Editorial

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Current status of stem cell therapy in urology

Jae Heon Kim, Yun Seob Song

Department of Urology, Soonchunyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

Stem cells have the ability to propagate through self renewal and generate mature cells of multiple lineages through differentiation [1,2]. Explorations of the potential value of stem cell therapy in urology have included studies of bladder dysfunction, erectile dysfunction (ED), stress urinary incontinence (SUI), and prostate and bladder cancer. Only a few pilot human translational studies study of stress incontinence and diabetes induced ED have been reported. Recently, Alwaal et al. [3] introduced the current status of stem cell treatment in benign urological diseases including ED, Peyronie disease, infertility and SUI.

The prowess of stem cell therapy has been indicated in bladder dysfunction models including bladder outlet obstruction, chronic ischemia, diabetes, cryo-injury, pelvic nerve injury, and spinal cord injury (SCI). Except for cryo-injury and pelvic nerve injury, models have demonstrated overactive urodynamics, indicative of improved inter-contraction interval and maximal voiding pressure [1,2]. Underactivity models including cryo-injury and pelvic nerve injury models have demonstrated improvements of intravesical pressure. Marked smooth muscle differentiation has been reported in three studies. Concerning SCI-induced bladder dysfunction, a meta-analysis affirmed that stem cell-based cell therapyproduces partial bladder recovery including improvement of voiding pressure, inter-contraction interval, and residual urine [4].

For ED, stem cell injection into the corpus cavernosum or periprostatic implantation improves erectile functions in diabetic, hyperlipidemic rat models, as well as in neurogenic ED models. A recent meta-analysis indicated that stem cell therapy in neurogenic ED models recovers erectile function [5]. Periprostatic implantation with acellular scaffolds can promote cavernous nerve regeneration, but is less effective for smooth muscle cell recovery. ED models have provided evidence that homogenous clonal stem cells can overcome the inherent impediment of the heterogenous nature of isolated cells, providing optimism of the clinical value of stem cell therapy of ED.

Successful ED therapy primarily relies on the improvement of functional and histological components. No direct evidence concerning the identification of stem cell differentiation has yet been described, suggesting the importance of paracrine action as a principle therapeutic mechanism in stem cell therapy of ED. Currently, two phase I–II stem cell clinical trials are recruiting patients with ED. One trial (NCT01089387) seeks to evaluate the efficacy of intracavernous injection of bone marrow stem cells in postradical prostatectomy patients. The other trial (NCT01601353) will evaluate the effect of intracavernous injection of adipose-derived stem cells in organic ED (vasculogenicand neural).

Relative to other fields in urology, research on stem cell-related gene therapy for ED has been less robust. The few studies to date have involved stem cells and vascular endothelial growth factor $(VEGF)_{164}$ or $VEGF_{165}$, endothelial nitric oxide synthase, and fibrous growth factor. Many oncology studies have focused on cancer

Corresponding Author: Yun Seob Song
Department of Urology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 140-743, Korea
TEL: +82-2-709-9375, FAX: +82-2-709-9378, E-mail: yssong@schmc.ac.kr

stem cells to investigate the specific cancer risk, whereas less therapeutic effort for future possible translational studies has been made. Lee et al. [6] reported prostate tumor migration of systemically transplanted HB1.F3.CD stem cells; in combination with the prodrug 5-fluorocytosine, the volume of tumor implant was significantly reduced, which suggested a new possible treatment option of a new selective chemotherapeutic strategy against prostate cancer. Wang et al. [7] reported that the enhanced antitumor effects *in vitro* elicited by Ad/PSCAE/UPII/E1A plus cisplatin were closely related to increased Fas expression and cleavage of caspase-8 and Bid, and the decrease in the ratio of anti- to proapoptotic proteins followed by activation of caspase-9 and caspase-3, which may contribute to the activation of extrinsic and intrinsic apoptotic pathways.

Although many experimental urology-focused studies have shown relatively favorable functional outcomes, clinical applications of stem cells continue to be thwarted mainly due to poor differentiation of the cells into the targeted histologic component and inflammation-mediated graft rejection. Nonetheless, the potential for stem cells has been increasing due to their unique abilities of targeted-site specific migration, plasticity and potential for tissue repair or regeneration. Additional studies are needed to confirm the detailed mechanisms and to optimize the ideal treatment strategies for the varied stem cell applications.

Among the obstacles for clinical application of stem cells, the realistic issues are the selection and culture of stem cells, tumorigenesis, route of delivery, metabolic memory and limitation of gene therapy. Issues concerning the selection of stem cells are the choice of cells (embryonic, adult or induced pluripotent stem cells), reflecting ethical considerations and plasticity. To overcome problems associated with reduced transdifferentiation plasticity, the recent discovery of induced pluripotent stem cells has shed light on the molecular basis of stem cells. For adult counterpart stem cells, embryonic or fetal mesenchymal stem cells (MSCs) are not always superior to adult MSCs regarding the formation of new differentiated smooth muscle cells or vascular cells, despite the nominally higher plasticity of immature stem cells.

Recently, direct lineage conversion has been issued as a promising approach for disease modeling and regenerative medicine. Although the discrete mechanism of reprogramming of somatic cells to pluripotency has not been fully clarified, the expected role of direct lineage conversion is promising.

Regardless of their tissue origin, a concern with all stem cell types is tumorigenesis—the possibility of formation of nascent tumors or facilitated growth or pre-existing tumors. Many studies have provided confidence regarding the remote possibility of tumorigenesis. But, these studies relied on animal experimental models. Indeed, information from animal models is principally important for regulatory applications for stem cell-based human clinical studies.

Local injection and transplantation of stem cells have been effective in ED and bladder dysfunction models. Systemic administration by intravenous or intracardiac route could be more helpful in cancer models. There is the concern of capillary clogging by larger cell types, a complication that could result in hemodynamic compromise, interference with pulmonary gas exchange, and respiratory distress. Intravenously injected stem cells are localized mainly to the pulmonary capillary bed, hence local injection may have a better effect than intravenous injection. But, autologus transplantation itself could be more of an issue than transplantation itself. The exact culture conditions to direct autologous nontargeted stem cells to transdifferentiate into targeted cells are yet to be established.

Before the administration of stem cells, metabolic memory has to be considered. Stem cells harvested from a pathological host, such as diabetes, act differently than from a healthy host. Although gene therapy can be efficacious and is a particularly promising therapeutic option, effective gene transfer into stem cells including long-term transgene expression must be achieved without inducing detrimental effects on their biological properties including cell viability. This area still has many challenges and obstacles, such as local inflammatory response and random transgene expression, in addition to other safety issues that limit its use at the clinical level. Another big pitfall in performing stem cell studies using experimental animal models is that, in most cases, researchers cannot perform an intermediary examination including *in vivo* functional studies or *in vivo* radiologic monitoring.

Currently, even with the data from well designed and performed experimental studies and the promise of novel pilot studies, the aforementioned limitations remain to be overcome. Moreover, to perform experimental studies using stem cells, more efforts have to be made on defining and establishing basic parameters including characterization of stem cells with homogenous cultures, standardization of disease model, cell survival, and measurement of outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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