10 YEARS OF BREAKTHROUGHS A HEALTHIER FUTURE

RHAPSODY for precision therapy and prevention of diabetes

31

New candidate genes in insulin target tissues : ELOVL2 as a protective enzyme against glycaemic deterioration?

Justine Lallement[1], Ana Rodriguez Sanchez-Archidona[3], Sofiane Rimani[1], Nadim Kassis[1], Kelly Meneyrol[1], Jessica Denom[1], Florence Mehl[2], Leonore Wigger[2], Hervé Le Stunff[1], Mark Ibberson[2], Bernard Thorens[3], Christophe Magnan[1], Céline Cruciani-Guglielmacci[1]

1. Université Paris Descartes, Sorbonne Paris Cité, Paris, France 2. Vital-IT Group, SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland 3.Centre for integrative Genomics, University of Lausanne, Switzerland

Facts & Figures

Start date :	01/04/2016
End date :	31/03/2020
Contributions	
IMI funding :	8 130 000 €
EFPIA in kind :	6 882 049 €
Other:	606 625 €
Total Cost :	15 618 614 €
Project website :	www.imi-rhapsody.eu

Challenge

Rhapsody is an European project which gathers scientists from academic, clinical and pharmaceutical research institutions. The goal of this project is to identify new biomarkers of type 2 diabetes and find new targets genes in insulin target tissues.

RNAseq was performed on mice tissues and integrated with phenotypic datas in a network analysis.

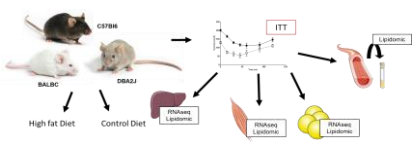


Figure 1. Mice from three different strains were fed with high fat or control diet (regular chow). At day 2, 10 or 30 of diet, we performed insulin tolerance test (ITT) and three days after, insulin target tissues and plasma samples were collected.

During a previous IMI project (IMIDIA), we found a significant positive correlation between *Elovl2* expression and insulin secretion in mouse islets from six different common strains (1).

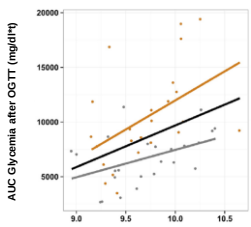


Figure 2. Scatter plot showing correlations between *Elovl2* islet gene expression and AUC glycaemia during OGTT

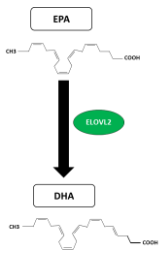


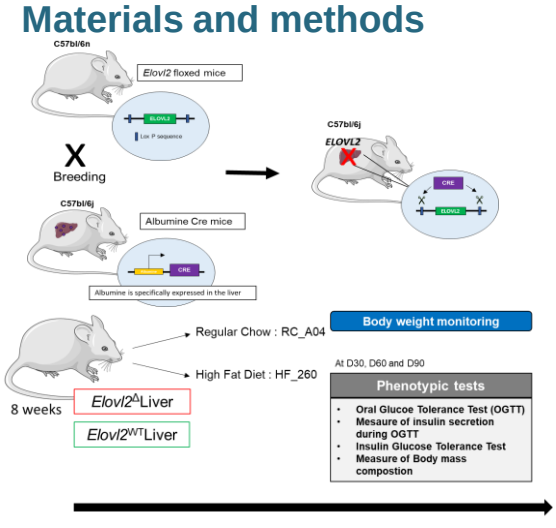
Figure 3. ELOVL2 catalyses the addition of carbons on w3-polyunsaturated fatty acids and is necessary for the endogenous production of DHA

Dietary w3-polyunsaturated fatty acids, especially docosahexaenoic acid (DHA), very abundant in fish oil, are known to influence glucose homeostasis by modulating peripheral insulin sensitivity (2).

These datas suggest a direct role of ELOVL2 in ensuring normal insulin secretion, however scarce data have been gathered about its role in peripheral insulin target tissues, especially in liver which highly expressed *Elovl2*.

Within the Rhapsody project, we aim to further investigate the role of ELOVL2/endogenous DHA axis in the liver.

Materials and methods



Results

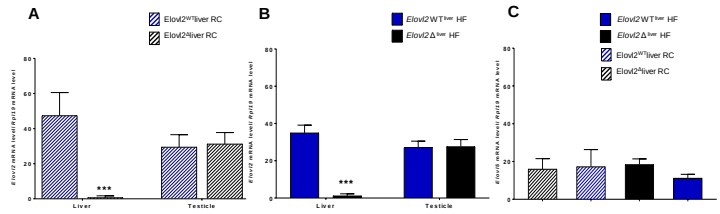


Figure 4. Validation of down regulation of *Elovl2* expression in the liver. Real-time PCR on *Elovl2* transcripts in the liver and in testicles in mice fed with regular chow (A) and high fat diet (B). Real-time PCR on *Elovl5* in the liver in mice fed with regular chow (C) and high fat diet (D). Data represents means ± SEM. *p<0,05, **p<0,01, ***p<0,001, (n=12 -18 mice per group).

The deletion of *Elovl2* is highly tissue-specific and there is no compensatory mechanism with ELOVL5.

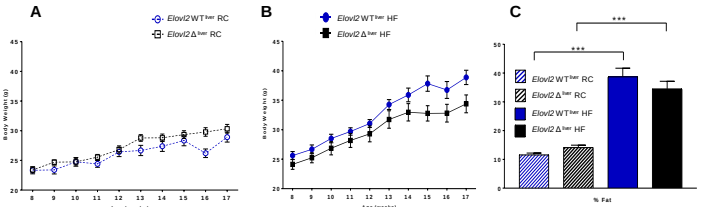


Figure 5. Effects of *Elovl2* deficiency in the liver on weight and body fat mass. Mouse Body weight fed with regular chow (A) or high fat diet (B). Body fat mass in % of total weight (C). Data represent means ± SEM. *p<0,05, **p<0,01, ***p<0,001, Control group vs KO mice (n= 6 -10 mice per group).

The Elovl2$^{\Delta}$liver mice don't display different body weight and fat mass compared to the control. High fat diet increases body fat mass both in Elovl2^{WT}liver and Elovl2$^{\Delta}$liver mice.

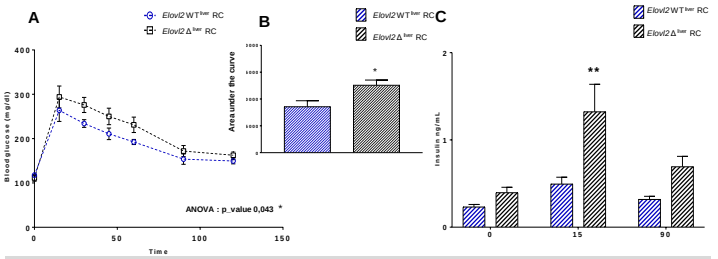


Figure 6. Effects of *Elovl2* deficiency in the liver on glucose tolerance and insulin secretion in mice 5 months old, fed with regular chow. Blood glucose measurements during an oral glucose tolerance test (OGTT) 2g/kg (A). Area under the curve values from OGTT (B). Blood insulin during OGTT (C). Data represent means ± SEM. *p<0,05, **p<0,01, ***p<0,001, Control group vs KO mice (n=4-15 mice per group).

Elovl2 deficiency in the liver decreases glucose tolerance and increases insulin secretion in mice fed with regular chow.

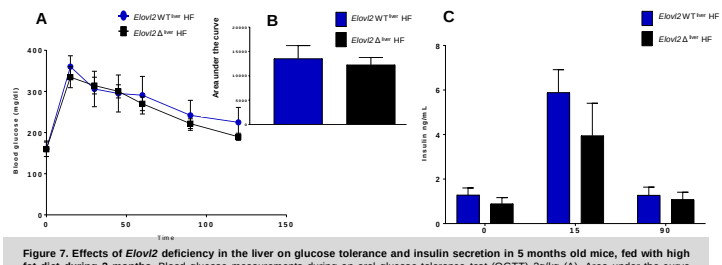


Figure 7. Effects of *Elovl2* deficiency in the liver on glucose tolerance and insulin secretion in 5 months old mice, fed with high fat diet during 3 months. Blood glucose measurements during an oral glucose tolerance test (OGTT) 2g/kg (A). Area under the curve values from OGTT (B). Blood insulin during OGTT (C). Data represent means ± SEM. *p<0,05, **p<0,01, ***p<0,001, Control group vs KO mice (n=4-15 mice per group).

Elovl2 deficiency in the liver doesn't impact glucose tolerance and insulin secretion in mice fed with high fat diet.

Value of IMI collaboration

IMI gave a financial support for this project and allow the collaboration between academics and industrials researchers, such as Servier.

Impact & take home message

This study identify Elovl2 as a promising target gene, involved in type 2 diabetes setting. Indeed, Elovl2 deficiency in the liver leads to glucose intolerance despite an increased insulin secretion in mice fed with regular chow, without difference in body weight and fat mass. These results suggest an impaired insulin sensitivity.

Perspectives : RNAseq analysis also show a significant negative correlation (p=0,009) between the *Elovl2* expression in adipose tissue and basal glycemia pointing towards a potential protective effect of adipose ELOVL2 on glucose homeostasis. We plan to further investigate ELOVL2 mechanism in adipose tissue using Cre-Lox mouse.

(1). Cruciani C. *et al.* (2017), Mol Metab, 345-351 (2). Chen C. et al (2015), Plos One..

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115881 (RHAPSODY). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This work is supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 16.0097. The opinions expressed and arguments employed herein do not necessarily reflect the official views of these funding bodies.