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Hepatocyte p110 α controls insulin signaling but is dispensable for free fatty acid and glucose sensing

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Abstract:

Background and aims: Class IA phosphoinositide 3-kinase (PI3K) is involved in insulin signaling through the production of the second messenger phosphatidylinositol 3,4,5 tri-phosphate (PIP3). Mouse with hepatocyte-specific deletion of p110 α ("p110 α hep-/-"), the catalytic subunit of PI3K α are glucose intolerant but protected from hepatic steatosis. We used a system biology approach to identify pathways regulated by p110 α *in vivo*.

Materials and methods: In this study, p110 α hep+/+ and p110 α hep-/- were used in different nutritional states : fed, fasted and refed. We combined transcriptomic, lipidomic, proteomic, metabolomic and histological approaches. *In vivo* studies were conducted under the EU guidelines for the use and care of laboratory animals, and they were approved by an independent Ethics Committee.

Results: As previously reported, we confirm that p110 α deletion leads to glucose intolerance without steatosis in response to aging and to high fat-induced obesity. We also provide evidence that "p110 α hep-/-" mice have normal circadian control of liver transcriptome. Then, we investigated the influence of hepatocyte p110 α -dependent signaling on liver transcriptome and proteome in fed and in fasted mice. In line with the role of PI3K α in insulin signaling, we

observed that major transcriptional targets of insulin are disrupted when p110 α is lacking in fed mice. This is associated with decreased phosphorylation of insulin-activated proteins. Interestingly, we show that this depends in a 50% reduction in PI(3,4,5)P3 production in response to insulin *in vivo*. However, we found that p110 α is dispensable for Chrebp-mediated glucose sensing in hepatocytes. More surprisingly, in fasted mice, p110 α deficiency is also very influential on liver transcriptome and lipidome. Gene ontology analysis revealed a major effect on PPAR α signaling. Given the well-established role of PPAR α in fasting, we further analysed the expression of PPAR α target genes in "p110 α hep-/-" mice. These genes, including the hepatokine FGF21, which is produced by hepatocytes in a PPAR α -dependant response to adipose lipolysis, were highly increased in "p110 α hep-/-" fasted mice. Conversely, p110 α is dispensable for the inhibition of PPAR α target during refeeding. This led us to postulate that, in "p110 α hep-/-" mice, the fasting-induced changes in PPAR α activity leading to an increase in FGF21 expression and secretion depends on adipose tissue fatty acid remodeling. Consistent with this hypothesis, we found that liver and adipose tissue fatty acid profile is modified in "p110 α hep-/-" mice in response to fasting.

Conclusion: Altogether, our data evidence that liver p110 α dependent effect on AKT is dispensable for glucose and free fatty acid signaling by CHREBP and PPAR α respectively. Moreover, we highlight lipolysis as the dominant signal for hepatocyte PPAR α activity.

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