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Commentary

Understanding & ameliorating enteropathy and malnutrition in impoverished areas

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Over 160 million (2017 estimates are 184 [range 176–193] million) children (including nearly one child in every 3 living in impoverished areas) suffer the often overlooked short and long-term consequences of malnutrition and stunted growth in early childhood [1]. In addition to inadequate diets, most children have repeated and multiple intestinal infections [2]. Together, destructive and inflammatory infections in a child with inadequate diet combine to further impair normal intestinal absorptive and barrier function that can cycle to acute life threatening severe acute malnutrition (SAM) or to more 'silent,' but even more widely devastating lasting outcomes like stunted growth, cognitive impairment and even later life costly metabolic syndrome [3]. We have tried to emphasize, in order to measure and address these as HAZdrop (the decrement in height-for-age Z score), COGhit (for the cognitive 'hit' that can be associated with early childhood enteropathy), and METsyn [4]. It is trying to understand what is happening in order to better treat and prevent this spectrum of 'enteropathy' that is the focus of the important work of Chama et al., working with children with SAM in Zambia [5].

This study involves analyses of the mRNA transcripts that are differentially expressed in the upper small bowel biopsy tissues of 27 children under 2 years of age with SAM and persistent diarrhea. Even though 1/3 of these children were HIV-infected, that was not what most distinguished the quartile with the most severe enteropathy (defined as decreased villus height, lactulose-to-rhamnose absorption ratio (LR), serum LPS and anti-DGP (deamidated gliadin peptide). Of great interest to us were the changes seen in nutrient transport transcripts such as ZIP zinc transporters as well as amino acid transporters. Additionally, transcripts associated with host response to enteric infections were not markedly altered in these SAM cases. These data suggest, that while there are likely recent and perhaps current enteric infections in these children, any host response to infection may be masked by the overwhelming host response to malnutrition, potentially further worsening the vicious cycle of malnutrition and infection [6].

Our group has also found ICK and several markers of intestinal cell proliferation and repair in response to acute malnutrition [7]. Of note, these changes were seen within minutes *in vitro* and within hours *in vivo*, suggesting a remarkably fast response of the host to nutritional status. In addition, we find that acute protein deficiency can substantially reduce intestinal cell proliferation and turnover. This ability of the host to pause proliferation and repair during brief periods of protein malnutrition also has implications for the ability to fight off intestinal infections, especially intracellular invasive pathogens such as *Cryptosporidium* [8] and *Shigella,* as epithelial turnover is an important host defense. These animal model studies could also help explain the lack of sufficient markers of host response to infections in these SAM children.

It is clear that a complex triangle of host, microbial and environmental influences are involved in understanding and ameliorating the critical short and long-term consequences of early childhood "environmental enteropathy" (EE) (Fig. 1) [9]. The host transcripts, as demonstrated in this report by Chama et al., provide a window into what the specific host responses are to its microbiota (with or without recognized 'pathogens') and to its environment (like diet or micronutrient deficiencies). The urinary metabolome provides an integration of host and microbiome responses to their combined environment. Understanding how these elements interact is critical to designing beneficial as opposed to harmful interventions. As an example, dietary nutrient or micronutrient interventions might 1) directly feed host growth, 2)"feed" the host's ability to resist pathogen effects (as by helping resist or kill pathogens or enhance barrier resistance), 3) "feed" beneficial microbiota, or, worrisomely, 4) preferentially "feed" pathogenic microorganisms. Others and we have seen the latter with the vitamin B components, tryptophan 'feeding' Cryptosporidium or Toxoplasma pathogens [10] or nicotinamide "feeding" enteroaggregative *E. coli* pathogens (unpublished data). Thus all possible basic, animal model and clinical/field studies are critical to dissect the potentially divergent outcomes of well intentioned interventions. Fortunately innovative scientific tools of metagenomics, transcriptomics, proteomics and metabolomics can now join with epidemiologic and systems biology to integrate and help build this understanding that is so critical to the lifelong health and development of children in greatest need.

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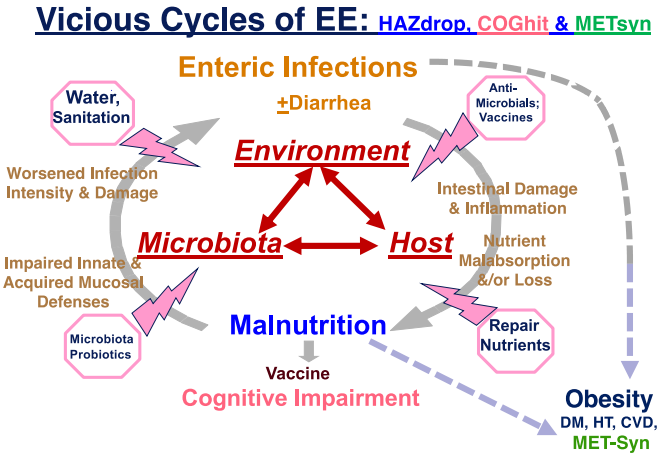

Fig. 1. Vicious cycles of "environmental enteropathy," (EE): HAZdrop (drop in height-for-age Z score over the first 2 years of life), COGhit (the cognitive impairment associated with early childhood enteric infections or EE) and METsyn (metabolic syndrome in later life associated with early childhood EE). This shows the complex interactions of environmental, microbial and host factors in disrupting intestinal absorptive and barrier functions as well as potential, likely 'interdependent' approaches to interventions to ameliorate the short and long-term outcomes of EE in early childhood.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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