Critical role of LKB1-Akt pathway activation in the proliferation of hepatocellular carcinoma

Researchers from the Metabolomics unit at CICbioGUNE-CIBERehd have recently observed that the enzyme LKB1, which had been initially considered a tumor suppressor, performs the opposite function in hepatocarcinoma cells derived from liver tumors of non-alcoholic steatohepatitis etiology (NASH). The study, published in the July issue of Hepatology, demonstrates that LKB1 is necessary for the survival of a cell-line (SAM-Deficient cell line) isolated from hepatocellular carcinoma (HCC) of mice lacking methionine adenosyltransferase 1A (MAT1-KO mice).

HCC from the MAT1A-KO mice has been chosen because these mice show a chronic reduction in the levels of SAMe, a hyperactivation of the enzyme LKB1 and spontaneously develop nonalcoholic steatohepatitis (NASH) and HCC. Moreover, MAT1A expression and synthesis of SAMe is reduced in patients with liver cirrhosis, who are at risk of developing HCC. The study demonstrates that LKB1 regulates Akt-mediated survival independently of PI3K, AMPK and mTORC2. In addition, LKB1 controls the apoptosis through phosphorylation and retention of p53 in the cytoplasm. Finally, the cytoplasmic localization of p53 and p-LKB1 (Ser428) in the HCC of MAT1-KO mice, and in human liver biopsies from HCC of NASH and ASH (alcoholic steatohepatitis) etiology, was also confirmed.

In short, the new cell line deficient in SAMe, SAMe-D, is a good model of HCC derived from NASH, in which LKB1 is the primary driver of a new regulatory mechanism and could be considered a practical tool for exploring new therapeutic strategies.