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PTEN Down-Regulation by Unsaturated Fatty Acids Triggers Hepatic Steatosis via an NF-κBp65/mTOR-Dependent Mechanism

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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-κB (NF-κB). Down-regulation of PTEN expression induced steatosis by affecting import, esterification, and extracellular release of fatty acids.** ***Conclusions:*** **Hepatic steatosis can be mediated by alterations of PTEN expression in hepatocytes exposed to high levels of unsaturated fatty acids. Furthermore, our data revealed interaction between mTOR and NF-κB, suggesting cross-talk between these 2 pathways.**

Enhanced fatty acid synthesis and liver steatosis are metabolic dysfunctions associated with obesity, diabetes, and hyperlipidemia. Hepatic steatosis is considered an important predisposing factor for liver inflammation, fibrosis, and cirrhosis, representing distinct clinical stages in nonalcoholic fatty liver diseases. The development of hepatocellular carcinoma (HCC) also might occur in the late course of these diseases. Furthermore, epidemiologic studies have shown that diabetes and obesity are important risk factors for HCC.[1]

Defects in the insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K)/Akt signaling pathway are associated closely with liver steatosis and insulin resistance.[2,3] A major regulator of the PI3K/Akt pathway is the phosphatase and tensin homologue deleted on chromosome 10 (PTEN), a tumor suppressor with phosphatase activity capable of dephosphorylating both proteins and phosphoinositides such as PtdIns(3,4,5)P_3.[4,5] Liver-specific deletion of PTEN in mice induces steatosis, steatohepatitis, and HCC, in addition to hypersensitivity to insulin and enhanced peripheral glucose metabolism.[6,7] Hypersensitivity to insulin in these mice is consistent with the fact that PTEN is a negative regulator of insulin signaling and peripheral insulin sensitivity.[8] Alterations in the expression/activity of the type-II SH2-domain-containing inositol 5-phosphatase (SHIP2), another PtdIns(3,4,5)P_3 phosphatase modulating insulin signaling,[8] does not lead to liver abnormalities.[9]

Loss of PTEN function in hepatocytes thus could represent an important mechanism triggering the development of steatosis and affecting insulin sensitivity. Frequent mutations/deletion of the PTEN gene have been reported in human cancers[4] but have not been associated with the metabolic syndrome. However, loss of PTEN function also can occur through down-regulation of its expression/activity. Indeed, posttranscriptional modifications can affect the activity, stability, or localization of this enzyme.[5] PTEN expression also is modulated by various transcription factors[10] and signaling cascades (eg, activated by transforming growth factor β or p38 mitogen-activated protein kinase).[10,11] However, most of these studies were performed in cell types with an uncharacterized role in insulin metabolism. The molecular mechanisms controlling PTEN expression in the liver in pathologic states such as obesity, insulin resistance, and diabetes still remain to be elucidated.

To determine whether alterations in PTEN expression/activity in the liver may be implicated in the development of steatosis, we examined the expression pattern of PTEN in livers of different rodent models and of human beings with metabolic syndrome. Because PTEN was found to be down-regulated in fatty hepatocytes, we then examined

Abbreviations used in this paper: FFA, free fatty acids; GFP, green fluorescent protein; HCC, hepatocellular carcinoma; HF, high fat; OA, mono-unsaturated oleic acid; PCR, polymerase chain reaction; siRNA, short interfering RNA; Tg, triglycerides; ZDF, Zucker diabetic fatty rats.

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