Publication of the Month

Excellence in Autoimmunity

June 06/10: Selection of autoimmune T cells

Hinterberger M, Aichinger M, Prazeres da Costa O, Voehringer D, Hoffmann R, Klein L
Autonomous role of medullary thymic epithelial cells in central CD4+ T cell tolerance
Nature Immunology 2010; 11:512-20

A major pathogenic mechanism of autoimmune diseases is an incorrect selection of T cells, allowing autoreactive T cells to leave the thymus and start an autoimmune reaction. The detailed knowledge of this negative selection is mandatory to be able to understand autoimmunity and possibly develop new therapeutic strategies in the therapy of autoimmune diseases.

Introduction:

Traditionally, the negative selection of autoreactive T cells has largely been attributed to the thymic dendritic cells and their antigen-presenting cell function. A second frequent cell type in the thymus is the medullary thymic epithelial cell. These cells are able to produce the whole spectrum of proteins of the body and, thus, serve as a reservoir for the selection process: the proteins are cut into peptides and presented to the newly developed T cells. When a T cell reacts with one of the antigens it will be destroyed by apoptosis. However, some of these autoreactive T cells are not destroyed but allowed to leave the thymus and work as regulatory T cells.

Content:

Hinterberger et al. aimed to evaluate whether the medullary thymic epithelial cells do also have an antigen-presenting function and if this function plays any role in the selection process, independent of the dendritic cells. With the help of the knock-down method the medullary cells of mice were genetically altered. The expression of the antigen-presenting MHC class II molecules was not totally eliminated but lowered down to about 10%, while the function as reservoir of autoantigens was not influenced. As a result, T cells which would have been eliminated in normal mice were accepted and could leave the thymus. In some organs of the knock-down mice mild autoimmune reactions appeared.

In a second approach, the knock-down method was used for the developing T cells themselves – again the MHC class II molecules were diminished but not completely eliminated. As a result, the avidity was lowered and, indeed, more autoreactive T cells got a function as regulatory cells than in normal mice. The lower avidity seemed to be the deciding factor if the T cell will be destroyed or can leave the thymus as a harmless regulatory immune cell.