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STK25 as a regulator of lipid accumulation

Akademisk avhandling

Som för avläggande av medicinsk doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula SU, Vita Stråket 12, den 7:e september, klockan 09:00

av Urszula Chursa

Fakultetsopponent:
Professor Bo Angelin
Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Amrutkar M, **Chursa U**, Kern M, Nuñez-Durán E, Ståhlman M, Sütt S, Borén J, Marschall HU, Blüher M, Mahlapuu M. STK25 is a Critical Determinant in Nonalcoholic Steatohepatitis. *FASEB J. 2016, 30(10): 3628-3643*

II. **Chursa U**, Nuñez-Durán E, Cansby E, Amrutkar M, Sütt S, Ståhlman M, Olsson BM, Borén J, Johansson ME, Bäckhed F, Johansson BR, Sihlbom C, Mahlapuu M. Overexpression of Protein Kinase STK25 in Mice Exacerbates Ectopic Lipid Accumulation, Mitochondrial Dysfunction, and Insulin Resistance in Skeletal Muscle. *Diabetologia. 2017, 60(3): 553-567*

III. **Chursa U**, Hammarstedt A, Smith U. STK25 regulates lipid accumulation and maturation of 3T3-L1 cells. *Manuscript.*

SAHLGRENSKA AKADEMIN
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STK25 as a regulator of lipid accumulation

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Abstract

Type 2 diabetes mellitus (T2DM) and nonalcoholic steatohepatitis (NASH), a progressive form of nonalcoholic fatty liver disease (NAFLD), have become widespread metabolic disorders that have reached epidemic proportions. Obesity, with ectopic lipid accumulation, is the main factor for the development and subsequent progression of T2DM and NASH. To develop effective pharmacological treatment strategies against these metabolic diseases, it is important to understand molecular mechanisms that control ectopic lipid deposition and insulin resistance.

Previous findings demonstrate that inhibition of serine/threonine protein kinase (STK25) leads to protection against HFD-induced liver steatosis and improved whole-body glucose tolerance and insulin sensitivity. In contrast, STK25 overexpression results in aggravated steatosis, promoting NAFLD and driving NASH development. Based on these studies, we investigated STK25 in the development of diet-induced NASH, described in *Paper I*. In this project, we found that mice fed methionine-choline deficient (MCD) diet were protected against NASH development following depletion of STK25. However, STK25 overexpression led to development of a more severe NASH phenotype when mice were challenged with MCD diet.

In *Paper II*, we found that overexpression of STK25 leads to increased ectopic lipid storage, fibrosis and inflammation in skeletal muscle of mice fed high-fat diet (HFD). Moreover, STK25-overexpressing mice had decreased *in vivo* insulin-stimulated glucose uptake, decreased endurance exercise performance and impairments in β-oxidation.

We also explored the role of STK25 in adipocyte lipid accumulation and maturation in *Paper III* using 3T3-L1 preadipocyte cells. We found that 3T3-L1 cells accumulated less lipid droplets and had several markers of adipocyte maturation reduced when STK25 was silenced prior to differentiation. Furthermore, we show a significant positive correlation between adipogenesis markers and STK25 expression in human adipose tissue.

Taken together, work in this thesis contributes to the concept that STK25 is a potential drug target for prevention and/or treatment of obesity-associated T2DM, NAFLD and NASH.

Keywords: STK25, T2DM, NAFLD, NASH, ectopic lipid accumulation, metabolism.

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