Göteborg, 2016

Roles of PI3-kinase and ARAP2 in regulating glucose metabolism

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Sahlgrens aula, Bruna Stråket 5, Göteborg
Torsdagen den 12 Maj , klockan 13.00

av Aditi Chaudhari

Fakultetsopponent:

Professor Matthias Wymann

Department of Biomedicine, University of Basel, Basel, Switzerland

Avhandlingen baseras på följande delarbeten

I. Hepatic deletion of p110α and p85α results in insulin resistance despite sustained IRS1-associated lipid kinase activity

Aditi Chaudhari, Katarina Ejeskär, Yvonne Wettergren, C. Ronald Kahn, and Victoria Rotter Sopasakis.

Manuscript

II. p110α hot spot mutations in E545K and H1047R exert metabolic reprogramming independently of p110α kinase activity

Aditi Chaudhari*, Daniel Krumlinde*, Annika Lundqvist, Levent Akyürek, Sashidhar Bandaru, Kristina Skålén, Marcus Ståhlman, Jan Borén, Yvonne Wettergren, Katarina Ejeskär, Victoria Rotter Sopasakis.

*Equal contribution

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III. ARAP2, a novel regulator of sphingolipid metabolism affects GLUT1 mediated basal glucose uptake

Aditi Chaudhari, Liliana Håversen, Reza Mobini, Linda Andersson, Marcus Ståhlman, Emma Lu, Mikael Rutberg, Per Fogelstrand, Kim Ekroos, Adil Mardinoglu, Malin Levin, and Jan Borén.

Submitted

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Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2016.

Abstract

Insulin signaling is mediated by a complex, highly integrated network which functions to control multiple metabolic and growth processes throughout the organism. A key enzyme in the insulin signaling network is phosphatidylinositol 3-kinase (PI3-kinase). PI3-kinase catalyzes the production of the lipid second messenger, phosphatidylinositol 3, 4, 5- triphosphate (PIP3), which is involved in various cellular functions such as cell growth, survival and apoptosis. In this thesis, we have investigated the impact of oncogenic mutations of PI3-kinase, as well as deletion of its key subunit isoforms on glucose metabolism. We also identified a PH-domain containing protein ARAP2, and investigated its role in lipid droplet formation.

In Paper I, we investigated the effect of combined hepatic deletion of the PI3-kinase subunits p110α and p85α (L-DKO) on insulin signaling and glucose homeostasis. L-DKO mice developed impaired glucose-tolerance, but surprisingly displayed intact IRS1-associated lipid kinase activity. The mice exhibited decreased body weight, but similar adipose tissue weight, hepatic glucose production as well as normal insulin tolerance, demonstrating a paradoxical milder phenotype compared to mice having only p110α deleted in the liver.

In Paper II, we investigated the effects of the hot spot mutations E545K and H1047R of p110α on hepatic and whole body glucose homeostasis. The expression of these mutations resulted in a reprogrammed cellular metabolism with marked accumulation of lipids and glycogen in the liver. Wild-type (wt) p110α expression did not result in hepatic lipid or glycogen accumulation despite having similarly increased expression of glycolytic and lipogenic genes. Furthermore, there was no difference in the kinase activity between the wt- and mutant-expressing mice, which suggest that the metabolic effects exhibited by the p110α mutants are linked to kinase-independent function(s) of the oncogenic p110α.

In Paper III, we identified ARAP2 as a PH-domain containing protein in the lipid droplet proteome. We show that knockdown of ARAP2 leads to diminished lipid droplet formation by decreasing the rate of triglyceride synthesis. The lower triglyceride synthesis rate resulted from decreased basal glucose uptake through lower expression of GLUT1, as well as reduced GLUT1 levels in the plasma membrane and lipid micro-domains. The effect on GLUT1 was mediated by increased glucosylceramide synthesis.

Keywords: Type 2 diabetes, phosphatidylinositol 3-kinase, metabolism, lipid droplets, ARAP2

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