COMMENTARY

Immunoglobulin A nephropathy: insights and progress

RICHARD A. LAFAYETTE

STANFORD, CALIF

Article on page 8

Application of Oxford classification, and overexpression of transforming growth factor-b1 and immunoglobulins in immunoglobulin A nephropathy: correlation with World Health Organization classification of immunoglobulin A nephropathy in a Chinese patient cohort

Hongxue Meng, Lei Zhang, Xiaoqiang E, Fei Ye, Huining Li, Changsong Han, Mitsunori Yamakawa, and Xiaoming Jin

Diseases of the kidney filter, the glomerulus, are generally recognized by clinical signs of hematuria and proteinuria. Many of these diseases can progress to cause kidney dysfunction, hypertension, and multiple complications. In this issue of *Translational Research*, investigators from northeastern China present data from a large population of individuals with immunoglobulin A nephropathy (IgAN) in an effort to evaluate a new pathologic classification and to evaluate other disease markers.[1] IgAN is the most common primary glomerular disease throughout the world, and it contributes significantly to the burden of chronic and end-stage kidney disease.[2,3] First described in 1968 by Berger and Hinglais,[4] IgAN is defined by predominant immunoglobulin (Ig) A antibody deposition in the glomerular mesangium with associated proliferation. Various populations have been studied, but rates of progressive kidney disease in affected individuals range from 5% to 40%.[3,5,6]

IgAN usually presents in late childhood or early adulthood, typically asymptomatically as microscopic hematuria with varying degrees of proteinuria. Urinary protein loss is usually mild in nature and only rarely is in the nephrotic range of 3.5 g/d or more. It can have a nearly pathognomonic presentation of gross hematuria during the onset of an acute upper respiratory tract or gastrointestinal infection, which has focused attention on the mucosal immune system as a key component in the development of the disease.[6]

Efforts continue to understand more completely the risk factors for IgAN. Currently, there are clear differences based on ethnicity and race, with higher incidences of IgAN among certain Asian and Latino populations, and lower incidences among those of Africandescent.[2,3,5] Efforts to define the underlying genetic predisposition have been complicated; however, there are kindreds enriched for IgAN and candidate genes have been suggested.[7,8] Interestingly, genewide association studies have found some interesting changes in genes associated with IgA itself and with the major histocompatibility complex loci, highlighting the immune nature of the disease.[8] These gene associations may ultimately explain some of the diversity of disease.

The susceptibility to risk also informs us of the potential pathophysiology of the disease. It is now felt that a major contributor to the risk of disease is high levels of IgA in the blood, particularly a form of IgA that is relatively galactose deficient.[7] IgA1—the major circulating form of the antibody—is glycosylated, as is the case for other immunoglobulins. Routine alterations in the glycosylation of the hinge region of IgA heavy chains result in galactose-deficient IgA (GDIgA1). Patients with IgAN have been found to have higher levels

DOI of original article: 10.1016/j.trsl.2013.06.007.

Glomerular Disease Center, Stanford University Medical Center, Stanford, Calif.

Submitted for publication August 20, 2013; accepted for publication August 25, 2013.

Reprint requests: Richard A. Lafayette, Glomerular Disease Center, Stanford University Medical Center, 300 Pasteur Drive, A155A, Stanford, CA 94305; e-mail: czar@stanford.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2013.08.007

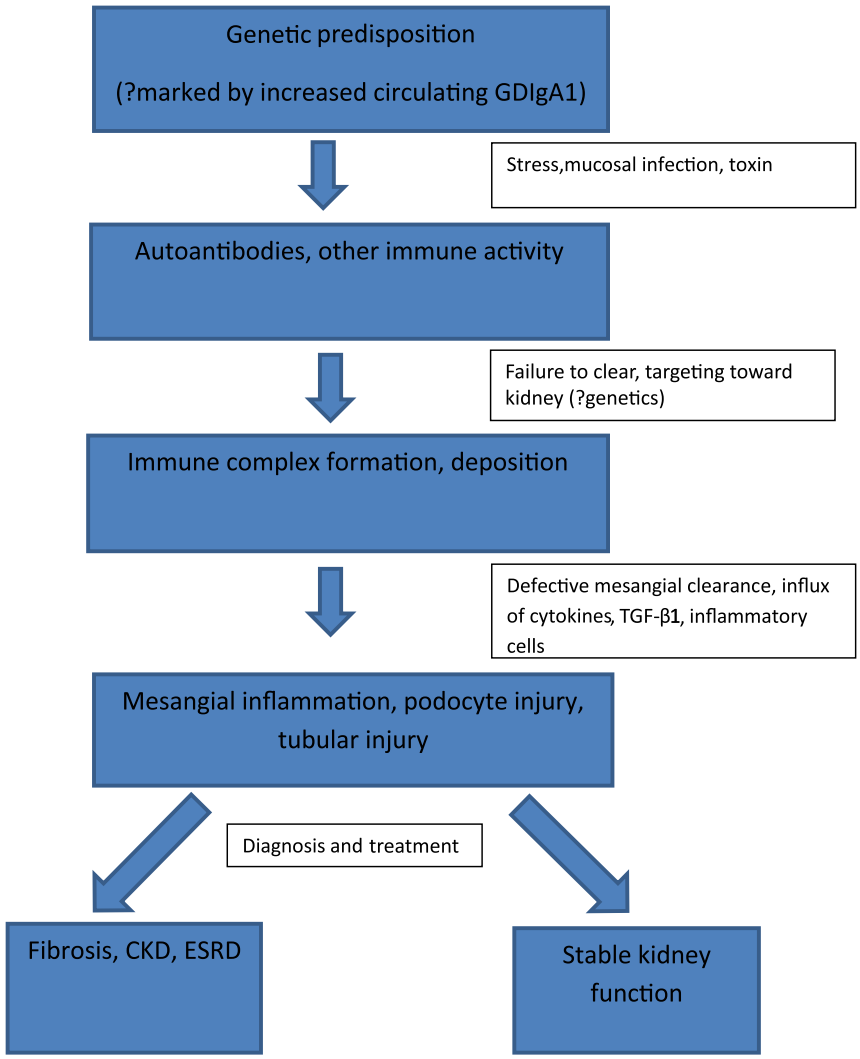

Fig 1. Pathogenesis of immunoglobulin A nephropathy. CKD, chronic kidney disease; ESRD, end-stage renal disease; GDIgA1, galactose-deficient IgA1; TGF-β1, transforming growth factor β1.

of GDIgA1 than healthy control subjects, and GDIgA1 is also typically found in immunedeposits in the glomerulus of patients with IgAN.[7,9] However, there is overlap of GDIgA1 levels between patients with IgAN and healthy individuals. Furthermore, unaffected family members of patients with IgA1 often have similarly elevated levels, suggesting hereditability of this trait.[10] Thus, it is argued that other factors must lead to active disease (Fig 1). It is felt that other susceptibility factors allow certain individuals to develop antibodies to galactose-deficient IgAN, perhaps during mucosal infections or injury, and that these antibodies, which can be both IgA and IgG, can then lead to immune complex formation.[7,11] These complexes, in turn, can be filtered and trapped in the glomerular mesangium, where they can lead to inflammation, injury, and scarring.[12] Some studies suggest it is the IgG-based immune complex with GDIgA1, larger in size than the IgA-based immune complex and better correlated with adverse outcomes, that has greater potential for kidney injury.[13] The immune complex has affinity to the extracellular matrix of mesangial cells, but the binding mechanisms are yet unknown. When the immune complex is *in situ*, mesangial cell growth and proliferation can occur. Mesangial cells or other resident or infiltrating cells also likely release cytokines that affect glomerular podocytes and lead to defects in the glomerular filter, allowing for glomerular bleeding, with hematuria and proteinuria.[14]

Clinically, patients are diagnosed with IgAN by kidney biopsy. Currently, no serologic or genetic test can distinguish IgAN reliably from other kidney disorders that cause blood and protein in the urine. As discussed earlier, individuals with IgAN have highly variable courses; some will maintain lifelong normal