New Insights into the Mechanisms Consequences of Progressive Tubulointerstitial (TI) Injury

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TI injury characterizes all progressive renal disease and correlates better than glomerular changes with renal function and prognosis. Glomerular changes are also important, but it is apparent that the GFR may cease not only from glomerulosclerosis but also when the glomerular circulation is bypassed ('shunt glomeruli') or when the outflow is blocked ('atubular glomeruli'). Much attention has focused on proteinuria as a mechanism to induce TI damage. Proteinuria can induce tubular injury and activation via oxidant generation, complement activation and cytokine exposure. Intrarenal angiotensin II may also lead to TI injury via both hemodynamic and nonhemodynamic effects. Recent evidence suggests chronic intrarenal ischemia may also have a central role in progression of TI disease. The pathogenesis of TI injury involves tubular cell proliferation and apoptosis, interstitial fibroblast activation, matrix deposition, macrophage infiltration and peritubular capillary rarefaction. Some of the major cytokines driving this response include PDGF-activation of the interstitial fibroblast and TGF-β-driven matrix deposition, and these processes appear to be linked.

Macrophage accumulation is also central to the inflammatory process and their recruitment appears to be mediated by chemokines, leukocyte adhesion molecules, and osteopontin. Progressive ischemia with capillary rarefaction also occurs, leading to local expression of angiogenic factors and attempted capillary repair. However, progressive loss of cellularity occurs in part by a FAS-dependent apoptosis of tubular cells, eventually culminating in a densely fibrotic lesion. Finally, while loss of renal function is the classic end-point, it is becoming increasingly clear that TI disease can also lead to alterations in sodium handling, and in several models salt-dependent hypertension can be induced in animals that have only mild to moderate TI disease. Thus, TI disease may be relevant not only to progressive renal disease but also to the mechanisms of some forms of salt-dependent hypertension.

Nephrology in type 2 diabetes

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Endstage renal failure in diabetic patients, mostly type II, has become the most frequent cause for renal replacement therapy in Western Europe, the USA and many Asian countries. The majority of patients with type II diabetes and renal failure suffer from diabetic glomerulosclerosis, but non-diabetic renal disease and atypical presentations, e.g. as irreversible acute renal failure or ischemic nephropathy play an increasingly important role. Known risk factors for the onset of diabetic nephropathy include (i) genetic predisposition (indicated by a history of hypertension and cardiovascular events in first degree relatives), (ii) quality of glycemic control, (iii) level of blood pressure and (iv) smoking. At the time when type II diabetes in diagnosed, an abnormal blood pressure profile is found in approximately 80%. In patients with established diabetic nephropathy, hypertension is the most important factor which promotes progression, and that is susceptible to intervention. Although less data are available for the type II diabetes (compared to type I diabetes), ACE inhibitors appear to be the antihypertensive agent of first choice, but monotherapy is rarely sufficient to achieve the blood pressure goal. Although, at least in principle, diabetic nephropathy is a preventable condition, currently only a minority of type II diabetic patients receives adequate medical treatment to prevent onset or progression of diabetic nephropathy. Consequently, novel approaches to patient management and interdisciplinary interaction are necessary to fulfill the postulate of the St. Vincent declaration concerning prevention of diabetic complications.