Göteborg, 2020

Investigating the role of Class-1 Phosphoinositide 3 Kinases (PI3Ks) in insulin signaling and obesity

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i K2320 C. Kylberg, Medicinaregatan 7, den 19:e maj, klockan 9:00

av Angela Molinaro

Fakultetsopponent:
Professor Massimo Federici
University of Rome Tor Vergata

Avhandlingen baseras på följande delarbeten

I. Breasson L., Becattini B., Sardi C., Molinaro A., Zani F., Marone R., Botindari F., Bousquenaud M., Ruegg C., Wymann M. P., Solinas G. **PI3Kγ activity in leukocytes promotes adipose tissue inflammation and early-onset insulin resistance during obesity.** *Science Signaling. 2017 Jul 18;10(488).*

II. Molinaro A., Becattini B., Mazzoli A., Bleve A., Radici L., Maxvall I., Rotter Sopasakis V., Molinaro A., Bäckhed F., Solinas G. **Insulin-driven PI3K-AKT signaling in the hepatocyte is Mediated by Redundant PI3Kα and PI3Kβ Activities and is promoted by RAS.** *Cell Metabolism. 2019 Jun 4;29(6):1400-1409.e5.*

III. Molinaro A., Becattini B. and Solinas G. **Insulin Signaling and Glucose Metabolism in Different Hepatoma Cell Lines Deviate from Hepatocyte Physiology Toward a Convergent Aberrant Phenotype.** *Manuscript submitted and under revision.*

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Abstract

Obesity and obesity related diseases such as type 2 diabetes, cardiovascular disorders, and different types of cancer are leading causes of mortality and morbidity in modern society. However, the mechanism that links obesity to these diseases remains largely unresolved. Class 1 phosphatidylinositide 3 kinases (PI3Kα; PI3Kβ; PI3Kδ and PI3Kγ) play a major role in several physiological processes such as the immune response, the metabolic insulin action, and tissues homeostasis. This thesis aims at a better understanding of the role of the different PI3K isoforms in obesity and insulin signaling.

PI3Kγ plays an important role in leukocyte recruitment during inflammation, in the inhibition of classical macrophage activation and in promoting diet-induced obesity and insulin resistance. In **PAPER I** we have investigated the PI3Kγ mechanisms of action and we have found that the activity of PI3Kγ in hematopoietic cells is dispensable in hepatic inflammation, liver steatosis, adiposity and macrophage recruitment in adipose tissue. However, PI3Kγ activity promotes insulin resistance, the pro-inflammatory M1 macrophage phenotype and neutrophils recruitment in the adipose tissue of obese mice. This observation challenges the concept that PI3Kγ activity is a general inhibitor of classical macrophage activation.

In **PAPER II**, we aim to define the role of class-1 PI3K isoforms and RAS in insulin signaling in hepatocytes. Our data lead to a new and improved mechanism for insulin signaling where insulin-driven PI3K-AKT signaling is mediated by the activities of PI3Kα and PI3Kβ, with RAS promoting PI3Kα-dependent insulin signaling. We conclude that PI3K inhibitors discriminating between PI3Kα and PI3Kβ should be used at doses below their hyperglycemic threshold to preserve isoform specificity and achieve optimal therapeutic index.

In **PAPER III**, we have found that compared to primary hepatocytes, three most commonly used hepatoma cell lines display aberrant insulin signaling, gluconeogenic genes expression, glucose production and different electrophoretic profiles, but similar among the hepatoma cell lines. We conclude that, because the hepatoma cell lines appear to converge to a common aberrant phenotype, these cells can be a valuable tool to study the metabolic aberrations in hepatocellular carcinoma.

General conclusion: Altogether this thesis supports the concept that the therapeutic effects of PI3K inhibitors on obesity, insulin resistance and tumor promotion could be largely dissociated from their deleterious effects on glucose homeostasis by using isoform-selective inhibitors discriminating between PI3Kα and PI3Kβ.

Keywords: Obesity, insulin signaling, PI3Ks, PI3K isoform-selective inhibitors.

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