

Stem cells in kidney disease: opportunities and challenges

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Chronic kidney disease (CKD) is increasingly being recognized as a global public health problem.¹ The prevalence and incidence of CKD is increasing at the rate of 6 to 8 percent per annum in the United States alone, largely as a consequence of increasing prevalence of diabetes and obesity.² The currently prevalent hypothesis for development of CKD is the imbalance between injurious mechanisms and regenerative repair.³ A sound understanding of renal development is imperative for understanding the processes of repair and regeneration in the kidney and how these can be manipulated to achieve complete regeneration and functional improvement.³ Human kidney develops from two structures derived from intermediate mesoderm; ureteric bud (UB) and metanephric mesenchyme (MM). The latter is heterogeneous and a specialized portion of it, called the cap mesenchyme (CM) constitutes the embryonic progenitor cell population. It undergoes mesenchymal to epithelial transition (MET) and gives rise to all parts of the nephron except for collecting ducts.⁴ The CM population is completely exhausted at birth in humans and no embryonic progenitors are observed in postnatal human kidney.⁴

Adult human kidney is an organ with limited normal cell turnover and no capacity for true regeneration.⁵ The possibility that stem cells contribute to the repair and regeneration of kidney following acute kidney injury (AKI) is of great interest for basic and translational research, as there are only limited therapeutic options available for CKD at present, i.e. dialysis and transplantation.^{3,5} Recent breakthroughs in the isolation and characterization of stem cells offer new opportunities for expanding the repertoire of therapeutic options for this chronic illness. Recent studies have shown that stem cells (SC) either derived from the bone marrow (BM) or resident in the renal tissue itself, may contribute to renal recovery after acute damage.⁶⁻¹⁵ Numerous studies reported recently have implicated endogenous bone marrow-derived stem cells (BMSC) in the repair of kidney damage, although the lineage and proportion of stem cells recruited is controversial at best.⁶⁻⁸ Whether endogenous BMSCs repopulate injured nephrons directly or act indirectly by a paracrine/endocrine mechanism also remains controversial.⁹⁻¹¹ Therapeutic administration of exogenous BMSCs in animal models of AKI suggests that a stem cell-based therapy may improve the recovery of both glomerular and tubular compartments.

Whereas the therapeutic benefit of sorted haematopoietic stem cells (HSC) remains uncertain, several studies showed a beneficial effect of mesenchymal stem cell (MSC) administration in models of acute tubular injury (ATI) and of endothelial progenitors in acute glomerular injury.¹²⁻¹⁵ Other studies have not found any functional improvement in a model of acute tubular injury.^{16,17} The later studies concluded that BM cells may be useful only for glomerular injury. While animal studies involving models of ischaemia-reperfusion (IR) or chemically-induced AKI have shown consistent improvement after MSC delivery, their effectiveness in chronic damage models is less clear. In a chronic UUO model, no influence of stem cell administration on renal damage, fibrosis or inflammatory cell influx was found.⁵

The use of embryonic stem cells (ESC) to improve kidney repair and function is associated with well known technical, legal and ethical issues. A recent study has shown that human amniotic fluid derived stem cells are capable of forming early nephron structures when injected into embryonic mouse kidneys. Such cells would avoid some of the ethical problems associated with ESC use. Hurdles still remain in terms of delivery of these stem cells as well as the immune rejection of allogenic stem cells.⁵

A number of studies have described potential stem/progenitor cells within the adult kidney of either mouse or humans.¹²⁻¹⁵ Such cells have been isolated, based upon cellular behaviour, surface marker expression or regional location using a variety of methods.⁵ Renal stem/progenitors have been described in both the renal epithelium and the interstitium. A few studies have demonstrated that both normal tubular turnover and tubular regeneration post IR injury was solely attributable to surviving tubular epithelial cells (TEC) in the adult mammalian kidney.¹⁶⁻¹⁸ This is in marked contrast with numerous other studies describing potential stem cells in the adult kidney.¹²⁻¹⁵ There is still some way to go in the kidney before the clear picture emerges.

In view of lack of definitive evidence for an endogenous renal stem cell and the apparent absence of embryonic progenitors after cessation of nephrogenesis, a novel approach to renal regeneration may involve reprogramming tubular epithelial cells to undergo epithelial mesenchymal transformation (EMT), to form a CM-like

population of cells capable of regrowing new nephrons through normal developmental pathways. These so called induced stem cells (iSC) could obviate the need for exogenous stem cells with their attendant problems.^{5,19}

Thus, there are many more questions than answers available at present regarding utility of stem cell in kidney diseases. Kidney is a complex, solid organ with a multitude of cells forming different anatomico-functional compartments. These cells and tissues differ in their proliferation rate, turnover and regenerative potential. Even the different compartments of the nephron exhibit different regenerative capacity. The question of what cell type is required is not a simple one to answer for such a complex organ and may vary depending on the renal disease. Stem cell delivery into this complex organ is also a formidable challenge. Direct introduction into the renal parenchyma only delivers cells into localized areas of kidney and global integration is not seen. Cells injected intravenously require an ability to reach home to the kidney and not be trapped in the vasculature of another organ. Stem cell research has largely been conducted using animal models. The pertinence of these animal studies to human disease also needs further studies. Few if any studies have been conducted on chronic renal diseases. The diversity of pathology present in CKD may also mean that no one cellular therapy will be applicable to all conditions.⁵

In summary, experimental studies suggest that the administration of exogenous SC or mobilization of endogenous BMSC improve AKI and accelerate regeneration. At present, the most promising approach is considered to be the administration of in vitro expanded MSC in the setting of AKI. Injected MSC have been shown to home to the injured kidney and to accelerate morphological and functional regeneration, possibly by a paracrine or even endocrine mechanisms, although their engraftment and transdifferentiation was not observed in the majority of the studies. A major mechanism in the effect of MSC has been attributed to the production of growth factors and cytokines with immunosuppressive, anti-inflammatory, anti-apoptotic and proliferative effects. A few phase I and II clinical trials have been designed or are in progress to evaluate the effect of MSC administration in renal transplantation, acute renal injury or chronic allograft nephropathy. The utility of MSC administration in CKD still warrants further investigation. In addition, different populations of resident SC have been identified in the adult kidney. It is still unclear whether these cells are involved in the normal cell turnover or in the regeneration process. The

possibility to expand and differentiate local progenitors or SC is another promising approach for regenerative medicine. However, it is still necessary to increase our understanding of normal renal development, renal turnover, response to injury and pathology. It is also imperative to increase our understanding of SC mechanisms and, in the view of possible mal-differentiation or transformation, to evaluate the safety of their use in long-term therapy, such as in CKD.

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