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EDITORIAL

Predicting Inflammatory Bowel Disease Symptoms Onset: Nitrous Take on Gut Bacteria Is No Laughing Matter

The gut microbiome is composed of microorganisms that generally live in symbiosis with our body and play a fundamental role in maintaining human health. Establishing these healthy host-microbiome interactions, especially during early childhood, is important in developing homeostatic immune, metabolic, and epigenetic functions that protect us from chronic gastrointestinal diseases later in life. Considered by some as our second genome, the genetic information contained within the gut microbiome holds tremendous potential for biomarker and therapeutic discovery. Next generation sequencing and functional systems biology technologies have dramatically advanced the potential for microbiome biomarker discovery by facilitating massive parallel identification of thousands of microbial species and the biochemical pathways that correlate with disease prognosis and outcomes. This has led to the recognition that dysbiosis is a key feature of human gastrointestinal disease, but there is currently little agreement on what constitutes dysbiosis or how this should be measured or interpreted because of geographic, ethnic, dietary, and age-related variations that complicate how best to define the healthy microbiome as a gold standard reference for clinical diagnosis. Deciphering poorly annotated genetic variance also remains a major unresolved hurdle in defining the healthy human microbiome because large amounts of the operative genomic variant are not readily identifiable using standard bioinformatics tools. This finding tends to be conveniently ignored in most microbiome studies and should lead us to complement purely annotation and database-driven biomarker discovery with annotation-agnostic workflows that identify new metagenomic content that is predictive of disease susceptibility and treatment outcomes.

In this issue of *Clinical and Molecular Gastroenterology and Hepatology*, Miyoshi et al[1] present an important proof-of-concept study that provides a new perspective on mining deep functional metagenomic data to predict inflammatory bowel disease (IBD) susceptibility. Microbiome-based studies such as those spearheaded by the National Institutes of Health Common Fund's Integrative Human Microbiome Project[2] have been actively targeting the clinical IBD arena with the goal of identifying host-microbiome signatures that aid in the diagnosis and risk profiling of susceptible patients, as well as identifying new precision-based microbial therapy for symptoms management. To date, these clinical studies have not yielded robust biomarkers that are independently validated across patient cohorts. In part, this may relate to challenges of working with highly heterogeneous clinical specimens and making those complex, multi-omic datasets fully "FAIR" (Findable, Accessible, Interoperable, and Reusable) for independent clinical validation studies. These findings prompted Miyoshi et al to take a more reductionist approach by using an interleukin 10 gene deficient (IL10 KO) mouse model of IBD where colitis is induced by maternal peripartum antibiotic exposure.[3] In carefully controlled studies, these investigators compared metagenomic profiles in fecal specimens collected longitudinally from animals where early life dysbiosis induced IBD in adulthood versus mice where no clinical symptoms were recorded. The study used pathway analysis of Kyoto Encyclopedia of Genes and Genomes biochemical annotation to identify dynamics of microbial nitrogen utilization as the major metagenomic predictor of disease induction in the IL10 KO model. This genetic pathway enrichment was demonstrated by using Nitrogen Source BIOLOG MicroPlates indicating functional significance.

Nitrogen metabolism pathways have previously been linked with active IBD,[4–6] but a deeper biochemical characterization is required to establish whether similar pathways are implicated in predicting disease progression in this model. Notably, elevated urea cycle metabolites in IBD stool may relate to homocitrulline and homoarginine levels being increased in situations where carbomoyl phosphate production exceeds incorporation into the urea cycle through synthetic combination with ornithine. Homocitrulline and homoarginine are formed in a synthetic pathway similar to the urea cycle but starting with lysine and inhibit arginase, which converts arginine to ornithine with co-production of urea. Both arginine and homoarginine are used by inducible nitric oxide synthase to produce nitric oxide and citrulline or homocitrulline, respectively. Conversely, increases in citrulline and homocitrulline might represent damage to the intestinal epithelium, which is sensitive to alterations in energy balance. Several nitrogen-based metabolites are intermediates in biosynthesis and degradation of creatine phosphate, which is an easy to mobilize energetic substrate. Both creatine and creatinine are metabolized by gut bacteria as carbon and nitrogen sources, and changes in fecal levels of creatine and creatinine are detected in antibiotic-treated mice. Perturbations in creatine synthesis also result in alterations in energy metabolism of colonic epithelial cells and negatively impact mucosal barrier integrity, which might be linked to elevated intestinal permeability being another reported early functional biomarker of clinical symptoms development in the IL10 KO model.[7] Alternatively, nitrogen metabolic pathways unique to microbial substrate processing, eg, OxyR, might be generating nitric oxide intermediates that are known to modulate intestinal barrier dysfunction and inflammation.[8,9]

In conclusion, elevated microbiome nitrogen metabolism might represent a new important functional biomarker of IBD disease susceptibility. Further studies are required to translate this early proof-of-concept finding and to decipher the disease mechanism.

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Conflicts of interest
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