EDITORIAL

A Low FUT(2) Diet For a High-Fat World: Connecting Intestinal Fucosylation With Western Diet–Driven Liver Disease

With the rise of the high-fat and sugar “Western diet,” many countries face a growing epidemic of obesity and its related comorbidities. Outside of extreme dietary changes in society, identifying and targeting genetic pathways that can improve metabolic function in the context of Western diet could help to reduce comorbidities. Metabolic disease is complex, involving the interaction of multiple organ systems and the gut microbiome. As a result, it is often difficult to determine the mechanism by which genetic modulators of metabolic disease function, making treatments difficult to establish.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhou et al. describe the effects of a specific form of glycosylation, α1-2-fucosylation, on obesity and steatohepatitis in the context of Western diet. α1-2-fucosylation occurs at high levels in the intestinal epithelium and requires a functional copy of Galactoside 2-alpha-L-fucosyltransferase 2 (Fut2). The authors found that wild-type mice exposed to Western diet exhibited decreased α1-2-fucosylation of proteins and other substrates in the intestinal epithelium. In contrast, Fut2 mutants on a Western diet gained less weight and had elevated energy expenditure, along with improved triglyceride and cholesterol levels, insulin sensitivity, and hepatic steatosis. These findings suggest that downregulation of α1-2-fucosylation, in the context of Western diet, could be a protective mechanism against metabolic dysregulation.

Strikingly, the protective effect of Fut2 loss is transmissible to cohoused wild-type mice, implicating the microbiome as a major driver of the observed metabolic effects. This finding is consistent with a known role of α1-2-fucosylation in regulating the microbiome. Analysis of circulating metabolites and the microbiome uncovered altered bile acid metabolism as a potential protective mechanism. Prolonged exposure to Western diet increased circulating metabolites and the microbiome uncovered altered bile acid metabolism in a functional manner. Moreover, although this study focused on the effects of intestinal α1-2-fucosylation, the lack of tissue-specific Fut2 mutant models in the literature complicates the interpretation of this and other studies. Further mechanistic understanding of the role of FUT2 in response to Western diet would be strengthened by future use of conditional alleles to drive intestinal epithelium-specific Fut2 loss.

In terms of translational relevance, several FUT2 alleles in humans have been well-characterized. As a result, a global FUT2 null mutation, as the one described, may be more representative of patients. Altered FUT2 function in humans is common, with nearly 20% of Whites lacking full FUT2 function. These patients, termed nonsecretors, display alterations in the gut microbiome and increased risk of obesity and its related comorbidities. Moreover, a previous study by this group found that Fut2 mutant mice showed increased sensitivity to ethanol-induced liver disease. Clearly, more research is required before inhibitors of fucosylation can be evaluated as therapeutics on fatty liver disease.

*RACHEL R. STINE, PHD*
University of Pennsylvania
Philadelphia, Pennsylvania

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Correspondence
Address correspondence to: Rachel R. Stine, PhD, University of Pennsylvania, Smilow Center for Translational Research, 3400 Civic Center Boulevard, 12-180, Philadelphia, Pennsylvania 19104. e-mail: stiner@pennmedicine.upenn.edu.

Conflicts of interest
The author discloses no conflicts.

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