

Lecture 11. T cells III: Regulatory T cells and the maintenance of tolerance

Learning Objectives and Summary



Fas-deficient lymphoproliferative (lpr) mice develop an autoimmune disease resembling human lupus, as well as profound enlargement of lymph nodes (see nodules, above)

From: <http://www.med.uvm.edu/medicine/immunobiology/TB1+BL.asp?SiteAreaID=604>

11. T cells III: Regulatory T cells and the maintenance of tolerance

Learning objectives:

1. To understand how naïve autoreactive T cells are regulated in the periphery
2. To learn about the various subsets of regulatory T cells
3. To understand the functions of critical molecules required for immune regulation (e.g., Foxp3, CTLA4 and Fas)
4. To understand the role of critical cytokines in immune regulation (e.g., IL-2, IL-10 and TGF- β)
5. To learn how activated T cells are regulated in the periphery
6. To understand how disorders of immune regulation are related to human autoimmunity

SUMMARY

1. A fraction of naïve T cells that are released into the periphery contain potentially pathogenic autoreactive specificities. Regulation of these T cells is required to avoid pathogenic autoimmunity.
2. Multiple subsets of autoreactive T cells have been described. Of these, the two most well characterized are natural T regulatory cells (nTreg) and IL-10-producing T regulatory cells (Tr1).
3. Development of nTregs occurs in the thymus. Failure of these cells to develop results in autoimmunity diseases affecting predominantly endocrine organs and the bowel. Development of nTregs is dependent on CD28 and possibly CTLA4 while survival of nTregs is dependent on CD28 and IL-2. Foxp3, a master transcriptional regulator, is required for the function of nTregs. nTregs mediate suppression via contact-dependent mechanisms.
4. Development of Tr1 cells is dependent upon exposure to antigen in the presence of IL-10. Tr1 cells produce IL-10 and mediate both antigen-specific suppression and “bystander” suppression.
5. Functional downregulation of activated T cells in the periphery involves multiple mechanisms. These include regulatory T cells as well as expression of inhibitory molecules, such as CTLA4 and Fas, on the surface of the activated T cells themselves.
6. Autoimmune diseases that are due to failure of T cell regulation include IPEX (Foxp3 deficiency), APECED (AIRE deficiency), and autoimmune proliferative syndrome (Fas deficiency). Genetic polymorphisms of many genes influence the onset or severity of autoimmunity.