The Role of Tubulointerstitial Inflammation in the Progression of Chronic Renal Failure

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Key Words

Inflammatory cells · Proteinuria · Chronic kidney disease · Oxidative stress · Atubular glomeruli · Vitamin D

Abstract

There is compelling evidence that interstitial inflammation plays a central role in the loss of renal function in chronic renal disease. The combined effects of interstitial inflammation, oxidative stress and local angiotensin II activity result in the disruption of glomerulus-tubule continuity, the development of pathogenic hypoxia, the generation of myofibroblasts and fibrosis, and the impairment of the protective autoregulation of glomerular blood flow that leads to glomerulosclerosis. The association between proteinuria and progression of chronic kidney disease is firmly established. Proximal tubular cells (PTC) exposed to high concentration of proteins produce proinflammatory and profibrotic factors. The activation of nuclear factor κ B and the signal transducer and activator of transcription results in the upregulation of a variety of cytokines and chemokines, overexpression of adhesion molecules and interstitial infiltration of inflammatory cells. Fibrosis is promoted by release of transforming growth factor β , which induces myofibroblast for-

mation and collagen deposition. Finally, the participation of vitamin D3 deficiency in the development of tubulointerstitial fibrosis is reviewed. The molecule $1,25\text{-(OH)}_2\text{D}_3$ modulates PTC proliferation, suppresses fibroblast activation and matrix production, reduces epithelial mesenchymal transition and downregulates the genes of the renin-angiotensin system, which are critical steps in the development of a scarred kidney.

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Tubulointerstitial Damage and Renal Function

The participation of tubulointerstitial lesions in the loss of kidney function was tacitly recognized since the availability of kidney biopsy made it possible to examine diseased kidneys before the development of end-stage renal injury. However, it was nearly 4 decades ago when Risdon et al. [1] reported that the severity of tubular damage had a more significant correlation with the reduction in creatinine clearance than glomerular damage scores. In subsequent studies, Bohle et al. [2] confirmed the association between tubulointerstitial fibrosis and renal function and extended these observations to immunoglobulin A nephropathy, poststreptococcal glomerulo-

Fig. 1. a Pathways of tubulointerstitial inflammation leading to end-stage renal disease. The combined effects of inflammation, oxidative stress and intrarenal angiotensin II activity produce interstitial capillary loss, tubular encroachment and disconnection from the glomeruli, afferent arteriopathy, cytokine-induced loss of autoregulatory capacity of glomerular blood flow and remodeling of glomerular arterioles. Structural alterations (**b, c**) are emphasized with a light grey background in the diagram (brown in the online version). AII = Angiotensin II; ROS = reactive oxygen species; EMT = epithelial mesenchymal transdifferentiation; SNGFR = single nephron glomerular filtration rate; SNBF = single nephron blood flow. **b** Intense inflammatory reactivity originating from a segment of adhesion of the glomerular tuft to the Bowman's capsule (arrow-head). The inflammation has constricted the corresponding tubule (indicated by *) that shows dilatation and atrophy. **c** Remodeling and increased media thickness in arterioles surrounded by inflammatory infiltrate in the proximity of the glomeruli with segmental sclerosis.

nephritis, mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and membranous nephropathy. Not only were the increments in interstitial volume and fibrosis reported to be correlated with renal functional impairment and worse prognosis, but also the reduction in peritubular capillaries, the morphological changes in tubular epithelia and the intensity of inflammatory infiltration in the interstitium correlated with renal functional deterioration.

Why the severity of tubulointerstitial disease should be better correlated with renal function and prognosis is not intuitively obvious. It may be due to the fact that in renal biopsies the tubulointerstitial areas are more representative of the extent of the kidney damage and less subject to

sample bias than glomeruli, because segmental changes may be missed in a given glomeruli by the biopsy section. Furthermore, atubular glomeruli may show relative integrity while the disconnected tubule is regularly atrophic and surrounded by inflammatory infiltrate and fibrosis and therefore more indicative of a nonfunctioning nephron.

Notwithstanding the considerations of sampling representativeness, and the fact that the association between interstitial inflammation (defined here as the accumulation of immunocompetent cells) and the chronic renal disease of any etiology [3] does not represent a proof of causality, the improvement resulting from therapies that directly or indirectly reduce the inflammatory infiltration strongly suggests a pathogenic role of inflammation in the development of a chronically scarred kidney.

Fig. 2. Hypoxia-induced renal damage. Reduced number of capillaries, postglomerular blood flow reduction, increased oxygen demand and anemia are responsible for a state of chronic hypoxia that generates oxidative, nitrosative and carbonyl stress. Hypoxia stimulates HIF that is enzymatically hydroxylated by the prolyl hydroxylases (PHD1, 2 and 3) and degraded rapidly by the proteasome. Nonhydroxylated HIF binds in the nucleus to HIF- β and activates genes involved in the adaptive response to hypoxia. PHD activity is inhibited by oxidative stress, thus favoring the HIF- β route. Nonspecific inhibition of PHD has adverse effects but disruption of PHD1 induces hypoxic tolerance [modified from 13].

Interstitial inflammation, oxidative stress and local angiotensin II activity are constantly associated [4] and their combined effects result in the disruption of glomerulus-tubule continuity, the development of pathogenic hypoxia and impairment of the protective autoregulation of glomerular blood flow that results in glomerulosclerosis (fig. 1). We shall discuss separately these mechanisms leading to renal scarring, recognizing that, in fact, they complement and support one another and lead to the development of fibrosis by the myofibroblast transformation of vascular pericytes [5] and/or the epithelial mesenchymal transdifferentiation of tubular epithelial cells [6]. This is a process in which transforming growth factor β (TGF- β) and matrix metalloproteinase 9-mediated E-cadherin disruption are actively involved [7]. The importance of this process is highlighted by the improvement in renal fibrosis by treatments that suppress epithelial mesenchymal transdifferentiation [6, 8].

Interstitial Inflammation and the Loss of Nephron Integrity

Tubulointerstitial inflammation may result from leakage of filtered urine to the interstitial space through capsular adhesions. The works of Kriz and LeHir [9] have exquisitely shown the formation of bridges between podocytes and the Bowman's capsule in sites of capsular adhesions and a remaining narrow urinary space allows

leakage of ultrafiltrate to tubulointerstitial areas. Periglomerular inflammation and fibrosis encroach the tubule, which results in tubular atrophy and eventual disconnection from its glomeruli and the formation of atubular glomeruli and aglomerular tubular remnants (fig. 1b). Angiotensin II is critically involved in this process since angiotensin-converting enzyme inhibitors prevent the formation of atubular glomeruli; a protective effect not observed with Ca antagonists despite lowering blood pressure to a comparable degree [10]. The significance of these structural changes were highlighted in the studies of Gandhi et al. [11] who showed in the remnant kidney model that 25 weeks after renal ablation, only 26% of the glomeruli have a normal connecting tubule and atubular glomeruli may represent 15–21% of the glomeruli that have some degree of sclerosis.

Tubulointerstitial Inflammation and Oxidative Stress

The role of hypoxia in the progression of chronic renal damage was postulated by Fine and Norman [12] who noted that tubulointerstitial inflammation and fibrosis were associated with loss of peritubular capillaries and proposed that hypoxia was a common denominator in chronic kidney damage. As recently reviewed [12, 13], the hypoxic milieu would be enhanced by an increment in vasoconstricting (or a reduction in vasodi-

Fig. 3. Activation of inflammatory and fibrogenic pathways in PTC by proteinuria. Proteinuria is assumed to induce chronic renal damage because of the demonstration that is capable to activate growth factors and proinflammatory cytokines in proximal epithelial cells (shown with a shaded background) as described in the text. MAC = Membrane attack complex; ICAM = intercellular adhesion molecule; VCAM = vascular cell adhesion molecule; IL-8 = interleukin-8.

lating) mediators, increased metabolic demands of hyperfunctioning remnant nephrons and anemia. As inflammation and fibrosis develops, the ongoing structural changes and the increased distance between tubular cells and peritubular capillaries will further impair diffusion and further augment the oxygen deficit. Hypoxia is a potent stimulus for the development of proinflammatory mediators, the increase of myofibroblast population and collagen deposition, and reduced matrix degradation [14]. Miyata and de Zeeuw [15] have recently reviewed the mechanisms of oxidative stress, nitrosative stress and carbonyl stress resulting from hypoxia, emphasizing the protective role of hypoxia inducible factor (HIF) and the modulation of this response by prolyl hydroxylases (fig. 2). Inhibition of these oxygen-

sensing molecules has resulted in an improvement of renal disease in experimental models of diabetic nephropathy and acute renal failure.

Tubulointerstitial Inflammation and Glomerular Blood Flow Autoregulation

The role played by the loss of the capacity to autoregulate the glomerular capillary blood flow to protect the glomeruli from the effects of systemic hypertension has been extensively studied by Bidani and Griffin [16]. In studies in the remnant kidney model, they demonstrated that the loss of a large number of functioning units results in the impairment of glomerular flow autoregulation. A linear relationship between systemic and glomerular capillary pressure is the consequence of the suppression of this adaptive response and therefore, a large reduction in systemic blood pressure is necessary to protect against hemodynamically-induced glomerulosclerosis. It should be realized that in the renal ablation model, the tubuloglomerular feedback is reset upwards in relation to the extension of renal ablation and is directed to sustain the glomerular hypertension and hyperfiltration (fig. 1), thus contributing to the 'adaptive and potentially maladaptive' responses of nephron loss [17].

An important contribution to the understanding of the relationship between tubulointerstitial inflammation and glomerular damage was offered by Sánchez-Lozada et al. [18] who demonstrated that the accumulation of inflammatory cells in tubulointerstitial areas was associated with proliferative phenotypical changes in afferent arterioles (fig. 1c) that result in rearrangement of extracellular matrix proteins and reduction in the response of vascular smooth muscle cells to contractile stimuli [19]. In addition to structural changes, inflammatory cytokines impair glomerular blood flow autoregulation, as demonstrated by the inhibition of both the proximal (myogenic) and distal (tubuloglomerular feedback) afferent arteriolar vasoconstriction by TGF- β in a dose-dependent manner [20].

Taken together, the studies discussed above give a mechanistic explanation for the lower blood pressure target levels currently considered optimal in the treatment of chronic kidney disease (CKD) when physiologic glomerular blood flow autoregulation is impaired or absent.

Proteinuria and Tubulointerstitial Injury

While the inflammation resulting from misdirected glomerular filtrate through capsular adhesions is a well-accepted cause of tubular encroachment and atrophy, the possibility that fibrosis and destruction of nephron architecture may be a consequence of the interstitial inflammatory cell accumulation induced by intense proteinuria is disputed by some investigators [9]. Nevertheless, proximal tubular cells (PTC) exposed to high concentration of proteins change their phenotype and produce proinflammatory and profibrotic factors [10, 21]. Proteinuria-induced tubulointerstitial inflammation plays a role in the development of salt-sensitive hypertension [21] and there is compelling evidence of the association between the severity of proteinuria and the rate of progression of CKD [22–24].

Proteinuria results in the upregulation of a large number of genes [25] generated by the PTC in response to the uptake of proteins. Megalin, the albumin-binding receptor, is subject to regulated intramembrane proteolysis that links protein reabsorption to gene regulation [26]. Figure 3 presents the proinflammatory effects resulting from the acute exposure of PTC to albumin. Critical in the proinflammatory response to albumin are the activation of nuclear factor κ B (NF- κ B) and the signal transducer and activator of transcription or STAT that are in turn responsible for the upregulation of a variety of cytokines and chemokines, and adhesion molecule overexpression. Protein kinase pathways stimulated by the generation of reactive oxygen species play a central role in the activation of these transcription factors [27]. The role of NF- κ B-induced upregulation of macrophage chemotactic factor 1 or MCP-1 and CCL5 (regulated upon activation, normal T-cell expressed, and secreted, or RANTES) are critically important. The role of CCL5 has been studied in experiments that suppressed the NF- κ B activation by intrarenal injection of recombinant adenovirus expressing a truncated form of I κ B α [28] and by DNA vaccination with naked DNA encoding for MCP1-1 and CCL5. These strategies, as well as the blockade of chemokine receptor-1 [29], have resulted in the amelioration of inflammatory infiltration, reduction of renal damage, and the slowing of renal scarring.

Complement activation products in the urine contribute to tubulointerstitial inflammation (fig. 3). C6-deficient rats are partially protected from tubular damage, and inhibition of complement activation and formation of membrane attack complex [30] offer protection against tubulointerstitial injury. However, local C3 synthesis by the PTC is unrelated to the development of proteinuria [31].

Table 1. Anti-inflammatory interventions that ameliorate experimental nonimmune chronic renal disease

Intervention	Disease model
RAS suppression (ACE inhibitors ¹ , ARBs blockers ¹ , angiotensinogen antisense mRNA, aliskerin)	Many animal models; transgenic Ren2 rat, aging nephropathy
Mycophenolate mofetil	Remnant kidney, obese Zucker rat, IRI, lead nephropathy, diabetic nephropathy
Rapamycin	Remnant kidney, diabetic nephropathy, PKD
Suppression of NF- κ B (PDTC, truncated form of I κ B α)	Remnant kidney
DNA vaccination for CCL2, CCL5	Adriamycin-induced nephropathy
Blockade of CCR-1 receptor	UUO, Adriamycin-induced nephropathy
NO donors	Remnant kidney, diabetic nephropathy, PAN
Antioxidants (melatonin, niacin)	Remnant kidney
PDE5 inhibition (sildenafil)	Remnant kidney, IRI, CyA toxicity
HIF activation (suppression of prolyl hydroxylases by cobalt chloride and other strategies)	IRI, remnant kidney, cisplatin toxicity
COX inhibitors	Diabetic nephropathy, IRI, PKD
IL-10 gene therapy	Remnant kidney
Vitamin D analogs	Remnant kidney
Erythropoietin	Remnant kidney, IRI, toxicity by cisplatin, CyA and radiocontrasts, UUO
Statins	UUO, Imai rat
PPAR- γ agonists	Remnant kidney, PAN

Interventions that directly or indirectly have been found to suppress inflammation and improve renal disease in specified experimental model (references available upon request).

RAS = Renin-angiotensin system; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; PDTC = pyrrolidine dithiocarbamate; CCL2 = MCP1 (macrophage chemotactic factor); CCL5 = RANTES; CCR-1 = chemokine receptor-1; UUO = unilateral ureteral obstruction; NO = nitric oxide; PAN = puromycin aminonucleoside nephrosis; PDE5 = phosphodiesterase 5; IRI = ischemia-reperfusion injury; CyA = cyclosporin A; COX = cyclooxygenase; PKD = polycystic kidney disease; IL = interleukin; PPAR- γ = peroxisome proliferator-activated receptor gamma.

¹ Used successfully in humans.

Despite the evidence that abnormal protein trafficking may damage the tubulointerstitium, the actual component of the filtered protein that carries the nephrotoxic potential still is unknown. One factor may be the association with lipids that accompany heavy albuminuria, especially in nephrotic syndrome. The addition of oleic acid markedly increases the inflammatory potential of bovine serum albumin [32]. Fatty acids activate peroxisome proliferator-activated receptors in a dose-dependent manner which results in apoptosis of PTC [33], suggesting that these elements are critical determinants of tubular atrophy [34]. The angiotensin AT2 receptor is involved in the apoptosis in PTC in chronic overload proteinuria [35]. Another factor that could have nephrotoxic potential is the generation of antigenic peptides resulting from proteasomal processing of reabsorbed albumin [36].

Vitamin D and Tubulointerstitial Fibrosis

Recent investigations have demonstrated the participation of vitamin D deficiency in the development of tubulointerstitial fibrosis. The PTC is the site of endogenous synthesis of 1,25-(OH)₂D₃. The recovery of 25-(OH)D₃ from the urine by megalin-facilitated endocytosis is hampered by a reduction of functioning renal mass.

Apart from its classical role in bone and mineral metabolism, 1,25-(OH)₂D₃ has recently been shown to modulate PTC proliferation [37]. In addition, vitamin D₃ suppresses fibroblast activation and matrix production, an effect mediated by upregulation of hepatocyte growth factor gene expression and receptor phosphorylation in renal fibroblasts [38]. 1,25-(OH)₂D₃ reduces epithelial mesenchymal transition by decreasing vitamin D recep-

tor and Smad3 protein levels and inhibition of β -catenin signaling, which are critical steps in TGF- β -mediated myofibroblast generation [39]. The beneficial effects of 1,25-(OH)₂D₃ in chronic renal disease are evidenced by the demonstration that, in the renal obstruction model, treatment with paracalcitol suppressed renal RANTES and tumor necrosis factor- α expression, inhibited renal infiltration of T cells and macrophages, reduced the accumulation of fibronectin and type I and type III collagen, and ameliorated the expression of α -smooth muscle actin, vimentin, and Snail1 [40]. Finally, vitamin D₃ downregulates the genes of the renin-angiotensin system that is critically involved in the development of a scarred kidney [41].

In conclusion, we have summarized mechanisms related to tubulointerstitial inflammation that may be involved in the progression of renal damage. These mechanisms may act in combination but their role in the progressive scarring of the kidney has not been fully elucidated. Each one in isolation provides insufficient explanation for chronic renal disease progression; tubular encroachment by misdirected filtrate does not extend to adjacent nephrons [5], interstitial accumulation of macrophages and lymphocytes in the overload proteinuria model does not lead to chronic renal damage [42] and long-standing proteinuria in cubilin-deficient patients (Imerslund-Gräsbeck syndrome) is not associated with renal functional impairment [43]. Nevertheless, as shown in table 1, many interventions addressed to mechanisms discussed in this review have proven beneficial in models of nonimmune experimental renal disease. The suppression of the renin-angiotensin system is a modality that has already been used successfully in humans, while the rest represents a variety of approaches with potential clinical significance.

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Editorial Comment

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The article by Bernardo Rodríguez-Iturbe and Guillermo García García follows in the footsteps of pioneering observations by Risdon and De Wardener (UK) in the 1960s and Bohle (Germany) throughout the 1980s by stressing the key role of tubulointerstitial inflammation and fibrosis in the progression of chronic kidney disease.

Since these initial observations, mechanistic hypotheses have been put forward by Bertani and Remuzzi (the nephrotoxicity of albuminuria), Fine and Norman (the nephrotoxicity of hypoxia) and Strutz and Nielson (the

epithelial mesenchymal transformation of renal tubules cells), to name a few. The current review updates the reader on a number of such mechanistic pathways but also introduces new potential modulators of renal fibrosis such as vitamin D₃. It is over 40 years since the initial observation of Risdon and De Wardener, though a huge body of research mechanisms are unraveling. It is hoped that the next 10 years will see some clinical translation of promising experimental observations to prevent progressive renal fibrosis.