Review Article

The Potential of Renal Progenitor Cells in Kidney Diseases: Preclinical Findings

Jeong Hyun Jo¹, Ki Hoon Kim¹ and Tae Min Kim^{1,2,*}

¹Graduate School of International Agricultural Technology, Seoul National University, Pyeongchang 25354, Korea

²Institute of Green-Bio Science and Technology, Seoul National University, Pyeongchang, 25354, Korea

Received June 20, 2019

Revised June 22, 2019

Accepted June 25, 2019

*Correspondence

Tae Min Kim

Graduate School of International Agricultural Technology, Institute of Green-Bio Science and Technology, Seoul National University, Pyeongchang-daero 1447, Pyeongchang 25354, Korea

Tel: +82-33-339-5896

Fax: +82-33-339-5747

E-mail: taemin21@snu.ac.kr

ORCID

<https://orcid.org/0000-0003-0015-2701>

ABSTRACT The kidney is a highly complex organ, and acute or chronic renal diseases can occur with various complications such as diabetes and hypertension. So far, no target specific treatment is available in acute or chronic renal failure, necessitating the development of alternative therapeutic strategy. Recent experimental findings suggest that the renal function and structure can be restored after being treated with various sources of stem/progenitor cells. In this review, we discuss up-to-date findings of the potential of renal progenitor/stem cells in alleviating renal injuries with a focus on preclinical studies. We also review cellular mechanisms underlying the therapeutic function of these cells.

Keywords: kidney, progenitors, regeneration

INTRODUCTION

Due to an increased incidence and associated morbidity, kidney disease is becoming a huge burden worldwide. Patients with diabetes or hypertension are at higher risk of acute kidney injury (AKI) (Togel and Westenfelder, 2012; Jha et al., 2013). Acute kidney injury (AKI) occurs by an acute loss of renal function due to ischemic, toxic or inflammatory insults. Current therapies for AKI mainly include supportive care and renal replacement therapy, which have been developed many years ago and these are not recognized as an efficient way due to the absence of specific therapeutic target (Jha et al., 2013). Recent studies demonstrated that various stem/progenitor cells have potential for enhancing tissue recovery after AKI, indicating that these cells may have therapeutic role in clinical uses (Hauser et al., 2010; Sedrakyan et al., 2012; Qi and Wu, 2013; Kuppe and Kramann, 2016). In this review, we

highlighted several key findings on the use of renal progenitor cells for renal recovery in animal models. We also discussed the cellular mechanisms underlying their function.

RENAL STEM/PROGENITOR CELLS

Several reports are available on using various types of stem/progenitor cells. These include mesenchymal stem cells (MSCs) derived from bone marrow (Qi and Wu, 2013; Kuppe and Kramann, 2016), adipose tissue, amniotic fluid (Hauser et al., 2010; Sedrakyan et al., 2012), as well as MSC-like cells or renal progenitor cells residing in kidney (Wang et al., 2013). Renal progenitor cells have been identified in rodents and human, and their ability to localize within the kidney after injury or during development, or and their role in regeneration has been reported (Biancone and Camussi, 2014). In adult kidneys, these

findings are mostly obtained by tracing a population of nephron cells that survive in tissue injury and differentiate into various subtypes of renal cells including tubular epithelial cells, podocytes, and collecting duct (Hansson et al., 2014; Rinkevich et al., 2014). In humans, CD133⁺CD24⁺ renal epithelial cells have been identified to represent renal progenitor cells, occupying around 2–4% of total renal cell (Romagnani et al., 2013). Most of these progenitor cells are able to differentiate into several types of renal epithelial cell, like a podocyte, renal tubular epithelial cells, adipocytes, and endothelial cells (Sagrinati et al., 2006; Ronconi et al., 2009). However, most of these progenitor cells do not meet the general criteria for stem cells, i.e., their potential in self-renewal, clonogenicity and multi-lineage differentiation (Biancone and Camussi, 2014). In the following section, we provide the characteristics of renal progenitor cells and their therapeutic role in animal model of AKI.

CHARACTERIZATION OF RENAL PROGENITOR CELLS

Renal resident stem cells have been identified within various regions of kidneys including the interstitium, the tubules, and Bowman's capsule. The markers that are specific to those cells are different among the regions. Generally, CD133⁺ cells can be found in the overall area of kidney, e.g., Bowman's capsule, proximal tubule, Henle's loop, and distal convoluted tubule (Bussolati et al., 2005; Sagrinati et al., 2006; Ward et al., 2011). In human kidneys, resident glomerular MSCs have been characterized as CD133 negative and CD146 positive, and

their ability to differentiate into endothelial, mesangial or glomerular cells has been reported (Bruno and Camussi, 2012). CD133⁺CD24⁺CD106⁺ cells are localized at the urinary pole of Bowman's capsule, and reported to have high proliferative potential, and differentiate into podocytes and tubular lineages. In addition, a distinct population of scattered CD133⁺CD24⁺CD106⁻ cells was localized in the proximal tubule as well as in the distal convoluted tubule, and reported to have a lower proliferative capacity, and displayed a committed phenotype toward the tubular lineage. Both showed higher resistance to injurious agent in comparison to all other differentiated cells of the kidney (Angelotti et al., 2012). It has also been reported that multipotent CD133/CD146 double positive cells are present in the adult decapsulated glomeruli, and that these cells express MSC markers as well as renal stem cell markers CD24 and Pax-2. The glomerular mesenchymal CD133⁻CD146⁺ cells exhibited self-renewal capability, clonogenicity, and multipotency. In addition to osteogenic, adipogenic, and chondrogenic differentiation, these cells were able to differentiate to endothelial and epithelial cells expressing podocytes markers such as nephrin, podocin, and synaptopodin. Another study demonstrated that CD133⁺CD146⁺ cells differed from those previously isolated from Bowman's capsule, as they expressed endothelial markers, such as CD31. Also, they were CD24 negative and lacked clonogenic potential, suggesting an endothelial commitment (Bruno et al., 2009). Functionally, these cells were able to enhance renal function in animal model of AKI, and were resistant to various injurious cues (Angelotti et al., 2012) (Fig. 1).

c-Kit⁺ cells, another population having potential to dif-

Fig. 1. Schematic of kidney injury regeneration by renal progenitor cells. Renal injuries by toxin, drugs, excessive bleeding, or co-morbidities such as diabetes has been shown to be recovered by renal progenitors of different populations in preclinical study.

ferentiate into renal lineages, are found in proximal tubular epithelial cells, Henle's loop, and focally or weakly in distal tubules, while negative in collecting tubules (Miliaras et al., 2004). Several mechanisms are involved in kidney regeneration by kidney-derived c-Kit⁺ cells, including cell engraftment and differentiation into renal-like structures, such as tubules, vessels, and podocytes. Moreover, paracrine mechanisms could also account for kidney regeneration, either by stimulating proliferation of surviving cells or modulating autophagy and podocyte cytoskeleton rearrangement through mTOR-Raptor and -Rictor signaling, which ultimately leads to morphological and functional improvement of kidneys (Gomes et al., 2018). Other populations expressing markers including Nestin, CD24, or NCAM-1 were also found to have the potential to alleviate the renal function and structure in various animal models of AKI and renal fibrosis (for detailed explanations, please

see Table 1).

CONCLUSION

Renal progenitor cells from fetal, infant, and adult kidneys have been shown to have potential to stimulate the recovery of AKI. However, current protocol for obtaining sufficient amount of renal precursor cells is technically difficult because most tissues are obtained from partial nephrectomy of renal cancer patients. Alternatively, generating renal lineage cells from induced pluripotent stem cells (iPSCs) would be another option considering the immune compatibility and the cell productivity. With better understanding of the biology of renal progenitor cells as well as bioengineering technique, renal progenitor cells will become an efficient tool for renal recovery from various injurious conditions.

Table 1. Therapeutic role of renal precursor cells in AKI

Markers	Cell source	Route	Model	Suggested mechanisms	Major findings	References
CD133 ⁺	Adult	IV	Glycerol-induced AKI in SCID mice	Release of Erythropoietin	Inhibition of pro-inflammatory cytokines and alleviation of fibrosis at day 60 post-injury	(Aggarwal et al., 2016)
CD133 ⁺ , CD24 ⁺ CD106 ⁺	Adult	IV	Glycerol-induced AKI in SCID mice	Engraftment within the kidney	CD106 ⁺ cells had regenerative potential and were resistant to apoptotic stimuli CD106 ⁻ cells proliferated upon tubular injury	(Angelotti et al., 2012)
CD133 ⁺ and CD133 ⁻ cells	Infant	IV	Rat AKI (Cisplatin, 7 mg/100 g)	Paracrine or endocrine factors from CD133 ⁺ or CD133 ⁻ cells	Improvement of renal function	(Santeramo et al., 2017)
NCAM-1 ⁺	Fetal	Intra-parenchymal	Mice CKD (5/6 nephrectomy)	Tubular integration	Inhibition of disease progression	(Harari-Steinb et al., 2013)
CD133 ⁺ , CD24 ⁺	Fetal	IV	Glycerol-induced AKI in SCID mice	Tubular integration	Improvement of renal function	(Lazzeri et al., 2007)
Nestin ⁺	Adult	IV	Ischemia-reperfusion injury in mice	Protect against ischemic acute renal failure partially through paracrine factor VEGF	Enhanced renal function and reduced tubular cell apoptosis	(Jiang, et al., 2015)
c-Kit	Neonatal	Supra-renal aorta	PAN-induced acute proteinuria in rats	Recovery of podocyte cytoskeleton and activation of phosphorylated mTOR Ser 2481 in renal tissue	Tubular epithelial cell recovery in a paracrine manner	(Gomes et al., 2018; Rangeet al., 2018)

AKI, acute kidney injury; BUN blood urea nitrogen; CKD, chronic kidney disease; IV, intravenous; mTOR, mechanistic target of rapamycin; PAN, puromycin amino nucleoside; SCID, severe combined immunodeficiency; VEGF, vascular endothelial growth factor.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2018R1D1A1A02085481).

ORCID

Jeong Hyun Jo: <https://orcid.org/0000-0002-2136-1492>

Ki Hoon Kim: <https://orcid.org/0000-0002-4913-6617>

Tae Min Kim: <https://orcid.org/0000-0003-0015-2701>

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