Association of Gene Polymorphism of Polymeric Immunoglobulin Receptor and IgA Nephropathy

Key words: gene polymorphism, polymeric IgR, IgA nephropathy

IgA nephropathy (also called Berger’s disease) is characterized by glomerular mesangial deposition of IgA (mainly IgA1) in renal biopsy specimens as determined by immunohistochemistry and is considered to be an immune complex-mediated glomerulonephritis. Epidemiologically, it is well known that there are geographic, ethnic and/or familial clusters of patients with IgA nephropathy. Dimeric and/or polymeric IgA1 in the glomerular mesangial areas have been observed in patients with IgA nephropathy. IgA nephropathy is defined as nephropathy showing proliferative changes in the glomerular mesangial cells and increases in the mesangial matrices, associated with deposition of IgA. However, 4% of the kidneys studied at autopsy showed IgA deposition in the glomerular mesangial areas even in the absence of clinically evident renal disease in the large autopsy study of Sinniah et al (1). Thus, it is possible that a variety of mechanisms may lead to deposition of IgA in the glomerular mesangial areas, and other factors may induce these deposits to cause glomerular injuries with subsequent production of clinical renal disease. It remains uncertain whether mesangial IgA (IgA1)-immune complexes (IC) or polymeric IgA1 directly cause glomerular injury, or they are only secondary to some other pathological process. If IgA-IC/polymeric IgA has direct effects on glomerular injury, it would appear that they contribute to pathogenesis by including complement activation such as in the classical inflammatory cascade of type III (IC type) allergy (2). However, the mechanisms of IgA-IC/polymeric IgA binding to the glomerular mesangial cells and/or areas are still obscure. Possible mechanisms of such binding include the following: 1) pinocytosis, 2) charge-dependent binding, 3) cytokine activity, 4) circulating or localized producing complement activation, 5) uteroglobin activity, 6) via the asialoglycoprotein receptor (ASGPR), 7) via the Fcα receptor (CD89), 8) via the polymeric immunoglobulin receptor (plgR), and 9) via other novel Fcα receptors. Leung et al (3) concluded that there was an absence of Fcα receptor (CD89), ASGPR, or plgR on human mesangial cells. They suggested that the predominant binding of human IgA1 to human mesangial cells is mediated by another mechanism, i.e. charge-dependent binding. However, Suzuki et al (4) investigated the characteristics of Fcα receptors in human mesangial cells to assess the role of polymeric IgA/IgA-IC in IgA nephropathy and confirmed the gene expression of Fcα receptor in cultured mesangial cells by RT-PCR and Southern blotting. Tsuge et al (5) identified two novel polymorphisms in the functional promoter region of the Fcα receptor gene frequencies of the homozygous +56CC genotype and +56C allele in patients with IgA nephropathy were significantly higher than those in both control groups, i.e. patients with other chronic proliferative glomerulonephritides and healthy adults. The frequencies of the −114CC genotype and −114C allele tended to increase in patients with IgA nephropathy compared with those in both control groups. It appears that polymorphisms of the Fcα receptor promoter region are associated with susceptibility to IgA nephropathy, suggesting the importance of the Fcα receptor gene and its expression in patients with IgA nephropathy.

The role of polymeric immunoglobulin receptor (plgR) in the pathogenesis of IgA nephropathy is still obscure. plgR is an integral membrane secretory component localized on the basolateral surface of secretory epithelial cells. It mediates the transepithelial transport of polymeric IgA. plgR is detected in most human secretory epithelia, including the intestines, bronchi, salivary glands, renal tubules and uterus. The plgR neutralizes extracellular and intracellular pathogens in mucous membranes by epithelial transport of polymeric IgA-pathogen complexes and then excretes them via epithelial transcytosis (3). It is reasonable to hypothesize that individual variations in mucosal immune response to common environmental antigens such as food, bacterial or viral antigens may participate in determining the development of this disease. Narita et al (6) examined the association of the gene polymorphism of plgR in patients with and without IgA nephropathy in order to explore the possibility that genetic predisposition to dysfunction of mucosal immunity and the IgA processing pathway may play a role in the pathogenesis of mesangial IgA1 deposition in this disease.

See also p 867.

The plgR genotype distribution was significantly different between the patients with IgA nephropathy and others. Allele frequency of A2 was higher in IgA nephropathy than in other renal diseases. Their report is the first demonstration of plgR gene polymorphisms in IgA nephropathy, which are associated with its clinical phenotype. Gene polymorphisms of plgR may be candidate gene markers of susceptibility to IgA nephropathy. It appears that genetic control of IgA binding to the glomerular mesangial cells/areas might be related to the patho-
genesis in patients with IgA nephropathy.

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