Title of the PhD project

Role of the Notch pathway in ASC-mediated Th17 cell promotion in obesity and type 2 diabetes (ASCODIL-17)

Disciplines: Sciences de la Vie et de la Santé
Laboratory:Inserm U 1060-Carmen/Hubert Vidal/ Equipe1: Adaptations Nutritionnelles, Environnement et Diabètes
Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Description

Scientific background and rationale:
Adipose tissue (AT) inflammation in obese subjects is considered as a causal event for insulin resistance and type 2 diabetes (T2D). This is related to infiltration of AT with immune cells, among which the T-helper 17 (Th17) cell subset, which mainly secretes IL-17A/F cytokines. Moreover, IL-17A is also known to favour insulin resistance development, and adipogenesis inhibition. Recently, we have discovered that adipose stem cells (ASC) from obese, but not lean donors, contribute to Th-17 promotion through contact-dependent interactions and soluble factor secretion¹. ASC-mediated IL-17A secretion was associated with increased secretion of IL-1β and IL-6. Interestingly, those pro-inflammatory cytokines inhibited in turn ASC adipogenesis and insulin-sensitivity of adipocytes derived from obese ASC.

Aim:
The goal of our research program is to characterize the mechanisms by which ASC from obese subjects polarize T cells towards the Th17 cell pathway and induce insulin-resistance.

Description of the project methodology:
We will focus on the Notch pathway because it has been implicated in Th-17-mediated auto-immune or chronic inflammatory diseases, as well as in type 2 diabetes. Therefore, we will use mice deficient for a Notch Ligand which is involved in ASC-mediated inflammation. Those mice will be subjected to a standard, or high fat/hypercaloric diet. Adipose tissues, as well as liver, and muscles will be harvested. Glucidic and lipidic metabolism will be explored in those tissues and in periphery as well, using functional and biochemical assays, immuhistochemistry, and RT-qPCR.

Expected results:
We expect that deletion of the Notch ligand will inhibit MSC-mediated Th17 promotion and inflammation as well in adipose tissues. This should improve adipogenesis, and decrease insulin-resistance inside adipose tissues, but also, inside muscles and liver. We also expect that obesity will be impaired.

Perspectives:
Identification of a putative marker, and/or therapeutic target , for insulin resistance/type 2 diabetes in obese individuals

Skills required:
Cell culture , animal studies ( but this can be teached during thesis) , Q RT-PCR, western blotting, immunofluorescence. Motivation, and in immunology

Bibliography:
Chehimi M, Vidal H, Eljaafari A. Pathogenic Role of IL-17-Producing Immune Cells in Obesity, and Related Inflammatory Diseases. J. Clin Med. 2017 6

Key-words:
Mesenchymal Stem cells, IL-17, obesity, type 2 diabetes, inflammation, Notch pathway

Contact: Application should include: CV, application letter, Names and addresses of two references. The application file should be sent before May 14, 2017 to: assia.eljaafari@univ-lyon1.fr . The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.