Proximal tubular cells: potential role in macrophage migration and crescent formation

Sir,
Tubulointerstitial disease is a consistent feature of progressive glomerular injury. However, the mechanism by which inflammatory events in the glomerulus involve the tubulointerstitium remain poorly understood. Recent data suggest that proximal tubular epithelial cells are important in the mediation of this process [1–3]. Proximal tubular cells play an important role in local macrophage proliferation; they are a major site of macrophage colony-stimulating factor (M-CSF) production [2,4]. There are also data suggesting that locally produced macrophage inflammatory protein and monocyte chemoattractant protein may be involved in the development of cellular crescents [3,5]. The aim of the present study was: (i) to document the anatomical connection among proximal tubular cells and crescents in primary crescentic glomerulonephritis; and (ii) to detect the location of macrophages in biopsy specimens from patients with primary crescentic glomerulonephritis.

Renal biopsy specimens from patients with crescentic glomerulonephritis without systemic disorders, independently of the aetiology, were analysed using the standard procedure on paraffin sections. A total of 158 glomeruli with crescents (both segmental and circumferential) and a urinary pole in the same section were separated from 573 analysed glomeruli. Eighty-two glomeruli from seven biopsies (random choice) were stained using the indirect immunoperoxidase method with CD68 monoclonal antibodies to detect macrophages; vimentin was used to detect fibroblasts, and CK (cytokeratin) and CK18 were used as markers for epithelial cells (Figures 1 and 2).

Summarizing the results of the optical microscopy, we noted involvement of the urinary pole in all glomeruli with circumferential crescents (63 glomeruli, 100%) and involvement of the urinary pole in the crescent formation in 92/95 (96.5%) of the glomeruli with segmental crescents. Zonal interstitial infiltrates positive for CD68 (macrophages) were found surrounding proximal tubules close to urinary poles (78.1 ± 29.2 cells on high magnification), and numerous positive cells were noted in cellular crescents. Intraglomerular macrophages were rare (3.4 ± 0.7 on glomerular cross-section), but we also noted positive staining of scanty proximal tubular cells (2.1 ± 0.5 positive cells on high magnification). Numerous fibroblasts were present in the cortical interstitium (65.3 ± 11.5), forming confluent infiltrates close to the glomerular urinary pole and crescent formations. A total of 8.5 ± 3 fibroblasts were detected on glomerular cross-section. CK and CK18 staining was positive (++) in proximal tubular cells (as normal), but scanty parietal glomerular epithelial cells and cells from crescent formations were also positive. Our results suggest: (i) there is a strong anatomical connection between crescent formations and urinary pole-proximal tubules; and (ii) this area is full of immune potent cells, macrophages and cells responsible for secondary fibrosis, fibroblasts. We suggest two possibilities. The first explanation is that crescents due to epithelial proliferation or macrophage clustering tend to migrate towards the urinary pole and then come into close contact with proximal tubular cells. The second possibility is that macrophages originating from the interstitium surrounding proximal tubules migrate to the nearest position, the urinary pole...
pole, and contribute to crescent formation. Recent studies support the second possibility [1–6]. It was reported that chemokines produced by proximal tubular cells promoted the infiltration [3,4]. Proximal tubular epithelial cells activate urinary complement proteins in situ and contribute to the mediation of tubulointerstitial injury [6]. The tubular epithelial cell is the major site of M-CSF production within the injured kidney; macrophage accumulation and local proliferation can occur in the tubulointerstitium in the absence of glomerular inflammation [2]. Proximal tubular cells also promote fibrogenesis by transforming growth factor-β1-mediated induction of peritubular myofibroblasts [1]. Most important is that recent studies performed on cultured cells and experimental nephropathies suggest the possibility of epithelial–mesenchymal transition of tubular epithelial cells, i.e. transdifferentiation. One study, done on a human renal biopsy, also suggested such a transdifferentiation [7]. Finally, is it possible that proximal tubular cells transdifferentiate and migrate towards the glomerular urinary pole and contribute to crescent formation?

Conflict of interest statement. None declared.

2. Isbel NM, Hill PA, Foti R et al. Tubules are the major site of M-CSF production in experimental kidney disease: correlation with local macrophage proliferation. Kidney Int 2001; 60: 614–625

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Croatia is not spared from diabetic nephropathy

Sir,
In the article by Rutkowski [1], Croatia was pointed out as having a peculiarly low proportion of patients with diabetes...