Defining the expression and metabolic regulation of alternative isoforms of the lipodystrophy protein seipin in developing adipocytes

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Introduction

- Disruption of BSCL2 gene, encoding the protein seipin, causes Congenital Generalized Lipodystrophy (CGL), the most severe lipodystrophy
- Seipin is an endoplasmic reticulum membrane protein and has a fundamental role in adipose tissue development and maintenance, as demonstrated by cellular and *in-vivo* models
- We have recently shown that seipin dodecamers create a scaffold for critical pro-adipogenic enzymes (lipin-1 and 1-acylglycerol-3-phosphate-O-acyltransferase 2, AGPAT2) to act in a single functional complex
- Sequences annotated in ENSEMBL suggest that several splice variants of seipin may exist, with distinct polypeptide structures
- Overall, seipin may play critical roles in both adipose tissue development and lipid storage, so influencing metabolic health

Loss of Bsl2/seipin causes lipodystrophy in humans

Seipin is an ER membrane protein that can bind enzymes regulating lipid synthesis and adipocyte development

Aims

- To examine the capacity of seipin to interact with other enzymes involved in lipid metabolism
- To investigate the expression and characteristics of seipin splice variants, specifically the long (seipin-L) and the short (seipin-S)

Methods

- Co-immunoprecipitation and immunofluorescence experiments to investigate the association of seipin with interacting partners
- Gene expression and proteomic analyses to examine seipin variants expression on adipocytes and ex-vivo tissue samples from mice fed a high fat diet (HFD)

Results

- In addition to AGPAT2 and GPAT3, seipin can interact with the key enzymes of lipid synthesis [AGPAT1](#) and [GPAT4](#)

- 2-dimensional analysis of proteins from differentiating adipocytes reveals altered patterns of seipin immunoreactivity, indicating the presence of different seipin isoforms

- Seipin transcripts have distinct tissue expression and their expression is influenced by high fat diet feeding

Conclusions

- Seipin binds to AGPAT1, AGPAT2, GPAT3 and GPAT4, and may act as a molecular scaffold to regulate both lipid synthesis and the generation of pro-adipogenic signals
- The isoforms of seipin expressed can be influenced by dietary fat intake in a tissue-specific manner
- Tissue specific alterations in the expression of seipin isoforms may influence lipid handling and so metabolic health in response to high-fat diet