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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Microbial Signals Link Westernized Diet to Metabolic Inflammation: More Evidence to Resolve Controversies

Host immune responses and the gut microbiota are tightly connected and collectively contribute to the regulation of metabolic homeostasis. Disturbance of this interplay is implicated in the development of the metabolic syndrome, a multifactorial condition characterized by insulin resistance, dysglycemia, hypercholesterolemia, hypertension, and hepatic steatosis. The underlying pathogenic mechanisms are complex and not completely understood; however, obesity or visceral adiposity stands as a primary trigger, driven by complex cellular mechanisms of de novo lipogenesis and insulin resistance. A main risk factor for obesity-associated metabolic syndrome is chronic consumption of low-fiber, high-fat Western-style diet (WSD). WSD is known to modulate host immunity to promote inflammatory processes in a variety of organs including gut, liver, and fat tissue. Macrophage polarization toward M1 phenotypes seems to play an important role in developing systemic inflammation. In addition, gut microbiota composition changes rapidly in response to dietary modification, and shifts in bacterial composition and function, often referred to as dysbiosis, have been described in patients with metabolic disease, suggesting that the influx of detrimental bacterial products or changes in bacterial metabolism promote chronic "low-grade" tissue inflammation. A decade ago, the scientific community started to unravel the complex role of gut microbial triggers in promoting obesity-associated metabolic disorders.[1]

In this issue, Tran et al[2] focus on studying the contribution of the gut microbiota and the downstream inflammatory signaling pathways in WSD-induced adipose tissue inflammation and metabolic disturbances. To confirm the relevance of gut bacteria to host phenotype, the authors used 3 approaches to modulate the microbiota composition, namely germ-free mice, conventional mice treated with antibiotics, and ex–germ-free mice colonized with the previously characterized 8-member minimal consortium, altered Schaedler Flora (ASF), known to mimic normal gut microbiota physiology. Interestingly, absence of microbiota resulted in the amelioration of metabolic disturbances such as dysglycemia and elevated serum cholesterol levels, as well as inflammation. In contrast to the first observations from Gordon and colleagues in germ-free mice demonstrating that the development of obesity requires the presence of gut bacteria,[3,4] Gewirtz and colleagues now confirmed recent studies that the absence of complex microbial communities did not reduce WSD-induced weight gain or adiposity.[5] However, microbiota eradication reduced innate immune cell infiltrates and pro-inflammatory cytokine expression in antibiotic-treated and germ-free mice. Furthermore, ASF and germ-free mice showed reduced levels of adipose tissue macrophages. With this put together, the authors provide solid evidence that WSD-induced adipose inflammation requires the presence of complex gut microbiota. To address the transmissibility of the inflammatory phenotype associated with the WSD-conditioned microbiota, the authors compared ex–germ-free mice transplanted with WSD-conditioned or chow diet–conditioned gut microbiota and subsequently maintained on chow diet. The transfer of WSD-conditioned microbiota did not recapitulate the phenotype in gnotobiotic mice, which could be explained by the insufficiency of microbial dysbiosis in driving the phenotype, or that WSD-dysbiotic microbial communities rapidly change when colonized mice are exposed to chow diet. To test a postulation for an alternative mechanism of WSD-induced metabolic disturbances, the authors studied influence of WSD in MyD88 knockout mice, where global toll-like receptor (TLR) signaling is dysfunctional. Interestingly, loss of TLR signaling protected the mice from WSD-induced inflammation, confirming the relevance of microbiota and molecules or products thereof in activating innate immune signaling pathways and in driving inflammation.

In light of these findings and the question of how microbiome-diet interactions impact host metabolism, the contribution of microbial signals is inevitable, but the cellular and mechanistic integration of these signals remains controversial. Although Tran et al supported the hypothesis that gut-related microbial signals activate peripheral tissue inflammation, the leaky gut syndrome with impaired epithelial barrier function remains unresolved in this study. Translocation of structural components of the gut microbiota, such as lipopolysaccharide, the major component of cell wall membrane in gram-negative bacteria, can activate innate immune signaling cascades leading to macrophage accumulation in adipose tissue and inflammation. This phenomenon is frequently referred to as systemic endotoxemia; however, the mechanisms of lipopolysaccharide translocation and distribution along the gut-liver axis leading to clinically relevant blood endotoxin levels are still not completely understood.[6]) Furthermore, microbiome-diet interactions lead to the generation of bioactive secondary metabolites such as short chain fatty acids or secondary bile acids, which are known to modulate gut barrier integrity and metabolic homeostasis.[7,8] Finally, the composition of energy dense foods is diverse, potentially exerting different metabolic responses in the host. For example, germ-free mice are resistant to diet-induced obesity when fed a cholesterol-rich, lard-based high-fat diet, whereas germ-free mice on a palm oil–based, high-fat diet developed obesity,

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suggesting microbiota independent mechanisms on energy expenditure and subsequent weight gain.[9] In addition, lard-based and palm oil–based fats have different effects on gut microbiota composition. Thus, obesity and obesity-associated metabolic dysfunction depend on complex interactions of diet, the intestinal milieu harboring a pleiotropy of different microbes and metabolites, as well as host functions, such as gut barrier regulation and immune activation locally as well as in peripheral organs. The relative contribution of these different mechanisms is still not clear and remains to be elucidated.

In summary, the work by Tran et al is a valuable addition to the currently conflicting reports on microbiome and metabolic disorders. Using different approaches to ablate gut microbiota improved the resolution of the required community complexity and proved that gut microbiome contributes to disease manifestation. Furthermore, the loss of TLR signaling proved that WSD-induced adiposity and inflammation required the interaction of gut microbiome with the dietary components that trigger downstream signaling. This work adds another piece to the puzzle and in the long run may help provide a deeper mechanistic understanding of gut microbiota functions and the modulatory activities of their bioactive metabolites. Ultimately, this will enhance our conception of microbiome-driven pathologies and suggest new approaches for treatment of patients with metabolic diseases.

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References

1. Cani PD. Microbiota and metabolites in metabolic diseases. Nat Rev Endocrinol 2019;15:69–70. Available from: https://doi.org/10.1038/s41574-018-0143-9.
2. Tran H, Bretin A, Adeshirlarijaney A, Yeoh BS, Vijay-Kumar M, Zou J, Denning TL, Chassaing B, Gewirtz AT. "Western diet"-induced adipose inflammation requires a complex gut microbiota. Cell Mol Gastroenterol Hepatol 2020;9:
3. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. PNAS 2004;101:15718–15723.
4. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 2013;341:1241214.
5. Rabot S, Membrez M, Blancher F, Berger B, Moine D, Krause L, Bibiloni R, Bruneau A, Gérard P, Siddharth J, Lauber CL, Chou CJ. High fat diet drives obesity regardless the composition of gut microbiota in mice. Sci Rep 2016;6:32484, Available from: https://doi.org/10.1038/srep32484.
6. Guerville M, Boudry G. Gastrointestinal and hepatic mechanisms limiting entry and dissemination of lipopolysaccharide into the systemic circulation. Am J Physiol Liver Physiol 2016;311:G1–G15, Available from: https://doi.org/10.1152/ajpgi.00098.2016.
7. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165:1332–1345. Available from: http://www.sciencedirect.com/science/article/pii/S009286741630592X.
8. Wahlström A, Sayin SI, Marschall H-U, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab 2016;24:41–50. Available from: http://www.sciencedirect.com/science/article/pii/S1550413116302236.
9. Kübeck R, Bonet-Ripoll C, Hoffmann C, Walker A, Müller VM, Schüppel VL, Lagkouvardos I, Scholz B, Engel KH, Daniel H, Schmitt-Kopplin P, Haller D, Clavel T, Klingenspor M. Dietary fat and gut microbiota interactions determine diet-induced obesity in mice. Mol Metab 2016;5:1162–1174. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27900259.

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Conflicts of interest
The authors disclose no conflicts.

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