THESIS TOPIC

Subject N° (to be completed by the ED):
FUNDING: □ Requested ☑ Acquired
Funding origin: 50% ARED / 50% CDE

Thesis title:
Role of metabolism in the acquisition of regulatory functions of B lymphocytes.

3 keywords: B lymphocytes, control of the immune response, auto-immune diseases.

Unit / team: Lymphocytes B et Auto-Immunité (LBAI, UMR 1227)

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Socio-economic and scientific context (approximately 10 lines):
Millions of people suffer from autoimmune diseases. Among these pathologies, in which the immune system reacts abnormally against our own constituents, systemic autoimmune diseases (lupus, Gougerot-Sjögren ...) are a group of chronic inflammatory diseases whose characteristic is the presence of auto-antibodies in the serum (directed against components of the Self) but also sometimes the presence of defective regulatory B lymphocytes (Breg). However, Bregs are one of the links involved in the dysfunction of immune responses, without knowing why. While each clinical entity can be considered “rare”, together they constitute the third leading cause of morbidity in the world. This is why these diseases were at the center of the European IMI PRECISESADS project for which the LBAI (UMR1227) participated in the collection of multiple biological data (genomics, transcriptomics, epigenomics, metabolomics, proteomics). These data, including information on energy metabolism, are now available since all 3,000 patients have been included. Recent publications strongly suggest that energy metabolism plays an underestimated role in the development of B lymphocytes and in the acquisition of their functions. Thus, the objective of this thesis will be to understand the role of energy metabolism in the development of Bregs and its influence on autoimmune responses.

Working hypothesis and aims (approximately 8 lines):
Energy metabolism governs the development of immune cells. The pentose phosphate pathway (PPP), the glutaminolysis and the fatty acid oxidation pathway are involved to meet the energy demands and functional needs of lymphocytes. Glucose-6-Phosphate is the entry point for the PPP pathway that generates riboses for nucleotide synthesis. During glutaminolysis, glutamine is metabolized into glutamate, the fate of which depends on the state of activation of the immune cell. Either it is completely oxidized to generate ATP or it is used to replenish the Krebs cycle for the biosynthesis of macromolecules. Beta-oxidation of fatty acids generates acetyl-CoA to enter the Krebs cycle and provides additional energy. Recent publications suggest that these pathways play an important role in the acquisition of Breg functions. We hypothesize that deregulation of energy metabolism could be responsible for the development of defective Breg and contribute to the production of pathogenic autoantibodies. Do the metabolic pathways involved vary between patients and controls? According to the type of autoimmune diseases? Can we act on these metabolic pathways to restore Breg functions? Is the transformation into lymphoma seen in some patients influenced by metabolic pathways?

Main milestones of the thesis (approximately 12 lines):
In a first step, we will establish the molecular signature of the metabolic pathways of B lymphocytes in pathological and normal situations thanks to the transcriptomic and metabolomic data of the PRECISESADS project. In a second step, thanks to the in vitro stimulation models that we have already published (Achour, 2017; Mohr, 2018; Amrouche, 2019), we will identify the metabolic pathways involved when B lymphocytes polarize into Breg to control the immune responses. Next, in order to assess the impact of metabolic pathways in autoimmunity settings, we will compare the expression of transcripts in deficient Bregs (lupus cells) versus efficient Bregs (control cells). Further, from a therapeutic perspective, we will determine the transcriptional changes in metabolic pathways that occur when Bregs functions are restored in vitro (Amrouche, 2019). In a final step, we will assess the influence of metabolic pathways in the transformation of B lymphocytes from patients with Gougerot-Sjögren into lymphoma. In particular, in B lymphocyte infiltrates within the salivary glands, we will evaluate the expression of modulators of metabolic pathways by the Hyperion technique based on an original multi-parametric analysis. We will complete this information with in vitro stimulation in order to identify the pathways responsible for the appearance of the "pro lymphoma" profile, and we will seek to characterize the way to slow down the orientation towards this profile through the use of specific drugs against the identified pathways.

Scientific and technical skills required by the candidate (2 lines):
The profile sought is that of a student with solid knowledge in immunology, and in cell culture techniques, proteomic analyzes, flow cytometry and molecular biology. Knowledge of bioinformatics is a benefit.

3 publications from the team related to the topic (last 5 years):

National and international collaborations:
- European Innovative Medicines Initiative (IMI) project "Molecular Reclassification to Find Clinically Useful Biomarkers for Systemic Auto-immune Diseases (PRECISESADS)"
- European Horizon 2020 Research and Innovation Programme "HARMONIzation and integrative analysis of regional, national and international Cohorts on primary Sjögren’s Syndrome (pSS) towards improved stratification, treatment and health policy making disease."
- European Innovative Medicines Initiative (IMI) project "NEW Clinical Endpoints in primary Sjögren’s Syndrome: an Interventional Trial based on stratifying patients (NECESSITY)"
- European IMI2 project "Taxonomy, Treatment, Targets and Remission. Identification of the Molecular Mechanisms of non-response to Treatments, Relapses and Remission in Auto-immune, Inflammatory, and Allergic Conditions (3TR)"