Regulation of metabolism and inflammation by two protein kinases – AMPK and STK25

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 5 september 2014, kl 9.00

av

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Avhandlingen baseras på följande arbeten:

I. Nerstedt A, Johansson A, Andersson CX, Cansby E, Smith U, Mahlapuu M. **AMP-activated protein kinase inhibits IL-6-stimulated inflammatory response in human liver cells by suppressing phosphorylation of signal transducer and activator of transcription 3 (STAT3).** *Diabetologia. 2010 Nov;53(11):2406-16.*

II. Nerstedt A, Cansby E, Amrutkar M, Smith U, Mahlapuu M. **Pharmacological activation of AMPK suppresses inflammatory response evoked by IL-6 signalling in mouse liver and in human hepatocytes.** *Mol Cell Endocrinol. 2013 Aug 15;375(1-2):68-78.*

III. Cansby E, Nerstedt A, Amrutkar M, Nuñez Durán E, Smith U, Mahlapuu M. **Partial hepatic resistance to IL-6-induced inflammation develops in type 2 diabetic mice, while the anti-inflammatory effect of AMPK is maintained.** *Manuscript.*

IV. Nerstedt A, Cansby E, Andersson CX, Laakso M, Stancakova A, Blüher M, Smith U, Mahlapuu M. **Serine/threonine protein kinase 25 (STK25): a novel negative regulator of lipid and glucose metabolism in rodent and human skeletal muscle.** *Diabetologia. 2012 Jun;55(6):1797-807.*

V. Cansby E, Amrutkar M, Manneras Holm L, Nerstedt A, Reyahi 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 Sep;27(9):3660-71.*

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Regulation of metabolism and inflammation by two protein kinases – AMPK and STK25

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Type 2 diabetes mellitus (T2DM) is a widespread metabolic disorder that has reached epidemic proportions globally, and is now considered to be one of the main threats to human health. The currently available treatment options in T2DM suffer from inadequate efficacy and durability, as well as liabilities, including hypoglycemia, weight gain, edema and gastrointestinal intolerance. Since the efficacy and patient compliance of existing treatments are in many cases unsatisfactory, there is a pronounced need for novel targets, which could complement current treatment.

Evidence accumulated during the last two decades indicates that excessive caloric intake and obesity lead to a chronic low-grade inflammation in metabolic tissues, and increased inflammation may be directly involved in the pathogenesis of T2DM. Therefore, novel pharmacological treatments targeting both the metabolic and inflammatory disruptions seen in T2DM are warranted.

AMP-activated protein kinase (AMPK) is a central master switch important for regulating energy homeostasis at cellular as well as whole body level. Recently, evidence for a role of AMPK in regulation of inflammatory balance has emerged. By using AMPK agonists AICAR and metformin in liver cell lines, primary hepatocytes and in mouse model system *in vivo*, we demonstrate that AMPK activation in liver leads to decreased inflammatory response to the proinflammatory cytokine IL-6. We further show that the anti-inflammatory action of AMPK was mediated via decreased phosphorylation of several downstream components of the canonical IL-6 receptor signalling pathway. Inhibition of the IL-6 signalling cascade in liver by AMPK supports a role of this kinase as a crucial point of convergence of metabolic and inflammatory pathways in hepatocytes.

Serine/threonine protein kinase 25 (STK25) is broadly expressed in mouse, rat and human tissues. When activated, this kinase is part of several cell processes, such as development, migration and apoptosis. We, for the first time, show that STK25 also has metabolic effects. By using small interfering RNA for *Stk25* in rodent muscle cell line L6, we demonstrate that STK25 is involved in regulation of glucose uptake and lipid oxidation. Furthermore, mice overexpressing STK25, when challenged with a high-fat diet, develop reduced glucose tolerance and insulin sensitivity compared to wild-type siblings. Increased triglyceride deposition in liver and skeletal muscle, and adipocyte hypertrophy, as observed in *Stk25* transgenic mice, suggest that the underlying cause of insulin resistance in conditions of excess dietary fuels is a shift in the metabolic balance from lipid oxidation toward lipid storage in peripheral tissues. Furthermore, *Stk25* transgenic mice show increased infiltration of inflammatory cells in liver.

Taken together, both AMPK and STK25 emerge as interesting targets for future treatment of T2DM, enabling to target the dysregulation of both metabolism and inflammation seen in connection with this disease.

Keywords: AMPK, STK25, Metabolism, Type 2 diabetes, Inflammation

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