Epidemiologic data indicate that nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of chronic liver disease in the world. Chronic nutrient overconsumption, inactivity, inherited genetic determinants, and other exposures increase the risk of hepatic fat accumulation (steatosis). If left unchecked, hepatic steatosis can tip changes in inflammatory and immune responses that exacerbate reactive oxygen species, fibrosis, and proinflammatory cytokine production leading to nonalcoholic steatohepatitis (NASH). This more worrisome disorder can lead to cirrhosis and liver failure in 10%–15% of patients. The mechanisms conferring risk and protection from NAFLD and NASH are not entirely understood.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Cansby et al. demonstrate the utility of a novel approach to reduce hepatic steatosis in mice. Their efforts focused on manipulating intracellular levels of serine/threonine kinase 25 (STK25), a protein kinase that decorates lipid droplets in hepatocytes and that they previously showed functions to regulate fatty acid mobilization and triglyceride synthesis across an array of tissues including pancreas, adipose, and skeletal muscle. Prior work showed that human hepatic STK25 mRNA and protein levels correlate with NASH severity, and several single nucleotide polymorphisms in the human STK25 gene correlate with hepatic steatosis. The investigative team also leveraged previous findings that STK25-overexpressing mice exhibited worsened NAFLD and that treatment with Stk25 antisense oligonucleotides (ASOs) reduced STK25 activity and reduced NAFLD severity. ASOs are short, synthetic, single-stranded oligodeoxynucleotides bound by complementary base pairing to a target mRNA, leading to endonuclease transcript knockdown and reduced mRNA of the targeted protein. Because STK25 is expressed in multiple tissues, the existing mouse models where STK25 is globally overexpressed or deleted did not permit direct examination of liver lipid metabolism. Therefore, a novel approach was needed to investigate specifically the effects of hepatic STK25.

To address this limitation, Cansby et al. targeted STK25 knockdown by using hepatocyte-specific triantennary N-acetylgalactosamine (GalNAc)–conjugated ASOs in chow-fed and high-fat diet–fed (45% fat) mice made obese after 21 weeks. GalNAc-Stk25 ASO, a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor, delivered by intraperitoneal injection (twice weekly for the last 6 weeks), enabled a targeted distribution to hepatocytes resulting in NAFLD resolution. Improvements in GalNAc-Stk25 ASO-treated mice included significantly reduced hepatic steatosis and fibrosis and improved necroinflammatory changes coupled with significant reductions in serum alanine aminotransferase and aspartate aminotransferase. Importantly, improvements exceeded those achieved on treatment with unconjugated parent ASO (Stk25 ASO), providing evidence that repression of STK25 levels selectively in hepatocytes is sufficient to solicit therapeutic benefit in diet-induced NAFLD. Although direct assessments of liver mitochondrial function were not reported, fatty acid β-oxidation measurements in naive mouse primary hepatocytes treated with GalNAc-Stk25 ASO versus GalNAc-control ASO suggest that enhanced lipid oxidation may be partly responsible for the effect. There were no observations of accelerated fat accumulation in other tissues such as skeletal muscle or white adipose, supporting this concept.

These findings shed new light on both targets and approaches to treat NAFLD. Continued advancements in gene (in)activation technologies such as ASOs and adeno-associated virus derived vectors, as well as gene-editing technologies such as CRISPR, will bring new opportunities to alter and/or cure monogenic liver disease. Exploitative binding to cell surface receptors is a tried and sometimes true method of targeted nucleic acid and amino acid polymers to desired tissues. However, the architecture and zonal distribution of liver metabolism and the polygenic nature of NAFLD present a unique set of challenges. Asialoglycoprotein receptor, as well as key enzymes mediating lipid, glucose, and amino metabolism, are zonally distributed across portal tracts. This distribution is deteriorated in disease states such as NAFLD and NASH, and it remains unknown how this altered zonation influences disease trajectories. Nonetheless, gene transfer technologies are maturing rapidly, and the ability to differentially modulate multiple targets concurrently for therapeutic effect may soon be within reach.

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