

New directions for IS

Immune synapses form after cognate antigen recognition by T cells. In *Cell*, Dustin and colleagues show that such immune synapses in naive T cells demonstrate dynamic activity and can transiently reorient through the opposing activities of protein kinase C- θ (PKC- θ) and WASP (the Wiscott-Aldrich syndrome protein). Neither PKC- θ nor WASP is required for the formation of immune synapses, but PKC- θ , which is present as punctae in the peripheral supramolecular activation cluster, directs the relocation of the immune synapse. T cells expressing PKC- θ form breaks in the symmetrical arrangement of their immune synapses and can translocate in the direction of the breaks. In contrast, WASP is needed to reform the symmetrical immune synapse structure. *In vivo* imaging shows that PKC- θ is required for dynamic sampling of dendritic cell networks by T cells. These data indicate that immune synapses are much more dynamic structures than previously thought. **LAD**
Cell 129, 773–785 (2007)

Advancing Aire expression

Expression of the transcription factor Aire in medullary TECs is essential for deletion of developing thymocytes bearing T cell receptors specific for tissue-restricted self antigens. In the *Journal of Experimental Medicine*, Anderson and colleagues identify a function for receptor activator of NF- κ B (RANK) signaling in the differentiation of Aire⁺ medullary TECs. Aire is upregulated coincidentally with the appearance of the activation marker CD80 on the surface of medullary TECs. CD80⁺ medullary TECs give rise to CD80⁺ medullary TECs, and passage through this precursor-product transition requires the presence of CD4⁺CD3⁻ thymocytes that resemble lymphoid tissue-inducer cells. Interaction between RANK ligand on thymic lymphoid tissue-inducer cells and RANK on medullary TECs sparks Aire expression, and RANK-deficient mice show autoimmunity and defective expression of Aire and tissue-restricted self antigens in the thymus. The molecular mechanisms linking RANK and expression of Aire remain to be identified. **CB**
J. Exp. Med. (14 May 2007) doi:10.1084/jem.20062497

LFA-1 redistributes Ras

The GTPase Ras functions in pathways that can lead to opposite effects, such as positive and negative selection of T cells. In *Nature Cell Biology*, Philips and colleagues demonstrate that 'compartmentalized' signaling by Ras in T cells is regulated by the integrin LFA-1. It is known that palmitoylated Ras traffics between the Golgi apparatus and the plasma membrane and that T cell receptor stimulation, with or without costimulation, induces Ras activation only at the Golgi. Here, live-cell imaging of T cells shows that stimulation of both the T cell receptor and LFA-1 are required for the activation of Ras at the Golgi and the plasma membrane; both require the exchange protein Ras-GRP1, whereas activation at the Golgi also requires phospholipase C. In addition, that LFA-1 signaling leads to increased activity of diacylglycerol and phospholipase D. Thus, 'outside-in' LFA-1 signaling via phospholipase D is required for activation of Ras at the plasma membrane in T cells. **DCB**
Nat. Cell Biol. 9, 713–719 (2007)

Thymic proteasomes

Proteasomes initiate the cleavage of peptides destined for presentation on major histocompatibility complex class I molecules. In *Science*, Murata *et al.* identify a thymic-specific proteasome subunit called β 5t, whose expression is confined to cortical thymic epithelial cells (TECs). This subunit seems to be incorporated instead of the prototypical β 5 subunit. As a result, the chymotrypsin-like catalytic activity of β 5t-containing proteasomes is decreased, thereby reducing the number of peptides with hydrophobic residues at their carboxyl termini. Mice lacking β 5t have normal thymic architecture and development of CD4⁺ single-positive thymocytes but have fewer CD8⁺ single-positive thymocytes. Notably, the authors show that major histocompatibility complex class I molecules are expressed in similar abundance on β 5t-deficient and wild-type cortical TECs. These results show that β 5t alters the thymic peptide repertoire presented to CD4⁺CD8⁺ double-positive thymocytes and can profoundly influence the positive selection of CD8⁺ single-positive thymocytes. **LAD**
Science 316, 1349–1353 (2007)

First things first

The transcription factors Blimp-1, Pax5, IRF4 and XBP-1 all seem to influence the differentiation of antibody-secreting cells (ASCs). In *Immunity*, Nutt and coworkers align distinct transcription factors with discrete stages of ASC development. Mice expressing a green fluorescent protein (GFP) reporter in place of functional Blimp-1 have smaller but nevertheless detectable amounts of serum and mucosal immunoglobulins. GFP upregulation occurs after T cell-dependent or T cell-independent B cell stimulation, even in the absence of Blimp-1. However, subsequent expression of the ASC marker syndecan-1 requires Blimp-1. Blimp-1-deficient GFP⁺ syndecan-1-positive 'pre-plasmablasts' produce immunoglobulins and have higher expression of XBP-1 and lower expression of Pax5 than do naive B cells. These data indicate that Pax5 downregulation occurs before the induction of Blimp-1 expression and characterize an intermediate stage of ASC differentiation. The molecular mechanisms enforcing suppression of Pax5 expression and function, which seem to be post-translational, remain to be defined precisely. **CB**
Immunity 26, 1–12 (2007)

TLR2 triggers T_H1

Toll-like receptors (TLRs), essential for innate immunity, are also expressed on T cells and can modulate naive T cell activation. In the *Journal of Immunology*, Saito and colleagues investigate whether TLR stimulation influences the biology of differentiated T helper cells. First evaluating T helper type 1 (T_H1) cells, they find that among all TLRs, only stimulation of TLR2 results in the production of interferon- γ (IFN- γ). Although ligands for TLR9 and TLR2 can act in synergy with antibody to CD3 to activate naive T cells, only TLR2 ligands stimulate T_H1 cells. IFN- γ produced by the T_H1 cells is enhanced substantially by interleukin 2 or interleukin 12. In addition to producing IFN- γ , stimulated T_H1 cells upregulate CD69 and CD70, the survival factors c-Myc and Bcl-x_L and, relative to that of T_H1 cells not stimulated by TLR2 ligands, have strong and sustained activation of the transcription factor NF- κ B and the Jnk, p38 and Erk kinases. Although T_H1 and T_H2 cells have equivalent expression of TLR2, ligands for TLR2 and all other TLRs fail to stimulate T_H2 cells. Thus, stimulation of TLR2 induces strong T_H1 responses through the production of T cell-derived IFN- γ and innate immune cell-derived interleukin 12. **DCB**
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