Regulating diversity

It is unclear whether the ability of the body to sense a broad array of antigenic peptides is because of the polymorphism of the *mhc*-encoded molecules or due to the diversity of CTLs generated by these MHC molecules. In *Science*, Messaoudi *et al*. compared the response of coisogeneic strains of mice, C57BL/6 and B6.C-H-2^{bm8}, to a peptide from *Herpesvirus hominis* type 1 and show that despite the equivalent ability of both MHC molecules to present this peptide, there was a marked difference in the CTL response. The qualitative difference was due to the broader diversity of V_β usage and CDR3β length of the CTLs in the bm8 strain. This resulted in a bigger pool in which to select CTLs with high avidity for the peptide-MHC. Thus, *mhc* polymorphism enhances immune defense by increasing the diversity of CTLs.

Science **298**, 1797–1800 (2002)

Bound to be killed

The 'missing self' hypothesis explains the propensity of NK cells to kill in the absence of MHC class I expression. However, NK cells are known to lyse MHC class I–sufficient cells. In the *Journal of Experimental Medicine*, Michaelsson *et al.* show that HLA-E, the ligand for inhibitory NK receptor CD94-NKG2A, preferentially binds to a peptide from the leader sequence of heat shock protein 60 (hsp60sp) when cells are subjected to stress. Binding of hsp60sp to HLA-E enhances the surface expression of HLA-E–hsp60sp but prevents recognition by CD94-NKG2A. This renders the cells more susceptible to NK cell killing, thus allowing NK cells to differentiate 'normal' and 'abnormal' cells even in the presence of HLA molecules

J. Exp. Med. **196**, 1403–1414 (2002)

Aging control

CD28-deficient T cells are typically found in the elderly and are predictors of immunoincompetence. CD28 transcription is regulated by a transcriptional initiator (INR) consisting of an α and a β motif. These motifs are, in turn, regulated by unknown proteins. In *The Journal of Biological Chemistry*, Vallejo *et al*. identified two major proteins, nucleolin and the A isoform of heterogeneous nuclear ribonucleoprotein-D0 (hnRNP-D0A), that bind to the α motif and are important in the transactivation of CD28 INR. Nucleolin and hnRNP-D0A are present in both $CD28^+$ and $CD28^-$ cells. However, the nucleolin–hnRNP-D0A complex that recognizes the CD28 INR is only found in $CD28^+$ cells. This suggests that post-transcriptional modifications of the α binding proteins and/or other minor proteins may further control CD28 transcription.

J. Biol. Chem. **277,** 46940–46949 (2002)

Disseminating CMV

Cytomegalovirus (CMV) infection induces transient immunosuppression. CMV-infected DCs are functionally paralyzed and could be crucial for CMV-triggered immunosuppression. In *Immunity*, Halary *et al.* also show that DCs may promote virus dissemination. DC-SIGN, which is expressed on the surface of DCs, captured CMV and mediated *trans*-infection of susceptible cells. Blocking DC-CMV interactions with anti–DC-SIGN antibodies prevented DC infection by primary CMV isolates. Furthermore, expression of DC-SIGN or its homolog DC-SIGNR promoted *cis*-infection of cells that are poorly susceptible to CMV infection. The virus ligand of DC-SIGN and DC-SIGNR was identified as envelope glycoprotein B. Together these data show that, similar to HIV, CMV binding to DC-SIGN is required for DC infection and *trans*-infection of target cells.

Immunity **17**, 653–664 (2002)

Silence of the genes

CD4 expression is strictly regulated in developing thymocytes and mature T cells. In *Cell*, Littman and colleagues identify three critical *cis*-elements within the intronic silencer that are required to repress CD4 expression at the $CD4^-CD8^-$ DN stage as well as in committed $CD8^+$ cytotoxic lymphocytes. Different mechanisms act at this locus, as the early DN repression is reversible and requires active repressor complexes to block gene expression, whereas in CTLs stable epigenetic silencing of the CD4 locus occurs. In *Molecular Cell*, the same group shows the DNA-binding proteins Runx 1 and Runx3 play essential roles to repress CD4 expression at the DN and CTL stage, respectively. However, additional unknown factors bind adjacent sites in the silencer to effect repression or to establish the stable heterochromatin state.

Cell **111**, 621–633 & *Mol. Cell* **10**, 1083–1096 (2002)

Functions of acetylated RelA

Does the acetylation of RelA that occurs in cells undergoing NF-κB activation influence NF-κB activity? In the *EMBO Journal*, Chen *et al*. show that the RelA lysines at positions 218, 221 and 310 are acetylated *in vivo* by the transcriptional coactivator protein p300, although other acetylases may also participate. Lysine→arginine mutation at these positions interferes with NF-κB activity. Modification of lysine 310 is necessary to activate transcription of reporter genes with κB enhancers, whereas acetylated lysine 221 confers DNA binding stability. Acetylation of lysines 218 and 221 blocked RelA association with newly synthesized IκBα, thereby preventing the inhibitor complex from forming and exporting RelA from the nucleus. Thus, RelA acetylation is required for proper NF-κB function.

EMBO J. **21**, 6539–6548 (2002)

Natural-born inhibitor

The anti-apoptotic proteins Bcl-2 and Bcl-x_L act to inhibit loss of mitochondrial membrane potential. In *Nature Cell Biology*, Shirane and Nakayama report how these proteins localize to the mitochondria. They show that the immunophilin protein, FKBP38, recruits both Bcl-2 and Bcl-x_L to mitochondria. Loss of FKBP38 function increases apoptotic activity, whereas its overexpression blocks apoptosis. Like other immunophilins, FKBP38 inhibits the phosphatase activity of calcineurin. Surprisingly, the pharmacological immunosuppressant FK506 is not required for this activity, suggesting that FKBP38 may be the natural physiological inhibitor of calcineurin. Although previous studies identified the pro-apoptotic factor Bad as a calcineurin substrate, dephosphorylation of Bad was not inhibited by FKBP38. Thus, it remains unclear at the moment how these two activities of FKBP38 are linked.

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