UKE Paper of the Month Februar 2019

Molecular and functional heterogeneity of IL-10-producing CD4+ T cells

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ABSTRACT: IL-10 is a prototypical anti-inflammatory cytokine, which is fundamental to the maintenance of immune homeostasis, especially in the intestine. There is an assumption that cells producing IL-10 have an immunoregulatory function. However, here we report that IL-10-producing $CD4^+$ T cells are phenotypically and functionally heterogeneous. By combining single cell transcriptome and functional analyses, we identified a subpopulation of IL-10-producing $Foxp3^{Neg}$ $CD4^+$ T cells that displays regulatory activity unlike other IL-10-producing $CD4^+$ T cells, which are unexpectedly pro-inflammatory. The combinatorial expression of co-inhibitory receptors is sufficient to discriminate IL-10-producing $CD4^+$ T cells with regulatory function from others and to identify them across different tissues and disease models in mice and humans. These regulatory IL-10-producing $Foxp3^{Neg}$ $CD4^+$ T cells have a unique transcriptional program, which goes beyond the regulation of IL-10 expression. Finally, we found that patients with Inflammatory Bowel Disease demonstrate a deficiency in this specific regulatory T-cell subpopulation.

STATEMENT: *This paper challenged a long-sanding dogma: all IL-10-producing $CD4^+$ T cells are regulatory. In contrast we show that IL-10-producing $CD4^+$ T cells are a functional heterogeneous population of cells and only the simultaneous expression of co-inhibitory receptors enable the separation between effector and regulatory sub populations in mouse and human. To prove this we used a newly developed technology - single cell RNA sequencing - which was never used before at UKE. Finally, we showed that IBD patients have a defect in this regulatory subset of IL-10-producing $CD4^+$ T cells. Together, these findings will pave the way to monitor and therapeutically target this cell subset in inflammatory diseases.*

BACKGROUND: This work is an example of collaborative research and involved the combined expertise of the SFB 841 and SFB 1192. This paper was indeed the result of a long collaboration within several UKE departments and also across different Universities in Europe and around the world.
Prof. Samuel Huber (co-last author) and Leonie Brockmann (first author) are part of the I. Department of Medicine while Prof. Nicola Gagliani (co-last author) is part of the I. Department of Medicine and of the Department of General, Visceral and Thoracic Surgery. All these authors have a strong interest in the basic aspect of T cell immunobiology, but also in translational science. In order to perform the single

cell RNA sequencing these authors collaborated with Dr. Christian Krebs at the III. Department of Medicine and with Prof. Eduardo Villablanca at the Karolinska Institute in Sweden. From 2017 to 2018, the postdoc program of UKE supported Leonie Brockman, while part of the project, especially the part related to single cell RNA seq, was supported by the ERC project of Nicola Gagliani.