Mutant CTLA-4 looks guilty

The risk of Graves disease, type 1 diabetes and autoimmune hypothyroidism is associated with a region on chromosome 2q33 that contains *CD28*, *CTLA4* and *ICOS*. However, the causal variants of these genes have not been identified. In *Nature*, Ueda *et al.* sequenced the 330-kb DNA region that contains these genes in subjects with Graves disease and localized the disease association to polymorphisms in a 6.1-kb region within the *CTLA-4* gene. Haplotypes that are susceptible to the disease have decreased mRNA expression of soluble CTLA-4. In NOD mice, a mutation in the *Ctla4* gene leads to decreased expression of a ligand-independent form of CTLA-4. Because CTLA-4 is an important negative regulator of T cell activation, these data provide new mechanistic insights into the basis of autoimmune diseases. *PL*
Nature doi:10.1038/nature01621 (30 April 2003)

Skin-deep lipids

Langerhans cells (LCs) initiate immune responses in the skin. Prostaglandin E_2 (PGE) is abundantly produced in the skin after antigen exposure, but whether this lipid mediator is involved in the activation and regulation of antigen-specific skin immune responses is unclear. In *Nature Medicine*, Kabashima *et al.* use mice deficient in each of the four PGE receptor subtypes to address this question. Although LCs express all four PGE receptor subtypes, only EP4-deficient mice showed impaired LC migration after challenge with antigen. Conversely, an EP4 agonist enhanced LC migration, increased the expression of costimulatory molecules and improved the ability of LCs to activate naive T cells. Loss of EP4 signaling impaired contact hypersensitivity to antigen *in vivo*. Thus, PGE2-EP4 signaling promotes LC migration and maturation. *JDKW*
Nature Medicine **9**, 744–749 (2003)

Zapping B cells

The tyrosine kinase ZAP-70 plays a crucial role in initiating TCR signals in natural killer and T cells. In *Immunity*, Tybulewicz and colleagues show that developing B cells also use ZAP-70 to convey receptor signals at the pre-B cell checkpoint, which marks the successful rearrangement of immunoglobulin heavy chain genes and initiates light chain gene assembly. Mice deficient in both ZAP-70 and the related kinase Syk display a complete block at the pro-B cell stage, whereas singly deficient Syk mutants generate reduced numbers of B cells. This defect was intrinsic to the developing B cells, as *Zap70*$^{-/-}$*Syk*$^{-/-}$ fetal liver cells failed to reconstitute B cell populations in irradiated recipient mice. ZAP-70 is expressed throughout B cell ontogeny. Thus, ZAP-70 and Syk appear to play redundant roles in mediating BCR signals. *LAD*
Immunity **18**, 523–533 (2003)

Regulating *Ikaros*

Ikaros is a zinc-finger DNA-binding factor that is required for normal, balanced hematopoietic lineage development. What regulates proper *Ikaros* gene expression during myeloid and lymphoid differentiation has remained unknown. In the *EMBO Journal*, Kaufman *et al.* identify three critical regulatory elements within the *Ikaros* gene that specify *Ikaros* expression. Two different promoters were identified that regulate *Ikaros* expression in granulocytes and B cells, respectively. Yet neither promoter could, by itself, induce *Ikaros* transcription in T cells. T lineage expression required a *cis*-acting element found between exons 3 and 4 in addition to the lymphoid-specific promoter. This element was necessary to confer high-level expression in mature T cells and reduced position-effect variation of *Ikaros* expression in the other hematopoietic lineages. The factors that bind these elements remain unknown. *LAD*
EMBO J. **22**, 2211–2223 (2003)

Nuclear architecture

Multiple layers of regulation govern tissue-specific gene expression, beginning with control of gene accessibility through higher-order chromatin structure. Little was known about factors that can regulate chromatin organization. In *Nature Genetics*, Cai *et al.* show that the nuclear factor SATB1 plays a critical role in establishing proper gene expression in developing thymocytes. SATB1-deficient thymocytes are blocked at the DP stage and show gross alterations in chromatin structure. SATB1 forms cage-like networks that tether chromatin loops, which are associated with active gene transcription. SATB1 binding was correlated with local histone acetylation modifications within the exposed chromatin domains, which were absent in the SATB1-null thymocytes. These results suggest SATB1 acts upstream of histone modifying enzymes and may regulate chromatin remodeling and accessibility. *LAD*
Nature Genetics **34**, 42–51 (2003)

Holy GRAIL of anergy

$CD4^+$ T cell anergy resulting from insufficient costimulatory signals is one form of peripheral tolerance. Anergy requires *de novo* protein synthesis, but the proteins in question have not been identified. In *Immunity*, Soares and colleagues examined differences in transcripts from T cell clones activated in the presence or absence of B7 costimulation. One transcript encoding a zinc-finger RING finger protein, called GRAIL (gene related to anergy in lymphocytes), was highly expressed in anergic cells and exhibited E3 ubiquitin ligase activity *in vitro*. Retroviral transfection of *GRAIL* into T cells inhibited IL-2 and IL-4 expression. Inhibition of cytokine production required E3 ubiquitin ligase activity and an intact endocytic pathway. These data suggest that GRAIL expression induced by an anergizing stimulus plays a pivotal role in anergy by inhibiting cytokine production. *JDKW*
Immunity **18**, 535–547 (2003)

TLR4-dependent IL-17

Interleukin-17 (IL-17) is a proinflammatory cytokine that is particularly critical for host defense against Gram-negative bacteria. For example, *Klebsiella pneumoniae* pulmonary infection blunts the G-CSF and MIP-2 response, decreases neutrophil recruitment, increases bacterial burden and worsens mortality in IL-17-deficient mice. In the *Journal of Immunology*, Happel *et al.* investigate the physiological trigger of IL-17. Using C3H/HeJ mice, which are LPS insensitive as a result of a mutation affecting the cytoplasmic tail of TLR4, they show that IL-17 production is TLR-4-dependent. Specifically, IL-23 produced by dendritic cells after exposure to *K. pneumoniae* induced IL-17 production by $CD8^+$ T cells. Therefore, TLR4 signaling induces IL-23 production required for CD8 T cell secretion of IL-17 in this Gram-negative pneumonia model. *JDKW*
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