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REVIEW ARTICLE

Urine-derived stem cells: A novel and versatile progenitor source for cell-based therapy and regenerative medicine

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Abstract Engineered functional organs or tissues, created with autologous somatic cells and seeded on biodegradable or hydrogel scaffolds, have been developed for use in individuals with tissue damage suffered from congenital disorders, infection, irradiation, or cancer. However, in those patients, abnormal cells obtained by biopsy from the compromised tissue could potentially contaminate the engineered tissues. Thus, an alternative cell source for construction of the neo-organ or functional recovery of the injured or diseased tissues would be useful. Recently, we have found stem cells existing in the urine. These cells are highly expandable, and have self-renewal capacity, paracrine properties, and multi-differentiation potential. As a novel cell source, urine-derived stem cells (USCs) provide advantages for cell therapy and tissue engineering applications in regeneration of various tissues, particularly in the genitourinary tract, because they originate from the urinary tract system. Importantly, USCs can be obtained via a non-invasive, simple, and low-cost approach and induced with high efficiency to differentiate into three dermal cell lineages. Copyright © 2014, Chongqing Medical University. Production and hosting by Elsevier B.V. All rights reserved.

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Introduction

Stem cells have shown potential as a therapeutic strategy for repair of various tissues, including genitourinary organs. Stem cell-based therapy for genitourinary tissue repair is most relevant to congenital conditions or disorders such as radiation damage, chronic inflammatory diseases, and tumors. Multiple types of stem cells have been used in pre-clinical animal models to repair or regenerate tissue, employing either trans-differentiation or paracrine effects to stimulate endogenous cells participating in tissue regeneration. These stem cells include pluripotent stem cells such as embryonic stem cells (ESCs); induced pluripotent stem cells (iPS),¹ multipotent mesenchymal stem cells (MSCs), including bone marrow-derived mesenchymal stromal cells (BMSC)^{2–6}; adipose-derived stem cells (ASCs)⁷; hair follicle stem cells⁸; and amniotic fluid stem cells.⁹

We recently found that a subpopulation of cells isolated from urine possess biological characteristics with stem cell characteristics, i.e. clonogenicity, cell growth patterns, expansion capacity, cell surface marker expression profiles, multipotent differentiation, pro-angiogenic paracrine effects, immune-modulatory properties, and easily-induced pluripotent stem cells. Thus, we have termed these cells “urine-derived stem cells” or USCs.^{10–12} These stem cells can be obtained from humans and different animal species, such as monkeys, pigs, and rabbits. Although stem cells

make up a small proportion of the total cell population, they play an important role in replacing aged, injured, and diseased cells and promoting tissue regeneration from organs where they originate. USCs consistently expressed MSC/pericyte markers and some key cell surface markers, but not hematopoietic stem cell markers (except for MHC-1), endothelial cell markers (CD31), or human leukocyte antigen (locus) DR (HLA-DR). Compared to other MSCs, USCs have several advantages: i) they can be obtained regardless of a person’s age, gender, or health condition (except in those urinary tract infection and anuria); ii) the cells can be collected using a simple, safe, low-cost and non-invasive procedure; iii) it is easier to isolate pure stem cells, which do not require an enzyme digestion process; iv) the cells display telomerase activity so that they are able to generate more cells, but not teratomas or tumors; and v) they differentiate into podocytes, smooth muscle, and endothelial and urothelial cells with higher efficiency.^{10–12}

Origin of USCs

The source of endogenous stem cells in the kidney may be the renal tubules or the papilla. Glomerular parietal epithelial cells function as stem cells in the glomeruli (Fig. 1), displaying self-renewal properties and the potential to give rise to podocytes and proximal tubular cells.^{13–28}

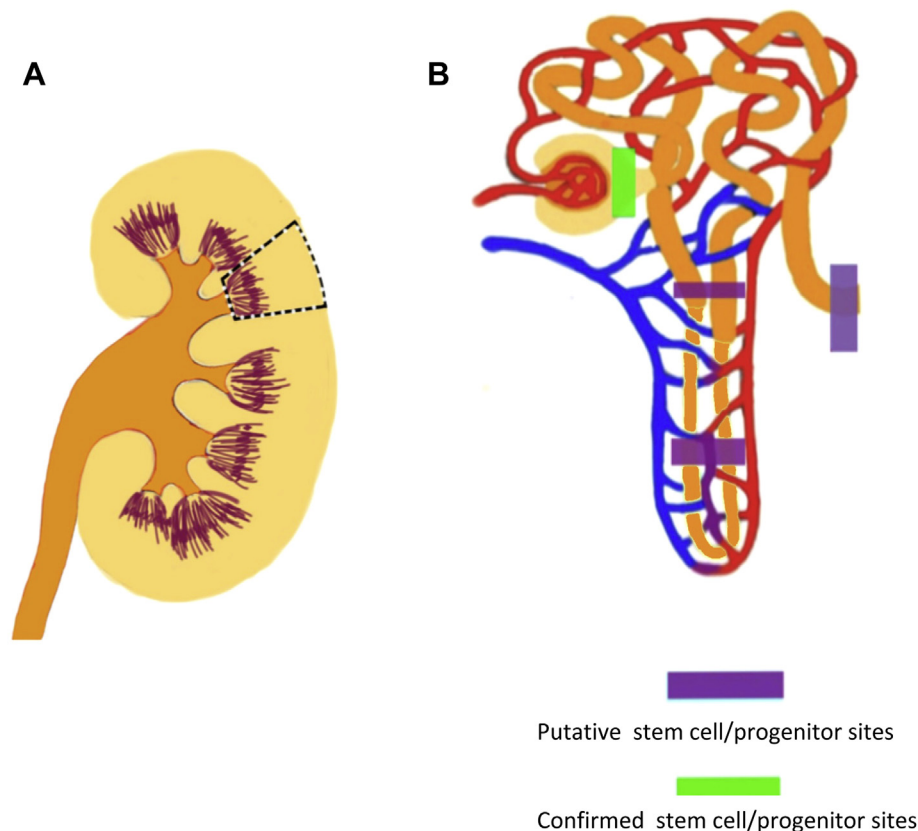


Figure 1 Possible sources of endogenous renal stem cells in the kidney. (A) The dotted area depicts the potential existence of renal stem cells, which are possibly the sources of urine-derived stem cells. (B) A detailed depiction of possible locations of urine stem cells.

The epithelial-mesenchymal transition (EMT) is a process by which epithelial cells lose their cell polarity to become mesenchymal stem cells; these multipotent stromal cells can differentiate into a variety of cell types in renal repair and regeneration. Parietal cells are commonly obtained from kidney tissue biopsies, but the isolation of pure parietal cells is difficult.^{29,30}

Identifying the origin of USCs will lead to a better understanding of the biological impact of this multipotent MSC population in the urinary tract system. There is strong evidence that USCs are most likely from glomerular parietal epithelial cells. USCs isolated from urine obtained from the upper urinary tract are similar to voided USCs in morphology, cell phenotypes, growth pattern, and differentiation capacity, suggesting that the voided USCs originate from the upper urinary tract.^{11,31} In addition, urine-derived cells from women who had received transplanted kidneys from male donors contained the Y chromosome and expressed normal renal cell markers (PAX2 and PAX8), podocytes, glomerular parietal cells, and specific gene and protein markers (synaptopodin and podocin),^{13–30,32–36} suggesting that USCs most likely originate from the kidney. Furthermore, USCs expressed CD146⁺/CD31⁻ at a rate similar to that expressed in parietal cells and podocytes in glomerulus, while renal tubule epithelial cells, bladder and ureter urothelial and smooth muscle cells did not, implying that USCs are likely transitional cells at the parietal cell/podocyte interface originating from renal tissue¹⁰ (Fig. 2).

Self-renewal of USCs

USCs can be obtained from voided urine and can generate a large number of cells from a single clone^{10,37} (Fig. 3). These cells form homogenous cell types and possess highly proliferative capacity because they maintain higher telomerase activity and longer telomere length compared to other types of MSCs¹⁰ (Table 1). Upto 75% of USCs collected from middle-aged individuals expressed telomerase activity (USCs-TA⁺) and retained long telomere length,³⁸ but USCs-TA⁺ decline to 50–60% of the USCs in people 50 years old or

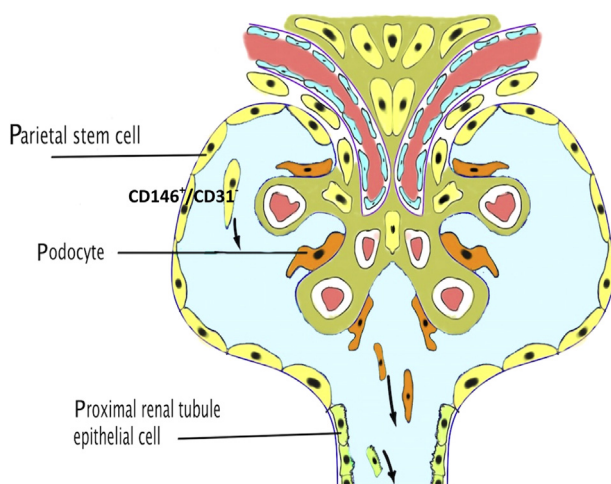


Figure 2 Renal cells, including parietal cells, podocytes, and renal tubule epithelial cells, are shed off into the urine in normal physiologic conditions.

older. USCs-TA⁺ can be maintained for upto 20 passages with 67 population doublings, indicating that a single USC can generate upto 2⁶⁷ cells within 14 weeks. In contrast, USCs-TA⁻ grow only for 8–10 passages with 34 population doublings. Importantly, either USCs-TA⁺ or USCs-TA⁻ display normal karyotypes in culture medium even after several passages. They did not form teratomas 3 months after renal subcapsular cell implantation.³⁸ We can now obtain 100–140 USC clones/24 h urine from each individual.³⁹ About 1.4 × 10⁹ cells are needed for potential use in bladder reconstruction with cell-seeded technology.⁴⁰ Thus, two urine samples containing 20–30 USC clones in 400 ml can provide ample cells (1.5 × 10⁹ USCs at p4) within 4–5 weeks to be used in cell-based therapy for genitourinary tissue or organ repair.

Multipotent differentiation of USCs

USCs can differentiate *in vitro* into multi-potential cells. After being induced in the appropriate culture condition, each type of differentiated USC expressed specific markers at the gene, protein, and cellular levels of osteogenic,⁴¹ chondrogenic and adipogenic myogenic,⁴² neurogenic⁴³ and endothelial cell types,¹⁰ respectively. Following implantation *in vivo*, induced USCs can form functional bone, cartilage, fat, muscle, endothelium, and urothelium tissue.¹⁰

For ureter, bladder, or urethral tissue engineering, urothelial, endothelial, and smooth muscle cells are needed for creating urothelial mucosa, blood vessels, and muscle wall. However, a challenge in urological tissue regeneration is generating urothelial cells from BMSCs or ASCs. Although BMSCs, the most commonly used MSC source, can efficiently differentiate into smooth muscle and endothelial cells,^{5,6,44–52} only 5–10% of BMSCs can give rise to the cells expressing urothelial gene and protein markers.⁵ One of the most likely reasons for this is that true stem cells in bone marrow stromal cells are very rare, depending on donor age (1/10⁴ cells in newborns, but 1/10⁶ in older individuals). In addition, it is very difficult to isolate pure stem cells from the large amount of somatic cells. Furthermore, it is less likely to induce stromal cells (mesodermal) to differentiate into urothelial cells (endodermal).

Using the same inductive medium as in the BMSC study,⁵³ we found that 60–70% of USCs differentiated into cells expressing uroepithelial cell-specific genes and protein markers (uroplakin-Ia/III), and had urothelial barrier function and tight junction ultrastructures. Urothelial differentiated USCs also expressed the genes and proteins for ZO-1, E-cadherin, and cingulin (associated with tight junctions) in a dose- and time-dependent manner. The barrier function of induced USCs reaches a maturity similar to that of urothelial cells isolated from bladder tissue 14 days after induction, significantly better than non-induced USCs, indicating that USCs possess stem cell plasticity.¹⁰

USCs can efficiently give rise to functional cells of the smooth muscle cell lineage. Myogenically-differentiated USCs expressed smoothelin, desmin, myosin, α-SM actin, and calponin at both the gene and protein levels. The mRNA and protein levels of these markers increased significantly with time in differentiation media. Functional studies demonstrated that these differentiated USCs have similar

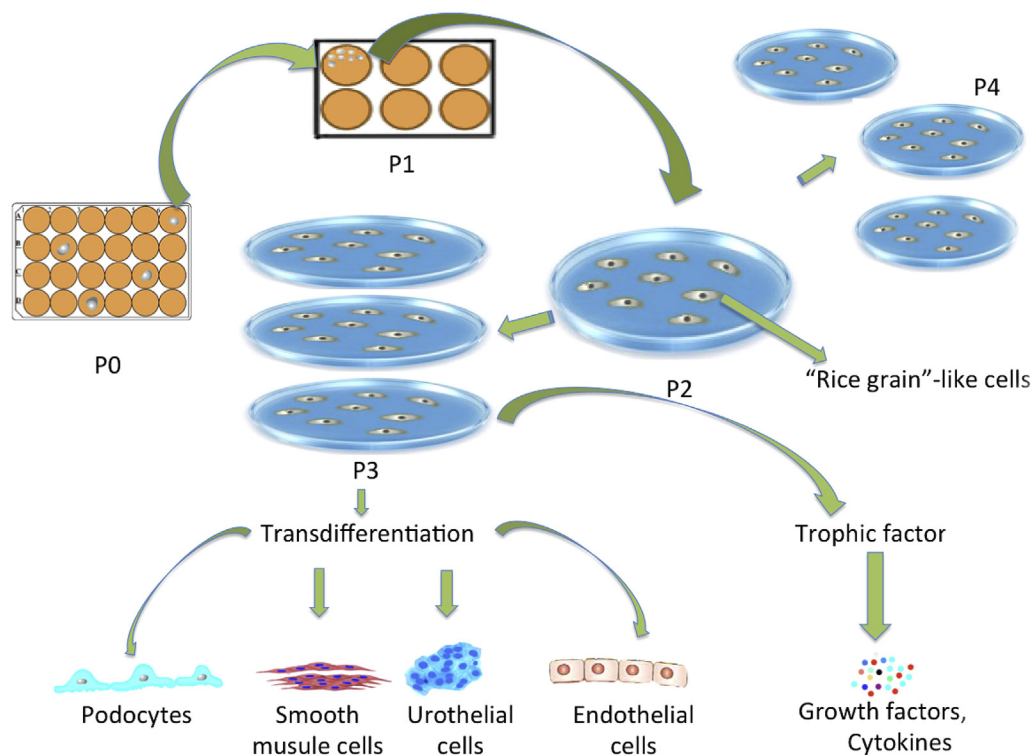


Figure 3 Cell proliferation, differentiation, and trophic factor secretion by urine-derived stem cells *in vitro*.

contractile properties as healthy smooth muscle cells *in vitro*. Myogenically-differentiated USCs formed multiple layers of smooth muscle cells beneath UC layers when subcutaneously implanted in a nude mouse model. The smooth muscle cells stained positively for α -SMA, desmin, and myosin. Scaffolds containing urothelial differentiated USCs generated stratified layers *in vivo* and stained positive for uroplakin-Ia and uroplakin-III (urothelial markers) and epithelial cell markers (Ck 7, Ck13, Ck20 and AE1/AE3).^{10,11}

We found that USCs differentiate into cells of the endothelial lineage when grown in endothelial differentiation medium containing 2 ng/ml VEGF for 12 days. Early *in vitro* vessel-forming was displayed 18 h after differentiated USCs (5×10^3 cells) were seeded onto Matrigel. The differentiated cells began to express the specific gene and protein markers of endothelial cells (CD31, vWF, KDR, FLT-1, eNOS and VE-cadherin). Induced USCs demonstrated intense immunofluorescent staining for these markers compared to non-differentiated USCs. Importantly, USCs can be efficiently differentiated into endothelial cells with barrier function. Neovessel formation occurred 4 weeks after induced USCs were subcutaneously implanted in an athymic mouse model.¹⁰

Immunoregulatory property of USCs

Regulatory T cells play an important role in induction of peripheral tolerance, inhibition of pro-inflammatory immune responses, and decreased immune reactions. USCs can impart profound immunomodulatory effects, by inhibiting proliferation of peripheral blood mononuclear cells (PBMC) and T and B cells, and secreting interleukin (IL)-6 and IL-8.⁵⁴

PBMNCs proliferated when mixed with other cells due to immune stimulation.⁵⁵ However, PBMC concentrations in USC wells were much lower than in BMSC culture wells. BrdU colorimetric ELISAs showed there was less BrdU labeled into the USC PBMC mixed culture wells compared to BMSC culture wells. CD80 and CD86 expressed on the surface of antigen-presenting cells interact with cytotoxic T lymphocyte antigen-4 expressed on activated T cells and mediate critical T cell inhibitory signals. Flow cytometry showed that 3.35% of the BMSCs were positive for CD80 (versus 1.05% of USCs), and 1.3% of the BMSCs were positive for CD86 (versus 0.55% of USCs). Human cytokine release arrays showed that IL-6 and IL-8 concentrations were elevated after stimulation by PBMCs in USC supernatant, which is higher than BMSC supernatant. IL-6 and IL-8 might be the main immunomodulatory cytokines to target in future studies aimed at preventing and treating diabetic bladder tissue lesions, other immune system disorders, or rejection of transplanted organs.

Trophic factors secreted by USCs and exogenous growth factors

USCs can secrete angiogenic growth factors and cytokines,^{56,57} but require a favorable microenvironment to do so. We demonstrated that use of genetically modified stem cells via transfection of the VEGF gene significantly promoted myogenic differentiation of USCs and induced angiogenesis and innervation.⁵⁸ However, virally delivered VEGF caused severe side effects in our animal model, including hyperemia, hemorrhage, and even death.⁴² Thus, a safer approach is needed for stem cell therapy to increase angiogenesis and promote muscle regeneration. Adding

Table 1 Comparison of USCs and other types of stem cells in genitourinary tissue repair.

Cell type/parameters	MSCs	USCs	ESC/iPS cells	Somatic cells from GU tissues
Original sites	Bone marrow or fat tissues	kidney		EC, SMC and UC from bladder
Self-renewal and expansion capability	Limited, PD~30, <passage 8	High, PD 60–70 > passage 15	Very high, PD > 200,	Limited, PD < 30, passage <8
Multi-lineage differentiation capability	Multipotent, but mainly limited within mesodermal cell lineages: i.e. osteocytes, adipocytes, chondrocytes	Multipotent differentiation potential; give rise to three dermal cell lineages	Pluripotent (can form all lineages of the body)	None
Urothelial and endothelial differentiation capability	Low (<10%)	High (60–85%)	Low	None
Telomerase activity (TA)/ telomere length	Cannot be detected	Upto 75% USC clones possess TA and relatively long telomeres	Possess TA and long telomeres	None
Harvesting methods	Invasive	Non-invasive, simple, cost-low, safe	Invasive to harvest somatic cells for iPS cells	Invasive
Stem cell isolation	Difficult	Very easy	Easy	None
Number of stem cells harvested	1 MSC/10 ⁴ bone marrow stromal cells in a newborn, 1 MSC/10 ⁶	100–140 USCs clones/24 h urine in adult		Unknown
Angiogenic trophic factors	Yes	Yes	Unknown	Moderate
Immuno-modulatory properties	Yes	Yes	Unknown	Moderate
Rejection after implanted <i>in vivo</i>	No rejection reaction as allogeneous or even xenogeneous cells (e.g. human BMSCs, USCs) implanted in rodent, rabbit, or canine models		Likely to be rejected	No rejection as autogeneous cells
Teratoma formation or oncogenic potential	No	No	Yes	None
Preclinical Study in renal insufficiency, ED, SUI, bladder or urethral reconstruction	Effective	Effective	None, due to safety concern	Effective
References	2–6,53	11,12,31,37,39,42,72	70	

Abbreviation: ESC, embryonic stem cell; GU, genitourinary; PD, population doubling; BMSC, bone marrow stem cell; MSC, mesenchymal stem cell; iPS, pluripotent stem cell; TA, telomerase activity; USC, urine-derived stem cell; SMC, smooth muscle cell; UC, urothelial cell; EC, endothelial cell; ED, erectile dysfunction; SUI, stress urinary incontinence.

exogenous angiogenic factors into biodegradable polymers as delivery vehicles can be beneficial to promote regeneration and tissue healing.⁵⁹ Alginate is one of the most commonly used natural hydrogels as an aqueous drug carrier for encapsulation because of its mild gelling conditions and tunable microsphere characteristics. Alginate microbeads also resist protein adsorption, making them attractive for *in vivo* studies.⁶⁰ Alginate microbeads deliver molecules in a controlled fashion, which can stably release active FGF-1 for at least 3 weeks *in vitro*. This sustained release of FGF-1 promoted neovascularization *in vivo* without any side effects.^{61–63} More recently, we found that a combination of growth factors (VEGF, IGF-1, FGF-1, PDGF, HGF and NGF) released locally from alginate microbeads induced USCs to differentiate into a myogenic lineage, enhanced revascularization and innervation, and stimulated resident cell growth *in vivo*.⁴² In addition, when cultured on 3D biomaterial, stem cells had significantly enhanced cell viability, proliferation, and differentiation *in vitro*; and promoted tissue formation *in vivo*, compared to cells cultured on 2-dimensional plates.⁶⁴

iPS cells reprogrammed from USCs

The ability to reprogram iPS cells from adult somatic cells could promote broad biomedical applications of stem cells, such as drug developments and tissue regeneration. Despite successful converting to iPS cells from various types of somatic cells, the process is time-consuming and inefficient. In our recent study, we created iPS cells from the urine of a child with Duchenne muscular dystrophy.⁶⁵ The cells found in the patient's urine were reprogrammed to iPS more rapidly and with greater efficiency than fibroblasts or other mesenchymal cells. Following the forced expression of the four reprogramming factors *oct4*, *sox2*, *klf4* and *c-myc*, urine cells from a healthy volunteer and a patient with Duchenne muscular dystrophy were successfully reprogrammed into iPS cells in 12 days, whereas it required more than 3 weeks to reprogram human skin fibroblasts. Cells harbored in the urine intrinsically expressed two canonical reprogramming factors, *c-myc* and *klf4*, together with highly active telomerase. The latter characteristic of urine cells contributes to improved reprogramming efficiency. Our data and other investigators' studies^{66–70} demonstrate the feasibility of rapid and efficient iPS cell generation from a sample of human urine, suggesting potential therapeutic uses of patient-derived iPS cells both for the treatment of various genetic defects via cell-based therapy and for drug screening.

Applications of USCs in animal studies

Diabetic erectile dysfunction

As with other MSCs,^{44–52,71} we recently determined that either human USCs or USCs genetically modified with FGF2 improved erectile dysfunction in a type 2 diabetic rat model.⁵⁶ USCs collected from human healthy donors and were transfected with FGF2 (USCs-FGF2). The implanted cells were injected into the cavernous tissue and tracked 1 and 4 weeks later. Implanted USCs or USCs-FGF2 had

significantly higher intracavernous pressure (ICP) and a higher ratio of ICP to mean artery pressure 28 days after ICP. Although few cells were detected within the implanted sites, histological and Western blot analyses demonstrated increased expression of endothelial and smooth muscle markers within the cavernous tissue following USC or USC-FGF2 injection. This study demonstrated that paracrine effects of USCs or USCs-FGF2 induced improvement of erectile function in type 2 diabetic rats by recruiting resident cells and increasing the endothelial expression and amounts of smooth muscle.

Urinary incontinence

Impairment of sphincter muscles or their neural and vascular support leads to stress urinary incontinence.⁵⁷ To determine the feasibility of using USCs, we studied the role of USCs or USCs over-expression of human VEGF165 in collagen-I gel on angiogenesis, cell survival, cell growth, myogenic phenotype differentiation of the implanted cells, and innervation following implantation *in vivo*. USCs were infected with adenovirus containing the VEGF and green fluorescent protein genes. A total of 5×10^6 cells, USCs alone, USCs plus endothelial cells, or human skeletal myoblasts (as control) suspended in collagen-I gel were subcutaneously implanted into nude mice. Extensive vascularization and more implanted cells was noted in VEGF-expressing USCs groups compared to the non-VEGF groups *in vivo*. Significantly more cells displaying endothelial markers (CD 31 and von Willebrand's factor) and myogenic markers (*myf-5*, *MyoD*, and *desmin*), and regenerated nerve fibers displaying neural markers (*S-100*, *GFAP* and *neurofilament*) were seen in grafts of VEGF-expressing USCs. Improved angiogenesis by VEGF-expressing USCs enhanced grafted cell survival, recruited resident cells, and promoted myogenic phenotype differentiation of USCs and innervation. This approach has important clinical implications for the development of cell therapies to treat stress urinary incontinence.

To provide site-specific delivery and targeted release of growth factors to implanted USCs, we prepared microbeads of alginate containing growth factors.⁴² The growth factors included VEGF, IGF-1, FGF-1, PDGF, HGF, and NGF. Radio-labeled growth factors were loaded separately and used to track *in vitro* release from the microbeads, as measured with a gamma counter over 4 weeks. In a separate experiment, *in vitro* endothelial differentiation of USCs via the released VEGF from the microbeads confirmed that the released growth factors from the microbeads were bioactive. Next, USCs and microbeads were mixed with the collagen gel type 1 (2 mg/ml) and subcutaneously injected into nude mice. Four weeks after subcutaneous injection, grafted cell survival was improved and more cells expressed myogenic and endothelial cell transcripts and markers compared to controls. Compared to controls, we observed more vessel formation and innervation in USCs combined with the six growth factors and incorporated in microbeads. In conclusion, a combination of growth factors released locally from the alginate microbeads induced USCs to differentiate into a myogenic lineage, enhanced revascularization and innervation, and stimulated resident cell growth *in vivo*. This approach could potentially be used for

cell therapy in the treatment of stress urinary incontinence. Our most recent studies demonstrated that implanted USCs restored sphincter function by increasing leak point pressure (LPP) in a rat model one week after vaginal distention injury (unpublished data).

Bladder or urethral reconstruction

The ideal stem cell sources for bladder repair would i) be able to differentiate into functional smooth muscle, urothelial, endothelial, and peripheral neurocytes with high efficiency. These promote bladder contractility and compliance, and restore histological structures with innate vasculature and innervation; ii) allow collection via a non-invasive, simple, safe, and low-cost method; iii) have universal or 'off the shelf' availability; and iv) generate tissue-specific or organ-specific stem cells from the urinary tract system. Currently, it is unknown whether such a 'perfect' stem cell exists. We do know, however, that certain cell types are more favorable than others. Although BMSCs or adipose stem cells are the most commonly used MSCs, they have some limitations in tissue engineering technology applications for lower urinary tract reconstruction, such as low differentiation capacity (<5% of urothelial cells of endodermal lineage), short lifespan *in vitro* (<10 passages in BMSCs), and the need for invasive collection procedures.

To be used successfully in tissue engineering approaches for lower urinary tract reconstruction, USCs must be directed to three types of bladder cells: smooth muscle, urothelial, and endothelial cells. Via trans-differentiation, USCs can give rise to all three types *in vitro* and *in vivo*.^{37,72} In addition, when both myogenically-differentiated USCs and urothelially differentiated USCs were co-cultured on decellularized collagen matrix (such as SIS or bladder submucosa), the urothelium and muscle layer structure *in vitro* is similar to that of the bladder wall.^{37,72} Further cystoplasty experiments in animal models are needed to test the feasibility and efficacy of USCs or the induced USCs.

In addition, we found that USCs differentiated into podocytes and renal tubule epithelial cells *in vitro* and significantly enhanced renal function after implantation of USCs by reducing collagen deposition and inhibiting fibrosis formation in a rodent model of chronic renal failure (unpublished data).

Future directions

To use stem cell therapy more efficiently for tissue repair or regeneration requires enhancing angiogenesis for survival of grafted cells, inducing innervation for functional recovery, and developing more suitable biomaterials in the future. Increasing the ratio of cell retention and improving long-term engraftment after cell implantation will lead to better genitourinary tissue regeneration. The grafted cells start to die within the first week, most probably due to ischemia, inflammation, or apoptosis due to detachment from the extracellular matrix. It is extremely important to increase viability of implanted stem cells early after cell transplantation. Controlled release of exogenous angiogenic factors, such as genetically modified stem cells,

significantly increase cell retention and induce better tissue formation. Because of safety concerns, use of viral gene transfection might not be optimal.

In addition, for tubule or hollow organ tissue engineering in urology, urothelial cells seeded on the luminal side of scaffold are often lost during surgery, washed out via the urine, or mechanically ejected via the urethral catheter. To solve these problems, several methods might help: **a)** using biomaterials with porous micro-structure to aid cell retention within the scaffold; **b)** keeping the cell-seeding scaffold construct wet in the culture media, and avoid drying it out during surgery; **c)** inducing angiogenesis or capillary network formation early in implantation with angiogenic growth factors released from nanoparticles or microbeads, adding growth factors (such as FGF2 or IGF-1) into binding scaffolds in the site, or pretreatment of hypoxic cells; and **d)** promoting revascularization (artery-capillary-venous system) at the middle or late stages after the implantation using biologically safe physical stimulation, including lower-frequency electrical stimulation or low-intensity ultrasound. These methods could extend the lifespan of implanted cells *in vivo* to provide better tissue repair with long-term release of paracrine factors and trans-differentiation, resident cell recruitment, anti-fibroblast formation, and anti-inflammatory and anti-apoptotic effects of MSCs. In addition, innervation is critical to create a functional bladder. Stimulating peripheral nerve growth into neobladder tissue might be more efficacious than attempting to create neurogenic differentiation of MSCs.

To achieve clinically successful results, USCs need further investigation. Although USCs restore tissue or organ function in rodent models, larger animal experiments are required before cell therapy could be attempted in clinical trials. Relevant questions include: **a)** What is the mechanism by which USCs generate tissue repair, trans-differentiation, or trophic effects? Is it necessary to induce USCs to differentiated target cells *in vitro*, or can undifferentiated stem cells achieve similar or better outcomes as pre-differentiated stem cells? **b)** As a novel stem cell source, can USCs be used for tissue repair and regeneration in non-urinary tract sites, such as skin, vessels, heart, lung, or liver tissue?

Summary and conclusions

As a novel cell source, USCs possess an excellent feasibility and safety profile for tissue regeneration, specifically for genitourinary tissue repair. These cells express telomerase activity and are highly expandable, but do not induce teratomas or tumors *in vivo*. USCs not only efficiently give rise to podocytes, myocytes, and endothelial and urothelial cells, they also secrete a battery of growth factors and cytokines. Preclinical outcomes of cell therapy with USCs have been positive in models of diabetic erectile function, stress urinary incontinence, urethra and bladder reconstruction, and renal insufficiency. USCs can be obtained via a non-invasive, simple, safe and low-cost approach. Besides genitourinary tissue repair, USCs might also be a viable cell source for cell-based therapy in treatment of tissue defects or diseases in other systems.

Conflicts of interest

All authors have none to declare.

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