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Epithelial-Mesenchymal Transition of Tubular Epithelial Cells in Crescentic Glomerulonephritis

L.Grcevska[1], G.Petrusevska[2], S.Dzikova[1]
Department of Nephrology[1], Institute of Pathology[2], University of Skopje, R.Macedonia

Introduction

Recent studies confirmed that proximal tubular cells, instead of glomerular, play an important role in local macrophage proliferation, they are major site of macrophage colony-stimulating factor. In the other studies performed on cultural cells and experimental nephropathies, as well as on human biopsies, epithelial – mesenchymal cell transdifferentiation (EMT) was presented, a phenomenon characterized by loss of epithelial markers in epithelial cells and acquisition of mesenchymal phenotype and of fibrosing properties.

The aim of our study was to:

- test that EMT is involved in human crescentic glomerulonephritis
- detect possible role of transdifferentiated tubular cells in crescent formation

Patients and methods

Optical microscopy

Renal biopsy specimens were stained using standard procedure on paraffin sections. The following glomeruli were selected and analyzed: with both segmental and circumferential crescents and obligatory with cross section of urinary pole.

Methods – indirect immunoperoxidase method

Macrophages were confirmed with anti CD 68 monoclonal antibodies, vimentin for mesenchymal cells and fibroblasts and cytokeratins (CK, CK 18) for tubular cells.

Results

The number of analyzed glomeruli was 573, but glomeruli with crescents 415 and glomeruli with crescents+urinary pole (necessary criterion for the study) only 158.

63 glomeruli were with circumferential crescents and the involvement of the urinary pole was 100%. 95 glomeruli were with segmental crescents and the involvement of the urinary pole was surprisingly high, 92/95 (96,5%). This fact documents anatomical connection between urinary pole (i.e. proximal part of the proximal tubule) and crescent formation. Zonal interstitial infiltrates positive on CD 68 (macrophages) surrounded proximal tubules close to urinary pole and crescent formation (78,1+-29,2 cells on high magnification), positive numerous cells were present in cellular crescents and rarely in glomerular tufts (3,4+-0,7). Macrophages were followed by fibroblasts, they were present in the cortical interstitium (65,3+-11,5) forming confluent infiltrates close to glomerular urinary pole and in crescent formation, as well as in glomerular tuft (8,5+-3). Some of the tubular cells were negative on CK and CK 18, i.e. they have lost their epithelial phenotype and they were positive on CD 68. Analyzing areas of cortical interstitium close to crescents formations and urinary poles CD68 positive tubular cells were 2,1+-0,5 on high magnification. The other parts of cortical interstitium presented only CK and CK 18 positive cells of proximal tubuli.

Discussion and conclusions

What may be the explanation for the connection crescent – urinary pole – proximal tubule?

1. Crescents due to epithelial proliferation or macrophage clustering migrate to urinary pole and proximal tubules or
2. Macrophages originated from the dedifferentiated proximal tubular cells (CD 68 positive tubular cells!) migrate to urinary pole and crescent formation.

Epithelial-mesenchymal transformation and more general, transdifferentiation are concepts originally belonging to developmental biology and oncology. Cell shifting between epithelial and mesenchymal phenotype, by turning on and off specific genes during early development, is a well recognized process that characterizes the embrional plasticity. EMT also can be a key element in development of metastasis of tumors derived from epithelial tissues, in fact mesenchymal cells have the ability to invade and migrate through the extracellular matrix, a property not present in the epithelial lineage. More recent evidence for transdifferentiation has been observed in almost all mature tissues, where the process seems to be mainly related to wound healing and fibrotic remodeling after inflammatory injury. In the kidney, for several years interstitial fibrosis has been considered a common mechanism of disease progression, that, at a certain point, becomes independent of the initial cause of disease and is linked to a pathological imbalance between extracellular matrix deposition and degradation, which is stimulated by a variety of cytokines and growth factors.

Given the complexity of the cell lineage, the origin of renal fibroblast remains controversial. At present the prevailing theory favors resident interstitial cellos, but other authors have previously postulated a fibroblast derivation from migrating leukocytes. Recent studies on cultured cells and experimental nephropathies have hypothesized that epithelial-mesenchymal transformation can occur in tubular epithelial cells.

Correspondence to: Ladislava Grcevska, MD, PhD, Department of Nephrology, Clinical Center Skopje, University of Skopje, Vodnjanska 17, 1000 Skopje, R. Macedonia, Tel: + 389 2 31 47 /190

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