Profile N° (à remplir par VAS) **FUNDING Planned**

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Sheet abstract of thesis 2023 **Disciplinary Fields** **Biologie fondamentale et Santé**

Thesis Title : (1-2 lines)
Crosstalk between ILC2 and their supportive niches, gatekeeper of bone marrow homeostatic functions?

3 keywords : (1 line) **ACRONYME** CINIMA
Bone marrow microenvironment / inflamation / aging and obesity

Unit/Team of supervising : (1-2 lines)
INSERM U1236 – MOBIDIC - Rennes

Name of the scientific director and co-director : (1 line)

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Socio-economic and scientific context : (10 lines)

Primarily present in mucous membranes, innate lymphoid cells (ILCs) are effector immune subpopulations that participate in the maintenance of tissue homeostasis through the induction of a rapid immune response. Type 2 ILCs (ILC2) share the expression of cytokines and transcription factors with Th2 lymphocytes. Thus, their activation promotes tissue repair and immune response to infections. In adults, ILC2s are derived from lymphoid progenitors present in the bone marrow (BM) and their final maturation is favored there. Maturation and activation of ILC2 are initiated in the peripheral residence tissues but their role in the BM is poorly understood. However, there is increasing evidence that the development of hematologic diseases is strongly associated with deregulation of hematopoietic niches in the bone marrow, especially during aging and obesity where a chronic inflammatory state exists.

Assumptions and questions (8 lines)

The BM microenvironment that promotes ILC2 development is not known. We propose to define the niches in the BM that promote their development by combining our knowledge of the factors required for ILC2 development and the characteristics of the mesenchymal cell (MC) subpopulations in the BM. Conversely, ILC2 are able to regulate tissue homeostasis by controlling the differentiation of MCs such as adipocytes. Deregulation of ILC2 contributes to many diseases such as airway hyperreactivity or obesity. The IL33/ILC2 axis is at the center of these adverse conditions. Interactions between IL33+ MCs and ILC2 in the periphery have been considered to mediate the anti-inflammatory reflex that controls tissue homeostasis. We believe that ILC2 perform the same functions in the BM. We therefore propose to decipher the mechanisms of interaction between BM CMs and ILC2 and their influence on inflammation during aging and obesity.

The main steps of the thesis and demarche (10-12 lines)

The thesis will proceed in three main steps. First, we will seek to identify MCs capable of supporting ILC2 development. To do so, we have set up tools in the lab to analyze subpopulations of BM MCs by cytometry and single cell sequencing. We will also use reporter mice systems that will allow us to precisely localize ILC2 to the cells of the microenvironment. We will then define with the same tools the role of interactions between mature ILC2 and MCs on hematopoiesis. In order to understand these interactions, we will use mice that show an early arrest of ILC2 development. Finally, we will characterize the interactions between ILC2 and the microenvironment during obesity and aging. To answer these questions, we will take advantage of the tools developed in the first two parts of the project to apply them in aged mice and mice on a high-fat diet.

Methodological and technical approaches considered (4-6 lines)

This study is based on the use of reporter mouse models allowing to trace the differentiating ILCs, as well as mice with ILC2 maturation defects. The interrelationships between MCs and ILC2 will be analyzed by flow cytometry and confocal microscopy. Molecular analyses will be performed on single cells by single cell RNAseq. These analyses will be performed in young and old mice, as well as in mice on a high-fat diet to place them in the context of obesity.

Scientific and technical skills required by the candidate (2 lines)

- strong knowledge in immunology and hematology
- competences in molecular and cellular biology, with an interest in bioinformatics approaches