Abstract

The process of immune "self-nonself discrimination" is of utmost importance for the survival of all species as the biodestructive force of immune system can be directed towards the host as much as to pathogens. Thus, to shift this balance towards the latter, T cells bearing self-recognizing receptors are removed in the thymus (central tolerance) or their reactivity is harnessed through various additional mechanisms in periphery (peripheral tolerance). If the selfreactive T cells are not deleted and persist in the body, the regulation of self-tolerance can be breached, leading to the onset of autoimmunity.

Presented thesis revolved around α-defensins, very effective bactericidal peptides that represent an important part of humoral innate immunity. There are two types of α-defensins: myeloid, expressed predominantly in neutrophils, and enteric, synthesized by intestinal Paneth cells. Data presented inhere are first to characterized the involvement of α-defensin-expressing cells in two types of autoimmune diseases, insulin-dependent diabetes mellitus (T1D) and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). The former relates to the identification of transcriptionally activated myeloid α-defensin-expressing eosinophils present in the thymus of diabetes prone rat. In addition, a new insight into molecular and cellular mechanisms underlying the development of T1D is provided based on our two original observations: (i) the presence of activated eosinophils with high level of myeloid α-defensins mRNAs in capillary blood of patients with T1D but not in the controls; and (ii) a comparative microarray analysis which established a distinct "default" setting of expression of several innate immune genes gene in the group of first-degree relatives of patients with T1D. In addition, a case study linked the onset of T1D in monozygotic quadruplets with enteroviral infection. The last set of data revealed a previously unknown mechanistic link between the AIRE-mediated expression of enteric α-defensins in the medulary thymic epithelial cells (mTECs) and immune homeostasis of the small intestine. Consequently, APECED patients with inactivated mutations in AIRE are seropositive for anti-defensin autoantibody and clinically manifest several gastrointestinal symptoms.

In conclusion, our data for the very first time characterize two distinct types of α-defensin-expressing thymic cells and provide the evidence for the involvement of myeloid α-defensin-expressing eosinophils and enteric a-defensins-expressing mTECs in distinct mechanisms of central tolerance.