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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.[1] 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[2] 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.[3] Analysis of circulating metabolites and the microbiome uncovered altered bile acid metabolism as a potential protective mechanism. Prolonged exposure to Western diet increased the synthesis of primary bile acids from cholesterol in the liver, which is mediated by Cholesterol 7 alpha-hydroxylase (CYP7A1). Increased bile acids are postulated to contribute to diet-induced liver damage.[4] In *Fut2* mutants, the size of the bile acid pool was significantly reduced, likely caused by a combination of reduced production and increased excretion. Compared with wild-type mice, Western-diet-fed *Fut2* mutants displayed reduced expression of *Cyp7a1* in the liver and decreased primary bile acid levels in plasma. Additionally, the microbiome of *Fut2* mutants contained higher levels of the gene encoding *hsdh*, which converts primary bile acids to secondary bile acids. The authors speculate that the induction of *hsdh* accounts for increased bile acid levels in the feces of *Fut2* mutants. Importantly, the protective effect in *Fut2* mutants was reversed with either antibiotic treatment or supplementation with 2'-Fucosyllactose, a product of FUT2, providing further evidence for the contribution of the gut microbiota.

Overall, this study provides an intriguing link between FUT2-driven α1-2-fucosylation and metabolic and liver disease in the context of Western diet. Although *Fut2* mutation in this context leads to physiological improvement, in other contexts, loss of α1-2-fucosylation is deleterious. For example, in mice fed a normal chow diet, *Fut2* mutation leads to liver disease in a subset of mice,[5] and altered α1-2-fucosylation status affects the microbiome makeup in a diet-dependent manner.[3] 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 several intestinal diseases including Crohn's disease, ulcerative colitis, and inflammatory bowel disease.[6,7] *FUT2* polymorphisms in nursing mothers can also lead to disruption of the developing microbiome in infants, because 2′-fucosyllactose is a major oligosaccharide found in breastmilk.[8] In adults, 2′-fucosyllactose supplementation is showing promise in alleviating symptoms of several *Fut2*-linked disorders. This study is unique in suggesting that *Fut2* loss could also confer protective effects under certain conditions. Moreover, a previous study by this group found that *Fut2* mutant mice showed increased sensitivity to ethanol-induced liver disease.[9] Clearly, more research is required before inhibitors of fucosylation can be evaluated as therapeutics on fatty liver disease.

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Conflicts of interest
The author discloses no conflicts.


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