Regenerative medicine in kidney disease

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The treatment of renal failure has changed little in decades. Organ transplantation and dialysis continue to represent the only therapeutic options available. However, decades of fundamental research into the response of the kidney to acute injury and the processes driving progression to chronic kidney disease are beginning to open doors to new options. Similarly, continued investigations into the cellular and molecular basis of normal kidney development, together with major advances in stem cell biology, are now delivering options in regenerative medicine not possible as recently as a decade ago. In this review, we will discuss advances in regenerative medicine as it may be applied to the kidney. This will cover cellular therapies focused on ameliorating injury and improving repair as well as advancements in the generation of new renal tissue from stem/progenitor cells.

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The term "regenerative medicine" is used to describe any biomedical approach to the replacement or regeneration of human tissues or organs for therapeutic purposes. Advances in our understanding of normal tissue development, turnover, regeneration, and repair have all contributed to the concept of regenerative medicine as a translational clinical approach. The generation of pluripotent stem cells (PSCs) from human somatic cells, the isolation of tissue-specific stem cells, and the reprogramming of nonstem cells to a stem cell state all bring the prospect of regrowing an entire organ via bioengineering. The presence of stem cell niches within adult organs has allowed us to understand normal turnover events. Hence, in its broadest sense, regenerative medicine also encompasses interventions to improve the ability of the body to repair itself, either via immunomodulation or the administration of biologicals. All of these options can be envisaged for any organ; however, the barriers to success increase as histological and functional complexity increases. Hence, the replacement of skin or the bioengineering of simple epithelial structures, such as bladder wall, have seen substantial progress. The kidney has been a far greater challenge. However, the last decade has seen significant changes in what we can achieve with this organ. Whereas all options were previously prophetic,[1] many are now reaching proof of concept. Much of this advance rests on fundamental biological insights into normal kidney development and postnatal repair.

Postnatal kidney repair

The kidney is not a static organ, rather it is repairing and remodeling itself throughout life. Relatively quiescent when unchallenged, acute injury can rapidly trigger extensive cellular proliferation.[2] This endogenous repair potential gives the kidney a capacity to repopulate and repair damaged structures, even though nephron formation has ceased shortly before birth.[3] This repair process has been clearly observed in several animal models subjected to acute injury. The most commonly used experimental model of acute kidney injury is the induction of transient ischemia via clamping of the renal artery. Performed unilaterally (provides a capacity to investigate the contralateral organ as a control) or bilaterally, this mimics clinical ischemia reperfusion injury.[4] This injury model in mice is known to result in a rapid inflammatory response with substantial epithelial cell death followed by a proliferation repair response that, over a 7-day period, results in a return to normal histology. A more chronic injury, unilateral ureteral ligation, results in tubular atrophy, interstitial expansion, and loss of renal parenchyma. However,

once the obstruction is removed, the tissue can remodel to repair damaged tubules without forming new nephrons.[5] This repair is accompanied by substantial cell proliferation within the epithelium.

The last decade has seen many efforts aimed at elucidating the precise cellular origin of the cells involved in this kidney repair, with this knowledge likely to form the foundation for new cell- or factor-based treatments. Potential cell types of value will be discussed herein. However, the innate ability of the kidney to repair itself is limited and reaches a barrier when faced with repetitive episodes of injury or chronic damage. This process, termed "maladaptive kidney repair," results in interstitial fibrosis, parenchymal loss, and therefore an irreversible loss of nephrons. To investigate the capacity of the renal epithelium to respond to repeated injury, Grgic *et al.*[6] tagged all renal epithelium derived from the $Six2^+$ cap mesenchyme to produce a receptor to diphtheria toxin. This allowed for the induction of selective and repetitive injury of the nephron epithelium of the postnatal kidney in these mice. A single damage event triggered the anticipated macrophage infiltration and tubular epithelial cell proliferation, with a complete resolution of pathology within 7 days. However, repeated injury resulted in a maladaptive response including myofibroblast proliferation, loss of vasculature (rarefaction), glomerulosclerosis, and fibrosis. Hence, whereas the primary response of the tubular epithelial is proliferation to elicit repair, repeated epithelial injury can also trigger a fibrotic response.[6,7] Overall, events such as DNA damage, increasing age, previous episodes of acute kidney injury, and sustained cells stress may induce tubular cells to enter into cycle arrest at the G2/M phase mediating the secretion of cytokines and growth factors that promote an inflammatory response. The molecular changes associated with this loss of repair suggest that the reexpression of a number of molecular pathways that are initially critical in nephron formation and patterning can contribute to the tubulointerstitial response to chronic injury. Pathways implicated include the notch and Wnt-signaling pathways and, more recently, the transcription factor Sox9.[8–10] Improvements in the regulation of this endogenous renal repair process or optimization of any cell therapy going forward will rely on understanding repair as well as unveiling the molecular mechanism of maladaptive kidney repair.

Cellular approaches to improving repair

A number of cell types are considered to be able to either contribute directly to renal repair after injury or substantially ameliorate renal injury without directly contributing to the renal epithelium. The successful delivery or regulation of these cell types is likely to be crucial for the development of new regenerative treatments for kidney disease. Experimental nephrology has focused on 4 possible origins for cells contributing to postnatal renal repair: (i) interstitial cell transdifferentiation to epithelium,[11] (ii) recruitment of cells from the bone marrow,[12–16] (iii) tubular cell dedifferentiation and proliferation in response to injury,[2,11,17] and (iv) repopulation of the renal tubules by an adult resident kidney stem/progenitor cell population.[18–20] Options (i) and (ii) involve nonepithelial cells presumably transdifferentiating into renal epithelium whereas options (iii) and (iv) propose a repair process involving epithelial cells within the renal epithelium itself. After many years of careful studies, there is little evidence for the first 2 options occurring.[21] The most definitive proof that renal repair involves cells within the renal epithelium of the nephron was provided by lineage studies showing no evidence of dilution of the cap mesenchyme-derived ($Six2^+$) tubular epithelium with a nonepithelial cell source.[22] This did not resolve whether any cell within the epithelium can contribute to repair or whether repair relied on a resident stem cell population within the tubules. This debate has become a major focus over recent years.

Endogenous tubular kidney progenitors. The presence of a resident tubular stem cell population ($CD133^+$ and $CD24^+$) within the human adult kidney has been proposed, with this viewed as a defined subpopulation resident within the tubular compartments.[18–20,23] Over the last decade, many studies have investigated the existence, location, and contribution of these renal progenitor cells (RPCs) to epithelial repair.[19,20,23,24] The delivery of such cells has also been reported to act as a successful therapy for both acute and chronic animal models.[18,20,23,24] Based on specific markers, it has also been possible to isolate and culture RPCs from human urine, providing a pathway for personalized disease modeling and drug screening.[25] As well as progenitors involved in tubular turnover, there is also evidence for progenitors with overlapping protein signatures that can contribute to the turnover of podocytes within the glomerulus.[26,27]

Some view the RPC population of the postnatal renal tubules as potentially representing a retained tubular progenitor, in part based on expression of markers such as Pax2 seen in the developing organ.[24] Although it is clear that RPCs do not have a capacity to regenerate an entire nephron, the concept is that each segment might contain a distinct tubular progenitor able to selectively contribute to repair via differential proliferation in response to injury. Evidence for this was seen in a mouse model by Rinkevich *et al.*[28] who reported clonal proliferation of epithelial cells in all nephron segments with each cell type only contributing to the turnover of that segment. This study did not prove that this proliferation involved the activity of a stem/progenitor cell versus all epithelial cells. Indeed, there is an ongoing debate around whether RPCs correspond to a stable subpopulation within the tubular epithelium or a transient cell state that appears in response to a homeostatic imbalance within the kidney (Figure 1). The confusion has come in part from an inability to directly compare between human and mouse. The CD24 epitope used in association with CD133 to identify a specific double positive population in humans is not present in the mouse. Conversely, the capacity to lineage trace, though available in the mouse, is not in the human. It is also possible that mouse and human kidneys are not using the same

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