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Multipotent mesenchymal stromal cells protect against kidney injury

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With rapid advances, cell therapy is being considered as an important part of the therapeutic arsenal against disease in many organ systems. Bone marrow, cord blood or adipose tissue-derived multipotent stromal cells (MSCs) are an important component of this growing field since they have been shown in many animal disease models to have beneficial effects. MSCs secrete a large number of growth factors and cytokines associated with inhibition of the inflammatory response. Furthermore, MSCs are not associated with as difficult ethical problems as are embryonic stem cells (ESCs). MSCs are immuno-modulatory and immuno-privileged, thereby allowing evaluation of allogeneic “off the shelf” use without immunosuppression. These properties make them a very promising cell type for therapeutic use.

The kidney is a challenging organ for cell therapy given its many specialized and diverse cell types and injury mechanisms which can vary greatly in type and timing from acute to chronic (1). It is well known that inflammation plays an important role in many forms of kidney disease. This provides a rationale for evaluating MSCs with their anti-inflammatory effects in this context. Indeed MSCs are being used in clinical trials for acute kidney injury as well as after kidney transplantation and for lupus nephritis (ClinicalTrials.gov).

A large number of preclinical studies have shown that MSCs have the capability to ameliorate injury and accelerate repair. There is evidence that homing to sites of injury facilitates repair. Nevertheless there are data to suggest that even when few injected cells are found in the target organ, there is also protection possibly mediated by factors released from the MSCs. It was convincingly demonstrated by several groups that the beneficial effects of MSCs did not require the infusion of whole cells but could be mediated by conditioned medium (2) or by microvesicles carrying RNA (3). However, there is no role for direct transdifferentiation of MSCs to renal epithelial cell types (4,5) and the presence in the kidney of MSCs injected peripherally is transient (6). The beneficial effects of MSCs in pre-clinical studies have been attributed to many paracrine activities resulting in, for example, growth factor secretion, immuno-modulation and reduction of apoptosis (7).

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In this issue of *Cytotherapy* four groups have contributed experimental studies that add to our enthusiasm about the potential clinical utility of MSCs.

Luo *et al.* (8) show that MSCs generated from embryonic stem cells are effective in ameliorating cisplatin-induced acute kidney injury. MSC therapy has been previously shown to mitigate cisplatin toxicity (9) but the Luo *et al.* study is different in that the authors used MSCs derived from embryonic stem cells (ESCs) and found them to have similar renoprotective effects as MSCs derived from bone marrow. Deriving MSCs from ESCs may provide a more stable source of MSCs for cell therapy. Future studies will be required to show that MSCs derived from ESCs constitute a pure differentiated population and as safe as MSCs from other sources given the small but real risk of tumor formation by even small amounts of undifferentiated ESCs that may contaminate the MSC preparation.

Plotnikov *et al.* (10) report that human MSCs decreased inflammation and oxidative stress in a rat pyelonephritis model of kidney inflammation. MSC treatment was associated with reduced kidney tissue tumor necrosis factor α , reactive oxygen species (ROS) production, malonyldialdehyde, nitrite/nitrate ratio and myeloperoxidase activity. Furthermore the MSCs were even more effective in reducing markers of inflammation and ROS when incubated *ex vivo* with activated leukocytes before administration to the animals. This adds to the growing data on preconditioning of MSCs to enhance their secretome and their antiinflammatory actions when infused into animals (11).

Reinders *et al.* (12) examined the characteristics of MSCs collected from patients with end stage renal disease (ESRD). Patients with renal failure often receive an allograft and MSCs have been suggested to be beneficial in solid organ transplantation (13). MSCs derived from patients with ESRD have characteristics similar to MSCs from healthy donors. This includes an overlapping expression profile of surface markers, similar morphology and differentiation capacity, as well as immuno-modulatory capacities such as inhibition of mononuclear cell proliferation and inhibition of cytokine secretion. Furthermore there is a broad overlap between microRNA levels between ESRD and healthy donor MSCs. This is of particular interest given that microRNAs have been reported to play critical roles in differentiation and the processes of MSC functionality (14). These data are different from those in the mouse where uremia was associated with decreased expression of vascular endothelial growth factor, vascular endothelial growth factor receptor-1 and stromal cell-derived factor-1 α , increased cellular senescence and decreased proliferation (15). In kidney transplantation it is possible that patients might require repeat treatments with MSCs over time due to episodic immune rejection episodes. It may be more feasible to consider autologous MSCs as a treatment in these patients so that one can avoid the possibility of an allo-response that might impair their effectiveness over time.

Lastly, Ma *et al.* (16) report that human MSCs reduce albuminuria that results from doxorubicin (adriamycin)-induced nephropathy in the rat. MSC treatment resulted in reduction in serum levels of pro-inflammatory cytokines tumor necrosis factor α , interleukin (IL)-6 and prostaglandin E2 with increases in the anti-inflammatory IL-10 in the serum. There was decreased expression of cyclooxygenase-2 and prostaglandin E receptor subtype EP4 messenger RNA in MSC-treated groups. Histological evaluation revealed reduced

evidence of doxorubicin-induced injury to podocytes, reduced glomerular basement membrane changes and reduced mitochondrial abnormalities. In addition there was decreased inflammation in kidney tissue in the MSC-treated animals.

Together these four papers expand the evidence that MSCs have protective effects in various animal models of kidney disease and suggest that autologous MSC treatment may be feasible in patients with advanced renal disease who receive kidney allografts. The important question that remains is whether these animal studies are appropriate predictors of therapeutic efficacy in humans. Several early phase trials in humans have been conducted with limited published data available at this time. A dose-escalating phase 1 study was performed in patients at high risk for acute kidney injury. MSCs were given postoperatively after coronary artery bypass/and or cardiac valve surgery (6,17). A phase II trial multicenter follow up study is currently ongoing (ClinicalTrials.gov). A phase 1 study of autologous MSCs in humans for the treatment of allograft rejection and interstitial fibrosis/tubular atrophy in the kidney demonstrated clinical feasibility and findings suggestive of immune suppression (18). In both studies the MSCs appeared to be safe and feasible to administer to patients. A more extensive randomized clinical trial of the use of induction therapy with autologous MSCs versus anti-IL-2 receptor antibody in living-related kidney transplants was recently published (19). The MSC-treated group had a lower incidence of acute rejection, decreased risk of opportunistic infection, and better estimated glomerular filtration rate at one year. Thus the translation of extensive animal studies into therapeutic success in the clinic is beginning to be demonstrated.

The challenges to effective cell therapy with MSCs are many, including identification of the cell type best suited for clinical use and the optimal route and schedule of administration. Importantly there remains a great deal of uncertainty regarding the exact mechanisms of action of MSCs. It is likely that these mechanisms are multifaceted and it may be some time before we fully understand them. It is not unprecedented in medicine, however, to have effective therapies whose mechanisms of action are poorly understood. We should move forward and continue to explore the potential utility of MSC-based cell therapy for kidney disease and do so with optimism.

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