



## Commentary

# Application of mucosal functional genomics to childhood undernutrition and stunting: Insights into mechanisms and targeted interventions

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Despite extensive global health efforts, maternal and child undernutrition continue to account for substantial morbidity and mortality in low-income and middle-income countries [1]. This includes a high rate of mortality for children hospitalized with severe acute malnutrition (SAM), and lasting effects upon cognition in those with chronic undernutrition and stunting. Efforts focused upon improved nutrition and sanitation early in life have yielded only partial benefits, suggesting a critical knowledge gap in our understanding of underlying mechanisms [1]. This may include a common environmental enteric dysfunction (EED) underlying both acute and chronic forms of malnutrition [2]. While histopathologic features of EED were recognized as early as the 1960s, a comprehensive multi-omic approach using mucosal samples obtained during endoscopy has only recently been applied [2]. It was hypothesized that specific microbial shifts, and associated mucosal epigenetic, transcriptomic, and proteomic features, would be associated with refractory undernutrition.

In the August 2021 issue of *EBioMedicine*, Kelly et al [3] tested for duodenal transcriptomic variation in an elegant design which included both children and adults with EED and stunting living in the same disadvantaged community in Zambia, and hospitalized children with SAM. This allowed the investigators to test for common and distinct features of childhood EED with stunting and SAM. Histopathologic analysis confirmed core features of EED including villous blunting, paneth and goblet cell depletion, and an increase in intra-epithelial and lamina propria lymphocytes in both groups. Participants with a treatable fecal pathogen were excluded, supporting a likely role for the commensal microbial community in driving inflammatory responses. Core transcriptomic features of EED identified in both groups of children, relative to adults living in the same community, implicated dysregulated mucin production and xenobiotic metabolism/detoxification. In addition, children with SAM exhibited a robust

mucosal immune response, and suppression of a broad array of genes involved in epithelial barrier function, transport, and digestion. Collectively these results were in agreement with transcriptomic and proteomic features of undernutrition and stunting observed in other recent EED cohorts [4,5], and defined more pronounced digestive and immune dysfunction in those acutely ill with SAM. Future interventional studies will need to account for these differences, in particular in addressing the high mortality associated with SAM.

A prevailing hypothesis regarding EED pathogenesis has been that the gut microbial community drives host inflammatory responses linked to malnutrition, as noted in the current study [3]. A study of children with EED in Bangladesh utilized endoscopy to identify 14 microbial strains which were associated with the degree of stunting, and host inflammatory responses detected using mucosal and circulating proteomics [4]. Transfer of these microbes into germ-free mice triggered intestinal injury and weight loss. These data will inform efforts to develop microbiota-directed foods (MDF) designed to regulate specific microbial strains in animal models, and children with malnutrition [6]. MDF-2 has now been shown to be superior to a ready-to-use supplementary food (RUSF) in promoting weight gain, microbial shifts, and expression of host proteins linked to bone growth and neurodevelopment in malnourished children [7]. It will be important to validate non-invasive biomarkers to identify children at greatest risk for adverse consequences of malnutrition for enrollment in interventional studies of MDF, and potentially as early indicators of treatment response.

Recent studies have shown that specific microbial metabolites regulate the intestinal epigenetic architecture, potentially accounting for persistent suppression of genes regulating epithelial digestive, secretory, and detoxification functions as in the current report [3, 8]. These epigenetic mechanisms may contribute to the refractory nature of wasting and stunting in affected children. A birth cohort study of underweight infants and toddlers refractory to nutritional intervention in a rural district in Pakistan tested for associations between one epigenetic feature, the duodenal methylome, and the associated transcriptome linked to core histologic features and the degree of undernutrition [5]. Transcriptomic pathways regulating lymphocyte proliferation and epithelial transport and metabolism were associated with histologic severity and reduced weight gain. These changes in gene expression were in turn associated with differences in the global pattern of DNA methylation, and reduced weight at study entry during the first month after birth. These data prioritize studies to test mechanisms by which the prenatal environment, and

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early postnatal microbial colonization and nutrition, may regulate intestinal histone acetylation or DNA methylation resulting in persisting adverse immune and digestive responses to the environment. This may in turn inform interventions to modify the intestinal epigenetic architecture of the mother and child, improving long-term growth and development.

Host and microbial multi-omic features of EED and SAM from these recent paediatric cohort studies may now be used to prioritize mechanisms to test in animal and organoid model systems, and to refine the effectiveness of clinical interventions [3, 4, 5]. Data across cohorts suggest core EED features including reduced goblet cell function and epithelial antioxidant and detoxification pathways which should be prioritized for further research. For children hospitalized with SAM, the host immune response, and profound suppression of epithelial transporters, will need to be considered [3]. Ideally these studies will include pre-clinical work to test approaches including microbiota-directed foods to modulate these host pathways, linked to interventions in children characterized using validated clinical and biomarker features [4, 5].

### Contributors

**LAD is the sole author.**

### Declaration of competing interest

LAD declares travel funding from Crohn's & Colitis Foundation and holds patents related to IBD monitoring and IBD treatment with oligosaccharides.

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