IgA Nephropathy Today
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Almost 40 years have passed since Dr. Jean Berger first described primary IgA nephropathy as a new disease entity. This disease may lead to end-stage renal disease (ESRD) with its enormous economic impact on healthcare everywhere. Since the pathogenesis of IgA nephropathy is still obscure, specific treatment is not yet available. However, efforts by many investigators around the world have gradually clarified various aspects of the pathogenesis and treatment of this disease.

The objectives of the 11th International Symposium on IgA nephropathy (October 5–7, 2006) are (1) to discuss the most up-to-date findings on pathogenesis and treatment of IgA nephropathy and (2) to build friendship among us. This symposium is truly a small specialized meeting with the participation of international nephrologists and basic scientists involved in the large topic of IgA nephropathy. This article is a summary of the topics presented in the 11th International Symposium on IgA nephropathy.

This symposium was made possible by the generosity of our sponsors. Thanks go to the members of the Organizing and Scientific Committees, my colleagues in the Division of Nephrology at Juntendo University and the sponsors. Autumn 2006

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Pathogenesis of IgA Nephropathy

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Abstract

IgA nephropathy is generally considered to be an immune-complex-mediated or aggregated (polymerized) IgA (IgA1)-mediated glomerulonephritis. Since the pathogenesis of IgA nephropathy is still obscure, it is important to determine the initiation and progression of this disease using the spontaneous animal model. The ddY mouse strain can serve as a spontaneous animal model for IgA nephropathy. Genetic factors are considered to be involved in the initiation and progression of IgA nephropathy. It has been hypothesized that susceptibility genes for IgA nephropathy can be detected by a genome-wide scan using this model. The peak marker D10MIT 86 on chromosome 10 is located on the region syntenic to human 6q22–23 with IGAN1, which is responsible for familiar IgA nephropathy. There are several developmental and/or exacerbating factors in this disease. Among them, the loss of glomerular epithelial cells (podocytes) and interstitial mast cell infiltration are important factors for progression of glomerulosclerosis and tubulointerstitial injury in patients with IgA nephropathy.

Determination of Pathogenesis of IgA Nephropathy using ddY Mice, a Spontaneous Animal Model for IgA Nephropathy

Although the etiology and pathogenesis of IgA nephropathy are still obscure, much is known about serum IgA and mesangially deposited IgA (fig. 1). IgA is the most common immunoglobulin produced by lymphocytes and plasma cells lining the mucosal membranes, and is the main immunoglobulin directed against bacterial or viral antigens in exogenous secretions. Imai et al. [1] reported that the ddY mouse strain can serve as a spontaneous animal model for IgA nephropathy, since these mice show mesangioproliferative glomerulonephritis with severe glomerular IgA deposition. In these mice, at over 40 weeks of age
marked deposition of IgA and C3 occurs in the glomerular mesangial areas, in association with an increase in the levels of IgA and macromolecular IgA-immune complex in the serum [1, 2]. IgA nephropathy is generally considered to be an immune-complex-mediated or aggregated (polymerized) IgA (IgA1)-mediated glomerulonephritis. However, the antigens or stimulators that produce the aggregated (polymerized) IgA involved in this disease are still obscure. Several antigens originating in the respiratory, intestinal and/or biliary tracts and some dietary antigens have been implicated. Previous studies revealed that murine retroviral gp70 is involved in the pathogenesis of lupus nephritis in systemic lupus erythematosus (SLE)-prone NZB, NZB × NZWF1, BXSB and MRL/Mp-lpr/lpr mice [3, 4]. Takeuchi et al. [5] reported that the murine retroviral envelope glycoprotein, gp70, is deposited in the glomerular mesangial areas in ddY mice over 24 weeks, in the same way as IgG and IgA. Gp70 is also present in various lymphoid tissues. Thus, they suggested that gp70 derived from lymphoid tissues circulates as immune complexes and is deposited in the glomerular mesangial areas. It may be one of the pathogenic antigens involved in renal disease of ddY mice. We examined the deposition of the major retroviral envelope glycoprotein, gp70, in glomeruli of ddY mice by immunofluorescence [6]. Positive staining of gp70 was not observed in glomeruli of our strain of ddY mice at any age examined using two different anti-gp70 antisera and three

**Fig. 1.** Initiation of IgA nephropathy.
different staining conditions, whereas deposition of IgA, IgG and IgM was manifest in mice aged over 40 weeks. It appears that gp70 deposition may not be sine qua non for the pathogenesis of IgA nephropathy, and that ddY mice may have a heterogeneous genetic background, resembling the situation in humans.

Genetic factors are considered to be involved in the initiation and progression of IgA nephropathy on the basis of racial differences in prevalence and familial aggregation. It has been hypothesized that susceptibility genes for IgA nephropathy can be detected by a genome-wide scan using this model [7]. First, serial renal biopsies were performed at 20, 40 and 60 weeks of age in 361 ddY mice. The ddY mice were classified into three groups on the basis of onset of glomerular injury as follows: early onset at 20 weeks (31.9%), late onset at 40 weeks (37.9%) and quiescence at 60 weeks (30.2%). The severity of glomerular lesions in both onset groups correlated with the intensity of glomerular IgA deposition but not with serum IgA levels. A genome-wide scan using 270 microsatellite markers identified three chromosomal regions on chromosomes 1, 9 and 10, which were significantly associated with the glomerular injuries. Surprisingly, the peak marker D10MIT86 on chromosome 10 is located on the region syntenic to human 6q22–23 with IGAN1, which might be responsible for familial IgA nephropathy [7]. In addition, D1MIT16 on chromosome 1 was located very close to the locus of the selectin gene, which is a known candidate for human IgA nephropathy. It appears that the three-group ddY mouse model can be a useful tool for identifying susceptibility genes and also for examining their roles in the pathogenesis of IgA nephropathy.

**Mechanisms of Progression in IgA Nephropathy**

Factors previously reported to be associated with disease progression include male sex, age, prolonged duration, nephrotic range proteinuria, hypertension and glomerular sclerosis in patients with IgA nephropathy. Other developmental and/or exacerbating factors for patients with IgA nephropathy are: (1) complement activation; (2) blood coagulation activity and/or its inhibition in plasma; (3) activity of cytokines/growth factors; (4) activity of reactive oxygen species (ROS); (5) activation of adhesion molecules; (6) apoptosis; (7) podocyte injury (loss) and (8) interstitial mast cell infiltration (fig. 2). Among them, podocyte injury and interstitial mast cell infiltration from our data are reviewed in this chapter.

**Loss of Glomerular Epithelial Cells (Podocytes)**

It is widely assumed that glomerular mesangial cell proliferation and mesangial expansion represent major pathological mechanisms underlying
progression to glomerular sclerosis. Marked glomerular mesangial expansion is accompanied by a further increase in total glomerular volume. Broadening of the podocyte foot processes is associated with a reduction in the number of podocytes per glomerulus and an increase in the surface area covered by the remaining podocytes. Podocyte loss appears to contribute to progression of IgA nephropathy. Hypotheses concerning the cause of podocyte loss are: (a) glomerular hypertrophy and hypertension may cause podocyte injury, and (b) mesangial expansion beyond some critical point can presumably cause closure of capillary loops and obliteration of the podocytes [8]. Morphological studies on experimental models of progressive glomerular disease have identified the detachment of podocytes from the glomerular basement membrane (GBM) as a critical step in the development and progression of glomerulosclerosis. Several molecular mechanisms for the detachment have been proposed, including reorganization of the actin cytoskeleton in podocytes, apoptosis of podocytes and oxidation of the GBM [9]. To predict progression in patients with IgA nephropathy, we analyzed glomerular lesions except for sclerosis, adhesion and/or crescents in 34 patients with this disease by morphometric analysis. Levels of urinary protein excretion, creatinine clearance (Ccr), serum creatinine (sCr) and mean blood pressure at the time of renal biopsy were used as clinical parameters. The slope of $1/sCr$ was also used as a prognostic parameter. Renal

*Fig. 2. Progression of IgA nephropathy.*
specimens were obtained by echo-guided biopsy. In PAS-stained light microscopic renal sections, three mid sections of open glomeruli were selected and photographed. Stereologic estimation was performed as follows: absolute values of glomerular volume \( V(G) \), glomerular surface area \( S(G) \), podocyte and nonpodocyte cell number per glomerulus \( N(G(pod)) \) and \( N(G(Non-pod)) \), glomerular surface area covered by one podocyte \( S(G)/N(G(pod)) \) and glomerular volume occupied by one nonpodocyte cell \( V(G)/N(G(Non-pod)) \). There was a significant correlation between the levels of urinary protein excretion and the change of podocyte injury parameters \( N(G(pod)) \) and \( S(G)/N(G(pod)) \) or \( N(G(Non-pod)) \). \( N(G(pod)) \) was negatively correlated but \( S(G)/N(G(pod)) \) and \( N(G(Non-pod)) \) were positively correlated with urinary protein excretion. \( S(G)/N(G(pod)) \) and \( N(G(Non-pod)) \) were correlated with mean blood pressure. \( N(G(pod)) \), \( S(G)/N(G(pod)) \), \( N(G(Non-pod)) \), urinary protein excretion and mean blood pressure were significantly correlated with the slope of \( 1/sCr \). High specificity was observed for \( N(G(pod)) \), \( S(G)/N(G(pod)) \) and \( N(G(Non-pod)) \) urinary protein excretion. It appears that podocyte injury might provide additional prognostic information in patients with IgA nephropathy [10]. Further examinations are warranted to calculate the number of podocytes by electron microscopy to detect the outcome in patients with IgA nephropathy.

**Interstitial Mast Cell Infiltration**

Mast cells (MC) are derived from hematopoietic progenitors and migrate into inflammatory lesions. Human MC can be classified into two types according to their protease composition: those containing only tryptase (MC(T)) and those containing both tryptase and chymase (MC(TC)) [11]. MC(T) may play a role in immunological responses, whereas MC(TC) seem to play roles in angiogenesis and tissue remodeling. The role of MC in renal inflammatory and fibrotic processes has recently attracted considerable attention. Although the mechanism of the protection provided by MC is poorly understood, hormonal mediators released from MC are thought to protect against interstitial fibrosis. Heparin, e.g., is one of the molecules released by the secretory granules of MC and is well known for its anticoagulant activity and inhibition of the production of TGF-\( \beta \).

MC have been observed in the renal interstitium of patients with primary glomerular diseases. Their levels increase with progression of tubulointerstitial fibrosis in patients with IgA nephropathy. Kurusu et al. [12] reported that the number of MC in non-fibrotic tubulointerstitial fields can be a predictor of the renal prognosis of patients with IgA nephropathy. In vitro studies have revealed that MC also produce inflammatory mediators other than histamine, such as
fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). Accordingly, MC are assumed to contribute to the development of renal interstitial fibrosis in humans. Angiotensin II (Ang II) is closely involved in the pathogenesis of renal fibrosis and is generated by chymases as well as by angiotensin converting enzyme (ACE). It has been suggested that ACE works mainly in intravascular areas, while chymases work mainly in extravascular areas. Human MC have one α-chymase, which generates Ang II by cleaving the terminal His and Leu residues from Ang I, whereas rodents express various kinds of β-chymase [13]. Rat β-chymase destroys Ang II by cleaving it between Tyr⁴ and Ile⁵, but the mouse β-chymase MC protease 4 (mMCP-4) generates Ang II in the same way as human α-chymase [14]. Sakamoto-Ihara et al. investigated whether human MC contribute to renal fibrosis through local activation of the renin-angiotensin system by assessing their numbers in renal biopsy specimens from patients with IgA nephropathy or minimal change nephrotic syndrome (MCNS). In patients with IgA nephropathy and MCNS, the numbers of tryptase-positive MC (MC(T)) and MC positive for both tryptase and chymase (MC(TC)) were examined histopathologically. sCr, mean blood pressure and the severity of glomerular and tubulointerstitial lesions were also determined. MC(TC) numbers differed between IgA nephropathy patients and MCNS patients. IgA nephropathy patients had more MC(TC) than MC(T). MC were found around but not in the conglomerate of Ang II-positive infiltrating cells. In IgA nephropathy patients with the most severe pathology, the number of Ang II-positive cells was correlated with that of MC(TC) and MC(T). It appears that chymase-dependent Ang II synthesis due to human MC may be involved in the inflammatory and fibrotic processes of IgA nephropathy (submitted).

References


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Treatment for IgA Nephropathy

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Abstract

The Committee on IgA nephropathy in Japan has published new clinical guidelines (2nd edition) for the diagnosis and treatment of patients with this disease. The nonspecific therapeutic approach involves a reduction of dietary intake of protein in patients with IgA nephropathy who have developed renal failure. At present, the most important therapeutic goal in patients with IgA nephropathy is the control of hypertension. It has been assumed that removal of tonsillar tissues might reduce the production of polymeric IgA and decrease the frequency of renal parenchymal damage resulting from episodes of macroscopic hematuria and proteinuria. Although there have been no randomized controlled trials (RCT) of tonsillectomy, these are necessary to determine the efficacy of tonsillectomy in patients with IgA nephropathy.

Current Strategy of Treatment in Patients with
IgA Nephropathy in Japan

Nonspecific therapeutic approach involves reduction of dietary intake of protein in patients with IgA nephropathy who have developed renal failure. Long-term dietary restriction is generally considered to reduce the levels of urinary protein and ameliorate glomerular injuries in patients with IgA nephropathy.

Previous approaches to drug therapy of IgA nephropathy in Japan have included anti-platelet drugs, anticoagulants, prednisolone (PSL), immunosuppressants, fish oil, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB) and/or tonsillectomy. At present, the most important therapeutic goal in patients with IgA nephropathy is the control of hypertension. Blood pressure of less than 130/80 mm Hg is the therapeutic target in patients with IgA
nephropathy. Patients with more or less normal renal function, with or without proteinuria or hypertension, have been preferably treated with ACE inhibitors. Several investigators reported that ACE inhibitors reduce the levels of urinary protein excretion and preserve renal function on patients with IgA nephropathy. Furthermore, ACE inhibitors are recommended on the basis of their beneficial effects on the production of cytokines and extracellular matrix (ECM) components, even when hypertension is not present. ACE inhibitors are generally considered to have cardiac and renal protective actions, and they may improve glomerular hypertension due to dilatation of efferent arterioles in the kidneys and suppress glomerular sclerosis. Pulse therapy with high-dose corticosteroids has not been accepted in patients with IgA nephropathy, except in cases presenting as rapidly progressive glomerulonephritis characterized histologically by necrotizing and/or crescent formation, because the majority of patients with IgA nephropathy have an indolent course.

Tonsillectomy has been applied in patients with IgA nephropathy for two reasons [1]. First, tonsillar lymphocytes from patients with IgA nephropathy have been found to produce more polymeric IgA than healthy controls. Second, tonsillitis is a frequent precipitating event leading to macroscopic hematuria and, frequently, glomerular crescent formation, acute tubular injury, and/or a reduction in glomerular filtration rate (GFR). As a result of these observations, it has been assumed that removal of tonsillar tissues might reduce the production of polymeric IgA and decrease the frequency of renal parenchymal damage resulting from episodes of macroscopic hematuria [1].

The macroscopic hematuria seen in IgA nephropathy is commonly precipitated by mucosal stimulation (e.g. pharyngitis) suggesting the possibility of aberrant mucosal immunity in the pathogenesis of IgA nephropathy. The tonsils are also a significant source of under-glycosylated IgA1, implicated in the pathogenesis of IgA deposition. Tonsillectomy also decreases the levels of serum IgA. However, there have been no randomized controlled trials (RCT). No recommendations can be made regarding tonsillectomy for disease progression in patients with IgA nephropathy on the basis of currently available retrospective studies and case reports in Kidney Disease Outcomes Quality Initiatives, UK Renal Association, European Best Practice Guidelines, International Guidelines and CARI (Caring for Australasians with Renal Impairment) Guidelines [2]. The Canadian Society of Nephrology guidelines state that tonsillectomy could reduce proteinuria and hematuria in IgA nephropathy patients with recurrent tonsillitis. Tonsillectomy should be performed in patients with appropriate ENT (ear, nose, and throat) indications. Controlled trials are needed before tonsillectomy should be considered for any other group.

Kano et al. in my division investigated toll-like receptor (TLR) expression in tonsils from IgA nephropathy and determined their cell types. It is suggested