Göteborg, 2017

STK25 – a new key regulator of metabolic profile and a possible target for anti-diabetic drug

Akademisk avhandling

Som för avläggande av medicin doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg. Fredagen den 24 November 2017, kl 13.00

Av

Esther Nuñez-Durán

Fakultetsopponent: **Professor Ángela M. Valverde**

Alberto Sols Biomedical Research Institute (IIBm) (CSIC/UAM),
C/Arturo Duperier 4, 28029 Madrid, Spain

Avhandlingen baseras på följande delarbeten

I. Urszula Chursa, Esther Nuñez-Durán, Emmelie Cansby, Manoj Amrutkar, Silva Sütt, Marcus Ståhlman, Britt-Marie Olsson, Jan Borén, Maria E. Johansson, Fredrik Bäckhed, Bengt R. Johansson, Carina Sihlbom, and Margit Mahlapuu. **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*

II. Esther Nuñez-Durán, Belén Chanclón, Silva Sütt, Joana Real, Hanns-Ulrich Marschall, Ingrid Wernstedt Asterholm, Emmelie Cansby, and Margit Mahlapuu**. Protein Kinase STK25 Aggravates the Severity of Non-Alcoholic Fatty Pancreas Disease in Mice.** *Journal of Endocrinology 2017, 234(1):15-27*

III. Esther Nuñez-Durán, Mariam Aghajan, Manoj Amrutkar, Silva Sütt, Emmelie Cansby, Sheri L. Booten, Andrew Watt, Marcus Ståhlman, Norbert Stefan, Hans-Ulrich Häring, Harald Staiger, Jan Borén, Hanns-Ulrich Marschall, and Margit Mahlapuu**. *Stk25* Antisense Oligonucleotide Treatment Reverses Glucose Intolerance, Insulin Resistance and Nonalcoholic Fatty Liver Disease in Mice.** *Hepatology Communications*. Under review

SAHLGRENSKA ACADEMY
INSTITUTE OF MEDICINE

GÖTEBORGS UNIVERSITET

Göteborg, 2017

STK25 – a new key regulator of metabolic profile and a possible target for anti-diabetic drug

Esther Nuñez-Durán

Department of Molecular and Clinical Medicine, Institute of Medicine,
The Sahlgrenska Academy at University of Gothenburg, Sweden

Abstract

Type 2 diabetes (T2D) affects at least 285 million people worldwide and its prevalence is rapidly increasing. Understanding the molecular mechanisms controlling ectopic lipid deposition and insulin response in metabolic tissues is essential for developing new pharmacological strategies to effectively treat T2D. Obesity and overweigh are the main risk factors for developing T2D, but nonalcoholic fatty liver disease (NAFLD) also contributes to the pathogenesis of T2D. Today, achieving good glycemic control in T2D patients with the current treatment alternatives remains challenging and no specific therapy exists against NAFLD.

In this thesis, we describe protein kinase STK25 as a new key regulator of ectopic lipid deposition in skeletal muscle, liver and pancreas as well as whole-body metabolism. We have found that STK25 overexpression in mice challenged with a high-fat diet (HFD) results in an increased ectopic lipid deposition in skeletal muscle and pancreas, accompanied by an aggravated fibrosis and inflammation. The overexpression of STK25 also leads to impairments in β-oxidation and decrease in *in vivo* insulin-stimulated glucose uptake in skeletal muscle and reduced endurance exercise capacity in mice. The pancreas of *Stk25* transgenic animals shows a significant decrease in islet β/α-cell ratio and alterations in the islet architecture with an increased presence of α-cells within the islet core, together with an impaired insulin production during IPGTT after a HFD challenge. We also show that treatment with *Stk25* antisense oligonucleotides in obese mice protects against HFD-induced liver steatosis, glucose intolerance and insulin resistance. In addition, we found a significant positive correlation between nonalcoholic steatohepatitis (NASH) development and STK25 protein abundance in human liver biopsies. Furthermore, we have identified four common non-linked SNPs in the human *STK25* gene that are associated with altered liver fat: two associated with increased hepatic fat levels and two associated with decreased levels.

Taken together, our studies suggest that pharmacological inhibition of STK25 potentially provides a new-in-class therapeutic strategy for the treatment of NAFLD, T2D and related metabolic complications.

Keywords: Type 2 diabetes, insulin resistance, ectopic lipid accumulation, β-cell dysfunction, NAFLD, NASH, antisense oligonucleotides.

ISBN 978-91-629-0286-5 (PRINT)
ISBN 978-91-629-0287-2 (PDF)