchida A, et al. Restoration of bladder contraction by bone marrow transplantation in rats with underactive bladder. Biomed Res. 2007; 28:275. [PubMed: 18000341]
2. Huang YC, Shindel AW, Ning H, Lin G, Harraz AM, Wang G, et al. Adipose derived stem cells ameliorate hyperlipidemia associated detrusor overactivity in a rat model. J Urol. 2010; 183:1232. [PubMed: 20096880]

3. Woo LL, Tanaka ST, Anumanthan G, Pope JCt, Thomas JC, Adams MC, et al. Mesenchymal stem cell recruitment and improved bladder function following bladder outlet obstruction: Preliminary Data. J Urol. 2011
4. Liu J, Huang J, Lin T, Zhang C, Yin X. Cell-to-cell contact induces human adipose tissue-derived stromal cells to differentiate into urothelium-like cells in vitro. Biochem Biophys Res Commun. 2009; 390:931. [PubMed: 19852942]
5. Tian H, Bharadwaj S, Liu Y, Ma PX, Atala A, Zhang Y. Differentiation of human bone marrow mesenchymal stem cells into bladder cells: potential for urological tissue engineering. Tissue Eng Part A. 2010; 16:1769. [PubMed: 20020816]
6. Nitta M, Tamaki T, Tono K, Okada Y, Masuda M, Akatsuka A, et al. Reconstitution of experimental neurogenic bladder dysfunction using skeletal muscle-derived multipotent stem cells. Transplantation. 2010; 89:1043. [PubMed: 20150836]
7. De Coppi P, Callegari A, Chiavegato A, Gasparotto L, Piccoli M, Taiani J, et al. Amniotic fluid and bone marrow derived mesenchymal stem cells can be converted to smooth muscle cells in the cryo-injured rat bladder and prevent compensatory hypertrophy of surviving smooth muscle cells. J Urol. 2007; 177:369. [PubMed: 17162093]
8. Tanaka ST, Martinez-Ferrer M, Makari JH, Wills ML, Thomas JC, Adams MC, et al. Recruitment of bone marrow derived cells to the bladder after bladder outlet obstruction. J Urol. 2009; 182:1769. [PubMed: 19692058]
9. Chung SY, Krivorov NP, Rausei V, Thomas L, Frantzen M, Landsittel D, et al. Bladder reconstitution with bone marrow derived stem cells seeded on small intestinal submucosa improves morphological and molecular composition. J Urol. 2005; 174:353. [PubMed: 15947689]
10. Frimberger D, Morales N, Shamblott M, Gearhart JD, Gearhart JP, Lakshmanan Y. Human embryoid body-derived stem cells in bladder regeneration using rodent model. Urology. 2005; 65:827. [PubMed: 15833555]
11. Zhang Y, Lin HK, Frimberger D, Epstein RB, Kropp BP. Growth of bone marrow stromal cells on small intestinal submucosa: an alternative cell source for tissue engineered bladder. BJU Int. 2005; 96:1120. [PubMed: 16225540]
12. Drewa T, Joachimiak R, Kaznica A, Sarafian V, Pokrywczynska M. Hair stem cells for bladder regeneration in rats: preliminary results. Transplant Proc. 2009; 41:4345. [PubMed: 20005396]
13. Zhu WD, Xu YM, Feng C, Fu Q, Song LJ, Cui L. Bladder reconstruction with adipose-derived stem cell-seeded bladder acellular matrix grafts improve morphology composition. World J Urol. 2010; 28:493. [PubMed: 20091038]
14. Sharma AK, Hota PV, Matoka DJ, Fuller NJ, Jandali D, Thaker H, et al. Urinary bladder smooth muscle regeneration utilizing bone marrow derived mesenchymal stem cell seeded elastomeric poly(1,8-octanediol-co-citrate) based thin films. Biomaterials. 2010; 31:6207. [PubMed: 20488535]
15. Tian H, Bharadwaj S, Liu Y, Ma H, Ma PX, Atala A, et al. Myogenic differentiation of human bone marrow mesenchymal stem cells on a 3D nano fibrous scaffold for bladder tissue engineering. Biomaterials. 2010; 31:870. [PubMed: 19853294]
16. Jack GS, Zhang R, Lee M, Xu Y, Wu BM, Rodriguez LV. Urinary bladder smooth muscle engineered from adipose stem cells and a three dimensional synthetic composite. Biomaterials. 2009; 30:3259. [PubMed: 19345408]