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**Adult stem-like cells in kidney**

Hishikawa K *et al.* Adult stem-like cells in kidney

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**Abstract**

Human pluripotent cells are promising for treatment for kidney diseases, but the protocols for derivation of kidney cell types are still controversial. Kidney tissue regeneration is well confirmed in several lower vertebrates such as fish, and the repair of nephrons after tubular damages is commonly observed after renal injury. Even in adult mammal kidney, renal progenitor cell or system is reportedly presents suggesting that adult stem-like cells in kidney can be practical clinical targets for kidney diseases. However, it is still unclear if kidney stem cells or stem-like cells exist or not. In general, stemness is defined by several factors such as self-renewal capacity, multi-lineage potency and characteristic gene expression profiles. The definite use of stemness may be obstacle to understand kidney regeneration, and here we describe the recent broad findings of kidney regeneration and the cells that contribute regeneration.

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**Key words:** Stem cell; Label-retaining cells; rKS56; SP cells; CD24; CD133; Sca-1; Induced pluripotent stem; ES cell

**Core tip:** Controversies still persist whether kidney stem cells exist or not, but renal progenitor cell or system is reportedly presents suggesting that adult stem-like cells in kidney can be practical clinical targets for kidney diseases. In this mini-review, we describe the recent broad findings of kidney regeneration and the cells that contribute regeneration.

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**INTRODUCTION**

Recent developments inhuman pluripotent cells including both embryonic stem cells and induced pluripotent stem (iPS) cells[1] are promising for clinical development of cell therapies and tissue engineering[2-4]. There is an urgent need for stem cell and regenerative medicine approaches to kidney diseases, because patients with end-stage kidney disease require lifelong dialysis treatment or transplantation that incurs a significant cost. Several established protocols for derivation of cardiomyocytes and neurons were already reported, but that for kidney cell types are still controversial. Recently human iPS cells were successfully differentiated into kidney lineage *via* OSR1 (+) cells[5,6]. However metanephric progenitors were not induced from OSR1(+) cells[7], and efficient differentiation of human pluripotent cells into intermediate mesoderm was reported by treatment the cells with glycogen synthase kinase-3beta inhibitor[8]. Different from mammals, the capacity to regenerate kidney tissue is well confirmed in several lower vertebrates such as fish[9]. Kidney regeneration, such as the repair of nephrons after tubular damages, is commonly observed after renal injury even in humans[10,11]. Concerning adult mammal kidney, there are lots of evidences that suggest existence of renal progenitor system[12-19]. Collectively, these results suggest the potential role of adult stem-like cells in kidney for practical clinical treatment of kidney diseases. In this review, we describe the localization and recent functional findings of kidney regeneration and the cells that contribute regeneration.

**TUBULAR CELLS (LRC, RKS56, NFATC-1+, ALDHHIGH, CD24+/CD133+, MRPC)**

To identify the stem cells, BrdU-DNA labeling is commonly used to find slow-cycling cells because stem cells have a slow cell cycle. Slow cycling cells were also called label-retaining cells (LRC), and LRC in tubules were confirmed by several groups[20-22] (Table 1). In rat kidneys, LRC were distributed among renal epithelial tubular cells[20]. In 3 dimensional culture system, LRC formed tubule-like structure. Moreocver, injected LRC into cultured metanephros formed nephrons and collecing ducts[23]. rKS56 cells were established form proximal tubules (S3) by using microdiseection of a single nephron[24]. rKS56 cells expressed markers of an immature progenitor state such as c-Kit and Sca-1. When rKS56 cells were transplanted into acute kidney disease models, the cells differentiated into epithelium. A resident progenitor cells in proximal tubular (PTC) cell was identified by Nfatc1-P2-Cre reporter system[25]. Nfatc-1-labeled PTC cells were apoptosis-resistant and proliferated to repair the damaged proximal tubule segment. ALDH activity was used to isolate cells with progenitor-like characteristics from the tubular fraction of the renal cortex[26-29]. ALDHhigh cells displayed typical stem cell properties such as sphere formation and anchorage-independent growth. CD24/CD133 double-positive cells were localized in the tubular epithelium, and demonstrated clonogenic mutipotency and self-renewal ability[28]. Bombelli *et al*[30] recently proposed existence of CD133+/CD24- renal stem cells but Romagnani reported that CD133+ renal stem definitely co-express CD24 in human kidney[31]. Gupta *et al*[32] reported localization of stem-like cells around the tubules. They named the cells multi-potent renal progenitor cells (MRPC). By using similar culture condition used for culture of bone marrow–derived mult-ipotent adult progenitor cells, MRPS were isolated from rat kidney. The plasticity of MRPC was confirmed by expression of endothelial, hepatocyte, and neural markers by RT-PCR and protein expression. When MRPC were injected under the capsule of an uninjured kidney or arterially into acute kidney injury model, the cells differentiated into renal tubules. However, differentiation/induction of matured kidney cells from MRPC *in vitro* was not confirmed yet.

**RENAL PAPILLA (LRC, CD133+)**

To identify the stem-like cells in kidney, Oliver *et al*[33,34] performed pulse label of rat and mouse pups by BrdU, and confirmed the existence of LRC cells in the kidney. LRC cells was very sparse in the kidney, but they found numerous LRC cells in renal papilla[33]. In 3 dimensional culture, LRC cells in renal papilla spontaneously formed spheroids, and clones from single cell of LRC cells expressed both mesencymal and epithelial markers. The papillary cells also differentiated to myofibroblasts and neuronal cells. In acute kidney injury model such as ischemic injury, LRC cells in papilla migrated to the upper papilla and formed a compartment of rapidly proliferating cells suggesting that the cells contributed to repair of kidney tissue[34]. Papillary cells that expressed CD133 were also expressed nestin and embryonic cell markers (Oct3/4, Nanog, SOX2 and SSEA-4)[35].

**INTERSTITIAL SPACE (SCA-1+CD45-, SP, CD133+)**

Several groups have found adult stem-like cells in murine kidney interstitial space using different approaches. Stem cell angiten-1 (Sca-1)-positive and CD45-negative cells were isolated from whole kidney tissue by magnetic assisted cell sorting (MACS) and fluorescence activated cell sorting (FACS) sorting[36]. The cells were negative for hematopoietic stem cell and lineage markers and located in the renal interstitial spaces. The differentiation of the cells into multi-lineage (myogenic, osteogenic, adipogenic and neural) was also confirmed. In acute kidney injury model, injected Sca-1+CD45- cells contributed kidney repair. To isolate hematopoietic stem cell-rich population in a single step, Goodell *et al*[37] stained cells with Hoechst 33342 dye and isolated the cells by FACS. The cells isolated by this method were nemaed side population (SP) cells. This method was also used to purify a stem cell-rich population in various kinds of tissue. SP cells isolated from adult kidney demonstrated ability of self-renewal and differentiation into multiple lineages[38]. SP cells isolated from adult kidney located in interstitial spaces, and secreted reno-regenerative/protective factors (HGF, VEGF, and BMP-7)[39-42]. The injection of SP cells isolated from adult kidney cells into a model of acute kidney injury demonstrated the recovery of renal function[39,40]. Interestingly, Inowa *et al*[43] confirmed the existence of kidney SP cells in human[43]. Concerning CD133 positive cells, Bussolati *et al*[27] reported that the cells were localized to the interstitium, but not in glomeruli Kidney CD133 positive cells lacked expression of hematopoietic markaers and expressed Pax-2, an embryonic renal marker. Intravenous injection of kidney CD133 positive cells in SCID mice with glycerol-induced tubulonecrosis, the cells homed into the injured kidney and integrated in tubules.

**BOWMAN’S CAPSULE (CD24+CD133+PDX+, CD24+CD133+PDX-)**

Some parietal epithelial cells (PEC) are reported to be adult stem-like cells[44-47]. Sagrinati *et al*[45]confirmed the existence of PEC that expressed CD24, CD133 Oct-4 and Bml-1 in the Bowman’s capsule CD24+CD133+ PEC were isolated by culture of capsulated glomeruli plated on fibronectin-coated dishes. CD24+CD133+ PEC showed potential of self-renewal and a high cloning efficiency. Transplantation of CD24+CD133+ PEC into acute kidney injury model significantly improved not only morphologic but functional kidney damage. Further charcterization using podocyte marker (PDX) of CD24+CD133+ PEC revealed a hierarchial population of the cells in a precise sequence with Bowman’s capsule and exhibited heterogenous potential such as differentiation and regeneration[48]. CD24+CD133+PDX- cells localized to the urinary pole could differentiate into both tubular cells and podocytes, but CD24+CD133+PDX+ cells localized between the urinary pole and vascular pole could differentiate into only podocytes. Transplantation of CD24+CD133+PDX- cells reduced proteinuria and improved chronic glomerular damage in adriamycin-induced nephropathy models.

**FUNCTIONAL REGULATION OF ADULT STEM-LIKE CELLS IN KIDNEY**

As mentioned above, different kinds of adult stem-like cells in kidney have been reported, but their functional regulations were poorly understood. If it is possible to regulate multi-potent adult stem like-cell *in situ*, this can be a good regenerative treatment. Recently MyoR was reported to regulate regenerative function of kidney SP cells[49], and such a molecule can be a good target for pharmacological treatment for kidney disease.

**CONCLUSION**

Several adult stem-like cells in kidney reportedly demonstrated multi-potency. However, it is impossible to get enough cells for cell therapy from the patient. The adult stem-like cell in kidney is expected to play key role to preserve kidney function, and the cells may be the good targets for pharmacological treatment. For cell therapy, iPS or ES cells might be the applicable as in the case with neural and cardiac rengenertion.

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**Table 1 Localization and characteristics of adult stem-like cells in kidney**

|  |  |  |  |
| --- | --- | --- | --- |
| Localization | Characteristics  | Species  | Ref. |
| Tubular cells  | LRC | Rat | [20-23] |
| rKS56  | Rat | [24] |
| Nfactc-1+ | Mice | [25] |
| ALDHhigh/CD24+/CD133+ | Human  | [26-29] |
| MRPC  | Rat | [32] |
| Renal papilla | LRC | Rat, mice | [31,32] |
| CD133+ | Human | [33] |
| Interstitial space  | Sca-1+/CD45-  | Mice | [34] |
| SP cell  | Rat, mice, human  | [38-41] |
| CD133+  | Human  | [27] |
| Bowman’s capsule | CD24+/CD133+/PDX+ | Human  | [44-48] |
| CD24+/CD133+/PDX- | Human  | [44-48] |

LRC: Label-retaining cells; MRPC: Multi-potent renal progenitor cell; PDX: Podocyte marker.