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EDITORIAL

Something to mTORC About in NASH

Nonalcoholic steatohepatitis (NASH) is defined as hepatic lipid accumulation with accompanying inflammation and fibrosis in the absence of excessive alcohol intake or other overt cause. Patients with NASH have an elevated future risk of developing cirrhosis, end-stage liver failure, and hepatocellular carcinoma.[1] Liver failure secondary to NASH has emerged as one of the most common causes of liver transplantation in many areas of the world. Despite the prevalence of NASH, there are still no licensed drug therapies to treat the disease and the pathogenic mechanisms that drive the development and progression of NASH are still incompletely understood. The hallmark of NASH, the accumulation of lipid in the liver parenchyma, is likely driven by abnormalities in a variety of metabolic pathways including dysregulated adipose tissue lipolysis, increased de novo lipogenesis, impaired fatty acid oxidation, and suppression of very low density lipoprotein (VLDL) secretion. Whereas the accumulation of triglyceride may itself be relatively innocuous, the accumulation of other toxic lipid and phospholipid species may be causally linked to development of liver injury and progression of NASH. Indeed, many people exhibit simple steatosis without significant liver injury (nonalcoholic fatty liver [NAFL]) for prolonged periods of time, whereas other patients progress quickly to more serious forms of the disease for reasons that are still unclear.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Uehara et al[2] found that the hepatic activity of the mechanistic target of rapamycin complex 1 (mTORC1), which is increased in mouse models of NAFL, is conversely decreased in multiple mouse models of NASH. They found that reactivating mTORC1 in liver reduces hepatic injury and steatosis coincident with increased VLDL secretion and suppression of de novo lipogenesis. Work by this group has shown that mTORC1 regulates VLDL secretion by augmenting the synthesis of a phospholipid (phosphatidylcholine [PC]) that is an important constituent of VLDL particles.[3] The stimulatory effects on PC synthesis are mediated by increased abundance of CCTα, a critical enzyme in PC production. They showed that CCTα is required for the ameliorative effects of mTORC1 on VLDL secretion and liver injury in the mouse models of NASH. Finally, using a variety of genetic models, they disentangled the beneficial effects of mTORC1 on NASH end points and found that the activation of VLDL secretion rather than the suppression of de novo lipogenesis tracked with reduced liver injury. This mechanistic insight fits well with prior studies indicating that VLDL secretion may be decreased in subsets of patients with NASH[4] and studies conducted in mice demonstrating that suppressing VLDL secretion is a potent driver of liver injury, NASH biomarkers, and even development of hepatocellular carcinoma.[5] These findings provide new insight into the differential regulation of mTORC1 in NAFL versus NASH and suggest that impaired mTORC1 activity and its effects on PC synthesis and VLDL secretion may play a role in the pathogenesis of NASH.

Several unanswered questions remain related to this work. First, and most importantly, is mTORC1 deactivated during the progression to NASH in humans as well? Moreover, the mechanistic cause of mTORC1 deactivation in NASH also remains to be determined because the activity of AKT, a critical regulator of mTORC1, was not affected in liver of mice with NASH. Could deactivation of the mTORC1 pathway play a role in other metabolic alterations that are disparately affected in NASH versus NAFL? Recent work has suggested that mitochondrial function and activity is increased in early stages of NAFL, but decreased in later stage NASH.[6] Uehara et al[2] found no effect of mTORC1 activation on the expression of genes encoding fatty acid oxidation enzymes, but mitochondrial activity and function was not examined. Finally, can this pathway be safely modulated so as to be targeted therapeutically given the myriad pathways affected by mTORC1 signaling and the potential for exacerbating dyslipidemia by promoting VLDL secretion? Recent population studies have suggested that subpopulations of NASH patients with impaired VLDL secretion have lower risk of cardiovascular disease.[4] Because cardiovascular disease is the most common cause of mortality in people with NASH, this is an important consideration. Additional work is needed to address these questions and determine the therapeutic potential of these findings.

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