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Ceramide Salvage, Gut Mucosal IgA Signaling, and Diet-Induced NASH

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Nonalcoholic fatty liver disease (NAFLD) may arise from genetic and/or environmental factors that modulate enterohepatic signaling through gut-derived enterokines, cytokines, bile acids, and microbial products (including sphingolipids) that in turn regulate hepatic metabolic pathways.[1] Alterations within the enterohepatic axis may induce multiple parallel hits and promote NAFLD progression to nonalcoholic steatohepatitis (NASH), for example, by impairing immunologic tolerance to lipid droplet accumulation.[2]

Among those enterohepatic signaling mediators are bioactive sphingolipids, which include ceramides, sphingosine, and sphingosine-1-phosphate. All of these may be generated by multiple pathways, such as de novo synthesis, hydrolytic conversion (mediated by ceramidases, of which there are multiple family members), and a salvage pathway involving lysosomal sphingosine conversion into ceramides[3]—a step requiring monounsaturated fatty acid (MUFA). Salvage of dietary ceramides requires hydrolysis to sphingosine at the small intestinal brush border, enzymatically mediated by a specific neutral ceramidase encoded by N-acylsphingosine amidohydrolase 2 (*Asah2*). Germline deletion of *Asah2* eliminated degradation of dietary sphingolipids with reduced levels of metabolites throughout the intestinal tract.[4] Recent work has emphasized the role of altered sphingolipid metabolism in the adaptive response to diet-induced NAFLD and NASH, linking metabolomic biomarkers (including choline metabolites) in mice and subsets of patients with NASH,[5] suggesting that altered intestinal ceramide salvage in $Asah2^{-/-}$ mice might offer important new insights into the progression of experimental NAFLD.

In this issue of HEPATOLOGY, Gu et al. explore the role of altered intestinal ceramide salvage in $Asah2^{-/-}$ mice using a combination of dietary models of NAFLD/NASH. Among the key findings, they show that $Asah2^{-/-}$ mice exhibit decreased inflammation and fibrosis with either prolonged high-fat feeding (up to 14 months) or shorter periods of a high-sucrose, high-fat diet. They found that total hepatic triglyceride content was no different by genotype,

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although cholesterol ester content was reduced in *Asah2*$^{-/-}$ mice, and, perhaps surprisingly, there was no change in the overall abundance of hepatic ceramide or sphingosine-1-phosphate. On the other hand, hepatic choline content increased and intestinal sphingosine content decreased in *Asah2*$^{-/-}$ mice, as expected.[4] A deeper dive into the lipidomic profile of those mice revealed alterations in MUFA across lipid species, including cholesterol ester, triglycerides, and phospholipids and, in particular, decreased abundance of 16:1 and 18:1 fatty acids. In exploring the underlying mechanisms for both the protection against NASH and the shift in fatty acid distribution with decreased MUFA, the authors then examined the role of stearoyl-CoA desaturase1 (SCD1), a key metabolic regulator for de novo MUFA generation and an important metabolic control point with regard to obesity, insulin resistance, and NAFLD.[6]

Gu et al. report that *Asah2*$^{-/-}$ mice exhibit up to 900-fold reductions in hepatic SCD1 expression when fed a high-fat diet for 14 months and likewise demonstrated reduced SCD1 expression in the small intestine. They demonstrate developmental regulation of SCD1 expression with progressive suppression of hepatic SCD1 observed with age in *Asah2*$^{-/-}$ mice, along with a parallel change in MUFA content of lipid species. Those developmental changes raised the possibility that altered microbial taxa may contribute to some of the adaptive changes noted because antibiotic-treated wild-type mice exhibited both decreased SCD1 expression and a parallel reduction in hepatic 16:1 and 18:1 fatty acid content. To explore this connection further, the authors then demonstrated that lamina propria B cells from *Asah2*$^{-/-}$ mice were enriched in immunoglobulin M (IgM)$^{+}$ B220^{+} populations and demonstrated altered immunoglobulin A (IgA) secretion and increased IgA-associated bacteria. Transfer of those IgA-bound bacteria from *Asah2*$^{-/-}$ mice (or wild-type controls) into germ-free recipients resulted in a transmissible phenotype with reduced SCD1 expression and reduced abundance of hepatic 16:1 and 18:1 fatty acids. Germ-free mice colonized with IgA-bound bacteria from *Asah2*$^{-/-}$ mice also exhibited enrichment with Ruminococcaceae family, and IgA-bound bacteria from wild-type controls promoted enrichment with *Desulfovibrio.* The authors show that culture supernatants from *Desulfovibrio* increased SCD1 expression in primary hepatocytes, although the mediator(s) and pathways involved remain unknown. The demonstration of a transmissible liver phenotype resulting from altered intestinal lipid absorption is reminiscent of findings with impaired chylomicron assembly and secretion following intestine-specific deletion of microsomal triglyceride transfer protein.[7]

In a final series of experiments, the authors undertook studies to provide more mechanistic insights into the pathways linking altered SCD1 expression in *Asah2*$^{-/-}$ mice and mitigation of NAFLD/NASH. They focused on the Wnt-β-catenin pathway and found decreased expression of Wnt ligands (Wnt3a, Wnt7a, Wnt7b) and decreased nuclear β-catenin in *Asah2*$^{-/-}$ mice. They also show that direct administration of Wnt3a in wild-type primary hepatocytes increases neutral ceramidase expression and that adenoviral administration of SCD1 into *Asah2*$^{-/-}$ mice fed a high-fat, high-sucrose diet promoted a more fibrogenic and inflammatory injury phenotype. Studies have demonstrated a signaling network involving stellate cell and hepatocyte crosstalk that involves Scd2 (not Scd1) signaling by Wnt pathways along with MUFA-mediated, feed-forward, Wnt-dependent *Scd* transcription.[8] Those findings, together with the current work, suggest that the adaptive alterations in

hepatic MUFA distribution and SCD1 expression likely reflect multiple convergent signaling networks.

The findings from Gu et al. add to our understanding of enterohepatic lipid signaling and the role of altered microbial taxa in genetically altered mice with impaired lipid digestion. However, important questions remain. The *Asah2*$^{-/-}$ mice are germline null, and it is clear from the work in isolated hepatocytes from those mice that cell autonomous adaptations are a component of the phenotype. It is worth noting that germline *Scd1* and liver-specific *Scd1* knockout mice demonstrate distinct phenotypes with regard to hepatic lipid and glucose metabolism.[9] A related question is, why do high-fat-fed *Asah2*$^{-/-}$ mice gain less weight than wild-type controls, and what adaptive changes might be involved? The findings of altered microbial taxa and a transmissible phenotype raise questions regarding the mechanisms underlying the altered IgA response in the intestine of *Asah2*$^{-/-}$ mice. Finally, what are the signals involved in Ruminococcaceae and *Desulfovibrio* colonization and the related adaptive changes? An attractive unifying hypothesis (Fig. 1) is that the by-products of neutral ceramidase (sphingosine, potentially unique MUFAs) act at gut-associated immune organs to induce an innate immune response leading to plasma cell class switching away from IgA. The relative expansion of microbiota that would normally be targeted by IgA might in theory generate unknown secondary messenger(s) to activate hepatic SCD1, generate MUFA-rich lipid droplets, and signal through Wnt-β-catenin to promote fibrosis. The identification of neutral ceramidase in limiting steatohepatitis and fibrosis renders it a promising, novel target for NAFLD pharmacotherapy.

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Abbreviations:

Asah2	N-acylsphingosine amidohydrolase 2
IgA	immunoglobulin A
MUFA	monounsaturated fatty acid
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
Scd1	stearoyl CoA desaturase 1

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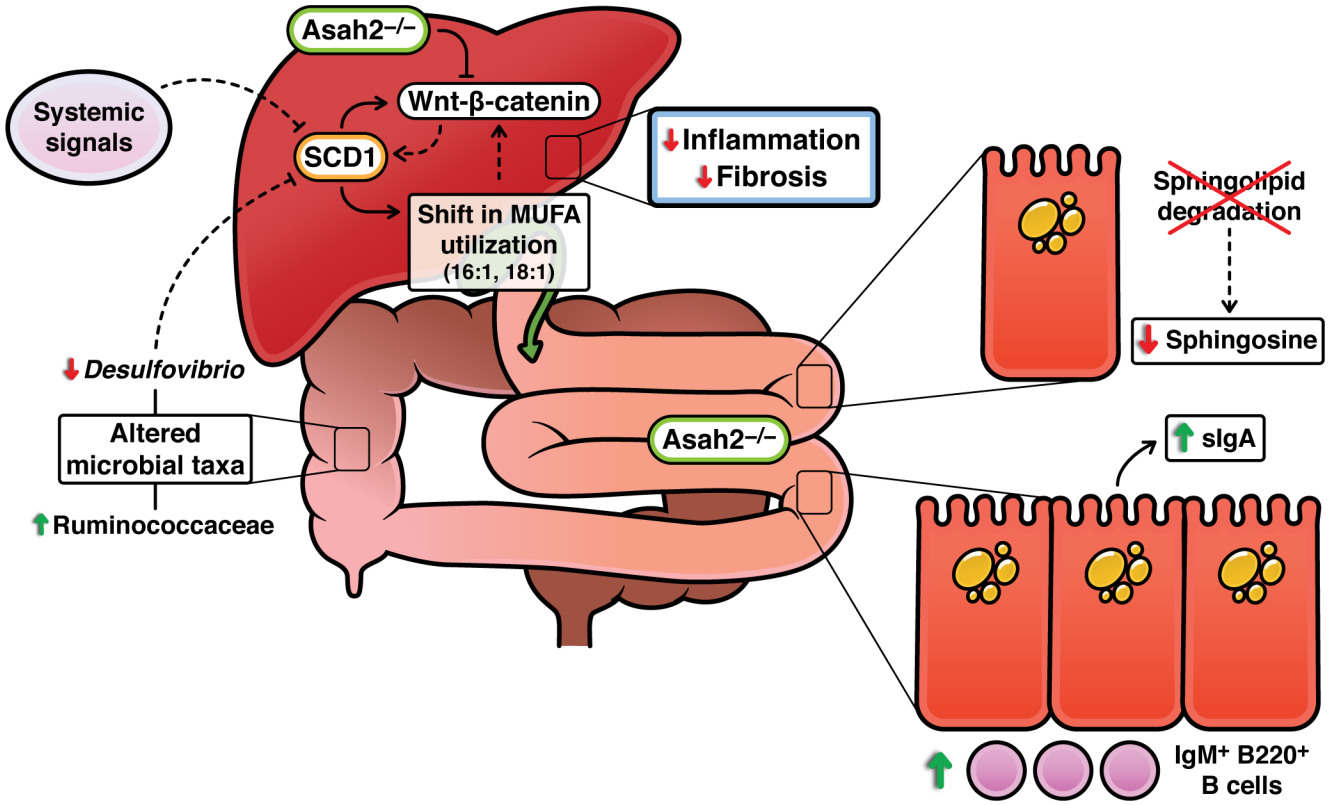

FIG. 1.

Germline deletion of neutral ceramidase (*Asah2* $^{-/-}$) mice mitigates inflammation and fibrosis in diet-induced NASH. The key pathways include impaired intestinal sphingolipid degradation and increased sIgA production with altered microbial taxa. Systemic (unknown) signals as well as microbial-derived products reduce up-regulation of hepatic SCD1 expression and cause a shift in MUFA utilization for complex lipid synthesis and lipid droplet formation. *Asah2* deletion modifies hepatocyte and potentially other cell-specific signaling events to mitigate feed-forward regulation of SCD1-Wnt-β catenin signaling. Abbreviations: *Asah2,* N-acylsphingosine amidohydrolase 2; IgA, immunoglobulin A; MUFA, monounsaturated fatty acid; NASH, nonalcoholic steatohepatitis; SCD1, stearoyl CoA desaturase 1; sIgA, secretory IgA.