Paracrine and differentiation mechanisms underlying stem cell therapy for the damaged kidney

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Submitted 15 March 2005; accepted in final form 22 March 2005

NATIVE KIDNEY ACUTE RENAL FAILURE (ARF) occurs in 2–5% of hospitalized patients and is associated with high mortality (11). Allograft ARF occurs in 30–50% of deceased donor kidney transplants and leads to longer hospital stays, a higher incidence of acute rejection, and reduced long-term graft survival (13). There is no specific therapy for ARF except for supportive care. A surge of evidence over the last decade supports an important role for inflammatory mediators, microvascular dysfunction, and apoptosis in the pathogenesis of the injury and extension phase of ARF (12). The mechanisms of recovery, less well understood, are felt to include a recapitulation of mechanisms originally involved in renal development. It is commonly believed that kidney progenitor cells, from either the kidney or an extrarenal source, repopulate the kidney during the recovery phase of ARF and drive the repair process (9). A popular model was that damaged/dead cells are removed and the kidney stem cells migrate to necrotic areas, differentiate, and repopulate the kidney. Indeed, injured human kidney transplants from female donors into male recipients were found to have Y chromosome staining of tubular epithelial cells, demonstrating that they were of recipient origin (5). In support of this model are studies in mice in which labeled bone marrow was tracked with fluorescent protein detection (1).

In this issue of AJP-Renal Physiology, Tögel et al. (14) present data that administration of bone marrow-derived mesenchymal stem cells (MSCs) either at the time of reperfusion or 24 h later had a marked functional and structural improvement on recovery from ischemic ARF in rats (14). Importantly, fibroblast administration did not have a protective effect within the 3 days of study. Elegant experiments tracking the administered cells found early lodging of these cells in the lung, liver, and kidney. Two-photon laser confocal microscopy demonstrated that MSCs were found in the intravascular, subcapsular, and occasional peritubular capillary locations, but the utility of this technique is limited to ~100 μm in depth. Using immunostaining, MSCs were found in liver, lungs, bone marrow, and spleen at 2 h, with persistence in lung but not in kidney at 24 h. To increase detection sensitivity, further staining of kidney and confocal analysis revealed that at 2 h MSCs were found in glomerular capillaries, but not at 24 or 72 h. Examination of Y chromosomes in kidneys of female rats infused with male MSCs did not detect MSCs in the kidney by either staining or PCR methods. In addition to demonstrating the effectiveness of immediate and delayed stem cell therapy for ischemic ARF in rats, the above-mentioned paper provides strong evidence against a transdifferentiating (“direct differentiating”) mechanism. The authors speculate that paracrine means, by default, are the more likely mechanism, and invoke possible pathways including stem cell regulation of T cells, which can in turn produce either deleterious or protective effects on the course of ARF depending on which pathways are activated (17). They find both an inhibition of select molecules that could mediate injury and repair as well as an increase in others, such as IL-10. However, we do not know whether the molecular responses described directly mediate the mesenchymal cell-induced kidney protection or are simply a response to the improvement. The data presented to rule out cell differentiation as a mechanism of stem cell action are important. However, in the absence of a demonstrated mechanism, strong negative findings must be questioned as to whether there is a true absence or the technologies being applied are insensitive for detection.

Studies using MSCs for cardiac damage have also suggested an important role for a paracrine mechanism and have invoked the SDF and CXC chemokines as important mediators of this process (4). SDF-1 could be an important mediator of migration of CXCR4-expressing cells into the postischemic kidney (15). An alternative mechanism beyond differentiation and paracrine effects are via cell fusion (16). Tögel et al. (14) found that distant organs like the lung and liver trap the stem cells, as well as the glomerulus, and the stem cells are not detected in the major area of kidney damage, the corticomedullary junction. This raises the possibility that events in the vulnerable corticomedullary junction are downstream of injury and recovery mechanisms at the level of the glomerulus. It is also
possible that distant organs orchestrate the course of ARF (2). The microenvironment surrounding injured tissue appears to play a strong role in the effect of the stem cell (6). What is clear, despite ambiguity on mechanisms, is that stem cells have profound beneficial effects on ARF and other damaged organs. The very early effects of stem cells on the course of ARF point to an early effect on the injury and extension phase rather than purely on recovery. This paradigm shift suggests that microvascular effects involving interactions at the leukocyte-endothelial level could be major mechanisms of stem cell action. Clearly, human trials are needed for this promising approach.

REFERENCES


