Gut microbiome

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A high-protein diet prevents weight regain

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Sustained weight loss and weight maintenance are key challenges for the treatment of obesity. Here, the authors show that a high-protein diet following weight loss can protect against weight regain, through a process dependent on the gut microbiome.

Long-term sustained weight loss and weight maintenance — the holy grail of weight loss therapy — is difficult for individuals to attain, mainly because the body is unforgiving. It 'conspires' to retain fat mass by affecting appetite and thermogenesis in ways that are still poorly understood[1]. This has been exemplified by a previous study of the participants of the 'The Biggest Loser', a televised weight-loss competition[2], in which participants underwent body composition and resting metabolic rate assessments at baseline, the end of the competition (30 weeks) and at a 6-year follow-up. The results demonstrated an increase in appetite and changes in adaptive thermogenesis (that is, a lower resting metabolic rate) in all participants. At the six-year follow up, most participants had gained their weight back. Participants with weight regain at or above their pre-competition weight were now forced to diet just to maintain their baseline, pre-competition weight. Although these results might not be very encouraging, they do highlight the need for a better understanding of what drives or maintains these metabolic changes in response to weight loss, as such information could have a considerable impact on the fight against obesity.

In this issue of *Nature Metabolism*, Zhong et al. address this problem in a mouse model of obesity by investigating the role of post-weight-loss diet composition and the gut microbiome on weight regain and fat accumulation[3]. In response to short-term dietary restriction, mice always had increased body fat mass and weight gain that exceeded the weight of ad libitum-fed controls. This change could not be explained by increased food intake alone. In fact, refeeding after the short dietary restriction led to increased intestinal lipid absorption and free fatty acids by white adipose tissue (WAT), as well as increased fatty acid and triglyceride synthesis. Moreover, increased respiratory exchange rate indicated a decrease in total lipid oxidation and preservation of body fat mass.

A key observation the authors made was that refeeding with a high-protein diet instead blocked excessive fat accumulation after a short-term dietary restriction. This change corresponded with decreased intestinal lipid absorption, lipid anabolism and changes in respiratory exchange rate that were consistent with increased total lipid oxidatiton. Although mice placed on a high-protein diet consumed fewer calories, the authors performed a critical paired-feeding experiment, even administering the appropriate amount of food during the dark phase (that is, the eating period), to determine whether these physiological changes can be solely explained by the caloric intake differences. However, the mice on a high-protein diet still had decreased fat accumulation and improved fatty-acid utilization as compared to pair-fed controls.

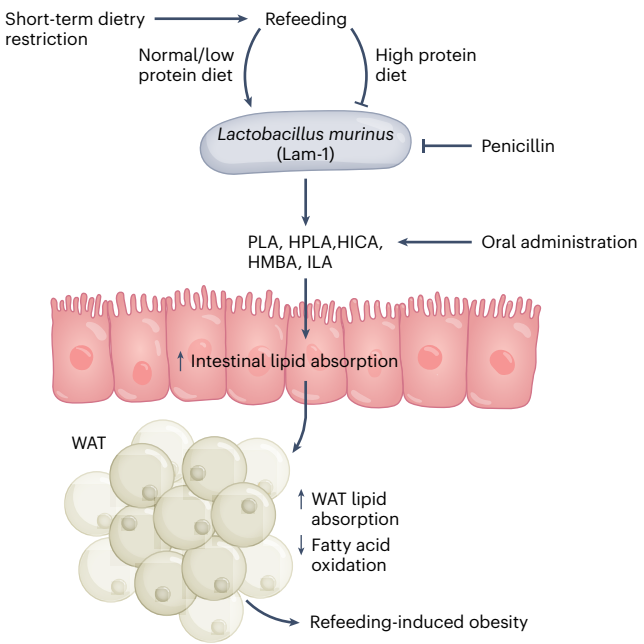

Fig. 1 | A high-protein diet protects from weight regain through changes in the gut microbiome. Feeding mice with a high-protein diet after caloric restriction prevents excessive body fat accumulation in mice. This occurs by the suppression of the gut bacteria *L. murinus* (Lam-1) and its purported metabolites DL-3-phenyllactic acid (PLA), 4-hydroxyphenyllactic acid (HPLA), 2-hydroxyisocaproic acid (HICA), 2-hydroxy-3-methylbutyric acid (HMBA) and 1-indole-lactic acid (ILA). Lam-1 and its purported metabolites lead to increased intestinal and white adipose tissue (WAT) lipid absorption and decreased fatty acid oxidation, all of which triggers refeeding-induced obesity after a short-term dietary intervention.

To understand why a high-protein diet had protective effects, the authors looked at the gut microbiome. A variety of microbiome analytics demonstrated that refeeding after a short-term dietary restriction led to increase in *Lactobacillus* species in the caecal microbiome. Cultures specific to *Lactobacillus* spp. of the caecal content led to the isolation of a *Lactobacillus murinus* species, which the authors named Lam-1 (Fig. 1). Lam-1 was markedly increased in all refeeding scenarios but was suppressed when the mice were refed with a high-protein diet. Antibiotics highly specific to Lam-1 suppressed refeeding-induced fat accumulation after a short-term dietary intervention. Remarkably, gnotobiotic mice treated with Lam-1 alone or as part of a reduced community, as well as specific-pathogen-free mice, had increased intestinal lipid absorption and fatty acid uptake in white adipose tissue. A potential mechanism of Lam-1-induced intestinal increase in fatty acid absorption involves five specific metabolites: DL-3-phenyllactic acid (PLA), 4-hydroxyphenyllactic acid (HPLA), 2-hydroxyisocaproic acid (HICA), 2-hydroxy-3-methylbutyric acid (HMBA) and 1-indole-lactic

acid (ILA). Administration of these five metabolites together (but not alone) increased intestinal fat absorption without altering food intake, upregulated fatty-acid uptake in white adipose tissue and increased the body fat percentage of the mice.

The immediate implication of the study is that macronutrient composition may be more important than previously thought. Dietary weight-loss studies have not found any specific dietary macronutrient profile to be particularly advantageous for the treatment of obesity, indicating that compliance with any low-calorie diet to be the best predictor of weight loss[4–6]. Thus, clinicians advise individuals to pick a diet that they can adhere to regularly. If the results of this study are translatable to humans, people seeking sustained weight-loss outcomes may need to transition to a high-protein diet if they notice that they are stagnating or starting to gain weight. More long-term implications of the study are related to determining whether a *Lactobacillus* species such as Lam-1 or its five offending metabolites can explain weight regain and retained body fat mass in humans. Although there is a reluctance to using antibiotics to treat obesity (because it could promote multi-antibiotic-resistance strains), a better understanding of how a high-protein diet suppresses Lam-1 – perhaps by promoting a competitor or eliminating its luminal niche – could help to promote additional therapeutic agents.

As with all studies using a mouse model to understand metabolic disease, there are limitations to extrapolating these results to humans. First, the length of dietary restriction was short, at three days for most interventions. Thus, whether this study reveals a physiological phenomenon that is applicable to individuals who want to have sustained weight loss is not immediately clear. In addition, unlike humans, mice did not have a change in their resting metabolic rate with refeeding-induced weight regain, perhaps suggesting that that the weight loss portion of the experiments was not long enough or that the adaptive thermogenesis in response to weight loss observed in humans does not occur in mice. Importantly, the host caecal environment has cyclical fluctuations in the composition of the microbiome and luminal metabolites[7,8], yet it is not clear whether Lam-1 and its metabolites are present at all time points or affect host metabolism in specific times.

These caveats do not detract from this fascinating paper that generates many important hypotheses that warrant further investigation. It will be important to determine whether these findings focused on refeeding after short-term dietary restriction are applicable to the inability to maintain sustained weight loss in humans. Determining whether a high-protein diet has similar positive outcomes in individuals who seek to keep weight off will be the most clinically impactful next experiment. As the study demonstrates that a single bacterial strain can contribute to changes in lipid homeostasis and body fat mass, do other bacteria with similar properties exist, particularly in humans? With the use of novel tools for functionally manipulating the gut microbiome[9], investigators could determine whether the production of the Lam-1-associated metabolites (that is, PLA, HPLA, HICA, HMBA and ILA) might affect host metabolic processes. Importantly, why would host lipid homeostasis be affected by the presence or absence of a microorganism or its metabolites? What is the environmental signal that the host is detecting through the fluctuation of this microorganism and its metabolites, and why is the appropriate response by the host an increase in lipid absorption and retention? Addressing these questions could help to change our fundamental understanding of microbe–host interaction and host metabolic homeostasis, and at the same time will get us closer to finding effective strategies for body weight maintenance following weight loss.

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Competing interests

A.Z. is a cofounder of, and equity holder in, Endure Biotherapeutics.