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tem cell therapy holds great promise for the repair of injured tissues and organs, including the kidney. Although still surrounded by uncertainties, such as the role of specific stem cell or progenitor populations, the relative contribution of local versus circulating cells or the modes of action, recent years have witnessed considerable progress in bringing stem cells closer to the bedside in nephrology. Concerning the kidney, most studies on repair have concentrated on the tubulointerstitial compartment, and less information is available for glomerular repair.

In this issue of JASN, Kunter et al. demonstrate that intrarenal administration of bone marrow–derived mesenchymal stem cells (MSC) can be used as cell therapy in the anti-Thy1.1–mediated model of antibody-mediated mesangiolysis and glomerular capillary destruction. Importantly, recovery of the glomerular lesions is accelerated when MSC are instilled locally 2 d after the induction of disease. The study elegantly demonstrates that these beneficial effects are not mediated through replacement of damaged glomerular cells by differentiated MSC but rather are caused by paracrine effects. The authors convincingly show that these actions are specific for MSC and dependent on local delivery.

MSC are a rare minority of cells in the bone marrow and are important for nourishing other bone marrow cells. MSC are approximately 10 times less abundant than hematopoietic stem cells. Recent data indicate that MSC probably also are distributed widely outside the bone marrow in a perivascular niche, and it is hypothesized that such local stem cells may contribute to local tissue repair (1). MSC from the bone marrow can be cultured from bone marrow aspirates, and after expansion, these cells still have the capacity to differentiate into a variety of mesenchymal phenotypes, including muscle and connective tissue.

Cytokines that enhance endothelial and epithelial survival, such as vascular endothelial growth factor (VEGF), fibroblast growth factor, or hepatocyte growth factor, have been shown to ameliorate glomerular and tubular injury in experimental models (2). However, for resolution of glomerular injury, a mix of several cytokines is probably required, suggesting that cytokine therapy with a single protein or gene is destined to fail. Moreover, the balance between beneficial and harmful effects of cytokines such as TGF-β1, for example, seems to depend on the cytokine microenvironment (3). Kunter et al. show that expanded MSC are a source of VEGF and TGF-β1 but not PDGF-BB. Also in bone marrow, the nourishing function of MSC depends on local cytokine production. Therefore, administration of MSC that produce naturally processed cytokines may offer a strategy that could act as a multidrug delivery system.

The current observations with MSC in experimental glomerulonephritis are in line with previous studies of MSC in ischemia-reperfusion injury in the kidney. Regeneration of tubular necrosis depends on proliferation of endogenous tubular epithelium, and local or bone marrow–derived stem cells probably have no major role in regeneration (4). However, administration of exogenous MSC could accelerate regeneration, also here through a paracrine mode of action (5,6).

In addition to the release of angiogenic and anti-inflammatory cytokines, there is accumulating evidence that MSC have strong immunosuppressive activity (7). Human MSC modulate the immune response by altering the cytokine response of dendritic cells and T cells, by interfering with the development of immunocompetent dendritic cells, and by favoring the development of regulatory T cells (8,9). Also here, the mode of action seems to involve the generation of soluble mediators with paracrine actions, including IL-6, macrophage colony stimulating factor, and prostaglandin E2. In addition, several of the mediators that are associated with repair, such as TGF-β1 and VEGF, are known for their immunomodulatory functions.

It is interesting that, in the same model of experimental glomerulonephritis as described by Kunter et al., bone marrow–derived cells have been shown to contribute to repopulation of the injured endocapillary compartment (10,11). Infusion of mononuclear bone marrow cells cultured with VEGF could reduce glomerular injury in the anti-Thy1 glomerulonephritis model, whereas incorporation of these cells in the glomerulus was found (12). We recently demonstrated that so-called endothelial progenitor cells mostly are myeloid progenitors (13). Importantly, such progenitors may differentiate into cells with monocyte and dendritic cell–like characteristics when they encounter an inflammatory microenvironment, even though they may appear as classical endothelial cells with respect to surface markers (13). This transformation to cells with more destructive potential may prohibit the use of progenitor cells as a clinical therapy in inflammatory diseases in which they are intended to repair structural damage to the glomerulus (Figure 1). However, the data by Kunter et al. open the possibility of adminis-
terting MSC in adjunct to endothelial or myeloid progenitors, thereby preventing a skew in differentiation toward inflammatory phenotypes.

These immunosuppressive and anti-inflammatory properties have initiated the clinical evaluation of MSC in patients with refractory graft-versus-host disease after allogenic bone marrow transplantation (14). However, it is not yet time to proceed to clinical trials with MSC in renal disease. It takes 4 to 8 wk of expansion to obtain a purified MSC fraction from bone marrow aspirate. Currently, the clinical MSC protocols still use FCS for expansion, which probably is less of an issue in a potentially fatal condition such as graft-versus-host disease but would have to be resolved for application in renal medicine. Also, the characterization of these cells has not been developed fully and still depends on differentiation assays, which makes sorting and selecting of the cells difficult. Finally, the best source of MSC has not been well established. MSC can be derived and expanded from the bone marrow but also from, for example, fat tissue. Kunter et al. use both autologous and allogenic cells. Whether allogenic cells can be used in humans as well is not known. Infusion of allogenic donor MSC can prime naïve T cells and as such accelerate, for example, rejection of bone marrow, whereas recipient autologous MSC promote tolerance and acceptance of the transplant (15).

Another issue is the physical properties of MSC. As also shown in the study by Kunter et al., MSC are large cells and are approximately the same size as mesangial cells. As a result, they lodge in the glomerular capillary bed and may induce microinfarction of the glomerulus. For example, administration of high dosages of MSC in the heart was associated with cardiac damage (16). Here, the dosage of MSC administered may turn out to be critical, not to outweigh the beneficial paracrine effects. It has been suggested that systemic MSC can be recruited to sides of inflammation (17). Nevertheless, as also illustrated in the current study, MSC most likely will have to be administered locally to prevent entrapment in other microcirculatory beds and the spleen and to avoid the administration of high dosages. Even with the limitations described herein, these new results described by Kunter et al. pave the way for future investigations into the possibilities of safe and effective use of MSC in renal medicine.

References


See the related article, “Transplanted Mesenchymal Stem Cells Accelerate Glomerular Healing in Experimental Glomerulonephritis,” on pages 2202–2212.