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# Hepatocyte PI3K $\alpha$ controls the PPAR $\alpha$ -FGF21 axis and regulates whole body fatty acid homeostasis

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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 $\alpha$  ("p110 $\alpha$  hep<sup>-/-</sup>"), the catalytic subunit of PI3K $\alpha$ , are glucose intolerant but protected from hepatic steatosis. We used a system biology approach to identify pathways regulated by p110 $\alpha$  in vivo.

As previously reported, we confirmed that p110 $\alpha$  deletion leads to glucose intolerance without steatosis in response to aging and to high fat diet-induced obesity. Interestingly, we showed that "p110 $\alpha$  hep<sup>-/-</sup> mice" have normal circadian control of liver transcriptome. Then, we investigated the influence of hepatocyte p110 $\alpha$ -dependent signaling on liver transcriptome in fed and in fasted mice. In line with the role of PI3K $\alpha$  in insulin signaling, we observed that major transcriptional targets of insulin are disrupted when p110 $\alpha$  is lacking in fed mice. More surprisingly, in fasted mice, p110 $\alpha$  deficiency is also very influential on liver transcriptome and lipidome. Gene ontology analysis revealed a major effect on PPAR $\alpha$  signaling. Given the well-established role of PPAR $\alpha$  in fasting, we further analyzed the expression of PPAR $\alpha$  target genes in "p110 $\alpha$  hep<sup>-/-</sup> mice". These genes, including the hepatokine FGF21, which is produced by hepatocytes in a PPAR $\alpha$ -dependent way in response to adipose lipolysis, were highly increased in "p110 $\alpha$  hep<sup>-/-</sup>" fasted mice. This led us to postulate that, in "p110 $\alpha$  hep<sup>-/-</sup> mice", the fasting-induced changes in PPAR $\alpha$  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 $\alpha$  hep<sup>-/-</sup> mice" in response to fasting. Importantly, in obesity induced by a high fat diet, this bilateral metabolic dialogue between the white adipose tissue and the liver is inhibited, and the hepatic PPAR $\alpha$ -FGF21 axis can no longer be activated in fasting.

Altogether, our data evidence that liver PI3K $\alpha$  regulates the PPAR $\alpha$ -FGF21 pathway in hepatocytes, which impacts the white adipose tissue function during fasting. Thereby, hepatic insulin signaling controls the PPAR $\alpha$ -dependent dialogue between the liver and the white adipose tissue.

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