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Mechanisms of tubulointerstitial injury in IgA nephropathy

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Background. IgA nephropathy (IgAN) runs a highly variable clinical course, with frequent involvement of tubulointerstitial damage. A subgroup of IgAN with severe tubulointerstitial damage is often associated with the most rapid progression to end-stage renal failure. In IgAN, mesangial sclerosis and tubulointerstitial damage were found to be correlated with the increase in pore size of the glomerular barrier.

Methods. The direct toxicity of proximal tubular epithelial cells (PTEC) by IgA in IgAN is still unresolved. Activation of PTEC by mediators released from infiltrating cells or resident kidney cells that induce tubular inflammation is the common final pathway in most chronic renal diseases. We hypothesize that mediators released from human mesangial cells (HMC) triggered by IgA deposition may lead to PTEC activation.

Results. We found that IgA binding to PTEC was less than one tenth that of HMC. The binding was nonspecific and exhibited no increased cell proliferation or enhanced synthesis of cytokines or adhesion molecules. However, when PTEC were cultured with IgA-HMC spent medium prepared from IgAN patients, there was enhanced proliferation of PTEC and increased synthesis of cytokines and adhesion molecules.

Conclusion. These findings implicate a glomerulotubular cross-talk with mediators released from the mesangium, contributing to the pathogenesis of tubulointerstitial damage in IgAN. There are preliminary data to suggest that the expression of angiotensin II subtype-1 receptor and angiotensin II subtype-2 receptor in PTEC differs from that of HMC. These novel findings may provide clinicians new therapeutic approach for selective blockade of the tubulointerstitial injury in IgAN.

IgA nephropathy (IgAN), the most common primary glomerulonephritis worldwide, is associated with a substantial risk of progression to end-stage renal failure (ESRF) [1]. Proteinuria is a well-recognized risk factor for progression in different glomerular diseases. However, the prognostic value of high-grade proteinuria is more complicated in IgAN. First, heavy proteinuria is not common in IgAN [2]; nephrotic syndrome, an unusual presenting symptom, occurs in only 5% of all IgAN [3]. Second, it has been reported that the severity of proteinuria may not always bear any significant correlation with the severity of renal histopathologic changes [4, 5]. One of the possible explanations is the existence of a variant of IgAN associated with a nephrotic syndrome that resembles lipoid nephrosis in its responsiveness to steroid [6].

Certain clinical, laboratory, and pathologic parameters have been identified as predictors of poor outcome in IgAN. These include older onset of disease, arterial hypertension, high glomerular histopathologic scores, the extent of global glomerular and interstitial sclerosis, tubulointerstitial fibrosis, persistent microscopic hematuria, nephrotic-range proteinuria, and renal insufficiency at the time of first diagnosis [7, 8]. These factors are concluded from retrospective analysis of large cohorts of patients. Indeed, for most patients with IgAN, these prognostic indicators are weak on an individual basis. Notably, most nephrologists observed renal progression correlates more closely with the severity of tubulointerstitial lesions than with the degree of glomerular lesions [9, 10]. With marked tubular atrophy, the remaining time to ESRF was 3.5 ± 2.7 for those with and 8.2 ± 4.2 years for those without [11]. In addition, infiltration of circulating inflammatory cells, including mononuclear and polymorphonuclear leukocytes, to the renal interstitium is one of the early and prominent histopathologic changes preceding the induction of glomerular or tubulointerstitial injury. Inflammation elicited by these infiltrating cells plays an important role in subsequent development of glomerular and tubulointerstitial damage [12].

WHAT LEADS TO TUBULOINTERSTITIAL CHANGES: PROTEINURIA, MONOCYTIC/MACROPHAGE INFILTRATION, TUBULAR IGA DEPOSITION, OR OTHER MECHANISMS?

The pathogenetic cascade of IgAN can be conveniently divided into 3 phases: (*1*) synthesis of "pathogenetic IgA;" (*2*) mesangial IgA deposition and mesangial inflammatory injury; and (*3*) tubulointerstitial injury. While the pathogenetic significances of abnormal glycosylation of the IgA molecule and the mesangial binding of IgA via known IgA receptors still remain unclear, IgA deposited in the mesangium clearly induces local release

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of cytokines, complement, and angiotensin II (Ang II), leading to inflammatory injury [3, 13]. The question that has not been explored is how would mesangial IgA deposition lead to tubulointerstitial injury in IgAN? Four pathogenetic mechanisms of tubulointerstitial injury may operate independently or synergistically, namely: monocytic/macrophage infiltration, proteinuria, direct inflammatory effect of IgA, and a glomerulotubular cross-talk.

The involvement of infiltrating inflammatory cells in the tubulointerstitium is important in mediating tubular injury and renal fibrosis [14]. As a consequence, resident kidney cells can become activated during the inflammatory process. In recent years, much attention has focused on the role of proximal tubular epithelial cells (PTEC) in orchestrating the infiltration of inflammatory cells and the renal fibrosis via production of inflammatory mediators upon activation. Mediators released by infiltrating cells are directly responsible for the activation of PTEC, which, in turn, may amplify the inflammatory cascade by local production of chemotactic mediators that attract even more inflammatory competent cells. The outcome of such a chain reaction is the generation of a positive feedback loop of activation that may lead to the overproduction of extracellular matrix components, resulting in fibrosis and ultimately loss of kidney function. Therefore, a cytokine "cross-talk" network between PTEC and interstitial immunocompetent cells can be envisaged to be the major driving force of tubulointerstitial injury. The key role of tubular epithelial cells in progressive renal diseases have been reviewed, and collective data from the literature have clearly demonstrated the ability of tubular epithelial cells in producing a wide variety of inflammatory mediators [15]. Proteinuria is the major stimulus of PTEC activation and subsequent chemotaxis of infiltrating immunocompetent cells in most glomerular diseases [16]. Our novel finding that "conditioned" supernatant from PTEC stimulates the proliferation of mesangial cells provides experimental evidence to suggest a tubuloglomerular "cross-talk" mechanism, involving different soluble factors, is likely to operate in different glomerular and interstitial nephritis [17]. However, proteinuria may be one of the several contributory factors in tubulointerstitial injury in IgAN because heavy or nephrotic-range proteinuria is uncommon [2, 3].

The other possible contributory factor is the direct toxic effect following tubular binding of IgA. IgAN patients have increased urinary IgA concentration that correlates with serum creatinine concentration, as well as the urinary protein excretion [18]. By immunofluorescence, tubulointerstitial deposits were previously reported in 10% to 35% of proximal tubules, consisting of C3 in all, and IgA in 11% of IgAN patients in one study [19]. However, other investigators noted that IgA deposits are rarely detected in the tubulointerstitium [20, 21]. The scarcity of tubular IgA deposition in IgAN is illustrated in Figure 1.

DOES URINARY IGA BIND TO TUBULAR EPITHELIAL CELLS TO EXERT INFLAMMATORY INJURY IN IgAN?

The increase in glomerular barrier pore size that allowed the passage of proteins to the tubular lumen was observed in various glomerular diseases [22]. Normally, the glomerular barrier is impermeable to proteins. However, it is possible that the tubular lumen could be exposed to the high-molecular-weight IgA from patients with IgAN, especially when the glomerular size barrier was impaired in IgAN [23]. Hence, it remains interesting and important to ascertain in IgAN whether IgA is capable of binding to PTEC, and to elicit similar inflammatory responses as those observed in human mesangial cells (HMC).

Our preliminary data demonstrated that there was minimal binding of IgA from IgAN patients to cultured PTEC [24]. The amount of IgA binding to PTEC was less than 10% that of mesangial cells. The representative immunofluoresence staining of IgA binding to HMC or PTEC is shown in Figure 2. As for the expression of documented IgA receptors in PTEC, there was absence of known IgA receptors in cultured PTEC except the transferrin receptor. Competitive binding assay of IgA to PTEC using different ligands (including transferrin) for known IgA receptors further confirms that known IgA receptors were not expressed in PTEC. The lack of cell proliferation and absence of inflammatory mediator production from PTEC stimulated with IgA from IgAN patients suggest that the low level of IgA bound to the PTEC is a nonspecific binding in the cell culture experiment. Our data support the previous observation that IgA deposits are rarely detected in the tubulointerstitium in IgAN [20].

HYPOTHESIS: A GLOMERULOTUBULAR CROSS-TALK IN IgAN VIA HUMORAL FACTORS

Failing to demonstrate a specific binding of IgA to PTEC and the infrequent occurrence of high-grade proteinuria in IgAN, we postulate a new mechanism that may be operative upon mesangial IgA deposition that subsequently leads to tubulointerstitial atrophy and fibrosis in IgAN. It has been documented that inflammatory cytokines, including Ang II, are released from mesangial cells following binding to IgA in IgAN. We hypothesize that these mediators alter the glomerular barrier pore size that allows the passage of these inflammatory mediators to the tubular lumen. These mediators then activate the PTEC, which in turn may amplify the inflammatory cascade by local production of chemotactic