The Continuing Story of Renal Repair with Stem Cells

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Renal stem cells are still a hot topic, but their location and mechanism of action continue to elude. The therapeutic potential of intrinsic stem cells to the recovery of damaged kidney has been suggested by a number of recent experiments, whereas the role of various other kinds of administered stem cells is still controversial. There are two large questions to address regarding the role of stem cells in kidney repair. The first is whether the restoration of nephrons requires either intrinsic renal progenitor cells, bone marrow–derived stem cells, or both. The second pertains to the role of stem cells in the repair process itself, specifically whether stem cells replace damaged tubular cells by transdifferentiation or accelerate repair by an indirect mechanism.

In the early 2000s, pluripotent bone marrow–derived stem cells were thought to contribute directly to regeneration of the kidney.1,2 Bone marrow contains at least three stem cell lineages: Hematopoietic stem cells (HSC), mesenchymal stem/stromal cells (BMSC), and endothelial progenitor cells. Crude preparations of bone marrow–derived stem cells seem to have a high capacity for transdifferentiation and therefore are able to replace damaged renal tissue with tubular epithelial cells, mesangial cells, endothelial cells, and even podocytes. In these studies, double staining of green fluorescence protein or Y chromosomes from bone marrow–derived stem cells in addition to kidney cell–specific surface markers provided evidence of transdifferentiation and repair, although the issue of cell fusion looms large and is still controversial.

In other studies, the injection of BMSC protects the kidney from toxin or ischemia/reperfusion injury and attenuates lost renal function, whereas injected HSC do not have the same effect.3 In both approaches, however, bone marrow–derived stem cells seemed to contribute relatively small numbers of cells (3 to 22%) to regenerating renal tubular and glomerular cell populations; that is, the majority of reparative cells were derived from intrinsic kidney cells. In studies from this period, the notion of transdifferentiation was used with loosely defined meaning. The definition of transdifferentiation in the stem cell field is the complete conversion of a cell from one lineage to another lineage with clearly altered tissue-specific markers and functions. However, the completeness of this definition has not been demonstrated in many studies.

If recent studies argue against the direct differentiation of most bone marrow–derived stem cells into kidney cells, then some other mechanism must contribute to kidney repair. Duffield et al.,4 for example, reported that adoptively transferred BMSC are not detected in the kidney, lung, or spleen, whereas injection of BMSC ameliorated repair of the kidney in the ischemia/reperfusion model. Togel et al.5 also demonstrated that administration of BMSC significantly improved renal function in the ischemia/reperfusion model, but none of the cells differentiated into tubular or endothelial cells.

In this issue of JASN, Bi et al.6 provide another mechanism. They demonstrate that adoptive transfer of BMSC into the peritoneal cavity or passive transfer of condition medium from cultured BMSC accelerates recovery from cisplatin-induced acute renal failure in mice. This is new evidence that humoral factors from BMSC—and not BMSC per se—are necessary for recovery from acute kidney injury. Furthermore, injected BMSC localize in the vasculature of the lung but not in the kidney at all. These results suggest that the local presence of BMSC in the kidney is not necessary for repair and that the humoral factors secreted by BMSC at remote locations are sufficient to protect or repair injured nephrons. Although many of us assume that tissue regeneration after acute kidney injury may subtly orchestrate the temporal and spatial expression of various growth factors or cytokines as in the developmental stage, it is of great interest that systemic administration of condition medium from BMSC affords this renoprotective effect as well, presumably activating intrinsic stem cells in the kidney through endocrine or paracrine action. What these intrinsic renal cells are and what in the conditioned medium are the critical mediators of this signaling are not yet clear.

The candidate factors are plentiful. We know from other experiments that the therapeutic effects of angiogenic growth factors such as vascular endothelial growth factor (VEGF)7 and hepatocyte growth factor (HGF)8 have been reported in tissue injury followed by fibrosis. VEGF and HGF are secreted by BMSC, and administration of VEGF or HGF improves hemodynamics, increases capillary density, accelerates tissue repair, and inhibits fibrosis in injured tissues. BMSC also seem to have immunomodulatory properties and inhibit alloantigen-induced differentiation, maturation, and
activation of dendritic cells. They also decrease IL-2 production and IL-2 receptor expression in activated T cells; induce regulatory T cells; and suppress the activation, proliferation, chemotaxis, and antibody production of B cells. These immunosuppressive actions of BMSC are not fully understood; however, some speculate that secreted, soluble factors suppress inflammation and mediate the beneficial actions in tissue repair.

What are the cellular targets of this conditioned medium? Presumably they are renal stem cells or progenitor cells. Kidney stem cells have been described in the renal papilla,6,11 Bowman’s capsule,12 and the S3 segment of the proximal tubule.13–15 CD133+/CD24+ stem cells in or near Bowman’s capsule can differentiate into epithelial and endothelial cells. Oct4+, Pax-2−, and CD90-expressing cells in the proximal tubules differentiate into tubular cells.15 Multipotent renal progenitor cells expressing Pax-2, Sca-1, and Musashi-1 have been isolated from microdissected S3 segments.14 Taking advantage of the slow cycling of stem cells, a population of proximal tubular epithelial cells have also been isolated in important experiments.15 Further studies, of course are necessary to identify the beneficial effects of soluble factors in the condition medium of BMSC on kidney repair, and confirmatory experiments are needed in other models of acute kidney injury and experimental glomerulonephritis. For the future, more vertical research is needed to identify mechanisms of kidney regeneration is needed, and a high priority should be placed on the identification of the therapeutic targets and factor cells in and around the nephron.

DISCLOSURES

None.

REFERENCES


See the related article, “Stromal Cells Protect against Acute Tubular Injury via an Endocrine Effect,” on pages 2486–2496.

Anti–Endothelial Cell Antibodies in Vasculitis

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Anti–endothelial cell antibodies have been described in association with small vessel systemic vasculitides since the late 1980s. Opinions have waxed and waned about their importance. An early study from this group suggested they were present in 59% of 168 samples from patients with Wegener’s granulomatosis or microscopic polyangiitis,1 while a contemporaneous study by Varagunam using a similar patient cohort...