ABSTRACT

Kctd17, a novel regulator in hepatic insulin resistance and nonalcoholic fatty liver diseases

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Obesity-induced fatty liver predisposes to non-alcoholic steatohepatitis (NASH), which has no approved pharmacotherapy, making it the fastest growing indication for liver transplantation. Fatty liver develops in part due to excess hepatic *de novo* lipogenesis (DNL), an insulin-stimulated cell-autonomous synthesis of fatty acids, a conundrum as obesity is commonly associated with insulin resistance and glucose intolerance. We show that the serine/threonine phosphatase PHLPP2 terminates insulin action in the liver by dephosphorylating Akt Ser473 to repress DNL but not gluconeogenic pathways. In obesity, endogenous PHLPP2 is degraded – to understand this regulation, we performed LC-MS/MS which identified glucagon/PKA-dependent PHLPP2 phosphorylations at Ser1119 and Ser1210, which recruit the adaptor KCTD17 and ubiquitin E3 ligase Cullin3. Hepatic *Kctd17* expression is increased in murine obesity, and *KCTD17* is correlated with excess hepatic fat in patients. Knockdown of hepatic *Kctd17* in obese mice prevents PHLPP2 degradation, allowing repression of DNL and fat accumulation, while overexpression of Kctd17 in healthy mice provokes fatty liver. These results demonstrate that modulators of the PHLPP2/KCTD17 axis can reverse obesity-induced hepatic steatosis and may be utilized to treat NASH.