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**Key Points:**

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Immunoglobulin-A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. The working model for the pathogenesis of IgAN involves a multistep process starting from the production of galactose deficient and polymeric immunoglobulin A-1 (gd-IgA1) that enters systemic circulation from gut-associated lymphoid tissue (GALT). Galactose-deficient IgA are targeted by endogenous IgG, leading to the formation of circulating immune complexes that deposit in the mesangium leading to glomerular inflammation. Disease onset and relapses are often associated with gut infections, supporting the hypothesis that the gut plays an important pathogenic role. In the presence of microbial pathogens or food antigens, activated dendritic cells in the gut mucosa induce T-cell dependent and independent B-cell differentiation into IgA secreting plasma cells. In IgAN patients, this promotes the systemic release of mucosal gd-IgA1. Not all bacterial strains have the same capacity to elicit IgA production, and little is known about the antigen specificity of the pathogenic gd-IgA1. However, efficacy of treatments targeting gut inflammation support a pathogenic link between bowel immune system and IgAN. Herein we will review the evidence supporting the role of gut inflammation in IgAN pathogenesis.

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# The Gut and Kidney Cross Talk in Immunoglobulin-A Nephropathy

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**Abstract**

Immunoglobulin-A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. The working model for the pathogenesis of IgAN involves a multistep process starting from the production of galactose deficient and polymeric immunoglobulin A-1 (gd-IgA1) that enters systemic circulation from gut-associated lymphoid tissue (GALT). Galactose-deficient IgA are targeted by endogenous IgG, leading to the formation of circulating immune complexes that deposit in the mesangium leading to glomerular inflammation. Disease onset and relapses are often associated with gut infections, supporting the hypothesis that the gut plays an important pathogenic role. In the presence of microbial pathogens or food antigens, activated dendritic cells in the gut mucosa induce T-cell dependent and independent B-cell differentiation into IgA secreting plasma cells. In IgAN patients, this promotes the systemic release of mucosal gd-IgA1. Not all bacterial strains have the same capacity to elicit IgA production, and little is known about the antigen specificity of the pathogenic gd-IgA1. However, efficacy of treatments targeting gut inflammation support a pathogenic link between bowel immune system and IgAN. Herein we will review the evidence supporting the role of gut inflammation in IgAN pathogenesis.

## Introduction

Immunoglobulin-A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide.[1] Clinical presentation generally involves episodic macrohematuria intercurrent with mucosal infections and varying degree of proteinuria. Disease progression is variable: some patients have a mild presentation with normal kidney function, sometimes achieving complete remission of proteinuria with supportive care alone, while up to 50% of patients progress to irreversible kidney damage and end-stage kidney disease (ESKD).[2] Histologically, the disease is characterized by mesangial and paramesangial deposition of immune complexes with dominance or co-dominance of IgA by immunofluorescence microscopy. Since its initial description by Berger and Hinglais in 1968,[3] significant advances have been made in understanding the pathogenesis of this disease, and evidence now points toward a multi-hit autoimmune process also known as the four-hit hypothesis, which starts with the production of a galactose deficient and polymeric immunoglobulin A-1 (gd-IgA1) and then formation of gd-IgA1 immune complexes in the circulation that ultimately deposit in the glomerular mesangium, leading to inflammation and progressive glomerular injury.[4]

The mechanisms behind the production of gd-IgA1 are not entirely clear, but studies have revealed that the origin of gd-IgA1 is likely mucosal.[5–8] Interactions between commensal bacteria and the intestinal mucosa seem to be essential in regulating IgA production in the gut, though it is not clear how this interaction may influence *O*-glycosylation and production of gd-IgA1. Importantly, these findings formed the basis for the development of drugs that target the gut mucosa to treat patients with IgAN.

Recently, a novel targeted-release form of the corticosteroid budesonide that has been engineered to target the Peyer's patches in the distal ileum,[9–11] was approved by the United States Food and Drug Administration (FDA) to become the first disease-specific therapy in IgAN.[12]

Herein, we will review the processes that regulate IgA production in the gut mucosa, as well as the evidence that links gut mucosal alterations to IgAN. We will also explore the relationship between this disease and other gastrointestinal conditions such as inflammatory bowel disease (IBD) and celiac disease (CD).

## *IgAN: epidemiology, genetic susceptibility, and clinical presentation*

### *Epidemiology and genetic susceptibility*

IgAN is the most common cause of kidney failure secondary to a primary glomerular disease worldwide. It is common in Asia, has lower prevalence in Europe, and is very infrequent among populations of African ancestry.[13] In Eastern Asia, IgAN is diagnosed in 40-50% of native kidney biopsies which heavily contrasts with African registries that show prevalence as low as 2.8%.[14] Differences in screening policies may partially explain such disproportion. In Japan, screening for IgAN by assessment of proteinuria and hematuria with urine dip-stick has been used since 1972 for every child and worker since 1983.[15] This aids to capture and prompts kidney biopsies in asymptomatic patients with isolated microscopic hematuria with or without proteinuria that would have

otherwise passed unnoticed. However, differences in screening practices do not fully explain the geographic variability of the disease.

IgAN can present sporadically or in familial form. For the latter, autosomal dominant transmission with incomplete penetrance, or a combined model where the activation of genes is dependent on environmental factors represent reasonable explanations.[16] Genome-wide association studies (GWAS) have identified several susceptibility and protective genetic loci. Using seven single nucleotide polymorphisms (SNP), a genetic risk score detected significant differences in the distributions of risk alleles among different ethnicities. The frequency of risk alleles was highest in East Asians and lowest in African Americans,[17] mimicking the distribution maps discussed before. The genetic risk score was based on a previous GWAS which identified five IgAN susceptibility loci on Chr.6p21 (HLA-DQB1/DRB1, PSMB9/TAP1, and DPA1/DPB2 loci), Chr.1q32 (CFHR3/R1 locus), and Chr.22q12 (HORMAD2 locus).[18] Intriguingly, these loci have been associated with other autoimmune diseases, including inflammatory bowel disease. Several other GWAS have identified various susceptibility loci that link IgAN to potential environmental and alimentary hits.[19–21] These loci, which include, among others TLR9, DEFA, and TNFSF13, encode fore genes implicated the immunogenic response to antigens in the intestinal mucosa. DNA methylation studies suggest that environmental and alimentary changes in IgAN may induce aberrant methylation of the DNA, leading to an abnormal expression of the genes involved in T cell regulation. This translates into decreased $CD4^+$ T cell proliferation and Th1/Th2 imbalance observed in patients with IgAN.[16,22]

*Clinical presentation*

Historically, the clinical archetype of IgAN presentation includes episodic macroscopic hematuria shortly after a mucosal infection involving the upper respiratory or gastrointestinal tract. In reality, clinical presentation is exceedingly variable. Macroscopic hematuria for example, while common in younger patients, is rarely seen in patients who are over 40 years of age.[23] Disease progression is also heterogeneous and it is poorly understood why some patients have mild forms of the disease, while others experience rapidly worsening kidney function which is often irreversible. The degree of proteinuria and time-average proteinuria correlates with the risk of disease progression.[24] While progression is generally slow, it may lead to ESKD in up to 40-50% of patients within 20-40 years from diagnosis.[1,25] In a cohort study of 251 adults with IgAN, progression to ESKD was seen in 53% and death was observed in 39% over a 20-year follow-up period with life expectancy reduced by 10.1 years.[26]

Treatment of the disease is primarily based on supportive care with strict blood pressure control, weight loss, smoking cessation, and management of dyslipidemia. Targeted treatment with renin-angiotensin-aldosterone-system (RAAS) blockers, which have major anti-hypertensive, anti-proteinuric, and antifibrotic effects are fundamental in the management of IgAN.[27,28] More recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as potential adjunct therapy in patients who have failed to

achieve proteinuria reduction.[29] Immune modulating agents are usually spared for patients with refractory proteinuria. In countries like Japan tonsillectomy has been used as a therapeutic alternative in IgAN. However, despite observational data from a subset of Japanese patients with IgAN suggest that tonsillectomy in combination with steroid pulse may increase the rate of remission of hematuria and proteinuria, a randomized controlled trial (RCT) failed to corroborate such finding.[30,31] European studies have also been unsuccessful in demonstrating any beneficial effect of tonsillectomy in IgAN.[32]

The FDA recently approved a targeted release formulation of budesonide as the first disease specific treatment for IgAN.[12] Interim data from a phase III trial shows reduction of proteinuria by 27% when compared to placebo, and a statistically significant 7% increase in eGFR.[33] An extensive hepatic first pass metabolism,[34] and its direct effect in modulating the immune function of cells of cells that are largely responsible for mucosal IgA production,[35] may give this medication substantial advantage over systemic formulation of corticosteroids which are associated with significant toxicities.

For patients who develop ESKD, kidney transplantation is the treatment of choice. However, after kidney transplant, the disease recurs in a significant subset of patients. A recent multicenter retrospective study on 504 transplant recipients with IgAN showed a cumulative incidence of recurrence of 23% at 15 years[36] and graft loss was higher in patients with recurrent IgAN compared to those without recurrence.

## Gut and Kidney Axis in IgAN

*Current Understanding of IgAN Pathogenesis*

Current evidence indicates that kidney injury in IgAN is the product of four sequential pathogenic processes starting with the production and accumulation of circulating gd-IgA1.[4] The presence of aberrant IgA1 glycoforms *per se* does not translate in kidney injury. Significantly elevated levels of abnormal IgA1 glycoforms have been detected in asymptomatic relatives of patients with IgAN.[37] Two additional processes then have to occur to initiate the glomerular disease, first the generation of autoantibodies against gd-IgA1, and the formation of immune complexes of autoantibodies and gd-IgA1.[38] Though predominantly IgG1 and IgG3, antibodies against gd-IgA1 can also be of IgM or IgA isoforms.[23] Furthermore, poly-IgA complexes may include also molecules that are not autoantibodies. Interactions between IgA and the transmembrane glycoprotein CD89 expressed by myeloid cells can induce shedding of soluble CD89 and prompt the formation of circulating CD89-IgA complexes.[39,40] Mice expressing human IgA1 and CD89 have circulating and mesangial deposits of CD89-IgA which associates with disease features of IgAN (mesangial deposits, hematuria and proteinuria).[41] **Figure 1** illustrates the multi-hit model of IgAN.

The effector mechanisms of the immune complexes have not been fully elucidated yet. Several studies have indicated that pathogenic gd-IgA1 can activate the complement system through the alternative and lectin pathways. High levels of C3 split products have been confirmed in the circulation of patients with IgAN,[42] and terminal complement components co-localize with IgA in kidney biopsies of patients with the disease.[43] In a

study on 60 kidney biopsies of patients with IgAN, mannose-binding lectin was observed in 25% of the cases.[44] Additionally, evidence of lectin pathway activation was associated with higher degree of histologic damage and with significantly more proteinuria. Therefore, complement represents an important effector mechanism in IgA nephropathy, at least in some patients. However, other, complement-independent mechanisms may also play a role. Activation of mesangial cells by immune complexes of polymeric IgA1 unleashes a pro-inflammatory and pro-fibrotic cascade mediated by tumor necrosis factor (TNF), transforming growth factor-β (TGFβ), IL-6 and angiotensin II (Ang II).[13]

*Gut Associated Lymphoid Tissue and IgA*

IgA is the most abundant immunoglobulin isotype produced at mucosal sites and comprises roughly two thirds of all immunoglobulins.[1,45] Similarly to IgM, IgA can also form polymers, though more than two thirds of IgA molecules in circulation are found as monomers. The mucosal associated lymphoid tissue (MALT) is largely responsible for IgA production, with the gut associated lymphoid tissue (GALT) secreting up to 5 grams of IgA into the intestinal lumen every day.[11] The GALT is the best-defined portion of the MALT, and comprises the Peyer's patches, predominant on the distal ileum, and isolated lymphoid follicles that also seem to increase in density distally in the gut.[46] Peyer's patches and isolated lymphoid tissue are covered by a monolayer containing microfold cells (M cells) which serve as a site for antigen uptake. In the presence of microbial pathogens or food antigens, activated dendritic cells induce B-cell differentiation into IgA secreting cells by T-cell-dependent and -independent

mechanisms (**Figure 2**).[47,48] Dendritic cells that have engulfed luminal antigens move to interfollicular regions where they prime $CD4^+$ T cells into follicular helper T-cells (Tfh). Tfh then interact with $IgM^+$ B-cells that undergo class differentiation to $IgA^+$ cells through activation-induced cytidine deaminase. Dendritic cells can also mediate IgA1 class switch independent of T-cell mediation by secreting factors such as B-cell–activating factor (BAFF), and A proliferation-inducing ligand (APRIL).[11,49] BAFF and APRIL are crucial ligands in the process of IgA class switch in the lamina propria of the intestinal mucosa.[50] Furthermore BAFF has been found to be elevated in the serum of patients with IgAN and to correlate positively with proteinuria.[51–53] BAFF and APRIL antagonists such as atacicept and blisibimod are being evaluated in clinical trials for the treatment of IgAN (NCT04716231, NCT02062684).

Secretion of gd-IgA1 in patients with IgAN is predominantly polymeric,[54] which suggests that its origin is mucosal as circulatory IgA is usually monomeric. The presence of secretory IgA in mesangial deposits of patients with IgAN implicates the gut in the disease pathogenesis. The association between secretory IgA and different pathological phenotypes of the disease was evaluated in 57 patients with IgAN and compared to 48 controls without the disease. Interestingly, levels of secretory IgA were not only significantly higher in patients with IgAN than in healthy controls, but they correlated with disease activity. Patients with focal proliferative sclerosing IgAN had higher levels than patients with mild mesangial proliferative IgAN. Furthermore, there was a statistically significant association between the levels of secretory IgAN to serum creatinine and proteinuria.[55] Other investigators demonstrated that mesangial

complexes were at least partly formed by secretory IgA. Secretory IgA was found to be part of mesangial deposits in 15% of the biopsies in this study.[56]

Another piece of evidence linking GALT to IgAN comes from the higher frequency of intestinal-activated B cells seen in patients with IgAN when compared to healthy controls. By comparing subpopulations of B cells expressing CCR9 and integrin ß 7, a group of investigators showed that patients with IgAN have higher circulation of $IgA^+$ gut-homing B lymphocytes.[51] CCR9 and integrin ß 7 have been identified as gut homing molecules and have been used to study the role of gut-homing lymphocytes in the pathogenesis of intestinal diseases such as IBD.[57] In a more recent study, another group of investigators also found increased numbers of gd-$IgA1^+$ cells expressing CCR9.[58]

Evidence of increased circulation of mucosal isoforms of IgA1 that correlates with disease activity, in addition to consistent findings of increased proportions of B-cells expressing gut homing characteristics implicate that GALT is key in the pathogenesis of IgAN (**Figure 3**).

*Aberrant Glycosylation of IgA1: pathogenic or normal variant?*

In humans, two subclasses of IgA, namely IgA1 and IgA2, can be found. Circulatory IgA are mainly IgA1, but IgA2 can also be found at a significantly smaller proportion. The two isotypes differ structurally by the presence of *O*-glycans located at the hinge

region.[59] O-glycans are modifications of serine and threonine by the addition of N-acetylgalactosamine (GalNac) residues.[60] In contrast to IgA2, the hinge region of IgA1 has nine potential O-glycosylation sites which make it susceptible to unique-IgA1 specific proteases produced by several bacterial species.[59,61] Of these nine sites that have the potential for *O*-glycosylation, usually three to six are glycosylated.[62,63] The variability in the glycosylation status of IgA1 contributes to the heterogeneity of the IgA1 molecules. *O*-glycosylation includes the addition of galactose and sialic acid to GalNac in a stepwise process that involves several glycosyltransferases and chaperones like Cosmc.[61,64] Normal serum IgA1 contains little or no galactose deficient *O*-glycans.[61] The absence of galactose in the *O*-glycan sites of the hinge region of IgA1 molecule of patients with IgAN may predispose GalNac residues to be recognized by anti-glycan antibodies.

While there is agreement that gd-IgA1 play an important role in the pathogenesis of IgAN, the mechanisms behind its increased presence in patients with IgAN are less clear. One important still unanswered question is whether variations in glycosylation happen in response to specific antigens, or if there is an inherited defect in the enzymes responsible for the process. Significant differences in the *O*-glycosylation profile were found in patients with IgAN and healthy controls for antigen specific IgA1 against a Helicobacter pylori (mucosal antigen), and tetanus toxoid (systemic antigen).[8] While this evidence seems to implicate that gd-IgA1 may originate as a response to specific antigens, genetic studies have correlated increased levels of gd-IgA1 to decreased expression of genes related to core-1 β1,3-galactosyltransferase (C1GalT1) which adds galactose to GalNAc as well as the chaperone of this enzyme - Cosmc.[65]

**Gut Microbiota and IgAN**

The term microbiota describes the population of microbes at a particular anatomical site, whereas microbiome is used to describe the collective genes encoded by all microbes at that site.[66] In the past few decades, the impact of commensal microbes in immune mediated disorders affecting the gut has gained growing interest. The immunoregulatory role of intestinal microbiota has also been proposed as a key factor in the acquired immunodeficiency seen in patients with chronic kidney disease (CKD) and ESKD.

Kidney disease promotes dysbiosis through multiple factors including the shifting cells into a more acid environment, fluid overload which may result in intestinal congestion, and the use of medications such as oral iron which may promote pathogen overgrowth.[67] Dysbiosis favors inflammation and disruption of the intestinal barrier leading to translocation of bacteria from the intestinal lumen into the circulation.[67] Increased bacterial permeability from a “leaky gut” can promote activation of proinflammatory cells outside the gut which in turn can have a role in the progression of CKD. For example, in murine models of Alport’s nephropathy, disease progression was accelerated after exposure to a synthetic mimic of bacterial DNA.[68] Activation of renal macrophages and TNF-α production were fundamental in inducing kidney disease progression, as the TNF inhibitor Etanercept overcame the effect of the bacterial mimic. Another study in mice looked at the effects of microbiota in the development and progression of CKD by depleting gut microbiota using broad spectrum antibiotics. The

investigators found that depletion of gut microbiota decreased levels of proinflammatory cytokines and fibrosis markers, attenuating renal injury.[69]

The notion that gut microbiota had a role in the pathogenesis of IgAN came from experimental models on mice with genetic predisposition to IgAN in which the lack of intestinal clearance of alimentary components and intestinal microbiota increased IgA production, systemic circulation, and mesangial deposits.[48] In 2014, De Angelis and collaborators showed for the first time that gut microbiota was different between IgAN patients with progressive disease and non-progressors.[70] When compared to healthy controls, both groups had statistically significant lower counts of *Bifidobacterium.* While the clinical implication for IgAN is unknown, it has been proposed that *Bifidobacterium* species may help suppress the effect of pro-inflammatory cytokines in patients with celiac disease.[71]

Since then, several other studies have identified substantial differences in the gut microbiota of patients with IgAN as compared to healthy controls. A recently published case-control study on 20 patients with IgAN found several microbiome taxonomic differences between patients with IgAN and healthy controls both in stool and blood. In comparison with healthy controls patients with IgAN had higher proportions of the species of the genera *Bacteroides*, *Escherichia-Shigella*, and some *Ruminococcus.*[72] Another study that analyzed fecal gut microbiota in 52 Chinese patients with IgAN and 25 healthy controls found abundance of *Bacteroides* compared to healthy controls.[73] The study also highlighted that gut microbial modifications may be associated with the

clinical severity of IgAN, pointing that patients with higher urine red blood cell counts or proteinuria levels had a higher percentage of *Escherichia-Shigella* and a lower percentage of *Bifidobacterium*. Interestingly, the investigators determined that some genus such as *Prevotella* and *Bifidobacterium*, were related to increased levels of serum gd-IgA1.

Experimental evidence also supports the fact that commensal bacteria may be critical in the pathophysiology of IgAN. A form of glomerulonephritis resembling IgA nephropathy was reproduced in mice overexpressing BAFF. Interestingly this finding was dependent on the presence of commensal bacteria.[74] These mice had high levels of circulating polymeric under-glycosylated IgA. Additionally, there was evidence of serum IgA specific to commensal bacteria cultured from the mice and in mice which were colonized with limited commensal bacteria (altered Schaedler flora [ASF]).

Intestinal IgA production depends on colonization by a gut microbiota and not all the strains have the same IgA-inducing capacity. *Bacteroides ovatus* has been recently identified as the species that best induced gut IgA production.[75] The affinity of gd-IgA1 to mucosal antigens is not very well known, but there are several reports of increased IgA levels specific to intestinal microbiota, mucosal vaccines, and food.[5,11,72,76–78] Altogether, these data raise the intriguing hypothesis that intestinal microbiota affects pathogenic gd-IgA1 formation and that these antibodies are specific to certain intestinal bacteria.

Fecal matter transplantation (FMT), probiotics, and antibiotics, may modulate disease activity in patients with IgAN by modifying the composition of the gut microbiota. Microbiota modulation by FMT has been shown in murine studies to alter the IgAN phenotype in antibiotic treated humanized IgAN mice. Mice who had FMT transplantation from healthy human controls were found to significantly reduce albuminuria compared to mice who received FMT from patients with IgAN.[79]

**IgAN and Bowel Disease**

Many case reports and series have suggested an association between IBD and IgAN. The most compelling evidence supporting a link between these diseases comes from a Swedish population-based cohort study on 3,963 biopsy proven IgAN cases and 19,978 matched controls showing that patients with IgAN had more than three times higher risk of developing IBD than controls (adjusted HR, 3.29; 95% confidence interval [95% CI], 2.73 to 3.96).[80] This study also showed that a diagnosis of IBD in patients with IgAN was associated with increased risk of ESKD. Several GWAS have identified shared susceptibility loci between IBD and IgAN,[81,82] which suggests that there may be a shared genetic predisposition between these two diseases.

The pathogenic mechanisms that tie IBD and IgAN have not been fully elucidated. Intestinal inflammation with associated increased intestinal permeability and modifications to the gut microbiota, are shared pathogenic features between these two

conditions.[83] Furthermore, it is unclear whether IgAN associated to IBD van be considered a primary form of IgAN as opposed to secondary IgAN as seen in liver disorders, neoplastic, or inflammatory diseases. Measurement of gd-IgA1 in serum and kidney tissue have been proposed as a potential biomarker that may help establish diagnosis and differentiate between primary and secondary forms of the disease. In a case series, investigators used a specific monoclonal antibody against gd-IgA1 (KM55 mAB) in patients that were suspected to have secondary forms of the disease to detect the presence of gd-IgA1 in mesangial deposits.[84] Interestingly this case series included one patient with Crohn's disease that show presence of KM55 mAB. Lack of correlation between intestinal disease and IgAN activity supported the idea that the case represented primary rather than secondary IgAN. However, the role of KM55 to differentiate between primary and secondary forms of IgAN remains controversial as other studies have identified positive staining for gd-IgA1 using KM55 in kidney biopsies of patients with secondary IgAN.[85]

Celiac disease has also been linked with IgAN, especially since the pathogenesis of CD involves an IgA class tissue transglutaminase autoantibody (tTG) that may be found in systemic circulation and extra intestinal organs. Interestingly, tTG targeted IgA deposits have been found in kidney biopsies of patients with and without celiac disease who had been diagnosed with IgAN.[86] Transglutaminase 2 (TG2) and the transferrin receptor 1 (TfR1) are key in inducing the immune response against gliadin, a subcomponent of gluten, that is seen in patients with CD. Intriguingly, the interactions between TG2 and TfR1 have been deemed crucial to enhance mesangial inflammation following

deposition of IgA1 complexes in IgAN.[87] Gliadin has been shown to bind to soluble CD89 in a mouse model of IgAN expressing CD89 and IgA1. Restriction of gluten resulted in decreased expression of TG2 and TfR1 along with decreased IgA1-CD89 complex formation, decreased mesangial deposits, and hematuria.[88]

A recently published cohort study in Finnish population interestingly found that the prevalence of Celiac disease in patients with IgAN had significantly decreased in the past few decades when compared to data from the 1970's. A possible explanation for this findings is that early detection of celiac disease and early restriction from gluten may slow down progression of IgAN and hence decrease the measurable association between both diseases.[89]

**Conclusion**

Existing evidence concurs to support that the gut has an important role in the pathogenesis of IgAN. With this, therapeutic interventions targeting the gut for patients with IgAN who are at risk of progression have started to arise. Many questions remain unanswered in respect to the mechanisms behind gd-IgA1 production. Whether gd-IgA1 is antigen specific, or whether specific microbiome members can potentiate its production, remains unknown. Answers to these questions may pave the way towards new therapeutic interventions in patients with IgAN.

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## Author Contributions

Luis Sanchez Russo: Conceptualization; Writing - original draft; Writing - review and editing. Arun Rajasekaran: Writing - original draft; Writing - review and editing. Sofia Bin: Writing - original draft; Writing - review and editing. Jeremiah Faith: Conceptualization; Writing - original draft; Writing - review and editing. Paolo Cravedi: Conceptualization; Writing - original draft; Writing - review and editing.

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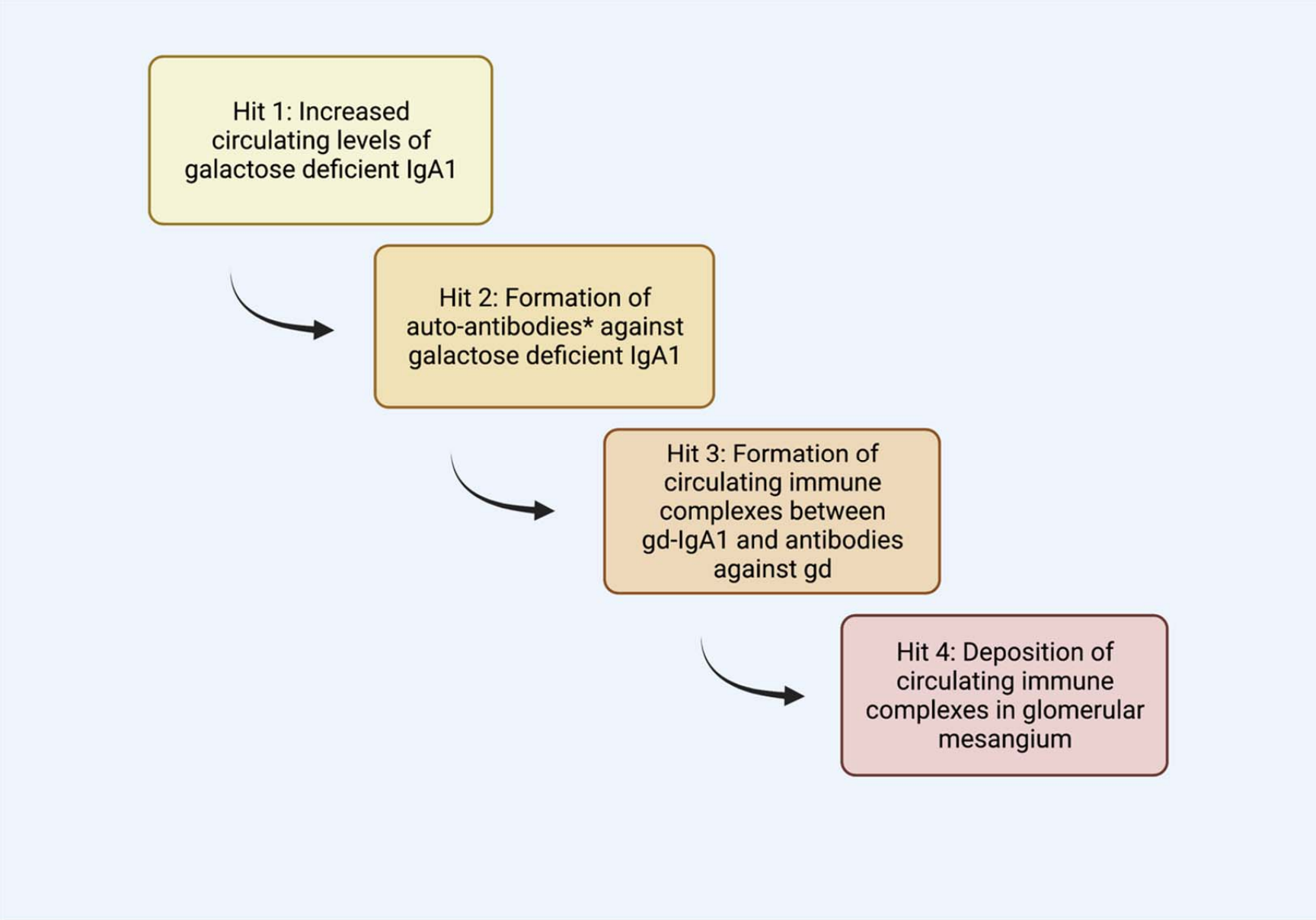


**Figure 1:** 4-hit hypothesis of immunoglobulin-A nephropathy disease pathogenesis.
* Though predominantly IgG1 and IgG3, antibodies against gd-IgA1 can also be of IgM or IgA isoforms.

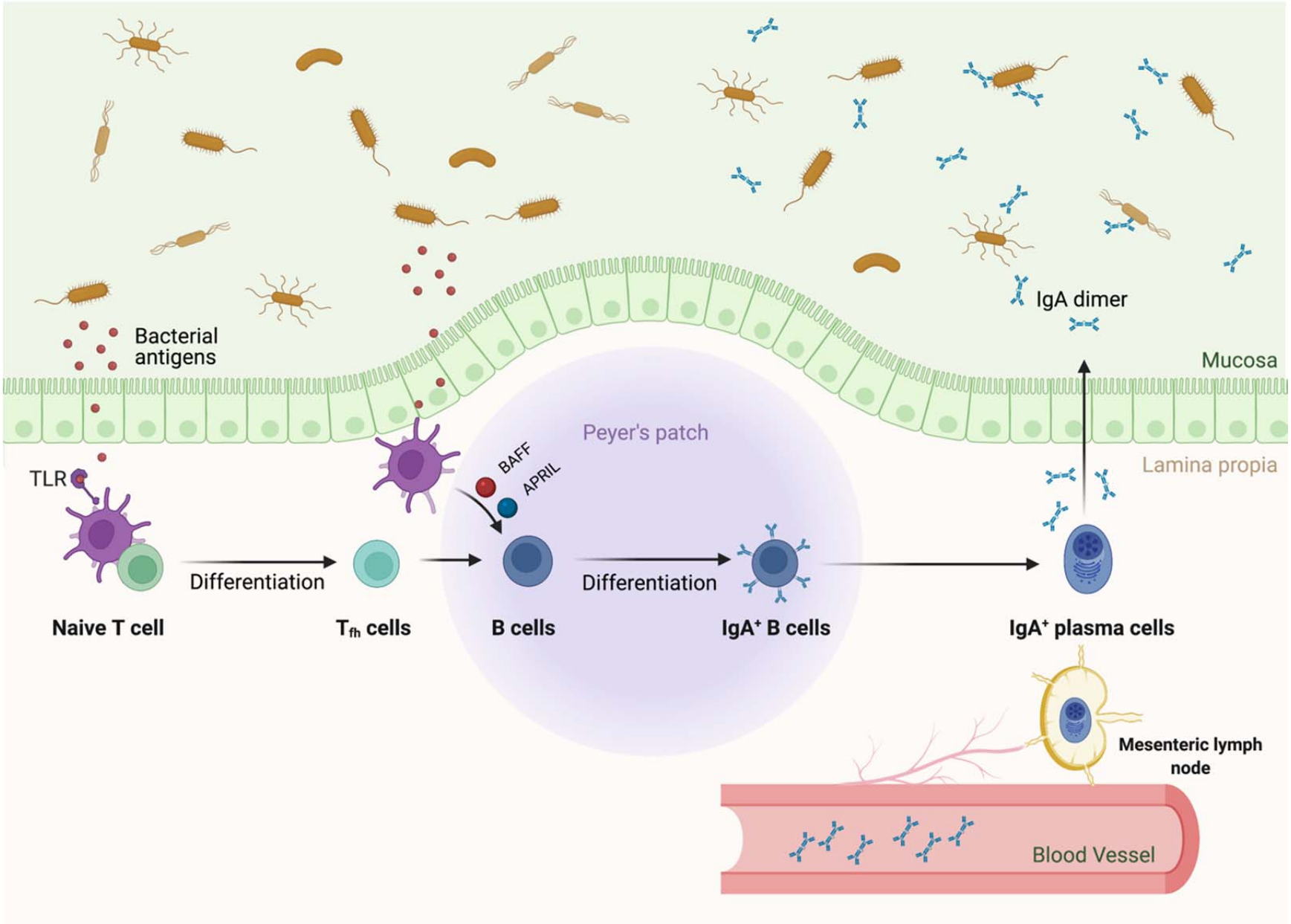


**Figure 2:** Schematic representation of B-cell class switch from naïve cells to $IgA^+$ B-cells in the Peyer's patches. Antigen exposure from commensal bacteria induces class switch from B-cells by T-cell dependent and independent pathways. After encounter with bacterial antigens, Toll-like receptor (TLR) ligand recognition promote naïve T-cell differentiation to T follicular helper cells ($T_{fh}$ Cells). $T_{fh}$ cells promote B-cell differentiation into $IgA^+$ B-cells in Peyer's patches. Microbial antigens can also promote release of B cell stimulating factors such as B-cell–activating factor (BAFF) and A proliferation-

inducing ligand (APRIL) which can promote IgA class switch in a way that is independent from T cells. Adapted from "IgA-mediated Gut Microbiota Regulation" by BioRender.com. Retrieved from https://app.biorender.com/biorender-templates.

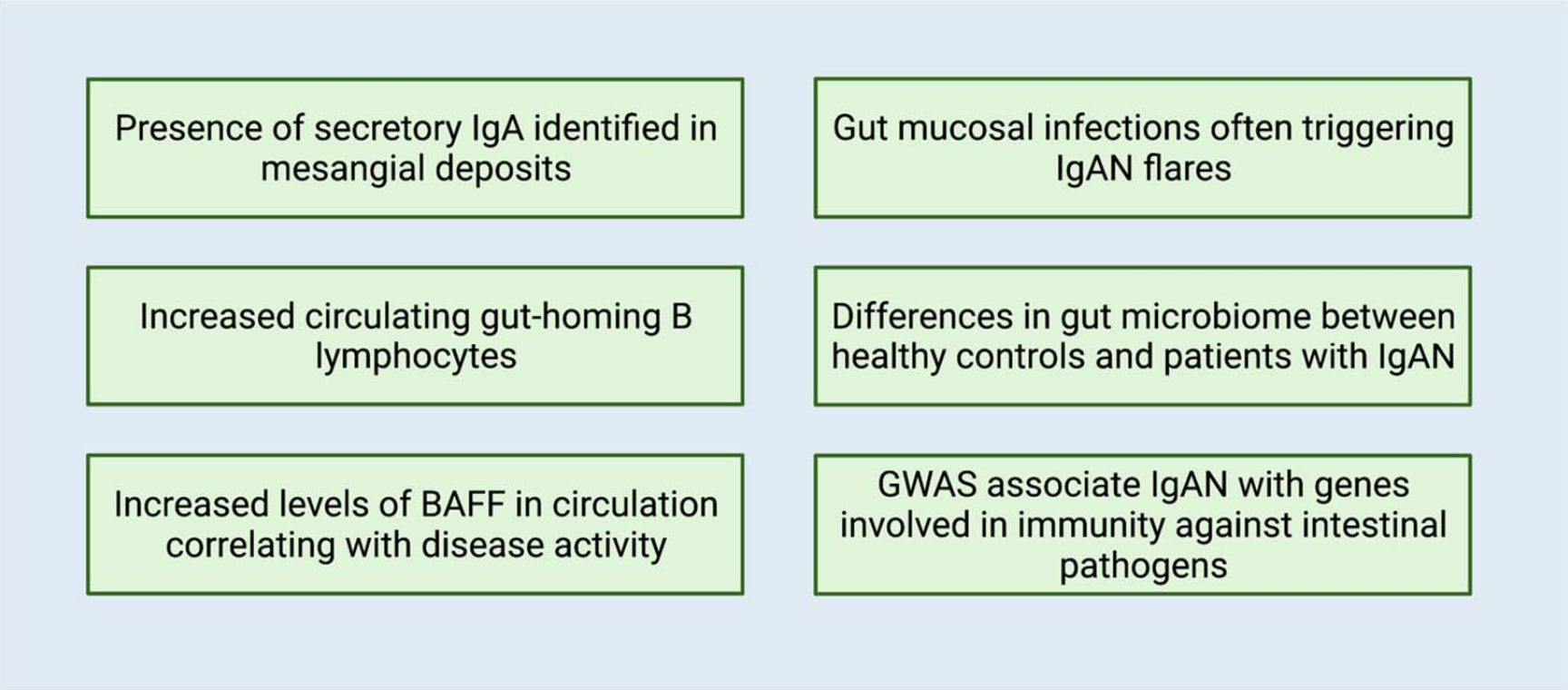


**Figure 3:** Findings that suggest a connection between IgA nephropathy and the gut mucosa abnormalities. GWAS: genome wide association studies. IgAN: Immunoglobulin A nephropathy. BAFF- B-cell–activating factor.