

ISN Forefronts Symposium 2015: IgA Nephropathy, the Gut Microbiota, and Gut–Kidney Crosstalk



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IgA nephropathy (IgAN) represents the most common form of primary glomerulonephritis worldwide, especially in East Asia; even with current treatments, it can lead to end-stage renal disease within 10 years in approximately 20% of adult patients. Genome-wide association studies in IgAN have identified susceptibility genes that are involved in the maintenance of the intestinal epithelial barrier, intestinal inflammation, and the intestinal response to mucosal pathogens, indicating a gut–kidney connection. However, the role of gut microbiota in mediating gut–kidney communication is still underappreciated. Here we highlight current clues that link microbiota with IgAN, and suggest contact points where the microbiota may exert its influence on the onset and progression of IgAN. More specifically, bacterial lipopolysaccharide potentially affects 2 essential components involved in IgAN pathogenesis: the overproduction and hypogalactosylation of IgA1. Short-chain fatty acids can modulate the inflammatory process and protect against renal damage; however, this protection is lost when the intestinal microbiota changes, becomes imbalanced, and becomes dysbiotic. Gut microbiota is also involved in the production of uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which may accelerate kidney disease progression.

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KEYWORDS: gut microbiota; gut microbiota-derived uremic toxins; IgA nephropathy; intestine-kidney crosstalk; lipopolysaccharide; short-chain fatty acids

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After being described by Berger and Hinglais in 1968,¹ IgA nephropathy (IgAN) has become a leading form of primary glomerulonephritis and a major cause of end-stage renal disease (ESRD), leading to dialysis and kidney transplantation on a global scale.² The predominant feature of this disease is the deposition of IgA-containing immune complexes in the glomerular mesangium, along with local inflammation, mesangial proliferation, glomerular fibrosis, and subsequent loss of kidney function. IgAN can vary significantly among affected individuals in regard to clinical features, renal biopsy findings, rate of disease progression, and prognosis. Some patients exhibit only benign hematuria or mild proteinuria for many years, whereas 30% to 50% of patients can show rapid progression and develop ESRD

within 20 years. Although 4 large-scale genome-wide association studies (GWAS)^{3–6} have been performed that examined IgAN, the loci discovered could explain only a relatively small proportion (about 6%–8%) of the overall disease risk.⁶ To date, the etiology of IgAN is only partially defined, and the triggering event(s) is even less well understood.

It has been demonstrated that the mucosal immune system, including the gastrointestinal mucosa, plays an essential part in the pathogenesis of IgAN (reviewed elsewhere⁷), and it is now widely accepted that the gut is an important source of chronic inflammation in chronic kidney diseases (CKD)⁸. Most GWAS-identified IgAN susceptibility genes are directly or indirectly related to the risk of inflammatory bowel disease (IBD),⁶ indicating a potential role for a gut–kidney connection in the development of IgAN. However, the specific factors that elicit mucosal immune dysregulation, stimulate gut inflammation, and/or initiate intestine-to-kidney crosstalk remain inconclusive. Increasing evidence suggests that the gut microbiota is an important triggering factor.

The human intestinal tract is home to more than 100 trillion microorganisms collectively as the gut

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microbiota. As a “symbiotic organ,” the intestinal microbiota contributes to the host’s nutrient absorption, metabolic activity, and immune homeostasis. Thus far, the bidirectional influence between intestinal microbiota and renal disease has been proposed by several studies. For example, metabolites of beneficial bacteria, short-chain fatty acids (SCFAs), can modulate inflammation via epigenetic modification, and play a protective role in ischemia-reperfusion induced acute kidney injury.⁹ However, other potentially toxic bacterial metabolites such as p-cresol sulfate and indoxyl sulfate are also well-known uremic toxins and can elicit the release of pro-inflammatory cytokines and thereby accelerate kidney injury. Gut microbiota-derived trimethylamine N-oxide not only takes part in the development of atherosclerosis but has also been implicated in CKD progression. Lipopolysaccharide (LPS), derived from the cell wall of Gram-negative bacteria, is highly correlated with the severity of systemic inflammation, even without clinically detectable infection. LPS involvement in the hyperproduction and hypogalactosylation of IgA1 has also been described. On the other hand, it is likely that renal dysfunction can, either directly or indirectly, affect the composition of the intestinal microbiota, as well as the intestinal mucosal barrier.

In contrast to previous reviews, here we highlight the growing body of basic and clinical evidence that connect the pathogenesis and progression of IgAN to the gut microbiota. A better understanding of gut microbiota’s influence on the development of IgAN would greatly facilitate our exploration of new diagnostic, therapeutic, and prognostic approaches to targeting these bacteria.

Clinical and Genetic Evidence Indicate Gut-Kidney Connection in IgAN

The susceptibility of IgAN dramatically changes by geographic region and race/ethnicity. The IgAN prevalence, based on renal biopsy registries, is estimated to be 5% in the Middle East,^{10,11} 10%–35% in Europe,^{12–16} and up to 50% in East Asia (mainly Japan¹⁷ and China¹⁸). The incidence of ESRD among Asian Americans is 4-fold higher compared with that in European Americans, and is almost 7-fold higher compared with that in African Americans.¹⁹ In addition, several investigations reported a familial aggregation tendency for IgAN.^{20–25} Close relatives of IgAN patients tend to have higher risk of urinary abnormalities,²⁶ as well as higher levels of galactose-deficient IgA1 in their circulation.²⁷ All of these observations indicate that genetic background makes a substantial contribution to the development of this disease.

To explore the molecular mechanisms that underlie disease heritability, genome-wide linkage analysis has been applied to IgAN,^{28,29} as have GWASs. To date, 4

large-scale GWASs^{3–6} have identified distinct IgAN susceptibility loci (Table 1). These risk alleles could partially explain the geographical distribution of IgAN and provide insight about key factors involved in IgAN pathogenesis. However, GWASs could explain only a relatively small proportion (approximately 6%–8%) of the overall disease risk.⁶ It is worth noting that most IgAN risk alleles take part in physiological processes involving intestinal inflammation, maintenance of the intestinal epithelial barrier, and production of intestinal mucosal IgA in response to microbial antigens. These risk genes are, either directly or indirectly, associated with IBD, suggesting a strong gut–kidney connection in the pathogenesis and progression of IgAN, as well as a potential role of the microbiota as a triggering factor.

There are more clinical observations to support the gut–kidney axis hypothesis. Kidney involvement is common in patients with gastrointestinal disease. A high frequency of IgAN has been reported among patients with Crohn’s disease and ulcerative colitis (2 main forms of IBD).³⁰ A large number of patients with IBD have increased numbers of IgA-producing cells in the gut, as well as elevated serum IgA levels and hematuria.³¹ About 20% of IBD patients also have various kinds of renal diseases, including fistula, urolithiasis, tubular lesion, and a small chance of glomerulonephritis.⁷ It has been described in several case reports that successful treatment of inflammatory colitis can lead to disappearance of glomerular IgA deposition and to remission of mesangial proliferation.³² Conversely, it has been reported that patients with IgAN can show abnormal duodenal histopathological patterns,³³ or signs of intestinal inflammation.³⁴

The relevance of celiac disease (CD) to IgAN represents another research topic regarding a gut–kidney connection. Patients with IgAN show increased intestinal permeability and higher mucosal sensitivity to food antigens (such as gluten) in general.³⁵ The presence of high levels of IgA against food antigens has raised the issue of a potential pathophysiological association between IgAN and CD. Although several hypotheses postulate that food antigens may be involved in the triggering of IgAN, experimental IgAN can be induced by dietary gliadin or gluten in mice.³⁶ In sparse clinical cases, the introduction of a gluten-free diet in IgAN patients has led to favorable outcomes³⁷ or complete clinical remission.³⁸ However, more studies on the co-occurrence of IgAN and CD have yielded inconsistent results. In a study by Welander *et al.*,³⁹ 7 of 27,160 CD patients (0.026%) were found to have developed IgAN. Although this prevalence was 3-fold higher than that in the control cohort (0.008%), the incidence of IgAN among individuals with CD was extremely low. In a study by Collin *et al.*,⁴⁰ 8 of 223

Table 1. IgA nephropathy susceptibility genes identified by genome-wide association studies⁶

Risk locus	Gene	Function
1p13	<i>VAV3</i>	<i>VAV3</i> encodes guanine nucleotide exchange factors essential for adaptive immune function, colonic enterocyte differentiation, and IgA production.
1q32	<i>CFHR1/3</i> (deletion)	<i>CFHR1/3</i> encodes Factor H-related peptides that modulate the activity of the alternative complement pathway.
6p11	<i>ITGAM, ITGAX</i>	<i>ITGAM</i> and <i>ITGAX</i> encode integrins α M and α X mark intestinal dendritic cells that maintain a balance between inflammation and tolerance
6p21	<i>TAP1, TAP2, PSMB8, PSMB9</i>	encode interferon-induced subunits of the immunoproteasome that mediate intestinal nuclear factor- κ B activation in inflammatory bowel disease
6p21	<i>HLA-DP</i>	Major histocompatibility complex class II molecules, implicated in immune regulation
8p23	<i>DEFA1, DEFA3, DEFA5, DEFA6</i>	<i>DEFA</i> gene clusters encode anti-microbial peptides, α -defensins, and provide innate defense against microbial pathogens
9q34	<i>CARD9</i>	<i>CARD9</i> involves in both innate and adaptive immune responses by regulate intestinal nuclear factor- κ B activation; <i>CARD9</i> mediates intestinal repair and bacterial infection after intestinal epithelial injury
17p13	<i>TNFSF13</i>	<i>TNFSF13</i> encodes APRIL, a powerful B-cell-stimulating cytokine that is induced by intestinal bacteria and involves in IgA class switching
22q12	<i>HORMAD2</i>	The risk allele has a protective role against Crohn's disease (1 of the main forms of inflammatory bowel disease)

Adapted from Kiryluk K et al. *Nat Genet.* 2014;46:1187–1196, and Feehally J. *Nat Rev Nephrol.* 2016;12:147–156.

IgAN patients (3.6%) were found to have CD, and researchers thus hypothesized that IgAN patients are predisposed genetically to be susceptible to CD. In another study, Moeller *et al.*⁴¹ tested 99 biopsy-proven IgAN patients and 96 unaffected controls matched for age and sex. However, the levels of CD-characteristic serologic markers (for example, IgG and IgA antibodies to gliadin and transglutaminase 2) showed no significant difference between IgAN patients and unaffected individuals.

The Multi-hit Pathogenesis Model of IgAN

The origin and composition of IgA-containing immune complexes are key issues in relation to IgAN pathogenesis. However, they are still under debate, despite years of investigations. The high recurrence rate of IgAN after transplantation,⁴² together with the fact that transplantation of donor kidney with mesangial deposits into a recipient without IgAN can lead to the elimination of mesangial IgA accumulation,⁴³ suggests an extrarenal cause of IgAN. Because IgA represents the most abundant Ig produced by the mucosal barrier immune system, especially in the gastrointestinal tract, it is likely that the mucosal immune system plays a critical role in the pathogenesis of IgAN.

There are 2 subclasses of human IgA molecules, namely, IgA1 and IgA2. IgA1 is the predominate

subclass in the circulation of healthy individuals, and this subclass is also found in circulating immune complexes and mesangial deposits of patients with IgAN.^{44,45} A number of investigations^{46–50} have reported the presence of hypogalactosylated structures at the IgA1 hinge region in IgAN patients, a particular glycosylated pattern also known as galactose-deficient IgA1 (gd-IgA1). More specifically, compared with the IgA1 structure normally seen in individuals without IgAN, the serum and mesangial IgA1 of IgAN patients is characterized by a different pattern of O-glycosylation in the IgA1 hinge region, with less galactose attached (Figure 1).

A multi-hit pathogenic model of IgAN^{46,51,52} has been proposed to explain the IgAN pathogenesis, integrating current findings that include gd-IgA1 overproduction, gd-IgA1 autoantibody generation, IgA1-containing immune complex formation and deposition, and subsequent complement system activation (reviewed elsewhere⁵³). According to this model, there are 4 “hits” during the pathogenesis of IgAN. In the first hit, the excessive production of IgA1 with galactosylation defects results in an elevated Gd-IgA1 level in the circulation. In the second hit, the high level of Gd-IgA1 activates an antoimmune response, leading to the generation of anti-glycan antibodies that recognize *N*-acetylgalactosamine epitopes on Gd-IgA1. Binding of Gd-IgA1 and anti-glycan antibodies leads to the formation and deposition of IgA1-containing immune complexes in the glomerular mesangium, which is the third hit. Finally, the fourth hit is the stimulation of mesangial proliferation by the immune deposits, as well as local production of cytokines such as interleukin-6 (IL-6) and transforming growth factor- β (TGF- β)^{54,55}, with local inflammation and complement system activation. Although this model is something of an oversimplification, it provides a plausible conceptual framework for describing the sequence of pathogenic events, and one that the available GWAS data can help to refine.^{45,46}

According to this framework, the overproduction and hypogalactosylation of IgA1 in the first hit, which together lead to an elevated level of circulating Gd-IgA1, are central to the disease process. Although Gd-IgA1 might need co-factors to trigger the initiation of immune complexes,^{27,56} it represents an indispensable part of IgAN pathogenesis. We discuss the influence of gut microbiota on Gd-IgA1 later.

The Gut Microbiota and Microbiome

There are more than 100 trillion microbial cells that colonize our gastrointestinal tract, which comprise the gut microbiota. This intestinal microbiome constitutes a symbiotic ecosystem that co-evolved with the host. Under physiological conditions, 6 bacterial phyla,

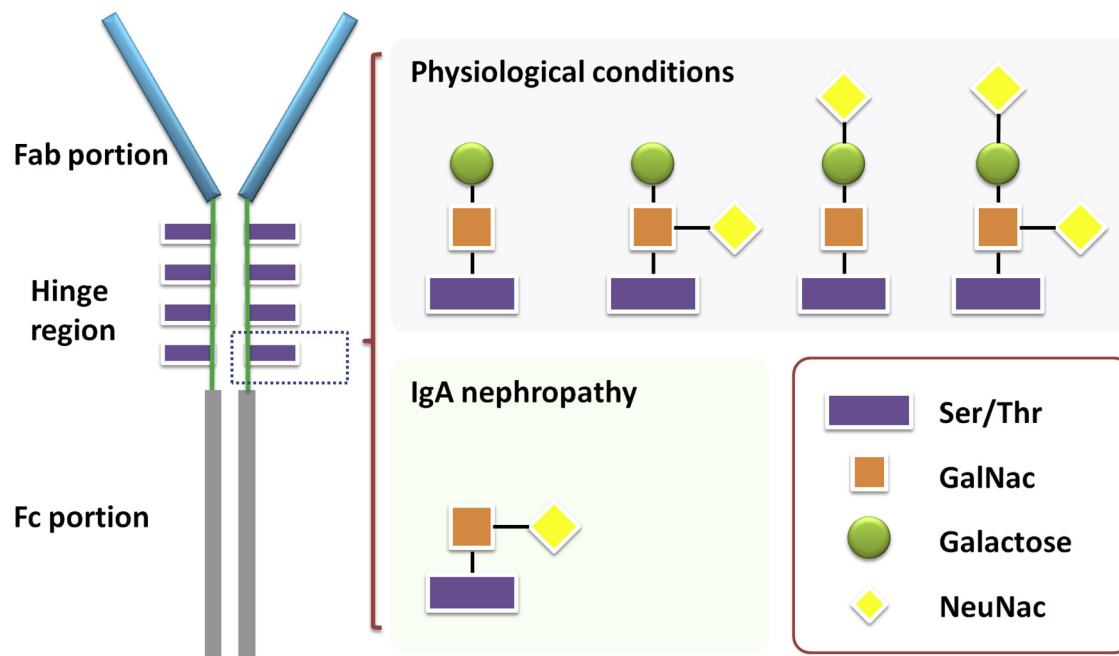


Figure 1. Galactosylation patterns of IgA1 hinge region under physiological conditions and under IgA nephropathy (IgAN). Under physiological conditions, *N*-acetyl-galactosamine (GalNAc) is attached to the oxygen atom of a serine (Ser) or threonine (Thr) by a polypeptide transferase GALNT enzyme. A galactose is then added to the O-glycoside via β 1,3-galactosyltransferase. Galactosylated O-glycoside can be further sialylated by sialyltransferase in 3 different forms or can remain free of *N*-acetylneuraminic acid (NeuNac). In IgA nephropathy, the most predominant abnormalities are defective galactose fixation or forward GalNAc sialylation.

including Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia, dominate our gut microbiota; among them the phyla Bacteroidetes and Firmicutes contribute more than 90% of all species.

The microbiota participate in important metabolic activities of the host, including digestion of complex polysaccharides,^{57,58} regulation of the immune system,^{59–61} synthesis of certain endogenic vitamins and amino acids,⁶² and metabolism of bile acids,⁶³ among others. The symbiotic ecosystem also confers protection against infection by potential pathogens by competing with exotic microorganisms. The maintenance of an appropriate mix of probiotics and opportunistic pathogen is essential to the health of the host. In recent years, the development of next-generation sequencing applied to the gut microbiota, including 16S rRNA sequencing, metagenome sequencing, and metatranscriptome sequencing, has provided a great opportunity for identifying the composition and function of bacteria in the human gut and investigating its association with human health. There is increasing evidence that altering the balance of the gut microbiota can profoundly affect human health and disease. The gut microbiome plays an important role in IBD,⁶⁴ obesity,⁶⁵ type 2 diabetes,⁶⁶ type 1 diabetes,⁶⁷ rheumatoid arthritis,⁶⁸ colorectal cancer,^{69,70} and cardiovascular disease.^{71,72} It also seems reasonable to speculate that the same may be true for IgAN.

The Role of the Gut Microbiota in IgAN

A bidirectional influence between the intestinal microbiota and kidney diseases has been proposed.⁷³ Gut microbiota–derived metabolites, such as SCFAs, and uremic toxins *p*-cresol sulfate and indoxyl sulfate, have either anti-inflammatory or pro-inflammatory effects, and play substantial roles in the development and progression of acute kidney injury and CKD. The translocation of bacterial products (LPS, metabolites, or the bacteria themselves) across the intestinal barrier activates the innate immune response, and enhances the systematical inflammatory response that can be linked to IgAN, CKD, and ESRD.⁷³

A small number of studies have directly focused on the relationship between renal disease and the gut microbials. Vaziri *et al.* analyzed the intestinal microbial flora of 24 patients with ESRD compared with 12 healthy controls, and identified bacteria from the Brachy bacterium, Catenibacterium, Enterobacteriaceae, Halomonadaceae, Moraxellaceae, Nesterenkonia, Polyangiaceae, Pseudomonadaceae, and Thiothrix families that showed a remarkable increase in patients with ESRD.⁷⁴ Further investigation confirmed that, compared with healthy controls, ESRD patients showed significant expansion of urease, uricase, indole-producing and *p*-cresol–producing bacteria, and reductions in SCFA-producing bacteria.⁷⁵ De Angelis *et al.* also described the intestinal microbiota and metabolome composition differences among IgAN progressors and

nonprogressors, as well as healthy controls.⁷⁶ Current studies are still in their infancy, with limited investigations as well as limited sample size, and further basic and clinical investigations will be necessary to establish a relevant or causal biological association between gut microbiota and renal disease.

Gut Microbial–Derived LPSs Alter the Production and Galactosylation of IgA1

As outlined in the multi-hit pathogenesis model, overproduction of hypogalactosylated IgA1 may play an essential role in the development of primary IgAN and may be associated with faster progression of kidney disease.⁷⁷ In this section, we consider the gut microbiota's influence on the production and galactosylation of IgA.

IgA production can be T-cell dependent.⁷ In response to T-cell regulation, B cells mature into plasma cells and reach the mucosal lamina propria, releasing 2 forms of dimeric IgA1 or IgA2. Either form can bind to other IgA molecules of the same kind, forming dimeric IgA (dIgA) or polymeric IgA (pIgA) proteins. dIgA or pIgA can bind to the polymeric Ig receptor (pIgR) that is located on the basolateral surface of the mucosal epithelium; dIgA or pIgA is then transported from the basolateral surface to the apical surface by transcytosis. dIgA then detaches from pIgR but retain the pIgR secretory component, constituting the dominant mucosal secretory form of IgA (sIgA). IgA production can also be modulated by T-cell–independent mechanisms. In this condition, epithelial cells, stromal cells, and dendritic cells secrete cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), transforming growth factor- β (TGF- β), tumor necrosis factor ligand superfamily member 13B (TNFSF13B, also known as B-cell–activating factor [BAFF]), and so forth. These cytokines activate plasma cell maturation and promote class switching from IgM to IgA1.

Recurrent or chronic bacterial infections can potentially stimulate the mucosal immune response, promoting IgA production, and are considered pathogenic triggers in IgAN. Even without exogenous invasion, commensal bacterial dysbiosis and overgrowth of harmful bacteria would activate T-cell–dependent IgA production, stimulating the overproduction of IgA. In addition, possible associations between LPS exposure and hypogalactosylation of IgA have been reported. A study by Qin *et al.* showed that bacterial LPS activated TLR4 in cultured peripheral B lymphocytes from patients with IgAN as well as from healthy controls, inducing methylation of the chaperone Cosmc, which is essential for the activity of galactosyltransferase, reducing its activity and hence the galactosylation of IgA1.⁷⁸

Gut Microbial–Generated SCFAs Have a Protective Role in Renal Injury

SCFAs are the main metabolites produced by certain colonic anaerobic bacteria by the fermentation of dietary fiber and resistant starches. SCFAs are a subset of organic fatty acids with 1 to 6 carbons: acetate (2C), propionate (3C), and butyrate (4C) constitute the most abundant SCFAs. Although SCFAs are essentially waste products for the microbes, they have been shown to have physiological functions and to play an important role in the maintenance of health and the development of disease. Available evidence demonstrates that SCFAs serve as nutrients for colonic epithelia (i.e., colonocytes), regulate intracellular pH,⁷⁹ modulate blood pressure,⁸⁰ and have anti-inflammatory, antimicrobial, as well as antitumorigenic roles.⁸¹

Two important SCFA signaling mechanisms have been identified, namely, inhibition of histone deacetylases (HDACs) and activation of G-protein–coupled receptors (GPCRs). In a series of well-designed experiments, Andrade-Oliveira *et al.*⁹ showed that treatment with SCFAs, especially acetate, can reduce ischemia-reperfusion kidney injury. It is tempting to hypothesize that, other than providing an energy source to the kidney, SCFAs may reduce inflammation and may promote apoptosis to decrease energy consumption, diverting energy toward cellular regeneration. As reported in a previous study,⁷⁵ patients with ESRD showed significant reductions in SCFA-producing bacteria, which may relate to the loss of the renoprotective effect of SCFAs. However, another study reported that oral administration of SCFAs at elevated levels in mice resulted in dysregulated T-cell responses and tissue inflammation of the renal system.⁸²

Given the fact that SCFAs can act either as immune tolerance promoters or as inflammatory inducers, more experimental studies and clinical trials are needed to fully address the influence of SCFAs on IgAN.

Gut Microbial–Produced Uremic Toxins Accelerate Kidney Disease Progression

Patients with CKD or ESRD have progressively elevated levels of plasma uremic toxins. Certain intestinal bacteria can produce advanced glycation end-products with uremic toxins, including phenols⁸² and indoles.⁸³ Aronov *et al.*⁸⁴ compared plasma from hemodialysis patients with and without intact colons, and confirmed the colonic origin of 5 uremic solutes: α -phenylacetyl-l-glutamine, 5-hydroxyindole, indoxyl glucuronide, p-cresol sulfate, and indoxyl sulfate. These are prototypical members of a large group of protein-bound uremic toxins that are resistant to clearance by dialysis.⁸⁵ Animal studies have shown that the biological effect of these molecules includes

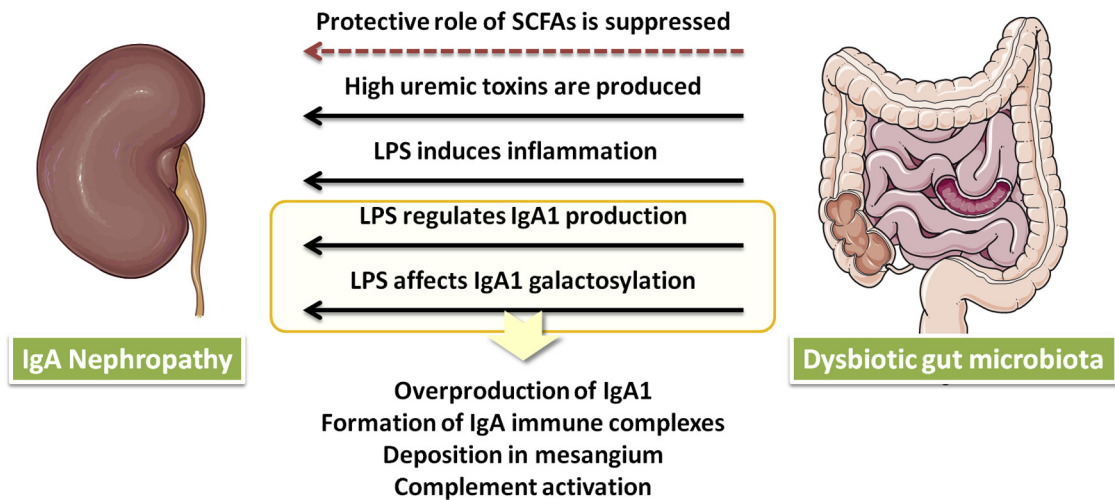


Figure 2. Possible roles of dysbiotic intestinal microbiota in the development of IgA nephropathy (IgAN). The dysbiotic intestinal microbiota leads to contraction of short-chain fatty acid–producing intestinal microbiota, and overgrowth of uremic toxin–forming bacteria. Gut microbiota–derived endotoxin is involved in the hyperproduction and hypogalactosylation of IgA1 and thus substantially contributes to the development of IgAN. LPS, lipopolysaccharide.

induction of pro-inflammatory responses, leukocyte stimulation, and endothelial dysfunction, thus playing a potentially substantial role in the development and progression of multiple causes of acute kidney injury and CKD. Moreover, gut-derived trimethylamine N-oxide is not only considered to be an independent risk factor for cardiovascular disease^{71,72} but is also related to CKD progression and mortality.⁸⁶ Investigations highlight the role of uremic toxin–producing gut bacteria and their potential as therapeutic targets.

Conclusion

Increasing evidence from clinical, genetic, epigenetic, and immunologic studies support a role for gut microbiota dysbiosis in the pathogenesis and progression of IgAN (Figure 2). Bacterial LPS can elicit a systemic inflammatory response and is implicated in the hyperproduction and hypogalactosylation of IgA1. The renal protective role of SCFAs can be lost when the balance of microbiota changes. Gut microbes that produce uremia toxins such as p-cresol sulfate, indoxyl sulfate, and trimethylamine N-oxide may increase CKD progression, whatever the underlying cause.

Technological developments in high-throughput sequencing, metagenomic sequencing, and metabolomic profiling offer an unprecedented opportunity to identify and to define the patterns of gut microbiota that occur in, and may influence, disease. It will be worthwhile to carry out microbiome and metabolome analyses in IgAN patients compared with healthy controls to determine whether there is an association between IgAN-related gut microbiota and disease phenotype. If the IgAN-related microbiota can be administered to germ-free animals and can be shown to

induce disease, this would strengthen the likely causal relationship between the intestinal microbiota and IgAN pathogenesis. The aim of identifying gut microorganism biomarkers for early diagnosis of and therapy for IgAN is another worthwhile goal.

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

- Berger J, Hinglais N. [Intercapillary deposits of IgA-IgG]. *J Urol Nephrol (Paris)*. 1968;74:694–695.
- Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368:2402–2414.
- Feehally J, Farrall M, Boland A, et al. HLA has strongest association with IgA nephropathy in genome-wide analysis. *J Am Soc Nephrol*. 2010;21:1791–1797.
- Gharavi AG, Kiryluk K, Choi M, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nature Genet*. 2011;43:321–327.
- Yu XQ, Li M, Zhang H, et al. A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. *Nature Genet*. 2012;44:178–182.
- Kiryluk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nature Genet*. 2014;46:1187–1196.
- Floege J, Feehally J. The mucosa-kidney axis in IgA nephropathy. *Nature Rev Nephrol*. 2016;12:147–156.
- Lau WL, Kalantar-Zadeh K, Vaziri ND. The gut as a source of inflammation in chronic kidney disease. *Nephron*. 2015;130:92–98.

9. Andrade-Oliveira V, Amano MT, Correa-Costa M, et al. Gut bacteria products prevent AKI induced by ischemia-reperfusion. *J Am Soc Nephrol*. 2015;26:1877–1888.
10. Demircin G, Delibas A, Bek K, et al. A one-center experience with pediatric percutaneous renal biopsy and histopathology in Ankara, Turkey. *Int Urol Nephrol*. 2009;41:933–939.
11. Monfared A, Khosravi M, Lebadi M, et al. Distribution of renal histopathology in Guilan: a single-center report. *Iran J Kidney Dis*. 2012;6:173–177.
12. Berthoux F. [Annual incidence of glomerulonephritis in the extended Rhone-Alpes region in 1987–1988]. *Presse Med*. 1990;19:1417.
13. Gesualdo L, Di Palma AM, Morrone LF, et al. The Italian experience of the National Registry of Renal Biopsies. *Kidney Int*. 2004;66:890–894.
14. Hanko JB, Mullan RN, O'Rourke DM, et al. The changing pattern of adult primary glomerular disease. *Nephrol Dial Transplant*. 2009;24:3050–3054.
15. Schena FP. Survey of the Italian Registry of Renal Biopsies. Frequency of the renal diseases for 7 consecutive years. The Italian Group of Renal Immunopathology. *Nephrol Dial Transplant*. 1997;12:418–426.
16. Kurnatowska I, Jedrzejka D, Malyska A, et al. Trends in the incidence of biopsy-proven glomerular diseases in the adult population in central Poland in the years 1990–2010. *Kidney Blood Press Res*. 2012;35:254–258.
17. Sugiyama H, Yokoyama H, Sato H, et al. Japan Renal Biopsy Registry: the first nationwide, Web-based, and prospective registry system of renal biopsies in Japan. *Clin Exp Nephrol*. 2011;15:493–503.
18. Zhao M-h, Zou W-z, Liu G, et al. The changing spectrum of primary glomerular diseases within 15 years: a survey of 3331 patients in a single Chinese centre. *Nephrol Dial Transplant*. 2009;24:870–876.
19. Kiryluk K, Li Y, Sanna-Cherchi S, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet*. 2012;8:e1002765.
20. O'Connell PJ, Ibels LS, Thomas MA, et al. Familial IgA nephropathy: a study of renal disease in an Australian aboriginal family. *Aust N Z J Med*. 1987;17:27–33.
21. Levy M. Familial cases of Berger's disease and anaphylactoid purpura. *Kidney Int*. 2001;60:1611–1612.
22. Julian BA, Quiggins PA, Thompson JS, et al. Familial IgA nephropathy. Evidence of an inherited mechanism of disease. *N Engl J Med*. 1985;312:202–208.
23. Scolari F, Amoroso A, Savoldi S, et al. Familial clustering of IgA nephropathy: further evidence in an Italian population. *Am J Kidney Dis*. 1999;33:857–865.
24. Paterson AD, Liu XQ, Wang K, et al. Genome-wide linkage scan of a large family with IgA nephropathy localizes a novel susceptibility locus to chromosome 2q36. *J Am Soc Nephrol*. 2007;18:2408–2415.
25. Karnib HH, Sanna-Cherchi S, Zalloua PA, et al. Characterization of a large Lebanese family segregating IgA nephropathy. *Nephrol Dial Transplant*. 2007;22:772–777.
26. Schena FP, Scivittaro V, Ranieri E, et al. Abnormalities of the IgA immune system in members of unrelated pedigrees from patients with IgA nephropathy. *Clin Exp Immunol*. 1993;92:139–144.
27. Gharavi AG, Moldoveanu Z, Wyatt RJ, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. *J Am Soc Nephrol*. 2008;19:1008–1014.
28. Gharavi AG, Yan Y, Scolari F, et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22–23. *Nature Genet*. 2000;26:354–357.
29. Bisceglia L, Cerullo G, Forabosco P, et al. Genetic heterogeneity in Italian families with IgA nephropathy: suggestive linkage for two novel IgA nephropathy loci. *Am J Hum Genet*. 2006;79:1130–1134.
30. Szigeti N, Kovacs T, Degrell P, et al. [Secondary IgA-nephropathy in gastroenterological diseases]. *Orvosi Hetilap*. 2007;148:313–318.
31. Wang J, Anders RA, Wu Q, et al. Dysregulated LIGHT expression on T cells mediates intestinal inflammation and contributes to IgA nephropathy. *J Clin Invest*. 2004;113:826–835.
32. Hubert D, Beaufile M, Meyrier A. [Immunoglobulin A glomerular nephropathy associated with inflammatory colitis. Apropos of 2 cases]. *Presse Med*. 1984;13:1083–1085.
33. Almroth G, Axelsson T, Müssener E, et al. Increased prevalence of anti-gliadin IgA-antibodies with aberrant duodenal histopathological findings in patients with IgA-nephropathy and related disorders. *Uppsala J Med Sci*. 2006;111:339–352.
34. Honkanen T, Mustonen J, Kainulainen H, et al. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. *Kidney Int*. 2005;67:2187–2195.
35. Smerud HK, Fellstrom B, Hallgren R, et al. Gluten sensitivity in patients with IgA nephropathy. *Nephrol Dial Transplant*. 2009;24:2476–2481.
36. Coppo R, Mazzucco G, Martina G, et al. Gluten-induced experimental IgA glomerulopathy. *Lab Invest*. 1989;60:499–506.
37. Woodrow G, Innes A, Boyd SM, et al. A case of IgA nephropathy with coeliac disease responding to a gluten-free diet. *Nephrol Dial Transplant*. 1993;8:1382–1383.
38. Koivuviita N, Tertti R, Heiro M, et al. A case report: a patient with IgA nephropathy and coeliac disease. Complete clinical remission following gluten-free diet. *NDTPlus*. 2009;2:161–163.
39. Welander A, Sundelin B, Fored M, et al. Increased risk of IgA nephropathy among individuals with celiac disease. *J Clin Gastroenterol*. 2013;47:678–683.
40. Collin P, Syrjänen J, Partanen J, et al. Celiac disease and HLA DQ in patients with IgA nephropathy. *Am J Gastroenterol*. 2002;97:2572–2576.
41. Moeller S, Canetta PA, Taylor AK, et al. Lack of serologic evidence to link IgA nephropathy with celiac disease or immune reactivity to gluten. *PLoS One*. 2014;9:e94677.
42. Berger J. Recurrence of IgA nephropathy in renal allografts. *Am J Kidney Dis*. 1988;12:371–372.
43. Silva FG, Chander P, Pirani CL, et al. Disappearance of glomerular mesangial IgA deposits after renal allograft transplantation. *Transplantation*. 1982;33:241–246.
44. Pabst O. New concepts in the generation and functions of IgA. *Nature Rev Immunol*. 2012;12:821–832.
45. Mestecky J, Raska M, Julian BA, et al. IgA nephropathy: molecular mechanisms of the disease. *Annu Rev Pathol*. 2013;8:217–240.

46. Kiryluk K, Novak J. The genetics and immunobiology of IgA nephropathy. *J Clin Invest.* 2014;124:2325–2332.
47. Allen AC, Harper SJ, Feehally J. Galactosylation of N- and O-linked carbohydrate moieties of IgA1 and IgG in IgA nephropathy. *Clin Exp Immunol.* 1995;100:470–474.
48. Novak J, Julian BA, Tomana M, et al. IgA glycosylation and IgA immune complexes in the pathogenesis of IgA nephropathy. *Semin Nephrol.* 2008;28:78–87.
49. Hiki Y, Horii A, Iwase H, et al. O-linked oligosaccharide on IgA1 hinge region in IgA nephropathy. Fundamental study for precise structure and possible role. *Contrib Nephrol.* 1995;111:73–84.
50. Moldoveanu Z, Wyatt R, Lee J, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. *Kidney Int.* 2007;71:1148–1154.
51. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol.* 2011;22:1795–1803.
52. Kiryluk K, Novak J, Gharavi AG. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. *Annu Rev Med.* 2013;64:339.
53. Magistroni R, D'Agati VD, Appel GB, et al. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. *Kidney Int.* 2015;88:974–989.
54. Novak J, Julian BA, Mestecky J, et al. (eds). Glycosylation of IgA1 and pathogenesis of IgA nephropathy. *Semin Immunopathol.* 2012;34:365–382.
55. Lai KN. Pathogenesis of IgA nephropathy. *Nature Rev Nephrol.* 2012;8:275–283.
56. Kiryluk K, Moldoveanu Z, Sanders JT, et al. Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch–Schönlein purpura nephritis. *Kidney Int.* 2011;80:79–87.
57. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. *Science.* 2001;292:1115–1118.
58. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science.* 2005;307:1915–1920.
59. Cebra JJ. Influences of microbiota on intestinal immune system development. *Am J Clin Nutr.* 1999;69:1046S–1051S.
60. Braun-Fahrlander C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med.* 2002;347:869–877.
61. Hooper LV. Bacterial contributions to mammalian gut development. *Trends Microbiol.* 2004;12:129–134.
62. Hill MJ. Intestinal flora and endogenous vitamin synthesis. *Eur J Cancer Prev.* 1997;6(Suppl 1):S43–S45.
63. Hylemon PB, Harder J. Biotransformation of monoterpenes, bile acids, and other isoprenoids in anaerobic ecosystems. *FEMS Microbiol Rev.* 1998;22:475–488.
64. Frank DN, St Amand AL, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A.* 2007;104:13780–13785.
65. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nature Rev Endocrinol.* 2015;11:577–591.
66. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature.* 2012;490:55–60.
67. Knip M, Siljander H. The role of the intestinal microbiota in type 1 diabetes mellitus. *Nature Rev Endocrinol.* 2016;12:154–167.
68. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med.* 2015;21:895–905.
69. Wang T, Cai G, Qiu Y, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *ISME J.* 2012;6:320–329.
70. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Rev Microbiol.* 2014;12:661–672.
71. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell.* 2016;165:111–124.
72. Wang Z, Roberts AB, Buffa JA, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell.* 2015;163:1585–1595.
73. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol.* 2014;25:657–670.
74. Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int.* 2013;83:308–315.
75. Wong J, Piceno YM, Desantis TZ, et al. Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. *Am J Nephrol.* 2014;39:230–237.
76. De Angelis M, Montemurno E, Piccolo M, et al. Microbiota and metabolome associated with immunoglobulin A nephropathy (IgAN). *PLoS One.* 2014;9:e99006.
77. Zhao N, Hou P, Lv J, et al. The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. *Kidney Int.* 2012;82:790–796.
78. Qin W, Zhong X, Fan JM, et al. External suppression causes the low expression of the Cosmc gene in IgA nephropathy. *Nephrol Dial Transplant.* 2008;23:1608–1614.
79. DeSoignie R, Sellin JH. Propionate-initiated changes in intracellular pH in rabbit colonocytes. *Gastroenterology.* 1994;107:347–356.
80. Natarajan N, Pluznick JL. Olfaction in the kidney: 'smelling' gut microbial metabolites. *Exp Physiol.* 2016;101:478–481.
81. Tan J, McKenzie C, Potamitis M, et al. The role of short-chain fatty acids in health and disease. *Adv Immunol.* 2014;121:91–119.
82. Bone E, Tamm A, Hill M. The production of urinary phenols by gut bacteria and their possible role in the causation of large bowel cancer. *Am J Clin Nutr.* 1976;29:1448–1454.
83. Macfarlane GT, Macfarlane S. Bacteria, colonic fermentation, and gastrointestinal health. *J AOAC Int.* 2012;95:50–60.
84. Aronov PA, Luo FJ, Plummer NS, et al. Colonic contribution to uremic solutes. *J Am S Nephrol.* 2011;22:1769–1776.
85. Martinez AW, Recht NS, Hostetter TH, et al. Removal of P-cresol sulfate by hemodialysis. *J Am Soc Nephrol.* 2005;16:3430–3436.
86. Tang WH, Wang Z, Kennedy DJ, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res.* 2015;116:448–455.