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Immune abnormalities in IgA nephropathy

Micaela Gentile[1,2], Luis Sanchez-Russo[1], Leonardo V. Riella[3], Alberto Verlato[1], Joaquin Manrique[4], Simona Granata[5], Enrico Fiaccadori[2], Francesco Pesce[6], Gianluigi Zaza[5] and Paolo Cravedi[1]

[1]Translational Transplant Research Center and Department of Medicine, Icahn School of Medicine at Mount Sinai, NY, USA, [2]UO Nefrologia, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy, [3]Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [4]Nephrology Service, Complejo Hospitalario de Navarra, Pamplona, Spain, [5]Nephrology, Dialysis and Transplantation Unit, University of Foggia, Foggia, Italy and [6]Nephrology, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari "A. Moro", Bari, Italy

Correspondence to: Paolo Cravedi; E-mail: Paolo.cravedi@mssm.edu

ABSTRACT

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and it is characterized by mesangial IgA deposition. Asymptomatic hematuria with various degrees of proteinuria is the most common clinical presentation and up to 20%–40% of patients develop end-stage kidney disease within 20 years after disease onset. The pathogenesis of IgAN involves four sequential processes known as the "four-hit hypothesis" which starts with the production of a galactose-deficient IgA1 (gd-IgA1), followed by the formation of anti-gd-IgA1 IgG or IgA1 autoantibodies and immune complexes that ultimately deposit in the glomerular mesangium, leading to inflammation and injury. Although several key questions about the production of gd-IgA1 and the formation of anti-gd-IgA1 antibodies remain unanswered, a growing body of evidence is shedding light on the innate and adaptive immune mechanisms involved in this complex pathogenic process. Herein, we will focus on these mechanisms that, along with genetic and environmental factors, are thought to play a key role in disease pathogenesis.

LAY SUMMARY

Immunoglobulin A (IgA) nephropathy (IgAN) is a kidney disease caused by the deposition of antibodies (IgA) in the glomerulus, the filtering portion of the kidney. As a result, filtering properties of the kidneys are lost and larger molecules like proteins cross from the blood into the urine. Up to 20%–40% of patients develop end-stage kidney disease (requiring dialysis or transplant) within 20 years after disease onset. New treatment options have become available over the last few years. This paper reviews the IgAN immune abnormalities that are targeted by the new therapies.

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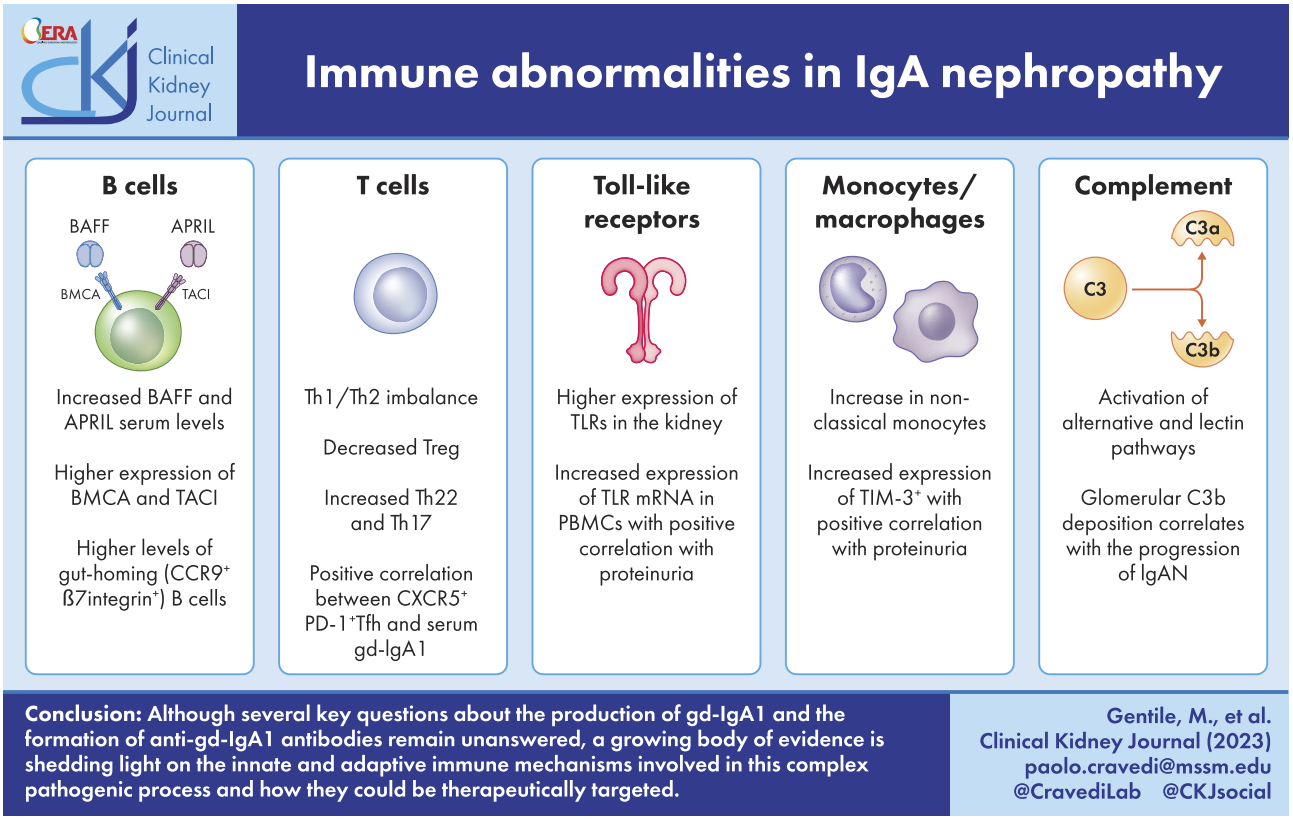
GRAPHICAL ABSTRACT



Keywords: adaptive immunity, galactose-deficient IgA1, innate immunity, IgA nephropathy

INTRODUCTION

Immunoglobulin A (IgA) nephropathy (IgAN) is characterized by mesangial deposition of aberrantly glycosylated IgA, and is now recognized as the most common primary glomerulonephritis globally [1]. IgAN was first described by Jean Berger in 1969 [2], and has an annual incidence of 2–10 cases per 100 000 people with most of the cases occurring during the second and third decades of life [3]. The prevalence varies widely from West-to-East, ranging from 12% to 25% of all native kidney biopsies in North America and Europe, and up to 40% in Japan [4]. Although variability in screening policies may account for some of this difference, genetic and environmental factors are thought to play a role as well [5].

Clinical presentation is heterogeneous and varies widely among different age groups. The classical clinical phenotype includes hematuria intercurrent with gastrointestinal or upper respiratory tract infections. Gross hematuria is more commonly seen in younger patients, while asymptomatic hematuria with various degrees of proteinuria is the most common presentation in older adults [1]. Nephrotic syndrome is observed in about 5% of cases [6, 7]. Disease progression is usually slow, but up to 20%–40% of patients develop end-stage kidney disease (ESKD) within 20 years after diagnosis [1]. The severity and time-average of proteinuria are considered major predictors of kidney function loss [8] along with histopathologic features listed in the Oxford Classification [9].

The "four-hit hypothesis" in IgAN offers a concise account of what is currently known about the pathogenesis of the disease (Fig. 1). This hypothesis postulates that the development of IgAN starts with increased circulating levels of an aberrantly glycosylated galactose-deficient IgA (gd-IgA1), followed by the formation of immune complexes with anti-gd-IgA1 antibodies that ultimately deposit in the glomerular mesangium, leading to kidney injury [1]. The origin of gd-IgA1 is still unclear, but data converge to indicate that the gut-associated lymphoid tissue (GALT) plays a key pathogenic role. Interactions between microbiota and intestinal mucosa have been deemed essential for the development of IgA in the gut, but it is not clear how changes to the microbiota and dysbiosis affect the production of aberrant gd-IgA1 [10]. However, the presence of gd-IgA1 in circulation is by itself not sufficient to cause IgAN. The fact that gd-IgA1 is also found in healthy subjects [11] underlines the presence of additional abnormalities that have to take place before the disease develops [12]. Herein, we will review the immune alterations that, along with genetic and environmental factors, play a key role both in the onset and progression of IgAN.

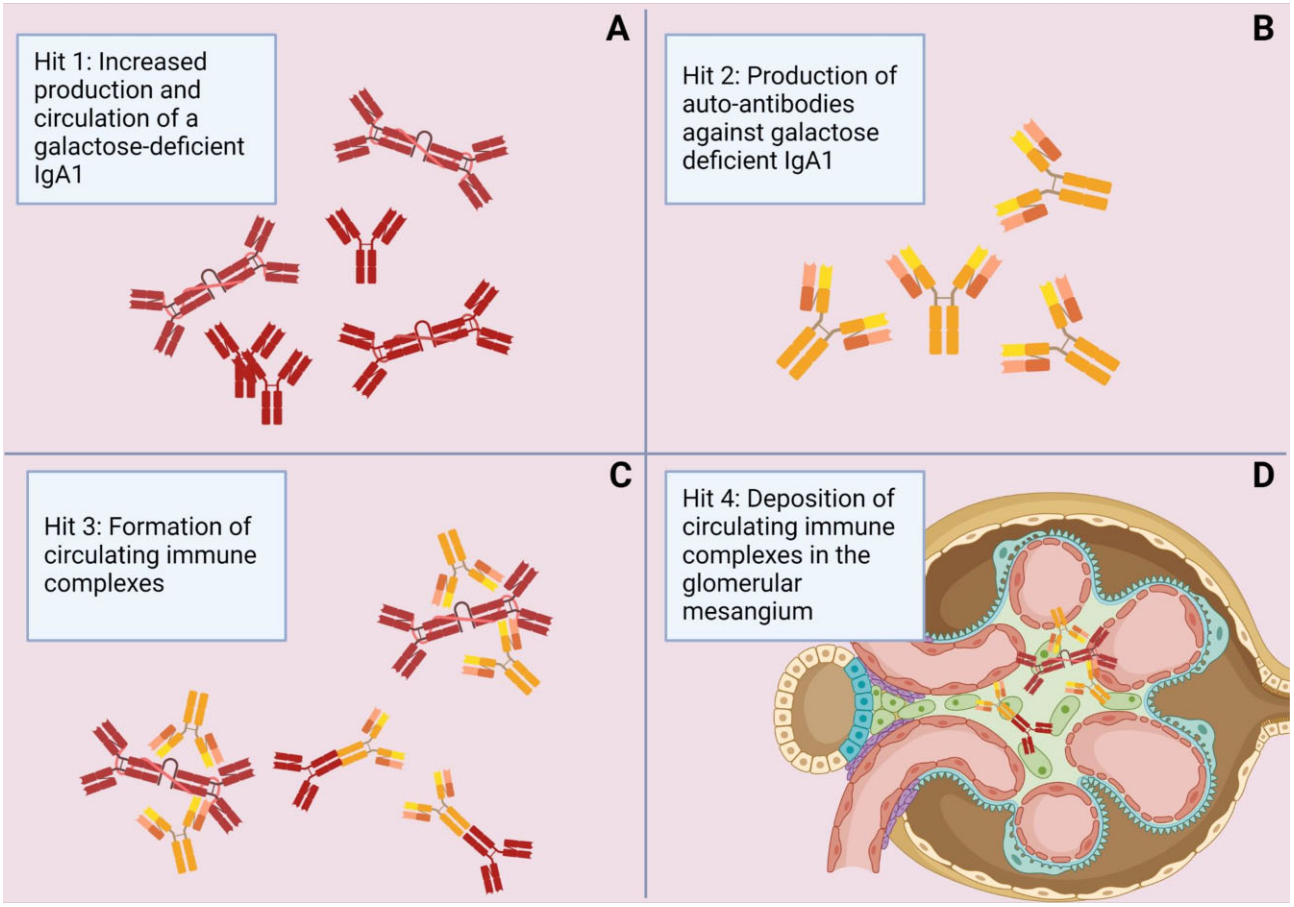


Figure 1: Representation of four hit hypothesis involved in the pathogenesis of IgA nephropathy.

THE FOUR-HIT HYPOTHESIS AND THE ROLE OF GALACTOSE-DEFICIENT IgA

Hit 1: increased production and circulation of gd-IgA1

IgA is the predominant antibody subtype in external secretions and plays an important role in mucosal immunity (Fig. 2) [13]. In humans and higher primates, IgA exists in two subclasses: IgA1 which is found in mucosal surfaces and systemic circulation, and IgA2 which is mostly limited to the mucosal surfaces [14]. The two isotypes differ in the numbers of N-linked carbohydrates in the heavy chain and in their hinge region (HR): compared with IgA2, IgA1 contains a unique extended HR characterized by nine serine and threonine residues and usually three to six of them have O-linked glycans attached. These O-glycans are formed by an N-acetylgalactosamine (GalNac) with β1,3-linked galactose that can be sialylated with one molecule of sialic acid [12]. Both the total number and the structure of attached O-glycans contribute to the heterogeneity of IgA1 [15]. Variations in O-glycosylation impact the biological functions of the immunoglobulin, including its ability to nonspecifically bind to bacteria which enables IgA to participate in innate immunity [16].

Circulating levels of gd-IgA1 have been found to be consistently higher in patients with IgAN compared with healthy controls and other immune- and nonimmune-mediated kidney diseases. Furthermore, the levels of gd-IgA1 correlate with IgAN disease progression in some series [17–19]. The detailed structure of gd-IgA1 with site-specific attachment of Gal-deficient O-glycans specific for the disease has not been identified [15]. The available assays [20–22] used to detect the gd-IgA1 in the serum cannot discriminate among different O-glycoforms, and quantitative analyses using liquid chromatography–mass spectrometry is required [11].

The high levels of gd-IgA1 seen in patients with IgAN may be the result of post-translational modifications of IgA1 [23] or altered expression of key glycosyltransferases involved in the galactosylation process. Premature sialylation by ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2 (ST6GALNAC2) prevents addition of galactose to GalNac. Gd-IgA1 cells have been found to have elevated expression of ST6GALNAC2 [24]. Decreased expression of core 1 β1,3-galactosyltransferase (C1GALT1), controlled by chaperone 1 (C1GALT1C1) have also been found in gd-IgA producing cells.

The site of gd-IgA1 production is still unclear, although there is evidence on the involvement of Peyer's patches and mesenteric lymph nodes. [25] The IgA produced at the mucosal surface (secretory IgA) is exclusively polymeric as opposed to the monomeric isoforms of IgA normally found in circulation [14]. The presence of secretory IgA in the mesangial deposits in 15%–30% of IgAN patients [26, 27] suggests the mucosal involvement in the pathogenesis of the disease, although the mechanisms that lead to the deposition of secretory IgA remain unclear. Circulating levels of secretory IgA have also been found to be higher in patients with IgAN compared with healthy controls with a

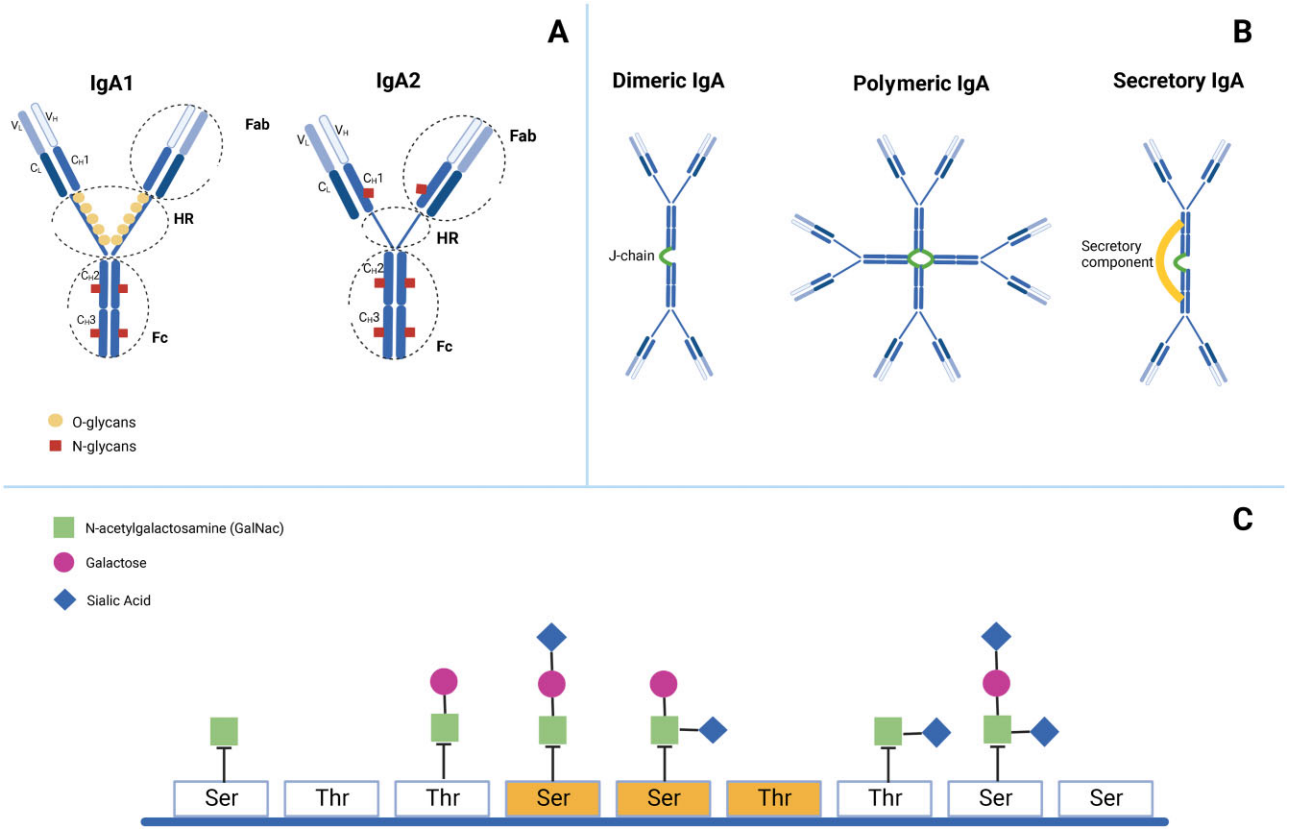


Figure 2: IgA forms and subclasses (**A** and **B**, modified from 'Perše M, Večerić-Haler Ž. The role of IgA in the pathogenesis of IgA nephropathy. *Int J Mol Sci* 2019;20:6199'). Schematic representation of the nine serine and threonine residues in the hinge region that serve as potential O-glycosylations (up to six are O-glycosylated). Six different type of O-glycans can be found in the IgA1 HR. The residues highlighted in yellow are the frequent sites with galactose-deficient O-glycan (**C**).

positive correlation to disease activity [28]. Serum levels of gd-IgA1 directed against mucosal pathogens are increased in IgAN compared with healthy controls [29].

Hit 2: antiglycan antibodies target gd-IgA1

High levels of serum gd-IgA1 are not sufficient *per se* to induce glomerular injury. The disease requires the formation of IgG or IgA1 autoantibodies that recognize the terminal GalNac of gd-IgA1 as a neoepitope [17, 30]. These autoantibodies share an unusual sequence in the variable region of their heavy chains that enhances binding to galactose-deficient glycans of gd-IgA1 [31], probably due to a somatic mutation [32]. These autoantibodies are mainly IgG isotype, and serum levels of anti-gd-IgA1 IgG correlate with proteinuria [30] and with serum levels of gd-IgA1 [31, 33]. Several studies have shown a clear association between anti-gd-IgA1 IgG, disease progression and absolute risk for ESKD [34, 35].

The mechanisms that lead to the formation of anti-glycan antibodies are not completely understood. It is conceivable that in patients with IgAN an infection with bacteria that express the GalNac molecule on their surface facilitates production of glycan-specific antibodies that cross-react with gd-IgA1. This molecular mimicry between bacteria and gd-IgA1 might explain the fact that hematuria is often concomitant with mucosal infections [12, 36].

Hit 3 and hit 4: formation of immune complexes and mesangial deposition

Circulating immune complexes can be detected in patients with IgAN. These circulating immune complexes are composed of gd-IgA1, anti-gd-IgA1 antibodies and complement C3 [1, 37]. A recent study [38] showed that patients with IgAN have significantly higher levels of poly-IgA immune complexes compared with healthy controls, consistent with previous evidence [39] of increased polymer/monomer IgA ratio in immune complexes in IgAN patients (0.64 ± 0.13 vs 0.39 ± 0.01, in controls; $P < .001$). These complexes are not efficiently cleared from circulation so they tend to deposit in the renal mesangium [12]. Immunofluorescence microscopy often fails to detect IgG colocalizing with IgA, but the presence of IgG has been confirmed using confocal microscopy with an IgG-specific nanobody in a recent study by Rizk *et al.* [40]. These investigators also corroborated the presence of IgG-specific antibodies against gd-IgA1 by extracting immune deposits from frozen kidney biopsy specimens of patients with IgAN. These specific antibodies were found even in cases where regular immunofluorescence microscopy was negative for IgG [40, 41]. The results of this study highlight the role of IgG–gd-IgA1 immunocomplexes in the pathogenesis of IgAN.

Deposition of immune complexes in the glomeruli provokes activation of mesangial cells and release of aldosterone, angiotensin II, pro-inflammatory cytokines [interleukin (IL)-6] [42]

and growth factors [transforming growth factor (TGF)-β] [43]. The result is mesangial cell proliferation and complement pathway activation which ultimately cause glomerular injury and interstitial fibrosis [1, 44].

BAFF AND APRIL

B-cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL) [1], produced by antigen-exposed dendritic cells and intestinal epithelial cells [45], are critical factors in the maintenance of the B cell pool and in humoral immunity and are involved in the pathogenesis of several human autoimmune diseases [46]. BAFF maintains B cell homeostasis while APRIL modulates the function and survival of antigen-experienced B cells.

BAFF overexpression in mice induces autoimmune diseases similar to human systemic lupus erythematosus and IgAN. McCarthy *et al.* [47] showed that BAFF transgenic (BAFF-Tg) mice have increased levels of total IgA, aberrantly glycosylated IgA and mesangial IgA deposits with the development of proteinuria. The presence of commensal bacteria was essential to produce the IgAN phenotype and commensal-bacteria-reactive IgA antibodies were found in the blood of these mice, suggesting that overreactive B cells and mucosal microbiota both play a very important role in the pathogenesis of IgAN.

Several human studies (Table 1) have reported increased serum levels of BAFF and APRIL in patients with IgAN that correlate with gd-IgA1 levels and disease severity [48–51]. *Ex vivo* stimulation with APRIL of lymphocytes from IgAN patients led to an increased production of gd-IgA1 compared with lymphocytes from healthy controls [50]. Also, an enhanced expression of BCMA and TACI mRNA and protein was observed in B cells derived from IgAN patients [50]. Recently, Sallustio *et al.* [51] compared BAFF and APRIL levels in 44 patients with IgAN with 23 healthy controls and 22 patients with non-IgA glomerulonephritis, and reported that patients with IgAN had higher serum levels of BAFF, APRIL and gd-IgA1 along with higher circulating levels of gut-homing ($CCR9^+$, $\beta7$ $integrin^+$) B cells. A recent study has confirmed increased of expression of gut homing receptors in B cells in IgAN patients compared with controls [52]. The relationship between commensal bacteria, dietary antigens and high BAFF levels is not clear, but elevated BAFF levels have been associated with specific fecal metabolites, especially phenols, in individuals consuming high beef diet who had increased populations of phenol-producing anaerobic *Bacteroides* [51].

Altogether, these data support the hypothesis of a strong link between gut mucosal hyperresponsiveness and the activation of specific subtypes of B cells through BAFF and APRIL, resulting in an increased production of gd-IgA1. Evidence on the pathogenic role of BAFF/APRIL in IgAN led to the hypothesis that drugs initially developed for other immune disease [53, 54] can serve as a disease-modifying agents also in IgAN. Ongoing phase II and III clinical trials are testing the efficacy of BION-1301, an anti-APRIL monoclonal antibody (NCT03945318), and blisibimod, a selective inhibitor of BAFF (NCT02052219). The role of atacicept, a humanized recombinant TACI-IgG Fc fusion protein with anti-BAFF and anti-APRIL activity, is being explored in another phase II trial (NCT04716231). However, given the role of these cytokines in the maintenance of the B cell pool and humoral immunity, these drugs will likely not selectively inhibit IgA production.

TARGETING B CELLS AND PLASMA CELLS AS A THERAPEUTIC STRATEGY FOR IgAN

Despite the evidence suggesting that B cells have an important role in the pathogenesis of IgAN and the successful use of B cell depleting therapy in case reports [55–57], mainly of IgA vasculitis [58, 59], a randomized controlled trial comparing rituximab with conventional therapy in IgAN did not show any benefits despite effective B cell depletion [60]. Moreover, there were no differences in serum levels of gd-IgA1 and anti-gd-IgA1 between the two groups. Possible explanations to the lack of efficacy on B cell depleting agents may be due to the production of anti-gd-IgA1 IgG or IgA by plasma cells in the bone marrow or the reduced effects of rituximab in depleting mucosal B cells [60]. The stable presence of $CD20^-CD19^+CD27^{high}$ IgA-secreting cells of mucosal origin has been reported in patients treated with rituximab [61]. B cell precursors resident in the mucosa may be self-sufficient in adults and not replenished by CD20 B cells immigrating from systemic circulation [62].

A targeted-release formulation of the corticosteroid budesonide has been engineered to target the Peyer's patches in the distal ileum. This medication has been approved by the Food and Drug Administration to treat patients with IgAN based on the results from a randomized controlled trial showing a significant reduction of proteinuria in treated patients compared with the placebo group [63]. Although the mechanisms of action are not clearly understood, it is thought that budesonide inhibits the local activation of B cells and thereby attenuates the gd-IgA1 production, with less systemic steroid absorption [64, 65].

The proteasome inhibitor bortezomib has also been tested in IgAN to clear plasma cells. In a single-center open-label pilot trial in eight patients with IgAN, three patients had complete remission of proteinuria (<300 mg/day) [66]. Though further studies are needed, it is possible that bortezomib could be useful in decreasing production of gd-IgA1 antibodies and inhibiting nuclear factor kappa B (NF-κB) expression.

T CELLS

Th1 and Th2

Abnormalities in T helper 1 (Th1) and Th2 cell numbers and function have been reported in IgAN (Table 1), but the data are not clear. A murine model of IgAN showed more Th1 in animals with signs of illness [67], and an *in vitro* study [68] in humans found a higher IL-2/IL-5 ratio in patients with IgAN compared with controls, suggesting a Th1 shift. In contrast, other studies revealed an increase of Th2 and IL-4 in patients with IgAN [69, 70] and a correlation between Th2 cytokines and reduced glycosylation of IgA1 [71]. In particular, IL-4 has been associated with downregulation of 1 β*1,3-galactosyltransferase (Cosmc)* gene, chaperone, that may lead to reduced glycosylation of IgA1 in IgAN patients [72].

Th17 and Th22

Th17 and Th22 may also play a pathogenic role in IgAN, although the mechanisms remain unknown [73]. Th17 cells are increased in patients with IgAN compared with healthy controls [74] as well as serum levels of Th17 cytokines IL-17A and IL-21. A positive correlation between IL-17A levels and proteinuria has also been observed [75]. The number of Th22 cells and plasma levels of IL-22 are higher in patients with IgAN compared with healthy controls and non-IgAN controls. Furthermore, the number of

Table 1: Human studies about abnormalities of adaptatitve immunity in IgAN.

	Authors	Classes of subjects	Principal findings in IgAN patients
B cells and BAFF-APRIL axis	Xin *et al.* 2013 [48]	• 153 IgAN patients • 55 healthy controls • 20 disease controls	• Higher BAFF levels compared with controls • Levels were associated with severity of histologic damage
	Li *et al.* 2014 [49]	• 30 IgAN patients • 30 healthy controls • 30 minimal change disease	• Positive correlation between serum levels of BAFF, TLR9 and IgA1 levels and mesangial IgA deposition density
	Zhai *et al.* 2016 [50]	• 166 IgAN patients • 77 healthy controls	• Increased plasma APRIL levels • Positive correlation between plasma APRIL levels and gd-IgA1 levels • Higher expression of BCMA and TACI
	Sallustio *et al.* 2021 [51]	• 44 IgA patients • 23 healthy controls • 22 non-IgA glomerulonephritis	• Increased serum BAFF levels with positive correlation with specific microbiota metabolites • Increased serum APRIL levels • Higher levels of gut-homing ($CCR9^+$ $\beta7$ $integrin^+$) regulatory B cells. Memory B cells and IgA^+ memory B cells
	Zachova *et al.* 2022 [52]	• 30 IgAN patients • 30 healthy controls • 18 membranous nephropathy controls	• Gd-IgA1 cells from IgAN patients express predominantly λ chains compared with controls • IgAN patient's blood was enriched with λ^+ gd-IgA1, $CCR10^+$ and CCR9 + cells, which preferentially home to the upper respiratory and digestive tracts
T cells	Sallustio *et al.* 2016 [68]	• 24 IgA patients • 24 healthy controls	• Aberrant methylations in three regions involved in the response of $CD4^+$ T cells • Higher IL-2/IL-5 ratio with Th1/Th2 imbalance
	Yang *et al.* 2017 [69]	• 60 IgAN patients • 25 healthy controls	• Lower levels of Th1 and Treg (with reduced levels of IFN-γ and IL-10) • Higher levels of Th2 and Th17 (with higher levels of IL-5 and IL-17)
	Zhang *et al.* 2014 [70]	• 24 IgAN patients • 12 healthy controls	• Higher % of $CD4^+CXCR5^+$, $CD4^+CXCR5^+ICOS^+$, $CD4^+CXCR5^+PD\text{-}1^+$ Tfh • Increased levels of IL-17A, IFN-γ, IL-2, IL-10, IL-4, IL-21 • Positive correlation between $CD4^+CXCR5^+PD\text{-}1^+$ Tfh and serum IL-21, gd-IgA1 and 24-h urinary proteins
	Peng *et al.* 2013 [74]	• 32 IgAN patients • 32 healthy controls • 16 MPGN patients	• Higher Th22, Th17 and plasma IL-22 • Positive correlation between Th22 and proteinuria
	Lin *et al.* 2012 [75]	• 63 IgAN patients • 36 healthy controls	• Decreased $CD45^-FoxP3^{high}$ Treg • Increased Th17 and decreased Treg/Th17 • Positive correlation between Th17 and proteinuria • Increased IL-17A, IL-21, IL-23, IL-1β, IL-6 and decreased IL-10
	Gan *et al.* 2018 [76]	• 44 IgAN patients • 16 healthy controls • 5 renal carcinoma patients	• Increased Th22 • Positive correlation between Th22 and MESTc score
	Yang *et al.* 2015 [77]	• 20 IgAN patients • 20 healthy controls	• Decreased iTreg • Reduced serum levels of IL-10, TGF-β, increased IL-17
	Huang *et al.* 2014 [79]	• 35 IgAN patients • 35 healthy controls	• Decreased $CD4^+CD25^+$ Treg with negative correlation with IL-4 and proteinuria and positively with eGFR • Increased IL-2, IL-4, IL-6

IFN: interferon; MPGN: membranoproliferative glomerulonephritis.

Th22 cells is higher in patients with IgAN with proteinuria and high grade histological lesions defined in the Oxford Classification of IgA nephropathy (MESTc score) [74, 76].

Tfh

Studies on the role of Tfh are limited [73], but evidence exists showing an increased percentage of circulating Tfh cells and higher serum levels of IL-2, IL-4, IL-10, IFN-γ, IL-17A and IL-21 in IgAN patients compared with healthy controls. Tfh cell percentages negatively correlate with estimated glomerular filtration rate (eGFR), but positively correlate with gd-IgA1 and proteinuria [70].

Treg

IgAN patients display abnormalities in Treg number and function. Yang *et al.* [77] showed that the number of Treg in patients with IgAN was lower compared with healthy controls, and other studies found lower mRNA expression of *TGF-β1* and *FoxP3* genes

Table 2: Human studies about abnormalities of innate immunity in IgAN.

	Authors	Classes of subjects	Principal findings in IgAN patients
TLRs	Coppo *et al.* 2010 [82]	• 47 IgAN patients • 40 healthy controls	• Higher expression of TLR-4 in mononuclear cells with positive correlation with proteinuria
	Saito *et al.* 2016 [84]	• 49 IgAN patients • 20 IgA vasculitis patients • 20 basement membrane nephropathy	• Increased mRNA expression of *TLR-2*, *TLR-3*, *TLR-4*, *TLR-5*, *TLR-7*, *TLR-9* with positive correlation with proteinuria
Monocytes	Hou *et al.* 2021 [90]	• 48 IgAN patients • 18 healthy controls	• Increased expression of TIM-3$^+$ on CD14$^+$ monocytes with positive correlation between proteinuria and negative correlation with eGFR
	Esteve Cols *et al.* 2020 [91]	• 22 IgAN patients • 12 healthy controls	• Reduced of classical monocytes • Reduced expression levels of CD89 on non-classical monocytes with positive correlation with poor renal function
	Sendic *et al.* 2021 [92]	• 13 IgAN patients • 13 healthy controls • 13 ADPKD patients	• Higher proportion of non-classical monocytes • Positive correlation between MCP-1 and UACR

ADPKD: autosomal dominant polycystic kidney disease; UACR: urine albumin-creatinine ratio.

in IgAN patients [78], as well as increased serum levels of IgA, IL-2, IL-4 and IL-6 [79], overall suggesting an imbalance between Treg and T effector cells.

INNATE IMMUNITY AND TOLL-LIKE RECEPTORS

Innate immune cells express pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) which are responsible for the detection of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [80, 81]. Increased expression of TLR-4 on PBMCs has been associated with higher disease activity in IgAN patients [82] (Table 2). Patients with IgAN also express up-regulation of TLR-4, TLR-7, TLR-8 and TLR-9 in the kidney [83] and increased mRNA expression of *TLR-2*, *TLR-3*, *TLR-4*, *TLR-5*, *TLR-7* and *TLR-9* in PBMCs, with a positive correlation with proteinuria [84]. *In vitro*, TLR-9 activation enhances the production of APRIL and IL-6 in human IgA1-secreting B cells [85]. Therefore, activation of TLRs by infections may exacerbate IgAN by activating cells of the innate immune system that, in turn, affect glomerular function, either directly, or through increased autoimmune response. TLR-4 has also been involved in the activation of NF-κB [86] and in B cell proliferation [87]. Animal studies have showed a relationship between high TLR-4 levels and conversion of B cells from IgM$^+$ to IgA$^+$ [84].

Intriguingly, TLR-4 is also constitutively expressed by podocytes and mesangial cells [88] and *in vitro* studies have shown that stimulation of mouse mesangial cells with human secretory IgA increases *TLR-4* mRNA and protein levels, suggesting a direct role of TLR-4 in mesangial cell injury [89].

MONOCYTES AND MACROPHAGES

Monocytes and macrophages play a role in mediating kidney injury in IgAN [90] (Table 2). CD89, the main receptor for IgA expressed on the surface of myeloid cells, has been found as a component of immune complexes in patients with IgAN [91]. A study comparing 22 patients with IgAN with 12 healthy controls showed a reduction in circulating classical monocytes (CD14$^+$CD16$^-$) in patients with IgAN but no differences in intermediate monocytes (CD14$^+$CD16$^+$) or non-classical monocytes (CD14^{low}CD16$^+$) [91]. Consistently, a prospective study [92] found a higher proportion of non-classical monocytes in 13 IgAN patients compared with 13 healthy controls and 13 patients with polycystic kidney disease, accompanied by increased level of IL-6 and a positive correlation between monocyte chemoattractant protein-1 (MCP-1; a chemotactic factor for monocytes) levels and albuminuria in IgAN.

The infiltration of macrophages into the tubulointerstitial compartment of the kidney correlates with fibrosis and unfavorable kidney outcomes in patients with IgAN [93]. A recent paper showed a higher expression of TIM-3$^+$ (T-cell immunoglobulin and mucin-domain-containing protein-3, an immunoregulatory molecule) on CD14$^+$ monocytes in 48 patients with IgAN compared with 18 healthy controls with a positive correlation with proteinuria and a negative correlation with eGFR [90]. Lastly, CD68$^+$TIM-3$^+$ cells are abundant in kidney immune infiltrates in IgAN patients. These data suggest that Tim3$^+$ monocytes may play a role in IgAN pathogenesis and could be tested as a biomarker for disease activity.

COMPLEMENT

The complement system is an important component of innate immunity that can be activated through three pathways. The classical pathway (CP) is triggered by cross-linking, cell-bound IgM or IgG antibodies, while activation of the alternative pathway (AP) occurs spontaneously by the association of C3 with a water molecule. Activation of the lectin pathway (LP) is triggered by carbohydrates present on bacteria surface and follows a route similar to that of the classical pathway [94]. These three pathways converge in the formation of a terminal membrane attack complex (MAC, C5b9) that directly lyses pathogens or damaged self-cells [95, 96].

Several studies have provided evidence of the activation of the AP and LP as effector mechanisms of kidney injury in IgAN [97]. Components of AP are found in renal biopsies of patients with IgAN, especially C3 (90%), complement factor H (CFH, 30%–90%) and properdin (75%–100%), and regulators such as CFH-related proteins (CFHR) [97]. Glomerular C3 deposition correlates with the progression of IgAN and the presence of complement components may distinguish between IgAN and IgA depositions that can be found in healthy subjects [98, 99]. A factor B inhibitor,

iptacopan (LNP023), is being studied in the placebo-controlled APPLAUSE-IgA study (NCT04578834) [100] to test the hypothesis that AP inhibition reduces disease severity.

A genome-wide association study has identified a deletion of the gene encoding the CFHR [101], which appears protective against IgAN [102]. It is unclear how loss of function of CFHRs may be protective in IgAN but it is believed that it could enhance the regulating capacity of CFH, thus reducing AP activity [97].

The identification of C4d in the absence of C1q in kidney biopsies of patients with IgAN strongly suggests that the LP is also an effector mechanism of injury in this disease [97]. Polymeric IgA has strong mannan-binding lectin (MBL) binding and gd-IgA1 may trigger LP activation due to interaction with ficolin [97]. A study on 323 patients with IgAN found increased circulating levels of ficolin, MBL-associated protease (MASP-1) and MBL-associated protein (Map-19) compared with healthy controls [103]. Based on the pathogenic role of LP in IgAN, LP inhibitors have been tested in clinical trials. Lafayette *et al*. [104] showed an improvement in proteinuria and stability of eGFR in high-risk patients with advanced IgAN treated with narsoplimab (OMS71), a humanized monoclonal antibody targeting MASP-2. Based on these data, a randomized, double-blind, placebo-controlled trial of narsoplimab is ongoing for patients with IgAN and persistent proteinuria (ARTEMISAN-IGAN, NTC030608033).

The activation of AP and LP converge to the activation of the terminal pathway (TP). An animal model of IgAN showed a possible role of C5a/C5aR signaling in the pathogenesis of IgAN. C5aR knockout mice had less proteinuria, and C3 and IgA deposition in the glomeruli [105]. In humans, MAC glomerular deposition has a positive correlation with the degree of glomerulosclerosis, tubular atrophy and interstitial inflammation in IgAN [106]. However, terminal complement inhibition with the humanized recombinant monoclonal anti-C5 antibody eculizumab has not shown efficacy in patients with IgAN [107–109], suggesting that major IgAN effector mechanisms of complement cascade are upstream C5.

IgAN RECURRENCE AFTER KIDNEY TRANSPLANTATION

IgAN has a high rate of recurrence (20%–40% clinical but 60% on biopsy) [110, 111] but its impact on allograft survival is small [112], possibly because the immunosuppressive drugs used to prevent rejection may also inhibit the IgAN. In the largest study (TANGO consortium) involving over 500 patients with IgAN that underwent kidney transplantation, the 10-year death-censored graft survival was 76% in patients with recurrence compared with 89% in those without recurrence [112]. The mean time to IgA recurrence was 3.4 years after transplantation [112]. While initial smaller studies suggested that maintenance steroids was associated with lower recurrence rate, the TANGO study did not show any association between steroid withdrawal and higher risk of recurrence [112]. The role of gd-IgA1 in recurrence is controversial, since they remain elevated only in some recipients regardless of the immunosuppressive therapy [113, 114]. The successful use of budesonide in IgA recurrence has been reported only in six patients so far [115, 116]. The fact that kidneys from donors with subclinical IgAN are clear of IgA deposits shortly after transplantation into recipients with non-IgAN renal diseases [117] points to the importance of persistent IgA immune complex production and deposition in the pathogenesis of IgAN.

The role of BAFF and APRIL has been investigated in transplant recipients with IgAN relapse. Penagos *et al*. have shown increased serum levels of APRIL at 6 months after transplant up to 3 years post-transplant in patients in with IgAN recurrence [110], while BAFF levels were reduced. The authors speculate that TACI, a positive regulator for APRIL and a negative regulator of BAFF, may be implicated in IgAN recurrence. Intriguingly, genetic mutations that inactivate TACI cause selective IgA deficiency [118]. Although additional studies are needed to understand the pathogenesis of IgAN relapse, these data suggest that targeting APRIL and TACI may have a therapeutic role in kidney transplant patients with IgAN recurrence.

CONCLUSIONS

The immune abnormalities that lead to the accumulation of aberrant forms of gd-IgA1 and to the formation of immune complexes that mediate glomerular injury in IgAN are not fully understood. However, a growing knowledge of these pathogenic mechanisms, together with the availability of small molecules and biologics targeting innate and adaptive immunity, has resulted in a dramatic increase in the number of ongoing clinical trials in IgAN that are expected to provide new tools to improve patients' outcomes. We believe that it will be important to accompany clinical studies with mechanistic analyses to better understand disease pathophysiology, which could be obtained also from negative trials. Sharing clinical samples across investigators will be instrumental to further deepen our understanding of disease pathophysiology and to design hypothesis-driven studies.

CONFLICT OF INTEREST STATEMENT

Paolo Cravedi is an advisor for Chinook Therapeutics and Calliditas Therapeutics. The other authors have no conflict of interest to declare.

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