Neonatal overfeeding alters hepatic insulin sensitivity during lactation and leads to long-term insulin resistance and fatty liver in mice: Key role of *Mogat1*

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BACKGROUND:

Excessive energy intake and rapid weight gain early in life are associated with obesity, type 2 diabetes, hepatic steatosis and other features of the metabolic syndrome. The monoacyglycerol acyltransferase (MGAT) is an enzyme involved in an alternative pathway for triglyceride (TAG) synthesis and storage. It has been recently proposed to have potential implications in the pathogenesis of insulin resistance (IR).

OBJECTIVE AND HYPOTHESES:

To understand the mechanisms that contribute to *(1)* the development of early IR, and *(2)* the long-term programming of metabolic disease in a mouse model of childhood obesity.

METHODS:

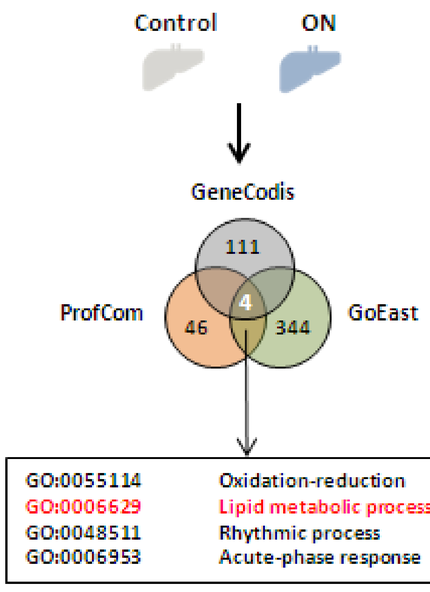
We have previously described a mouse model of neonatal overfeeding (ON) and accelerated growth. Despite similar caloric intake after weaning, ON mice with aging developed:

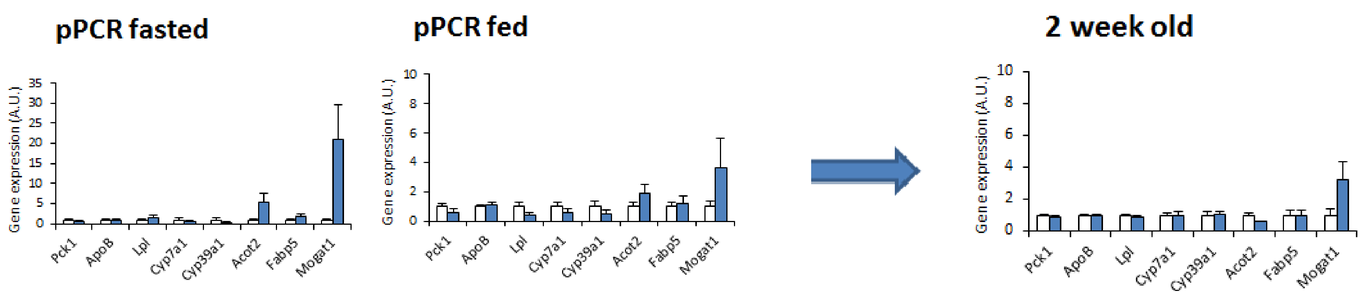
- Obesity
- IR and Glucose intolerance
- Hepatic steatosis

To gain insight about the mechanisms that lead to IR and hepatic steatosis, we performed gene expression profiling (Affymetrix) in livers from Control and ON mice.

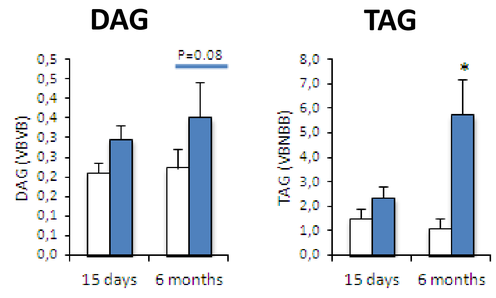
RESULTS:

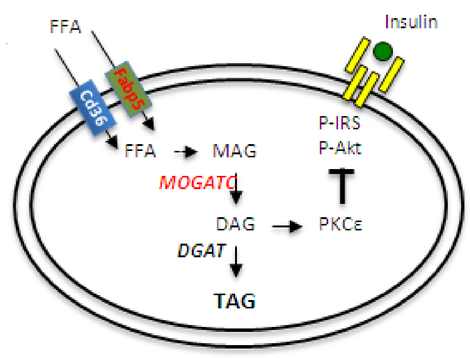
ONTOLOGIC ANALYSIS

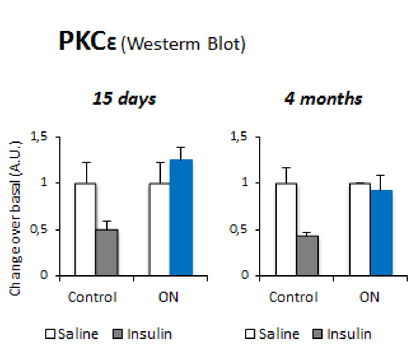




- Early alterations in genes related with lipid metabolism (*Mogat1*)
- Increased in DAG and TAG hepatic content
- We also found no changes on other pathways that could contribute to lipid synthesis and storage in the liver : synthesis *de novo*, lipid oxidation or VLDL transport (*data not show)*

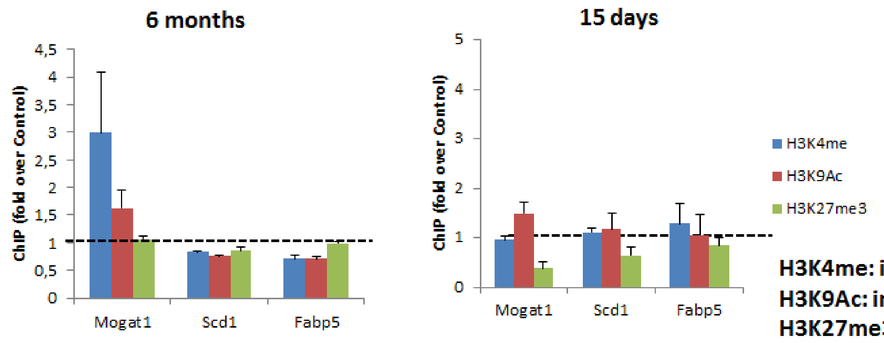






Mogat1 could cause insulin resistance and hepatic steatosis via PKCε

- We found no changes in the DNA metyhlation pattern (*data not show)*
- ChIP assays showed changes in histones methylation and acethylation pattern that up regulate *Mogat1* expression



H3K4me: increases transcription
H3K9Ac: increases transcription
H3K27me3: represses transcription

CONCLUSIONS:

Initially, the up regulation of gene expression and activity in hepatic lipid transport could be a physiologic adaptative response of ON mice to the increase influx of free fatty acids during lactation. However, the permanent changes in gene expression result later on into a maladaptative response leading to insulin resistance despite a healthy diet. Mogat1 might be a key player in the development of IR and hepatic steatosis. Therefore, targeting MGAT activity in the liver might be a novel potential strategy to improve hepatic insulin sensitivity.

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No conflict of interest

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