ImmunoTools *special* Award 2017

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The Role of PTPN2 in Dendritic Cells in Intestinal Inflammation

Inflammatory Bowel Disease (IBD) characterized by chronic and/or relapsing intestinal inflammation consists of two main forms: Crohn's Disease and Ulcerative Colitis. Currently, more than 15'000 people are affected by IBD in Switzerland. IBD patients suffer from severe abdominal pain, diarrhoea, and the occurrence of extra-intestinal manifestations affecting skin, eye or joint is very common. More than 200 gene loci have recently been associated with altered susceptibility for developing IBD. Variants within the gene locus encoding Protein Tyrosine Phosphatase non-Receptor type 2 (PTPN2) are associated with increased risk to develop IBD, but also with other inflammatory disorders, including rheumatoid arthritis, type 1 diabetes and psoriasis. The role of PTPN2 in T cells and intestinal epithelial cells has been investigated previously but its role in dendritic cells (DCs) remains unclear. Understanding the DC specific role of PTPN2 is of particular interest, since DCs play a crucial role in activation of T cells and orchestrating immune responses in general. In the intestine, DCs are important for maintaining tolerance against commensals and food antigens, thus preventing exacerbated immune reactions.

The aim of our is to address the role of PTPN2 during intestinal inflammation with a focus on its role in DCs. We will address how PTPN2 affects cytokine production and antigen presentation in DCs and how this affects colitis severity.

We generated mice with a specific loss of PTPN2 in DCs (PTPN2xCD11cCre mice). Even without any treatment, these mice develop symptoms of systemic loss of tolerance, characterized by severe skin inflammation, splenomegaly as well as inflammatory infiltrations in the liver and the lung. These symptoms start to develop around 10-15 weeks of age but onset and severity of the symptoms varies between individuals, and results in sudden, spontaneous death in some mice. Further, PTPN2xCD11cCre mice show increased numbers of effector/memory T cells within $CD4^+$ and $CD8^+$ T cells in the spleen. However, severity of DSS-induced acute and chronic colitis was not affected upon loss of PTPN2 in DCs. *Ex vivo*, PTPN2-deficient

BMDCs differentiated from bone marrow cells show increased phosphorylation of nuclear factor (NFκB) p65, as well as enhanced expression levels of TNF and the co-stimulatory molecules CD80 and CD86. These results indicate a role of PTPN2 in DCs in T cell activation.

In the next step, we will analyse immune cell populations across different organs by flow cytometry in PTPN2xCD11cCre mice of different age (after weaning, 10 weeks, 25 weeks). In order to determine immune cell frequencies, a wide range of fluorescently-labelled cell surface markers will be used, including but not limited to CD3, CD11b, CD11c, CD24, CD64, Ly6C, Ly6G, MHC class II. These antibodies to mouse antigens would be invaluable to discriminate and sort DCs and DC subsets from other myeloid cell populations. The effect of PTPN2 in DCs on T cell activation and polarization will be evaluated by intracellular cytokine staining.

The results obtained from these studies will help to understand the DC specific role of PTPN2 in IBD pathogenesis and ultimately, our findings will generate a better understanding of the mechanisms involved in IBD pathogenesis. Understanding how presence of the disease-associated variant in PTPN2 affects immune responses will help to develop novel, more efficient treatment options not only for IBD, but inflammatory disorders in general.