

Update on immunoglobulin A nephropathy, Part I: Pathophysiology

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Author contributions: Salvadori M and Rosso G both contributed to this paper.

Conflict-of-interest statement: No conflict of interest is declared by any of the authors.

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Received: June 23, 2015
 Peer-review started: June 23, 2015
 First decision: August 4, 2015
 Revised: August 24, 2015
 Accepted: August 30, 2015
 Article in press: August 31, 2015
 Published online: September 6, 2015

Abstract

Immunoglobulin A (IgA) nephropathy is one of the most common glomerulonephritis and its frequency is probably underestimated because in most patients the disease has an indolent course and the kidney

biopsy is essential for the diagnosis. In the last years its pathogenesis has been better identified even if still now several questions remain to be answered. The genetic wide association studies have allowed to identifying the relevance of genetics and several putative genes have been identified. The genetics has also allowed explaining why some ancestral groups are affected with higher frequency. To date is clear that IgA nephropathy is related to auto antibodies against immunoglobulin A1 (IgA1) with poor O-glycosylation. The role of mucosal infections is confirmed, but which are the pathogens involved and which is the role of Toll-like receptor polymorphism is less clear. Similarly to date whether the disease is due to the circulating immunocomplexes deposition on the mesangium or whether the antigen is already present on the mesangial cell as a "lanthanitic" deposition remains to be clarified. Finally also the link between the mesangial and the podocyte injury and the tubulointerstitial scarring, as well as the mechanisms involved need to be better clarified.

Key words: Immunoglobulin A; Immunoglobulin A galactosylation; Genome-wide association studies; Auto antibodies; Complement in renal diseases; Mesangial linked growth factors

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Core tip: For few glomerular diseases a new pathogenetic pathway has been recognized in the recent years as happened for the immunoglobulin A (IgA) nephropathy. Finding in the genetics allowed identifying several loci putative for the disease progression. Spectrometry mass studies and 3 dimension studies have allowed bettering clarifying the molecules involved at glomerular level. Molecular studies of the mesangium allowed identifying new receptors responsible for the IgA immune complexes deposition and for the binding to the mesangial structure. Finally molecular and cellular studies opened new ways to understanding the

link and the cross-talk between the glomeruli and the tubulointerstitial structure.

Salvadori M, Rosso G. Update on immunoglobulin A nephropathy, Part I: Pathophysiology. *World J Nephrol* 2015; 4(4): 455-467 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v4/i4/455.htm> DOI: <http://dx.doi.org/10.5527/wjn.v4.i4.455>

INTRODUCTION AND EPIDEMIOLOGY

The immunoglobulin A (IgA) nephropathy (IgAN) is represented by a proliferation of glomerular mesangial cells jointed with the presence of IgA deposition in the mesangial area. The IgAN represents the most frequent glomerulonephritis and is represented by extremely different clinical signs and histopathologic features^[1]. Because of the typical histopathological and immunological picture and the heterogeneous clinical aspects, the diagnosis of IgAN is principally based on the pathologic picture at the renal biopsy. As a consequence, the IgAN frequency is probably underestimated and the disease is the most prevalent glomerulonephritis in those countries where renal histology is more frequently used in the diagnostic algorithm. Its estimated frequency is approximately 2.5 cases/year per 100000 adults^[2]. IgAN is worldwide diffused even if with different frequencies. IgAN has prevalence for male sex in the Caucasian race^[3-5]. It is more frequent in some races (Asians, Hispanics, whites, American Indians) while is less frequent in other races as African and American blacks^[6]. Recently new epidemiological findings, supported by the genetics, have allowed confirming that the disease incidence varies greatly according the geographical location. Indeed the IgA nephropathy is found in up to 40% of native kidney biopsies in Eastern Asia, but in less than 5% of native biopsies in central Africa^[7]. In addition to the different criteria in performing renal biopsy, genetics is thought to play a significant role in explaining some geographical differences^[8]. In addition, a diagnostic difficulty is represented by the huge difference in clinical presentation. Indeed, clinically, IgAN may present an asymptomatic course. Such patients are occasionally diagnosed during the work up for other diseases as hypertension or reduced glomerular filtration rate (GFR). Other patients present with macroscopic hematuria, often related to upper respiratory tract infections. In addition, some patients may present with rapidly progressive disease. Generally, the progression of the disease is related to the presence of well-known clinical risk factors that impact on the evolution of most glomerulonephritis as hypertension, proteinuria above 1 g/d, impaired renal function, smoking and obesity^[9-11].

It is now clear that IgAN may be present in subjects apparently health as documented by biopsies of kidneys suitable for transplantation, or by data of autopsies

not related to renal diseases^[12,13]. This is further documented by the fact that most persons affected by IgAN may have a benign course or spontaneous resolution as documented by subjects followed for 10 years after diagnosis in China and in Spain^[14,15]. Moreover, after transplantation of an IgAN kidney into a non IgAN recipient, disappearance of the glomerular changes has been documented, suggesting that the defect leading to IgAN is not related to the kidneys^[16]. In addition, the high recurrence rates following kidney transplantation confirm that the key pathogenetic alteration in IgAN might reside outside the kidney^[17].

PATHOGENESIS

As aforementioned, the IgAN is characterized by mesangioproliferative changes in the glomeruli with typical IgA deposits in the mesangial area. Deposits of IgG and C3 are also frequently present. The glomerular IgAs eluted from biopsies of patients affected by IgAN belong almost always to the IgA1 subclass and are principally polymeric. Interestingly, they are poorly glycosylated. In particular, these abnormal IgA1s exhibit a defect of galactose molecules that are normally linked to O-glycans in the hinge region. Defective glycosylated IgA1s exhibit higher blood levels in patients affected by IgAN than in normal subjects. However, this high circulatory level of galactose-deficient IgA1s (Gd-IgA1) *per se* is not able to determine the renal disease. Different steps or processes are needed for the clinical development and manifestation of the IgAN. New findings concerning these processes have been recently discovered, they are under the genetic control and genetics and immunobiology of IgAN are strictly linked^[7,18].

A genome-wide association study (GWAS) performed by Gharavi *et al.*^[19] recently found five susceptibility loci for IgAN and allowed to identify the molecules responsible for the above mentioned steps.

These are represented by: (1) abnormal IgA1 glycosylation; (2) antibody production towards the abnormal IgA1; (3) binding of the anti-glycan antibodies to the abnormal IgA1 and consequent production of immune-complexes; and (4) deposition of the immune-complexes in the mesangial area and induction of the renal damage.

INSIGHTS FROM GENETICS

After the GWAS finding already mentioned^[19], more recently a GWAS again has identified more candidate genes offering new views on the hits involved into the IgAN pathogenesis. The hits involved are represented by the antigen elaboration and presentation, the immunity mucosa-related, and the complement activation.

Antigen elaboration and presentation

The GWAS mentioned identified three different candidate loci that might impact on this pathway. They all have

Table 1 Common genetic determinants for immunoglobulin A nephropathy

Genetic locus	Genes	Function
6q21	<i>HLA-DRB1</i> , <i>HLADQA1</i> and <i>HLA-DQB1</i> <i>PSMB8/9</i> and <i>TAP2</i>	Class II major histocompatibility complex Regulators for antigen processing and presentation
1q32	<i>CFHR1/3</i>	Modulators for complement activation and inflammation
22q12	<i>HORMAD2</i>	Unknown
17q13	<i>TNFSF13</i>	Important for B cell development and IgA isotype switching
8p23	<i>DEFA1</i>	Encoding α -defensins as a type of endogenous antimicrobial mediators
1p13	<i>VAV3</i>	Regulators for lymphocyte development and antigen presentation
9q34	<i>CARD9</i>	Participant in antigen-induced signalosome formation (<i>CARD9</i> - <i>BCL 10</i> - <i>MALT1</i>) and NF- κ B activation
16p11	<i>ITGAM</i> and <i>ITGAX</i>	Mediators for immune cell adhesion and phagocytosis

IgA: Immunoglobulin A.

been identified on chromosome 6p21, are located on major histocompatibility complex (MHC) and are called: *HLA-DRB1/DQB1*, *HLA-DPB1/DPB2* and *TAP1/PSMB9*.

A strength link was identified in a different HLA region that includes the *HLA-DRB1-DQA1* genes^[19]. The same region had been previously associated with several autoimmune diseases^[20-27]. Another MHC locus has been found in the region that includes the *HLA-DPA1*, *BPB1* and *DPB2* genes.

Immunity mucosa-related: The clinical association of hematuria and infective episodes related to mucosal sites allowed to suspect that abnormalities in the IgA production might be responsible for the IgAN^[28].

GWAS identified three loci involved in the mucosal pathogenesis of the IgAN. A locus is located on chromosome 17p13. This locus contains the gene *TNFSF13* that codes a proliferation-inducing ligand (APRIL). APRIL might determine the proliferation of IgA-producing cells^[29,30] and APRIL serum levels may be higher in subjects affected by IgAN^[31].

A second locus on chromosome 22q12 affects the circulatory IgA load and the susceptibility to develop IgAN^[19]. This locus includes several genes among which the genes *LIF* and *OSM*, that encode cytokines^[32]. The cytokines encoded by these genes belong to the interleukin 6 (IL-6) family and influence the immunoregulation^[33,34].

On the *DEFA* gene cluster located on the chromosome 8p23, another locus related to IgAN has been identified. It encodes the small peptides secreted by the mucosal cells with antimicrobial properties called α -defensin^[35]. While α -defensin 1, 3 and 4 are secreted by neutrophil, α -defensin 5 and 6 are secreted into the gut by the Paneth cells.

Complement activation

On chromosome 1q32 is located the locus that contains the gene encoding complement factor H (CFH). GWAS found that the deletion of two CFH related genes (*CFHR3* and *CFHR1*) is a protective genetic factor for IgAN^[19].

Indeed, the deletion of *CFHR3* and *CFHR1* is associated with the lacking of their products and CFHR1 is a competitive antagonist of CFH in regulating

the complement activity^[36]. As a consequence, the association of elevated CFH levels with the absence or low levels of CFHR1 determines a strong inhibition of complement activation. In addition, the relationship between mesangial C3 deposits and different CFH, CFH and CFHR1 levels suggests that these proteins are related to the pathogenic IgA-IC deposition^[37].

In addition to the above mentioned pathways, recently performing a GWAS in 20612 patients affected by IgAN, other relevant possible genes have been found; four in *ITGAM-ITGAX*, *VAV3* and *CARD 9* and two in the *HLA-DQB1* and *DEFA* loci. Most loci carry genetic risk correlation with local intestinal pathogens, supporting the possibility that host pathogens might favor the IgAN in genetically predisposed patients^[38]. All the candidate genes and their function are summarized in Table 1.

FOUR HITS FOR GENERATION OF RENAL INJURY

Several authors^[7,18] have formulated the so called "four hits" pathogenesis of the IgAN. According several studies the IgAN pathogenesis is multivariate and implies the co-existence of several factors. Indeed, after an increase in galactose-deficient circulating IgA1 (Gd-IgA1), an antibody production against these IgA1 is essential for the disease initiation. Later on IC are formed that may deposit in the kidney and activate an inflammatory response (Table 2).

Step 1: Regulation of IgA1 glycosylation and genetic impact on galactose-deficient circulating IgA1

The IgA1 hinge region is located between the constant region domains CH1 and CH2 of the $\alpha 1$ heavy chains. This region contains O-glycosylation sites composed of serine/threonine (Ser/Thr) and Proline residues. In normal condition only some of these sites are glycosylated^[39,40]. A key role in the IgA O-glycosylation is exerted by core 1 β 1, 3 galactosyl-transferase (C1 β 3Gal-T) and its molecular chaperone core 1-1-phosphateuridylyltransferase (Gal-T)-specific chaperone (Cosmc). Patients affected by IgAN have

Table 2 Summary of the four hits involved in the pathogenesis of immunoglobulin A nephropathy with distinction of the pathogenetic process (putative environmental factors involved, putative genetic factors involved, potential clinical biomarkers and potential novel therapeutic approaches)

Hit	Pathogenic process	Putative environmental factors involved	Putative genetic factors involved	Potential clinical biomarkers	Potential novel therapeutic approaches
1	Hereditary increase in circulating galactose-deficient IgA1	Potential role of mucosal exposure to infectious of dietary antigens	Strong evidence for high heritability of serum galactose-deficient IgA1 level Potential role of chromosome 22q12.2	Serum galactose-deficient IgA1 level (HAA-based ELISA)	Suppression of synthesis of galactose-deficient IgA1 Enzymatic boost of galactose transfer to IgA1 hinge- region O-glycans Suppression of sialylation of galactose-deficient O-glycans
2	Circulating antibody directed against galactose-deficient IgA1	Potential role of mucosal exposure to infectious or dietary antigens	Potential role of three MHC-II loci in antigen presentation and humoral response to galactose-deficient IgA1 O-glycans	Serum anti-glycan antibodies (dot blot assay)	Alteration of processing and presentation of galactose-deficient IgA1 O-glycopeptides Specific B-cell depletion therapy
3	Formation of pathogenic IgA1-containing immune complexes	Unknown	Unknown	Circulating and/or urinary immune complexes	Competitive blockade of immune complex formation by non-cross-linking anti-glycan antibodies or specific glycopeptides
4	Mesangial deposition of IgA1 containing immune complexes, cell activation and initiation of glomerular injury	Unknown	Protective effect of common deletion in CFHR1 and CFHR3	Circulating and/or urinary complement degradation products, or novel markers of glomerular injury	Suppression of the alternative complement pathway Targeted CFHR1/3 depletion Blocking mesangial cell signaling induced by nephritogenic IgA1-containing immune complexes

HAA: Helix Aspersa; ELISA: Enzyme-linked immunosorbent assay; CFHR3: Complement factor H receptor 3; IgA: Immunoglobulin A.

more elevated blood levels of IgA1 with the O-glycans poorly galactosylated and having either GalNAc as terminal molecule or GalNAc containing the secretory J component (Figure 1)^[41]. A recent study, using cell lines from a human B-lymphoma documented that the T 2 helper cytokine IL-4 may control the glycosylation of the IgA^[42]. Indeed, the IL-4 stimulation decreased the messenger RNA (mRNA) levels of both core the enzyme (C1β3Gal-T) and its molecular chaperone. Studies on animals confirmed the relevance of cytokines on IgA glycosylation^[43,44]. O-glycan specific lectin initially allowed identifying the defective IgA1 O-glycosylation in IgAN^[45]. More recently, other techniques as the liquid chromatography and the 3D mass spectrometry have allowed us to an improved understanding of the O-glycosylation process and the molecules involved^[46,47].

The origin of the poor galactosylated IgA1s is still a not resolved question. Several studies have documented a significant difference in IgA1s generated in the systemic compartment with respect to the IgA1s generated on the mucosal surface^[48]. Mucosal IgAs are predominantly polymeric (pIgA), while systemic IgAs are monomeric. Interestingly, in the IgAN the pathogenic IgA immune complexes (IgA-IC) principally contain poor galactosylated pIgA with the J secretory component^[49].

The high serum level of mucosal-type IgAs in the IgAN patients might suggest that mucosal sites are the origin of poor galactosylated IgA1s. In contrast, in IgAN either systemic pIgAs directed against antigens typical of the mucosa and systemic pIgA plasma cells in systemic sites have been described^[50,51]. Hence the

hypothesis that the overproduction in the serum of poor galactosylated IgA1 might be the result of the movement of mucosal IgA1 committed B cells from the mucosa to the systemic compartment. A mucosal B cell mis-homing to systemic sites is the most likely mechanism^[52].

The abnormal activity of Toll-like receptors (TLRs) might be another factor that contributes to the increased response to mucosal antigens in IgAN. Indeed, the association of increased Toll-like receptor 4 in circulating cells and signs of renal diseases have been reported by several studies^[53]. Other studies examining the single nucleotide polymorphism, found an association between the TLR-9 polymorphism and the IgAN progression. This suggests that the involvement of TLR-9/MyD88 might exert its effect over the progression of IgAN^[54].

Step 2: Synthesis of antibodies directed against GdIgA1

The synthesis of abnormally glycosylated IgAs is not "per se" enough to justify the mesangial lesions that characterize the IgAN. Indeed, comparing the IgA glycosylation of IgAs eluted from serum with those eluted from biopsy specimens we may observe that Gd-IgAs eluted from kidney biopsies are less glycosylated when compared to the glycosylation rate of serum IgAs from the same IgAN patients^[55,56]. This fact highlights a GdIgA1 tropism for the mesangium which might contribute to explain the recurrence of IgA deposits on kidney allograft. Moreover, a study documented that in families affected by IgAN an abnormal glycosylation may be present both in IgAN patients and in asymptomatic relatives^[57]. The latter observation confirms that the

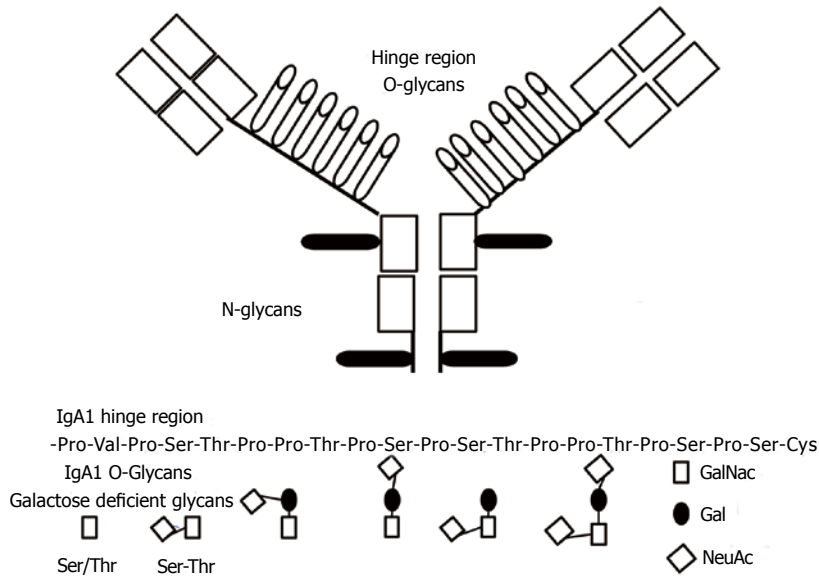


Figure 1 Immunoglobulin A1 and its hinge region with O-linked glycans (white) and N-linked glycans (black). Under the aminoacids chain of the hinge region. Sites of attachment are in bold. IgA: Immunoglobulin A.

presence of abnormally glycosylated IgAs does not “*per se*” justify the mesangial lesions and that other factors should be associated.

Recent studies suggest that auto antibodies recognizing the abnormally glycosylated IgA1s are essential in the pathogenesis of the disease^[58,59]. These findings document that IgAN is an autoimmune disease due to the mesangial deposition of immunocomplexes containing GdIgA1. Other molecules such as sCD89, fibronectin, collagen and laminin are also found in IgA1 containing immune complexes, even if their role remains to be determined^[60].

Circulatory auto antibodies (IgG and/or IgA) bind to Gd-IgA1s and form large pathogenetic immune complex^[61]. A better understanding of these antibodies is provided from an elegant experiment that used Epstein Barr virus (EBV-immortalized) lymphocytes from subjects affected by IgAN^[62]. These B cells are able to product IgG that bind Gd-IgA1 and a subsequent analysis of the cloned chains of these IgG auto antibodies identified as their unique feature the complementary-determining region (CDR) 3 of the heavy chains^[61]. In particular the third portion in CD3 is typically serine in patients with IgAN. Whether bone marrow or mucosal tissues are at the origin of IgA1s in circulating immune complexes is still now a matter of controversy. The acute onset of the disease is often accompanied by a concurrent infection of the upper respiratory tract and in this site cells are present able to produce polymeric IgA1s, typical of the pathogen IgA^[29]. However, in other studies, polymeric IgA1s and J chain producing cells have been found in the bone marrow of subjects affected by IgAN^[63-65]. The aforementioned mis-homing with transposition of plasma cells from the mucosa to systemic sites might explain this finding^[52].

Recently Barratt *et al*^[66,67] postulated the so called hypothesis of the “right antibodies in the wrong place at the wrong time”. According this hypothesis, the “right” antigen represented by the mucosal derived Gd-

IgA is in the systemic compartment that is the wrong place. Later on, when a large quantity of Gd-IgA1 is in circulation, a large quantity of the right antibody anti Gd-IgA1 is secreted at the wrong time.

The stimuli leading to the production of these auto antibodies remains to be explained.

A hypothesis might be that these antibodies are secreted against pathogen cell surface GalNac-containing glycoconjugates cross-reacting with GdIgA1, realizing a molecular mimicry^[68]. A prevalence of IgA1 autoantibody response^[61] anti GdIgA1 may justify the fact that some patients have only IgA1 antibody in the glomeruli^[69].

In conclusion, a portion of the IgA1 molecules secreted by the plasma cells in patients affected by IgAN is Gal-deficient and is identified by the anti-glycan IgG (or IgA1) antibodies^[70]. The formed IC, due to their size, cannot reach and bind the asialoglycoprotein receptor (ASGP-R) in the liver, and be metabolized. Moreover, the terminal GalNac residues, which might interact with the ASGP-R, are covered by specific antibodies that prevent such interaction^[71]. As a consequence, a larger fraction of the IgA-IC may reach the glomerular capillaries overlying the mesangium.

Summarizing the two steps above described in the IgA pathogenesis, in the first time a high quantity of under-galactosylated IgA1 is present in the blood. At this regard several points remain to be clarified. The plasma cell defect is inherited or acquired? In addition, to justify the systemic presence of GdIgA1 high quantity, a plasma cell mis-homing from mucosa to systemic sites is needed or not?

In the second step we have the IgG auto antibodies production anti the GdIgA1. At this regard several questions remain to be answered.

Are these antibodies the result of a molecular mimicry triggered by infections?

In addition, are these antibodies the result of a Toll-like receptor polymorphism?

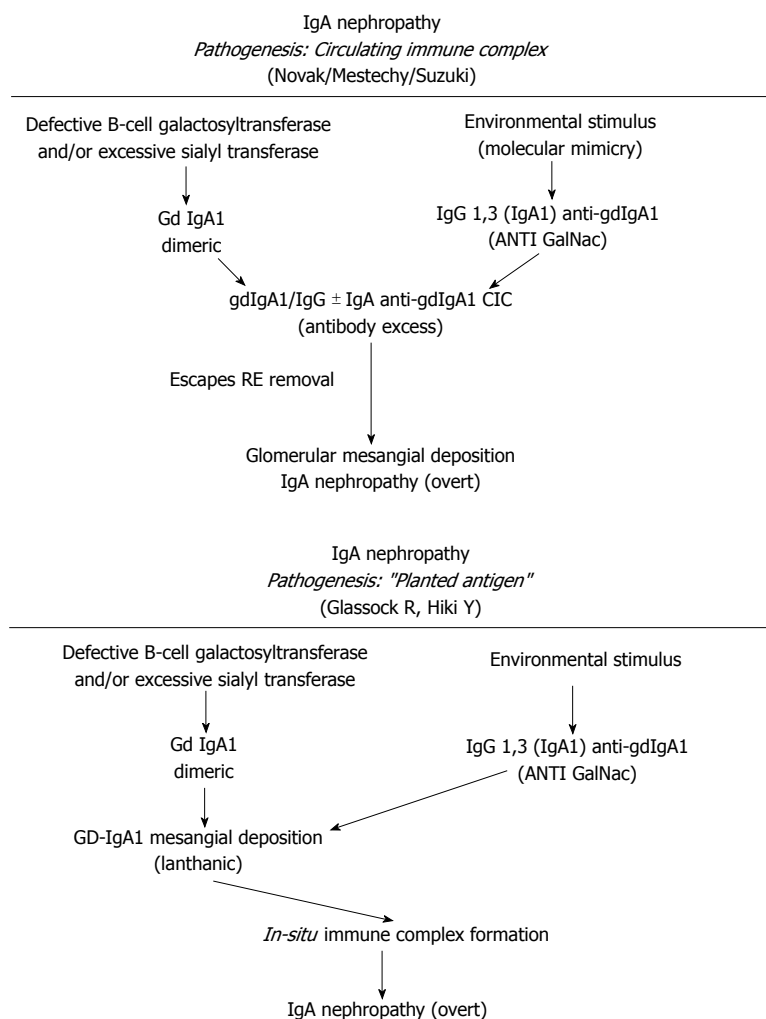


Figure 2 Schematic representation for the possible pathways involved in the generation of a circulating immune complex pathogenesis for the immunoglobulin A nephropathy. CIC: Circulating immune complex; Gd IgA1: Galactose deficient immunoglobulin A1.

Figure 3 Schematic representation for the possible pathways involved in an *in situ* pathogenesis for the IgA nephropathy. IgA: Immunoglobulin A; Gd-IgA1: Galactose deficient immunoglobulin A1; ANTI GalNac: ANTI N-acetylgalactosamine.

Finally, is there a genetically determination induced by somatic mutations in the IgG heavy chains?

Step 3: Formation of pathogenic immune complexes containing IgA and their mesangial deposition

Circulating anti-glycan auto antibodies recognize Gd-IgA1 and pathogenic immune complexes are formed as a consequence. IgA1s must be within an immune complex to activate the mesangial cell proliferation; indeed not complexed GdIgA1s do not stimulate the proliferation of mesangial cells^[72-74]. Additional components from serum need to be present to form stimulatory complex^[72].

Several models have been proposed to explain the IgA1 immune complex depositions on the mesangial cells. Immune complexes containing IgA1/IgG or IgA could directly deposit on mesangial cell^[61,62,75]. Another hypothesis is that poor glycosylated IgA1 might be present in the mesangial area as lanthanic deposits and later newly generated anti-glycan antibodies might bind and realize immune complexes *in situ* capable to activate mesangial cells^[3] (Figures 2 and 3). In addition, a further theory is that self-aggregated Gd-IgA1s might deposit or bind to specific receptors in the mesangial area realizing "planted" depositions that are not pathogenic

"*per se*". When an exposure to similar environmentally derived antigens occurs, an auto-antibody production and the involvement of several mediators cascade lead to the disease^[76,77]. Further studies led to identify the relevance of IgA receptors (IgA-R) in the deposits. Several IgA-Rs have been recognized^[78-80]. In the IgAN pathogenesis, two IgA-R expressing cells have been principally involved: (1) mesangial cells which have been documented to be implicated in kidney injury; and (2) myeloid cells (essentially kidney infiltrating macrophages) which have been documented to modulate the extent of the inflammatory response. Studies from several groups have ruled out that the mesangial expression of receptors as ASGP-R, CD 89 and pIgAR might have a role^[81]. In addition, although on the mesangial cells is located the Fc alpha mu receptor (Fca/μR), neither IgM nor the recombinant Fca/μR inhibit the IgA1 binding to mesangium^[82]. The transferrin receptor (TfR1 or CD71) has been identified as the mesangial IgA1 receptor implicated and the pIgA1 binding to TfR1 induces mesangial cells activation^[83,84]. Moreover, TfR1 co-localizes with deposited IgA in the IgAN biopsies^[85]. The same group documented that both glycosylation and size of IgA1 are relevant factors for the TfR-IgA1 interaction. This probably is the first step of the

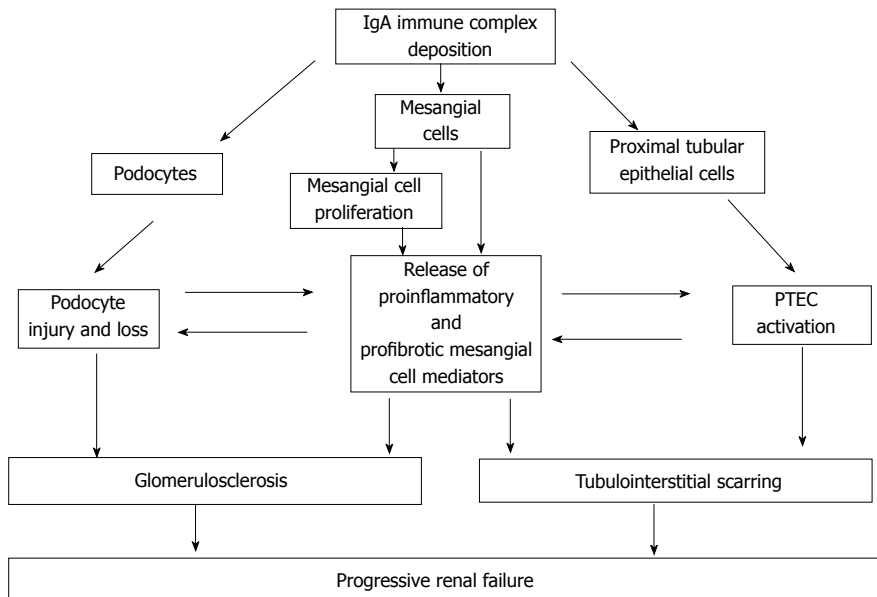


Figure 4 Pathways to glomerular damage and tubulointerstitial injury in Immunoglobulin A nephropathy. Deposition of IgA-ICs in the mesangium leads to activation of mesangial cells, triggering mesangial cell proliferation and release of proinflammatory and profibrotic mediators. Podocyte loss accentuates glomerular scarring and filtered mesangial cell-derived mediators and IgA-ICs stimulate PTEC to adopt a proinflammatory and profibrotic phenotype, which in turn drives tubulointerstitial scarring. IgA: Immunoglobulin A; PTEC: Proximal tubule epithelial cells.

IgAN injury^[86]. Finally, as an alternative hypothesis, has been proposed that the soluble form of the Fcα receptor (sCD89) might “*per se*” generate complexes with Gd-IgA1^[87]. The formation of circulating Gal deficient pIgA1 immune complexes (IgA1-CIC) induces an alteration in the interaction between IgA and CD89 that are found in the mesangial deposits and is implicated in the diseases exacerbation through the activation of pro-inflammatory cytokines and the secretion of chemokines^[88,89].

Step 4: Mesangial and glomerular cells activation, glomerular injury and fibrosis

The renal damage after mesangial cell deposition of immune complexes may be distinguished into three phases: (1) mesangial cell activation; (2) podocyte injury; and (3) tubulo-interstitial scarring. All these kinds of renal injuries may be mediated by different pathways as the complement activation, the innate immunity activation, and the non-complement mediators of IgA nephropathy (Figure 4).

Mesangial cells are activated by IgAs and may transform into inflammatory and fibrotic cells after the exposure to IgA-IC. Indeed, the mesangial cells binding to IgA-IC containing poorly galactosylated IgA1 triggers the proliferation and the programmed death of the mesangial cells. In addition a reduced synthesis of vascular endothelial growth factor (VEGF), an abnormal integrin production and an abnormal production of extracellular matrix increase the renal damage^[86,90-92].

The role of complement in the activation of the mesangial cells in IgAN has been recently reviewed by Maillard *et al.*^[93]. In IgAN, polymeric or aggregated IgA1s, principally Gd-IgA1s, may stimulate the alternative complement pathway, determine the C3 deposition and

the production of the complement terminal complex (C5b-C9)^[94-97]. Similarly the same pathways might be locally stimulated on the mesangial cells by polymeric Gd-IgA1s as well as by the secretory IgAs (SIgA)^[97]. In addition, the complement involvement by the alternative and the mannan binding lectin (MBL) pathways may be activated by the polymeric IgA1, thus participating to the pathogenesis of the IgAN and characterizing a more severe disease.

Components of the innate immunity are similarly involved in the pathogenesis of the IgAN. Some studies have documented that the TLRs are able to induce the IgA production by the B cells^[98]. It has also been documented a link between the TLRs stimulation, the overproduction of Gd-IgA1s, the more aggressive aspects of IgAN and the activation of the enzyme and molecules involved in the IgA glycosylation^[54,99,100].

Mesangial injury: IgA1-ICs containing secretory IgA with a high sialic acid content and anionic IgA-IC stimulate mesangial cells, may stimulate the p42/p44 mitogen activated protein kinase, activator protein 1, and NF-κB signal transduction. Similarly other chemokines and cytokines are up-regulated, among which the IL-6, the transforming growth factor β (TGFβ), the tumor necrosis factor α (TNFα) and the monocyte chemo attractant protein (MCP-1)^[101-103].

The platelet derived growth factors (PDGFs) are among the growth factors most involved in the mesangial cell proliferation^[104]. The PDGFs are five potent mitogens and chemoattractants that play important roles in the mesangio-proliferative diseases, principally in the IgA nephropathy. The PDGF-BB and PDGF receptors (PDGFR-β) are over expressed in the experimental

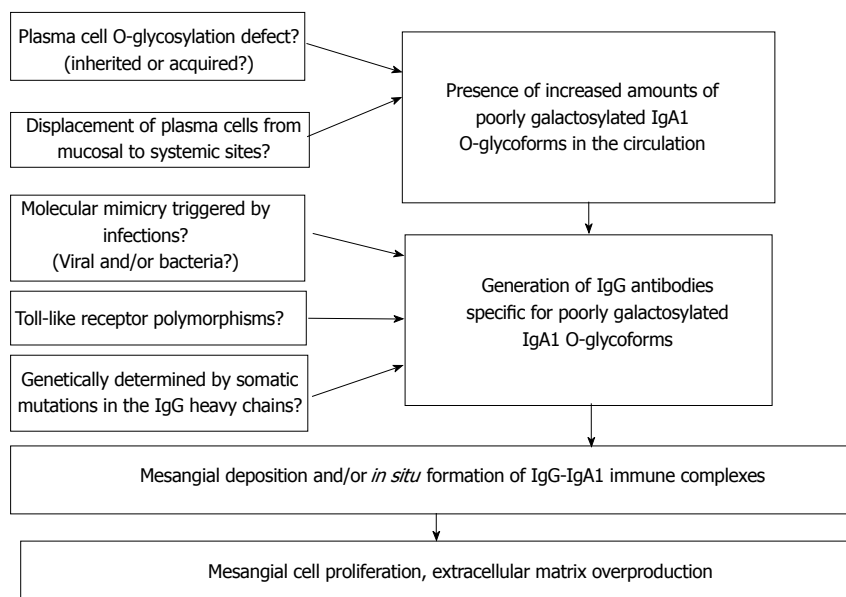


Figure 5 Doubts and different possibilities in generating the first two steps. IgA: Immunoglobulin A; IgG-IgA1: Immunoglobulin G-Immunoglobulin A1.

mesangio-proliferative nephritis and in the human IgAN^[104].

The pathogen IgA1s are also able to activate the renin-angiotensin-aldosterone system (RAAS) intrarenally^[105]. This system too is involved in the IgAN injury.

Finally a protective affect against mesangial cell activation by IgA-IC is exerted by bone morphogenetic protein 7 (BMP-7)^[106]. BMP-7 suppresses TNF α induced synthesis of proinflammatory cytokines, and has an anti-fibrotic effect through antagonism of the cellular actions of TGF β ^[107,108].

Podocyte injury: Podocyte necrosis and detachment from the glomerular basal membrane has been reported in the IgAN and the degree of podocytopenia is closely related to the increasing severity of glomerular lesions^[109]. Nephritin is a key component of the podocyte slit diaphragm and is essential for the maintenance of an intact glomerular filtration barrier. Interestingly, nephritin mRNA and extracellular nephritin expression are reduced in the IgAN^[110,111]. In addition, evidence from *in vitro* studies suggests that the podocyte injury in the IgAN is likely to be mediated by both the mesangial cell derived soluble mediators and by the direct contact with filtered IgAs^[112,113].

It has also been documented that IgA1-IC in IgAN patients might up regulate the production of CXCL1 and TGF beta from the mesangial cells. CXCL1 and TGF beta might exert a synergistic effect upon the podocytes, inducing podocyte dysfunction and podocyte death^[114].

Tubulointerstitial scarring: It has until recently been thought that the mechanisms of the subsequent tubulointerstitial injury were generic and common to all forms of chronic kidney diseases. Recent studies have

documented that specific mechanisms are operating in the IgAN.

Among the factors that are up regulated after stimulation of mesangial cells, the TGF β is the most involved in generating fibrotic tissue related to the cell damage. It is generated by growth factors involved in the connective tissue generation^[115,116]. In addition to producing fibrotic tissue, TGF β also acts favoring the transformation of the tubular cells into a fibrotic phenotype.

With an increasing damage to the perm selective barrier, increasing amounts of high-molecular weight IgA-ICs enter the urine. In IgAN these IgA-ICs are enriched by GdIgA1s that reflects their localization within the mesangium^[117]. Therefore the proximal tubule epithelial cells (PTEC) are constantly exposed to filtered IgA-ICs because of the impairment of the glomerular size barrier.

Recent studies suggest that there may be a direct and specific interaction between filtered IgA-ICs, mesangial cell-derived mediators, and PTEC. Indeed, when the mesangial cells are activated by the IgAs, they release mediators, which subsequently lead to up-regulation of angiotensin II production, inflammatory changes and apoptosis of PTECs^[118]. Similarly, the mesangial cell derived TNF α is known to activate the tubular cells inducing pro-inflammatory mediators, thus establishing an IgAs specific glomerular-tubular cross-talk^[119]. There is also convincing *in vitro* evidence that the filtered mesangial cell-derived mediators also may determine a proinflammatory and profibrotic transformation of PTEC^[118-121]. As a consequence, an IgA specific pathogenetic effects might exist, which further accelerate the progressive lost of renal function. In addition, a recent study documents that^[122] IgAN might be associated to the Epithelial-mesenchymal

transition and the apoptosis of renal tubular epithelial cells favoring the renal scarring.

CONCLUSION

Figure 5 summarizes the four steps along which the IgAN pathogenesis develops. Every step is far to be completely understood. From one side several questions remain to be answered, from the other side new disease specific therapeutic approaches might be opened.

The first step is the presence in circulation of elevated levels of Gd-IgA1. This step is under the control of several putative genetic factors. Still opened questions are whether the IgA under-glycosylation defect is genetically or environmentally generated and whether there is an abnormal plasma cell mis-homing from mucosal to systemic areas.

Second step is represented by the production of auto antibodies against Gd-IgA1. GWAS has identified the possible role of MHC-II loci involved either in the process of antigen elaboration or in the antibody response. Open questions at this regard are whether a molecular mimicry is triggered by infections and which is the role of Toll-like receptors and their polymorphisms. In addition, is not clear whether a somatic mutation genetically determined for the IgG heavy chains structure does exist.

The third step is the production of pathogenic immune complexes containing IgA and their following localization on the mesangium. Open questions are the exact composition of the immune complexes and whether there is a circulating immune complexes deposition or the Gd-IgA1 are already present in the mesangium as a lanthanic deposition followed by binding of auto antibodies.

The fourth step is represented by the renal injury IgA induced and caused by the mesangial IC deposition. The role of podocyte injury in determining the renal lesions is far to be clarified and similarly the tubulointerstitial scarring pathogenesis seems to be peculiar of IgAN, but still not completely clarified.

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P- Reviewer: Roberto S, Tanaka H, Watanabe T **S- Editor:** Qiu S
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