Discovery of the role of the ELOVL2/docosahexaenoic acid axis in the regulation of insulin secretion and survival of rodent and human pancreatic beta cells

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Facts & Figures

Start date:	04/11/2013
End date:	12/05/2018
Contributions	Servier, Boheringer Ingelheim, Astra Zeneca
IMI funding	IMIDIA, RHAPSODY
EFPIA in kind:	servier
Project website	www.imidia.org www.imi-rhapsody.eu

Challenge

The project challenges were:

- the validation of IMIDIA database for the definition of new islet biomarkers associated to glucose tolerance and insulin secretion in mice fed with chow or high fat diet,
- Once defined Elovl2 as new biomarker of islet function, to determine its role under glucolipotoxicity conditions, and the mechanism involved on its protection effect;
- Determine the *in vivo* supplementation effects of Elovl2 product, the DHA (omega 3 fatty acid).

Approach & Methodology

To create the mice database 6 mice strains have been fed with chow or high fat diet, physiological tests have been performed and correlated to gene expression changes (RNAseq performed on isolated islets of Langerhans).

The role of new candidate genes has been investigated in rodent cell lines (INS-1, MIN6) under conditions of glucolipotoxicity (GL, high glucose and high palmitate concentrations). The cell death has been determined by caspase activity and by western blot, CPT1 role has been determined using pharmacological inhibitors or genetic tools (siRNA, adenoviral over expression). The main results have been validate in dispersed human islets.

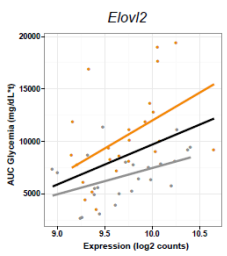
To determine DHA supplementation's role in islets *in vivo*, mice have been fed with high fat diet (HFD) supplemented or not with DHA. Physiological tests have been performed (ITT, OGTT) and islets have been isolated to determine *ex vivo* their secretion ability.

Value of IMI collaboration

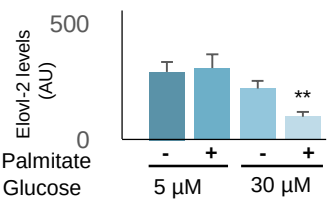
IMIDIA and RHAPSODY financed the project and allow the collaboration with many other scientists, in particular with P. Marchetti's group who gave us access to human islets. IMI gave us also the opportunity to develop collaboration with pharma.

Results

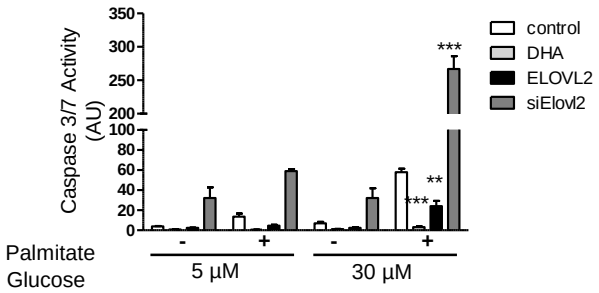
A- In mice, Elovl2 expression is correlated to insulin secretion

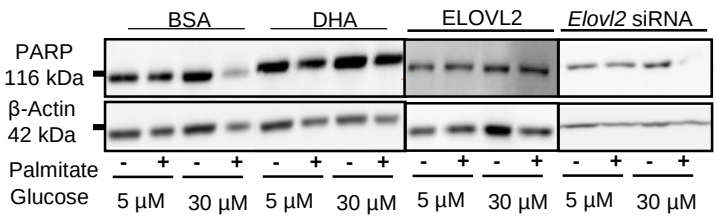


B- Elovl2 expression in INS-1 cells under GL

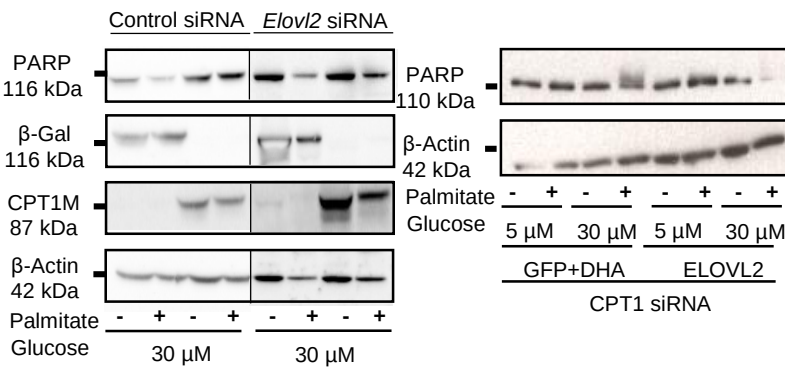


C- Elovl2 expression in INS-1 cells modulates the cell death induction under GL

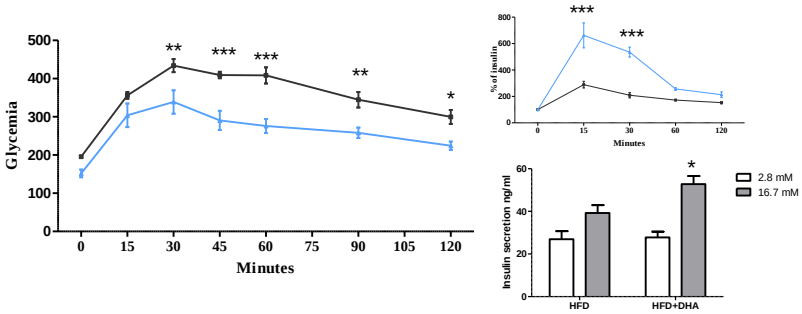




D- CPT1 modulates Elovl2-effects on GL induced apoptosis in INS1 cells.



E- *In vivo* DHA supplementation in high fat diet fed mice.



Impact & take home message

This project uncover for the first time the role of Elovl2 (and its product the DHA) as new biomarker of Islets function.

Bellini L, Campana M et al, Diabetologia. 2018 May 12.
Cruciani-Guglielmacci C, Bellini L et al, Mol Metab. 2017 Jan 26;6(4):340-351.

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