Adult stem-like cells in kidney

Keiichi Hishikawa, Osamu Takase, Masahiro Yoshikawa, Taro Tsujimura, Masaomi Nangaku, Tsuyoshi Takato

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 present 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.

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

INTRODUCTION

Recent developments in human pluripotent cells including both embryonic stem cells and induced pluripotent stem (iPS) cells are promising for clinical development of cell therapies and tissue regeneration. However, 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 present 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.

Core tip: Controversies still persist whether kidney stem cells exist or not, but renal progenitor cell or system is reportedly present 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.

Hishikawa K, Takase O, Yoshikawa M, Tsujimura T, Nangaku M, Takato T. Adult stem-like cells in kidney. World J Stem Cells 2015; 7(2): 490-494. Available from: URL: http://www.wjgnet.com/1948-0210/full/v7/i2/490.htm DOI: http://dx.doi.org/10.4252/wjsc.v7.i2.490
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+, ALDH**\textsuperscript{HIGH}, CD24\textsuperscript{+}/CD133\textsuperscript{+}, 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. Moreover, injected LRC into cultured metanephros formed nephrons and collecting ducts[21], rKS56 cells were established form proximal tubules (S3) by using microdissection of a single nephron[22]. 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[23]. Nfatc1-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]. ALDH\textsuperscript{HIGH} 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 multipotency and self-renewal ability[28]. Bombelli et al[30] recently proposed existence of CD133+/CD24\textsuperscript{-} renal stem cells but Romagnani reported that CD133\textsuperscript{-} 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 multi-potent 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.

**RENNAL PAPILLA (LRC, CD133\textsuperscript{-})**

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 mesenchymal 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\textsuperscript{+}CD45\textsuperscript{-}, SP, CD133\textsuperscript{-})**

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 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\textsuperscript{+}CD45\textsuperscript{-} cells contributed
Hishikawa K et al. Adult stem-like cells in kidney

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

| Localization          | Characteristics | Species   | Ref. |
|-----------------------|-----------------|-----------|------|
| Tubular cells         | LRC             | Rat       | [20-23]|
|                       | rK56            | Rat       | [24]  |
|                       | NiAct-1’        | Mice      | [25]  |
|                       | ALDH4A+/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.

To isolate hematopoietic stem cell-rich population in a single step, Goodell et al. stained cells with Hoechst 33342 dye and isolated the cells by FACs. The cells isolated by this method were named 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. SP cells isolated from adult kidney located in interstitial spaces, and secreted renoge-nenerative/protective factors (HGF, VEGF, and BMP-7). The injection of SP cells isolated from adult kidney cells into a model of acute kidney injury demonstrated the recovery of renal function. Interestingly, Inowa et al. confirmed the existence of kidney SP cells in human. Concerning CD133 positive cells, Bussolati et al. reported that the cells were localized to the interstitium, but not in glomeruli. Kidney CD133 positive cells lacked expression of hematopoietic markers 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. Sagrini et al. confirmed the existence of PEC that expressed CD24, CD133 Oct-4 and Bmi-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 characterization using podocyte marker (PDX) of CD24+CD133+ PEC revealed a hierarchical population of the cells in a precise sequence with Bowman’s capsule and exhibited heterogeneous potential such as differentiation and regeneration. 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, 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 regeneration.

**References**

1. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006; 126: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]
2. Song JH, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med 2013; 19: 646-651 [PMID: 23584091 DOI: 10.1038/nm.3154]
3. Humes HD, Weitzel WF, Bartlett RH, Swaniker FC, Paganini EP, Luderer JR, Sobota J. Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. Kidney Int 2004; 66: 1578-1588 [PMID: 15458454 DOI: 10.1111/j.1523-1755.2004.00923]
4. Tumlin J, Wali R, Williams W, Murray P, Tolwani AJ, Vinnikova AK, Szerlip HM, Ye J, Paganini EP, Dworkin L, Finkel KW, Kraus MA, Humes HD. Efficacy and safety of renal tubule cell therapy for acute renal failure. J Am Soc Nephrol 2008; 19: 1034-1040 [PMID: 18272842 DOI: 10.1681/ASN.2007080095]
5. Song JH, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med 2013; 19: 646-651 [PMID: 23584091 DOI: 10.1038/nm.3154]
6. Humes HD, Weitzel WF, Bartlett RH, Swaniker FC, Paganini EP, Luderer JR, Sobota J. Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. Kidney Int 2004; 66: 1578-1588 [PMID: 15458454 DOI: 10.1111/j.1523-1755.2004.00923]
nephrogenic intermediate mesoderm from human pluripotent stem cells. Nat Commun 2013; 4: 1367 [PMID: 23340407 DOI: 10.1038/ncomms2378]

6 Araoka T, Mae S, Kurose Y, Uesugi M, Ohla A, Yamanaka S, Osafune K. Efficient and rapid induction of human iPSCs/ESCs into nephrogenic intermediate mesoderm using small molecule-based differentiation methods. PLoS One 2014; 9: e84881 [PMID: 24454758 DOI: 10.1371/journal.pone.0084881]

7 Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, Nishinakamara R. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell 2014; 14: 53-67 [PMID: 24332837 DOI: 10.1016/j.stem.2013.11.010]

8 Lam AQ, Freedman BS, Morizane R, Lerou PH, Valerius MT, Bonventre JV. Rapid and efficient differentiation of human pluripotent stem cells into intermediate mesoderm that forms tubules expressing proximal tubular markers. J Am Soc Nephrol 2014; 25: 1211-1225 [PMID: 24357672 DOI: 10.1681/ASN.2013080381]

9 Diep CQ, Ma D, Deo BC, Holm TM, Nayelow RW, Arona N, Wingert RA, Bollig F, Djordjevic G, Lichman B, Zhu H, Ikeno T, Ono F, Engert C, Cowan HA, Hukriede NA, Handin RL, Davidson AJ. Identification of adult nephron progenitors capable of kidney regeneration in zebrafish. Nature 2011; 470: 95-100 [PMID: 21270795 DOI: 10.1038/nature06969]

10 Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest 2006; 116: 288-296 [PMID: 16453013 DOI: 10.1172/JCI27699]

11 Ma LJ, Nakamura S, Aldigeri JC, Rossini M, Yang H, Liang X, Nakamura I, Marcantoni C, Fogo AB. Regression of glomerulosclerosis with high-dose angiotensin inhibition is linked to decreased plasminogen activator inhibitor-1. J Am Soc Nephrol 2005; 16: 966-976 [PMID: 15728787 DOI: 10.1681/ASN.2004060492]

12 Blanpain C, Horsley V, Fuchs E. Epithelial stem cells: turning processes of the kidney. Nat Rev Nephrol 2011; 7: 179-187 [PMID: 21281626 DOI: 10.1038/nrneph.2011.14]

13 Remagnani P, Vaziri ND. Stem cells in renal diseases. Kidney Int 2009; 76: 997-1003 [PMID: 19463812 DOI: 10.1038/kint.2009.148]

14 Aggarwal S, Moggio A, Bussolati B. Concise review: stem/progenitor cells for renal tissue repair: current knowledge and perspectives. Stem Cells Transl Med 2013; 2: 1011-1019 [PMID: 24167320 DOI: 10.5966/scit.2013.0097]

15 Zhu XY, Lerman A, Lerman LO. Concise review: mesenchymal stem cell treatment for ischemic kidney disease. Stem Cells 2013; 31: 1731-1736 [PMID: 23766020 DOI: 10.1002/stem.1449]

16 Masahima A, Yamashita S, Nojima Y. Identification of renal progenitor-like tubular cells that participate in the regeneration processes of the kidney. J Am Soc Nephrol 2003; 14: 3136-3146 [PMID: 14638912]

17 Vogeseder A, Karadeniz A, Kaisling B, Le Hir M. Tubular cell proliferation in the healthy rat kidney. Histochim Acta 2005; 124: 97-104 [PMID: 16133123 DOI: 10.1007/s00418-005-0023-y]

18 Fujiky J, Goto T, Sakamaki M, Fukasawa H, Miyaji T, Yamamoto T, Hishida A. Kinetics and characterization of initially regenerating proximal tubules in S3 segment in response to various degrees of acute tubular injury. Nephrol Dial Transplant 2006; 21: 41-50 [PMID: 16077144 DOI: 10.1093/ndt/gfl035]

19 Ma I, Allan AL. The role of human aldehyde dehydrogenase in normal and cancer stem cells. Stem Cell Rev 2011; 7: 292-306 [PMID: 21103958 DOI: 10.1007/s12015-010-0920-4]

20 Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Gaudino A, Camussi G. Isolation of renal progenitor cells from adult human kidney. Am J Pathol 2005; 166: 545-555 [PMID: 15681837 DOI: 10.1016/S0002-9440(10)62276-6]

21 Sallustio F, De Benedictis L, Castellano G, Zaza G, Loverre A, Costantino V, Grandaliano G, Schena FP. TLR2 plays a role in the activation of human resident renal stem/progenitor cells. FASEB J 2010; 24: 514-525 [PMID: 19843711 DOI: 10.1096/fj.09-136481]

22 Lindgren D, Bostrom AK, Nilsson K, Hansson J, Sjoland J, Muller C, Jensstrom K, Nilsson E, Lundberg G, Axelsson H, Johansson ME. Isolation and characterization of progenitor-like cells from human renal proximal tubules. Am J Pathol 2011; 178: 828-837 [PMID: 21281815 DOI: 10.1016/j.ajpath.2010.10.026]

23 Bomelli S, Zipeto MA, Torsello B, Bovo G, Di Stefano V, Bagarin C, Zordan P, Viganò P, Cattoretti G, Strada G, Bianchi C, Perego RA. PKH(high) cells within clonal human nephrospheres provide a purified adult renal stem cell population. Stem Cell Res 2013; 11: 1163-1177 [PMID: 24012544 DOI: 10.1016/j.scr.2013.08.004]

24 Remagnani P, Remuzzi G. CD133+ renal stem cells always express CD242 in adult human kidney tissue. Stem Cell Res 2014; 12: 828-829 [PMID: 24467938 DOI: 10.1016/j.scr.2013.12.011]

25 Gupta S, Verfaillie C, Chmielewski D, Kren S, Eidman K, Connaire J, Heremans Y, Lund T, Blackstad M, Jiang Y, Luttun A, Rosenberg ME. Isolation and characterization of kidney-derived stem cells. J Am Soc Nephrol 2006; 17: 3028-3040 [PMID: 16988061 DOI: 10.1681/ASN.2006030275]

26 Oliver JA, Mauroff O, Cheema FH, Martens TP, Al-Awqati Q. The renal papilla is a niche for adult kidney stem cells. J Clin Invest 2004; 114: 795-804 [PMID: 15372013 DOI: 10.1172/JCI20921]

27 Oliver JA, Klinakis A, Cheema FH, Frierdich J, Sampogna RV, Martens TP, Liu C, Efstratiadis A, Reddy CA, Reddy BS. NFATc1 identifies a population of proximal tubule cell progenitors. J Am Soc Nephrol 2009; 20: 2315-2327 [PMID: 19762493 DOI: 10.1681/ASN.2008111203]

28 Ward HH, Romero E, Welford A, Pickett G, Bacallaro R, Gattone VH, Ness SA, Wandlering-Ness A, Roitbak T. Adult human CD133(1+) kidney cells isolated from papilla integrate into developing kidney tubules. Biochim Biophys Acta 2011; 1812: 1344-1357 [PMID: 21255643 DOI: 10.1016/j.bbadis.2011.01.010]

29 Dekel B, Zangi L, Shezen E, Reich-Zeliger S, Eventov-Friedman S, Katchman H, Jacob-Hirsch J, Amariglio N, Rechavi G, Margalit R, Reisner Y. Isolation and characterization of nontubular sea-1(+) multipotent stem/progenitor cells from adult mouse kidney. J Am Soc Nephrol 2006; 17: 3309-3314 [PMID: 17090369 DOI: 10.1681/ASN.2005020195]

30 Goodell MA, Brote K, Paradis G, Conner AS, Mulligan RC. Isolation and functional properties of murine hematopoietic stem cells that are replicating in vivo. J Exp Med 1996; 183: 1797-1806 [PMID: 866936]

31 Hishikawa K, Marumo T, Miura S, Nakashima A, Matsuzaki Y, Shibata K, Kohike H, Komori T, Hayashi M, Nakaki T, Nakauchi
Hishikawa K et al. Adult stem-like cells in kidney

H, Okano H, Fujita T. Leukemia inhibitory factor induces multi-lineage differentiation of adult stem-like cells in kidney via kidney-specific cadherin 16. *Biochem Biophys Res Commun* 2005; 328: 288-291 [PMID: 15670782 DOI: 10.1016/j.bbrc.2004.12.167]

39 Hishikawa K, Marumo T, Mura S, Nakanishi A, Matsuaki Y, Shibata K, Ichiyamagi T, Kohike H, Komori T, Takahashi I, Takase O, Imai N, Yoshioka M, Inowa T, Hayashi M, Nakai T, Nakauchi H, Okano H, Fujita T. Musculin/MyoR is expressed in kidney side population cells and can regulate their function. *J Cell Biol* 2005; 169: 921-928 [PMID: 15967813 DOI: 10.1083/jcb.200412167]

40 Challen GA, Bertoncello I, Deane JA, Ricardo SD, Little MH. Kidney side population reveals multilineage potential and renal functional capacity but also cellular heterogeneity. *J Am Soc Nephrol* 2006; 17: 1896-1912 [PMID: 16707564 DOI: 10.1681/asn.2005111228]

41 Marumo T, Hishikawa K, Matsuaki Y, Imai N, Takase O, Shimosawa T, Okano H, Fujita T. Angiotensin II type 1 receptor blockade prevents decrease in adult stem-like cells in kidney after ureteral obstruction. *Eur J Pharmacol* 2007; 573: 216-220 [PMID: 17692840 DOI: 10.1016/j.ejphar.2007.07.032]

42 Nishinakamura R, Sakaguchi M. BMP signaling and its modifiers in kidney development. *Pediatr Nephrol* 2014; 29: 681-686 [PMID: 24217785 DOI: 10.1007/s00467-013-2671-9]

43 Inowa T, Hishikawa K, Takeuchi K, Kitamura T, Fujita T. Isolation and potential existence of side population cells in adult human kidney. *Int J Urol* 2008; 15: 272-274 [PMID: 18304230 DOI: 10.1111/j.1442-2042.2007.01984.x]

44 Lasagni L, Romagnani P. Glomerular epithelial stem cells: the good, the bad, and the ugly. *J Am Soc Nephrol* 2010; 21: 1612-1619 [PMID: 20829409 DOI: 10.1681/asn.2010010048]

45 Sagrinati C, Netti GS, Mazzinghi B, Lazzeri E, Liotta F, Frosali F, Ronconi E, Meini C, Gacci M, Squecco R, Carini M, Gesualdo L, Francini F, Maggi E, Anunziato F, Lasagni L, Serio M, Romagnani S, Romagnani P. Isolation and characterization of multipotent progenitor cells from the Bowman’s capsule of adult human kidneys. *J Am Soc Nephrol* 2006; 17: 2443-2456 [PMID: 16885410 DOI: 10.1681/ASN.2006010089]

46 Lazzeri E, Crescioli C, Ronconi E, Mazzinghi B, Sagrinati C, Netti GS, Angelotti ML, Parente E, Ballerini L, Cosmi L, Maggi L, Gesualdo L, Rotondi M, Anunziato F, Maggi E, Lasagni L, Serio M, Romagnani S, Vannelli GB, Romagnani P. Regenerative potential of embryonic renal multipotent progenitors in acute renal failure. *J Am Soc Nephrol* 2007; 18: 3128-3138 [PMID: 17978305 DOI: 10.1681/ASN.2007020210]

47 Park HC, Yasuda K, Kuo MC, Ji N, Ratliff B, Chander P, Goligorsky MS. Renal capsule as a stem cell niche. *Am J Physiol Renal Physiol* 2010; 298: F1254-F1262 [PMID: 20200095 DOI: 10.1152/ajprenal.00406.2009]

48 Ronconi E, Sagrinati C, Angelotti ML, Lazzeri E, Mazzinghi B, Ballerini L, Parente E, Becherucci F, Gacci M, Carini M, Maggi E, Serio M, Vannelli GB, Lasagni L, Romagnani S, Romagnani P. Regeneration of glomerular podocytes by human renal progenitors. *J Am Soc Nephrol* 2009; 20: 322-332 [PMID: 19092120 DOI: 10.1681/asn.2008070709]

49 Kamiura N, Hirahashi J, Matsuaki Y, Idei M, Takase O, Fujita T, Takato T, Hishikawa K. Basic helix-loop-helix transcriptional factor MyoR regulates BMP-7 in acute kidney injury. *Am J Physiol Renal Physiol* 2013; 304: F1159-F1166 [PMID: 23515721 DOI: 10.1152/ajprenal.00510.2012]

**P- Reviewer:** Kita K, Yarema KJ  **S- Editor:** Ji FF  **L- Editor:** A  **E- Editor:** Lu YJ
