

Renal Epithelial Cells: Differentiation and Plasticity

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Epithelia, which make up the nephron, exert critical functions in the kidney. Within the glomerulus, podocytes maintain normal glomerular architecture and barrier function. Along the tubule, epithelial cells participate in the conversion of glomerular filtrate into a concentrated urine whose composition is adjusted to maintain the organism in a steady state. Important progress has been made in the past decade in our understanding of the biology of these cells. It concerns mainly the differentiation of epithelial cells in both prenatal and adult kidney, the role of epithelial cells in the onset and progression of kidney lesions, and the mechanisms whereby kidney lesions are eventually repaired.

The fifth *Journées Gabriel Richet*, entitled “Renal Epithelial Cells: Differentiation and Plasticity,” was held in Le Coudray Montceaux near Paris on June 14 to 15, 2002. This symposium provided a forum for experts in epithelial cell biology and kidney pathophysiology to meet and discuss most recent breakthroughs in these different fields. Emerging information is summarized below and is presented in detail in this special issue of the *Journal of the American Society of Nephrology*.

In embryonic kidney and lung, specific epithelial-mesenchymal interactions result in different aspects of epithelial bud branching. Vainio pointed out that localization of type XVIII collagen, a component of extracellular matrix (ECM), would be a key regulator of this process. Evidence for this hypothesis includes (1) in organogenesis studies, type XVIII collagen expression seems limited to the tip of the epithelial bud in embryonic lung and to the stalk of ureteric bud in embryonic kidney, and (2) in tissue recombination experiments allowing the interaction of ureteric bud with lung mesenchyme, type XVIII collagen expression is repatterned from the stalk to the tip region, and this process is accompanied by the expression of specific markers of lung development. Further information regarding differentiation of epithelial bud cells and transformation of mesenchymal cells into epithelial cells was provided by Rossert. He emphasized that particularly important is the specific spatiotemporal expression of transcription factors, such as *Pax2*, *Eya1*, and *Six2*. Actually, although a large body of information has accumulated regarding the role of these

factors in early phases of cell differentiation, less is known about their involvement in the terminal phases.

In adult kidney, epithelial cells from the cortical collecting duct are differentiated in two ways: principal cells are involved in water, sodium, and potassium transport, and intercalated cells mediate acid-base transport. For the first time in 1970, Hagege and Richet demonstrated that intercalated cells exhibit two morphologic forms *in vivo*, their respective number changing as a function of the acid-base status. These cells, now referred to as α and β cells, have been shown to secrete H^+ and HCO_3^- , respectively. Recently, Al-Awqati, using a model of metabolic acidosis *in vitro*, confirmed the previous observation of Hagege and Richet and suggested the possibility of a conversion of β cells to α cells. Mechanisms underlying epithelial “plasticity” were described in detail: acid media induce ECM localization of a specific protein, hensin, which, in turn, reverses the polarity of H^+ and HCO_3^- flux.

Podocytes are involved in numerous hereditary diseases that affect the glomerulus and are characterized by proteinuria. As illustrated by Gubler, the identification of gene mutations in these inherited diseases has demonstrated the importance of the podocyte slit diaphragm in the permselectivity process. Proteins that form the barrier include mainly nephrin, podocin, and CD2AP. Recent studies on actinin-4 gene mutations have emphasized the additional role of podocyte cytoskeleton. Podocyte injury seen in acquired diseases of the kidney may also lead to alterations in permselectivity, thus resulting in proteinuria. For instance, in membranous glomerulonephritis, a major cause of nephrotic syndrome, the accumulation of immune deposits in close contact with podocyte foot processes results in alterations of the podocyte phenotype, which, in turn, is responsible for the development of proteinuria. Surprising is that antigens that are involved in the formation of such deposits are not well characterized. Ronco reported the first case of membranous glomerulonephritis in which the target antigen was identified as a constitutive antigen expressed on podocyte (neutral endopeptidase). In glomerulonephritis, podocytes play a key role not only in the initiation of glomerular lesions but also in the propagation of pathways leading to glomerulosclerosis. Bruneval advanced the intriguing possibility that podocytes and parietal epithelial cells may transdifferentiate into macrophagic cells and myofibroblasts. Epithelial to mesenchymal transition would be implicated in crescent formation and progression toward fibrosis, for instance, in human pauci-immune crescentic glomerulonephritis, as suggested by the coexpression of myofibroblast and epithelial markers in glomerular lesions.

Once glomerular lesions are established, proteinuria extends,

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promoting in turn tubulointerstitial inflammation and fibrosis. Cellular signaling pathways involved in this process were described in detail by Zoja. Urinary proteins bind to megalin and cubilin at the apical pole of epithelial cells in proximal tubules. Subsequent endocytosis leads to protein kinase C activation, reactive oxygen species production, and eventually NF- κ B translocation into the nucleus. This transcription factor plays a key role in the expression of genes that are involved in inflammation and fibrosis. It is interesting that besides tubular fluid composition, tubular fluid flow by itself would modify the phenotype of epithelial cells in the proximal tubule. Essig reported that *in vitro* or *in vivo* exposure of these cells to laminar flow induces a reorganization of the actin cytoskeleton and thereby reduces the expression of fibrinolytic activity. This could be one of the events underlying ECM remodeling after destruction of nephrons in various nephropathies. Indeed, under these conditions, tubular flow rate is increased in remaining functional nephrons.

Recovery of renal function after severe injury depends on the replacement of necrotic epithelial cells with functional epithelium. New epithelial cells may originate from kidney-resident and/or bone marrow-derived stem cells. That bone marrow-derived stem cells participate in tubular regeneration has been observed after acute tubular necrosis in both experi-

mental models and in humans. By analyzing kidneys that have been transplanted from female to male individuals, Poulsom provided evidence that circulating Y chromosome-positive cells repopulate tubules and exhibit a tubular epithelial phenotype. Nevertheless, the number of these bone marrow-derived stem cells is limited, and repair process is rather related to dedifferentiation, migration, and proliferation of surviving epithelial cells. Bonventre reported that gene expression in these dedifferentiated cells recapitulates gene expression patterns typical of the developing nephron. These genes encode transcription factors, growth factors, adhesion molecules, and chemokines. Of particular interest in this context is the recent identification of kidney injury molecule-1, a transmembrane glycoprotein expressed on dedifferentiated proximal tubule epithelial cells undergoing regeneration after ischemia injury and possibly involved in their migration and proliferation.

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