SORBONNE UNIVERSITÉ

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Title of the research project :

Thesis supervisor (HDR) :

Name : Surname :

Title :

email :

Professional adress :
(site, dresse, bulding, office…)

Research Unit

Name :

Code *(ex. UMR xxxx)* :

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) :

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :

Project DOLOREG

Very little is known on the role of endogenous opioids on the regulation of the immune response. Endogenous opiods are major regulators of pain that function as analgesic and several reports describe the production of those molecules in primary leukocytes [1]. They signal through various opioid receptors on sensory neurons to block nociception (peripheral sensation of pain). Met-enkephalin (MENK), the opioid peptide derived from proenkephalin (Penk) cleavage, was shown to either inhibit or enhance T cell proliferation, both being reversible by Naloxone, an antagonist of all opioid receptors [2]. Our survey of publicly available datasets and our own results generated in the team of Dr B Salomon show that murine regulatory T cells are enriched for Penk mRNA relative to other subsets at steady state. Several lines of experimental evidence led us to conclude that Penk might be positively regulated in Treg by the transcription factor BATF through TNFR-mediated signaling (1) . Moreover, we recently observed that Treg of the tumor up regulated Penk relative to Tconv at the protein level (unpublished), suggesting a role for Penk in the tumor micro-environment. Furthermore, CD4+ T-cell-derived enkephalins are involved in the regulation of nociception in the context of infection-induced inlammation and inflammatory bowel diseases [4,5]. Earlier results showed that Treg were involved in pain control in models of peripheral nerve injury in Treg-depleted mice [6,7] but the data were confounded by the major inflammation that arise in those Treg-depleted mice. More recently, a role for TNFR2 expressed by Treg on nociception in the same model of peripheral nerve injury was suggested [8] but the evidence were indirect and the mechanism by which TNFR2 and Treg would control pain was not adressed. However, nothing is known on the role of enkephalins produced by Treg in cancer. Thus, our observations exposed above raise two questions: 1) are enkephalins produced by Treg involved in their suppressive function in cancer? and 2) are those T-cell derived enkephalins also involved in the regulation of pain in cancer? Our project will address the hypothesis that **Treg might be central in the control of both the immune and the nociceptive responses to cancer**. For the present project, we will address this unexplored issue using various models of ectopic tumor growth in mice deficient for Penk only in Treg, coupled to high throughput cellular and molecular techniques. Given the confounding literature and the lack of information regarding enkephalins and cancer, we have planned an extensive set of experiments to determine whether TNFR2 regulate enkephalin production by Treg and whether those regulate pain via TNFR2-mediated production of enkephalins. Results from these different set of experiments should demonstrate that endogenous opioids are novel players of immunosuppression and should reveal a crucial role for TNFR2 in regulating immunosuppression and pain in cancer. We will have acceeess to up to date animal models in which the expression of Penk will be followed by flow cytometry and ablated specifically in Treg. These models will be used to decipher in vivo the role of Penk in immunosuppression and pain control. Furthermore, single cell RNA equencing will be performed in the tumor micro environment to determine which cells and pathways are important in those process. Further details will be given after selection of suitable candidates. **For this project, we are looking for a motivated immunologist with a solid appetite for animal experimentaions and technically challenging experimentations. A deep knowledge/interest for flow cytometry and cell culture is mandatory. An interest in Bioinformatics would be an asset while French language is not required. A good English level is therefore absolutely required. This project is supported by a grant from Sorbonne University.**

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