ImmunoTools *special* Award 2014

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The role of Th2 and eosinophils in control of joint inflammation

Rheumatoid arthritis (RA) is the most severe chronic inflammatory joint disease. It is characterized by a high level of chronicity and the failure to spontaneously resolve inflammation despite absence of the inflammatory trigger. Ineffective resolution is therefore a major clinical challenge and unmet need in understanding arthritis.

To date, the factors leading to resolution of arthritis remain obscure. In this project, we aim to define a cellular and molecular pathway, which fosters the resolution of inflammatory arthritis. We will therefore revisit a part of the immune response, which is well known for allergy but largely unexplored in the field of arthritis. Considering the inverse association between atopy and RA, we suspect that Th2 cells, alternatively-activated macrophages (AAM) and eosinophils, which form a well known functional cluster in allergy may at the same time foster the resolution of inflammatory diseases like arthritis.

In support of this concept, we show that a robust activation of the Th2-AAM-eosinophil axis mitigates the course of inflammatory arthritis, suggesting that this pathway can impact this severe inflammatory joint disease. Furthermore, previous and our own human data not only suggest spurious activation of Th2 associated cytokines IL-4 and IL-13 in very early arthritis but also a substantial number of Th2 cells present in the joints of patients with RA. We therefore aim to define the role of the Th2-AAM-eosinophil axis in the resolution process of arthritis in more detail. To do this, we have developed a model, where we expose arthritic mice to the activation of the Th2-AAM-eosinphil axis by challenging them with the helminth Nippostrongylus brasiliensis (Nb). We will use this method in several different arthritis models in order to define its effect on the resolution of disease. In this context, we will also include more advanced arthritis models, where inflammation can be timely switched on or turned off. Furthermore, we will define the molecular and cellular mechanism of the resolution process elicited by Th2-AAM-eosinophil axis activation. We will examine the role of IL-4 and IL-13 in linking Th2 with the activation of AAMs and eosinophils. Furthermore,

we will dissect the role of eosinophils, basophils and type 2 innate lymphoid cells in this process using genetic or pharmacological approaches. With respect to human investigations, we will make use of a specific study (Retro), where we have collected data on drug tapering and stopping in RA patients, allowing us to analyze the Th2-AAM-eosinophil axis in patients with true resolution of the disease or where the disease is only suppressed by anti-inflammatory drugs. Analyses will comprise serum levels of cytokines related to the Th2-AAM-eosinophil axis, immunophenotyping of blood cells as well as analyses from synovial biopsies. Hence, the ImmunoTools reagent especially the diverse cell surface markers and ELISA kit would be a huge benefit for our study. Taken together, these analyses will allow us to get a com-prehensive view on the mechanisms of resolution in arthritis and potential strategies to foster this process.