ABSTRACT

The process of self-nonself discrimination by the immune system is a fundamental attribute of healthy organisms. Since T-cell receptors (TCRs) are generated by the random process of somatic recombination without regard to its targets, the newly developed T-cell clones could recognize either self or nonself antigens. The mechanisms of central tolerance robustly limit the self-reactive repertoire within the T-cell population via deletion of clones that express self-reactive TCRs or their deviation into the regulatory T-cells (Tregs). These processes occur mainly in the thymic medulla where the TCR reactivity to self-antigens is tested by various types of antigen-presenting cells, mainly medullary thymic epithelial cells (mTECs), dendritic cells (DCs), and B-cells. The cooperation between these cell-types has been shown to be essential for the establishment of thymic tolerance. A key molecule regulating the production of self-antigens is the autoimmune regulator (AIRE), which is thought to be expressed primarily by mTECs and its mutations are associated with the development of severe autoimmune disorders. In this context, the presented thesis describes the novel regulatory pathways important for the development of a functional and "harmless" repertoire of T-cells and for enforcement of tolerance. First, we have shown that signaling through Toll-like receptors (TLRs) on mTECs leads to the influx of monocyte-derived DCs to the thymic medulla and subsequent regulation of Tregs development. Consistently, the abrogation of TLR signaling in TECs resulted in decreased frequency and functionality of Tregs, leading to aggravated mouse experimental colitis. Second, we demonstrated that gastrointestinal symptoms associated with AIRE loss-of-function are associated with the defective central tolerance to enteric α-defensins. Third, and consistent with the notion that the processes of central tolerance are complemented by the various mechanisms of peripheral tolerance, we have identified a novel population of peripheral lymph node resident AIRE-expressing cells, which share several characteristics with innate lymphoid cells type 3 (ILC3) and can efficiently present endogenously expressed antigen to peripheral $CD4^+$ T-cells. Lastly, we have developed a new mouse model that enables cell-specific depletion of AIRE and thus allows to study the function of AIRE in a much broader physiological context.