

EDITORIAL

Tightening the Case for Gut Microbiota in
Autism-Spectrum Disorder

Autism-spectrum disorder (ASD) is a developmental behavioral disorder often accompanied and aggravated by a range of gastrointestinal and cognitive dysfunction. The concern for ASD reflects its increasing incidence and the disproportionate burden of this and other cognitive disorders on those affected and the family and community around them. Is there a role for us to help from the distant fields of gastroenterology and hepatology?

The etiology of ASD probably occurs during gestation, with evidence that maternal diet and inflammatory events result in systemic products that alter central nervous system neurodevelopment of regions critical to the cognition of social interaction.¹ Emerging candidates for such products include the cytokines interleukin 6 and interleukin 17A and certain bioactive amines, notably serotonin.^{2–5} Because select intestinal commensal microbiota can induce or attenuate production of these molecules, the intestinal mucosa and microbiome may be a modifier of ASD penetrance. Mouse models of ASD indeed provide some precedents for this idea, although this is early and incomplete evidence, and the outlook for addressing this concept in at-risk human mothers is experimentally and ethically fraught.

In children with ASD, an important question is whether these or other processes modify disease progression or phenotype. Because functional gastrointestinal disorders are a common and probably increased comorbidity in ASD, these patients may provide clues to such processes because distinct cytokines, bioactive amines, and microbiome constituents are biomarkers and probable modifiers of certain adult functional gastrointestinal disorders. Studies of ASD patients with gastrointestinal dysfunction have been small scale to date, but have associated this patient subset with increased levels of serotonin and certain microbial taxa, although the latter findings have been inconsistent among studies.

The study by Luna et al⁶ in this issue of *Cellular and Molecular Gastroenterology and Hepatology* tightens the case for a microbial hub and serotonin and cytokine spokes in the gastrointestinal dysfunction of ASD. Compared with ASD-unaffected children, children with ASD and gastrointestinal dysfunction had increased mucosal tissue levels of select microbial taxa, mainly members of the genus *Clostridium*. Notably, several of these taxa were associated with ASD patients in cross-sectional case-control studies. In the Luna et al⁶ study, mucosal production of cytokines and serotonin-pathway bioamines also were measured. Bioinformatic analysis established a layered network of relationships between these microbial taxa, serotonin pathway metabolites, and several inflammatory cytokines. Again, these same metabolites and cytokines predominate

with those associated with the ASD disease state in prior cross-sectional studies.

In these frontier times of microbiome science, several strengths in design and analysis distinguish this study. First, its care in patient phenotypic selection (gastrointestinal dysfunction and stratification of the pain subset) and bio-specimen choice (mucosal biopsy vs fecal) ensure that the collected data are closest to the clinical state and biologic site in question. Second, deep 16S metagenomic sequencing and optimized pre-analytic bioinformatics permit deeper resolution of microbial taxa. Third and most exciting is the simultaneous assessment of the mucosal ecosystem in single biopsy specimens, including microbial composition and bioamine and cytokine production. Such simultaneous measurement permits the follow-through with powerful bioinformatic analyses to construct potential functional relationships between microbiota and clinical relevant properties of the mucosal site.⁷

Important and challenging questions loom as this pathogenic ecologic network is advanced from association to causation. What are the direct mucosal cell types and functions targeted of this network for the microbiota, and via what microbial products? For example, perhaps certain microbiota act on local enteroendocrine cells for serotonin production, or by direct microbial metabolism of enteral tryptophan. Or, others may elicit epithelial or mucosal hematopoietic cell cytokine production that may in turn elicit mucosal bioamine secretion.⁸ Conversely, levels of some microbiota may instead be altered secondarily by the altered ecologic state of the dysfunctional intestine, and not involved causally in the functional biology. However, no worries, this is life as usual in frontier times. The exciting study by Luna et al⁶ increases confidence for this path ahead, and its promise for clarifying ASD pathogenesis and uncovering targetable elements for intervention.

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Conflicts of interest

The author discloses no conflicts.

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