Cell Host & Microbe
Previews

Fighting Undernutrition: Don't Forget the Bugs

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http://dx.doi.org/10.1016/j.chom.2013.02.015

Severe acute malnutrition is a major cause of child death in developing countries. In a recent study, Smith et al. (2013) monitored a large twin cohort in Malawi to unveil a causal relationship between gut microbiota and weight loss in undernutrition.

Undernutrition is a major worldwide health issue, affecting 18% of children under 5 years of age and associated with about one-third of child deaths in developing countries (WHO, 2010). Wasting is a form of acute undernutrition demonstrated by a low weight-for-height score that can be categorized as either moderate acute malnutrition (MAM) or severe acute malnutrition (SAM) (Black et al., 2008). Kwashiorkor, also called nutritional edema, is a form of SAM characterized by bilateral edema, dermatitis, and hepatic metabolic disruptions as a result of severe nutrient deficiencies (Williams, 1933). Undernutrition has been associated with a range of long-term health defects, including stunting, recurrent infections, and cognitive impairment. To avoid these irreversible consequences, undernutrition needs to be treated before the child is 2 years of age (Ahmed et al., 2009a). The pathogenesis of kwashiorkor has been mainly attributed to protein deficiency, but recent evidence suggests that other causes remain to be identified (Ahmed et al., 2009b).

In a new study, Smith et al. (2013) investigated the relationship between the gut microbiota and kwashiorkor. In order to distinguish the influence of the genetic background from environmental factors, the team monitored 317 Malawian twin pairs (15% monozygotic) during their first 3 years of life. In this initial twin cohort, 50% remained healthy, 43% became discordant for a form of malnutrition, and 7% became concordant for acute malnutrition. As soon as any infant was diagnosed with SAM, both siblings were treated with ready-to-use therapeutic food (RUTF), which consists of peanut paste, sugar, vegetable oil, and fortified milk, allowing the team to also control the effects of treatment in the healthy twin. The scientists then selected 9 control pairs of twins and 13 discordant pairs for kwashiorkor to profile their gut microbiome using DNA-based metagenomic sequencing. This revealed that age and family membership were the main sources of variability. From the very first few minutes of life, microorganisms that newborns encountered in the birth canal, the external environment, and diet colonize the gut. Over the first 2 years, babies acquire a complex gut ecosystem that increases in diversity, which was reflected in this study by an increasing number of identified genes as children got older. Surprisingly, the trajectory over time of well-nourished twins was different from that of the twins discordant for kwashiorkor. This divergent trajectory could only be transiently corrected by RUTF treatment. The team was not able to identify a specific microbial signature characteristic of kwashiorkor infants, but this may be due to the difficulty of recruiting enough discordant twins for this particular disease. Another possible explanation is that SAM is associated not with a single microbial ecosystem but more likely with various submicrobiotypes, illustrating the complexity and variability of the gut microbiome (Sonnenburg and Fischbach, 2011).

In a second set of experiments, Smith et al. (2013) tested the causal relationship between the gut microbiome and the host metabolism by transplanting the microbiota of three selected twin pairs into germ-free recipient mice fed a representative Malawian diet. For two of the three kwashiorkor donors, this resulted in massive weight loss in recipient mice over 3 weeks following the transplant. This was not observed in mice receiving a "healthy" microbiota or if mice were fed a standard chow diet, indicating that weight loss resulted from the interaction between the Malawian diet and the kwashiorkor microbiota. The team also screened these discordant pairs of donors for common pathogens in fecal transplants and showed that the pathogens could not cause the discordant weight loss. Instead, they identified a number of bacteria that were differentially found in healthy and kwashiorkor recipient mice, of which *Bilophila wadworthia* was significantly more present in the kwashiorkor gut microbiota. The RUTF treatment improved body weight in kwashiorkor recipient mice, and this was associated with a number of positive microbial changes that enhanced the overall microbiotype, as illustrated by a higher abundance of Bifidobacteria and Lactobacilli species. Similar changes, although less pronounced, were observed in mice receiving the healthy gut microbiota.

A metabolomic study of fecal and urine samples collected from these animals revealed that RUTF treatment of kwashiorkor infants was associated with a number of transient metabolic changes, particularly in fecal amino acids, which is consistent with the protein deficiency associated with this syndrome. These metabolic modulations could not be correlated to a specific alteration of the microbial ecosystem, suggesting that RUTF treatment induced a modification of the microbial metabolism, rather than the microbial community, as microbial metabolism can adapt to modulations of the environment (Fischbach and Sonnenburg, 2011).The global metabolic impact of RUTF on host metabolism assessed in the urinary profiles of healthy and kwashiorkor recipient mice confirmed the transient effect of dietary intervention on host homeostasis. Modulation of various endogenous metabolic pathways and microbial cometabolism reflected the transgenomic impact of the

dietary intervention that acts both at gut microbiome and at host metabolism levels. Hence, the most significant finding of this work was to demonstrate strong interactions between two environmental factors (i.e., diet and gut microbiota) to determine the health status. As illustrated in Figure 1, this interaction can be modeled like a topographic map where diet and gut microbiota are two interdependent parameters determinant for health, which is achieved when the host metabolism moves around an optimal metabolic space (Holmes et al., 2008). Although other crucial factors (e.g., genetic background, drug exposure, pathogens, stress, etc.) contribute to define the topographic layout, this study shows how critical diet and gut microbiome can be when the variation from other factors is tightly restrained. Moreover, other factors can be impossible or difficult to control at a population level, and diet may be the easiest intervention to maintain an individual's optimal metabolic space. However, this work also illustrates that modifying the metabolism by a dietary intervention alone cannot be sustainable and that interactions between nutrition and the microbial ecosystem must be considered when designing therapy. Only when a synergy between diet and the gut microbiota is reached can an optimal metabolic state be achieved.

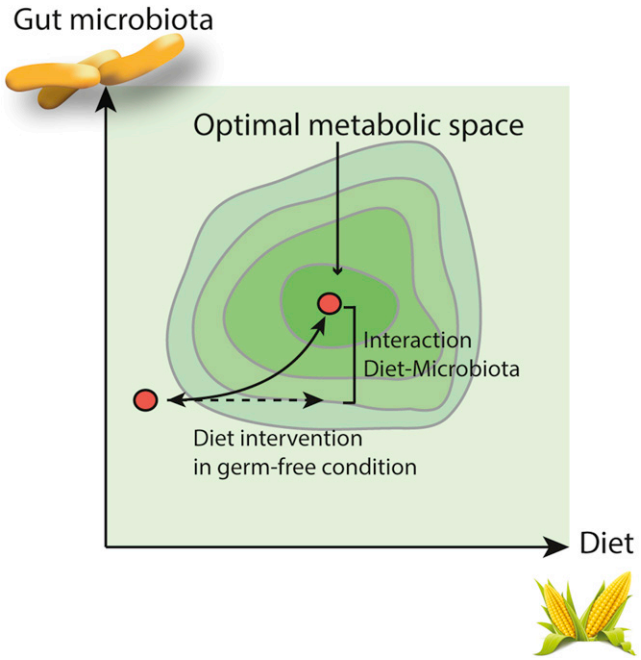

Figure 1. Interaction between Gut Microbiota and Diet in the Context of Undernutrition
Diet and gut microbiota are two interdependent parameters that are crucial for an individual's health, which is determined by his metabolic status (red dots). A healthy situation is obtained when the metabolic status moves around an optimal metabolic space, represented at the top of a topographic map (dark green). The more an individual drifts from his optimum, the more he tends toward disease. Although other factors (e.g., genes, pathogens, stress, etc.) can be critical, the interaction between diet and gut microbiota needs to be considered in addition to a dietary intervention alone in order to maintain homeostasis and long-term health.

In essence, by using germ-free animal models in combination with state-of-the-art metagenomics and metabolomics technologies, this significant piece of work demonstrates a causal relationship between the gut microbiota and underweight in SAM. Beyond the scientific conclusions, it paves the way to address future challenges, of which deciphering the underlying mechanisms between the gut microbiota and host health is a major step toward personalized nutrition.

ACKNOWLEDGMENTS

The author thanks Glenn Gibson and Olivier Cloarec for helpful comments.

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