

Genetics and Immunopathogenesis of IgA Nephropathy

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Abstract IgA nephropathy (IgAN) is the most common glomerulonephritis in the world. The hallmark of IgAN is underglycosylation in the hinge region of IgA1. Increasing evidence supports the underglycosylated IgA-containing immune-complex including IgG antibodies against the glycans of the hinge region of IgA1 are key factors for mesangial deposition and then trigger inflammation and glomerular injury. The polymeric IgA is produced after aberrant mucosal IgA response. The displacement of mucosal B cells to systemic lymphoid organs and bone marrow may arise from abnormal trafficking of lymphocytes along the mucosa–bone marrow axis involving changes of chemokines and adhesion molecules. This review will summarize the works on the genetics, the mucosal and systemic IgA immune response, mechanism of underglycosylation of IgA1, and the pathological effect of mesangial IgA deposition in IgAN.

Keywords IgA nephropathy · Underglycosylation · IgA · Immune complex · Glomerulonephritis

Introduction

IgA nephropathy (IgAN), also called Berger's disease, was first described by Berger and Hinglais in 1968 based on the

characteristic finding of diffuse deposition of IgA- and IgG-containing immune-complexes (ICs) with mesangial proliferation immunohistologically [1]. It is the most common primary glomerulonephritis throughout the world. About 10% of the general population and other systemic diseases are associated with glomerular IgA deposits [2]. The clinical significance of such IgA deposition is unclear. Among them, Henoch–Schonlein purpura (HSP) nephritis is indistinguishable with IgAN on renal biopsy. IgAN and HSP diseases are considered variants of the similar disease process [3].

IgAN occurs at any age, most common in second and third decades of life. The male-to-female ratio is around 2 to 6:1. Disease prevalence is higher in Caucasians and Asians than that of Blacks and Indians. Although genetic differences may partly explain variations in disease prevalence, a definite diagnosis of IgAN is made by renal biopsy and its indication and practices varied in different countries. Thus, true incidence of IgAN is unknown [4]. In the early stage of the disease, many patients are asymptomatic. Abnormal urine sediment and proteinuria are found by routine healthy examination. The most common clinical presentation is macroscopic hematuria accompanied by variable degree of proteinuria. Although IgAN is a very slowly progressive disease, about 25–50% of the patients progress to end-stage renal disease (ESRD) within 25 years of diagnosis [5]. It is the main cause of ESRD in patients with primary glomerulonephritis who require renal-replacement therapy. Severe glomerular pathological changes, proteinuria of more than 1 g per day for more than 6 months, persistent microscopic hematuria, impaired renal function, and hypertension are considered as poor prognostic factors [2]. Nevertheless, IgAN recurs with milder disease severity in more than 50% of patients within 2 years of kidney transplantation [6].

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Genetic Factors

The cause of primary IgAN is unknown. IgAN now is considered a complex disease contributed by multiple genes with modest effect in combination with environmental factors. While most IgAN patients are sporadic cases, familial aggregation of IgAN has been reported. Genome-wide linkage study of familial IgAN was considered the most promising approach to identify susceptibility genes. Gharavi et al. analyzed 30 IgAN families (24 from Italy and six from the USA) and identified linkage of IgAN to chromosome 6q22-23 (called *IGAN1*), with a maximal logarithm of the odds ratio (LOD) score of 5.6. Only 60% of patients are linked to *IGAN1*, suggesting other genes may be involved in the development of disease [7]. The second study by Bisceglia et al. analyzed 22 Italian families showed linkage to 6q22-23 *IGAN1* and two other loci on chromosome 4q26-31 (called *IGAN2*) and 17q12-22 (called *IGAN3*) with a peak LOD score of 1.83 and 2.56, respectively [8]. Although no specific genes have been identified in these three candidate loci containing IgA susceptibility genes, family-based association studies to identify some potential candidate genes such as transient receptor potential channel 3 (*TRPC3*) gene, the interleukin-2 (*IL2*) gene, the *IL21* gene located in 4q26-31; histone deacetylase (*HD5*) gene, the granulin (*GRN*) gene located in 17q12-22 involved in immune response are in progress [9].

On the other hand, numerous association studies have been performed to identify susceptibility genes of IgAN by a candidate gene approach based on the disease pathogenesis. The genes associated with susceptibility to IgAN and/or disease progression are summarized in Table 1 according to the immunological and biological pathways. Innate immune response provides an immediate defense of a wide range of individual pathogen without antigen specificity or immunological memory. It acts through the recognition of pathogen-associated molecular patterns (PAMPs) by macrophages, dendritic cells (DCs), and other leukocytes to perform phagocytosis. Toll-like receptors (TLRs) are a family of pathogen pattern recognition receptors that sense PAMPs and trigger the production of pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)- α , IL-6, interferons (IFNs), and chemokines [10]. A genome-wide scan identified *myeloid differentiation primary response gene 88* (*MyD88*), a TLR signaling adaptor, as a candidate gene in ddY mice, a spontaneous IgAN model [11]. CD14 acts as a co-receptor with TLR4 to sense bacterial lipopolysaccharide (LPS). An association was observed between *TLR9* and *CD14* gene polymorphisms with disease progression in patients with IgAN [11, 12]. These findings suggest that activation of the TLR/MyD88 pathways by the exposure of microbial pathogens might affect the severity of IgAN.

Fc receptors are cell surface receptors that bind Fc portion of antibodies to facilitate phagocytosis of neutralized pathogens, to clear antigen-antibody complexes, to provide signaling, and to regulate immune response. Fc α R1 (CD89) is the IgA Fc receptor expressed on blood myeloid cells and mesangial cells. Two functional gene polymorphisms in the promoter region of *Fc α R* gene yielded controversial results on the risk of IgAN [13, 14]. An association between soluble CD89 levels with disease progression was found [15]. On the other hand, mesangial IgG deposition and circulating IgG-containing ICs are observed in patients with IgAN [16]. Therefore, pathologic roles of IgG and IgG Fc γ receptors in IgAN have been discussed. The major classes of human IgG Fc γ receptors have been identified with different affinities to IgG that vary from high (Fc γ RI) to low (Fc γ RIII). *Fc γ RIIA*, *IIIA*, and *IIIB* (*CD16*) gene polymorphisms were associated with susceptibility to IgAN and severity [17, 18].

Chemokines are a group of secreted proteins that attract cells bearing chemokine receptors into inflammatory tissue (chemotaxis). C-C chemokine receptor CCR5 has several ligands such as CCL5/RANTES, CCL3/MIP-1 α , CCL4/MIP-1 β , and CCL8/MCP-2 and is highly expressed on T cells. Chemokines and chemokine receptors have been shown to be involved in the resolution or progression of renal disease [19]. In human, homozygous 32 base pair deletion in *CCR5* gene (*CCR5*- Δ 32) generates a non-functional receptor and a reduced chemotactic response [20]. *CCR5* Delta32 mutation was associated with late progression to ESRD with dialysis and a better renal survival in patients with IgAN [21, 22].

Selectins are adhesion molecules involved in the leukocyte-endothelial cell interaction. Activated endothelial cells express E-selectin. P-selectin is expressed in platelets and activated endothelial cells. L-selectin (CD62L) is expressed in leukocytes [23]. Accumulation of leukocytes within the glomeruli and interstitium of kidney is considered an important mechanism in glomerulonephritis. The study showed up-regulated expression of P-selectin in the high endothelial venule-like vessels in renal interstitium in patients with IgAN [24]. Abnormalities in leukocyte homing in the mucosa–bone marrow axis also contribute to the pathogenesis of IgAN [25]. Functional single nucleotide polymorphisms (SNPs) in *E-selectin* (*SELE*) and *L-selectin* (*SELL*) gene were associated with susceptibility to IgAN and rapid progression to ESRD [26, 27]. These results were consistent with the findings of a genome-wide scan of ddY mouse which showed significant association between three chromosome regions on chromosome 1, 9, and 10 and glomerular injuries. The peak marker *D10MIT86* on chromosome 10 was located on the region syntenic to human *IGAN1* on chromosome 6. *D1MIT16* marker on chromosome 1 was very closely located at the locus of *selectin* gene [28].

Innate immunity links to adaptive immunity by antigen presentation of DCs to T cells. Adaptive immunity provides

Table 1 Candidate genes and the involved biological pathways in IgA nephropathy

Immune and biological response	Chromosome	Genes	Effect	Ref
Adaptive immunity				
Antigen presentation	6p21.3	HLA-B, -DRA, -DRB1, -DQA, DQB	D, P	[29, 162, 163]
Immunoglobulin class switch	11q13.3	IGHMBP2 ^a	D, N	[40, 41]
Cytokine	19q13.2	TGFB1 ^a	D, P	[36, 164, 165]
	12q15	IFNG ^a	D	[37, 166]
	5q31.1	IL4	P	[166]
	1q32.1	IL10 ^a	D, P, R	[33–35]
IgA transfer in epithelium	1q32.1	PIGR ^a	D	[38, 167]
Innate immunity				
Toll-like receptor	3p21.2	TLR9	P	[11]
	5q31.3	CD14	P	[12]
Fc receptor	1q23	FCGR2A, FCGR3A, FCGR3B	P	[17, 18]
	19q13.42	FCAR (CD89) ^a	D, N	[13–15]
Pro-inflammatory cytokine	6p21.33	TNF ^a	D, P	[168, 169]
	2q13	IL1B, IL1RN	D, P	[168, 170, 171]
Chemokine receptor	3p21.31	CCR5 ^a	P	[21, 22]
Adhesion molecule	1q24.2	SELE, SELL ^a (selectin) ^a	D	[26, 27]
Glycosylation of IgA	7p22.1	C1GALT1 ^a	D, P	[42–45]
	17q25.1	ST6GALNAC2 ^a	D, P	[45]
	Xq24	Cosmc (C1GALTC1)	N	[172]
Secretory proteins and IgA deposition	11q12.3	SCGB1A1 (Uteroglobin, CC10)	D, P, N	[48–50, 52]
Renal structure				
Mucin protein	3q29	MUC20	P	[61]
Serine protease inhibitor	18q21.33	SERPINB7 (Megsin)	D, P	[55–59]
Renin–angiotensin system	17q23.3	ACE ^a	D, P	[65, 173, 174]
	1q42.2	AGT	P	[66, 174]
	7q36.1	NOS3 (eNOS)	P	[65]

^a It has been proved to be functional gene polymorphisms by altering promoter activity or protein production

D development of IgAN, *P* progression of IgAN, *N* no association, *R* recurrence of IgAN, *HLA* human leukocyte antigen, *IFNG* interferon- γ , *IL4* interleukin-4, *TGFB1* tumor necrosis factor- β 1, *TNF* tumor necrosis factor- α , *IL1B* interleukin-1 β , *IL1RN* interleukin-1 receptor antagonist, *PIGR* polymeric immunoglobulin receptor, *CCR5* chemokine (C–C motif) receptor 5, *IGHMBP2* immunoglobulin μ binding protein 2, *TLR9* Toll-like receptor 9, *FCGR2A* Fc γ receptor IIA, *FCGR3A* Fc γ receptor IIIA, *FCGR3B* Fc γ receptor IIIB, *FCAR* Fc α receptor, *SELE* E-selectin, *SELL* L-selectin, *SCGB1A1* secretoglobulin, family 1A, member 1, *C1GALT1* core 1 β -1,3-galactosyltransferase, *ST6GALNAC2* GalNAc α -2,6-sialyltransferase II, *MUC20* mucin 20, cell surface-associated, *SER-PINB7* serpin peptidase inhibitor, clade B (ovalbumin), member 7, *ACE* angiotensin I converting enzyme, *AGT* angiotensinogen, *NOS3* nitric oxide synthase 3 (endothelial cell)

specific immune response with long-lasting immune memory, including production of antibodies against pathogen by B cells (so-called humoral immunity) and T cells-mediated immune response (so-called cellular immunity). There have been reports of positive association of certain human leukocyte antigen (*HLA*) and cytokines (*IFNG*, *IL4*, *IL10*, *TGFB1*, *TNFA*, *IL1B*, *IL1RN*) genes polymorphisms on disease susceptibility or progression (Table 1). The first genome-wide association study (GWAS) in UK, screening over 300,000 SNPs on the genome, yielded a strong association on chromosome 6p in MHC region (rs 3115573 and rs3130315, odds ratio (OR; 95% CI) 1.62 (1.39 to 1.90), *P* value = 1×10^{-9}). Further analysis showed the associ-

ation signals across the HLA-B, DRB1, DQA, and DQB loci [29].

Few studies evaluated with T helper 1 (Th1) and T helper 2 (Th2) profiles in IgAN. CD4⁺ Th1 cells produce cytokine interferon- γ (IFN- γ) that activates macrophages-mediated defense mechanism and inflammation. CD4⁺ Th2 cells secrete IL-4, IL-5, IL-10, and IL-13 cytokines that are essential for production of appropriate antibodies though B cells class switch recombination (CSR). Cytokine expression studies of peripheral blood mononuclear cells (PBMCs) showed increased levels of IFN- γ , IL-10, and transforming growth factor- β (TGF- β ; two cytokines important in IgA CSR), as well as enhanced Th2 cytokines

production at single cell level analysis in patients with IgAN [30–32]. *IL10* gene G-1082A polymorphism was associated with development, disease progression, and an increased recurrence of IgAN after renal transplantation [33–35]. The association between *TGF β* gene polymorphism and disease susceptibility was reported. Patients with high TGF- β levels showed a poor renal survival [36]. A family-based association study demonstrated that the *IFNG* +874A allele, strictly associated with *IFNG* 13-CA repeat allele, conferred susceptibility to IgAN, without influencing renal survival [37]. Different reports showed that *IFNG* +874A and *IL10* -1082G allele in IgAN patients correlated with lower IFN- γ and higher IL-10 cytokine production respectively, a Th2 cytokine response [9, 37].

The mucosal immune system provides frontline protection at the interface between the host and the environment and also regulates the tone of entire immune response. The dominant antibody in the mucosal immune system is IgA. A significant association between IgAN and *PIGR* gene encoding polymeric immunoglobulin receptor (pIgR) was found by the first partial GWAS in Japan, covering over 80,000 SNPs [38]. pIgR is a transmembrane protein expressed in the basolateral surface in glandular epithelium. It mediates the transport of polymeric immunoglobulins via transcytosis, particularly dimeric IgA or polymeric IgM, across mucosal epithelium to the lumen of gut, respiratory tract, or salivary gland. Secretory IgA arrests microbial pathogens and toxins at epithelial borders. Although it has been shown that defect in pIgR expression might result in impaired IgA secretion and high IgA serum levels in mice [39], no relationship between *PIGR* gene polymorphisms and serum IgA levels was found in patients. The author assumed that *PIGR* A580V polymorphisms might affect the binding of pIgA-PIGR [38].

The same study group further demonstrated a significant association of the gene encoding the immunoglobulin μ -binding protein 2 (*IGHMBP2*) with IgAN [40]. As the gene product is involved in immunoglobulin-class switching, and patients with 34448A allele higher serum levels of IgA, *IGHMBP2* gene polymorphism might influence CSR to IgA, resulting in a higher risk of IgA nephropathy. However, the association of *IGHMBP2* to IgAN was not significant in UK Caucasian or Chinese Han populations [41].

Incompleteness of *O*-glycosylation in the IgA1 hinge has been implicated as a central mechanism in the development of IgAN. Although underglycosylation was reported to be an acquired abnormality, genes for enzymes of *O*-glycosylation, *C1GALT1* (a galactosyltransferase), and *ST6GALNAC2* (a sialyltransferase) were associated with susceptibility to IgAN and disease outcome [42–45]. Reduced expression of *C1GALT1* was seen in homozygous 1365G/G individuals, compared with those with G/A or A/A genotypes [44]. The ADG haplotype of *ST6GALNAC2* gene conferred reduced

promoter activity and was associated with the degree of deficiency of α 2,6-sialic acid of IgA1 molecules in IgAN patients [46].

Uteroglobin (UG), also named Clara cell protein CC10, is a steroid inducible protein with potent immunomodulatory and anti-inflammatory effect and high affinity to fibronectin (Fn). UG knockout and antisense transgenic mice developed pathological and clinical features similar to fibronectin nephropathy and IgAN [47]. Several association studies of *uteroglobulin* (*SCGB1A1*) G38A gene polymorphism with IgAN yielded controversial conclusion [48–51]. A meta-analysis of six studies including 930 patients and 768 healthy controls showed no significant association between *uteroglobulin* 38A and risk for IgA nephropathy with OR (95%CI) 1.05 (0.71–1.54) for AA genotype, 0.96 (0.84–1.11) for A allele. *Uteroglobulin* G38A polymorphism was not associated with disease progression either [52].

Two novel proteins upregulated in the kidney of IgAN were identified. Megsin (SERPINB7) belongs to the serpin (serine protease inhibitor) superfamily, which is predominantly expressed in the glomerular mesangium [53, 54]. The genetic variations within the 3'-untranslated region of the megin gene were associated with susceptibility to IgAN and disease progression [55–59]. However, reversal results were seen between Chinese and Korean population. Further studies are required to resolve the reasons of disparity and to define the roles of megin in disease mechanism. On the other hand, a mucin protein MUC20 is highly expressed in the kidney upon injury [60]. The higher repeated times (SL/LL alleles) in the variable number of tandem repeats polymorphism of *MUC20* gene was associated with progression to ESRD in IgAN patients [61]. The repeated numbers of *MUC20* might affect not only the amount of glycosylation but also other physico-chemical property. Epithelial mucins function in cell protection via the interaction with bacteria/IgA and adhesion modulation via interaction with adhesion molecules (selectins). Mucins might also regulate cell growth and differentiation through signaling in ERK cascade and β -catenins pathway [60]. Further studies will be needed to define the roles of mucins in mucosal immunity, cell signaling, and proliferation in the pathogenesis of IgAN.

Renin-angiotensin system plays an important role in the progression of primary glomerulonephritis to ESRD. The carriers of *angiotensin I converting enzyme* (*ACE*) deletion (DD) genotype had significantly higher mean ACE activity than insertion (II) genotype individuals [62]. A meta-analysis of 20 association studies with conflicting results revealed *ACE* DD genotype is a risk for disease susceptibility in Asians with OR 2.37 (95% CI 1.04–5.41) but not in Caucasians and disease progression in Asians (OR 1.75) and Caucasians (OR 1.9) [63]. Patients with DD genotype also had a poor response to ACEI/ATRA

therapy in a randomized controlled trial [64]. The combination of *ACE* DD genotype and *endothelial nitric oxide synthase* (*eNOS*) 894 GG genotype was associated with an unfavorable outcome in a Caucasian cohort [65]. The T allele in *angiotensin* M235T polymorphism was associated with increased serum angiotensinogen concentrations and progressive loss of renal function of IgAN without the effect on hypertension [66, 67].

Microarray analysis represents the latest approach to gain information on global gene expression. A whole-genome expression analysis showed upregulation of genes in canonical WNT- β -catenin and PI3K/Akt pathways in PBMCs in IgAN patients. Hyperactivation of these pathways explained the enhanced proliferation of PBMCs in IgAN patients [68]. Up-regulation of the *apolipoprotein B messenger RNA-editing enzyme catalytic polypeptides 2* (*APOBEC2*) gene, a member of the cytidine deaminase of DNA/RNA editing enzyme, was also found in tonsils of patients with IgAN [69]. The expression of APOBEC2 is specific to skeletal and cardiac muscle. APOBEC2 does not have any RNA or DNA deaminase activity, but a recent report showed that it inhibit TGF- β signaling during early embryogenesis [70]. This result has not been confirmed by other studies.

The genetic approach appears to support important roles of dysregulated mucosal immune response, defective IgA glycosylation, and renin-angiotensin system activation in the pathogenesis of IgAN. Meta-analyses of combined datasets to confirm present data in correlation with biological function are expected. Genetic studies may further lead us to refine prognosis and treatment responsiveness (pharmacogenetics) in an individual and to find potential pathogenic pathways and novel treatments for IgAN.

IgA Immune System

IgA is the most abundant immunoglobulin in the body and in mucosal secretions. The majority of IgA is produced at mucosal tissues and secreted as secretory IgA (SIgA), with little entering the circulation. A small amount of IgA is produced by the plasma cells in the bone marrow and enters circulation, most in monomeric form (mIgA). The mucosal and systemic compartments are tightly linked and regulated, the so-called “mucosa–bone marrow axis” and two compartments function dependent on each other [25]. IgA is divided into two subclasses, IgA1 and IgA2, which differ by the absence of an 18-amino acid sequence in the hinge region of IgA2 [71]. This difference explains the resistance of IgA2 against degradation by bacterial proteases in mucosal surface. IgA1 comprises 85% of total serum IgA. IgA⁺ plasma cells are mainly of IgA1 subclass, 93% in the spleen,

peripheral lymph nodes, tonsils, nasal mucosa, 60–80% in bronchial mucosa, exocrine glands, duodenal, and gastric mucosa, in contrast to a dominance of IgA2 (64%) in the colon [72].

IgA system is different between human and mice. Murine IgA lacks a hinge region with *O*-glycosylation sites. Serum IgA in mice is exclusive polymeric in nature. A homologue of IgA receptor Fc α RI is not present in mice. These differences have limited the development of animal models for IgAN. The ddY mouse is a well-known model of spontaneous IgAN. These mice develop glomerulonephritis with IgA deposition in the mesangium [73].

Biological Function of Circulating IgA and IgA Receptors

The biological activities and physiological functions of circulating IgA are still poorly understood. It seems that circulatory IgA plays a paradoxical role in immune regulation. The major role of serum monomeric IgA (mIgA) has a powerful anti-inflammatory effect, such as down-regulation of IgG-mediated phagocytosis, chemotaxis, bactericidal activity, and cytokine release [74]. There are five types of IgA receptors: Fc α R, Fc α / μ receptor, pIgR, the hepatic asialoglycoprotein receptor (ASGPR), and transferrin receptor (CD71). Fc α RI (CD89) is expressed on Kupffer cells in liver, neutrophils, monocytes, and eosinophils. Fc α RI plays an essential anti-inflammatory role in physiology by transmission of inhibitory signals following binding of mIgA to Fc γ -associated Fc α RI. However, in pathology, Fc γ -associated Fc α RI favors the pro-inflammatory role. The polymeric IgA complexes result in enhanced IgA binding to Fc α RI on blood monocytes, which activate monocytes. This also leads to the generation of soluble IgA–Fc α RI complexes due to cleavage of the Fc α RI extracellular domain and then release of IgA–Fc α RI complexes into circulation. Soluble IgA–Fc α RI complexes deposit in tissue such as renal mesangium though binding of IgA1 to the other receptors such as CD71 and initiate inflammation [74].

Underglycosylation of IgA in IgA Nephropathy

Elevated serum levels of IgA were observed in about half of the patients with IgAN [75]. In patients with IgAN, the IgA in the mesangial deposits and in circulation as immune-complex is exclusively IgA1 subclass [76]. One of the most consistent abnormalities in IgAN is underglycosylation of IgA1 in serum and mesangium, which is rarely found in normal individuals. IgA1 is aberrantly galactosylated with deficient in galactose (Gal) in the hinge region *O*-linked glycans, resulting in truncated *O*-glycans as Tn antigen or

sialyl-Tn antigen [77–80] (Fig. 1). The undergalactosylated IgA1 has increased affinity for extracellular matrix, such as fibronectin, type IV collagen, which promotes mesangial deposition [81]. Studies demonstrated that undergalactosylated IgA1 in aggregates or immune-complexes also induced mesangial proliferation, complement activation, altered integrin expression, enhanced inflammatory response, and increased synthesis of extracellular matrix components [82, 83]. The binding of IgA to mesangial cells triggers the release pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor- α (TNF- α) [82–84]. Using a lectin-binding assay to detect underglycosylated IgA1 in serum might have potential as a non-invasive diagnostic test for IgAN [85].

The hinge region of IgA1 contains six *O*-linked glycosylation sites with serine and threonine residues, which are the sites of attachment of *O*-linked glycans consisting of *N*-acetylgalactosamine (GalNAc) with a β 1,3-linked galactose (Gal) and sialic acids, such as *N*-acetylneuraminic acid (NeuNAc) [71] (Fig. 1). The synthesis of *O*-glycan is initiated by adding GalNAc to serine or threonine residues by the enzyme *N*-acetylgalactosaminyltransferase 2 (GalNAcT2). Gal is attached to GalNAc by core 1 β 1,3-galactosyltransferase (C1GalT1) with its chaperone Cosmc [86, 87]. Sialic acid NeuAc is linked to GalNAc by α 2,6-

GalNAc-sialyltransferase I or II (ST6GalNAcI or ST6GalNAcII) or linked to Gal by an α 2,3-Gal-sialyltransferase.

Using Epstein-Barr virus (EBV)-immortalized B cell lines established from circulating IgA1-producing B cells, underglycosylation of IgA1 was only seen in IgAN patients, not in normal individuals or disease controls. Suzuki et al. demonstrated that premature sialylation due to enhanced ST6GalNAc activity and/or reduced galactosylation due to decreased C1GalT1 activity might contribute to underglycosylation of IgA1 in IgAN [77]. Furthermore, low expression of Cosmc gene was found in peripheral B lymphocytes of patients with IgAN. Cosmc expression levels negatively correlated with glycosylation levels of IgA1 and proteinuria [88].

At present, little is known about the control of IgA1 *O*-glycosylation in B cells. Evidence shows that glycosylation of IgA is regulated by external stimuli and cytokines. Using Th1- or Th2-prone mice, a study demonstrated that cytokines might determine the severity of IgAN by regulating IgA glycosylation. Increased Th2 cytokines can decrease glycosylation levels of IgA, which results in more significant renal insufficiency [89]. IL-4 stimulation in a human B cell line yielded higher IgA1 production, a significantly decreased Cosmc mRNA levels, decreased C1GalT1 mRNA levels and activity, with defective galactosylation of the *O*-glycans of IgA1 hinge region [90].

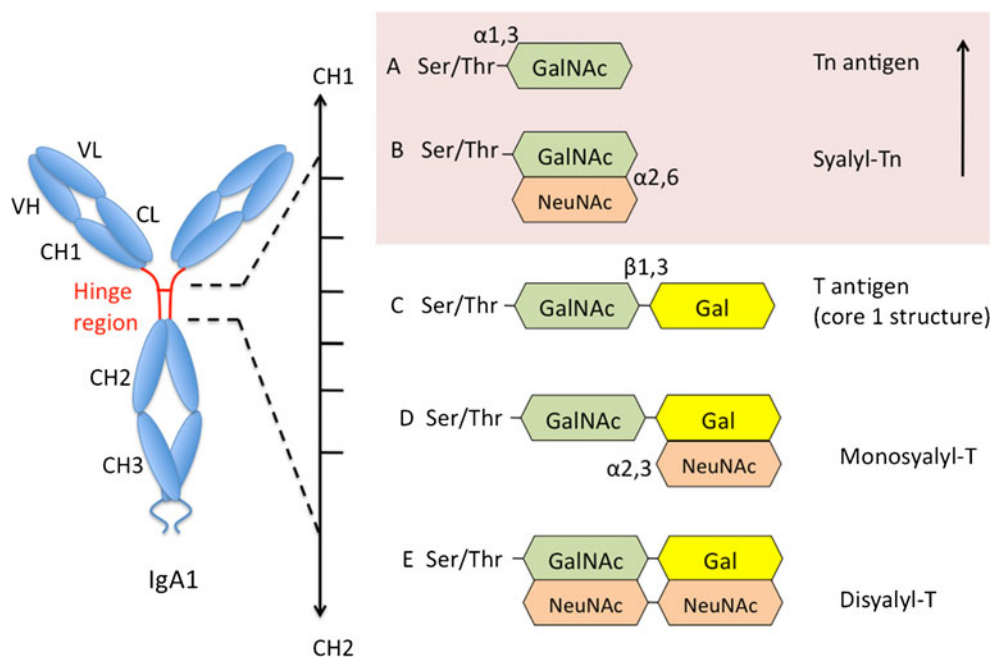


Fig. 1 The structure of IgA1 and *O*-linked carbohydrates in the hinge region. A hinge region consists of 18 to 23 amino acids and nine potential *O*-glycation sites between the CH2 and CH3 domains. *N*-acetylgalactosamine (GalNAc) is α 1,3-linked to serine (Ser) or threonine (Thr) residues in the hinge region of the IgA1. Sialic acid *N*-acetylneuraminic acid (NeuNAc) is α 2,6-linked to GalNAc or α 2,3-linked to Galactose (Gal) residues. Abnormal IgA1 in patients with IgAN poses an increased proportion of the terminal as either **a**

GalNAc (Tn antigen) or **b** GalNAc-NeuNAc glucan structures (sialyl-Tn antigen). The T antigen, or the core 1 structure, is formed by an addition of Gal in β 1,3 linkage to the GalNAc of Tn antigen. Abbreviations: VL variable region of light chain, VH variable region of heavy chain, CL constant region of light chain, CH1, CH2, CH3, three domains of the constant regions of the heavy chain; the Ser/Thr residues of *O*-glycosylation sites in the hinge region are indicated by small bars

However, a significant inhibition of Cosmc expression was found using LPS stimulation of peripheral B lymphocytes of patients with IgAN [91]. Mechanisms of regulation of C1GalT1 and/or Cosmc activity in B cells of IgAN remain unclear.

Interestingly, *O*-glycosylation of IgA1 and IgD was differentially controlled during B cell maturation by analyzing their lectin binding activity. Defective *O*-glycosylation was seen in IgA1 not in IgD in patients with IgAN. It is general accepted that defective glycosylation arising at a later stage of B cell development and maturation due to aberrant immune regulation after acquired stimuli, rather than an inherited nature [92]. It is also now well recognized that aberrant glycosylation is limited to a small fraction of the total IgA1 and originates from a small B cell subset.

Mucosal IgA Response

Clinical observation showed that presence of macroscopic hematuria coincidently or immediately followed an upper respiratory tract or gastrointestinal tract infection. It provides a rationale for a connection between mucosal immune response after encounters of antigens and IgAN [4, 93]. IgA has a critical role in the mucosal defense against microbes. Human mucosa-associated lymphoid tissues are constituted by two compartments: gut-associated lymphoid tissue (GALT) and nasopharynx-associated lymphoid tissues (NALT) [94]. In rodents, NALT is found on both sides of the nasopharyngeal duct, and it is considered analogous to Waldeyer's ring, including palatine tonsils and adenoids, in human. NALT and GALT have similar immunological characteristics and biological functions, as well as to contain the same types of resident immune cells (Table 2). However, the homing receptors- and chemokines-mediated lymphocyte trafficking are different between GALT and NALT (Fig. 2). Bronchus-associated lymphoid tissues in

mice are not generally detectable in normal lungs of adult humans [95].

In GALT, mucosal antigens initiate IgA production by activating follicular B cells in germinal centers of Peyer's patches (PPs) through T cell-dependent reaction. Dendritic cells (DCs) located beneath specialized M cells take up microbial antigens and migrate to T cell zone to present antigen in MHC molecules to T cells (so-called follicular helper T cells). B–T interaction through CD40–CD40L interaction and cytokines (mainly IL-10, TGF-β) stimulation activate B cells which then express activation-induced cytidine deaminase and undergo CSR from IgM to IgA and somatic hypermutation (SHM) for affinity maturation [96]. More than 80% of plasma cells in the mucosa produce IgA [97]. The preferential generation of IgA by CSR are due to abundant production of activated TGF-β, IL-6, IL-10, IL-21, and retinoid acid in the mucosal environment [98].

On the other hand, TLR/MyD88 activation (including TLR2, TLR4, TLR5, and TLR9) by mucosal antigens could also stimulate lamina propria (LP) DCs (including iNOS⁺ DCs) and stromal cells to release innate signals (such as BAFF, APRIL, TNF-α, TGF-β, retinoid acid) to enhance CSR to IgA in activated B cells in a T cells independent (TI) manner. The conventional B2 cells and a specialized CD5⁺ B1a subset are involved in the TI response [99–101]. In TI response, engagement of TLRs by microbial ligands enhances IgA CSR and production through two independent TIR (Toll-IL1 receptor domain)/MyD88 and TACI (transmembrane activator and calcium-modulating cyclophilin-ligand interactor)/MyD88 signaling pathways [99]. CSR to IgA and intestinal IgA response were impaired both in mice and human lacking MyD88 [102].

The vast majority of IgA produced by mucosal B cells is as dimeric form (DIgA) joined by a J chain. DIgA is transported through intestinal epithelial cells after binding to pIgR via transcytosis and become secretory IgA (SIgA). High-affinity SIgA antibodies from T cell-dependent pathways

Table 2 The compartments and immunological features of human mucosa-associated lymphoid tissues (MALT)

	Gut-associated lymphoid tissue (GALT)	Nasopharynx-associated lymphoid tissue (NALT)
Inductive sites	Peyer's patches	Waldeyer's pharyngeal ring (adenoids and paired palatine tonsils)
	Isolated lymphoid follicles	Isolated lymphoid follicles
Main immunological function	CSR from IgM to IgA through TD and TI pathways	CSR from IgM to IgA through TD and TI pathways
Effector sites	Lamina propria of small intestine, colon	Nasal passages
Draining lymph nodes	Mesenteric lymph nodes	Cervical lymph nodes
Induced antigen-specific immunity following vaccination	Gastrointestinal tract	Respiratory tract, salivary gland, genito-urinary tract

CSR class switch recombination, TD T cell-dependent, TI T cell-independent, CCR C–C chemokine receptors
Mesenteric and cervical lymph nodes are not classified into MALT

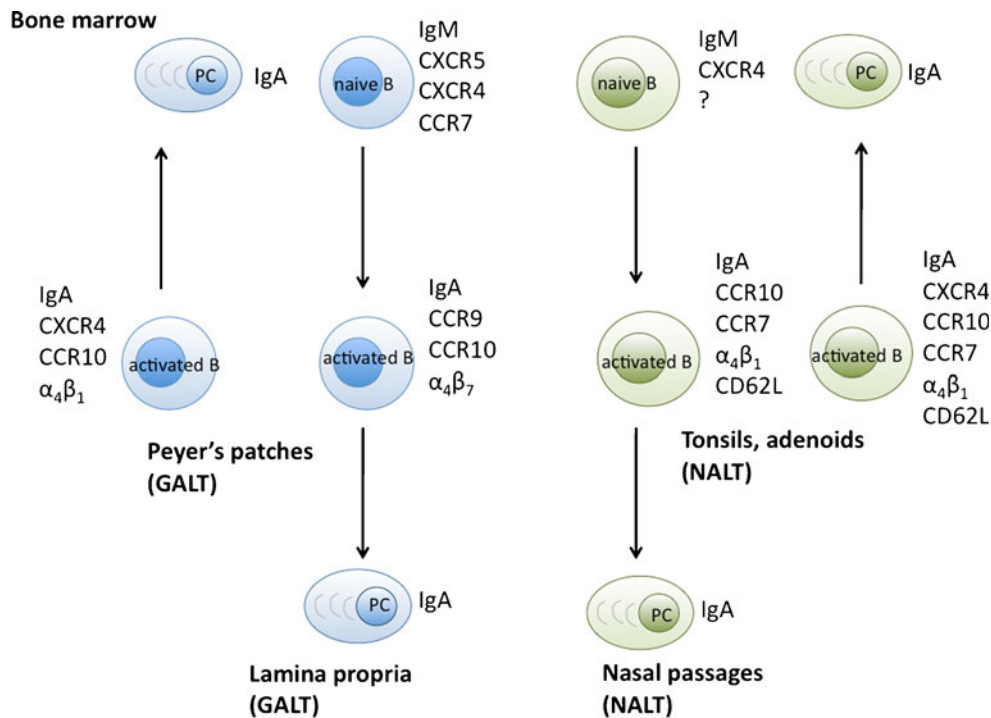


Fig. 2 A scheme of the trafficking of B cells between bone marrow, gut-associated lymphoid tissue (GALT), and nasopharynx-associated lymphoid tissue (NALT). Naïve B cells expressing surface IgM and chemokines receptors CXCR5, CXCR4, and CCR7 emerge from the bone marrow and migrate to Peyer's patches (PPs) of small intestine. Homing of activated B cells from PPs depends on the interaction of $\alpha_4\beta_7$ integrin with MADCAM1 expressed on the endothelium in the intestinal lamina propria. In the small intestine, CCR9-expressing B cells are attracted by the chemokine CCL25 secreted in lamina propria of small intestine, while CCL28–CCR10 interaction appears to be important in the colon. A small proportion of activated B cells expressing CXCR4 and

CCR10 that bind respectively to CXCL12 and CCL28 produced in the bone marrow. Integrin $\alpha_4\beta_1$ -VCAM1 (vascular cell-adhesion molecule-1) interaction also contributes to GALT-derived B cells homing to bone marrow. On the other hand, the homing receptors used in NALT are less understood. CXCR4–CXCL12 interaction might mediate B cells trafficking between bone marrow and NALT. The interaction of CD62L (L-selectin)–PNAd, $\alpha_4\beta_1$ integrin–VCAM1, CCR7–CCL19, CCL21, and CCR10–CCL28 might mediate the homing the NALT-derived activated B cells to bone marrow and other effector sites such as nasal passages [95, 138]. Chemokine receptor/chemokine: CCR9/CCL25; CCR10/CCL28; CCR7/CCL19, and CCL21; CXCR4/CXCL12; CXCR5/CXCL13

function in protection against invasion by pathogenic microbes in mucosal surfaces by neutralization, while low affinity SIgA antibodies from T cell-independent pathways are important to confine commensal bacteria in the intestinal lumen and prevent initial adherence through a process known as “immune exclusion” [103]. In pIgR knock-out mice, loss of pIgR-mediated transport of dimeric IgA resulted in intestinal SIgA deficiency, paralleled by increased levels of seral dimeric IgA [39, 104]. In addition, pIgR deficiency did not have any effect on the induction of a respiratory mucosal immune response or a systemic immune response [104].

Aberrant Mucosal Immunity and IgA Nephropathy

Common microbial or food antigen may trigger the dysregulated innate immune response. Antibodies to a wide spectrum of viral and bacterial infectious agents and diet antigens such as gluten, soy, and cow's milk protein antigens have been detected in sera or the glomerular mesangium from patients with IgAN [105–107]. However, no

consistent antigen associated with mesangial IgA deposition was identified. A variety of pathogens have been used in experimental animal of IgAN, including *Staphylococcus aureus* in Th2-prone mice [108], oral immunization of *Hemophilus parainfluenza* [109] and intranasal immunization of *Sendai virus* (a rodent parainfluenza virus) [110, 111]. Oral immunization of gliadin and other antigen can also induce a specific IgA mucosal immune response and reproduce IgAN in mice [112, 113]. A recent report showed significant presence of *Helicobacter pylori* in the palatine tonsils in patients with IgAN [114].

Up-regulation of TLR4, but not TLR3 and TLR7, in transcriptional levels and surface expression in peripheral monocytes were significantly increased in patients with IgAN, particularly in association with proteinuria and heavy microscopic hematuria [115]. In the ddY mice, nasal challenge with CpG DNA, the TLR9 ligands expressed in bacteria and viruses, led to Th1 polarization, increased serum and mesangial IgA, and aggravated renal injury [11]. Transgenic mice over-expressing BAFF developed renal IgA deposits similar to IgAN [100].

The roles of CD19⁺CD5⁺ B1a cells in IgAN are unclear, but B1a cells have been proved to be involved in autoimmune diseases [116]. A significantly higher percentage of CD19⁺CD5⁺ B1a cells were observed in peripheral blood B lymphocytes, tonsillar germinal centers, and in kidney in patients with IgAN [117–119]. Those B1a cells secrete higher levels of IgA and IFN- γ and are more resistant to Fas-mediated apoptosis in patients compared with controls and lupus patients, probably enhancing renal inflammation and tubulointerstitial injury [119].

A special subset of T cells bearing $\gamma\delta$ T cell receptors ($\gamma\delta$ T cells) appears to regulate IgA production in the mucosa, especially NALT. Human $\gamma\delta$ T cells express one of the six V γ gene segments and three V δ genes. A decrease of $\gamma\delta$ T cells expressing V γ 3 and V δ 3 in duodenal mucosa and bone marrow in patients with IgAN [120, 121]. On the contrary, a study showed that the percentage of $\gamma\delta$ T cells increased in PBMCs was correlated with the percentage of IgA⁺ B cells significantly in patients with IgAN. Isolated $\gamma\delta$ T cells from IgAN patients induced surface IgA expression on naive B cells and produced large amount of TGF- β [122]. The roles of $\gamma\delta$ T cells in the pathogenesis of IgAN remain to be defined.

Many studies suggest the involvement of tonsils in the pathogenesis of IgAN. Underglycosylation of IgA1 was found not only in serum and but also in renal deposits. The same pattern in glycosylation is found in IgA produced in vitro by tonsillar lymphocytes [123]. Tonsillar CD19⁺ B cells had decreased C1GalT1 gene expression in patients with IgAN [124]. Increased dimeric IgA-producing plasma cells, increased CD5⁺ B1a cells and decreased CD4⁺CD25⁺ T cells were observed in tonsils of IgAN patients [118, 125, 126]. However, from the point of view of treatment in IgAN, the benefits of tonsillectomy are not impressive and are considered insufficient to change the prognosis of patients with renal damage [127].

There is no question about the importance of IgA-mediated protection at mucosal surface. A pathogenic role of SIgA is suggested by the fact that SIgA is present in renal biopsies in 15% of the cases using a specific staining of secretory component [128]. It is oversimplified to assume IgAN as a consequence of overproduction of mucosal polymeric IgA which spilled into the circulation and deposited in the mesangium. Dysregulation of mucosal response might result in failure of mucosal antigen elimination, prolonged antigen exposure, and lead to excessive activation of systemic IgA immune response and glomerulonephritis.

“Mucosa-bone Marrow Axis”—Homing of Lymphocytes in IgA Nephropathy

The mechanisms underlying underglycosylation of IgA1 in IgAN are still unclear. The major site of the underglycosylated IgA production in IgAN remains uncertain. It is a general

agreement that circulatory IgA antibodies are mainly produced in the bone marrow. Large numbers of pIgA1-secreting plasma cells are found in the bone marrow of IgAN patients [129]. There are controversial results that the number of IgA-producing plasma cells was reduced [130] or normal [131] in intestinal mucosa in IgAN.

To have a better view on the development of IgA immune response, several groups have performed vaccination studies in IgAN patients. An impaired mucosal IgA response with normal IgG and IgM response were demonstrated after a neoantigen exposure, using nasal immunization of cholera toxin B subunit and oral immunization of live typhoid vaccine [132, 133]. However, systemic immunization of tetanus toxoid, influenza vaccine, or mucosal immunization with oral polio vaccine, the recall antigens, resulted in an enhanced and prolonged systemic IgA response [134, 135].

To investigate whether the site of antigen encounter influences IgA1 O-glycosylation, the glycosylation of serum IgA1 after subcutaneous immunization of tetanus toxoid, a systemic antigen, and after *H. pylori* infection, a mucosal antigen, was analyzed in patients with IgAN and healthy controls. The O-glycosylation of allergen specific IgA1 antibodies did not differ between patients and controls. Patients could produce full spectrum of IgA1 O-glycoforms. Moreover, IgA1 with high lectin binding, indicating underglycosylation, was produced in response to mucosal infection in all subjects [136]. The reasons for different glycosylation of IgA1 in mucosa and bone marrow remains poorly understood. Nevertheless, this important study raises a possibility of an increase in “mucosal-type” IgA1 in the serum in IgAN. It is more evident that “mucosal type” pIgA1 is produced in the bone marrow of patients with IgAN, namely a misdirected of IgA1 secreting plasma cells from mucosa to systemic sites, such as bone marrow [137]. Therefore, abnormalities in the cross-talk between mucosa and bone marrow may play an important role in the pathogenesis of IgAN.

Studies have revealed continued trafficking of antigen-specific lymphocytes and antigen-presenting cells between mucosa and bone marrow. Chemokines and adhesion molecules coordinate the migration of plasma cells from the site of antigen-driven differentiation in lymphoid tissues to target effector tissues. IgA-secreting plasma cells have trafficking pattern related to the site of production [138]. Differentiation and homing of plasma cells in the lamina propria of the small intestine is associated with the upregulation of $\alpha_4\beta_7$ integrin and C–C chemokine receptor 9 (CCR9) and CCR10, while the expression of $\alpha_4\beta_1$ integrin and CXC chemokine receptor 4 (CXCR4) is related to differentiation and homing of B cells to the bone marrow [95, 138] (Fig. 2). Limited studies focus on changes in the homing of lymphocytes between mucosal and systemic sites in IgAN. A study showed that activated CD3⁺ T cells

express $\alpha_4\beta_1$ integrin rather than $\alpha_4\beta_7$ integrin in patients with IgAN [139].

IgA-Containing Immune Complexes in Circulation and Kidney in IgAN

The roles of IgA-containing ICs in the pathogenesis of IgAN are supported by diffuse and generalized mesangial deposition of IgA, usually accompanied by deposition of complement C3 and variable deposition of IgG and/or IgM. Elevated levels of circulating IgA-ICs are seen in most patients with IgAN [140]. Underglycosylated IgA1-ICs are retained in the circulation for long period of time due to impaired immune-complex clearance and then deposited in the mesangium [141].

Some of the components of IgA-ICs have been identified, mainly underglycosylated IgA, as well as fibronectin (Fn), collagen, soluble Fc α RI (CD89), and IgG [142]. Uteroglobin (UG) has strong binding affinity to fibronectin. UG interacts with Fn and prevents IgA-Fn ICs formation in IgAN. UG knockout and antisense transgenic mice developed pathological and clinical features similar to fibronectin nephropathy and IgAN. Treatment with purified recombinant human UG in mice prevented abnormal glomerular deposition of Fn and IgA by binding of UG to Fn [47]. However, only about half of the patients with IgAN have IgA-Fn ICs [143]. The specific heparin-binding site on the Fn molecules with UG interacts is identified, which would be a potential drug target for IgAN [144].

Increased levels of IgA are associated with decreased expression of surface CD89 on monocytes in IgAN [145]. Elevated soluble CD89 due to shedding of surface CD89, a highly glycosylated 50 to 70-kDa protein, were detected in patients with IgAN but not in healthy controls. Another soluble CD89, a slightly glycosylated 30-kDa protein, complexed with pIgA present in patients with IgAN and healthy controls [146]. Human CD89 transgenic mice that express human CD89 on macrophages and monocytes had circulating IgA-CD89 ICs and develop spontaneous IgAN [147]. Furthermore, the disease can be transferred to immunodeficient recipients by injecting serum. SCID-Fc α RI transgenic mice, which do not develop IgAN spontaneously, develop manifestations of IgAN upon injection of IgA from patients with IgAN. But, IgA from healthy subjects did not result in IgAN in such mice [147]. This result provides an evidence of a pathogenic role of IgA-CD89 ICs in IgAN.

Mesangial IgG deposition is considered as risk factors for hypertension and renal failure in early IgAN [148]. The percentage of concomitant IgG deposition in renal biopsies shows large variation and is not universally present [106]. Immune-complexes composed of aberrantly glycosylated

IgA1 and IgG autoantibodies as well as free IgG autoantibodies are present in the circulation of subjects with IgAN [141]. Suzuki et al. showed that sera and culture supernatants of EBV-immortalized peripheral B cells of patients of IgAN contained elevated levels of IgG antibodies against the GalNac epitopes on the Gal-deficient hinge-region *O*-glycans of IgA1 [16]. The seral levels of the glycan-specific IgG antibodies correlated with proteinuria. The binding of the glycan-specific IgG to undergalactosylated IgA1 significantly favored the formation of immune-complexes. Moreover, these IgG autoantibodies contained a common A to S amino acid substitution in a region of IgG V_H molecule due to mutations of the variable region of *IGH* gene (*IgG V_H*). Whether these mutations arise from underlying genetic polymorphisms or from somatic hypermutation was unclear [16, 149]. It seemed that both undergalactosylated IgA1 and glycan specific IgG, representing disease-specific markers, are essential for the development and progression of IgAN. In addition, there is a speculation without evidence to support that IgG anti-IgA antibodies could be produced against bacterial or viral surface glycoproteins during infection and cross-react to the glycans on IgA1, a phenomenon known as “molecular mimicry” [137].

The mechanism of deposition of IgA-ICs in the mesangium in IgAN is poorly understood. There is no evidence to support the deposited IgA is directed against renal antigens. Mesangial cells do not express CD89, ASGPR, and pIgR [150]. The transferrin receptor (CD71) is identified as a mesangial IgA1 receptor, which is upregulated in mesangium in patients with IgAN but not in healthy controls. CD71 binds pIgA1, not IgA2, and has a higher affinity of underglycosylated IgA1 and IgA-ICs. Fc α / μ receptor is receptor for IgA and IgM which is expressed on mouse monocytes and B cells. Human mesangial cells express mRNA for Fc α / μ receptor after IL-1 stimulation, thereby implying another receptor for IgA deposition [151]. Whether Fc α / μ receptor is upregulated in mesangium and the binding of IgA to Fc α / μ receptor triggers inflammation in IgAN still has to be elucidated.

It is considered that pathogenesis of IgAN to occur in three phases. In the early primary phase, B cells produce pIgA that initiates glomerular IgA-ICs deposition. In the secondary phase, continuous activation of mesangial cells, the complement system and the recruited macrophages that produce cytokines and growth factors, such as IL-6, IL-8, TNF- α , TGF- β , chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor, platelet-derived growth factor (PDGF), leading to glomerulosclerosis. In the tertiary phase, interstitial infiltration of CD8⁺T cells and the sentinel $\gamma\delta$ T cells cause tubular injury and irreversible interstitial fibrosis leading to ESRD [152].

IgA1 deposition is commonly associated with C3 complement but rarely C1q (a marker of classical pathway activation) in the mesangium, suggesting complement

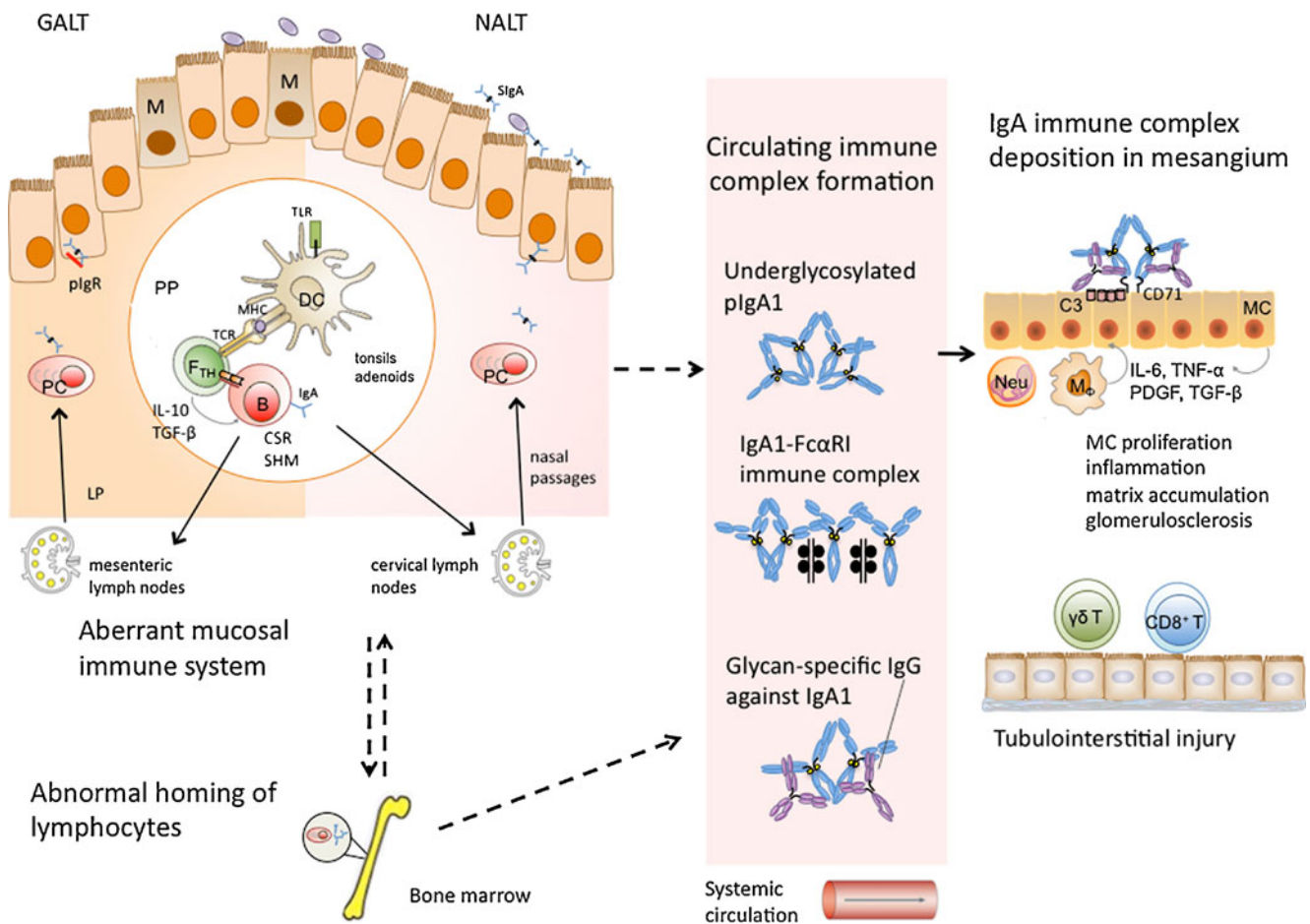


Fig. 3 Possible mechanisms underlying the development and progression of IgA nephropathy. T cells activated by dendritic cells (DCs) presenting mucosal antigens drive naïve B cells to undergo class switch recombination (CSR) from IgM to IgA in a T cell-dependent manner in the Peyer's patches of small intestine and tonsils/adenoids in the NALT. Activated B cells migrate to regional lymph nodes and home to lamina propria of small intestine or nasal passages in the NALT where they terminally differentiate into IgA-secreting plasma cells. A T cell-independent response of IgA production also occurs in the lamina propria of small intestine and nasal tissues in the NALT. Dimeric IgAs associated with pIgR are transported through the intestinal epithelium to become secretory IgA (SIgA) for pathogen defense. Aberrant mucosal immune response involving TLR signaling and impaired homing of IgA-producing plasma cells to bone marrow might lead to increased production of underglycosylated IgA1. Unglycosylated IgA1 tends to self-aggregate into polymeric form (pIgA1). Soluble FcαRI (sCD89), fibronectin, and IgG antibodies against the galactose-deficient glycans of the hinge region of IgA1 are also found in the circulating

immune-complex. The binding of IgA1-containing immune-complexes to glomerular mesangial cells is enhanced via CD71 (transferrin receptor). The continuous activation of mesangial cells, the complements (C3) and macrophages that produce cytokines and growth factors, such as IL-6, TNF- α , TGF- β , and PDGF, leading to matrix accumulation and glomerulosclerosis. Neutrophils infiltrated into the glomeruli further augment glomerular damage by the release of superoxide and proteolytic enzymes. Further recruitment of CD8⁺ cytotoxic T cells and the sentinel $\gamma\delta$ T cells contribute to tubulointerstitial injury. *GALT* gut-associated lymphoid tissue, *NALT* nasopharynx-associated lymphoid tissue, *M* cells microfold cells, *SIgA* secretory IgA, *TLR* Toll-like receptors, *PP* Peyer's patches, *LP* lamina propria, *DC* dendritic cells, *F_{TH}* follicular T helper cells, *CSR* class switch recombination, *SHM* somatic hypermutation, *PC* plasma cells, *pIgR* polymeric immunoglobulin receptors, *pIgA1* polymeric IgA1, *IL-6* interleukin-6, *TNF- α* tumor necrosis factor- α , *TGF- β* transforming growth factor- β , *PDGF* platelet-derived growth factor, *MC* mesangial cells, *Neu* neutrophils, *M ϕ* , macrophages

activation through alternative pathway in patients with IgAN. Complement activation through alternative pathway by IgA has been documented [153]. It has been shown that human IgA can also activate lectin pathway driven by mannose-binding lectin (MBL) [154]. It is supported by detection of MBL, mannose-binding lectin-associated serine proteases (MASP-1), C3, C4, and IgA in the mesangium in patients with IgAN [155]. In addition, a strong colocalization of SIgA, MBL, or

C4d in renal biopsies provides evidence for a pathogenic role of SIgA associated with lectin pathway activation in IgAN [128]. Glomerular deposition of MBL is associated with more pronounced renal damage histologically such as increased mesangial proliferation, extracapillary proliferation, glomerular sclerosis, interstitial infiltration, as well as with significantly more proteinuria [156]. Mesangial deposition of C4d is also associated with poor renal survival [157].

IgA Nephropathy and Henoch–Schonlein Purpura

HSP is the most common systemic vasculitis in children, which is characterized by purpuric rash, nephritis, gastrointestinal involvement, and arthralgia/arthritis. In contrast to the insidious onset and slow progressive nature in IgAN, HSP has an acute onset, self-limited, and rarely progressed to ESRD. The renal biopsy in HSP nephritis (HSPN) and IgAN patients are identical morphologically and glomeruli deposits contain exclusive IgA1. The glycosylation defects in serum IgA1 are similar in both IgAN and HSPN. Gal-deficient IgA1 and IgA-IgG immune-complexes were found in sera of patients with HSPN but not in HSP patients without nephritis [158, 159]. The expression of CD71 mesangial IgA receptor was also upregulated in HSP nephritis [160]. One with IgAN and one with HSP in identical twins after adenovirus infection have been reported [161]. It is evident that clinical symptoms are triggered or aggravated after an episode of upper respiratory tract infection in both diseases. However, the key factors deciding the direction of systemic or local action of IgA-containing immune-complexes after mucosal immunity activation have not been identified.

Conclusions

IgA nephropathy is an IgA1-containing immune-complex-mediated glomerulonephritis. Genetic factors are considered to be involved in the initiation and progression of IgAN. The cognate antigens of IgA remain unclear. Underglycosylation of IgA1 is the key mechanism in the disease pathogenesis. Aberrant mucosal immune response is linked to an enhanced systemic IgA response, which results in elevated serum levels of IgA1, polymeric, and underglycosylated in nature. Abnormal leukocytes trafficking between mucosa, bone marrow, and systemic lymphoid organs might also contribute to the production of “mucosal type” pIgA from the bone marrow. Glycan-specific IgG antibodies provide a second hit leading to the development or progression of IgAN. Underglycosylated IgA1-containing immune-complexes bind to mesangial cells via CD71 and results in mesangial inflammation, matrix accumulation, glomerulosclerosis, and further tubulointerstitial injury (Fig. 3).

Recent some breakthrough studies provide new insights into disease pathogenesis and lead to new methods of noninvasive diagnosis and monitoring patients with IgAN. It also points to new possibilities for future research on targeted therapy directed at inhibition of the interaction between glycan-specific IgG and underglycosylated IgA1 molecules in IgAN. Anti-Fc α RI or anti-CD71 antibodies are also potential therapeutic tools to prevent the progression of renal inflammation.

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