Zhang et al. Ann Nephrol 2018, 3(1):28-30
DOI: 10.36959/832/394 | Volume 3 | Issue 1

Annals of Nephrology

Commentary Open Access

Autologous Urine-derived Stem Cells for Kidney Tissue Repair

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Stem cell-based therapy offers an alternative treatment for chronic kidney diseases, including acute or chronic renal failure, diabetic nephropathy, polycystic kidney diseases and renal transplantation. Most studies have focused on endothelial progenitor cells or mesenchymal stem cells (MSCs), not embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [1] because the concern of teratoma formation or ethical issues hamper the further clinical application potential of ESCs or iPSCs. Available experimental evidences confirm that MSCs contribute to cellular repair and ameliorate renal injury in chronic renal failure via anti-inflammatory, anti-fibrotic, anti-apoptotic and pro-angiogenic potentials [2-4]. However, to obtain MSCs from bone marrow, fat, and other tissues, invasive tissue biopsies are usually required. In addition, stem cells often used in preclinical studies are isolated from healthy donors, not from patient tissues. For eventual clinical use, autologous stem cells would be the optimal cell source, to avoid immune rejection [5] and other adverse events associated with allogeneic or exogenous sources. Thus, autologous stem cells conveniently obtained from a non-invasive, safe, reproducible, and low-cost approach would be highly desirable as an alternative cell source for improve renal tissue regeneration for the patients with various kidney diseases.

Ideal cell candidate for cell therapy in the treatment of kidney dysfunction should be: i) The cells are easily accessible from a patient's own cells; ii) They could survive and exert the reparative function under diseases-stress after implanted; iii) They are able to potential in inhibiting inflammatory response, fibrosis and oxidative stress, and giving rise into podoctyes and renal tubule epithelial cells; iv) They are safe to use *in vivo* without any risk of oncogenicity. We were the first to discover a subpopulation of cells isolated from urine that possess biological characteristics of stem cells: Clonogenicity, cell growth patterns, expansion capacity, migration, cell surface marker expression profiles of mesenchymal stem cells, pro-angiogenic paracrine effects, immunomodulatory properties, easily-induced pluripotent stem (iPS) cells, and multipotent differentiation capacity [6,7]. We demonstrated that USCs originate from parietal epithelial cells in kidney glomeruli [8], because the USCs obtained from women receiving a sex-mismatched kidney transplant (male) contained the Y chromosome, expressed parietal epithelial cell markers (Pax2, Pax8, CD24, CD133 and claudin-1) [9,10] Importantly, USCs can differentiate into renal cells, such as podocytes and renal tubular epithelial cells besides giving rise to osteogenic, adipogenic chondrogenic, myogenic, and neurogenic cell lineages and endothelial cells *in vitro*, and formed relevant tissues *in vivo* [6,11,12]. USCs expressed podocyte markers (WT1, synaptopodin, podocalyxin and podocin) [11,13] after induction at a rate similar to that seen in parietal epithelial cells and podocytes that populate glomeruli. USCs displayed epithelial markers of renal tubular epithelial cells and tight junctions, and displayed barrier junctions after the induced medium. Furthermore, USCs secrete bioactive trophic factors *in vitro*; those factors significantly improved tissue regeneration via increasing implanted cell viability and recruited the resident stem cells participating in endogenous tissue regeneration *in vivo* [14].

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Accepted: August 23, 2018; **Published online:** August 25, 2018

Citation: Zhang D, Xing G, Tao L, et al. (2018) Autologous Urine-derived Stem Cells for Kidney Tissue Repair. Ann Nephrol 3(1):28-30

Although there are several cell types in urine, our culture system can easily isolate stem cells from other somatic cells [15]. A single USC clone can generate large numbers of pure stem cells [6,7]. Cell viability is better protected [7,16] because isolation of USCs does not require tissue dissociation procedures (such as digestive enzymes). USCs possess potent proliferation capacity. Up to 75% of USCs collected from middle-aged donors expressed telomerase activity (USCs-TA$^+$) and retained telomere length [17]. USCs-TA$^+$ possessed higher proliferative capacities and were maintained for up to 67 population doublings after 16-20 passages, indicating that a single USC can generate up to 2^{67} cells within 14 weeks [6]. After optimizing our methods, 100-140 USC clones/24 hr urine were consistently obtained from each individual [7]. Thus, a 24 hr urine sample can provide ample cells ($> 100 \times 10^6$) in 3 weeks for the purposes of cell implantation. Importantly, although USCs do display telomerase activity, these cells do not form teratomas or tumors after subcutaneous implantation or under the renal capsule for up to 3 months, indicating they have high proliferation potential but are a safe source for cell therapy [2,17]. In short, our data suggest that USCs with potent regeneration capacity are an optimal cell source for cell-based therapy in the treatment of kidney diseases, compared to other adult stem cells.

USCs obtained from healthy human donors have been used for tissue regeneration in various *in vivo* models. We recently tested the protective effects of USCs on pancreatic islets, the myocardium, the renal glomerulus, and the bladder detrusor muscle in high fat diet/streptozotocin-induced Type 2 diabetic rat models. USCs significantly inhibited fibrosis and apoptosis of the myocardium, glomerulus, and detrusor, but did not decrease fasting blood glucose significantly, suggesting that USCs may be most useful in treating complications of diabetes [2]. Our most recent study showed that human USCs significantly improved renal function in a rat model of chronic renal insufficiency induced by gentamicin combined with renal ischemic insult, with a 50% decline in serum creatinine at 2 weeks post-cell injection (5×10^6 cells/kidney) maintained over 9 weeks, compared to controls. The implanted USCs were detected around the glomerulus and interstitial area. Numbers of macrophages and amount of collagen deposited significantly decreased in renal tissue (unpublished data). Furthermore, use of implanted USCs restored erectile function in a rodent model of diabetic erectile dysfunction [18], and improved urethral sphincter function in a rat model of vaginal distention injury [19]. Our procedures with USCs have been successfully repeated by other [4,12,20-32]. They used human USCs for kidney [4,12,33], bladder, [29] cardiomyotic tissue [2], corpora cavernosa [34], bone [26,35], lungs [31], skin [13], neurogenic [11] and other types of tissue regeneration [13,35]. Importantly, our more recent studies that up to 30% of USCs from the patients with chronic diseases (such as diabetic nephropathy) possess normal regenerative function in cell proliferation, differentiation, and paracrine factor section (unpublished data). Taken together, these data show that patients-sourced USCs have therapeutic effects on tissue regeneration, particularly for renal tissue repair. In addition, these cells could be useful in assessment of renal function, and in the diagnosis and prognosis of different types of renal disease and renal failures.

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