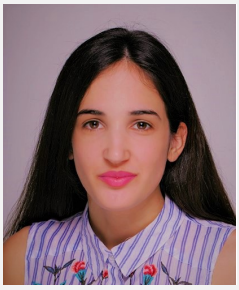
ImmunoTools *special* Award 2018



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Deciphering the role of activin-A during the differentiation of pathogenic Th17 cells in the context of central nervous system inflammation

Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that affects approximately 2.5 million worldwide. Studies in experimental autoimmune encephalomyelitis (EAE), a widely-used mouse MS model, have implicated Th17 cells as key drivers of autoimmune responses in the CNS. Encephalitogenic Th17 cells cross the BBB and exacerbate inflammatory responses, triggering a chronic self-sustaining neurodegenerative process. Although currently-available immunomodulatory therapies decrease entry and activation of CNS-reactive T cells, they do not halt MS and are associated with serious side effects. Hence, there is an imperative need to identify novel immunoregulatory factors that can restrain the highly pathogenic potential of autoreactive Th17 cells and ameliorate disease severity in the growing number of MS patients.

Activin-A is a cytokine that belongs to the TGF-β and has been implicated in critical biological processes. Our previous studies have uncovered a key immunosuppressive role for activin-A in the context of allergen-driven airway inflammation. Pertinent to human autoimmune diseases, activin-A is increased in the serum and synovial fluid of patients with rheumatoid arthritis and systemic lupus erythematosus (SLE) and correlates with SLE activity. Still, the precise in vivo role of activin-A in the suppression of encephalitogenic Th17 responses and autoimmune inflammation in the CNS remains elusive.

Preliminary findings/Hypothesis: Preliminary results from my PhD thesis reveal that activin-A is significantly increased in the CSF of MS patients, pointing to a role in CNS autoimmune inflammation. Notably, our in vivo findings also uncover that activin-A administration after disease onset, in a therapeutic regime, attenuates EAE severity and decreases mortality, associated with markedly decreased parenchymal and meningeal inflammation in SC sections and reduced demyelination.

On the basis of the aforementioned strong preliminary data, I would be extremely interested to further investigate the role of activin-A in the suppression of encephalitogenic Th17 responses and autoimmune CNS inflammation in vivo. Part of the proposed studies will also explore whether activin-A alters the phenotype of Th17 cells from pathogenic to suppressive in the context of CNS inflammation.

Methodology: To address my hypothesis, I will culture naive $CD4^+$ T cells in the presence of recombinant activin-A or control (PBS) and anti-CD3/CD28 and differentiate these cells with recombinant IL-6, IL-1b and IL-23 towards the Th17 subtype. Importantly, I will also examine the phenotype (CD3, CD4, CD8a, CD45) and cell activation status (CD25, CD44, CD62L) of these cells by flow cytometry as well as the cytokines that they secrete using commercially available ELISA Kits (IL-6, GM-CSF, TNF-a, IL-17A).

Significance: We strongly believe that our results will uncover activin-A as a novel therapeutic target that may be exploited to ameliorate MS severity and progression. In fact, we expect that administration of activin-A will significantly suppress autoimmune CNS inflammation, associated with decreased pathogenicity of CNS-reactive Th17 cells and alleviate EAE severity. Receiving the ImmunoTools Special Award is very important for the execution of the designed experiments during my PhD thesis, as it will provide our group with the necessary reagents, including flow cytometry antibodies, recombinant proteins and ELISA kits that will lead to the completion of our research plans.

ImmunoTools *special* AWARD for **Georgia-Artemis** includes 25 reagents

FITC - conjugated anti-mouse CD3e, CD4, CD25, CD44, CD45, CD62L

recombinant human cytokines: rh Activin A

recombinant mouse cytokines: rm IL-1b, rm IL-6

mouse ELISA-set (for one 96 plate): mouse GM-CSF, mouse IL-6, mouse IL-17A, mouse TNF-a

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