INFECTIONS

Feeding the microbial multitudes: co-infection in a malnourished host

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Childhood malnutrition is a global health issue influenced by poorly understood microbial interactions. A new model of co-infection in mice now sheds light on the complex interplay between pathogens, the host and the resident gut microbiota during malnutrition.

Refers to Bartelt, L. A. *et al.* Cross-modulation of pathogen-specific pathways enhances malnutrition during enteric co-infection with *Giardia lamblia* and enteroaggregative *Escherichia coli*. *PLoS Pathog.* **13**, e1006471 (2017)

Childhood malnutrition is a global health issue, which, at first glance, seems to have a relatively simple cause and solution: the availability of nutritious food. Counterintuitively, however, nutritional supplementation alone is a poor treatment for malnutrition[1] and inadequate sanitation is thought to be a key contributing factor to growth stunting and the failure of nutritional interventions[2]. Malnourished children have a dysbiotic gut microbiota, are more susceptible to enteric infections and frequently exhibit a persistent inflammatory pathology of the intestine known as environmental enteric dysfunction (EED)[3]. Contaminated environments and outright infection are both correlated with poor growth outcomes in children[2,4], but it is unclear how these many microbial exposures act together to influence growth and physiology in a malnourished host. A better understanding of this problem is crucial to design more effective interventions for malnutrition.

Now, in a new study, Bartelt *et al.*[5] provide some answers to this global issue. The researchers explored the interplay of a bacterial enteric pathogen (enteroaggregative *Escherichia coli*; EAEC) and a parasite (*Giardia lamblia*) in malnourished mice. Both of these pathogens are found in cohorts of malnourished children and can frequently coexist[4]; however, little is known about their interactions *in vivo*. Bartelt *et al.*[5] fed mice a low-protein diet and characterized the effect of each pathogen individually on host growth and immune responses, intestinal microbiota composition, as well as host and microbial metabolism. They then went on to demonstrate how these parameters were modulated during co-infection.

Malnourished hosts are already known to be vulnerable to microbial infections[6]. In the latest study, protein-deficient mice were more susceptible to single infection with either *G. lamblia* or EAEC[5]. In turn, each pathogen decreased the growth rate of its already-malnourished host, highlighting the important contribution of enteric infection to basic growth outcomes. Moreover, the resident bacterial microbiota seemed to have a pivotal role in this interaction. Malnourished mice had an altered intestinal microbiota that was permissive to *G. lamblia* colonization. Interestingly, within *G. lamblia*-infected mice, the relative abundance of Enterobacteriaceae — a family that often blooms in the gut during dysbiosis and inflammation — was a better predictor of growth outcomes than *G. lamblia* itself[5]. To demonstrate a causal role for the gut microbiota, the authors treated *G. lamblia*-infected mice with antibiotics, altering the bacterial community. Remarkably, although antibiotic-treated mice had the same parasite burden, they were entirely resistant to *G. lamblia*-induced growth defects[5].

These data strengthen the argument that microbial dysbiosis is a driving force behind growth stunting in children, and that enterobacteria probably have a role. In mice fed nutrient-deficient diets, faecal microorganisms transferred from severely malnourished children were found to exacerbate weight loss[7], whereas repeated exposure to certain non-pathogenic bacteria mimicked EED and increased growth stunting[6]. Moreover, both of these models found enterobacterial cocktails to be particularly potent for inducing growth defects, inflammation and intestinal damage[6,7], which corresponds well with observations in human studies. Bartelt *et al.*[5] make the intriguing observation that even parasite-associated weight loss during malnutrition might be driven by the bacterial microbiota, including enterobacterial blooms[5]. Exactly how these parasite–microbiota interactions unfold is a question that remains to be explored.

Although this question might seem challenging, there is yet another layer of complexity: malnourished children are frequently burdened with multiple pathogens at once[4]. Bartelt and colleagues began to address this issue by co-infecting malnourished mice with both *G. lamblia* and EAEC (FIG. 1). When combined during protein malnutrition, *G. lamblia* and EAEC drove a cumulative growth deficit, demonstrating how a burden of multiple pathogens could be hugely detrimental to the health and growth of children. Additionally, co-infected hosts had increased IL-1α levels, a marker of intestinal damage, and showed immune hallmarks of single infection from both *G. lamblia* and EAEC[5]. Collectively, these data remind us that co-infection probably has emergent properties that are complex and difficult to predict.

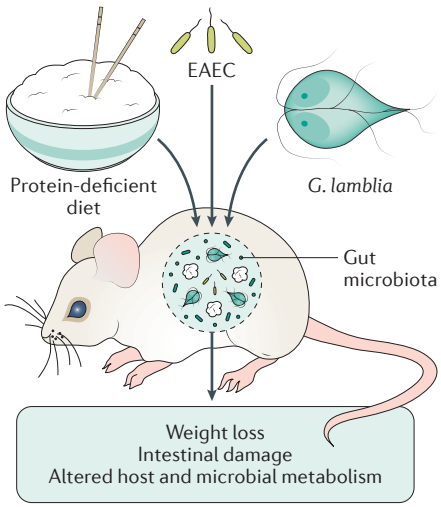

Figure 1 | **A model of co-infection.** In malnourished mice, co-infection with *Giardia lamblia* and enteroaggregative *Escherichia coli* (EAEC) exacerbates weight loss and intestinal injury, affects the gut microbiota and results in an altered metabolic state.

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When examining host–microorganism interactions, metabolism is another important aspect to consider. Intestinal microorganisms contribute to, and benefit from, host metabolism of nutrients; in addition, small metabolites might be used as signalling molecules by both microorganisms and their hosts[8]. In 2016, it was shown that the urinary levels of *N*-methylnicotinamide (NMND), a host metabolite of tryptophan, were predictive of growth outcomes in stunted children[9]. The enzyme that produces NMND is thought to regulate energy expenditure; increased NMND could therefore represent a beneficial metabolic adaptation to reduce energy expenditure and maximize growth in malnourished children[9]. Intriguingly, Bartelt *et al.*[5] also found increased NMND in the urine of *G. lamblia*-infected malnourished mice. Moreover, compared with uninfected mice, *G. lamblia*-infected mice displayed faster catch-up growth (also known as compensatory growth) when switched from low-protein to high-protein chow. This finding suggests that beneficial, microbially triggered metabolic adaptations might help compensate for growth impairment in malnourished individuals.

Adaptations, however, can only do so much. When EAEC infection was combined with *G. lamblia* infection, levels of NMND dropped back to normal[5]. Instead, malnourished mice suffering from a double burden of enteric infection had signs of metabolic exhaustion without any obvious compensatory mechanisms. Moreover, the microbial catabolism of proteins seemed to be increased, suggestive of a proteolytic microbiota fighting for its share of limited resources[5]. It is tempting to speculate how this metabolic environment might affect the catch-up growth of co-infected mice, or indeed children.

Collectively, this study[5] helps to unravel some of the complex microbial–host interactions that occur during infection and malnutrition. It offers new evidence for the role of the intestinal microbiota in growth stunting, and it provides a model in which metabolic adaptations to malnutrition can be explored. One day, metabolites such as NMND could be used to predict which children will respond well to nutritional interventions.

> “Malnourished mice had an altered intestinal microbiota that was permissive to *G. lamblia* colonization”

As always, there remains much that we do not know, including whether these findings are applicable to humans. Another question is how parasites, pathogens and the resident gut microbiota actually interact on a molecular and metabolic level. In 2017, it was shown that the helminth parasite *Heligmosomoides polygyrus* increased host susceptibility to co-infection with the bacterial pathogen *Salmonella enterica* subsp. *enterica* serovar Typhimurium (*S.* Typhimurium)[10]. This finding was not attributed to any host immune response, but to a helminth-altered metabolic environment that caused *S.* Typhimurium to increase its expression of virulence factors. The metabolism and gene expression of microorganisms such as *G. lamblia* and EAEC might be strongly affected by the presence of the other pathogen, ultimately contributing to their effect on a malnourished host.

It is fair to say that scientific understanding of complex host–pathogen–microbiota interactions remain murky at best. The elegant work of Bartelt and colleagues has enabled us to peer a little farther into the gloom and, importantly, taken us a step closer to understanding and addressing childhood nutrition around the world.

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Competing interests statement
The authors declare no competing interests.

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