


The Phenotypic Difference of IgA Nephropathy and its Race/Gender-dependent Molecular Mechanisms

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Abstract

IgA nephropathy (IgAn), defined by the pre dominant de position of IgA in the glomerular mesangium, is the most common form of GN throughout the world. However, its incidence, sex distribution, clinical presentation, and progression and pathogenic initiating factors are largely variable and do not fit such a simple definition. To assess the heterogeneity of this disease, we recently conducted a clinical survey on the presentation and clinical management of patients with IgAn in Europe and Japan. This clinical survey highlights similarities and differences in patients from different continents. The survey revealed obvious differences between nations in the frequency of gastrointestinal complications, including inflammatory bowel diseases (IBD) and celiac disease, which were more frequent in European patients. Such findings are compatible with susceptibility loci related to intestinal immunity and IBD in recent genome wide association studies (GWAS) on IgAn. However, most of the molecules in these mucosal-related loci fulfill the immunologic function not only of gut-associated lymphoid tissue (GALT), but also nasopharyngeal/bronchial-associated lymphoid tissues (NALT/BALT). Indeed, a similar frequency of macrohematuria coinciding with upper respiratory infection, a hallmark manifestation of this disease, was found in the survey, emphasizing the pathogenic roles of these molecules in the NALT/BALT of patients with IgAn. Recent experimental and clinical studies including GWAS on multiple common infections and IBD indicate immune crosstalk between GALT and NALT/BALT, and some related mediators, such as TNF superfamily ligands (APRIL/BAFF). This review explains the epidemiologic heterogeneity of this disease with the clinical survey, and discusses race and sex-dependent molecular mechanisms.

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Introduction

Whether IgA nephropathy (IgAn) is a single disease remains of debate, because of its variable clinical and pathogenic presentation, disease progression and complications, geographic and sex variation, and treatment response. It can be argued that IgAn is a glomerular pattern rather than disease because of its simple definition (1). Indeed, 5%–10% of kidney samples from the autopsies of trauma victims or people without a renal history showed mesangial IgA deposition (2–4), and 14%–17% of kidney donors without a renal history had evidence of mesangial IgA deposition with or without C3 (5).

IgAn is the most frequent biopsy-proven primary GN; however, its geographic prevalence varies. A systematic review suggests IgAn has an incidence of at least 2.5 per 100,000 in adults worldwide (6). However, the prevalence of IgAn is much higher in East Asia compared with North America and Europe (6,7). This is partly explained by the increased performance renal biopsies and national urine screening programs in East Asia. In Japan, Korea, and Taiwan, there is annual urinalysis as a part of a health check program that encourages the early referral of individuals, even with

persistent microscopic hematuria with or without mild proteinuria, which increases the frequency of IgAn diagnosis (7,8). A wide indication for a renal biopsy, even in individuals with microscopic hematuria, resulted in the identification of a large number of asymptomatic urinary abnormalities caused by IgAn, not only in Asia but also in Europe (9–11), suggesting the true prevalence of IgAn globally is underreported. An observational study of renal biopsies in patients with hematuria without overt proteinuria reported a high proportion of IgAn (62%), and 31% of these patients with IgAn have active glomerular lesions, including crescent formation (9). This may be a part of the reason why persistent isolated microscopic hematuria is a risk for ESKD (12).

IgAn in East Asia has a male to female ratio of 1:1 or <2:1, which is different from that in Europe and the United States. and reports ratios as high as 6:1 (13–15). This strongly indicates that environmental and/or genetic factors may have certain roles in the pathogenesis of IgAn. The contribution of race to the etiology of ESKD in patients with IgAn has been reported. Barbour *et al.* reported that individuals of Pacific Asian origin

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had a significantly increased risk of ESKD, even after adjusting for the effects of known prognostic variables, such as age, eGFR at biopsy, proteinuria, and mean arterial pressure (16). Although this risk may be explained by racial differences, the effects of Asian origin on disease progression may not be explained by specific factors related to IgAn, such as the number of nephrons at birth (17,18).

Differences in the renal progression of male and female patients with IgAn are still controversial. Recent Chinese studies reported that no significant differences were observed in the long-term renal survival of male and female patients, despite matching with prognostic factors such as eGFR and serum uric acid (19–21). Cattran *et al.* demonstrated that, in contrast with membranous GN and focal segmental glomerulosclerosis, baseline and follow-up urinary protein and patient sex did not influence IgAn progression (22). However, this is in contrast with a large meta-analysis (23). A recent study from Estonia has reported that renal progression occurs faster in males than in females, with a correlation between a higher Oxford MEST score and disease progression in male patients (24). It is now widely accepted that galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1 immune complex formed with autoantibodies against GdIgA1 are key effector molecules in IgAn, and are thus referred to as prognostic markers (25–28). A recent report indicates a significant difference in Gd-IgA1 level between United Kingdom and Chinese patients with IgAn and healthy subjects (29). Enzyme core 1 synthase, glycoprotein-N-acetylgalactosamine 3- β -galactosyltransferase (C1GALT1) is known to catalyze the transfer of galactose UDP-Gal to N-acetylgalactosamine O-linked esters of threonine and serine residues of IgA1 (30). The C1GALT1 gene is strongly associated with Gd-IgA1 level in both populations without sex bias (29,31); however, a different lead single nucleotide polymorphism (SNP) of C1GALT1 and a novel genetic interaction with GALNT12, which is a key enzyme for the O-glycosylation of N-acetylgalactosamine may exist only in Chinese patients (31), suggesting serum elevation of Gd-IgA1 is the result of different regulation with the same enzyme in different races. Berthouix *et al.* reported the serum levels of autoantibody against Gd-IgA1 are associated with IgAn progression (32). However, this French cohort comprised 75% male patients with IgAn, and the absolute renal risk for dialysis or death was correlated with a high number of male patients. Such a male-dominant elevation of antiglycan antibody with poor prognosis was not observed in Japanese patients (33). Therefore, the prognostic value of the serum level of anti-Gd-IgA1 antibody should be carefully evaluated in multiethnic cohorts, such as *via* an international collaborative study of an International IgAn prediction tool (34).

Clinical Features and Practice of IgAn in Japan and Europe: Results from An International Survey

To further understand the geographic heterogeneity of IgAn in Europe and Japan through a collaborative study between the Japanese Society of Nephrology and the European Renal Association-European Dialysis Transplantation Association (ERA-EDTA) may be helpful. A retrospective analysis comprising patients with biopsy-proven IgAn from 2016 to

2017 was performed to compare the clinical and therapeutic features of European countries (Europe) ($n=437$) and Japan ($n=470$). The questionnaire was distributed to leader institutions in both regions (24 from Europe and 24 from Japan) after approval from the ethics committee at each institution. Patients with IgAn were randomly selected from each institution for data collection.

Urinary Abnormalities and Renal Function before Renal Biopsy

The frequency of history of macrohematuria was similar between Europe and Japan (Table 1). Hematuria was rarely (3%–5%) associated with acute gastrointestinal disorders in both cohorts (Figure 1). However, the frequency of hematuria coincident with an upper respiratory tract infection was higher (23% and 30% in Europe and Japan, respectively) (Figure 1), without significant differences between the two cohorts. Many Japanese practitioners required a history of proteinuria (>300 mg/day) detected twice on urinalyses, performed more than 3 months apart, for the indication of renal biopsy. The rate of a renal biopsy being performed <1 year after the initial detection of proteinuria was higher in Europe (Table 1). The ratio of nephrotic syndrome before renal biopsy was much higher in Europe compared with Japan (21% and 4%, respectively). Moreover, multiple renal abnormalities were discovered during an annual health check-up in Japan (Table 1), and Japanese patients with IgAn were diagnosed at a relatively early stage.

In Europe, 21% of patients with IgAn had at renal biopsy an increase in serum creatinine (Table 1). The frequency of preserved eGFR at the time of renal biopsy (> 60 ml/min per 1.73m²) was low in Europe (55%) compared with Japan (71%). Moreover, 20% of the European cohort had an acute renal injury (Table 1). IgAn possibly progressed in Europe at the time of the renal biopsy.

Gastrointestinal Disorders and Upper Respiratory Tract Infections Coincident with Urinary Abnormalities

The frequent occurrence of episodic macroscopic hematuria with a concurrent upper respiratory or intestinal tract infection suggests the mucosal immune system plays an important role in IgAn progression (35,36). The ratio of gastrointestinal complications, such as Crohn's disease (CD), ulcerative colitis (UC), and celiac disease, were more frequent in Europe compared with Japan (17% vs 1%) (Table 2). Although the serum level of IgA was found to be elevated in patients with CD and UC compared with healthy controls (37), patients with IgAn and an elevated serum IgA at the time of renal biopsy were much less common in Europe compared with Japan (11% vs 34%) (Table 1). Of interest, there were no clear differences in the coincidence of episodic hematuria and gastrointestinal disorders or upper respiratory tract infections between Europe and Japan (Figure 1).

Differences in Status of Treatment between Europe and Japan

The major treatment options for adult IgAn are the use of renin-angiotensin system inhibitors, corticosteroids, nonsteroidal immunosuppressive agents, tonsillectomy (combined with high-dose intravenous corticosteroids), omega 3 fatty acids (fish oil), and antiplatelet agents. Because several clinic

Table 1. Clinical features of patients with IgA nephropathy obtained by questionnaire surveys in Europe and Japan

Feature	Europe	Japan
Numbers	437	470
Age, yrs	43.5	40.1
Sex, male/female, %	67/33	41/59
Ethnicity	93% White, others from Asian, American and African	All Japanese
History and persistent macrohematuria, %	23	29
Time between first detection of hematuria and renal biopsy (<1 year), %	54	34
History of single detection of proteinuria (>1 g/day), %	22	11
History of proteinuria (>300 mg/day) in twice detections greater than 3 months apart before renal biopsy, %	40	72
Nephrotic syndrome before renal biopsy, %	21	4
Time between first detection of proteinuria and renal biopsy (<1 year), %	72	40
Detection of increase of serum creatinine before renal biopsy, %	21	13
eGFR at the time of renal biopsy (> 60 ml/min per 1.73m ²), %	55	71
Significant (>20%) decrease in GFR at time of biopsy over the previous months, %	20	8
Elevated serum IgA at the renal biopsy, %	11	34
Family history of kidney disease / family history of IgAn, %	7 / (IgAn: 2)	16 / (IgAn: 2)
Renal abnormalities were discovered as part of a systematic screening program, %	10	74

IgAn, IgA nephropathy.

studies have confirmed a favorable effect of tonsillectomy (38), it has now become a common treatment option in Japan. In fact, approximately 53% of patients with IgAn in Japan underwent a tonsillectomy (Figure 2). Renin-angiotensin system inhibitors are a common treatment option in both Europe and Japan, conversely, major therapeutic differences between Europe and Japan are reported on the use of high-dose intravenous corticosteroids and oral corticosteroids (Figure 3). Note that >60% of Japanese patients with IgAn were treated with corticosteroids. Although several reports suggest a risk of adverse events after the use of corticosteroids in patients with IgAn (39), most patients with IgAn in Japan had completed corticosteroids during the 2-year study period, hence suggesting a rather safe treatment (Table 3).

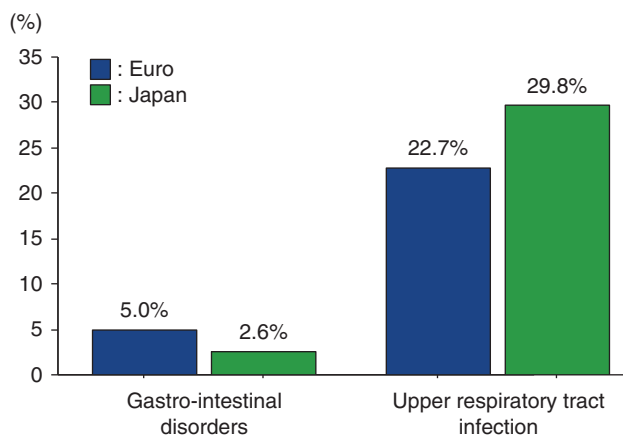


Figure 1. | The ratio of episodic hematuria coincident with an acute gastrointestinal disorder or upper respiratory tract infection. There are no clear differences between the ratio of episodic hematuria coincident with an acute gastrointestinal disorder between Europe and Japan. However, the ratio of episodic hematuria coincident with an upper respiratory tract infection was relatively high in both Europe and Japan (23% vs 30%, respectively). Euro, Europe.

Although a clinical study in a large cohort in Japan and a recent meta-analysis of 14 studies in mainly Asian countries confirmed a favorable effect of tonsillectomy (38,40), good outcomes of tonsillectomy for IgAn were not reported in European studies (41–43). Meanwhile, the novel targeted-release formulation of budesonide targeting small intestine was shown to reduce proteinuria in patients with IgAn in European countries (44). There are epidemiologic differences between Asia and European countries, such as sex ratios and frequency of intestinal complications, including CD, UC, and celiac disease. Thus, there is a possibility the effectiveness of tonsillectomy may depend on racial differences. However, the limited number of patients receiving tonsillectomy in Europe because of IgAn and not for ear, nose, and throat indications does not allow a comparison between the continents (41,43). Despite negative results (41,42) in small European studies, a report from Germany indicated that many patients with IgAn in the tonsillectomy group had progressive disease (serum creatinine >2 mg/dl) (42). Meanwhile, a Hungarian report showed the positive effects of tonsillectomy in 98 White patients with IgAn (45). Thus, further basic and clinical studies are required to determine the efficacy of tonsillectomy in different races. The European ear, nose, and throat guidelines do not support tonsillectomy in patients without repeated episodes of tonsillitis, hence this procedure remains not easily applicable in Europe.

Potential Underlying Molecular Mechanisms in Race/Sex difference in IgAn Mechanisms Related to Intestinal Disorders

This clinical survey highlights the similarities and differences in European and Japanese patients with IgAn and clinical care. The hallmark manifestation of IgAn is macrohematuria, which often coincides with an upper respiratory tract infection and is indicative of the pathogenic roles of the nasopharyngeal and bronchial mucosae. However, the survey also revealed obvious differences in the frequency

Table 2. Complications accompanied by IgA nephropathy

Complication	Europe (%)	Japan (%)
Gastrointestinal complications		0
Celiac disease	2	0
Crohn's disease	2	0.90
Ulcerative colitis	3	0
Irritable bowel syndrome	4	0.
Chronic, nondefined gastrointestinal symptoms	6	0.20
Total	17	1
Others		
Periodontitis	0.20	4
Atopic dermatitis	1	6
Bronchial asthma	4	3

of gastrointestinal complications between nations, including inflammatory bowel disease (IBD) and celiac disease in European patients with IgAn (Europe 17%; Japan 1%, Table 2). IBD, including CD and UC, have been considered disorders that primarily affect patients of European ancestry (46,47). Celiac disease is an autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals, especially of European ancestry (48). However, the incidence of IBD and celiac disease is increasing in non-European and non-White populations (49–51). Considering the altered etiology of IBD and celiac disease, the clear geographic difference in the prevalence of intestinal diseases in this survey may be more than coincidence and suggests a pathogenetic connection between gut inflammation in IgAn and the heterogeneity of European patients with IgAn.

Transgenic mouse models of IgAn overexpress a ligand for lymphotoxin β receptor or B cell-activating factor (BAFF), which are both essential molecules for IgA class switching and intestinal IgA production by resident IgA⁺ plasma cells,

and thereby demonstrate the overproduction of polymeric IgA in the intestinal mucosa results in high serum levels of IgA (approximately 100 times higher) and IgAn disease phenotypes (37,52). The polymeric immunoglobulin receptor (pIgR) is the key molecule for the luminal trafficking of mucosal dimeric IgA in the intestine and upper respiratory tract (53,54). Excessive IgA remaining in the intestinal lamina propria is therefore considered to be the result of overwhelmed pIgR, which leads to the leakage of mucosal IgA into the circulation of transgenic mice. Serum IgA elevation has been observed in patients with CD and UC (37,55), suggesting intestinal inflammation may interfere with IgA trafficking by pIgR. Intestinal inflammation in patients with IgAn with celiac disease may share the same mechanism of the mesangial deposition of intestinal IgA (56). Interestingly, certain Swedish reports suggest 33% of patients with IgAn have a mucosal sensitivity to gluten without the clinical manifestations of celiac disease (57,58). Furthermore, antigliadin antibodies were detected in association with high levels of IgA immune complexes in Italian patients with IgAn (59). More recently, a French IgAn cohort without the manifestations of celiac disease exhibited elevated serum antigliadin antibody (60), suggesting even subclinical intestinal inflammation may lead to glomerular IgA. A pathogenic mechanism was proposed using a humanized mouse model of IgAn, the α 1KICD89Tg mouse, that expresses human IgA1 and the human myeloid CD89 IgA Fc receptor. Under a normal diet, in their serum these mice displayed IgA1 antibodies to gliadin complexed with soluble CD89. A gluten-free diet resulted in a decrease of mesangial IgA1 deposits and hematuria. Disease severity depended on gluten and CD89, as shown by the reappearance of IgAn features in mice fed a gluten diet (61). However, a serological link with antigliadin antibody was absent in patients with IgAn in Japan and the United States (62,63). Moreover, most patients with IgAn do not usually complain of any gastrointestinal disorders,

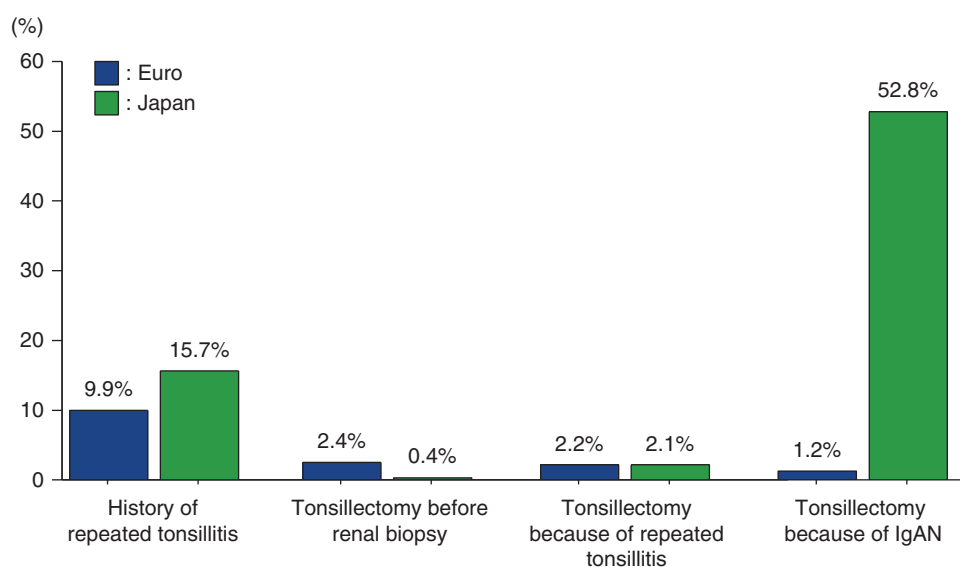


Figure 2. | History of recurrent tonsillitis and tonsillectomy. Although recurrent tonsillitis is relatively common in Japanese patients with IgA nephropathy (IgAn), the ratio of tonsillectomy because of recurrent tonsillitis is similar between Europe and Japan. However, tonsillectomy is a common treatment option in Japan, and approximately 53% of Japanese patients with IgAn underwent a tonsillectomy.

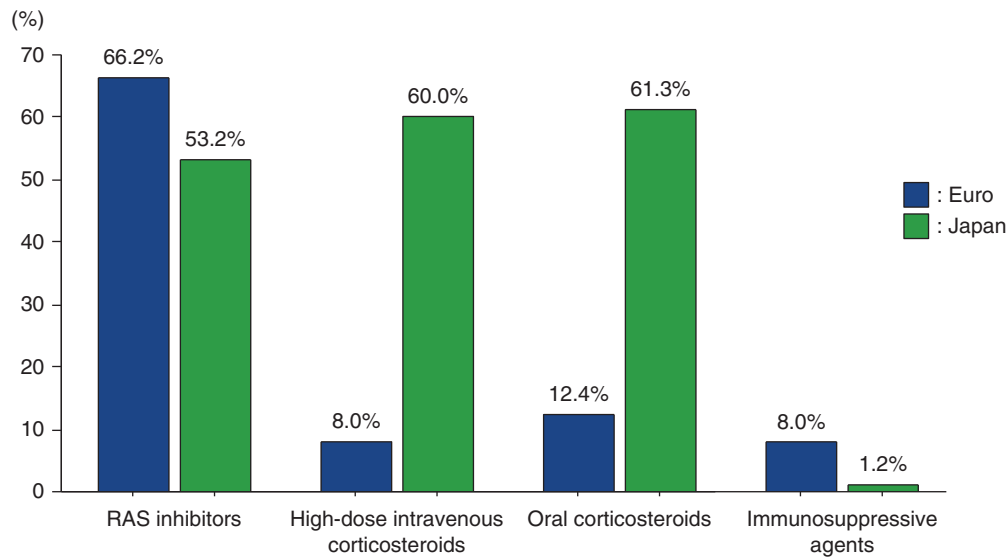


Figure 3. | Differences in the status of treatment between Europe and Japan. Treatment with renin-angiotensin system (RAS) inhibitors is common in both Europe and Japan. There are major differences in the use of high-dose intravenous corticosteroids and oral corticosteroids between Europe and Japan.

indicating certain specific environmental factors may facilitate such a link in European patients. In a direct comparison with patients with IgAn from various continents, abnormal levels of IgA directed against various alimentary antigens were found to be less frequent in Japanese versus European patients (0%–16% versus 19%–28%, respectively for IgA against different alimentary components) (64)

It is known that IgA transcytosis and trafficking by pIgR in mucosal cells are strikingly augmented by estradiol (65). This is thought to be a part of the reason why female patients are more resistant against pneumonia after trauma (66–69). In this regard, the presence of a sex-hormone-based difference in mucosal IgA trafficking should be carefully examined for sex bias in European patients with IgAn.

Immune Crosstalk between Nasopharyngeal/Bronchial- and Gut-associated Mucosal Tissues

A recent genome-wide association study (GWAS) on IgAn demonstrated a disease association with loci related to molecules responsible for intestinal immunity, maintenance of the intestinal barrier and IBD, reinforcing the importance of interstitial immune response in IgAn (70–72). However, most of the molecules in these mucosal immune-related loci fulfill the immunologic function not only of gut-

associated lymphoid tissue (GALT) but also nasopharyngeal/bronchial-associated lymphoid tissues (NALT/BALT), although much remains to be elucidated about NALT/BALT-mediated regulation of IgA immunity compared with that of GALT.

Although a genetic association at the variants rs2412971, intronic in *HORMAD2* at 22q.12.2 was reported in GWAS for IgAn involving Han Chinese and European cohorts (70–72), a GWAS for tonsillectomy revealed that the same SNP, rs2412971, is robustly associated with an increased risk of requiring a tonsillectomy (73), which is suggestive of *HORMAD2*-related susceptibility of infection or a hyperimmune reaction in the palatine tonsil. Indeed, on the telomeric side of *HORMAD2*, the two nearest neighboring genes, *LIF* and *OSM*, encode cytokines that are members of the IL-6 family and thus may play a role in the hyperimmune response or inflammation (73,74). Note that the GWAS for tonsillectomy demonstrated that rs2412971 is associated with a decreased risk of CD and IBD in the European population (75–77), revealing opposing effects of risk loci for IgAn in IBD. Epidemiologic studies with nationwide cohorts and a related meta-analysis primarily from European studies revealed a tonsillectomy is associated with an increased likelihood of developing CD and IBD (78–80). These results call into question a direct influence of tonsillectomy on GALT. A Danish nationwide cohort study demonstrated that a history of tonsillectomy in first- and second-degree relatives increases an individual’s risk of IBD (78), suggesting shared hereditary or environmental factors.

There is growing evidence of physiologic and pathologic crosstalk in IgA immunity between NALT/BALT and GALT (81,82) or mucosa and nonmucosal tissues (83). After intranasal immunization with inactive cholera toxin, lung dendritic cells stimulate the retinoic acid-dependent upregulation of $\alpha 4\beta 7$ and CCR9 gut-homing receptors on local IgA-expressing B cells (81). The migration of these B cells to the

Time	Europe (%)	Japan (%)
3–6 months	31	11
6 months to 1 year	32	47
1–2 years	21	36
2–3 years	9	5
3–5 years	6	0
>5 years	1	1

gut results in IgA-mediated protection against an oral challenge with active cholera toxin. Such homing plasticity of IgA⁺ B cells in NALT/BALT may underlie this crosstalk, although GALT-oriented IgA⁺ B cells home more efficiently to GALT, but not to spleen or NALT/BALT (84,85).

APRIL/BAFF Balance in B Cell Regulation in IgAn

Different GWAS for common infections and infection-associated procedures in patients with a European ancestry demonstrated certain independent genome-wide associations with tonsillectomy. These include HLA and genes of the TNF/receptor superfamily ligands, such as *TNFSF13B* and *TNFRSF13B*, which encode BAFF and the transmembrane activator and cyclophilin ligand interactor, respectively (86). BAFF and a proliferation-inducing ligand (APRIL) are members of the TNF superfamily, and are essential cytokines to IgA class-switch recombination and B cell differentiation and maturation in the mucosa, although pathophysiologic role sharing between APRIL and BAFF largely remains unknown (87). Transmembrane activator and cyclophilin ligand interactor is one of the shared receptors of BAFF and APRIL. Although the overexpression of BAFF leads to the intestinal accumulation of IgA⁺ plasma cells and subsequent murine IgAn (52), several GWAS carried out in patients with IgAn identified a strong associated loci at *TNFSF13* at 17p13 encoding APRIL, but not *TNFSF13B* (BAFF) (71,72). Moreover, APRIL targeted antibodies (88,89), but not BAFF (paper in revision), dramatically improved kidney injury as evidenced by decreased proteinuria and mesangial IgA deposition in spontaneous murine IgAn models (grouped ddY). Moreover, the serum levels of APRIL were correlated with the serum levels of GdIgA1 and IgAn prognosis (90,91). Such experimental and clinical results support the idea that IgAn is an APRIL-mediated disease rather than a BAFF-mediated disease.

The tonsillar expression of APRIL in patients with IgAn is significantly higher than in those with chronic tonsillitis (92). Such tonsillar APRIL expression involves germinal center B cells (92). Toll-like receptor (TLR)-mediated microbial sensing plays a critical role in IgA production in the mucosa via APRIL/BAFF activation (87). We previously reported that a specific SNP of TLR9 that recognizes the unmethylated DNA of microbiomes is significantly associated with the pathologic severity of IgAn (93). The expression of TLR9 in the tonsils is related to reduced serum IgA and GdIgA1 after a tonsillectomy, which represents a treatment response (94,95). Note the persistent stimulation of TLR9 induces APRIL expression in the B cells themselves, even in tonsillar B cells from patients who do not have IgAn (92). Indeed, tonsillar APRIL expression is significantly correlated with TLR9 in patients with IgAn (92). At least in the spontaneous murine IgAn model, TLR9 activation in NALT, but not GALT, is involved in nephritogenic aberrantly glycosylated IgA production and subsequent renal damage (96). The association between *TNFSF13* (APRIL) at 17p13 and *HOMA-D2(LIF/OSM)* at 22q12 in an independent population-based GWAS of the serum levels of IgA is worthy of note (97), because LIF/STAT1 signaling is involved in the overproduction of Gd-IgA1 in IgAn (98). These results suggest an aberrant innate immune activation of mucosal TLR9/APRIL in IgAn. Furthermore, in addition to the risk of tonsillectomy,

BAFF is known as a potential biomarker for active IBD and celiac disease (99,100). Further examinations with translational approaches are required to find a core molecular mechanism; however, assessment from the point of APRIL/BAFF balance in the crosstalk between NALT/BALT and GALT may be one of next challenges to explain the heterogeneity of IgAn.

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Author Contributions

Y. Suzuki conceptualized the study; H. Suzuki was responsible for data curation; H. Suzuki, R. Monteiro, and Y. Suzuki were responsible for formal analysis; Y. Suzuki was responsible for funding acquisition; H. Suzuki, R. Monteiro, and Y. Suzuki were responsible for investigation; H. Suzuki, R. Coppo, R. Monteiro, and Y. Suzuki were responsible for the methodology; R. Monteiro and Y. Suzuki were responsible for project administration; Y. Suzuki provided supervision; H. Suzuki and Y. Suzuki wrote the original draft; R. Coppo, R. Monteiro, and Y. Suzuki reviewed and edited the manuscript; H. Suzuki, R. Coppo, and R. Monteiro were responsible for validation.

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