NARRATIVE REVIEW

Stem cells in Urology

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Abstract

Stem cell research is rapidly expanding and has provided novel concepts in understanding and managing various diseases. Recent progress in translational and experimental urology has given insight about their utilization in the treatment and regeneration of urological structures. Chronic degenerative and neurological conditions affecting the lower urinary tract (LUT) are excellent targets for stem cell therapy. Their role has been particularly studied in bladder dysfunction, painful bladder syndrome, bladder outflow obstruction, stress urinary incontinence, erectile dysfunction, and urethral regeneration. However, the translation of this research in clinical domain is slow. Furthermore, regeneration of kidney using stem cells has been explored but remains challenging due to complexities of nephrons. Stem cells research in uro-oncology, especially bladder and prostate cancer, provided significant insight in understanding of pathogenesis processes and expanded potential therapeutic options. This review is centered to discuss application of stem cells and regenerative medicine in urology particularly human subject clinical studies and trials published in recent years.

Keywords: Stem Cell, Cystitis, Urology, Prostate, Nephrons, Kidney.

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Introduction

Stem cells have the capability of differentiation and self-renewal.[1] Considering these characteristics of stem cells, their utilization in treatment and regenerative strategies for urological structures is an active research area in recent times.[2] Both degenerative and neurological diseases affecting the lower urinary tract (LUT) are considered excellent targets for stem cell therapy (SCT) and have been explored in multiple pre-clinical and clinical trials. While searching literature for stem cells research, regenerative medicine and tissue engineering, we found 9,236 trials currently registered with clinicaltrials.gov.[3] Majority of these trials are on blood and lymph conditions (37.9 %), Neoplasms (32.6 %) and Immune system diseases (23.5%). Urinary tract, sexual organs and pregnancy collectively constitute only 4.3 % of all registered stem cell clinical trials. Furthermore, most of the published stem cells human trials in Urology are phase 1 /2 trials with small sample sizes without long term follow-up. This review aims to discuss application of stem cells and regenerative medicine in urology particularly human subject clinical studies/ trials published in recent years.

Bladder dysfunction

A variety of adult Mesenchymal stem cells (MSC) have been studied for bladder dysfunction.[4] Many of these trials were carried out in rodent models. Intravenous and intra-vesical administrations of stem cells were both used in spinal cord injury (SCI) model. By regenerating the damaged tissues, transported neural progenitor cells can restore bladder function.[4] Similarly, intravenously administered Bone marrow stem cells (BMSC) provided improvement in bladder function in rats by residing in the spinal cord nerve roots L3-L4.[4] Stem cell's success is also demonstrated in experimental models with improvement in histological, morphological and functional parameters.[5]

Various bladder dysfunction models have been studied including bladder overactivity, bladder outflow obstruction (BOO), chronic ischaemia, SCI, diabetes mellitus (DM) and bladder underactivity models etc.[6] These models reported marked smooth muscle differentiation following SCT. A meta-analysis[6] incorporating 8 studies with 224 subjects showed the effect of SCT on bladder recovery in SCI patients and found bladder recovery with improvement in non-voiding contraction, residual urine and voiding pressure.

Stem cells' role for tissue engineering and bladder regeneration is explored in a few studies. Stem cells obtained from embryoid bodies when implanted on sub mucosa of small intestine provided regeneration in partially cystectomized models.[7]

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Tissue-engineered urinary bladders created de-novo are also reported is clinical trials.[8] Autologous bladder cells were implanted into scaffolds made of polyglycolic acid and collagen and transplanted in cystoplasty patients. These engineered bladders exhibited excellent clinical parameters such as stable intravesical pressure, compliance, bladder capacity and preserved renal function which were stable up to 5 years follow up.[8]

Bladder outflow obstruction (BOO)

SCT for the management of BOO remains experimental. BOO leads to inflammation, hypertrophy, and later fibrosis. Mesenchymal stem cells (MSCs) injected into bladder diminish inflammatory markers, hypoxia, and collagen remodeling in rodent models[4] but the mechanism is not fully understood.

Interstitial cystitis/painful bladder syndrome

SCT in interstitial cystitis (IC)/painful bladder syndrome (PBS) was centered on the idea that their transplantation into bladder might repair the damaged neurons and epithelium.[9] However, further evidence has generated a new hypothesis, supporting that the transplanted stem cells prompt paracrine release of pro-angiogenic, anti-apoptotic, anti-inflammatory, and/or anti-oxidative factors.[10] Additionally, these paracrine bioactive factors are considered to boost the expression of stem cell trafficking genes, resulting in endogenous stem cells recruitment to the damaged tissues.[9, 10]

While the application of SCT for IC/BPS has been reported in numerous pre-clinical models, only one clinical trial to date has evaluated their efficacy for IC/BPS. Lander et al.[11] explored the effect of combined local and intravenous injections of autologous stromal vascular fraction (SVF) into the pelvic floor in 91 female and 18 male patients with IC/BPS. The study demonstrated good safety and efficacy with improvement in symptoms; however, it had various limitations. The molecular mechanism of SVF was not fully understood, study did not have a control group and there was lack of long term follow up.

Stress urinary incontinence

Stem cells with regenerative potential for the damaged external urethral sphincter (EUS) drew the attention of researchers to reverse the structural damage causing stress urinary incontinence (SUI).[12] Adult stem cells isolated from bone marrow, adipose tissue, or skeletal muscle are the commonly used for research on SUI.[12] A randomized clinical trial (RCT) compared periurethral injections of autologous fibroblasts & myoblasts with collagen gel in female patients with SUI.[13] This trial reported excellent outcomes at 12 months follow up, with 90% (38/42) patients demonstrating complete continence. This paper was later retracted by Lancet as investigations discovered that good clinical practice (GCP) guidelines were not followed.[13]

Despite the unfortunate fate of above RCT, researchers continued to explore applications of the SCT for SUI. Recently, Barakat B et al[14] published a review of clinical trials focussing on stem cell application, safety, and effectiveness in SUI. In this report, 17 clinical trials with a total of 715 patients were analyzed. Studies included in this review utilized various stem cell types such as adipose derived stem cells (ADSCs), bone marrow-derived mesenchymal stem cells (BMSCs), muscle derived stem cells (MDSC), human umbilical cord blood stem cells (HUCBs), urine-derived stem cells (UDSCs), and total nucleated cells (TNCs). Analysis and direct comparison between various types of stem cells used in the included trials was difficult due to technical variability and the number of injected cells in each trial. However, pooled results showed a regenerative potential of ADSCs to treat SUI and median postoperative improvement rate of 88% following ADSCs therapy. Similarly, published studies have shown remodelling of the damaged sphincter muscle and urethral bulking with new tissue by using MDSC-based therapy resulting in improved sphincter function.[12] Though promising, the overall data analyzed in this report was not enough for evaluating the long-term safety of stem cell therapies. Additionally, the published series have various limitations, including small sample size and limited follow up.[15-20] A summary of a few clinical trials is given in Table1.

Although, basic concepts and many trials supported stem cell utility in patients with SUI, following three areas will need further exploration in robust clinical trials before SCT is widely acceptable in routine management of SUI.

- Enhancement of the survival and metabolism of the injected cells
- Non-invasive tracking of stem cell's viability and functionality
- Exploration of alternative and/ or additional approaches (e.g., regenerative pharmacology)

Erectile dysfunction (ED)

Basic science and animal studies have shown promising results of SCT for erectile dysfunction (ED). By inducing angiogenesis and increasing cavernosal smooth muscle cells within corporal bodies, stem cells may reverse disease progression. This contrasts with current

Table-1: Summary of clinical trials; Stem Cell therapy in Stress Urinary Incontinence.

Author/year	n	Stem cells used	Follow up duration	Key Findings
Sharifaghdas et al. [15] (2016)	10 females	Autologus MDSCs	36 months	7 out of 10 patients either cured or experienced improvement in MUCP and on pad tests
Yiou et al. [16] (2013)	5 female 5 male	Freshly isolated myofibers (from Gracilis muscle)	12 months	Continence improved in 4 out of 5 women and their MUCP increased twofold.
Crr et al. [17] (2013)	38 females	Autologous MDSCs (from quadriceps muscle)	12 months	The high dose provided more favorable outcomes while majority of study participants had a 50% or > reduction in pad weight (89% vs. 62%) and less stress leaks (78% vs. 53%).
Gerulli et al. [18] (2012)	222 male pRP incontinence	MDSCs	12 months	Either continent (12%) or improvement (42%) of clinical symptoms.
Blaganje et al. [19] (2012)	38 females	Ultrasound guided myoblast injections+ Electrical stimulation	6 weeks	The results to the stress test were negative for 29 (78.4%) of the patients, 5 (13.5%) considered their SUI cured, and 29 (78.4%) reported improvement.
Sebe, et al. [20] (2012)	12 females	Autologous MPCs (from deltoid muscle)	12 months	10 out of 12 females were either dry or had improved incontinence while 50% have better QOL.

MDSC = Muscle Derived Stem Cells, MPCs= Muscle Progenitor Cells, MUCP = Maximum Urethral Closure Pressure, pRP: Post Radical Prostatectomy, SUI: Stress Urinary Incontinence, QOL= Quality of Life

modalities, which target on symptom control only.[21] In rat models of cavernosal nerve injury, migration of stem cells into major pelvic ganglia was observed after intravenous injection.[22] In diabetic, hyperlipidaemic and neurogenic rat models, stem cell injection directly into corpus cavernosum or peri-prostatic implantation improved erectile dysfunction.[22]

Only limited data is available on use of SCT for ED in humans. Clinical trials using different types of stem cells have been evaluated (Table 2). The results of these clinical trials suggest both a good safety profile and efficacy of stem cell-based therapies in improving erectile functions. [23-30]

Lokeshwar et al in a recent systematic review analyzed

Table-2: Summary of clinical trials; Stem cell therapy in Erectile Dysfunction.

Author/year	Study design	n	Stem cells used	Key findings
Mirzaei et al. [23] (2021)	Randomized single blinded clinical trial	20	Autologous MSCs	Improved sexual function and PSV and RI indices of penile arteries.
Protogerou, et al. [24] (2019)	Single center pilot study	8	MSCs derived from adipose tissue and platelet lysate (PL)	A statistically significant difference was observed in the IIEF-5 after the first month ($p < 0.05$) and the third month ($p < 0.05$).
Al Demour et al. [25] (2018)	Open label phase I clinical trial	4	BM-MSCs	4/4 good tolerance.3/4 patients had significant improvements in IIEF-15 and all 4 in EHS.
Haahr et al. [26](2018)	Open label phase I clinical trial	21	ADRC	53% of erections sufficient for intercourse. Not seen in incontinent or preop ED men
Yiou et alPhase 1= [27] (2016) Phase 2 = [28] (2017)	Phase I and II clinical trials	Phase I =12 Phase II= 12+6	BM-MNSCs	All patients tolerated injections well. IIEF-15 and EHS significant improvements
Levy et al . [29] (2015)	Open label phase I clinical trial	8	PM-MSCs	3/8 patients achieved erections at 3 months. Significant improvement only in PSV
Bahk et al. [30] (2010)	Single blind phase I clinical trial	10	UC-MSC	3/7 patients had morning erections at 3 mo. At 6 months follow up 2/7 Patients sufficent erection with PDE5 inhibitor

ADRC = Autologous Adipose Derived Regenerative Cell; BM-MNSCs = Bone Marrow Mononuclear Cells; BM-MSC = Bone Marrow Derived Mesenchymal Stem Cell; EHS = Erection Hardness Score; IIEF-15 =International Index of Erectile Function 15 item; PDE-5 = Phosphodiesterase type 5; PM-MSC = Placental Matrix Mesenchymal Stem Cell; PSV = Peak Systolic Velocity; RI= Resistance Index; MSCs = Mesenchymal Stem Cells; UC-MSC = Umbilical Cord-Derived Mesenchymal stem cell,
Note: no serious adverse events reports in all above trials.

five completed human trials and showed promise for SCT as a restorative treatment option for ED.[21] A recent single-blinded randomized clinical trial, recruited 20 diabetic patients with ED, refractory to conventional treatments and divided them into two groups.[23] The intervention group received intra-cavernosal injection of autologous mesenchymal stem cells (MSCs) derived from oral mucosa while control group received intra-cavernosal normal saline injection. International Index of Erectile Function (IIEF5) questionnaire was used to assess sexual function during follow up period along with colour Doppler ultrasound to measure peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI). This trial concluded that Intra-cavernosal injections of stem cells resulted in improvement of PSV and RI in cavernosal arteries and overall improved sexual function.

Urethral reconstruction

Regeneration of urethra, compared to urinary bladder is considered a less challenging task due to its relatively simple structure and function.[2] Urethral stricture is being treated by tissue engineered grafts using stem cells (with or without scaffolds). Raya Rivera et al.[31] used tissue engineered autologous tabularized urethra, constructed from stem cells isolated from bladder tissue and seeding them on a synthetic poly (lactic-co-glycolic) acid (PGLA) tubular meshwork. They used this engineered tissue for urethral reconstruction in 5 boys with urethral defects. At a median follow up of 71 months, 100% success was reported.[31]

El-Kassaby et al.[32] reported an acellular bladder matrix graft used as Onlay graft for urethral stricture. The patency of graft was observed in 8 out of 9 patients with a healthy urethral bed and 2 of six in patients with unhealthy bed.

Male infertility

Using germline progenitors (spermatogonial stem cells (SSC) which are able to generate spermatogonia and have self-renewal abilities, the male infertility can be treated. Brinster et al.[33] used a novel method to transplant adult SSC of a donor and injected into seminiferous tubules of sterile recipients in a mouse model and found recovery of spermatogenesis which was morphologically similar to native cells with preservation of architecture of testes after 1 month.

Kidney regeneration

Among the urological organs, regeneration of kidney is believed to be most tough task due to complex structure of nephrons. Using renal progenitor cells, scientists have made attempts to tissue engineer and use these cells for formation, repair and turnover of renal tissues.[34] Poulsom et al.[35] suggested that differentiated renal tubular and stromal cells can be developed from adult stem cells. Minuth et al[36] described an in vitro approach for generating bio artificial kidney by using renal progenitor cells derived from embryonic cortex of neonatal rabbits. Although studies are ongoing but are far from reaching the complexity of nephrogenesis and hence generation of bio artificial renal devices is still awaited in the future.

Urological cancers and stem cells

Cancer stem cells (CSCs) have limitless replication and ability of self-renewal and transformation into different types of tumours.[1] Stem cells' role in cancers has been studied in recent times especially, for bladder and prostate cancers. This has provided not only a new dimension into the understanding of pathogenesis of cancers but has opened a window of opportunity to expand therapeutic options as well.

Bladder Cancer

Urothelial carcinoma of bladder is envisaged a stem cell disease. Cancer stem like cells (CSCs) are believed to be the main culprit for the high recurrence rate in bladder cancer (BCa).[37] The development in CSCs field with robust genome screening has paved the path to discover more targeted therapies against tumour-initiating stem cell populations. One of the huge challenges however is great heterogeneity of the CSCs with variable molecular signatures in BCa patients. Due to these traits of stem cells, progression of tumour with cultivation of CSC can result from improper choice of cytotoxic drugs leading to resistance and disease progression.[38]

The potential therapeutic targets for bladder CSCs include targetting miRNAs, HSP90 inhibitors, telomerase inhibitors, blockade of CD47 and anti-programmed cell death (PD)-1/ programmed death-ligand 1 (PD-L1) have shown success in certain BCa patients.[38] It is anticipated that in BCa, identification of certain early prognostic and diagnostic CSC markers will be a major breakthrough. This may translate into innovative methods for clinical staging/ classification of BCa and isolation of more aggressive cancer phenotype.[37] However, CSCs-based therapies are in their infancy and still far away from clinical application. Nevertheless, with availability of concrete evidence in future, clinical applications of Stem cell-based therapies may play a major role for managing BCa.

Prostate Cancer

The cellular origin of Prostate cancer (CaP) is debatable. It is possible that PCa may have origin from Prostate Cancer Stem Cells (PCSCs) or dividing progenitor cells converting into PCSCs secondary to mutations or ever-changing tumour micro-environment.[39]

The miRNAs are known to play a pivotal role in PCSCs and may elucidate some regulatory mechanisms.[40] The discovered miRNAs in CaP act as tumour-suppressor genes in majority and are under expressed in PCSCs. This leads to dis-inhibition of several stem-cell properties, including tumour regeneration, clonogenic expansion and even metastasis.[40] Hence, PCSCs could account for castrate resistant CaP.

Up-regulated signaling pathways in stem cells constitute a potential target for drugs development. These signalling pathways are important in CaP, as these promote CSC proliferation with tumour growth, making a favourable tumour microenvironment for tumour expansion/metastasis and leading towards drug resistance.[41] Presently, the signalling pathways demonstrating therapeutic potential in PCSCs are Notch, Wnt, Hedgehog (Hh), and NF-κB and these are being tested in multiple clinical trials.[40]

Although there are still numerous avenues to be discovered, targeting of PCSCs signalling pathways may develop into an important adjunct to current conventional treatment strategies for CaP. Multidrug combination regimen targeting PCSCs can potentially transform CaP treatment and presumably be effective in early and / or progressive disease.[41]

Current challenges in clinical translation of stem cells in Urology

Although stem cells utilization for reconstructing urological structures and treating degenerative and malignant conditions seems promising, only limited application in clinical urology and every day practice has been made beyond the experimental territory. This is due to the regulatory issues of stem cell products and therapy as none of the stem cell treatment until now is approved by FDA for use in urological conditions.[2]

Another issue is limited application due to lack of knowledge regarding stem cells' exact mechanism of action for a certain condition, selection, culture and handling of these cells, their ideal method of administration, metabolic memory, and risk of tumorigenesis.[1] On the practical aspect, another challenge is to acquire differentiated urothelial and smooth muscle cells from progenitor stem cells as urological organs like urethra, bladder and ureter are composed of these 2 cell lines.

Conclusion

Stem cells therapy and regenerative medicine in an exciting field. Our understanding of diseases pathogenesis has improved by exploring stem cells in both benign and malignant urological conditions. Currently, applications of SCT in routine clinical practice are limited. However, with emergence of more robust clinical trials, stem cells have a potential to impact and modify current management standards of various urological diseases.

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