Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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The Gut-Kidney Axis in IgA Nephropathy

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IgA nephropathy (IgAN) is the most common primary cause of glomerulonephritis, and is a leading cause of kidney failure worldwide. Excess generation of polymeric forms of IgA1 deficient in sialic acid and galactose residues on O-glycan chains (gd-IgA1) leads to the formation of IgA immune-complexes that deposit in the glomerular mesangium. Clinical, genetic and experimental observations indicate that mucosal tissue is the source of pathogenic gd-IgA1. Genetic polymorphisms only explain 10% of the variability in disease risk, suggesting environmental factors play a major role in disease development. The intestinal microbiota is the most imposing environmental factor. Host-microbiota interactions are mostly mediated by the metabolic activity of microbes and the immune system of the host. Epithelial cells secreting mucus, IgA and antimicrobial peptides define the frontier between host and microbiota. The form of IgA secreted at the mucosal surface is polymeric, and in the intestine about 50% is of IgA1 isotype. To pass into the intestinal lumen, IgA binds to the secretory component. The secretory component is found associated with IgA deposits in up to 30% of IgAN biopsies. Other observations corroborating an intestinal mucosa origin of gd-IgA1 are the clinical association of inflammatory bowel disease, coeliac disease and liver cirrhosis with IgAN. Identified genetic risk polymorphisms for IgAN are involved in the mucosal immune system, notably the alpha-defensin locus for antimicrobial peptides. Corticosteroids targeting the intestinal mucosa are an effective treatment. The faecal microbiota of IgAN patients has been shown to be significantly different compared to both healthy controls and disease controls with other causes of kidney disease. Kidney failure has an independent effect on the microbiota, so it is important to compare with disease control groups matched for GFR. Over-abundance of mucin-degrading bacteria specifically adapted to live in the mucus-layer adjacent to intestinal epithelium, such as Akkermansia muciniphila and Ruminococci is emerging as a signature

dysbiosis of IgAN. Akkermansia muciniphila can degrade the O-glycan chains of IgA1 to generate gd-IgA1. This takes place in the intestinal lumen. We have shown that gd-IgA1 can return to the circulation across the intestinal epithelium by a process of retro-transcytosis. In the circulation of IgAN patients, mucosa associated invariant T cells (MAITs) are found to be activated and the number of B-lymphocytes homing to the intestinal mucosa is increased. This suggests a sub-clinical intestinal inflammation. IgAN could be the manifestation of an infection of the intestinal mucus layer involving mucin degrading bacteria that both activate the mucosal immune system and generate gd-IgA1. Apart from their direct effects on human IgA1, intestinal microbes can also influence the human immune system through vitamin B metabolism which stimulates MAIT cells and fermentation of short chain fatty acids (SCFA) which regulate T-cells. How environmental factors upstream of the microbiota such as diet, antibiotics and vitamin A (an important regulator of mucosal immunity) influence IgAN associated dysbiosis remains unknown.

Keywords: IgA nephropathy, Microbiota, Mucus, Mucosal immunology