Structural characterization and functional role of TGR5 in hepatic dysfunction and adipose tissue related diseases

Place of work: BioISI-FCUL and iMED-FFUL

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Abstract / MSc thesis project proposal

As obesity reaches epidemic proportions, Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming the most prevalent liver disease worldwide. Recently, it was shown that the adipose tissue (AT) comprises an important source of circulating exosomal miRNAs in both mice and humans, capable of regulating mRNA translation in the liver. In parallel, bile acids activate the metabolic receptor TGR5 in brown and white AT, thus increasing the energy expenditure and consequently preventing obesity and insulin resistance. Finally, TGR5 has been detected in exosomes; and exosomes released from brown AT contain miR-99b that targets *Fgf21* in the liver. Altogether, exosomal miRNAs, whose expression is likely to be modulated by TGR5, may represent a still unidentified link between AT and liver metabolism. A better understanding of the signaling pathways connecting metabolic impaired AT and hepatic dysfunction will help in identifying novel biomarkers and therapeutic targets for metabolic diseases. Therefore, under this Master Thesis project, the candidate will learn and use multiple computational and experimental approaches to identify novel agonist(s) of TGR5 and inquire this protein's role in adipose exosomes (ad-exos) pathways. The specific objectives of this project are:

OBJECTIVE 1: SCREEN, IDENTIFY AND EVALUATE NOVEL TGR5 AGONISTS

- *In silico* structural characterization of TGR5 structure and identification of the main structural determinants regulating the interaction between this protein and known agonists using molecular dynamics based approaches;
- Identification of novel TGR5 agonists using molecular docking screening campaigns with different purchasable compound libraries.

OBJECTIVE 2: EVALUATION OF AD-EXOS ROLE IN LIVER CELLS, *IN VITRO*

- Determine whether TGR5, or its activation by the identified agonist(s), modulate secretion of ad-exos, using different populations of adipocytes;
- Investigate the uptake of ad-exos by hepatocytes, kupffer cells and liver endothelial cells;
- Characterize the role of ad-exos in modulating NASH-associated pathogenic mechanisms in liver cells.

In the end of this project, the selected student will compile the results in the form of a Master thesis and in the form of a scientific paper to be submitted to an international peer-reviewed scientific journal.