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Commentary

Hepatic de novo lipogenesis is a major contributor to nonalcoholic fatty liver disease (NAFLD). In this issue of the *JCI*, Liu and Lin et al. identified Slug as an epigenetic regulator of lipogenesis. Their findings suggest that Slug is stabilized by insulin signaling, and that it promotes lipogenesis by recruiting the histone demethylase Lsd1 to the fatty acid synthase gene promoter. On the other hand, genetic deletion or acute depletion of Slug, or Lsd1 inhibition, reduced lipogenesis and protected against obesity-associated NAFLD and insulin resistance in mice. This study advances our understanding of how lipogenesis is regulated downstream of insulin signaling in health and disease.

Insulin-stimulated lipogenesis gets an epigenetic makeover

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Hepatic de novo lipogenesis is a major contributor to nonalcoholic fatty liver disease (NAFLD). In this issue of the *JCI*, Liu and Lin et al. identified Slug as an epigenetic regulator of lipogenesis. Their findings suggest that Slug is stabilized by insulin signaling, and that it promotes lipogenesis by recruiting the histone demethylase Lsd1 to the fatty acid synthase gene promoter. On the other hand, genetic deletion or acute depletion of Slug, or Lsd1 inhibition, reduced lipogenesis and protected against obesity-associated NAFLD and insulin resistance in mice. This study advances our understanding of how lipogenesis is regulated downstream of insulin signaling in health and disease.

Lipogenic regulation

Liver lipid accumulation is an early step in the development of nonalcoholic fatty liver disease (NAFLD), which can progress into nonalcoholic steatohepatitis (NASH) and cirrhosis. Liver fat can also drive excess gluconeogenesis and hepatic insulin resistance (1, 2). Thus, identifying the mechanisms that control liver lipid accumulation is a widely held research goal that is highly relevant to human disease.

There are multiple sources of liver lipids, including dietary fat, adipose tissue lipolysis, and de novo lipogenesis — the synthesis of new fatty acids from precursors such as carbohydrates. Among these sources of liver lipids, de novo lipogenesis is of particular interest, because it is uniquely elevated in individuals with NAFLD (3). Reducing lipogenesis has potential as a therapeutic intervention for NASH (4). As such, it is of great interest to determine the mechanisms that regulate lipogenesis under healthy and pathogenic conditions.

A major mechanism of lipogenic regulation is via transcriptional modulation. Indeed, the enzymes involved in hepatic de novo lipogenesis are highly transcriptionally regulated (5). One substantial inducer is the substrate, whereby glucose metabolites activate the transcription factor carbohydrate response element binding protein (Chrebp). A second important inducer is insulin. Hepatic insulin signaling promotes the maturation and nuclear localization of the sterol response element binding protein 1c (Srebp1c) and the posttranslational activation of the upstream stimulatory factor 1 (USF-1). Together, Chrebp, Srebp1c, and USF-1 promote the expression of the enzymes that generate, elongate, and desaturate fatty acids, including acetyl coA carboxylase and fatty acid synthase (encoded by *Acaca* and *Fasn*, respectively) (5). Hepatic insulin signaling also promotes the phosphorylation and nuclear exclusion of the FoxO transcription factors, thus releasing FoxO-mediated suppression of glucokinase (encoded by *Gck*) and allowing increased flux from upstream glucose into lipogenesis (6).

Epigenetic regulation of lipogenesis

Despite these known transcription factor–mediated pathways, the epigenetic regulation of lipogenesis — and its ability to mediate insulin-stimulated lipogenesis — is less well understood. In this issue of the *JCI*, Yan Liu, Haiyan Lin, and colleagues demonstrate a unique role for the transcription factor Slug (also known as Snai2 or Snail2) in the epigenetic activation of lipogenic gene expression, downstream of hepatic insulin signaling (7).

The authors found that Slug mRNA was induced and Slug protein was stabilized by hepatic insulin signaling in mice and primary murine hepatocytes. Slug expression in mouse liver was sufficient to induce liver triglyceride accumulation, whereas chronic or acute hepatocyte *Slug* knockout decreased liver triglycerides in both sexes. These phenotypes were associated with concomitant changes in the mRNA and protein expression of de novo lipogenesis enzymes, especially Fasn (7).

Slug protein has two important domains: a DNA-binding domain in its C-terminus that directs binding of the protein to specific target sequences in gene promoters and enhancers, and a SNAG domain that mediates binding of the protein to histone-modifying enzymes, including Lsd1. Lsd1 was the first enzyme identified as a histone demethylase, whereas histone methylation had previously been thought to be irreversible (8). Liu and Lin et al. demonstrated that Slug physically interacts with Lsd1, thus promoting the demethylation of histone H3 lysine 9 (H3K9) in the *Fasn* promoter, and allowing transcriptional activation. Mutant Slug that lacked the Lsd1-interacting domain was incapable of promoting H3K9 demethylation, *Fasn* expression, and liver triglyceride accumulation. A chemical inhibitor of Lsd1, GSK2879552, was able to block Slug-mediated induction of lipogenic gene expression and lipogenesis in primary murine hepatocytes (7). These data suggest that insulin-stimulated stabilization of the Slug-Lsd1 complex is an important contributor to postprandial hepatic lipogenesis.

Therapeutic targets in NAFLD

A major unresolved question is why lipogenesis is elevated in NAFLD and insulin resistance. Perhaps Slug provides some clues. In

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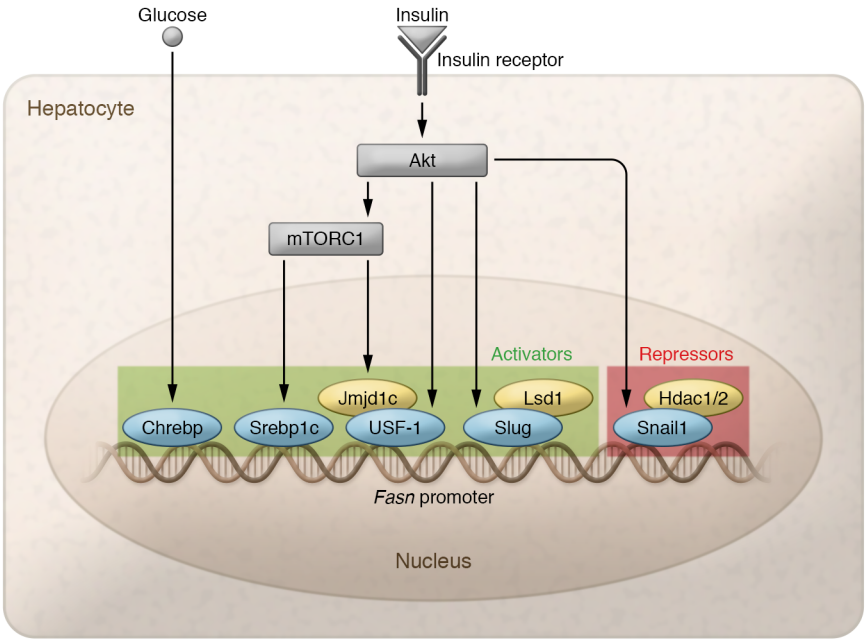

Figure 1. Model of insulin-stimulated lipogenesis. Insulin stimulates protein kinase B (AKT), which activates mammalian target of rapamycin (mTORC1) and transcription factors/repressors (blue). Multiple glucose- and insulin-regulated transcription factors and chromatin remodelers (yellow) collaborate to regulate postprandial de novo lipogenesis in liver.

two different human NASH cohorts, liver *Slug* mRNA expression was increased. Further, high fat diet–fed mice and genetically obese, leptin-deficient (*ob/ob*) mice induced *Slug* mRNA and protein expression (7).

Is the Slug-Lsd1 pathway a therapeutic target in NAFLD? Depleting Slug from adult *ob/ob* mice was sufficient to lower liver triglycerides in the absence of body weight changes. Further, treating WT mice with the Lsd1 inhibitor GSK2879552 (10 mg/kg, daily for five days) was also sufficient to reduce Fasn protein expression (7). Lsd1 inhibitors are currently in clinical trials for various forms of cancer (9). It will be of interest to determine whether such inhibitors are efficacious in preclinical models of NAFLD and NASH.

Recently, other epigenetic modifiers of insulin-regulated de novo lipogenesis have entered the fray. This same research group reported in 2018 that a related protein, Snail1, represses *Fasn* and lipogenesis by recruiting histone deacetylases that promote the deacetylation of H3K9 and H3K27 (10). Intriguingly, Snail1 is stabilized by hepatic insulin signaling, and may act as a brake on insulin-stimulated lipogenesis. A third insulin-regulated epigenetic modifier of lipogenesis was recently identified: Jmjd1c, a histone demethylase. Jose Viscarra, Yuhui Wang, and colleagues demonstrate that Jmjd1c promotes demethylation of H3K9 at the promoters of lipogenic genes, and this is associated with increases in expression of those genes (11). Moreover, the authors show that the recruitment of Jmjd1c to those promoters is induced by insulin signaling, via mTOR-mediated phosphorylation. Together, these findings suggest that insulin signaling engages multiple proteins in order to trigger the conversion of excess carbohydrate into fatty acids (Figure 1).

Where do we go from here? While considerable research has been dedicated toward the regulation of *Acaca* and *Fasn*, these are just two of many genes involved in the ultimate synthesis and storage of triglycerides. It will be of interest to apportion efforts toward investigating the transcriptional and epigenetic regulation of the other proteins involved, both upstream and downstream. Given the nonlinear relationship between fatty liver and hypertriglyceridemia, it will also be of interest to investigate whether the insulin-Slug pathway has a role in regulating the secretion or clearance of triglyceride-rich lipoproteins. There is much to be gained from investigating regulators of lipid homeostasis.

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1. Sunny NE, Parks EJ, Browning JD, Burgess SC. Excessive hepatic mitochondrial TCA cycle and gluconeogenesis in humans with nonalcoholic fatty liver disease. *Cell Metab*. 2011;14(6):804–810.
2. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. *Nat Rev Gastroenterol Hepatol*. 2017;14(1):32–42.
3. Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology*. 2014;146(3):726–735.
4. Esler WP, Bence KK. Metabolic targets in nonalcoholic fatty liver disease. *Cell Mol Gastroenterol Hepatol*. 2019;8(2):247–267.
5. Wang Y, Viscarra J, Kim SJ, Sul HS. Transcriptional regulation of hepatic lipogenesis. *Nat Rev Mol Cell Biol*. 2015;16(11):678–689.
6. Haeusler RA, et al. Integrated control of hepatic lipogenesis versus glucose production requires FoxO transcription factors. *Nat Commun*. 2014;5:5190.
7. Liu Y, et al. Hepatic Slug epigenetically promotes liver lipogenesis, fatty liver disease, and type 2 diabetes. *J Clin Invest*. 2020;130(6):2992–3004.
8. Shi Y, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. 2004;119(7):941–953.
9. Jambhekar A, Anastas JN, Shi Y. Histone lysine demethylase inhibitors. *Cold Spring Harb Perspect Med*. 2017;7(1):a026484.
10. Liu Y, et al. Insulin/Snail1 axis ameliorates fatty liver disease by epigenetically suppressing lipogenesis. *Nat Commun*. 2018;9(1):2751.
11. Viscarra JA, Wang Y, Nguyen HP, Choi YG, Sul HS. Histone demethylase JMJD1C is phosphorylated by mTOR to activate de novo lipogenesis. *Nat Commun*. 2020;11(1):796.