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Eating for trillions

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Abstract

Three studies investigate the bacteria in the guts of malnourished children and find that, when this microbiota is transferred into mice, supplements of certain microbes or sugars from human breast milk can restore normal growth.

Childhood undernutrition accounts for nearly half of all deaths in infants under the age of five worldwide, and efforts to restore adequate nutritional intake in early infancy have produced only modest outcomes. A proposed alternative is to alter the population of bacteria that inhabits the intestine, known as the gut microbiota, which modulates intestinal metabolic activity. Indeed, childhood malnutrition has previously been associated with an altered microbiota. Three papers (two in *Science* and one in *Cell*) now further establish that the composition of the microbiota is altered in chronically malnourished children. Furthermore, modifying these microbial communities in mice can ameliorate diet-associated growth deficits.

The time between conception and around three years of age is crucial for growth and development in humans. Decades of research into the developmental origins of health and disease has shown that environmental influences during this period can contribute to disease later in life. For instance, early-life nutritional deficits or excess can have lifelong consequences for metabolic and cardiovascular health. Because of the gut microbiota's symbiotic role in intestinal metabolism, changes in its composition are thought to contribute to these health problems.

The food that we consume influences which intestinal microbes flourish. Each microbial species has an optimal metabolic milieu that preferentially supports its growth. As such, a diet rich in plant fibre promotes a gut microbiota considerably different from that promoted by a diet rich in animal fats. In return, the microbiota converts otherwise indigestible dietary components, such as fibre, into useful compounds that fuel intestinal-cell growth and promote healthy immune development. But what happens to the gut microbiota when children are malnourished?

In the first of the three papers, Blanton *et al.* addressed this question. They studied the microbiota in stools collected from Malawian children with either no or varying degrees of growth impairment. They used the results from the children who grew normally to derive a model of healthy microbiota development. When they applied the model across the entire

cohort, the authors found that children who had impaired weight gain tended to have an immature microbiota compared with those of a healthy weight.

Blanton and colleagues next investigated whether the difference in the gut microbiota contributed to growth impairment. They used bacteria isolated from the children's faecal samples to colonize the intestines of germ-free mice, which are devoid of any microorganisms. The authors then fed the mice a nutrient-poor diet reflecting the typical Malawian diet.

After several weeks, mice harbouring a microbiota derived from donors with impaired growth (which we will call growth-stunted mice) gained significantly less weight than the control group given the microbiota of healthy children. However, if the two groups were housed in the same cage, microbes from the controls were rapidly transferred to the growth-stunted mice, restoring the animals' weight to healthy levels. The researchers traced this effect to two bacterial species — *Ruminococcus gnavus* and *Clostridium symbiosum*. When introduced into germ-free mice along with the microbiota from donors who had impaired growth, these species promoted a robust weight gain (Fig. 1).

To gain insight into how *R. gnavus* and *C. symbiosum* promoted growth, Blanton *et al.* examined the stools and livers of the mice using mass spectrometry. Levels of by-products of amino-acid breakdown were decreased in the livers of mice that had restored weight gain compared with those in growth-stunted mice. The authors speculate that the addition of the two species shifted the animals' metabolism away from energy extraction, which involves amino-acid breakdown, towards growth and lean-mass building.

In the second paper, Schwarzer *et al.* provide additional clues to how the gut microbiota might systemically stimulate growth in early childhood. The authors compared the growth of normal juvenile mice with those raised germ-free, and found that the presence of the microbiota promoted growth by facilitating the host's production of insulin-like growth factor protein. If the mice were placed on a nutrient-poor diet, microbial stimulation of this growth factor partially ameliorated growth deficits. Not all strains of bacteria could promote growth in this manner — different strains of one species, *Lactobacillus plantarum*, had differing effects on growth. These data highlight the fact that each microbe interacts with its host differently, warning that the beneficial effects of bacteria found to promote growth in mice might not be translated to humans.

In the third paper, Charbonneau and colleagues provide evidence that cultivating specific strains of bacteria is not the only way to stimulate microbiota-dependent growth. The authors studied the breast milk of mothers who had a malnourished child, and found that their milk tended to have lower amounts of specialized sugars called milk oligosaccharides. These sugars are of interest because they are abundant in human milk, but not in cow's milk. To investigate whether the sugars promoted microbiota-dependent growth, the researchers generated growth-stunted mice using a similar strategy to that of Blanton and colleagues. Adding a specialized 'sialylated' milk oligosaccharide to the growth-stunted animals' diet increased weight gain considerably, whereas treatment with other sugar types, or treatment of mice with an uncolonized gut, did not.

Unlike the other studies, Charbonneau *et al.* could not attribute the beneficial effects of milk oligosaccharides to a specific microorganism. Addition of the sugars did not dramatically alter the abundance of any one organism, although it did increase transcription of microbiotic genes involved in starch metabolism and other metabolic processes. The authors concluded that the resulting growth was likely to be a consequence of numerous complex interactions within the entire community. Additional studies will be required to delineate these interactions.

Supplementation of an infant's diet with milk oligosaccharides might promote healthy growth in children who do not receive the sugars through their mother's milk. However, manufacture of these oligosaccharides has proved difficult, which may be a barrier to widespread use.

It is becoming increasingly apparent that our diet, gut microbiota and health are inextricably linked. We must be conscious that, when we make dietary interventions, we affect the growth of trillions of bacteria. These three papers are a marked leap forward in our understanding of how the gut microbiota contributes to growth impairment in malnourished children, but by no means have they found a magic bullet for tackling growth stunting. Diet is just one of the many factors that govern growth in early life. Furthermore, because nutritional deficiencies can vary between communities, further studies should be performed on a population-by-population basis. Such research could optimize feeding regimens to take into account the beneficial effects of the microbiota.

References

1. Dewey KG, Adu-Afarwuah S. *Maternal Child Nutr.* 2008; 4:24–85.
2. Smith MI, et al. *Science.* 2013; 339:548–554. [PubMed: 23363771]
3. Blanton LV, et al. *Science.* 2016; 351:aad3311. [PubMed: 26912898]
4. Schwarzer M, et al. *Science.* 2016; 351:854–857. [PubMed: 26912894]
5. Charbonneau MR, et al. *Cell.* 2016; 164:859–871. [PubMed: 26898329]
6. Barker D. J. *Br. Med. J.* 1990; 301:1111.
7. David LA, et al. *Nature.* 2013; 505:559–563. [PubMed: 24336217]
8. Ma J, et al. *Nature Commun.* 2014; 5:3889. [PubMed: 24846660]
9. Schulz MD, et al. *Nature.* 2014; 514:508–512. [PubMed: 25174708]
10. Dewey KG. *J. Nutr.* 2001; 131:1879–1880. [PubMed: 11435501]

Figure 1. Help for a healthy gut

Three studies¹⁻³ analysed how changes in the bacteria that inhabit the gut (the gut microbiota) affect childhood growth. **a**, Juvenile mice whose guts are colonized by gut microbiota taken from healthy Malawian children experience robust weight gain, even if fed a nutrient-poor diet. This weight gain might be partially due to increased production of insulin-like growth factor protein, which is promoted by the presence of certain components of the microbiota. **b**, By contrast, mice harbouring microbiota from a child with impaired growth do not gain weight normally. **c**, By including two growth-promoting microbial species from the healthy

microbiota in the colonization step, or by supplementing the animals' diet with sugars called sialylated milk oligosaccharides, healthy weight gain can be restored.

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