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

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Challenge

Rhapsody is an European project which gathers scientists from academic, clinical and pharmaceutical 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 mouse tissues and integrated with phenotypic data in a network analysis.

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

Dietary ω3-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 data 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 DNA axis in the liver.

Materials and methods

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

Results

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

The Elovl2 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 liver and Elovl2 liver mice.

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

Value of IMI collaboration

IMI gave a financial support for this project and allow the collaboration between academics and industrial 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) Grouillet E. et al (2017) 31 03 069 061 (2) Chan E. et al (2016) Ripe Papmier This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 106913 (Rhapsody). This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA. The authors declare no conflict of interest. Research and Innovation (SME) under contract number 169897. The opinions expressed and argued employed herein do not necessarily reflect the official views of these funding bodies.