Hepatocellular loss of mTOR aggravates tumor burden in nonalcoholic steatohepatitis-related HCC

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Abstract

Obesity and associated nonalcoholic steatohepatitis (NASH) are on the rise globally. NASH became an important driver of hepatocellular carcinoma (HCC) in recent years. Activation of the central metabolic regulator mTOR (mechanistic target of rapamycin) is frequently observed in HCCs. However, mTOR inhibition failed to improve the outcome of HCC therapies, demonstrating the need for a better understanding of the molecular and functional consequences of mTOR blockade. We established a murine NASH-driven HCC model based on long-term western diet feeding combined with hepatocellular mTOR-inactivation. We evaluated tumor load and whole-body fat percentage via µCT-scans, analyzed metabolic blood parameters and tissue proteome profiles. Additionally, we used a bioinformatic model to access liver and HCC mitochondrial metabolic functions. The tumor burden was massively increased via mTOR-knockout. Several signs argue for extensive metabolic reprogramming of glucose, fatty acid, bile acid and cholesterol metabolism. Kinetic modeling revealed reduced oxygen consumption in KO-tumors. NASH-derived HCC pathogenesis is driven by metabolic disturbances and should be considered separately from those caused by other etiologies. We conclude that mTOR functions as tumor suppressor in hepatocytes especially under long-term western diet feeding. However, some of the detrimental consequences of this diet are attenuated by mTOR blockade.