Decoding Hidden Messages: Can Fecal Host Transcriptomics Open Pathways to Understanding Environmental Enteropathy?

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Yu et al. showed how human RNA could be isolated from feces and interrogated. They applied this technology to feces from 259 children in rural Malawi to show that host messenger RNA (mRNA) transcripts encoding immune and epithelial cell adhesion proteins associate with environmental enteric dysfunction (EED), defined as the percentage of lactulose excretion (%L), as a measure of barrier dysfunction, growth impairment, or both. The transcripts identified include those associated with broad immunologic responses (T-cell chemokines, immunoglobulin Fc fragments, interferon-induced proteins, neutrophil, and B-cell activators), mediators that dampen inflammatory responses of the rapidly renewing mucosal response to resident and/or pathogenic microbes as well as downstream cytokine signals. The investigators showed decreases in mucin expression and thereby down-regulation of MUC2 promoter that encodes for the mucin MUC2, which is expressed in the intestine and colon, and is more subject to degradation or functional modulations than inflammatory cells. Whether mucin down-regulation is the cause for the changes is traceable perhaps to variation in mucin-modulating microbiota such as *Akkermansia* or pathogens or both, select nutritional deficiencies, or even epigenetic methylation of CpG islands in specific regions of MUC2 promoter that down-regulate MUC2 expression, or a consequence (secondary to potential tumor necrosis factor-α-induced inhibitory effects on mucin transcription along with goblet cell depletion) of chronic inflammation. Furthermore, whether broad inflammatory activation signifies an appropriate attempt to repair a damaged mucosa, as the investigators suggested, or reflects a dysregulated mucosal response to resident and/or pathogenic microbes as may occur in conditions of immunocompromise, specific nutrient deficiency, or inflammatory bowel diseases, also is unclear. Future sequential measurements of fecal host transcriptomes layered on other innovative methods such as multipathogen molecular fecal diagnostics, microbiomics, and metabolomics (which show perturbed choline and tryptophan metabolism associated with undernutrition and metabolic adaptations for catch-up growth) should provide a more complete overview of the global biological system helping to resolve key questions about EED pathogenesis.

Nevertheless, this work describes an intriguing noninvasive method to interrogate the host responses to microbial and nutritional challenges. In this analysis of young children in impoverished areas, the data also were used to develop hypotheses about EED pathogenesis and potential approaches and biomarkers for assessing innovative
interventions to improve growth and development, not to mention potential long-term metabolic and cognitive consequences.

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