

## CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Notch and Nonalcoholic Fatty Liver and Fibrosis**

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Nonalcoholic fatty liver disease is a complex condition involving the progression from simple steatosis to inflammation (nonalcoholic steatohepatitis [NASH]) and then to severe fibrosis and hepatocellular carcinoma, which are the major predictors of death in patients with this disease. In parallel with the recent rise in obesity, the incidence of nonalcoholic fatty liver disease is increasing. However, at present, there is no approved drug treatment that specifically targets NASH.

Notch proteins are a family of receptors involved in cell differentiation during embryogenesis.<sup>1</sup> Notch proteins have also been implicated in metabolism. For example, activation of the Notch protein in hepatocytes increases the synthesis of intracellular triglycerides by stabilizing another protein, the mechanistic target of rapamycin complex 1 (mTORC1; which is usually activated by insulin signaling), which in turn activates the sterol regulatory element-binding protein 1c.<sup>1</sup>

A study recently reported by Zhu et al.<sup>2</sup> investigated the inhibition of Notch signaling as a therapeutic strategy against fibrosis caused by nonalcoholic fatty liver disease. Although under normal circumstances Notch signaling is abolished in hepatocytes after differentiation, the authors found an up-regulation of this signaling in the livers of persons with nonalcoholic fatty liver disease and in mice fed a NASH-inducing diet. Importantly, down-regulation and ablation of Notch signaling in these mice resulted in an amelioration of liver fibrosis (Fig. 1).

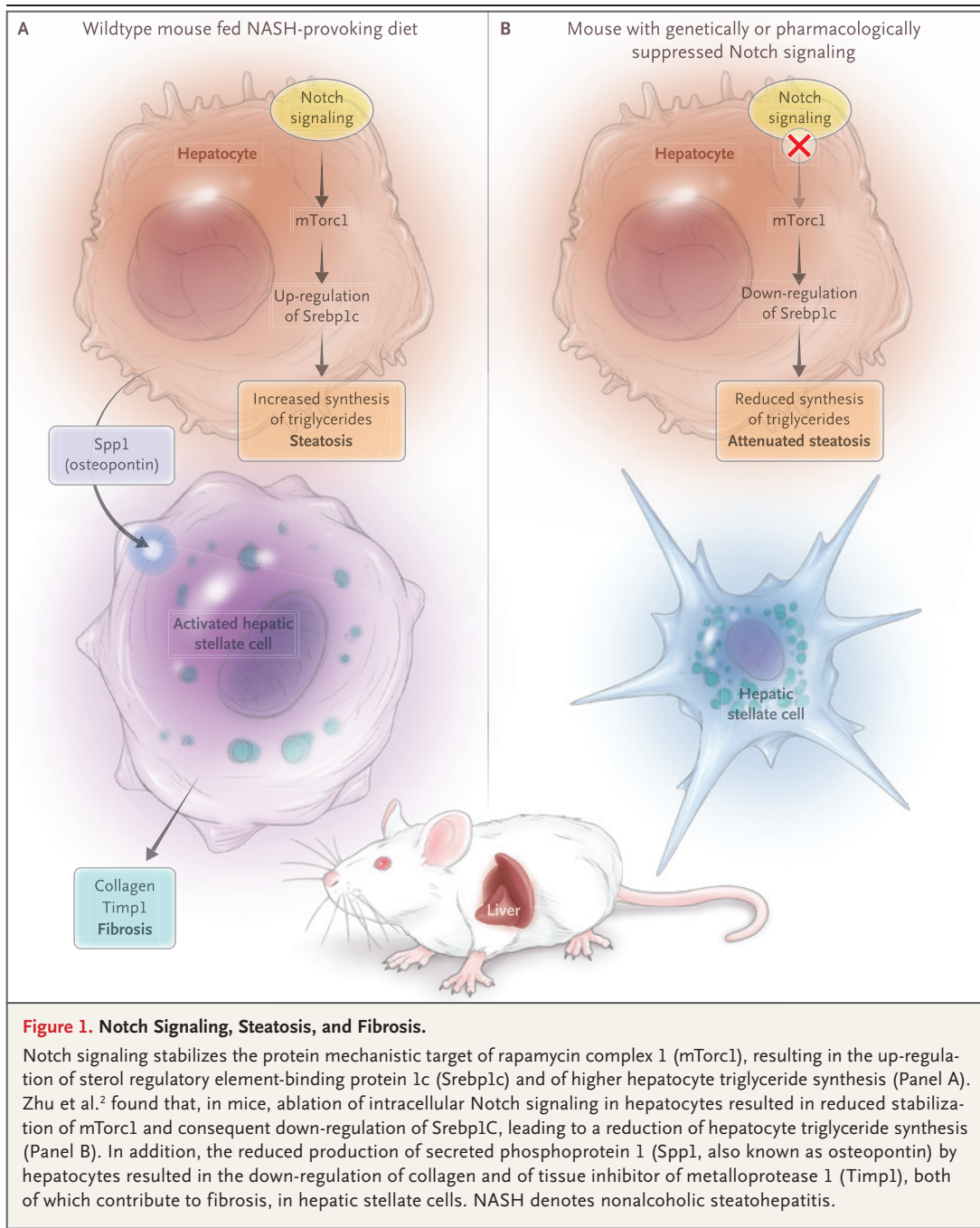
A mendelian randomization study with the use of human sequence variations (single-nucleotide polymorphisms) that have been associated with increased liver fat showed that hepatic steatosis has a causal role in liver fibrosis.<sup>3</sup> The results of the study by Zhu et al. are consistent with this

finding. They found that, in a mouse model of liver steatosis and fibrosis, ablation of Notch signaling resulted in a reduction in the incidence and severity of both steatosis and fibrosis. Notably, the authors observed no changes after Notch inactivation in liver fibrosis in mice fed a diet deficient in methionine and choline, which causes fibrosis independent of calories and lipid storage. These data support observations that excess liver fat is deleterious to the liver, that sustained Notch signaling induces liver fibrosis in the presence of lipid accumulation, and that suppression of Notch signaling or liver fat content may ameliorate liver fibrosis.

A strength of the study by Zhu et al. is that it started with the analysis involving specimens obtained from humans, followed by validation in mice. A limitation is that the mechanism linking Notch signaling with activation of hepatic stellate cells (the cells highly involved in fibrosis) was not fully elucidated, although the authors provided some data suggesting that down-regulation of a hepatocyte-secreted phosphoprotein (osteopontin) may be involved. Despite this limitation, the strategy of inhibiting Notch to treat nonalcoholic fatty liver disease has potential.

Cancer stem cells are the progenitors of cancer. They have a pivotal role in the development of cancer and its progression and recurrence. Notch signaling promotes enhanced tumor malignancy by contributing to the development of cancer stem cells and resistance to chemotherapy. It would be interesting to see whether Notch inhibition could improve the prognosis of patients with fibrosis-associated hepatocellular carcinoma or prevent disease recurrence.

Another line of inquiry is prompted by the genetics of susceptibility to nonalcoholic fatty liver disease. Naturally occurring genetic se-



quence variations increase liver fat and fibrosis by means of different mechanisms.<sup>4</sup> Might Notch inactivation reduce the incidence and severity of liver steatosis and fibrosis among persons with a specific genetic background? Another consideration is that long-term down-regulation of Notch could affect the biliary tract; the activation of

Notch signaling is known to induce the differentiation of cholangiocytes.<sup>5</sup> Perhaps a Notch-suppressing drug that is targeted specifically to hepatocytes or the intermittent administration of such a drug would obviate this risk.

In conclusion, down-regulation of Notch signaling represents a candidate therapeutic target

against fibrosis in patients with nonalcoholic fatty liver disease. Studies are needed to test this hypothesis in humans and to dissect the molecular mechanisms that link Notch signaling with fibrosis.

Disclosure forms provided by the author are available at NEJM.org.

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