The regulation of PTEN on insulin and lipid metabolism in bovine hepatocytes in vitro

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Short title：**PTEN regulate insulin and lipid metabolism**

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ABSTRACT

Background: Dairy cows with fatty liver or ketosis display decreased insulin sensitivity and defection in the insulin receptor substrate (IRS)/ PI3K/AKT signaling pathway. Phosphatase and tensin homolog (PTEN) is a well-known tumor suppressor and also a negative regulator of insulin signaling and peripheral insulin sensitivity. Hypothesis: PTEN may affect the insulin pathway-mediated hepatic glucose and lipid metabolism in dairy cows. Methods: Adenovirus vectors that over-express and silence PTEN were constructed, and then transfected into the hepatocytes isolated from calves to investigate the effect of PTEN on PI3K/AKT signaling pathway. Results: PTEN silencing increases the phosphorylation of AKT and the expression of PI3K, decreased the phosphorylation of IRS1, which increased the phosphorylation levels of glycogen synthase kinase-3β (GSK-3β) and expression of sterol regulatory element-binding protein-1c (SREBP-1c). Increased GSK-3β phosphorylation further up-regulated the expressions of the key enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6- phosphatase (G6-Pase) involved in gluconeogenesis. Furthermore, the expression of SREBP-1c target gene fatty acid synthase (FAS) also increased significantly. Interestingly, PTEN over-expression could reverse the above results. Conclusions and clinical importance: PTEN negatively regulates the enzymes involved in hepatic gluconeogenesis and lipid synthesis, which suggests that PTEN may be a therapeutic target for ketosis and fatty liver in dairy cows.