Involvement of Angiotensin II in Tubulointerstitial Disease

Angiotensin II as a mediator of tubulointerstitial injury

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Morphological alterations of the tubulointerstitial architecture currently are seen as a major determinant in the progression of chronic renal disease [1]. Structural changes such as the degree of tubulointerstitial fibrosis and tubular atrophy correlate better with the decline of renal function than glomerular lesions, even in primary glomerulopathies. Evidence suggests an evolution of the tubulointerstitial changes in chronic renal disease over time, with early compensatory hypertrophy of tubular changes and an increase in functional capacity, recruitment of inflammatory cells into the tubulointerstitial spaces and proliferation of interstitial fibroblasts [2]. In addition, tubular cells may transdifferentiate to fibroblasts under certain conditions, partly explaining tubular atrophy and the local increase in interstitial fibroblasts [1]. An increase in extracellular matrix synthesis by tubular cells and interstitial fibroblasts as well as a decrease in local turnover of such components finally leads to the irreversible development of tubulointerstitial fibrosis. Many of these diverse effects on tubular cells and fibroblasts are mediated by autocrine/paracrine release of growth factors, cytokines and chemokines [1–3]. Several pathophysiologically disturbances including proteinuria, reduction in functional nephron mass, local deposition of antibodies, alterations in tubular fluid reabsorption and an impairment in tubulointerstitial perfusion may all stimulate local release of such growth factors [1]. Furthermore, an increase in the amount of filtered growth factors occurring during proteinuria and cytokines, locally produced during immune and non-immune glomerular injury, being delivered to the tubulointerstitium, contribute to the ‘bathing’ of tubulointerstitial cells in profibrogenic factors [1,2].

A recent deluge of data suggests that angiotensin II (ANG II), commonly considered to be solely a vaso-constrictor, plays a pivotal role in many of these above-mentioned processes leading to tubulointerstitial scarring and tubular atrophy [3,4]. Cell culture studies investigating potential effects of ANG II on tubular cells and fibroblasts in the absence of haemodynamic alterations have contributed considerably to a better understanding of the multiple cellular actions of this small peptide (see Figure 1).

ANG II induces hypertrophy of proximal tubular cells but stimulates proliferation of cells isolated from the loop of Henle (for review, see [5]). The hypertrophic action of ANG II in proximal tubular cells is mediated through AT1 receptors, and depends on an oxygen radical-mediated increase in p27Kip1, an inhibitor of G1 phase cyclin–cycin-dependent kinase complexes [4,5]. Furthermore, ANG II also reduces protein degradation by inhibition of proteases [3]. ANG II mediates the transcription and biosynthesis of transforming growth factor-β (TGF-β), a major profibrogenic cytokine, in proximal tubular cells [6]. In addition, ANG II also stimulates TGF-β receptor type II, but not type I, transcription and surface expression, further amplifying the effects of ANG II-induced TGF-β expression [7]. ANG II also induces the transcription and synthesis of various chains of basement-associated collagen type IV including the α3(IV) chain with a quite restricted distribution [4,8]. In contrast, tubulointerstitial fibroblasts proliferate and secrete more of the interstitial collagen types I and III after exposure to ANG II (9) Figure 1). Interestingly, in the presence of ANG II, proximal tubular cells can secrete several growth factors including platelet-derived growth factor which, in turn, can stimulate proliferation of fibroblasts, suggesting a tubular–fibroblast cross-talk initiated by ANG II [1,4]. Recent studies indicate that ANG II is metabolized further directly on the surface of tubular cells into angiotensin IV (ANG IV; [10]). ANG IV itself binds to its own receptors (designated AT₄), resulting in induction of plasminogen activator inhibitor-1 with the final consequence of a decrease in matrix turnover [11]. This finding is important because the profibrogenic effect of ANG IV is not abolished by an AT₁ receptor antagonist [11]. Tubular cells may transdifferentiate into mesenchymal fibroblasts under certain conditions, partly explaining the tubular atrophy in chronic renal disease [1]. Since TGF-β may

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Fig. 1. Multiple effects of angiotensin II (ANG II) on tubulointerstitial cells such as tubular epithelium and fibroblasts. ANG II induces hypertrophy of proximal tubular cells and stimulates the synthesis of α1,2,3 (IV) chains. In contrast, fibroblasts proliferate after exposure to ANG II and synthesize more of interstitial collagen types I and III. Tubular cells as well as fibroblasts may produce several chemokines and cytokines such as TGF-β in the presence of ANG II. These factors may promote secondarily the influx of immunocompetent cells, for example macrophages/monocytes, into the tubulointerstitial space. ANG II can be degraded locally to angiotensin IV (ANG IV) on the tubular surface. ANG IV binds to its own receptors and inhibits matrix turnover by induction of plasminogen activator inhibitor-1. The inhibition of matrix degradation and the increase in synthesis cause tubulointerstitial fibrosis. Finally, evidence suggests that tubular cells, perhaps in the presence of ANG II-induced TGF-β, may transdifferentiate into fibroblasts, explaining the tubular atrophy of chronic tubulointerstitial disease. Thus, ANG II, as a single factor, may mediate many of the pathophysiological alterations observed in chronic tubulointerstitial injury.

Experimental studies provided convincing evidence that interference with the renin–angiotensin system (RAS) by angiotensin-converting enzyme (ACE) inhibitors or AT1 receptor antagonists reduces the development of tubulointerstitial fibrosis in various animal models including chronic aminonucleoside nephrosis [12], 5/6 nephrectomy [13], unilateral ureteral obstruction [14], chronic cyclosporin nephrotoxicity [15], radiation nephropathy [16], ageing [17] and chronic allograft nephropathy [18]. Moreover, treatment with an ACE inhibitor abolished the tubular increase in TGF-β expression after subtotal nephrectomy [19]. The most direct evidence for the role of the RAS in the development of tubulointerstitial fibrosis comes from animals in which components of the RAS were genetically altered [20]. For example, in mice bearing 0–4 functional copies of the angiotensinogen gene, unilateral obstruction leads to a different response depending on the expression of angiotensinogen: renal interstitial collagen and TGF-β expression increased from zero-copy mice to animals having four copies of angiotensinogen [20].

ACE inhibitor treatment currently is the only known pharmacological therapy to slow the progression of chronic renal failure in humans [4,21]. Although the precise effects of this treatment of tubulointerstitial morphology are not known because of a lack of follow-up biopsies, it is very likely that ACE inhibitors attenuate tubulointerstitial fibrosis, and prevent, at least to some extent, the development of tubular atrophy. Whether AT receptor antagonists have similar effects is controversially discussed and the subject of ongoing studies [21]. Therefore, every patient with chronic renal disease, independent of blood pressure, should be treated with an ACE inhibitor to slow the progression of chronic renal disease.

References

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