http://www.revistanefrologia.com

short review

Progress in understanding the pathogenesis of IgA nephropathy: New perspectives for the near future?

A. Segarra

Nephrology Department. Vall d'Hebron Hospital. Barcelona, Spain

Nefrologia 2010;30(5):501-7

doi:10.3265/Nefrologia.pre2010.Jul.10526

ABSTRACT

Progress in understanding the pathogenesis of IgA nephropathy has shown that probably there is no a single IgA nephropathy with the same pathogenic mechanism, clinical course and response to therapy. The evidence currently available suggests the existence of at least two possible mechanisms of IgA deposition in the renal mesangium. In a small percentage of patients, mesangial deposition of IgA1 colocalizes with secretory component, indicating that the deposited IgA1 in glomeruli originates completely or partly in the mucose-associated lymphoid tissue. This deposition pattern has been associated with activation of complement by the lectin pathway and has been associated with a worse prognosis, although this last statement needs to be confirmed in long-term studies. The mechanisms responsible for secretory IgA deposition are not known. In the majority of patients with IgA nephropathy secretory component is not detectable in the mesangium. In these cases, the presence of elevated circulating levels of galactose-deficient IgA, produced by bone marrow plasma cells would be a predisposing factor but not sufficient to induce nephropathy. To produce kidney disease, galactose-deficient IgA1 must be deposited in the renal mesangium, and once there, either by interaction with specific receptors (CD71?), by direct activation of complement or by being the target of an IgG autoimmune response anti-IgA, induce activation, proliferation and increased mesangial matrix synthesis and eventually cell injury. In parallel, galactose-deficient IgA, through interaction with the RR Fc alpha/gamma, may activate circulating lymphocytes and monocytes and enhance their response to chemoattractants produced by the mesangial cell, causing, thus, the inflammatory infiltrate to initiate and maintain the interstitial injury. In the next few years, advances recently added to the knowledge of the pathogenesis of nephropathy IgA1 could provide new variables that allow walking in the direction of having a classification of patients based not only in clinical and morphological criteria but also having a greater pathogenic basis.

Key words: Biomarkers. IgA nephropathy. Pathogenesis

Correspondence: Alfons Segarra Medrano
Servicio de Nefrología. Hospital Vall d'Hebron.
P.º Vall d'Hebron, 119-129. 08035 Barcelona. Spain.
alsegarr@gmail.com

Avances en el conocimiento de la patogenia de la nefropatía IgA: ¿nuevas perspectivas para un futuro inmediato?

RESUMEN

El avance en el conocimiento de la patogenia de la nefropatia IgA ha puesto de manifiesto que, probablemente, no hay un solo tipo de nefropatía IgA con mecanismo patogénico, curso clínico y respuesta al tratamiento únicos. Las evidencias disponibles en la actualidad sugieren la existencia de, al menos, dos mecanismos posibles de depósito de IgA en el mesangio renal. En un pequeño porcentaje de enfermos, el depósito mesangial de IgA1 colocaliza con componente secretor, lo que indica que la IgA1 depositada en el glomérulo se origina total o parcialmente en el tejido linfoide asociado a mucosas. Este patrón de depósito se ha asociado con la activación del complemento por la vía de las lectinas y se ha relacionado con un peor pronóstico, aunque esta última afirmación requiere ser confirmada en estudios a largo plazo. Los mecanismos responsables del depósito renal de IgA secretoria no se conocen. En la mayor parte de los enfermos con glomerulonefritis (GN) IgA no es posible detectar componente secretorio en el mesangio. En estos casos, la presencia de niveles circulantes elevados de IgA deficiente en galactosa, producida por células plasmáticas de la médula ósea (MO), sería un factor de predisposición, pero no suficiente para el desarrollo de nefropatía. Para que se produzca enfermedad renal, la IgA1 gal deficiente debe depositarse en

el mesangio renal y, una vez allí, bien por interacción con receptores específicos (CD71?), por activación directa del complemento o bien por ser la diana de una respuesta autoinmune IgG anti-IgA, inducir la activación, proliferación y aumento de síntesis de la matriz mesangial y, finalmente, la lesión celular. Paralelamente, la IgA1 gal deficiente, a través de la interacción con el RR Fc alfa/gamma linfomonocitario, podría activar los linfocitos y monocitos circulantes y aumentar su respuesta a los quimioatractantes producidos por la célula mesangial, causando, de esta manera, el infiltrado inflamatorio que iniciaría y mantendría la lesión intersticial. En los próximos años, los avances recientemente incorporados al conocimiento de la patogenia de la nefropatía IgA1 podrían proporcionar nuevas variables que permitieran caminar en la dirección de disponer de una clasificación de los enfermos que, además de considerar criterios morfológicos y clínicos tenga una mayor base patogénica.

Palabras clave: *Biomarcadores. Nefropatía IgA. Patogenia*

INTRODUCTION

In the human being, the first B cells with IgA expression initially appear in the 11th week after birth, as opposed to what occurs with IgG and IgM, which appear earlier. The usual serum level of IgA is undetectable at birth and adult levels are not reached until puberty. There are two IgA subclasses: IgA1 and IgA2, which differ because the IgA2 lacks a 13 amino acid sequence of in the "hinge" region. This structural difference explains the resistance of the IgA2 to the bacterial proteases and also why this subtype is more frequent in the mucosae. The IgA is found distributed in the organism in two compartments of different characteristics: the IgA which circulates freely in the plasma and the secretory IgA that is secreted in the mucosae.

In healthy individuals, 95% of the circulating IgA is monomeric IgA1, produced by plasma cells in the bone marrow and released directly into the bloodstream. In contrast, the IgA produced by the plasma cells associated to the mucosal lymphoid tissue is secreted in dimeric form made up of two IgA molecules bound by a chain, known as J-chain. For these dimers to be secreted to the mucosal surface, they should be bound to a specific receptor, the polymeric IgA receptor, present in the basal pole of the epithelial cells. After binding to the receptor, the IgA/RR dimer complex is internalise and transported towards the luminal pole of the epithelial cell. From there, it is released to the mucosal surface, so that the secreted IgA is made up of two IgA chains joined by a J-chain, preserving a fragment of the RR IgA-poly known as secretory component (SC).[1]

IgA nephropathy was described by Berger in 1968 as a glomerular disease characterised by the IgA deposit in the glomerular mesangium, with granular morphology associated to cell proliferation and mesangial matrix; clinically characterised by the presence of microscopic haematuria, associated or not to proteinuria and episodes of macroscopic haematuria.[2]

In Spain, according to the data of the Glomerulonephritis Register at the Spanish Nephrology Society (SEN), this diagnosis is 15% of the total of renal biopsies performed. In adults, this percentage is 17%, glomerulonephritis (GN) being the first cause of kidney disease subjected to biopsy. The annual incidence is estimated at 6-7 cases per million inhabitants.[3]

The IgA GN has a heterogeneous clinical prognosis. In the majority of cases (70%) the prognosis is benign. Some of the patients maintain normal kidney function for many years and approximately 8% manage to reach normal urine analysis levels. However, other patients present evolutions towards kidney failure. Ten percent of patients require kidney replacement therapy (KRT) 5 years after diagnosis and this percentage increases by 15, 20 and 30% at 10, 15 and 20 years respectively. Age, high arterial pressure, the absence of macroscopic haematuria outbreaks, increase in creatinine serum levels, glomerulosclerosis and interstitial fibrosis have a negative impact on the prognosis.[4]

PROGRESS IN IgA NEPHROPATHY PATHOGENESIS

In recent years, progress in understanding the pathogenesis of IgA nephropathy has proven that, probably, there is no one type of IgA nephropathy with a single pathogenic mechanism, case history and response to treatment.

The main hypothesis indicates that the development of the IgA nephropathy can be divided into three main stages: a) IgA deposit in the mesangium; b) generation of the mesangium lesion mediated by the interaction of the IgA1 complexes with specific receptors or through the activation of the complement, and c) progression of the mesangial IgA lesion towards chronic renal failure.[5]

Mesangial IgA deposit

The evidence available indicates that in 15-20% of the patients, the mesangial IgA1 colocalises with the SC, which reveals its total or partial origin from the lymphoid tissue associated to mucosae. The mechanisms responsible for kidney deposit of secretory IgA are unknown. This route coincides with the clinical data that relates the appearance of outbreaks of activity to respiratory tract infections. It has been described that biopsies with positive stain for SC are

frequently also positive for mannose-binding lectin (MBL), L-ficolin and C4d. This stain pattern indicates an activation of the complement through the lectin pathway and some data associates it with a worse prognosis. The reason for the MBL being present in some patients' renal biopsies, but not in all, is unknown. The relation between MBL renal deposits and circulating levels has not been proven, although it has been proven that only the polymeric IgA1 is able to interact with MBL and an association exits between MBL polymorphisms and the clinical pattern of IgA nephropathy, but not with the prognosis.[6-10]

In the majority of patients (70-80%), it is not possible to prove the presence of SC in the mesangium, therefore it is considered that the origin of the mesangial IgA1 are the plasma cells in the bone marrow. The main current hypothesis claims that the initial event in the pathogenesis is the mesangial deposit of an IgA1 with abnormal structure. Given that the renal deposits exclusively contain IgA1, the analysis of the possible structural defects in the IgA1 molecule is centred on the hinge region, present in IgA1 but not IgA2. Currently, the most proven theory is the production of an IgA1 molecule with glycosylation defects. The IgA1 hinge region, between the AA 223 and 240, contains serine and threonine which, under normal conditions, are glycosylated by the union of N-acetylgalactosamine (GalNAc). The Serine or Threonine/GalNAc complex, through the action of the beta-1,3 galactosyltransferase enzyme, incorporates galactose and forms the Gal-GalNAc disaccharide and this, through the action of the alpha-2,3 sialyltransferase enzyme, can incorporate one or two units of sialic acid.[11,12]

Several studies[11-14] have proven that a large number of IgA nephropathy patients presents a glycosylation deficiency in the hinge region of the IgA1 molecule and there is experimental evidence that this structural alteration of the IgA1 could directly affect the pathogenesis of the disease through several different mechanisms. Firstly, the hypoglycosylated IgA1 has the capacity of self-aggregation and forms polymeric aggregates with other IgA1 molecules. Secondly, the IgA1 polymers formed by self-aggregation, after interacting with the Fc alpha receptor on the surfaces of the lymphoid and mononuclear cells, can break its extracellular component and give rise to soluble polymeric IgA RR Fc alpha complexes that are deposited in the mesangium. Lastly, the hypoglycosylated region of the hinge exposes immunogens that generate the production of circulating IgG antibodies, giving rise to immune complexes IgA1 polymeric-IgG. The final result of these processes is the formation of macromolecular and immune complex aggregates that persist in the circulation since they cannot be recognised by the hepatic asialoglycoprotein receptors and are deposited in the renal mesangium due to their affinity to extracellular matrix proteins or through the interaction with specific mesangial receptors.[1,5]

It is considered that the origin of the galactose-deficient IgA are the bone marrow (BM) plasma cells, but there is no information on the factors that control the synthesis and whether it is continuous or only intermittent in response to certain stimuli. Neither is the actual prevalence of galactose-deficient IgA patients known, nor, at present, is there data available on the status of glycosylation of secretory IgA.

The cause of hypoglycosylation is not completely known. There is no evidence to date of mutations or deletions in the DNA which codes the synthesis of the hinge region or transcriptional alterations in the mRNA. The data at hand indicates that it could be due to a post-transcriptional defect. A recent study[15] has proven that the immortalised B-cells of patients with IgA nephropathy produce galactosylation deficient IgA, similar to that found in the renal mesangium. These cells also present reduced activity of beta-1, 3 galactosyltransferase and its chaperone (COSMC). From this data, it has been suggested that premature sialylation of the IgA, as a consequence of an increase in the alpha-2,3 sialyltransferase activity, could block the process of galactose incorporation, which would be also affected by a defect in the activity of beta-1,4 galactosyltransferase and its chaperone (COSMC).[15] However, studies performed to detect the presence of mutations in the genes of the beta-1,3 galactosyltransferase (C1 GALT1) and COSMC are inconclusive.[15-19] On the other hand, although there is evidence that both the alpha-2,6 sialyltransferase as well as the expression of its ST6 GALNA C2 gene are altered in the IgA nephropathy, it has not been proven that the enzymatic activity is increased while, as opposed to that observed in immortalised B-cells,[15] the expression of ST6 GALNA C2 in the B lymphocytes of patients with IgA nephropathy is reduced.[21] In recent studies,[21] an association has been described between two gene haplotypes that codify both galactosyltransferases (C1 GALT1/ST6 GALNA C2) and predisposition to IgA nephropathy. Similarly, it has been proven that the glycosylation defect is hereditary.[22] However, the presence of hypoglycosylated IgA cannot explain the appearance of nephropathy on its own, given that direct family members of IgA nephropathy patients present high levels of Gd IgA1 but do not develop nephropathy.[22] Accordingly, the presence of high levels of Gd IgA1 are considered an alteration that bestows higher risk of suffering IgA nephropathy, but is not sufficient to develop it. Another aspect to keep in mind is that in approximately 20% of IgAN patients no galactose-deficient IgA1 levels are detected. In these cases, the mechanisms that cause the renal deposit of IgA are unknown.

Activation and/or lesion to the mesangial cell by deposited IgA1

The second step necessary to the development of IgA nephropathy is the interaction of the IgA1 deposits with the

mesangial cells. The result of this interaction is the proliferation of mesangial cells, the increase in mesangial matrix synthesis and/or cellular lesion.

Two possible mechanisms of renal lesion have been identified that could operate either individually or simultaneously:

1. Polymeric IgA1 interaction with specific mesangial receptors.

2 Complement system activation through the traditional route, the alternative route or the lectin route.

Polymeric IgA interaction with specific mesangial receptors

Although several of the known IgA receptors have been proposed as IgA mesangial receptor candidates, none of them have been conclusively proven in the mesangium.[1,5,23] Recent data indicates that the transferrin TFR or CD71 receptor could develop the RR function for IgA1. CD 71 is expressed very little in quiescent mesangial cells, but it is found overexpressed in IgA nephropathy patients, colocalised with the IgA1 deposits and related to the severity of the kidney disease. CD71 is able to bind polymeric IgA1, but not monomeric IgA1, and several experimental data have shown that the polymeric IgA1-CD71 union causes an activation of the mesangial cell, which, as a result, proliferates and produces IL-6, TGF beta and other cytokines. Furthermore, the CD71 blockage through the monoclonal A24 antibody prevents stimulation of the mesangial cell induced by polymeric IgA.[24]

Complement activation

As opposed to IgA2 and monomeric IgA1, the polymeric IgA1 is able to activate the alternative route of the complement.[6] On the other hand, the polymeric IgA, in some patients, colocalises with MBL and can activate the complement through the lectin route.[7,8] There is evidence that in certain patients, the polymeric IgA, both circulating and mesangial, are found forming immune complexes with IgG. The existence of these complexes is known since 1997 and recently has regained interest on proving that the IgA1 hinge component, by presenting galactose deficiency, exposes residues of GalNAc in the circulation that could be immunogenic and provoke the synthesis of IC IgA1 gal def/IgG anti-IgA. These immune complexes could deposit in the mesangium, either through the recognition of the previously deposited anomalous IgA1 or through the direct deposit of circulating immune complexes, causing activation of the complement through the traditional route.

Progression of the mesangial IgA lesion towards chronic renal failure

Both the data from human biopsy histological studies as well as the experimental studies indicate that after initial stage of proliferation and increase of mesangial matrix, when any renal infiltration by inflammatory cells is hardly noticeable, progression of the IgA nephropathy to chronic renal failure is characterised by the appearance of lympho-monocyte infiltration that precedes interstitial fibrosis.[25,26] The mechanisms through which lymphocyte and monocyte chemoattraction is produced in the renal interstitial space are unknown. Nevertheless, by analogy with other processes, it must involve selectin expression in the peritubular capillaries followed by lympho-monocyte stimulation through specific chemokines and transendothelial migration mediated via interaction with integrins.

One hypothesis that has been developing over recent years indicates that kidney damage progresses when there is a reaction between two different receptors: Mesangial CD71 as an activation inducer of the mesangial cell and RR Fc alpha lympho-monocyte as mediator of the interstitial infiltration.[24,27]

Recent evidence shows that the RR Fc alpha could be involved in recruiting monocytes to the renal interstitial space and thus, mediating the kidney lesion progression. Firstly, several studies have shown that the leukocytes in IgA nephropathy patients have a large amount of polymeric IgA1 joined to the membrane RR Fc alpha.[24,26] This increase in expression has been attributed to the inability to internalise the IgA/RR complex. The RR Fc alpha, in the membrane, is associated to the RR Fc gamma which, in turn, is found in connection with ITAM in the cytoplasmic domain. The interaction of monomeric IgA1 with the RR Fc alpha-Fc gamma complex induces cell inhibition. In contrast, the union of polymeric IgA2 induces cell activation. This capacity of the polymeric IgA to activate the mononuclear leukocytes is currently considered one of the pathogenic mechanisms responsible for the infiltration of the renal interstitial space and progression of the kidney lesion.[24] The importance of the Fc alpha/gamma complex as a possible progression mechanism has been recently proven in a transgenic mouse model that expresses the human RR Fc alpha.[26] In this model, the mouse polymeric IgA interacts with the human RR Fc alpha, although with low affinity and forms complexes that are deposited in the renal mesangium and cause haematuria and proteinuria. The infusion of polymeric IgA/RR Fc alpha to "wild type" mice, which do not express human Fc alpha, reproduces the disease. Using this model, we can compare the evolution of the IgA nephropathy between two types of mice: those that expressed the Fc

alpha/gamma complex and those that only expressed Fc alpha but not Fc gamma. Although every animal presented IgA mesangial deposits and haematuria, only those expressing Fc alpha/gamma presented proteinuria and accumulation of macrophages in the glomerulus and periglomerular region. Furthermore, only the macrophages that expressed Fc alpha/gamma were able to migrate toward the renal interstitial space by being passively transferred. Evidence that the union of polymeric IgA1 or pathologic IC IgA1 with the gamma RR Fc of the monocytes causes their activation and increase their response to the cytokines produced by the mesangial cells is an additional fact that indicates the importance of signalling through gamma Fc in the progression of renal lesions. Stimulation of the neutrophiles through the alpha Fc union with dimeric IgA has also been recently proven in models of inflammatory bowel disease.[27]

In brief, the evidence currently available suggests the existence of, at least, two possible IgA deposition mechanisms in the renal mesangium. In a small percentage of patients, the IgA1 mesangial deposition colocalises with a secretor component, which indicates that the IgA1 deposited in the glomerulus originates totally or partially in the lymphoid tissue associated to mucosae. This pattern of deposition has been associated with the activation of the complement through the lectin pathway and has been related with a poorer prognosis, although this last affirmation requires confirmation in long term studies. The mechanisms responsible for kidney deposit of secretory IgA are unknown. In most Gn IgA patients, the secretory component in the mesangium cannot be detected. In these cases, the presence of high circulating levels of galactose-deficient IgA, produced by plasma cells in the BM, would be a predisposing factor, but no sufficient for the development of nephropathy. For kidney disease to occur, the gal deficient IgA1 should deposit in the renal mesangium and, once there, either interact with specific receptors (CD71?), through direct activation of the complement or by being the target of an IgG anti-IgA autoimmune response, induce activation, proliferation and increase of mesangial matrix synthesis and, lastly, the cellular lesion. Similarly, the gal deficient IgA1, through interaction with the RR Fc alpha/gamma of lymphocytes and monocytes, could activate the circulating lymphocytes and monocytes and increase their response to the chemo-attractants produced by the mesangial cell, causing the inflammatory infiltration that would initiate and maintain the interstitial lesion.

Are there new perspectives for the near future?

Considering that most of the prognostic factors used to predict the risk of a long term loss of renal function (including the recently described Oxford classification for the evaluation of kidney damage[29]) identify a predominantly advanced and chronic lesion, we need studies to identify prognostic variables from data obtained at the moment of diagnosis or before the appearance of irreversible renal fibrosis lesions. Consecutively, studies have been published that analyse the possible prognostic significance of a large number of histologic and/or biochemical variables, with inconclusive results.[30] Currently, there is data that allows us to make out that over the coming years, the recent progress that has been made in understanding the pathogenesis of IgA1 nephropathy could provide new variables for new patient classification not only based on morphologic and clinical criteria but also with a larger pathogenic base, in this way, contribute to reaching this objective. Among the numerous variables that could be considered possible candidates, some are especially attractive due to the possibility of short term analysis:

1. Techniques for measuring the levels of circulating galactose-deficient IgA1 are being standardised. When they become available for clinical use, they will allow for study of representative groups of patients with IgA nephropathy, determining the true prevalence and the prognostic significance of the glycosylation defects of the IgA1 molecule.

2. On the hand, the evidence of IgA1/CD 71 interaction opens the way to analysing whether the expression of CD71 can be a good index of mesangial activation.

3. The hypothesis that the circulating lymphocytes and monocytes that co-express surface Fc alpha/gamma and IgA are responsible for starting and maintaining the interstitial infiltration would present the possibility of studying whether quantification of these cell populations (circulating and/or in the renal biopsy) could have prognostic significance.

4. Detection of the presence and/or title of IgG antibodies directed against the IgA Gal def could be useful to identify patients in which the autoimmune mechanisms would relevantly contribute to the renal lesion and, therefore, would perhaps be better potential candidates for treatment with steroids and other immunosupressants. This aspect would have great relevance given the controversy that currently exists among nephrologists on the usefulness and indications of steroid treatment in IgA nephropathy.

5. In the study of histopathological characteristics of the renal biopsies, it is possible to find deposition patterns in which only the following are identified:

IgA, patterns with IgA and C3, IgA and C4d deposits and patterns with IgA, MBL C1q and C4d. The different deposition patterns could correspond to pathogenic variants with different course, prognosis and responses to treatment or it could be the reflection of different stages of the same process. There are data that relate C4d deposition with MBL, L-ficolin and secretory component, which suggests a pathogenic link between the IgA system associated to mucosae and a specific kidney lesion route. The presence of C4d has been associated with a poorer prognosis. For both reasons, it seems extremely justified to perform clinical studies that relate a certain deposition pattern with a pathogenic mechanism, the prognosis or response to treatment. Meanwhile, if the evidence of complement activation is related with the clinical progress of the disease, the question arises as to whether this situation could be identified through non invasive techniques, such as quantification of the C5b-9 levels in urine.

6. Lastly, the detection of podocyte damage either in the renal biopsy or in the urine samples, could contribute to identifying patients with evolution to irreversible lesions.

REFERENCES

1. Monteiro RC, Van De Winkel JG. IgA Fc receptors. Annu Rev Immunol 2003;21:177-204.
2 Berger J, Hinglais N. Les depots intercapillaires d'IgA-IgG. Journal d'Urologie et Nephrologie 1968;74:694-5.
3. www.senefro.org. registro español de glomerulonefritis.
4. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol 2004;24:179-96.
5. Monteiro RC. New insights in the pathogenesis of IgA nephropathy. Nefrologia 2005;25(Suppl 2):82-6.
6. Wyatt RJ, Kanayama Y, Julian BA, Negoro N, et al. Complement activation in IgA nephropathy. Kidney Int 1987;31:1019-23.
7. Oortwijn BD, Rastaldi MP, Roos A, et al. Demonstration of secretory IgA in kidneys of patients with IgA nephropathy. Nephrol Dial Transplant 2007;22:3191-5.
8. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M, Fujita T. Glomerular deposition of mannose-binding lectin (MBL) indicates a novel mechanism of complement activation in IgA nephropathy. Nephrol Dial Transplant 1998;13:1984-90.
9. Roos A, Rastaldi MP, Calvaresi N, Oortwijn BD et al Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. J Am Soc Nephrol; 2006;1724-34.
10. Espinosa M, Ortega R, Gómez-Carrasco JJM, et al. Mesangial C4d deposition: a new prognostic factor in IgA nephropathy. Nephrol Dial Transplant 2009;24:886-91.
11. Hiki Y, Tanaka A, Kokubo T, Iwase H, et al. Analyses of IgA1 hinge glycopeptides in IgA nephropathy by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. J Am Soc Nephrol 1998;9:577-82.
12. Coppo R, Amore A. Aberrant glycosylation in IgA nephropathy (IgAN). Kidney Int 2004;65:1544-7.
13. Giannakakis K, Feriozzi S, Perez M, Faraggiana T, Muda AO. Aberrantly glycosylated IgA1 in glomerular immune deposits of IgA nephropathy. J Am Soc Nephrol 2007;18:3139-46.
14. Moldoveanu Z, Wyatt RJ, Lee JY, Tomana M, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney Int 2007;71(11):1148-54.
15. Suzuki H, Moldoveanu Z, Hall S, Brown R, et al. IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. J Clin Invest 2008;118:629-39.
16. Li GS, Zhang H, Lv JC, Shen Y, Wang HY. Variants of C1GALT1 gene are associated with the genetic susceptibility to IgA nephropathy. Kidney Int 2007;71(5):448-53.
17. Li GS, Nie GJ, Zhang H, Lv JC, Shen Y, Wang HY. Do the mutations of C1GALT1C1 gene play important roles in the genetic susceptibility to Chinese IgA nephropathy? BMC Med Genet 2009;10:101.
18. Pirulli D, Crovella S, Ulivi S, Zadro C, et al. Genetic variant of C1GalT1 contributes to the susceptibility to IgA nephropathy. J Nephrol 2009;22:152-9.
19. Buck KS, Smith AC, Molyneux K, El-Barbary H, Feehally J, Barratt J. B-cell O-galactosyltransferase activity, and expression of O-glycosylation genes in bone marrow in IgA nephropathy. Kidney Int 2008;73:1128-36.
20. Ding JX, Xu LX, Zhu L, Lv JC, Zhao MH, Zhang H, Wang HY. Activity of alpha2,6-sialyltransferase and its gene expression in peripheral B lymphocytes in patients with IgA nephropathy. Scand J Immunol 2009;69:174-80.
21. Zhu L, Tang W, Li G, Lv J, Ding J, et al. Interaction between variants of two glycosyltransferase genes in IgA nephropathy. Kidney Int 2009;76:190-8.
22. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol 2008;19:1008-14.
23. Leung JC, Tsang AW, Chan DT, Lai KN. Absence of CD89, polymeric immunoglobulin receptor, and asialoglycoprotein receptor on human mesangial cells. J Am Soc Nephrol 2000;11:241-9.
24. Moura IC, Benhamou M, Launay P, Vrtovsnik F, Blank U, Monteiro RC. The glomerular response to IgA deposition in IgA nephropathy. Semin Nephrol 2008;28:88-95.
25. Alexopoulos E, Seron D, Hartley RB, Nolasco F, Cameron JS. The role of interstitial infiltrates in IgA nephropathy: a study with monoclonal antibodies. Nephrology, Dialysis, Transplantation 1989;4:187-95.
26. Grossetête B, Launay P, Lehuen A, Jungers P, Bach JF, Monteiro RC. Down-regulation of Fca receptors on blood cells of IgA nephropathy patients: Evidence for a negative regulatory role of serum IgA. Kidney Int 1998;53:1321-35.
27. Launay, P, Grôssetete B, Arcos Fajardo M, et al. Fc alpha Receptor (CD89) Mediates the Development of Immunoglobulin A (IgA) Nephro-

pathy (Berger's Disease). Evidence for pathogenic soluble receptor-IgA complexes in patients and CD89 transgenic mice. J Exp Med 2000;191:1999-2010.

28. Van der Steen L, Tuk CW, Bakema JE, Kooij G, et al. Immunoglobulin A: Fc(alpha)RI interactions induce neutrophil migration through release of leukotriene B4. Gastroenterology 2009;137:2018-29.
29. Goto M, Wakai K, Kawamura T, Ando M, Endoh M, Tomino Y. A scoring system to predict renal outcome in IgA nephropathy: A nationwide 10-year prospective cohort study. Nephrol Dial Transplant 2009;24:3068-74.
30. Roufosse CA, Cook HT. Pathological predictors of prognosis in immunoglobulin A nephropathy: A review. Curr Opin Nephrol Hypertens 2009;18:212-19.

Received: 8 Jun. 2010 | Accepted for publication: 8 Jun. 2010