Review Article

IgA Production and Tonsillar Focal Infection in IgA Nephropathy

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IgA nephropathy (IgAN), the common primary glomerulonephritis, is a tonsillar focal infection characterized by the qualitative abnormality of IgA in circulation and IgA deposition in the renal mesangium. Mesangial deposition of IgA, which is composed predominantly of poorly galactosylated polymeric IgA1 (pIgA1), seems to be the initiating event in the pathogenesis of IgAN. The origin of poorly galactosylated IgA, however, remains unclear. Recent studies suggest that the mesangial polymeric IgA1 deposition could be derived from mucosally primed plasma cells. B cells may undergo IgA class switching to acquire the expression of IgA via T-cell-dependent or T-cell-independent pathways in mucosa-associated lymphoid tissue and then differentiate to IgA plasma cells or home in on systemic sites. Dendritic cells, including plasmacytoid dendritic cells and another type of antigen-retaining cell, follicular dendritic cells, have an irreplaceable role in IgA class-switch mechanisms by producing IgA-inducing signals. Furthermore, an increased number of pIgA1-secreting plasma cells in the bone marrow and tonsils, as well as increased IgA class switching, have been found in IgAN, providing a link between the mucosal immunity and IgAN. The favorable effect of tonsillectomy on patients with IgAN showed that tonsillar focal infection may be closely related to pIgA1 deposition in glomerular mesangium of patients with IgAN and at least a part of pIgA1 may originate from affected tonsils. Therefore, the indication for tonsillectomy should be considered in patients with IgA nephropathy, especially at a mild or early stage, to prevent future renal deterioration. In this paper, we focus on IgA class switching and the role of tonsils with focal infection in IgAN. [J Clin Exp Hematopathol 52(3): 161-170, 2012]

Keywords: immunoglobulin A nephropathy, pathogenesis, IgA class switching, follicular dendritic cell, tonsillectomy

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is a common cause of glomerulonephritis and of end-stage renal failure, and was first described by Professor Berger in 1968. It is characterized by an overrepresentation of poorly galactosylated IgA1 molecules in the serum and mesangial deposition of IgA immune complexes accompanied by mesangial proliferative glomerulonephritis (Fig. 1A). It remains unclear where the poorly galactosylated IgA1 originates and whether there are any effective treatments for patients with IgAN.1 Recent evidence suggests that the mesangial deposition of polymeric IgA1 in IgA nephropathy is derived from mucosally primed plasma cells (Fig. 1B). This may provide a link between the mucosal immunity and IgAN. On the other hand, IgA class switching is a significant source of IgA production. In this review, we discuss the pathogenesis of IgAN, the abnormal production of IgA in IgAN, the role of dendritic cells (DC) and follicular dendritic cells (FDC) in IgA class switching, and the relationship between tonsillar focal infection and IgA nephropathy, as well as the effectiveness of tonsillectomy on adult and child IgAN.

THE PATHOGENESIS OF IgA NEPHROPATHY

Overview of the pathogenesis of IgA nephropathy

Mesangial deposition of IgA, which is predominantly polymeric IgA1 (pIgA1), seems to be the initiating event in the pathogenesis of IgAN. Then, IgA accumulation in the mesangium appears to be the principal trigger for the development of mesangial proliferative glomerulonephritis, which is mediated predominantly through IgA-induced activation of resident mesangial cells and local complement activation.2 Up to 60% of patients with IgAN present with recurrence of glomeru-
ular IgA deposition after renal allograft, which indicates that mesangial IgA is probably derived from a circulating pool of pathogenic IgA. In addition, the association of episodic macroscopic hematuria with mucosal infections originally led to the suspicion that IgAN may be intimately linked with abnormal mucosal antigen handling, particularly because both mesangial IgA and serum IgA immune complex (IgA-IC) predominantly contain pIgA, which is normally produced at mucosal surfaces rather than in systemic immune sites.

**IgA immune system in humans**

There are two subclasses of human IgA, IgA1 and IgA2, both of which can exist in monomeric or polymeric (pIgA) forms (Fig. 2). Human IgA1 and IgA2 subclasses are encoded by two distinct Ca1 and Ca2 genes and possess a seemingly identical receptor-binding profile, but a different distribution in the body. The major difference between IgA1 and IgA2 is the presence of an 18-amino-acid hinge region in IgA1, which could have activity as a protease of Streptococcus, Neisseria, and Haemophilus species. Its hinge region of heavily glycosylated IgA1 contains several sites of O-linked glycan attachments. Therefore, the physicochemical properties of IgA1 are always variably affected by the tight clustering and variability of sialic acid, galactose, and N-acetylgalactosamine residues. Polymeric IgA consists of two or more IgA monomers linked by a joining protein, the J chain. Secretory IgA (sIgA) on mucosal surfaces has an additional protein, secretory component (Fig. 2).

**Abnormalities of the IgA molecule in IgAN**

The most noteworthy finding in IgA nephropathy is an increased occurrence of IgA with poor galactosylation in the circulation. The principal O-glycosylation abnormality involves reduced galactosylation of the IgA1 hinge region O-glycans, leading to an increased frequency of truncated O-glycans. The changes in O-glycosylation only become apparent after antigen encounter and are therefore likely to be linked in some way to B-cell maturation and class switching to IgA1 synthesis in IgAN. A similar abnormality in galactosylation has been demonstrated for IgA1 produced in vitro by tonsillar lymphocytes, suggesting that the tonsils may contribute to the circulating pool of under-galactosylated IgA1 in IgAN. Furthermore, there seems to be some relationship between IgAN and IgA class switching in tonsil.

**Mechanisms of IgA-immune complex formation**

Aberrantly, galactosylated and siaiylated IgA1 molecules have an increased tendency to exhibit both IgA1 self-aggregation and formation of antigen–antibody complexes with IgG antibodies directed against IgA1 hinge epitopes, favoring the generation of IgA-IC. The inability of IgA to fix complement effectively may also promote IgA-IC formation and persistence in the circulation, as complement interrupts immune complex lattice formation and is involved in complex internalization by phagocytes. Complement could form the membrane attack complex, which causes perforation and dissolution of the target cells. The presence of aberrantly galactosylated IgA-IC has also been reported in the urine of patients with IgAN, but not in patients with non-IgAN proteinuric glomerular disease.

**Characteristics of the mesangial deposition of IgA**

The mesangial deposition of IgA has been shown to bind secretory component and therefore to consist at least partly of J-chain-containing pIgA molecules such as SlgA. Studies have demonstrated aberrant O-glycosylation of mesangial IgA1 in eluted mesangial IgA and SlgA deposition on mesangium. The reported under-galactosylation was also seen in matched serum IgA1 samples, but mesangial IgA1 exhibited a more marked defect, suggesting that altered O-glycosylation is a factor directly promoting mesangial deposition. It has been proposed that such changes in IgA1 O-
Galactosylation may affect the sialic acid content or distribution and hence the electrostatic charge of IgA1.

**PRODUCTION OF IgA IN IgA NEPHROPATHY**

The production of poorly galactosylated IgA1 in IgAN may result from a defect in B cells. Decreased activity of core 1 β-1,3-galactosyltransferase (C1GalT1), which is the key enzyme for galactosylation, has been shown in B cells.21 There is, however, no poor galactosylation in other O-glycated immunoglobulins except IgA, suggesting the aberrant galactosylation may occur at the later stage of B-cell development and may be secondary to aberrant immunoregulation.10 For the Th2 cytokines, interleukin (IL)-4 decreases messenger RNA and activity levels of C1GalT1.22 Besides deactivation of C1GalT1 in B cells, an increasing number of pIgA1 plasma cells are found in the bone marrow and tonsils in IgAN, and there is elevated IgA1 synthesis by these plasma cells in spontaneous culture.16,23 More importantly, poor galactosylation is particularly apparent in IgA1 produced against mucosal antigens (*Helicobacter pylori*) compared with systemic antigens (tetanus toxoid).24 This observation suggests the fascinating possibility that, in IgA nephropathy, there is no real defect in IgA1 O-glycosylation, but rather an increase in “mucosal-type” IgA1 in serum, possibly related to the migration of mucosal B cells to bone marrow, where they produce their “correct” poorly galactosylated IgA.23 This is consistent with the observation that homing of lymphocytes between mucosal and systemic sites is altered in IgA nephropathy,26,27 and this may ultimately explain how mucosally derived plasma cells might take up residence in systemic immune sites.28 The initial site of antigen encounter heavily influences the ultimate phenotype of T and B cells, and despite displacement, such plasma cells might be expected to continue to produce mucosal-type antibodies in systemic sites.29

**MECHANISMS OF IgA CLASS SWITCHING**

Class-switch recombination for IgA class switching

B cells could diversify their antibody repertoire through three main genetic alterations that occur in two distinct phases of B-cell development. For the antigen-independent phase in the bone marrow, B-cell precursors could generate new B cells to express IgM or further differentiate and express IgD by assembling the exons that encode immunoglobulin heavy (H) and light (L) chain variable regions from individual variable (V), diversity (D), and joining (J) gene segments through V(D)J recombination.30 In the antigen-dependent phase when B cells migrate to secondary lymphoid organs,31 mature B cells diversify their antibody repertoire to IgA or IgG and IgE through somatic hypermutation and class switching32,33 in the germinal centers of secondary lymphoid follicles in the presence of antigen. As described above, B cells may develop IgA class switching to acquire the expression of IgA in mucosa-associated lymphoid tissue (MALT) via T-cell-dependent or T-cell-independent pathways and then transmit to IgA plasma cells or home in on systemic sites.

**Signals for IgA class switching**

The switching process requires a variety of transcription factors and enzymatic activity expressed by several cell-type-
specific and general DNA repair enzymes, particularly activation-induced cytidine deaminase (AID),\(^{24}\) an inducible apolipoprotein-B mRNA-editing enzyme, and a catalytic component 1 family member encoded by AICDA.\(^{35}\) IgA switching may circumvent the need for T-cell help, which provides CD40-CD40 ligand (CD40L)/CD154, T-cell receptor (TCR)-major histocompatibility complex (MHC) interaction and, instead, rely on proliferation- and survival-inducing cytokines of the tumor necrosis (TNF) family, such as B-cell-activating factor of the TNF family/B-lymphocyte stimulator (BAFF/BLyS) secreted by monocytes, DCs, macrophages, and FDCs,\(^{36}\) and a proliferation-inducing ligand (APRIL) secreted by activated (e.g., after lipopolysaccharide exposure) DCs or macrophages. Transforming growth factor (TGF)-\(\beta\) and IL-21 were also found to be involved in IgA switching.

**T-cell-dependent IgA class switching**

Antigens incite a humoral immune reaction through B-cell proliferation, AID expression, and antibody repertoire diversification through somatic hypermutation and CSR in germinal centers. In general, germinal-center reactions are highly dependent on cognate interactions between antigen-specific B cells and CD4+ T cells that express CD40L, a TNF family member that engages CD40 on B cells,\(^{37}\) also as MCH engages TCR. Antigens exposed on the surface of FDCs select germinal-center B cells expressing a high-affinity B-cell receptor and promote IgD+ cells that differentiate into long-lived memory B cells and antibody-secreting plasma cells.\(^{38}\) T-cell-dependent antibody responses are strongly biased towards IgA and involve activation of B cells by antigen in the organized lymphoid tissue of gut Peyer’s patches (PPs) and tonsils.\(^{39}\) Together with CD40L, TGF-\(\beta\) is essential for the induction of T-cell-dependent IgA class switching.\(^{39,40}\)

**T-cell-independent IgA class switching**

T-cell-independent IgA class switching may be found in B-1 cells in mice and IgM+ memory B cells in humans. IgM+ memory B cells can be detected in the circulation and in the marginal zone of the spleen, gut PPs, and tonsils. B cells express mutated V(D)J genes, and undergo CD40-independent IgA production in response to bacterial polysaccharides, a canonical T-cell-independent antigen.\(^{40,41}\) T-cell-independent antigens can also provide additional B-cell-stimulating signals through DCs. During this process, DCs release soluble class-switch-inducing factors related to CD40L, including BAFF and APRIL.\(^{39,42}\)

**Regionalized class-switch mechanism**

Human IgA responses are dominated by IgA1 in both tonsils and the regional secretory effector sites. This suggests that mucosal B-cell differentiation in those parts of the body mainly takes place from slgD–IgM-CD38+ centrocytes by sequential downstream CH-gene switching.\(^{35}\) Tonsillar crypt epithelium is activated to secrete the innate switch factor BAFF and the thymic stromal lymphopoietin (TSLP) - a cytokine that further promotes CSR and a broad reactivity of local B cells by activating BAFF-producing DCs.\(^{46}\) Conversely, the relatively enhanced IgA2 expression in PPs and the distal human gut altogether, including the mesenteric lymph nodes, could reflect a direct switch from \(\alpha_{I} \) to Ca2. Such regional microbial influence on B-cell differentiation is supported by the observation that \(\alpha_{I}/\alpha_{I}\) deletion is more frequently detected in diseased than in clinically normal tonsils and adenoids,\(^{47}\) and extrafollicular IgD-producing plasma cells are relatively numerous in recurrent tonsillitis and adenoid hyperplasia.

**THE ROLE OF DENDRITIC CELLS IN IgA CLASS SWITCHING**

DCs have an irreplaceable role in IgA class-switch mechanisms. MALT DCs belong to a TNF-\(\alpha\)-inducible nitric oxide synthase (iNOS)-producing DC subset,\(^{48,49}\) which preferentially expresses iNOS in response to the recognition of commensal bacteria by toll-like receptor (TLR). Then, iNOS could regulate the T-cell-dependent IgA CSR through expression of transforming growth factor-\(\beta\) receptor, and the T-cell independent IgA CSR through production of APRIL (also called Tnfsf13) and BAFF (also called Tnfsf13b). One study has shown that IgA CSR is impaired in iNOS-deficient (iNOS2/2; gene also called Nos2) mice. Furthermore, adoptive transfer of iNOS1 DCs rescues IgA production in iNOS2/2 mice.\(^{50}\) The presence of a naturally occurring TNF-\(\alpha\)/iNOS-producing DC subset may explain the predominance of IgA production in the MALT, which is critical for gut homeostasis.

**HUMAN DENDRITIC CELL SUBSETS AND THE ROLE OF FOLLICULAR DENDRITIC CELLS AND PLASMACYTOID DENDRITIC CELLS IN IgA CLASS SWITCHING**

In terms of the DC subsets, there are Langerhans cells, the first immunological barrier to the external environment at the skin, plasmacytoid DCs (pDCs), an excellent producer of type I interferons (IFNs; IFN\(\alpha/\beta\)) involved in antiviral responses, myeloid DCs (mDCs) including conventional DC type 1, which is active in CD4+ T-cell priming, and conventional DC type 2, a producer of TGF-\(\beta\) for tolerance that is active in cross-presentation to CD8+ T cells, and monocyte-derived DCs (Mo-DCs), which are active in inflammation, tissue repair, and homeostasis.
FDCs reside in the lymphoid follicles of all lymphoid tissues and are critically involved in germinal-center development, immunoglobulin class switching, memory B-cell generation, selection of somatically mutated B cells with high-affinity receptors, affinity maturation, induction of recall responses, and regulation of serum IgG and IgE levels.\(^{51-53}\) FDCs are unique accessory cells that trap ICs and serve as a source of antigen for germinal-center B cells.\(^{54}\) Thereby, ICs on FDCs can promote AID production, class switching, and maturation of naive IgM\(^+\) B cells.

Some reports have indicated the involvement of FDCs and pDCs in IgA induction: The percentage of B cells bearing CD23 (also known as an FDC marker in light zone) was found to be significantly higher in patients, most likely representing in vivo B-cell activation due to chronic antigenic stimulation.\(^{55}\) FDCs could send additional IgA-inducing signals to follicular B cells by releasing CD40L-related factors known as BAFF and APRIL upon “priming” by mucosal signals, such as commensal TLR ligands and retinoic acid. Mucosal FDCs also release a large amount of active TGF-\(\beta1\), BAFF, and APRIL, and then promote follicular B cells from PPs and mesenteric lymph nodes to undergo switching to IgA.\(^{56}\)

**RELATIONSHIP BETWEEN TONSILLAR FOCAL INFECTION AND IgA NEPHROPATHY**

Normal human tonsils contain 60% IgG-secreting plasma cells and 40% IgA-secreting plasma cells, while in tonsils of patients with IgAN, these proportions are reversed.\(^{50}\) Furthermore, compared with the tonsils of nondiseased controls, those of patients with IgAN demonstrate some evident abnormalities.\(^{57}\) The IgA deposits in glomerular mesangium in patients with IgAN appear to be exclusively of the IgA1 subclass,\(^{58}\) and the IgA produced by tonsillar lymphocytes in these patients is mainly pIgA1. The serum IgA levels increase in about half of patients with IgAN\(^{61}\) and tonsillectomy could decrease these serum levels of IgA antibody, suggesting an intimate relationship between tonsillar focal infection and IgAN.

Tonsillectomy can also improve the urinary findings, maintain stable renal function, decrease mesangial proliferation and IgA deposition, and have a favorable effect on long-term renal survival in some IgAN patients. Furthermore, tonsillectomy maintains normal immune responses and does not increase the incidence of upper respiratory tract infections, suggesting that tonsillectomy can be used as a potentially effective treatment.\(^{64}\) Taken together, it should be emphasized that at least a part of IgAN and pIgA1 deposited in glomerular mesangium may be of tonsillar origin.

**Tonsillar bacterial infection and histologic findings in IgAN**

Some reports have suggested that *Haemophilus parainfluenza* (*H. parainfluenza*) antigens stimulate tonsillar T and B lymphocytes in patients with IgAN to produce cytokines and IgA antibody, and an immune response to *H. parainfluenza* antigens may play a role in the pathogenesis in some IgAN cases.\(^{65,66}\) Microfold cells (membrane cell, M cells) in human tonsils lie between the crypt epithelial cells to take up antigen and then promote mitogen-triggered T cells, leading to the production of Th1- and Th2-type cytokines for support of cell-mediated and antibody responses, resulting in the generation and dissemination of antigen-specific memory B cells, mainly dimeric IgA-producing effector B cells.\(^{67}\)

Some studies have demonstrated that coccoid *Helicobacter pylori* (*H. pylori*) was present in tonsillar crypts, and the prevalence of *H. pylori* was greater in the IgAN group than in the recurrent pharyngotonsillitis group. Bacterial colonies were visible in tonsillar crypts for macroscopy. Tonsillar crypts contained some bacterial colonies, horny layers of stratified squamous epithelium, and chronic inflammatory cells. *H. pylori* was present at the periphery of the bacterial colony and the horny layers of the stratified squamous epithelium.\(^{68}\) In the serum, a greater level of anti-\(H. pylori\) IgA antibody was also found in IgAN patients than in controls without renal disease.\(^{69}\)

There are significant differences in histological structure, proportion of constitutional cells, and expression profile of cell adhesion molecules between tonsils with and without IgAN. The most characteristic features of tonsils with IgAN include enlarged primary T nodules composed predominantly of small T lymphocytes, which are defined as small but apparent nodules accumulating T lymphocytes (Fig. 3). These nodules play a major role in the antigen triggering, helper T-cell-dependent stimulation, and subsequent maturation of antigen-responsive B cells into antibody-secreting plasma cells.\(^{70}\) Some reports have suggested that tonsillectomy suppresses a decrease in regulatory (suppressor) T cells and corrects abnormal cell-mediated immune responses in patients with IgAN.\(^{71}\)

One study has shown reduced reticulization of tonsillar crypt epithelium in patients with IgAN compared with that in controls who exhibited recurrent tonsillitis or tonsillar hyper trophy. Non-reticulated crypt epithelium was frequently observed in IgAN tonsils, and even exceeded 50% of the total crypt epithelia in the advanced stage of IgAN, compared with 7% in controls. Therefore, it has been speculated that the low
level of reticulization in IgAN patients may induce the unusual immunity responsible for the pathogenesis of IgAN. However, few articles have mentioned the tonsillar histological features in IgAN, and further investigation is necessary.

**Relationship between tonsillar IgA and glomerular deposition of IgA**

Bene *et al.* reported that an increment in the IgA population was paralleled by augmentation of the number of dimeric IgA-secreting cells (75% of IgA plasma cells) being stained for both cytoplasmic IgA and J chain in IgA patients’ tonsils. Similar results suggested that the number of CD5+ B cells isolated from the tonsillar germinal centers of IgAN patients was increased. These CD5+ B cells are likely IgA1 antibody-producing cells. IgA antibodies deposited in glomeruli specifically bind with tonsillar cells obtained from patients with IgAN, meanwhile, IgA produced by tonsillar B cells binds to the glomerular mesangium of IgAN. Taken together, these results demonstrate that abnormal immune response of the tonsils is a central feature of the abnormal pIgA biology in IgAN, which supports the hypothesis favoring a tonsillar origin of the mesangial IgA deposits.

**APPLICATION OF TONSILLECTOMY FOR IgA NEPHROPATHY**

**Effect of tonsillectomy for adult or child IgA nephropathy**

Because of IgA production in tonsillar tissue and the frequent association of the onset of symptoms of IgAN with mucosal infection, studies have been performed to explore the effectiveness of tonsillectomy as an adjuvant therapy. Some studies demonstrated the effectiveness of tonsillectomy in combination with steroid pulse therapy, with very favorable results. Hotta *et al.* reported that combined treatment of tonsillectomy and steroid therapy was associated with clinical remission in 329 patients with IgA nephropathy. Similar results were demonstrated by Komatsu *et al.*, who reported that combined therapy of tonsillectomy and pulse steroid was superior to pulse steroid alone with regard to remission of proteinuria. Tonsillectomy stopped gross hematuria in more than two-thirds of patients. Furthermore, a new report from a longitudinal study in Japan showed that tonsillectomy was associated with a favorable renal outcome of IgA nephropathy in terms of clinical remission and delayed renal deterioration even in non-steroid-treated patients. The urinary protein and microhematuria decreased significantly from 6 months after tonsillectomy compared with those before operation. The clinical remission rate of urinary findings and the stable renal function rate in tonsillectomized patients with IgAN were significantly higher than those in nontonsillectomized patients. One study reviewed 6 pediatric cases of IgAN with mild to moderate disease and recurrent tonsillitis, showing that tonsillectomy can be a useful adjuvant treatment to improve urinary symptoms (including proteinuria, and gross and microscopic hematuria) and renal function. Tonsillectomy decreased the levels of serum IgA and salivary secretary IgA, especially in children, several months or years after operation. However, these changes neither cause significant immune deficiency nor increase the incidence of immunomodulated diseases, such as infections of the upper respiratory tract. On the other hand, Rasche *et al.* described that tonsillectomy had no beneficial effect on preventing end-stage renal disease (ESRD).

**Indication and limitation of tonsillectomy for IgAN nephropathy**

In general, the efficacy of tonsillectomy in patients with hematuria-type IgAN, especially those presenting hematuria after tonsillar infection, is good. Tonsillectomy is mainly indicated for patients with mild or moderate IgAN. Xie *et al.* reported that tonsillectomy combined with steroid pulse therapy may be effective in IgAN patients with a baseline creatinine level of ≤ 2 mg/dL, whereas when serum creatinine > 2 mg/dL, tonsillectomy may not change the renal outcome, even if combined with steroid therapy. IgAN is a common indication for tonsillectomy in Japan, but is less common in other countries.
CONCLUSION

IgAN remains the most common primary glomerulonephritis, but there is no effective advisable therapy because of limited knowledge about the precise pathogenesis of this disease. Qualitative abnormality of IgA in circulation, formation of IgA-IC and deposition in mesangium, complement activation, and damage to mesangial cells seem to be the major steps in the pathogenesis of IgAN. An abnormal increase of pIgA1 in circulation and mesangial deposition of IgA seem to be initiating events in the pathogenesis of IgAN. Extensive research is needed to clarify whether and how mucosally primed plasma cells and IgA class switching enhanced by FDCs in MALt have a relationship with the pathogenesis of IgAN. In particular, some results provide a link between tonsillar focal infection and IgAN, so tonsillectomy should be considered as a therapeutic strategy in patients with IgAN, especially at a mild or early stage.

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