PTEN down-regulation by unsaturated fatty acids triggers hepatic steatosis via an NF-kappaBp65/mTOR-dependent mechanism

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Abstract

BACKGROUND & AIMS: Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a tumor suppressor and a regulator of insulin sensitivity in peripheral tissues. In the liver, PTEN deletion increases insulin sensitivity, but induces steatosis, steatohepatitis, and hepatocellular carcinoma. Here, we investigated the pathophysiologic mechanisms regulating PTEN expression in the liver and the development of steatosis. METHODS: PTEN expression was evaluated in the liver of rats and human beings having metabolic syndrome. Signaling pathways regulating PTEN expression and lipid accumulation in hepatocytes were examined in vitro. RESULTS: PTEN expression is down-regulated in the liver of rats having steatosis and high plasma levels of fatty acids, as well as in steatotic human livers. Unsaturated fatty acids inhibited PTEN expression in HepG2 cells via activation of a signaling complex formed by the mammalian target of rapamycin (mTOR) and nuclear factor-kappaB (NF-kappaB). Down-regulation of PTEN expression induced steatosis by affecting import, esterification, and extracellular release of fatty acids. CONCLUSIONS: [...]