4) ROLE OF THE SALIVARY AND FECAL MICROBIOMA IN THE PATHOGENESIS OF PRIMARY IGA NEPHROPATHY

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Rationale
Immunoglobulin A nephropathy (IgAN) is one of the most common forms of primary glomerular disease. Recent insight suggests that the composition of the gut microbiota can globally influence the immune system and disease development in nonmucosal organs (Chervonsky AV et al Nat Immunol 2010). The human gut microbiota is estimated to consist of at least $10^{14}$ bacteria and archaea, composed of approximately 1,100 prevalent species, with approximately 160 such species per individual. In its entirety, the microflora is estimated to contain 150-fold more genes than our own host genomes.

Mucosal IgA production occurs in the Peyer's patches (PPs), mesenteric lymph nodes (MLNs), and isolated lymphoid follicles (ILF). These are the major inductive sites for IgA production and the balance of various factors in the mucosal microenvironment plays an important role in regulating the synthesis of IgA. In IgAN polymeric IgA-containing immune complexes are deposited in the kidney glomeruli, triggering renal injury. In the case of IgAN, the source of the IgA has been variously speculated to involve mucosal tissues, tonsils, and bone marrow. In IgAN, the IgA itself is not generally viewed as being autoreactive per se, but rather it has a strong propensity to form macromolecular complexes that accumulate as immuno-deposits in the glomerular mesangium. Despite considerable investigation into the biochemical abnormalities of IgA1 from patients with IgAN, the origin and localization of sites secreting the aberrant IgA1, and the downstream effector mechanisms triggered by mesangial IgA1 deposition, the etiology of IgAN remains poorly understood. More recently, signaling induced by the TNF family members B cell activation factor (BAFF) has been implicated in the pathogenesis of IgAN. In the presence of excess BAFF, as in BAFF-Tg mice, some B cell subsets expand abnormally and B cell tolerance to self-antigen is perturbed and these mice develop an IgA-driven nephritis, and the development of this condition, which is commensal microbiota dependent, involves a breakdown in the normal barrier between the mucosal and peripheral compartments. The evidence supporting a role for the enteric flora in the gut-kidney axis has been increasing as reported by recent studies (Douglas D. et al., JCI 2011).

Purpose of the study
Along structural IgA abnormalities, hyperproduction of IgA is thought to play a role in the pathogenesis of primary IgA nephropathy. The generation of IgA in the mucosal compartments is a dominant immunological process that is crucial for homeostasis between the gut commensal flora and the local immunological environment.

We will test the hypothesis that IgA production in patients with IgA nephropathy is deregulated, in part, by mean of a quali-quantitative unbalancing in salivary and fecal microbiota. Moreover, we will study the hypothesis that changes in microbiota may influence the progression of IgAN and may be different in subclasses of IgAN patients (progressor vs not progressor vs patients with segmental necrotizing lesions).

Aim of our study will be to determine if changes in salivary and fecal microbiota could promote, at least in part, the Galactose-deficient IgA1 commonly observed in the primary IgA nephropathy patients, and contributing to kidney failure progression.

This new “integrated” approach may lead to better understand the “link” between human mucosal immunity and microbiota in the pathogenesis of IgAN.

Protocols and logistics
We would like to characterize the microbiota in IgAN patients starting from VALIGA cohort to test this hypothesis. We only require a one-time samples of saliva (shipped and collected in RNALater Solution), feces (shipped and collected in RNALater Solution) and whole blood for plasma and serum.

Received samples will be used for:

- Combining functional and structural genomic and metabonomic approaches based on culture-independent (e.g., pyrosequencing, DGGE) together with GC-MS/SPME analyses, in order to determine the metabolic changes triggered by salivary and fecal microbiota in the primary IgA nephropathy patients;
- Sequencing of circulating 16S rRNA, in order to characterize either Gram⁺ and Gram⁻ Bacteria composition;
- Measuring circulating levels of BAFF and April;
- Serum Gd-IgA1 levels.

We will provide all participating centers with tubes and supplies for collecting and shipping the samples. The shipment will be billed to our courier account.

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