Abstract

The ability of the immune system to tolerate self-antigens while mounting appropriate responses to pathogens is indispensable for the survival of the organism. Despite years of research, many details of the mechanisms of self-tolerance are still not well understood.

The objective of this thesis is to extend our knowledge of the mechanisms of immune tolerance. The core of the PhD thesis consists of five publications related to two main research directions. The first one addresses the mechanisms of peripheral immune tolerance established by regulatory T cells (Tregs). We showed that Tregs increase the quorum of self-reactive CD8+ T cells required for the induction of autoimmunity. In addition, we identified a novel subset of antigen-stimulated $CD8^+$ T cells, which expand in the absence of Tregs. We called them super-effector T cells. We revealed that the administration of IL-2 phenocopies the absence of Tregs, i.e., it induces super-effector T cells, and enhances $CD8^+$ T cell response in autoimmunity and cancer. Our results provide strong evidence that the major suppressive mechanism of Tregs is limiting IL-2 availability for $CD8^+$ T cells. Furthermore, in a collaborative project, we have shown that MyD88 signaling in thymic epithelial cells contributes to the development of Tregs and thus to the establishment of tolerance.

The second project deals with Bardet-Biedl Syndrome (BBS) ciliopathy. Despite multiple indications that ciliary disorder might influence the hematopoietic compartment, immune system of patients with BBS has not been studied before. We observed that BBS patients have higher incidence of certain autoimmune diseases, and altered blood components. Moreover, we revealed that BBSome deficiency alters the B-cell development in mice. Interestingly, some of the hematopoietic system alterations were caused by the BBS-induced obesity whereas others were caused by intrinsic defects in the bone marrow stromal cells. Because the molecular functions of particular BBS proteins were not clear, we performed a meta-analysis of published clinical data of BBS patients. This revealed that the identity of the causative gene partially predicts the clinical outcome of the BBS disease.

Overall, we provide new insights into the mechanisms of the tolerance and homeostasis of immune cells in health and disease.