MICROBIOLOGY

Fighting Obesity with Bacteria

Intestinal bacteria from lean humans can confer protection against fat gain in experimental mice.

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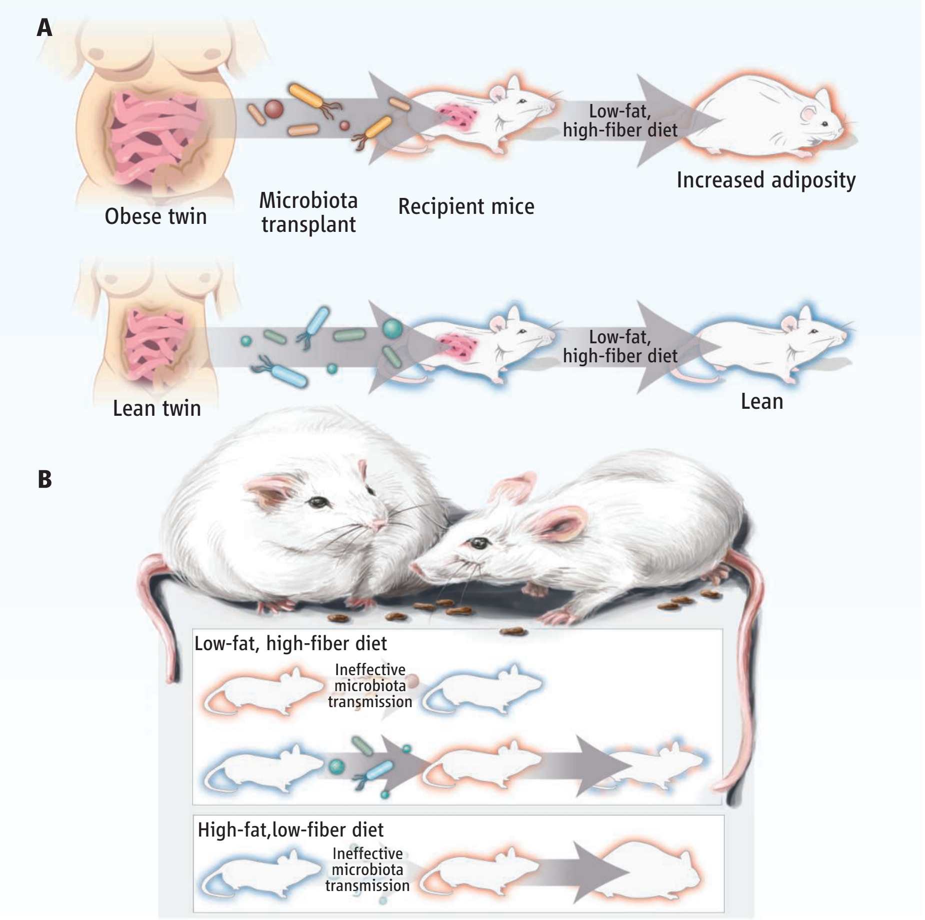
The human large intestine harbors a complex community of microorganisms (microbiota) that affect many aspects of our physiology and health (*1*). Numerous lines of evidence, particularly from rodent models, have suggested that the intestinal microbiota may play a role in the development of obesity. On page 1079 of this issue, Ridaura *et al*. (*2*) demonstrate that the microbiota from lean or obese humans induces similar phenotypes in mice and, more remarkably, that the microbiota from lean donors can invade and reduce adiposity gain in the obese-recipient mice if the mice are fed an appropriate diet.

Ridaura *et al*. recruited four human female twin pairs discordant for obesity and transferred the intestinal microbiota in fecal samples from each of them into the intestines of germ-free mice. Animals receiving a transplant from the obese (Ob) twin donors developed increased adiposity compared to those receiving transplants from lean (Ln) twin donors. Differences in mouse adiposity could also be reproduced after inoculation of germ-free mice with collections of cultured bacteria grown from twin-pair fecal samples. Cohousing of mice harboring cultured bacteria from an obese twin (Ob^{ch}) with mice harboring cultured bacteria from a lean twin (Ln^{ch}) prevented the development of increased adiposity in the Ob^{ch} mice. This occurred in tandem with successful colonization of Ob^{ch} intestines by bacteria from the Ln^{ch} mice. By contrast, Ob^{ch} microbes did not transmit to Ln^{ch} mice, and these animals remained lean. This indicated that transmissibility of intestinal microbes and adiposity phenotype were tightly linked.

Analysis of the bacterial communities showed that members of the Bacteroidetes phylum, particularly *Bacteroides* spp., could pass from the Ln^{ch} mice and colonize the Ob^{ch} mice, suggesting that these bacteria were largely responsible for protection against increased adiposity. However, cohousing of Ob^{ch} mice with lean mice inoculated with a relatively simple mix of just 39 defined bacterial strains, including many of the *Bacteroides* species that were previously correlated with reduced adiposity, did not reduce adiposity in the Ob^{ch} mice. This indicates that more complex bacterial interactions underlie protection against increased body mass and associated metabolic disturbance.

Ridaura *et al*. also identified diet as an important factor in the transmission of microbiota and associated host phenotype. Lean twin–derived bacterial strains effectively colonized and ameliorated excess adiposity in Ob^{ch} mice when the recipients were fed a low-fat, high-fiber diet. This was not the case when the mice were fed a diet that was high in saturated fat but low in fiber.

The findings support some emerging hypotheses regarding potential mechanisms by which the microbiota can affect host weight gain. One of the main activities of the intestinal microbiota is to break down and ferment dietary fibers into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. The host absorbs these acids, and humans obtain perhaps 5 to 10% of daily energy requirements from them (*3*). Ridaura *et al*. show that the microbiota in Ln mice produces greater amounts of SCFAs, particularly propionate and butyrate, and digests more of the plant fiber present in the mouse's



Please pass the microbiota. (**A**) Germ-free mice inoculated with microbiota from obese or lean human twins take on the microbiota characteristics of the donor. Those receiving the obese microbiota (red outline) had an increase in adiposity, whereas those receiving the lean microbiota (blue outline) remained lean. (**B**) If fed an appropriate diet, mice harboring the obese microbiota, when cohoused with mice harboring the lean microbiota, are invaded by the lean microbiota and do not develop increased adiposity (blue and red outline). By contrast, the obese microbiota does not effectively colonize mice harboring the lean microbiota, and these mice remain lean.

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Published by AAAS

diet than the microbiota of Ob mice. Thus, increased weight gain in Ob mice does not result from increased energy harvest. Rather, the finding supports previous studies showing that although SCFAs are a source of energy, they promote leanness by inhibiting fat accumulation in adipose tissue, raising energy expenditure, and enhancing production of hormones associated with feelings of satiety (*4–6*). Other putative mechanisms include a role for the microbiota in metabolizing bile acids, branched-chain amino acids, and acylcarnitines, which have all been linked to either insulin resistance or obesity in humans and mice.

A key question is the translatability of the findings to a human clinical context. *Bacteroides* species, correlated with reduced adiposity by Ridaura *et al.*, have repeatedly been implicated in protection against obesity in mice (*7*). However, evidence from human studies is mixed (*8*). Indeed, *Bacteroides*, and the propionate that they produce, can be more abundant in overweight and obese individuals than in lean counterparts (*9*). Furthermore, *Bacteroides* have been associated with diets high in animal protein and saturated fats (*10*) and are notably reduced in lean African individuals consuming diets high in fiber compared to Europeans consuming typical Western diets (*11*). Given these potential discrepancies, it will be important to verify in humans the activity of bacteria that are beneficial in mouse models.

Perhaps the most intriguing finding of Ridaura *et al*. is that microbial protection from increased adiposity is only possible against the backdrop of a suitable host diet. It may be that future microbiota-based therapies for an obese individual will require an alteration in diet to aid colonization by beneficial microbes. This offers a potentially synergistic approach, whereby reduced caloric intake and increased fiber consumption not only have a positive impact on energy balance but might also promote transplanted microbial communities that are associated with leanness.

Fecal transplants in humans have been used to beneficially alter the microbiota in a variety of ailments (*12*). Notably, a recent study showed that fecal transplants from lean individuals into obese counterparts improved insulin sensitivity in some obese recipients (*13*). The procedure is not risk free, however, with the potential for introducing pathogens to the recipient. The mouse model presented by Ridaura *et al*. is therefore timely, as it offers the potential to test human-derived bacterial strains, and accompanying dietary regimens, within a controlled mammalian host environment. The study is a step toward the ultimate goal of developing relatively simple mixtures of bacteria for testing as anti-obesity therapeutics.

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