RESEARCH ARTICLE SUMMARY

IMMUNOMETABOLISM

T cell–mediated regulation of the microbiota protects against obesity

Charisse Petersen, Rickesha Bell, Kendra A. Klag, Soh-Hyun Lee, Raymond Soto, Arevik Ghazaryan, Kaitlin Buhrke, H. Atakan Ekiz, Kyla S. Ost, Sihem Boudina, Ryan M. O'Connell, James E. Cox, Claudio J. Villanueva, W. Zac Stephens*, June L. Round*

INTRODUCTION: The gut microbial metagenome encodes a diverse array of functions that complement host genes involved in metabolism. In support of this idea, the gut microbiomes of obese individuals are characterized by reduced species richness and metabolic capacity. Thus, maintenance of the diversity and collective functional capacity of the microbiota is likely vital to the promotion of optimal metabolic health throughout life. One mechanism to maintain a diverse microbiota is through T cell–dependent immunoglobulin A (IgA) production. However, the relationship between IgA and the development of obesity remains unknown. Although studies of obesity and metabolic syndrome have highlighted a direct role for inflammation, overweight individuals also evince some diminished immune responses, such as reduced levels of mucosal IgA. Thus, microbiota maintenance through IgA may affect functions within both the microbiome and, subsequently, the host metabolism.

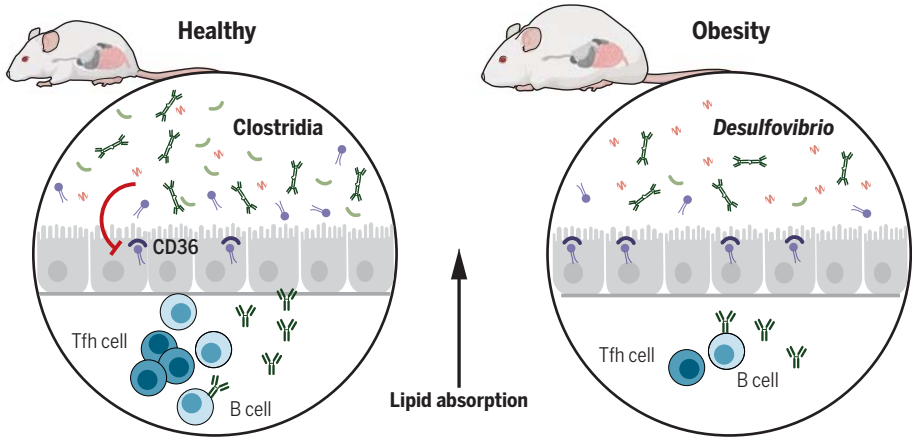
RATIONALE: Young mice whose T cells have disabled Myd88 signaling (T-*Myd88*$^{-/-}$ mice) exhibit reduced follicular T cell responses and defective IgA targeting of their gut bacteria that altered the composition of the microbiota. As these knockout mice aged, they developed obesity and insulin resistance despite eating a normal mouse diet. We identified that the development of age-dependent obesity was reliant on the microbiota. On the basis of the similarities of the metabolic phenotype with human disease, we reasoned that this model would provide a platform to understand how the interaction between the host immune system and the microbiota influences metabolic disease.

RESULTS: T-*Myd88*$^{-/-}$ mice experienced noticeable weight gain between 5 and 6 months of age. Like in humans, weight gain was accompanied by fatty liver disease, inflammatory adipose tissue, and insulin resistance that could be accelerated by placing mice on a high-fat diet. The depletion of the microbiota through antibiotic treatment rescued this weight gain. The cohousing of T-*Myd88*$^{-/-}$ mice transferred the weight gain to wild-type mice, suggesting that the composition of the microbiota was driving the obesogenic phenotype. The major feature of the microbiota formed within T-*Myd88*$^{-/-}$ mice was a reduction in Clostridia colonization. Metatranscriptomic analysis further revealed the reduced functional capacity of several Clostridia species. Cohousing experiments demonstrated that outgrowth of the bacterial genus *Desulfovibrio* could lead to decreased colonization of Clostridia. The replacement of Clostridia into knockout animals rescued weight gain. The composition of obesogenic microbiota was driven by defective T follicular helper cell (T_{FH} cell) responses and inappropriate IgA targeting of Clostridia. The colonization of germ-free mice with the protective Clostridia resulted in leanness, which was opposed by the addition of *Desulfovibrio*. T-*Myd88*$^{-/-}$ mice absorbed more long-chain fatty acids (LCFAs), suggesting that the microbiota regulates lipid absorption. Clostridia-colonized germ-free animals down-regulated CD36, a receptor that mediates the binding to and uptake of LCFAs, whereas the addition of *Desulfovibrio* up-regulated the expression of this receptor. Last, incubation of cell-free supernatant isolated from Clostridia with intestinal epithelial cells was able to down-regulate the expression of CD36 in culture, suggesting that a secreted bacterial molecule regulates host gene expression.

ON OUR WEBSITE

Read the full article at http://dx.doi.org/10.1126/science.aat9351

CONCLUSION: Reduced T cell responses within the guts of T-*Myd88*$^{-/-}$ mice results in loss of Clostridia colonization and function, as well as the outgrowth of *Desulfovibrio*, which collectively leads to metabolic disease. We observed similar changes to the microbiota in individuals with metabolic syndrome and obesity. Our findings reveal opposing microbial regulators of CD36 expression and fat accumulation within the gut. The mechanism by which Clostridia and *Desulfovibrio* alter CD36 remains unknown, and future studies will be needed to elucidate this interaction. Much work in the area of immunity in metabolic disease has been focused on the role of chronic inflammation. However, these studies highlight the importance of a robust immune response within the gastrointestinal tract to prevent metabolic disease, which remains unexplored in humans. Future investigations should be focused on studying the interaction between gut immunity and the microbiota in individuals with metabolic disease as these studies could uncover additional biomarkers and therapeutic interventions. ■



Innate immune signaling within T cells regulates the microbiota to protect from obesity. T_{FH} cells regulate IgA production, which appropriately sculpts the microbiota. Loss of this instruction leads to expansion of *Desulfovibrio* that negatively affects the colonization of beneficial Clostridia. Clostridia function to temper expression of CD36 and lipid absorption. Thus, a reduction in beneficial Clostridia can lead to obesity.

The list of author affiliations is available in the full article online.
*Corresponding author. Email: zac.stephens@path.utah.edu (W.Z.S.); june.round@path.utah.edu (J.L.R.)
Cite this article as C. Petersen *et al.*, *Science* **365**, eaat9351 (2019). DOI: 10.1126/science.aat9351