Institutionen för Medicin, Solna

Studies on peripheral tolerance in Aire deficient mice

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ABSTRACT

Autoimmune diseases such as diabetes mellitus and multiple sclerosis are increasing today, but the mechanism behind these diseases remains largely unknown. Autoimmunity arise when the immune system of an individual start to attack its own organs and tissues. Immune cells go through a selection in central and peripheral organs where they are taught to be non-reactive to self structures, a process referred to as tolerance. In this thesis we have investigated the function of the autoimmune regulator (AIRE), a gene that is important for the establishment of tolerance. The autoimmune polyendocrine syndrome type 1 (APS I) is a rare severe autoimmune disease caused by a single mutation in the AIRE gene. These patients suffer from a range of endocrine and non-endocrine manifestations such as hypoparathyroidism and chronic mucocutaneous candida infections. Aire deficient mice have been created in order to enable the investigation on how tolerance is lost in APS I patients. These mice have revealed that AIRE is involved in the deletion of autoreactive T-lymphocytes in the thymus. AIRE is thought to induce the expression of tissue specific antigens (TSAs) that are presented to T-lymphocytes in the thymus. However, Aire deficient mice display a phenotype suggesting that additional tolerance mechanisms are affected.

In the first paper presented in this thesis we show that AIRE is involved in the regulation of T-cell dependent B cell responses and that Aire−/− mice display an increased activation of B cells. This increased activation was demonstrated to be due to increased serum levels of the B cell activating factor of the TNF-family (BAFF) in Aire−/− mice and APS I patients. The increased levels of BAFF were in turn found to be due to uninhibited signaling of IFN-γ through the STAT1-pathway in absence of AIRE. In the second paper it was demonstrated that AIRE is expressed by a specific dendritic cell in the marginal zone of the spleen. These dendritic cells were found to regulate the activation of T lymphocytes in germinal center reactions and displayed a phenotype suggesting their involvement in tolerance mechanisms. In the third project we demonstrated that the expression of Aire in the marginal zone dendritic cells was regulated by IFN-γ. Upon IFN-γ stimulation both the expression of Aire and the TSA insulin was quickly down-regulated while the expression of inflammatory cytokines was up-regulated. These data suggest that the marginal zone dendritic cells are able to participate in tolerance induction during steady state and switch to an immunogenic state during an immune response. In the last project we investigated the development of the marginal zone dendritic cell in the bone marrow and found that AIRE is expressed in a precursor cell to the dendritic cell in the spleen. Further, it was found that in absence of AIRE the regulation of transcription factors important for the development of this particular dendritic cell subset was impaired.

The findings from this thesis suggest that AIRE play an important function in the periphery and adds to the view that AIRE regulates both central and peripheral tolerance.