The Gut-Renal Connection in IgA Nephropathy

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Summary: The connection between a dysregulated gut-associated lymphoid tissue and IgA nephropathy (IgAN) was supposed decades ago after the observation of increased association of IgAN with celiac disease. Pivotal studies have shown a role for alimentary antigens, particularly gliadin in developing IgAN in BALB/c mice, and a reduction in IgA antigliadin antibodies and proteinuria was reported after gluten free-diet in patients with IgAN. Recently a genome-wide association study showed that most loci associated with IgAN also are associated with immune-mediated inflammatory bowel diseases, maintenance of the intestinal barrier, and response to gut pathogens. Transgenic mice that overexpress the B-cell activating factor develop hyper-IgA with IgAN modulated by alimentary components and intestinal microbiota. Mice expressing human IgA1 and a soluble form of the IgA receptor (sCD89) develop IgAN, which is regulated by dietary gluten. Recent observations have confirmed gut-associated lymphoid tissue hyper-reactivity in IgAN patients with IgA against alimentary components. Interesting results were provided by the NEFIGAN randomized controlled trial, which adopted an enteric controlled-release formulation of the corticosteroid budesonide targeted to Peyer's patches. After 9 months of treatment, a reduction in proteinuria was observed with stabilized renal function and limited adverse events. The gut-renal connection is an area of promising new treatment approaches for patients with IgAN.

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The relationship between IgA nephropathy (IgAN) and the mucosal immune system has been considered since the identification of this renal entity by Berger and Hinglais[1] 50 years ago. IgA, which is predominant in the mesangial deposits of IgAN, is produced mostly by the mucosal-associated lymphoid tissue (MALT) and is the most represented immunoglobulin in mucosae.[2,3] The clinical hallmark of IgAN is the manifestation of gross hematuria, often coincident with an upper respiratory-tract infection, hence most of the interest has been focused on the oropharyngeal and tonsillar-associated lymphoid tissue in the past, however, some associations between IgAN and intestinal disorders were reported decades ago.[4] In some patients the mucosal infection triggering hematuria involves the intestine, with acute diarrhea, or in patients with Crohn's disease it involves the ileocecal region.[5] Patients with celiac disease and inflammatory bowel diseases have an increased frequency of IgAN, indicating a connection stronger than sheer chance.[4,6,7] Some experimental models and pilot studies in patients with IgAN in the 1980s suggested that alimentary antigens and particularly gluten may have a role in the pathogenesis of IgAN.[8,9] However, because the clinical association between celiac disease and IgAN was not constant and the role of tonsils seemed more relevant, also for the possibility eradication of antigens and lymphatic tissue producing IgA by tonsillectomy, as suggested by several studies from Japan,[10,11] the role of gut and gut-associated lymphoid tissue (GALT) was shadowed and no longer considered for several years.

Recent data have suggested investigators reconsider old theories of a role of dysregulated GALT in which the genetic conditioning, the gut dysbiosis, and the reaction to diet components may play a combined role in the development and progression of IgAN. This hypothesis led to a search for innovative treatment approaches to IgAN focused on corticosteroids specifically targeting GALT in the Peyer's patches and possible dietary components and intestinal microbiota modulations.

THE GUT-ASSOCIATED IMMUNE SYSTEM AND IgAN

MALT is represented in induction areas of organized lymphoepithelial tissue, including the oral tonsils and Waldeyer's pharyngeal ring MALT, the nasal-associated lymphoid tissue or bronchial-associated lymphoid tissue or gut- and Peyer's patches–associated lymphoid tissue (GALT).[12,13] The synthesis of IgA in these mucosal areas is initiated by T-cell–independent or T-cell–dependent mechanisms[14] (Fig. 1). T-cell–independent production of IgA is initiated by the adsorption through the intestinal mucosa of alimentary antigens or microorganism components or products, and intestinal epithelia Toll-like receptors (TLRs) are triggered. Activated dendritic cells, with the support of intestinal epithelial and stromal cells, produce interleukins (interleukin-6 and interleukin-10), transforming growth factor-β, B-cell activating factor (BAFF), and a proliferative inducing ligand (APRIL). BAFF and APRIL, after binding to TNF-receptor homolog

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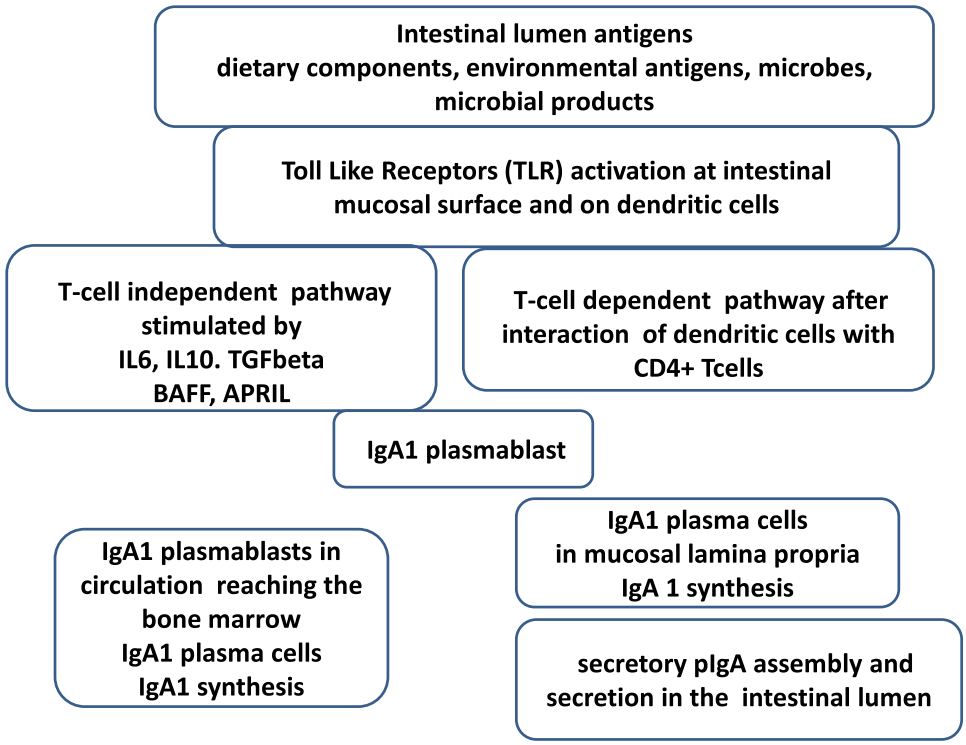

Figure 1. GALT activation by antigens present in the intestinal lumen: T-cell–dependent and T-cell–independent synthesis of IgA1 in GALT. IL, interleukin; TGFbeta, transforming growth factor β.

transmembrane activator, are particularly active in promoting the differentiation and proliferation of B cells with class switching from IgM to IgA1. Primed B cells migrate to the MALT effector area, the mucosal lamina propria, where they release dimeric IgA, formed by two IgA molecules and a joining chain.[15] IgA dimers and polymers (pIgA) bind to the polymeric Ig receptor on the basolateral surface of the mucosal epithelium and undergo transcytosis to the apical surface, where, after binding to the secretory component, are secreted into the lumen as secretory IgA (sIgA). The bacteriostatic effects of sIgA are potentiated by antimicrobial peptides secreted into the intestinal lumen (eg, defensins). sIgA plays a pivotal role in intestinal homeostasis between the host and commensal bacteria, regulating the intestinal microbiome and preventing pathogen overgrowth. Under normal circumstances, ingested dietary proteins do not activate immunologic mechanisms because sIgA prevents antigen entry.[16] Antigens escaping the IgA barrier enter the oral tolerance mechanism[17] (Fig. 2). The switch from IgG to IgA immune response leads to the formation of poorly complement-fixing IgA immune complexes (IgAIC), instead of flogogenic IgGIC. Secretory IgA molecules do not activate the classic complement pathway and facilitate a tolerant noninflammatory relationship between the subject and the intestinal microbes. Polymeric IgA variants predominate in secretions, with both IgA1 and IgA2 subclasses, while a large part of the IgA in circulation is synthesized in the bone marrow, mostly in a monomeric form and of IgA1 subclass. pIgA are produced mostly in the mucosal lamina propria.

Increased plasma levels of IgA are frequent in patients with IgAN (35%-50% of cases), with a significant increase in the pIgA fraction (25% of total IgA compared with 10% in healthy controls).[2,18] In the renal deposits of patients with IgAN the predominant variant is pIgA, and sIgA also is detectable, suggesting a mucosal origin,[19] however, the IgA1 subclass is mostly represented.[3] Because the immune response to mucosa presented antigens is exaggerated in patients with IgAN, although the systemic immune response is not modified,[20] the current hypothesis is that lymphocytes are sensitized at the mucosal level and then migrate to bone marrow to differentiate into IgA1-producing plasma cells.[21] However, the mucosa is the area where IgA molecules initiate their commitment, which will end in the production of IgA antibodies with abnormal glycosylation,[22] macromolecular immune complexes, and mesangial deposit formation.

Patients with IgAN present with a peculiar defective galactosylation of IgA1. IgA1 subclass has short O-linked oligosaccharide chains in the hinge region, made by a N-acetyl galactosamine core extended with β1,3 linked galactose by the β1,3 galactosyltransferase (which needs a specific chaperone, Cosmc) and covered with sialic acid. In patients with IgAN there is a prevalence of truncated IgA1 O-glycoforms with reduced galactosylation (galactose deficient or galactose-deficient IgA1