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EDITORIAL

Ste20-like Kinase STK25: A Potential Target in Prevention and Therapy of NASH-Associated Hepatocellular Carcinoma?

High caloric food intake, frequently referred to as Western diet, and lack of exercise have propelled a dramatic increase of metabolic syndrome and obesity worldwide.[1] The primary hepatic consequence of this development is nonalcoholic fatty liver disease (NAFLD), which is already affecting about 25% of the adult population globally and is still on the rise. Nonalcoholic steatohepatitis (NASH) is a more severe form of NAFLD and characterized by massive lipid accumulation, liver inflammation, and hepatocyte ballooning and may already include variable stages of fibrosis. NASH is a progressive disease that can lead to advanced fibrosis or cirrhosis and is associated with an increased risk of developing hepatocellular carcinoma. In light of the increasing prevalence of NAFLD and NASH, NASH will become a leading cause of hepatocellular carcinoma in the United States.[2] Consequently, there is an urgent need for a detailed molecular understanding of NASH pathogenesis. The definition of relevant factors involved in the progression from benign steatosis to NASH may facilitate the identification of new predictors and potential targets for improved treatment of NASH-related hepatocellular carcinoma.

Recently, the liver lipid droplet-decorating serine/threonine protein kinase STK25, a member of the mammalian sterile 20 kinase superfamily, has been identified as a new regulator of hepatic lipid partitioning and metabolism, systemic glucose levels, and insulin homeostasis.[3] Whereas STK25-overexpressing mice showed a severe metabolic phenotype upon high fat diet, Stk25-deficient mice were protected from liver steatosis and had improved glucose tolerance, reduced hepatic glucose production, and overall improved insulin sensitivity. In addition, STK25 is involved in inflammation, oxidative and endoplasmic reticulum (ER) stress, and autophagic degradation, representing key processes that support the development of NASH-associated liver cancer. Although these characteristics of STK25 are highly suggestive, the specific role of STK25 in NASH-associated hepatocellular carcinoma was unknown, prompting researchers around Margit Mahlapuu and colleagues to launch an important investigation that is published in this issue of *Cellular and Molecular Gastroenterology and Hepatology*.[4] They discovered a distinct tumor-promoting role for STK25 in 2 relevant mouse models of NASH-induced liver cancer. In a first model, a single injection of the procarcinogen diethylnitrosamine was applied in Stk25 null and wild-type control mice that both received a high fat diet. A second model was set up by administration of carbon tetrachloride together with a choline-deficient L-amino acid-defined diet to induce NASH-associated hepatocellular carcinoma. In both experimental models, macroscopic inspection and quantification of liver histology demonstrated that Stk25 null mice developed fewer tumor nodules and a reduced tumor burden, suggesting that STK25 ablation affected both tumor growth and initiation. Corroborating these observations on a more molecular level, liver sections of tumor-bearing Stk25 null mice showed reduced liver cell damage, smaller lesions, reduced numbers of tumor marker-positive cells, and reduced levels of Grp78 and EpCAM, which correlate with tumor grade or poor prognosis, respectively. To unravel the mechanisms behind these findings, the authors first investigated hepatocyte apoptosis and compensatory proliferation. Hepatocyte turnover, an important promoter of carcinogenesis in liver cancer, was significantly reduced in Stk25 null mice. Moreover, the authors found significantly reduced angiogenesis as determined by the CD31 positive area in tumor tissue. Besides reduced carcinogenesis, the authors demonstrated in several histopathologic examinations that the ablation of STK25 improved NASH-related liver parameters including lipid accumulation, inflammation, and fibrosis. Improved histopathology correlated with lower levels of alanine aminotransferase in the plasma of Stk25 null mice. Moreover, genetic ablation of STK25 suppressed ER stress and accumulation of reactive oxygen species. This in turn decreased the levels of oxidative stress and oxidative DNA damage, stimulated mitochondrial activity, and protected against the deposition of oxidized lipids. On the molecular level, the authors demonstrated that these alterations upon STK25 ablation involved the reduced activation of the ERK pathway. To investigate cell-autonomous mechanisms behind the antitumorigenic effect of STK25 deficiency, the authors adopted an in vitro model of human HepG2 hepatoma cells that had been treated with oleic acid to mimic NASH-comparable conditions. In this model, the small interfering RNA-mediated suppression of STK25 was able to reduce both apoptosis and proliferation. Moreover, an observable shift in epithelial to mesenchymal transition markers back to a more epithelial phenotype was associated with a reduced migratory potential, providing further support that STK25 could be a suitable target for pharmacologic intervention.

In summary, the results of Kurhe et al[4] clearly indicate a protumorigenic role of STK25 in NASH-associated hepatocarcinogenesis. These findings qualify STK25 as a promising therapeutic target in NASH and in prevention and treatment of NASH-associated liver cancer and will certainly stimulate efforts to identify suitable kinase inhibitors that facilitate an effective blockade of STK25 activity. In line with the diverse roles of STK25 in lipid storage and metabolism, this study already suggests that elimination of STK25 affects both tumor initiation and outgrowth. Further investigation

in alternative experimental models of hepatocellular carcinoma, including those with inducible or conditional elimination of STK25 function, is required to further define the roles of STK25 in carcinogenesis of hepatocellular carcinoma and to elaborate effective options for therapeutic strategies targeting STK25.

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References

1. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol 2019;16:411–428.
2. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59:2188–2195.
3. Amrutkar M, Chursa U, Kern M, Nuñez-Durán E, Ståhlman M, Sütt S, Borén J, Johansson BR, Marschall H, Blüher M, Mahlapuu M. STK25 is a critical determinant in nonalcoholic steatohepatitis. FASEB J 2016;30:3628–3643.
4. Kurhe Y, Caputo M, Cansby E, Xia Y, Kumari S, Anand SK, Howell BW, Marschall HU, Mahlapuu M. Antagonizing STK25 signaling suppresses the development of hepatocellular carcinoma through targeting metabolic, inflammatory and pro-oncogenic pathways. Cell Mol Gastroenterol Hepatol 2022;13:405–423.

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Conflicts of interest
The author discloses no conflicts.

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