

# Pathogenesis of IgA Nephropathy

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**Immunoglobulin A (IgA) nephropathy is an immune-complex-mediated glomerulonephritis characterized by the presence of immunoglobulin A deposits in mesangial and paramesangial regions. The patients with IgA nephropathy present with varying clinical symptoms (eg, microhematuria with preserved renal function or progressive deterioration of renal functions resulting in end-stage renal disease). The factors involved in the pathogenetic mechanisms of IgA nephropathy include (1) environmental factors, (2) genetic factors, (3) abnormality of the IgA1 molecule, and (4) various inflammatory mediators. The gene polymorphism studies for human leukocyte antigen (HLA), renin-angiotensin-aldosterone system, and selectin gene clusters, suggest a certain degree of genetic predisposition in patients for IgA nephropathy. Also, the genome-wide screening in familial IgA nephropathy showed linkage of IgA nephropathy to the 6q22-23 chromosome. Besides genetic influence in its pathogenesis, aberrant galactosylation in serum IgA and IgA1 eluted from kidneys with IgA nephropathy has been observed, and conceivably such abnormalities induce the expression of various cytokines, interleukin (IL)-6, platelet-derived growth factor (PDGF), tumor necrosis factor (TNF)- $\alpha$ , and transforming growth factor (TGF)- $\beta$ 1 in the renal cells, which contributes to further glomerular injury. Despite an enormous amount of information available in the literature, further studies are needed to delineate the precise pathogenetic mechanisms involved in primary IgA nephropathy and also to facilitate the development of newer therapeutic interventions.**

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**I**MMUNOGLOBULIN A (IgA) nephropathy is an immune-complex-mediated glomerulonephritis characterized by the presence of immunoglobulin A deposits in mesangial area and the patients manifest with varying clinical features (eg, recurrent microhematuria with preserved renal function or progressive deterioration of renal function resulting in end-stage renal disease). For many years after the description of IgA nephropathy by Berger and Hinglais in 1968, IgA nephropathy basically was considered to be a benign condition; however, it is now recognized that 15% to 40% of patients eventually will develop end-stage renal disease.<sup>1</sup> Epidemiologic studies suggest its prevalence to be higher in Asia, Australia, Finland, and Southern Europe (20% to 40% in a series of total renal biopsy examinations) and lower in the United Kingdom, Canada, and the United States (2% to 10%).<sup>1</sup> The significant differences of prevalence may be owing partly to renal biopsy practice; for example, in Japan, the recurrent microhematuria routinely is screened in school-aged children, and in adults renal biopsy procedure is frequently per-

formed in patients with microhematuria and mild proteinuria.

Paramount to the pathogenesis of IgA nephropathy are the environmental and genetic differences that can explain the regional differences in disease prevalence and give us some clues as to the development and progression of IgA nephropathy. In this article, we summarize molecular pathobiology of IgA nephropathy, with emphasis on environmental and genetic factors, abnormality of the IgA molecule, and various inflammatory mediators that are involved in its progression to end-stage renal disease.

## ENVIRONMENTAL FACTORS

The pathogenesis of primary IgA nephropathy remains unknown, and no consistent causative infectious organism or environmental agents have been identified. The onset of the disease frequently is associated with upper respiratory infections such as *Haemophilus parainfluenzae*, and its colonization in respiratory mucosa may be related to the development of IgA nephropathy. Suzuki et al<sup>2-5</sup> reported the glomerular deposition of outer membrane antigens of *H. parainfluenzae* (OMHP) and the presence of IgA-class antibody against OMHP in patients with IgA nephropathy. They also found that the administration of OMHP antigens orally or intraperitoneally into C3H/HeN mice resulted in glomerular deposition of OMHP antigens from 30 or 40 weeks of age and levels of IgA antibodies against OMHP were increased significantly compared with controls. In addition, there was a significant correlation between mesangial prolifera-

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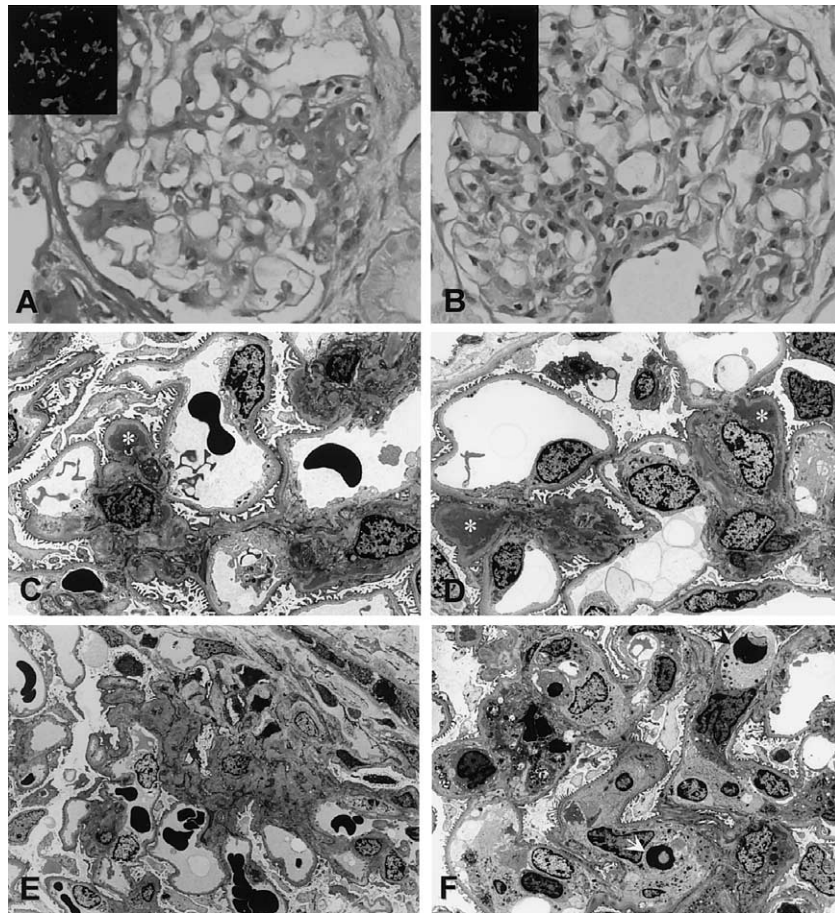
tion and glomerular deposition of IgA.<sup>6</sup> In regard to treatment, tonsillectomy may be beneficial, but further comprehensive studies are needed to attest to this assertion and so is the case for the potential use of antibiotics in anti-OMHP antibody-positive IgA nephropathy patients. Another relevant environmental factor is gluten, which commonly is found in food, and it has been postulated to be involved in the development of IgA nephropathy. The finding of increased levels of IgA against food antigens in patients with IgA nephropathy suggested its potential association with celiac disease.<sup>7</sup> Attention was directed initially to anti-gluten antibodies, then to IgA anti-endothelial antibodies (IgA-EMA).<sup>8</sup> Pierucci et al<sup>8</sup> reported that 16 of 36 patients with IgA nephropathy (44.4%) showed EMA positivity. Among patients with positive EMA, 12 patients were IgG1-EMA positive, 2 patients were IgA-EMA positive, and 2 patients were positive for both isotypes. The role of a gluten-free diet in the natural history of IgA nephropathy, at least in EMA-positive patients, needs to be investigated further in terms of patients' management.

#### GENETIC FACTORS

IgA nephropathy generally is considered to be a nonfamilial disorder; however, there have been many studies reporting the familial clustering of the disease, and several lines of evidence suggest a genetic predisposition to develop IgA nephropathy. Julian et al<sup>9</sup> evaluated familial aggregation of IgA nephropathy in patients derived from central and eastern Kentucky. The pedigrees included 14 patients and an additional 17 members of the pedigrees had clinical glomerulonephritis; autopsy examination revealed another 6 with chronic nephritis. Familial nature of this disease is strengthened further by studies on patients with Henoch-Schönlein purpura. It has been reported that a family member of a given patient with Henoch-Schönlein purpura has increased incidence of developing either IgA nephropathy or the full-blown system form of disease, suggesting that the genetic background or similar environmental factors may lead to development of both diseases.<sup>10,11</sup> In addition, the histologic findings of IgA nephropathy and purpura nephritis may be indistinguishable from primary IgA nephropathy and it indicates that Henoch-Schönlein purpura is a systemic form of the same disease process (Fig 1).

#### IMMUNOGENETIC STUDIES RELATED TO HUMAN LEUKOCYTE ANTIGEN

Several reports indicated the familial occurrence of patients with IgA nephropathy, and a strong association with human leukocyte antigen (HLA)-BW35 have been observed in these patients.<sup>12-14</sup> Similarly, comparison of HLA between the familial and sporadic form of IgA nephropathy revealed an increased incidence of HLA-DRB1\*08 in familial IgA nephropathy in an Italian population<sup>15</sup>; however, other reports failed to show such association.<sup>9,16</sup> Also, a weak link between the patients with the sporadic form of IgA nephropathy and certain HLA antigens has been described. Li et al<sup>17</sup> reported the possible association of the DQw7 allele at the DQB1 locus with susceptibility to IgA nephropathy in Caucasians. Here again the ethnic background and differences and differential prevalence of HLA locus has been reported. Fennessy et al<sup>18</sup> reported a decreased frequency of DQB1\*0201 in patients from Britain ( $P = .008$ ) and similarly of DQB1\*0602 in Finnish patients ( $P = .01$ ). But in Italian patients no association between DQ markers and IgA nephropathy was observed. Matthews et al<sup>19</sup> investigated the hypothesis that alternative alleles of one or more genes in the central major histocompatibility complex predispose carriers to IgA deficiency or IgA nephropathy. Australian Caucasian patients and controls were typed at HLA loci, single nucleotide polymorphisms, and microsatellites in the major histocompatibility complex. Alleles of the D6S273 microsatellite exhibited strong associations with IgA deficiency and IgA nephropathy. D6S273\*129 and \*139 were more frequent in IgA deficiency and less frequent in control cohort subjects of IgA nephropathy. The reverse was true for D6S273\*133 and \*131.<sup>19</sup> Akiyama et al<sup>20</sup> analyzed the extent of linkage disequilibrium in the region of chromosome 6p21.3 in a Japanese population and noted extended linkage disequilibrium blocks within the class II locus. They designed a case-control association study of single-nucleotide polymorphisms (SNPs) in each of those linkage disequilibrium blocks, and determined that SNPs located in the HLA-DRA gene were associated significantly with an increased risk for IgA nephropathy ( $P = .000001$ ; odds ratio = 1.91; 95% confidence interval, 1.46-2.49).



**Fig 1. IgA nephropathy and purpura nephritis in brothers.** Two Japanese 18-year-old men developed anaphylactoid purpura in the lower extremities, abdominal pain, microhematuria, and nephrotic syndrome. (A, inset) Renal biopsy examination revealed typical deposition of IgA with mesangial pattern by immunofluorescence, and mesangial proliferative lesions are seen associated with adhesion to Bowman's capsule (periodic acid-Schiff stain). Electron microscopic examination revealed hemispheric electron dense deposits in the (C) mesangial area, and (E) segmental sclerotic lesions associated with proliferation of Bowman's epithelial cells and fibrosis. His elder brother also manifested with microhematuria and mild proteinuria, while he did not develop purpura. (B, inset) Renal biopsy examination revealed that he also had IgA deposition in the mesangial area, and proliferation of mesangial cells and expansion of mesangial matrix is also seen (periodic acid-Schiff stain). Electron microscopy revealed typical mesangial electron dense deposits of IgA (D). Interestingly, proliferative lesions are associated with prominent apoptotic bodies (arrow, A), which usually is not found in IgA nephropathy but in purpura nephritis, although the elder brother did not develop anaphylactoid purpura. The cases suggest that common genetic susceptibility may exist in the pathogenesis of IgA nephropathy and anaphylactoid purpura.

#### GENE POLYMORPHISM OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The study of polymorphism of the angiotensin-converting enzyme (ACE) gene consisting of insertion (I) or deletion (D) of a 287-bp DNA fragment revealed that DD phenotype deletion polymorphism in the ACE gene, particularly the homozygote DD, is a risk factor for progression to chronic renal failure in IgA nephropathy. Moreover, this deletion polymorphism predicts the ther-

apeutic efficacy of ACE inhibition on proteinuria and, potentially, on progressive deterioration of renal function.<sup>21-23</sup> In addition to the ID polymorphism of the ACE gene, Pei et al<sup>24</sup> examined whether the M235T polymorphism of the angiotensinogen gene and the A1166C polymorphism of the angiotensin II type 1 receptor gene may be associated with disease progression in 168 Caucasian patients with IgA nephropathy. They found that patients with the angiotensinogen MT and TT

genotypes had a faster rate of deterioration of creatinine clearance than those with the MM genotype and, similarly, patients with angiotensinogen MT and TT genotypes had higher maximal values of proteinuria than those with the MM genotype. Neither the ACE I/D nor the angiotensin II type I A1166 gene polymorphism was associated with disease progression or proteinuria in univariate analysis. Multivariate analysis, however, detected an interaction between the angiotensinogen and ACE gene polymorphisms with the presence of ACE/DD polymorphism adversely affecting disease progression only in patients with the angiotensinogen/MM genotype.<sup>24</sup>

#### SNPS IN THE SELECTIN GENE CLUSTER

The accumulation of leukocytes in glomeruli and renal interstitium play a key role in the progression of various forms of glomerulonephritis and diabetic nephropathy. Selectins are involved in rolling action of leukocytes on the surface of endothelial cells and Takei et al<sup>25</sup> designed a case-control association study that was based on linkage disequilibrium among SNPs in the selectin gene cluster on chromosome 1q24-25. They found 2 SNPs in the E-selectin gene (SELE8 and SELE13) and 6 SNPs in the L-selectin gene (SELL1, SELL4, SELL5, SELL6, SELL10, and SELL11) that were associated significantly with IgA nephropathy in Japanese patients.<sup>25</sup>

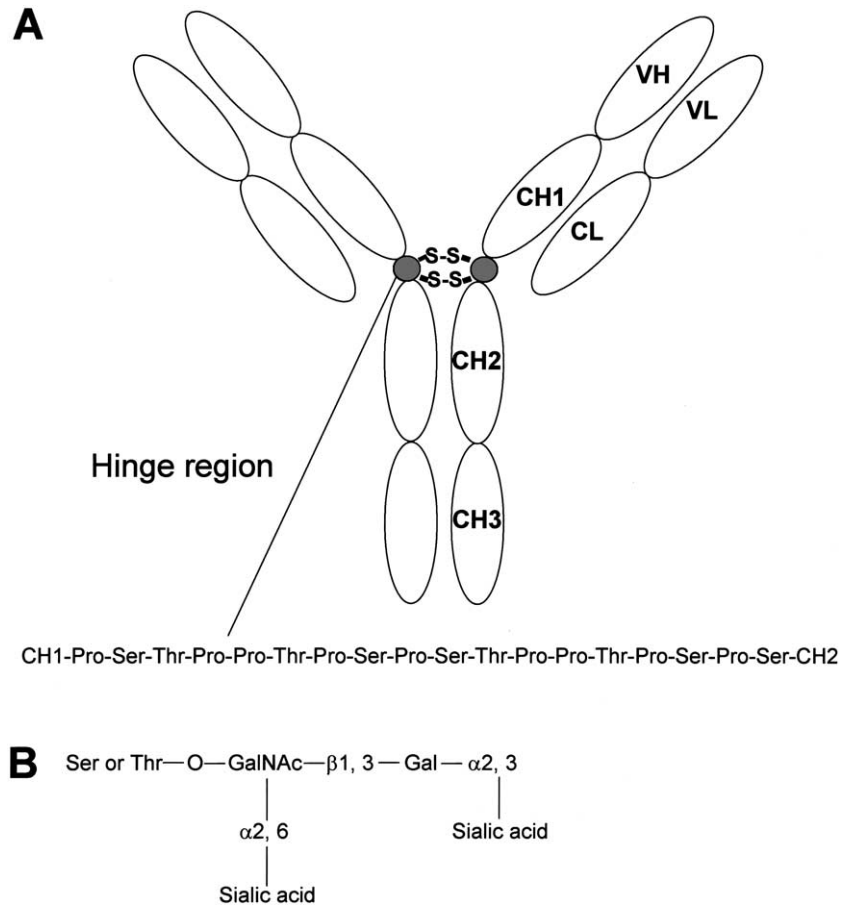
#### GENOME-WIDE SCREENING OF THE SUSCEPTIBILITY GENES

Although IgA nephropathy generally is not considered a hereditary disease, striking ethnic variation in prevalence and familial clustering, along with subclinical renal abnormalities among relatives of IgA nephropathy, suggests the existence of undefined IgA nephropathy susceptibility genes. By genome-wide analysis of linkage in 30 multiplex IgA nephropathy kindred from Italy and the United States, Gharavi et al<sup>26</sup> show linkage of IgA nephropathy to 6q22-23, a 6.5-cM region bounded by the D6S1702 and D6S262 polymorphic markers, under a dominant model of transmission with incomplete penetrance, with a LOD score of 5.6 and 60% of kindred linked.

#### ABNORMALITIES OF IGA MOLECULE

In humans, 2 isotype subclasses of IgA, IgA1 and IgA2, are produced and a predominant expres-

sion of IgA1 in mesangial deposits, serum, and bone marrow culture supernatants has been shown in IgA nephropathy.<sup>27</sup> Furthermore, an excess of  $\lambda$  light chains in both mesangial deposits and serum IgA has been observed, and IgA isotype dysregulation is confined to the bone marrow compartment.<sup>27,28</sup> In addition to the overproduction of IgA1 mainly in bone marrow, the abnormalities of glycosylation of IgA1 molecules were investigated extensively. A notable feature of IgA1 is the presence of multiple O-glycosylation sites within the hinge region and these sites are not present in other immunoglobulins. Both serum and eluted IgA1 from kidneys with IgA nephropathy revealed a reduced content of galactose and sialic acid (Fig 2).<sup>29-32</sup> Allen et al<sup>33</sup> measured the activity of  $\beta$ 1,3 galactosyltransferase, an enzyme responsible for galactosylation of O-linked sugars. They showed that B cell lysates in IgA nephropathy had significantly lower  $\beta$ 1,3 galactosyltransferase activity than controls. Furthermore, B cell  $\beta$ 1,3 galactosyltransferase activity showed a negative correlation with WGA lectin binding of serum IgA in patients with IgA nephropathy, WGA binding being specific for ungalactosylated moieties.<sup>33</sup> Recent studies suggest the presence of novel IgA receptors in mesangial cells (MCs). MCs bind both monomeric and aggregated IgA1; however, the activation of mesangial cells, revealed by *c-jun* expression, was dependent on the aggregation of the IgA1 molecule. These processes are independent of Fc $\alpha$ R1 (CD89), suggesting the presence of a new IgA receptor on mesangial cells.<sup>34</sup> Novak et al<sup>35</sup> also investigated the interactions of the circulating immune complexes, composed of galactose-deficient IgA1 and IgG or IgA1 antibodies specific for the galactose-deficient IgA1, with MCs. The binding by MCs appeared to be restricted to IgA1 or asialo-IgA1 and was not Ca<sup>2+</sup> dependent. Furthermore, MCs and HepG2 cells internalized and catabolized IgA1-containing circulating immune complexes. By using reverse-transcription polymerase chain reaction with asialoglycoprotein receptor- or CD89-specific primers, messenger RNAs of the 2 respective genes were not detected, thus internalization of circulating immune complexes is mediated by the receptors different from CD89 or asialoglycoprotein receptor and had a higher affinity for IgA-circulating immune complexes than for uncomplexed IgA.



**Fig 2.** The structure of (A) IgA1 molecules and the structure of (B) O-linked carbohydrates within the hinge region of normal IgA1. The IgA heavy chain contains the hinge region between CH1 and CH2. N-acetyl glucosamine (galactose NAc) is O-linked to serine (Ser) and threonine (Thr) residues within the hinge region of IgA molecule. Sialic acid is linked to galactose (Gal) through  $\beta 2, 3$  link and to GalNAc through  $\beta 2, 6$  link. CH1, CH2, and CH3, constant regions of the heavy chain; VH, variable region of the heavy chain; CL, constant region of the light chain; VL, variable region of the light chain.

#### MEDIATORS OF PROGRESSION OF IGA NEPHROPATHY

##### Mannose Binding Protein

Once IgA1 is deposited in the kidney, IgA1-containing immune complex induces various types of cytokine expression. Amore et al<sup>36</sup> reported that IgA glycoforms of IgA nephropathy patients were associated with increased exposure of mannose, suggesting a defective N-linked glycosylation. Mannose binding protein and mannose binding protein-associated serine protease, namely MASP-1, were detected in mesangial deposits and were associated with C3b/C3c and C5b-9 but not with IgG, IgM, C1q, C4c, or properdin.<sup>37,38</sup> The lectin pathway, which is initiated by mannose binding protein and MASP, is one of the possible routes to activate the complement cascade in IgA nephropathy.<sup>39,40</sup> Recently, Hisano et al<sup>41</sup> found that alternative pathway-involved complement activation is associated with mesangial deposits of

IgA1 alone in patients with IgA nephropathy, whereas in the patients with mesangial deposits of IgA1 and IgA2, both the alternative and lectin pathways were involved in complement activation.

##### Interleukin 6

Libetta et al<sup>42</sup> reported that incubation of mesangial cells with serum of patients with IgA nephropathy increased the average interleukin (IL)-6 release from 8.5 pg/mL to 274.1 pg/mL. Adsorption in  $\beta$ -D-glucose and N-acetyl-D-glucosamine caused a decrease in the activity of patients' serum, to 17.0 and 63.7 pg/mL, respectively. Thus, the serum of IgA nephropathy patients contains specific lectins that stimulate IL-6 release by mesangial cells.<sup>42,43</sup> Furthermore, soluble IgA aggregates are catabolized by cultured rat mesangial cells and induce production of tumor necrosis factor (TNF)- $\alpha$  and IL-6, and proliferation of mesangial cells.<sup>44</sup> IL-6 is produced by human mesangial and

tubular cells, and its urinary levels have been proposed as a marker of mesangial proliferation and tubulointerstitial damage<sup>45</sup> as well as a prognostic predictor.<sup>46</sup> The degree of histologic damage increased with the positive rates of platelet-derived growth factor (PDGF), IL-6, or IL-6 receptor and the number of PCNA-positive cells in the glomeruli. They also reported that, in the IL-6 receptor-positive patients, total urinary protein excretion, serum creatinine, urinary  $\beta$ 2-microglobulin, and systolic blood pressure were significantly higher than in the IL-6 receptor-negative patients.<sup>47</sup>

#### TNF- $\alpha$

TNF- $\alpha$  is another proinflammatory cytokine that is induced by soluble IgA aggregates in rat mesangial cells.<sup>44</sup> Total TNF and IL-6 levels have been increased in IgA nephropathy in patients before therapy and usually become normalized after immunoglobulin therapy. Although levels of soluble TNF receptor of type I (sR55) and type II (sR75) increased after immunoglobulin therapy. These data suggest that the overproduction of proinflammatory cytokine is unbalanced by their natural antagonists in IgA nephropathy and Henoch-Schönlein syndrome.<sup>48</sup>

#### PDGF

PDGF also is implicated in the proliferation of mesangial cells and in IgA nephropathy patients.<sup>49</sup> Compared with normal control kidneys, an increased expression of PDGF-BB/PDGF- $\beta$  receptor messenger RNAs and the corresponding proteins were observed in all biopsy specimens with IgA nephropathy.<sup>50,51</sup> Interestingly, the up-regulation was related to the degree of glomerular proliferation and the extent of fibrosing interstitial lesions.<sup>50,51</sup>

#### Transforming Growth Factor- $\beta$ 1

TGF- $\beta$ 1 has been implicated in the fibrosing process of various renal diseases, especially in diabetic nephropathy. In IgA nephropathy, renal localization of TGF- $\beta$ 1 correlates with the severity of tubulointerstitial damage. In patients with significant proliferative glomerular lesions and minor tubulointerstitial alterations, TGF- $\beta$ 1 positivity was confined to areas of glomerular proliferation. Whereas in cases with more severe histology including sclerosing lesions, the TGF- $\beta$ 1 immunoreactivity was less prominent.<sup>50</sup> Haramaki et al<sup>52</sup>

found that urinary excretion of total and mature TGF- $\beta$ 1 was reduced in patients with IgA nephropathy after treatment with prednisolone (0.8 mg/kg/d) for 1 month. The activation rate of urinary TGF- $\beta$ 1 also decreased significantly after steroid therapy, suggesting urinary TGF- $\beta$ 1 excretion may be a useful marker to assess disease activity of IgA nephropathy and responsiveness to steroid therapy.

#### Uteroglobin

In IgA nephropathy, high levels of circulating IgA-fibronectin (Fn) complexes, and glomerular deposition of IgA, complement C3, Fn, and collagen are observed. Two independent mouse models (gene knockout and antisense transgenic), both manifesting deficiency of an anti-inflammatory protein, uteroglobin, developed similar lesions as seen in human IgA nephropathy.<sup>53</sup> They further showed that Fn-uteroglobin heterodimerization prevented abnormal glomerular deposition of Fn and collagen, and abrogated both the formation of IgA-Fn complexes and their binding to glomerular cells.<sup>53</sup> In human IgA nephropathy, the single nucleotide polymorphism at the 38th nucleotide (A to G) from the transcription initiation site of uteroglobin exon 1 affected the progression of IgA nephropathy by modulating the level of uteroglobin expression, and GG genotype may be a genetic marker for rapid disease progression to end-stage renal failure, especially in the IgA nephropathy patients with heavy proteinuria or high blood pressure.<sup>54-57</sup>

#### CONCLUSIONS

Because the etiology of IgA nephropathy still is unknown, specific, effective and curable treatment is not available for patients with IgA nephropathy. To slow the progressive deterioration and preserve renal functions, several treatments, such as ACE inhibitors, corticosteroids, n-3 polyunsaturated fatty acids, and tonsillectomy,<sup>58,59</sup> are available in clinical practice. To develop the curable and effective therapeutic modalities, the elucidation of molecular mechanism of IgA nephropathy would be essential. Both the genetics and molecular biology approaches are in progress as briefly summarized in this article and such efforts would enhance our understanding of the etiology and pathogenesis of primary IgA nephropathy further.

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