
See related articles, “The IL-23/Th17 Axis Contributes to Renal Injury in Experimental Glomerulonephritis,” on pages 969–979, and “IL-23, Not IL-12, Directs Autoimmunity to the Goodpasture Antigen,” on pages 980–989.

Microvesicles from Mesenchymal Stromal Cells Protect against Acute Kidney Injury

Joseph V. Bonventre
Renal Division, Brigham and Women’s Hospital, Boston, Massachusetts

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The role of mesenchymal stromal cells (MSCs) in modification of kidney injury has been widely debated in the past decade. Administration of MSCs in the hands of many laboratories confers a protective effect against acute kidney injury, although the explanation for this effect has varied among investigators and evolved over time. Initially, it was thought that these cells home to the kidney and replace damaged epithelial cells. Subsequently, it was clarified that the cells do not replace epithelial cells but mitigate injury and/or hasten repair, perhaps by paracrine processes. Protection is also seen with conditioned media from these cells, further supporting the view that paracrine effects, perhaps through pro-proliferative or anti-inflammatory factors, mediate protection. MSCs are also implicated in repair of the permeability barrier of the glomerulus in animal models of Alport disease and also reduce mortality and improve kidney function in an experimental model of sepsis in vivo.

The mechanism for the protective effects proposed by the authors of this latter sepsis study includes reprogramming of macrophages through release of prostaglandin E2, which then acts on the macrophages through the EP2 and EP4 receptors. In general, the nature of the factors responsible for the beneficial paracrine protection in animals has remained elusive.

The Food and Drug Administration has approved human trials to evaluate the use of MSCs for the treatment of acute kidney injury. In an interim report of a Phase 1 safety trial, five patients who were older than 65 yr and had underlying renal disease and multiple comorbid conditions that are predictive of a poorer outcome were administered an infusion of allogeneic MSCs at the end of on-pump coronary artery bypass surgery or cardiac valve repair. No therapy-related adverse events were noted in these patients, although the period of follow-up is short and one of the five patients died at home after discharge. None of the patients required dialysis.

In this issue of JASN, Bruno et al. demonstrate that microvesicles derived from human MSCs are as effective as MSCs in accelerating recovery from glycerol-induced acute kidney injury in SCID mice in vivo and stimulate proliferation and inhibit apoptosis of tubular epithelial cells in vitro. They then demonstrate that RNase treatment of the microvesicles abolishes these effects both in vitro and in vivo. The authors propose that microvesicles activate a proliferative response in surviving tubular epithelial cells after injury through the transfer of mRNA. Microvesicles are membrane-derived, secreted microparticles that are produced by a number of different types of cells. These microparticles transfer proteins, nucleic acids, lipids, viruses, and prions and hence have a variety of pleiotropic effects on cells with which these microvesicles interact.

There is a growing interest in the importance of microvesicle-mediated transfer of genetic information and proteins between cells. Embryonic stem cell-derived microvesicles reprogram hematopoietic stem/progenitor cells through mRNA and protein transfer. Consistent with the observations of others that microvesicles contain a subpopulation of cellular mRNAs, Bruno et al. examined the mRNA in the microvesicles of human-derived MSCs and found a subset of transcripts rather than a random sampling of cellular mRNA. How this selectivity occurs is not known. The uptake of vesicles into renal epithelial cells is mediated by cell surface receptors on the vesicle. Bruno et al. present data suggesting that membrane expression of CD44 and CD29 are important in this context.

Why would it be advantageous to transfer genetic material to tubular epithelial cells? Bruno et al. show that incubation of tubular epithelial cells in culture with microvesicles results in enhanced proliferation and decreased apoptosis. Because the source of epithelial cells that replace the dead tubular epithelial cells in vivo are other surviving cells of the epithelium, it would be advantageous to promote this proliferation and prevent apoptosis. Bruno et al. show that injection of MSCs or MSC-derived microvesicles 3 d after glycerol injection...
also had significant protective effects on the kidney as reflected by lower blood urea nitrogen and serum creatinine concentrations on days 5 and 8 with decreased histopathologic evidence of injury. This protection is also associated with increased evidence for proliferation on days 4 and 5 in kidneys treated with either microvesicles or MSCs.

Although these results are consistent with direct effects of MSCs and microvesicles on the epithelial cells, it is possible these transferred materials affect another cell type, such as the endothelial cell, which might result in vasodilation and reduction of the vasoconstriction known to be an important factor in glycerol-induced acute kidney injury. This would allow sufficient oxygen delivery to and waste product removal from viable epithelial cells that then manifest their endogenous proliferative tendencies after injury to the epithelium. If there is less vasoconstriction, then there will be less injury, decreased apoptosis, enhanced blood flow to the injured parts of the nephron, and facilitated proliferation of viable cells to replace dead cells.

Microvesicles can also serve to affect coagulation and/or leukocyte–endothelial adhesive interactions and hence modify inflammation and small vessel occlusion. Microvesicles may also modulate vascular permeability and smooth muscle proliferation. The authors found, within 1 h after infusion, that the microvesicles are detectable within the endothelial cells of large vessels and within the lumen of the tubules. Microvesicles are detected in tubular cells at 3 h and later. Microvesicles are not detected in tubular cells of injected normal control rats, suggesting the tubules from glycerol-treated animals have increased ability to take up the microvesicles.

RNase treatment also significantly reduced the effects of microvesicles on the kidney, indicating that mRNA transfer is instrumental in mediating this protection. Using immunocytochemistry, the authors demonstrate that two human proteins, POLR2E and SUMO-1, encoded by mRNA in the microvesicles, are found in the nuclei of kidney tubules of microvesicle-treated mice with acute kidney injury. This finding demonstrates the transferred mRNAs are transcribed into protein. The particular mRNA or mRNAs responsible for this protection against acute kidney injury were not identified by this study.

In conclusion, Bruno et al. report that microvesicle-induced transfers of cellular material to the kidney are just as effective as MSCs in protecting against injury. Furthermore, microvesicles induce proliferation and reduce apoptosis of epithelial cells in vitro. Their work furthers our understanding of the possible ways that MSCs may be organ-protective without directly replacing parenchymal cells and increases the possible directions one might pursue in developing therapeutic approaches for kidney disease.

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**REFERENCES**


**DISCLOSURES**

None.

See related article, “Mesenchymal Stem Cell-Derived Microvesicles Protect Against Acute Tubular Injury,” on pages 1053–1067.