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Editorial

Urine Derived Stem Cells as a Novel Cell Source for Urethral Tissue Regeneration - ∂

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As a tubularized organ in the distal portion of the urinary tract, the urethra can often develop strictures due to congenital defects (e.g. hypospadias), injury, and infections. In particular, urethral stricture is a common urological problem in men. Urethral strictures thus present a significant economic impact and burden, because they are relatively frequent and repeated surgical intervention is often needed. The main causes of urethral stricture are trauma to the urethra, gonorrheal infection and idiopathic inflammatory diseases. Trauma, such as straddle injuries, pelvic bone fracture and iatrogenic injures (e.g. urinary catheterization or other instrumentation and complications due to irradiation for prostate cancer) can result in strictures of the anterior and/or posterior segments of urethra. Urethral stricture often results in scar tissue formation and poor blood supply in or around the urethra, which leads to fibrosis and changes in collagen deposition, or in the ratio of smooth muscle to extracellular matrix in the underlying tissue. Strictures can block the flow of urine and as a result, they cause a high incidence of associated complications. These complications include acute urinary retention, irritation on voiding, recurrent urinary tract infections, bladder or urethral stones, hydronephrosis, and renal failure.

Surgical treatments for urethral stricture depend upon the length, location and degree of scar tissue associated with the stricture. Although many different reconstructive procedures have been used, they are most applicable to strictures less than 3 cm in length in which the stricture can be removed and the two ends of the urethra reconnected. It is a big challenge to treatment of severe, long urethral strictures. When the stricture is longer, urethral repair requires fresh autologous tissue, such as foreskin or oral mucosa, to replace the excised segment (substitution procedures). However, fresh tissues for substitution are not always available, and if the urethral stricture is too long, even this type of repair is not possible. Tissue-engineered tubular urethral tissues are an alternative for replacement of lost or deficient urethral tissues with functionally equivalent ones, and may improve the outcome of reconstructive surgery for urethral strictures [1-6].

Two types of urethral tissue engineering technologies are often used: non-cell seeded or cell free and seeded tissue engineered urethra [2,7-10]. The non-cell seeded technology is suitable for urethra repair via onlay patch or for replacement of short segment urethra [11]. Cell seeded technology with autologous cells seeded on biodegradable scaffolds achieves better outcomes in longer segment urethra repair [4,12], compared to non-seeded scaffolds in urethral tissue regeneration. A convenient cell source and optimal biomaterial scaffold are both critical for urethra tissue engineering. Currently, autologous bladder cells or oral mucosa cells [13] obtained from tissue biopsy are most commonly used for urethral tissue engineering. In patients with urethral stricture, however, it might be difficult to insert an endoscope into the urethra to obtain adequate bladder cells via tissue biopsy. Additionally, even if an endoscopy can be performed, the tissue biopsy procedure itself may lead to donor-site morbidity. Furthermore, it might not be possible to harvest healthy cells in certain patients who have infections in the urethra, bladder or even the gums or other oral tissues, as this poses a high risk of bacterial or fungal contamination of the biopsy sample. In addition, despite reports of successful isolation of autologous urothelial cells from urine or bladder washes for use in urological tissue engineering, the success rate of cultures of these cells is low (55%), and they also have limited expansion capability in culture[14-15]. Importantly, while an immortalized urothelial cell line may generate a large amount of cells, these cells have limited clinical applications, since immortalized cells carry the risk of tumor formation in vivo.

A stem cell source with high self-renewal and multi-potent differentiation capacities that can be obtained via a simple and non-invasive approach would be highly desirable. We recently found that a subpopulation of cells isolated from urine possess characteristics similar to mesenchymal stem cells (MSCs), i.e. clonogenicity, cell growth patterns, expansion capacity, cell surface marker expression profiles and multipotent differentiation capacity [5,16-29]. These urine-derived cells are positive for the MSC surface markers CD29, CD44, CD54, CD73, CD90, CD105, CD146, and CD166. In addition, these urine-derived stem cells also express some embryonic stem cell markers, including Oct4, c-Myc and klf4; however, they do not express markers associated with hematopoietic stem cells, such as CD31, CD34, CD45, CD11b, CD14, CD19 and HLD-DR [30]. We have demonstrated that these stem cells derived from urine are capable of multipotent differentiation to bone cells, cartilage cells, fat cells, and muscle cells [5-18,30-32]. Thus, we have termed these cells "urine-derived stem cells" or USCs. USCs can be obtained from voided urine or from urine in the upper urinary tract through a nephrostomy tube, and they can generate a large number of cells from a single clone [18-31]. Additionally, about 57-75% of the USCs collected from middle-aged individuals expressed telomerase activity (USCs-TA+) and retained long telomere length. USCs-TA+ possessed higher proliferative capacities and could be maintained for up to 67 population doublings, indicating that a single USC can generate more cells, up to 267 cells within 14 weeks, compared to 35 PD (235 cells) for USCs that do not express telomerase (USCs-TA-). Now that we have improved the cell isolation methods used to obtain USCs, five to ten USC clones/100 ml urine can be consistently obtained from almost every freshly voided urine sample [30]. To prepare a cell-seeded biomaterial scaffold for use in urological tissue regeneration, the cell concentration for seeding must be about 50x106 cells/cm3,33. Thus, the number of cells from one 200 ml urine sample can provide enough cells to create a cell-seeded scaffold 0.5x2x10cm3 in size. Our recent study showed that USCs give rise to functional urothelial cells 5, 18, 31, 32, SMCs5, 18, 31, 32, and endothelial cells [30]. Induced USCs seeded on different biomaterials (small intestine submucosa [5], bladder submucosa [34] or bacterial cellulose polymer18) all formed urethra structure with urethelial layer and smooth muscle layer on the scaffolds in vitro and also remained such a contracture after subcutaneously implanted in a rodent animal.

Taken together, USCs provide a novel cell source for urethra reconstruction via tissue engineering technology. Importantly, these cells can be collected using a simple, safe, low-cost and non-invasive procedure. Because of their high proliferation capacity and differentiation potential, USCs are also a viable cell source for bladder tissue engineering [5,18] and cell therapy for the treatment of stress urinary incontinence [32-35] vesicoureteral reflux, erectile dysfunction, renal dysfunction and other diseases that are suitable for stem cell therapy.

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