Journal of the Formosan Medical Association (2014) 113, 201–209

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

REVIEW ARTICLE

Stem cells and kidney regeneration

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Received 25 July 2013; received in revised form 13 November 2013; accepted 9 December 2013

KEYWORDS
bioengineered kidney;
endothelial progenitor cell;
kidney regeneration;
renal progenitor cell;
stem cell

Kidney disease is an escalating burden all over the world. In addition to preventing kidney injury, regenerating damaged renal tissue is as important as to retard the progression of chronic kidney disease to end stage renal disease. Although the kidney is a delicate organ and has only limited regenerative capacity compared to the other organs, an increasing understanding of renal development and renal reprogramming has kindled the prospects of regenerative options for kidney disease. Here, we will review the advances in the kidney regeneration including the manipulation of renal tubular cells, fibroblasts, endothelial cells, and macrophages in renal disease. Several types of stem cells, such as bone marrow-derived cells, adipocyte-derived mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells are also applied for renal regeneration. Endogenous or lineage reprogrammed renal progenitor cells represent an attractive possibility for differentiation into multiple renal cell types. Angiogenesis can ameliorate hypoxia and renal fibrosis. Based on these studies and knowledge, we hope to innovate more reliable pharmacological or biotechnical methods for kidney regeneration medicine.

Introduction

Kidney disease and its related complications are an important issue of public health worldwide.[1–6] The incidence and prevalence of end stage renal disease (ESRD) in Taiwan are among the highest in the world.[5,6] In Taiwan, dialysis is a heavy financial burden that consumed about 7% of Taiwan's annual budget for national health insurance in 2011.[5] Effective strategies are urgently needed to restore the renal function by kidney regeneration as well as to prevent acute kidney injury (AKI) and chronic kidney disease (CKD) progression.[7–13]

Broadly defined, kidney regeneration includes both renal repair and regrowth of partial or whole nephron in kidney disease. Neonephrogenesis, the process to regenerate every component of nephron, is a distinctive feature of

Conflicts of interest: All contributing authors declare no conflicts of interest.

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0929-6646/$ - see front matter
http://dx.doi.org/10.1016/j.jfma.2013.12.001

lower branches of the animal kingdom but does not occur in the mammalian kidney.[14] The reconstruction of the human kidney is more difficult than the regeneration of any other organ because of its complicated anatomical structure and no neonephrogenic zone of renal tissue to form new nephrons.[15] However, many studies in kidney regeneration, primarily from animal models, have identified methods of renal cell modulation pharmacologically or genetically to promote kidney regeneration.[16] Stem cell or progenitor cell therapy is also viewed as a promising strategy in regenerative medicine. Recent research has also identified that restoring the renal microvasculature might be effective in repairing the structure of diseased kidney.[17] In this review, we will describe the mechanisms of kidney regeneration and recent progress in different strategies of regenerative nephrology (Fig. 1).

Mechanisms of kidney regeneration

The nephron is the functional unit of kidney and there are almost one million nephrons in each adult kidney. The essential components of the nephron include the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct. The nephron is also encircled by abundant blood vessels.[18] A variety of kidney diseases result in injury of different cell types including podocytes, tubular epithelial cells, mesangial cells, or endothelial cells. Although the sublethal injury impairs renal function at various degrees, it also activates the mechanisms responsible for the regeneration of injured kidney tissues.[18]

According to current studies, there are four key processes of kidney regeneration, including reprogramming of endogenous renal cell, migration of bone marrow-derived cell (BMDC) and macrophage into kidney, renal progenitor cell differentiation, and neoangiogenesis. Growing evidence has shown that the regeneration process is similar to renal development through cell dedifferentiation. The genes vital during nephrogenesis may regulate cellular regeneration and tissue repair following injury in adult kidney.[19,20] In kidney following ischemia—reperfusion injury (IRI), the surviving tubular epithelial cells recapitulate an immature mesenchymal phenotype with re-expression of vimentin and Pax2, a process of dedifferentiation also termed as reprogramming.[21—23] The dedifferentiated cells regain the ability to proliferate and repopulate the denuded area. In addition, BMDCs migrate to the kidney after kidney injury and can inhibit renal cells apoptosis by an anti-inflammation effect and enhance renal cell proliferation.[24,25] Macrophages may scavenge the dead tissues in acute phase and promote regeneration of tubular epithelial cells during repair.[24—26] Different renal progenitor cells, either from local residence or recruited from circulation, have the potential to differentiate into target cells and promote surviving renal cell proliferation and kidney repair after injury.[16] Neoangiogenesis is stimulated through vascular growth factors and endothelial progenitor cells (EPCs), and can ameliorate oxidative stress and reduce nephron loss.[19]

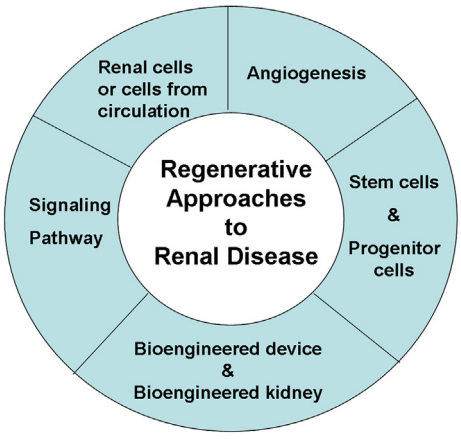

Figure 1 Regenerative approaches to renal disease.

Cells involved in kidney regeneration

Many cells are involved in kidney regeneration. First, injured proximal tubular epithelial cells can dedifferentiate and proliferate.[21] Using genetic fate-mapping techniques, Humphreys et al[18] indicated that the intrinsic, surviving tubular epithelial cells is the predominant source of new cells in repair of the postischemic nephron. Second, distal tubular cells can release growth factors such as epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), and these reparative growth factors then act on receptors in the proximal tubular epithelial cells to promote regeneration via paracrine effect.[27] Third, wound-healing or proreparative macrophages can produce a variety of growth factors including Wnt7b to promote tubular epithelial cell proliferation, angiogenesis, and kidney repair.[24—26]

Moreover, the integrity of the renal vasculature can have a profound impact on kidney regeneration following injury. Recent study identified that a novel developmental gene and protein, SCUBE1, is expressed in endothelial cells. *In vitro*, suppression of SCUBE1 can inhibit the proliferation of tubular epithelial cells.[28] Normal kidney pericytes can maintain the stability of microcirculation.[29] Although sustained activation of pericytes/perivascular fibroblasts promotes kidney fibrosis, transient activation of pericytes surrounding damaged tubules might be a normal repair process and beneficial to functional recovery after AKI.[8,30] Renal fibroblasts produce cytokines such as fibroblast growth factors-1 and -7 to stimulate proliferation of renal tubular epithelial cells, supporting the beneficial role of activated pericytes during kidney repair after AKI.[31] In addition, replacement of renal tubular epithelial cells cannot occur unless the reconstitution and stabilization of the tissue structure because surviving tubular epithelial cells need collagen framework to support their proliferation and migration to repopulate the denuded area.[31]

Reprogramming the kidney: a novel strategy for kidney regeneration

Cell reprogramming is defined as a switch in gene expression of one kind of cell to that of another cell type.[32]