Antigen-specific islet infiltration

Whether T cell antigen receptor (TCR) specificity for an islet antigen is required for T cell entry into the pancreatic islets is unclear. In *Immunity*, Vignali and colleagues address this question by adoptively transferring bone marrow transduced with multicistronic retroviral vectors encoding islet antigen–specific and/or irrelevant TCRs into lethally irradiated NOD SCID mice. Although T cells expressing islet antigen–specific TCRs accumulate in the islets of these 'retrogenic' mice, T cells expressing irrelevant TCRs are not detected in the islets, even in the presence of T cells expressing islet antigen–specific TCRs. However, T cells expressing an irrelevant TCR do accumulate in the islets of mice expressing the irrelevant TCR cognate antigen under the rat insulin promoter. When used to generate retrogenic mice, most TCRs cloned from islet—but not splenic—T cells facilitate T cell entry into the islets. Thus, specificity for an islet antigen seems to be required for T cell accumulation within the pancreatic islets. ***CB***

***Immunity* 31, 643–653 (2009)**

Inducing anergy

Clonal anergy triggered by suboptimal lymphocyte stimulation contributes to peripheral tolerance. In the *Journal of Clinical Investigation*, Zhang *et al.* show the histone deacetylase Sirt1 to be necessary for executing the anergy response in $CD4^+$ T cells. Sirt1 acts by deacetylating c-Jun, a component of the transcription factor AP-1, and thereby inhibits AP-1 activity. $Sirt1^{-/-}$ T cells express more interleukin 2 and proliferate more extensively than wild-type T cells stimulated under similar conditions. Sirt1 expression increases in T cells activated without co-stimulation. $Sirt1^{-/-}$ mice show exaggerated immune responses upon immunization, and signs of spontaneous autoimmunity. These studies identify Sirt1 as an enforcer of anergy induction. *LAD*

J. Clin. Invest. **119**, 3048–3058 (2009)

Some are better than others

Peripheral tissue antigen presentation in the thymus is essential for negative selection of autoreactive T cells and central tolerance induction. In the *EMBO Journal*, Trucco and colleagues show that specific knockdown of the insulin gene *Ins2* in Aire-expressing medullary thymic epithelial cells (mTECs) from *Ins1*-deficient mice is sufficient to induce development of spontaneous diabetes in mice around 3 weeks after birth. Although bone marrow–derived thymic antigen–presenting cells and macrophages have been proposed to take up, transport and cross-present circulating insulin molecules in the thymus, circulating insulin secreted by normal pancreatic islet beta cells in these mice was not effective in mediating negative selection of insulin-specific T cells. Thus, mTECs seem to be more efficient, or even indispensable, for effective autoantigen presentation and generation of a self-tolerant T cell repertoire. ***IV***

***EMBO J.* 28, 2812–2824 (2009)**

Written by Christine Borowski, Laurie A. Dempsey & Ioana Visan

Regulating HLA-G expression

HLA-G, a nonclassical major histocompatibility class I molecule, can protect target cells from the cytolytic activity evoked by natural killer and cytolytic T cells by binding to inhibitory receptors ILT2 and ILT4. HLA-G expression contributes to maternal tolerance to prevent rejection of the developing fetus; yet tumor expression of HLA-G impairs anti-tumor responses, indicating that expression of HLA-G must be tightly regulated. In the *Journal of Immunology*, Flajollet *et al.* use a comparative proteomic approach to examine the transcriptional control of *HLA-G* expression. A Kruppel-type zinc finger protein, ras-responsive element binding protein 1 (RREB-1), is expressed in HLA-G–negative cells, where it binds to the *HLA-G* proximal promoter to silence *HLA-G* expression. RREB-1 recruits the chromatin remodeling proteins HDAC1 and CtBP1/2 to the *HLA-G* promoter. This repressor complex leads to a nonpermissive chromatin environment that restricts RNA polymerase access and thereby prevents *HLA-G* transcription. How RREB-1 expression is regulated by inflammatory or hormonal signals awaits future elucidation. *LAD*

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A biased view

Breakdown of self-tolerance requires several steps that alone are insufficient to sustain development of autoimmune diseases. In the *Journal of Experimental Medicine*, Hsu *et al.* show that a Zap70 tyrosine kinase mutant mouse, in which residues Tyr315 and Tyr319 are mutated to alanine (YYAA mouse) have hyporesponsiveness to TCR stimulation, impaired regulatory T cells development and defective positive and negative selection, a phenotype similar to a previously described ZAP-70 hypomorphic mutant (SKG mouse). The YYAA mouse produces rheumatoid factor antibodies but, unlike the SGK mouse, does not develop autoimmune arthritis. The two mutants showed differences in TCR signaling strength leading to differentially skewed TCR repertoires. These differences in repertoire, and not the quality of the immune response or defective peripheral tolerance, seem to be the cause of distinct predispositions for the induction of autoimmune arthritis in the two mutant strains. ***IV***

***J. Exp. Med.* 206, 2527–2541 (2009)**

Aire drives thymocyte migration

By promoting expression of tissue-specific antigens in medullary thymic epithelial cells (mTEC), autoimmune regulator (Aire) facilitates deletion of self-reactive thymocytes. In the *Journal of Immunology*, Peterson and colleagues suggest that Aire also controls thymocyte migration. $Aire^{-/-}$ thymi express less of chemokines capable of stimulating the receptors CCR4 and CCR7, which are expressed on $CD4^+CD8^+$ thymocytes and are essential for their corticomedullary migration. Aire controls expression of CCR4 ligand mRNA cell-autonomously, but seems to influence CCR7 ligand expression in a non–cell-autonomous manner. When overexpressed in a TEC cell line, Aire induces secretion of the CCR4 ligands CCL5 and CCL22 and the CCR7 ligand CCL19. Supernatants from Aire-overexpressing TEC cell lines facilitate $CD4^+CD8^+$ thymocyte migration, and fewer $CD4^+CD8^-$ thymocytes emigrate from $Aire^{-/-}$ thymi than from wild-type thymi in an *in vitro* assay. The molecular mechanisms through which Aire drives chemokine expression remain to be revealed. *CB*

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