Progress in Understanding How the Kidney Repairs after Acute Injury

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Kidney injury is a major cause of in hospital morbidity and mortality and nephrotoxicity an important complication of many therapeutic agents. The kidney has great capacity to repair after even a severe insult, but whether adult stem or progenitor cells contribute to epithelial renewal after injury and the cellular origin of regenerating cells remains controversial. Understanding the mechanisms of nephron repair is critical for the design of new therapeutic approaches to treat kidney disease. The widespread expression of many mesenchymal markers after injury suggests that many if not most of the cells in the immediate region of injury that survive the insult participate in the repair response. Nevertheless it has been proposed that a subpopulation of cells with progenitor/stem cell characteristics exists. This could involve direct replacement of lost epithelial cells through rapid proliferation or alternatively through indirect (paracrine) effects to potentiate proliferation or dedifferentiation of other resident cells. Circulating bone-marrow derived cells do not participate in kidney repair via direct replacement of lost epithelial cells but most likely act in a paracrine manner. These cells likely do contribute directly to the recovery of endothelium, and angiogenesis itself is an important factor in renal repair.

Using genetic fate-mapping techniques we generated transgenic mice in which 94-95% of tubular epithelial cells, but no interstitial cells, were labeled with either beta-galactosidase (LacZ) or red fluorescent protein (RFP). Two days after ischemia-reperfusion injury (IRI), 50.5% of epithelial cells co-express Ki67 and RFP, indicating that differentiated epithelial cells that survived injury undergo proliferative expansion. After repair was complete, 66.9% of epithelial cells had incorporated BrdU, compared to only 3.5% of cells in the uninjured kidney. Despite this extensive cell proliferation, no dilution of either cell fate marker was observed after repair. These results indicate that regeneration by surviving tubular epithelial cells is the predominant mechanism of repair after ischemic tubular injury in the adult mammalian kidney.