

Protein Kinase STK25 is a Regulator of Hepatic Lipid Partitioning and Whole Body Metabolism

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

- I. Cansby E, Amrutkar M, Mannerås Holm L, Nerstedt A, Stenfeldt E, Borén J, Carlsson P, Smith U, Zierath JR, Mahlapuu M. **Increased expression of STK25 leads to impaired glucose utilization and insulin sensitivity in mice challenged with a high-fat diet.** *FASEB J* 2013, 27(9):3660-3671.
- II. Amrutkar M, Cansby E, Chursa U, Nuñez-Durán E, Chanción B, Ståhlman M, Fridén V, Mannerås Holm L, Wickman A, Smith U, Bäckhed F, Borén J, Howell BW, Mahlapuu M. **Genetic Disruption of Protein Kinase STK25 Ameliorates Metabolic Defects in a Diet-Induced Type 2 Diabetes Model.** *Diabetes* 2015, 64(8):2791–2804.
- III. Amrutkar M, Cansby E, Nuñez-Durán E, Pirazzi C, Ståhlman M, Stenfeldt E, Smith U, Borén J, Mahlapuu M. **Protein kinase STK25 regulates hepatic lipid partitioning and progression of liver steatosis and NASH.** *FASEB J* 2015, 29(4):1564-1576.
- IV. Amrutkar M, Kern M, Nuñez-Durán E, Ståhlman M, Cansby E, Chursa U, Stenfeldt E, Borén J, Blüher M, Mahlapuu M. **Protein Kinase STK25 Controls Lipid Partitioning in Hepatocytes and Correlates with Liver Fat Content in Humans.** *Diabetologia* 2016, 59(2):341-353.

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In past decade, type 2 diabetes (T2D) and associated metabolic complications have become a major global threat for human health with epidemic increase in incidence. Currently available treatments for T2D have several limitations and side effects making it difficult safely reach adequate metabolic control. Therefore, it is important to identify novel therapeutic targets for metabolic regulation, which could complement current treatments for T2D.

T2D is closely associated with ectopic lipid deposition. Recent evidence suggests that hepatic lipid deposition is not merely a consequence of the metabolic syndrome but rather that non-alcoholic fatty liver disease (NAFLD), and progression to non-alcoholic steatohepatitis (NASH), exacerbate hepatic and systemic insulin resistance and actively contribute to the pathogenesis of the metabolic syndrome. However, no pharmacological treatment is approved for NAFLD/NASH, to date.

Serine/threonine protein kinase 25 (STK25) is broadly expressed in mouse, rat and human tissues. Previous studies by our research group in the rat myoblast cell line L6 by small interfering RNA (siRNA) have shown that STK25 is involved in regulation of glucose uptake and lipid oxidation. Studies presented in this thesis work demonstrate that the transgenic mice overexpressing STK25 challenged with a high-fat diet display a shift in the metabolic balance in peripheral tissues from lipid oxidation to lipid storage, resulting in a systemic insulin resistance. In contrast, *Stk25* knockout mice show better-preserved systemic insulin sensitivity via an opposite shift in the metabolic balance in peripheral tissues from lipid storage to lipid utilization.

We found that STK25 coats lipid droplets in mouse liver and human hepatocytes. Our studies performed in mouse liver, and in hepatocytes from both mouse and human, suggest that STK25 regulates hepatic lipid partitioning by controlling β -oxidation and very low-density lipoprotein (VLDL)-triaclylglycerol (TAG) secretion. Increased activity of STK25 reduces liver lipolytic capacity, which in turn results in lower availability of lipids for hepatic β -oxidation and VLDL-TAG secretion, leading to enhanced lipid storage. Upon inactivation of STK25 reciprocal increase in liver lipolytic capacity, β -oxidation and VLDL-TAG secretion was seen, which likely account for the reduced hepatic lipid storage. We also found a statistically significant positive correlation between *STK25* mRNA expression in human liver biopsies and hepatic fat content.

Taken together, our studies suggest that inhibition of STK25 enables the reduction of ectopic lipid deposition and improves insulin sensitivity and glucose utilization in peripheral tissues. Our studies highlight STK25 as a potential drug target for prevention and/or treatment of T2D, NAFLD and NASH.

Keywords: NAFLD, NASH, Liver lipid metabolism, Type 2 diabetes, STK25

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