Collecting duct epithelium and injury: Not all cells are created equal

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Studies by Butt et al. in the developing fetus provide new and timely insights into the regulation of repair and fibrosis in the injured kidney. Using a clinically relevant model, they have examined the response of the medullary collecting duct to ureteral obstruction, with some unexpected findings.


The kidney’s response to injury is analogous to the generalized models of wound healing, a process designed to repair injury and restore tissue function. However, whereas acute wounds go through a linear series of events, chronic non-healing wounds do not. Some areas of chronic wounds are in different phases at the same time, and progression to the next phase does not occur in the same coordinated manner. What makes this process even worse in renal disease is that the kidney has a very limited capacity for repair after prolonged injury. After acute injury, as long as a scaffold of basement membrane exists, individual cells, especially tubular epithelia, can regenerate by proliferation. Likewise, in some cases at least, these can be supplemented by circulating stem cells.¹

Conversely, more advanced injury is associated with destruction of tubular basement membranes and tubular atrophy, both of which appear irreversible.² The end result of this process is the failure of the wound to heal and accumulation of excess matrix, so-called scarring. Although we recognize that the extent of tubulointerstitial fibrosis in particular correlates well with decline in renal function, we often forget that it is not the fibrosis itself that is important, but rather the destructive effects of fibrosis on tubules and capillaries² (Figure 1).

These processes involve hematogenous cells, connective tissue cells such as fibroblasts, and associated resident macrophages and lymphocytes. Although monoclonal antibodies have long been used to phenotype the infiltrating hematogenous cells in various forms of inflammation, the absence of specific markers for fibroblasts has meant that their enumeration has been difficult. Other than the myofibroblast, there is no formal nomenclature to describe these cells.

Despite the inherent problems, we have been able to determine that the fibroblast is central to both wound healing and the pathogenesis of organ fibrosis. Fibroblasts are present in many tissues in the body, normally in a relatively quiescent state, and are mainly responsible for the production and turnover of extracellular matrix molecules. For more than 30 years we have known that during tissue repair, fibroblasts change phenotype to a contractile, hyperproliferative, and upregulated producer of extracellular matrix. Recognized from its de novo expression of α-smooth muscle actin, the so-called myofibroblast has been described in all forms of progressive renal disease. Not surprisingly, considerable interest has therefore centered on the regulation of this cell and in particular the factors that control its differentiation, kinetics, and matrix production. These studies have led us to recognize that the fibroblasts present in various connective tissues represent a heterogeneous population of cells. Their activity and differentiation are dependent on a combination of growth factors and other soluble mediators, extracellular matrix components, and mechanical stress.³

An underlying basis for this heterogeneity may lie in the diverse origins of these cells.

Electron microscopy studies have always shown that there is a resident population of renal fibroblast-like cells. Until relatively recently, it was assumed that fibroblasts were derived solely from their local proliferation and migration from adjacent tissues, in particular the perivascular region.⁴

It was therefore significant when Bucala et al.⁵ isolated a population of so-called fibrocytes in healing skin wounds that expressed both the hematogenous cell marker CD34 and procollagen I. In sex-mismatched bone marrow transplants, the authors demonstrated mismatched DNA in these cells to confirm that they were of donor origin. Likewise, there are now also reports that bone marrow-derived fibrocytes traffic to areas of renal fibrosis.⁶

Fibroblasts may also be derived from epithelial–mesenchymal transition (EMT). The concept of EMT comes from studies of embryonic development, in which EMT and the reverse process, mesenchymal–epithelial transition, are central mechanisms facilitating the derivation of a multitude of functionally specialized cells in the kidney.⁷ In the adult, such transitions were largely unknown. Of late, however, it has been noted that embryonic EMT can be recapitulated during certain adult disease states such as cancer and fibrosis, whereby dramatic morphological and functional changes take place to allow cells to develop a migratory and invasive capacity.

During EMT, epithelial cells lose polarity and cell–cell contacts and undergo dramatic cytoskeletal remodeling. Concurrent with the loss of epithelial-cell adhesion and cytokeratins, cells undergoing EMT acquire mesenchymal-cell expression profiles. Migration of these cells into the surrounding interstitium is facilitated by the degradation of basement membranes.

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Unilateral ureteric obstruction has become the most recognized model of renal tubulointerstitial fibrogenesis, its popularity driven by the absence of confounding glomerular pathology and its easy adaptation to genetically modified mice. Almost all studies have focused on the cortex, despite the obvious involvement of the renal pelvis.

Elegant experiments in a murine model of unilateral ureteric obstruction have attempted to address the relative importance of the various potential sources of fibroblasts. Using bone marrow chimeras and transgenic reporter mice, Iwano et al. were able to estimate that circulating precursors and EMT contributed 15% and 36% of the fibroblast burden, respectively. For technical reasons, only proximal tubule epithelium was transfected in this study, meaning that the role of EMT in other nephron segments remains poorly defined.

The study by Butt et al. (this issue) therefore provides interesting insights into both EMT and the pathophysiology of fetal ureteric obstruction in general. Using ultrasound for guidance, the authors have been able to obstruct a single ureter in fetal monkeys during the early second trimester. This is an important model because there are substantial differences between the wound healing process in the fetus and that in the adult. Ureteric obstruction in the fetus is accompanied not only by interstitial fibrosis, as in the adult, but also by disrupted nephrogenesis resulting in decreased glomerular endowment. Given the considerable gestational differences between species, the authors’ findings in a nonhuman primate are highly relevant to the human condition.

Fetal medullary collecting ducts contained two morphologically and biochemically distinct cell populations: principal and intercalated cells, recognized by their staining for water channel AQP2 and carbonic anhydrase II (CAII), respectively. Unlike in the adult kidney, Butt and colleagues have been able to identify a resident population of fetal cells coexpressing α-smooth muscle actin and CAII, which migrate in response to injury. Conversely, the population of fetal principal cells, some 80% of the collecting ducts, proliferate locally in response to injury, do not acquire fibroblastic features, and presumably did not migrate to the interstitium. Their response seems to be more consistent with an attempt to repair gaps in the injured epithelial layer.

In the past, studies of EMT have focused on the proximal tubule, which is derived from the embryonic mesenchyme. Importantly, the study by Butt et al. leads us to consider the process in cells with other derivations.

The role of EMT is not without controversy. Even though transitional cells are well described, there are few practical demonstrations of their migrating through the basement membrane. Ultrastructural demonstration of this is difficult given that so few cells are affected at any one time. The use of confocal microscopy by Butt et al. has to some extent overcome this by combining histochmistry and resolution.

The significance of these findings is far from certain, but they do once again highlight the plasticity of cell phenotype and the possibility of different programmed responses to injury. Like so much in medicine, this work raises many more questions. Further studies may help us determine whether CAII/α-smooth muscle actin-positive cells are a population of progenitor cells that can differentiate into either principal cells or myofibroblasts. Likewise, depletion of these cells may have implications for subsequent injury.

REFERENCES