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IMMUNOMETABOLISM

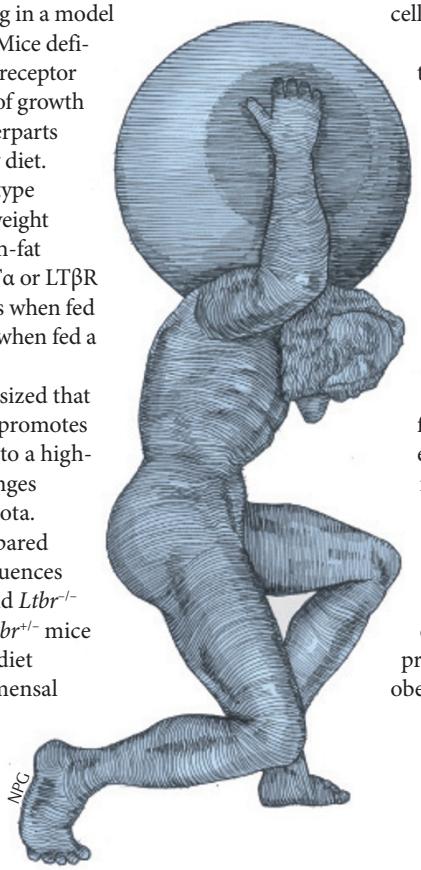
Immune decisions weigh heavily on us

Obesity is associated with changes in the composition of the intestinal microbiota, but it remains unclear how dietary changes promote alterations in the microbiota. Reporting in *Nature Immunology*, Upadhyay *et al.* show that lymphotoxin-driven immune mechanisms reshape the intestinal microbiota in mice fed a high-fat diet. Notably, these modifications in the microbiota appear to promote excessive weight gain and obesity.

As previous studies have linked the lymphotoxin-α (LTα) gene locus to obesity and type 2 diabetes, Upadhyay *et al.* examined the effects of lymphotoxin signalling in a model of diet-induced obesity. Mice deficient in either LTα or its receptor LTβR had similar levels of growth to their wild-type counterparts when fed a normal chow diet. However, whereas wild-type mice showed excessive weight gain in response to a high-fat diet, mice deficient in LTα or LTβR had similar body weights when fed a normal chow diet and when fed a high-fat diet.

The authors hypothesized that lymphotoxin signalling promotes weight gain in response to a high-fat diet by inducing changes in the intestinal microbiota. Indeed, when they compared 16S ribosomal RNA sequences in the stools of $Ltbr^{+/-}$ and $Ltbr^{-/-}$ mice, they found that $Ltbr^{+/-}$ mice that were fed a high-fat diet showed decreased commensal community diversity, whereas $Ltbr^{-/-}$ mice maintained a diverse microbial community regardless of whether they were fed normal chow or a high-fat diet. These findings are in keeping with other data that suggest the 'obese microbiome' of humans is characterized by a loss of commensal diversity. Other notable features of the microbiota in $Ltbr^{-/-}$ mice included under-representation of the Erysipelotrichi class (a class that has previously been reported to be over-represented in obesity) and a moderate overgrowth of segmented filamentous bacteria (SFB), which are known to promote T helper 17 cell development in mice.

> “lymphotoxin signalling promotes weight gain in response to a high-fat diet”



Further support for the idea that alterations in the microbiota account for the resistance of lymphotoxin-deficient mice to diet-induced obesity came from experiments in which the intestinal microflora was manipulated. First, the authors showed that gnotobiotic wild-type mice that were maintained on a high-fat diet and gavaged with caecal contents from either $Ltbr^{+/-}$ or $Ltbr^{-/-}$ mice fed a high-fat diet gained more weight when exposed to the caecal contents from the $Ltbr^{+/-}$ mice. Second, when fed a high-fat diet and co-housed with $Ltbr^{+/-}$ mice (which leads to the sharing of microbial communities), $Ltbr^{-/-}$ mice experienced excessive weight gain, presumably as a result of acquiring obesity-inducing microorganisms. The finding that an obese phenotype can be transmissible raises interesting questions concerning how genetic and environmental factors contribute to obesity.

Upadhyay *et al.* found that in mice fed a high-fat diet, lymphotoxin signalling regulates the intestinal microbiota by inducing the upregulation of interleukin-22 (IL-22), IL-23 and antimicrobial peptides in the intestine. Notably, treatment with IL-22 in $Ltbr^{-/-}$ mice maintained on a high-fat diet reduced the abundance of SFB in their stools and promoted weight gain. The authors suggest that RORγt^{+} innate lymphoid cells in the intestine — which are known to produce IL-22 in a lymphotoxin-dependent manner during bacterial infection — may also generate IL-22 in response to a high-fat diet. In support of this idea, they showed that mice deficient in RORγt are also resistant to diet-induced obesity.

It has been controversial whether the diet can directly modify microbial communities independently of the host genotype. This study suggests that diet-induced changes in the commensal microbiota are not simply caused by altered nutritional qualities in the diet, but are also heavily influenced by the genetic make-up of the host.

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ORIGINAL RESEARCH PAPER Upadhyay, V. *et al.* Lymphotoxin regulates commensal responses to enable diet-induced obesity. *Nature Immunol.* 26 Aug 2012 (doi:10.1038/ni.2403)