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Brave New Restriction

Cells of Old World monkeys are protected from HIV-1 infection by the intracellular 'restriction factor' TRIM5-α. Human cells are not protected because their cyclophilin A (CypA) binds to the HIV-1 capsid, allowing the virus to evade TRIM5-α. The New World owl monkey cannot be infected but, paradoxically, Luban and colleagues show in *Nature* that 'knocking down' CypA with RNA interference allows infection. This is because of their unusual *TRIM5*: owl monkeys' only copy of *TRIM5* is disrupted between exons 7 and 8 by a retrotransposed *CypA* cDNA. Thus, 'knocking down' CypA also knocks down TRIM5. The ability to resist HIV-1 infection in CypA knockdown owl monkey cells (or normal human cells) can be restored by transfection with chimeric TRIMCyp but not regular CypA. This explains the innate resistance of owl monkeys to HIV-1 infection. *JDKW*

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Anti-inflammatory DCs

Dendritic cells in the lungs determine whether the immune system is aggravated by or 'ignores' inhaled antigens. In the *Journal of Experimental Medicine*, Jan de Heer *et al.* report that lung plasmacytoid dendritic cells (pDCs) are important in the suppression of inflammatory responses to inert inhaled antigens. Depletion of lung pDCs resulted in the development of asthmatic features when mice were tested with a protocol that normally tolerizes them. In the absence of pDCs, antigen-specific T cell proliferation and effector cytokine production were enhanced. Antigen-loaded pDCs suppressed an asthmatic response when transferred into mice subjected to an immunogenic asthma protocol, apparently through the generation of suppressive T cells. Thus, pDCs could prevent overzealous lung immune responses to innocuous antigens. *PTL*

J. Exp. Med. **200**, 89–98 (2004)

Herding ELKS for NF-κB activation

NF-κB activation in response to inflammatory cytokines occurs by phosphorylation and subsequent degradation of its inhibitor IκB. This pathway requires the kinase IKK. In *Science*, Verma and colleagues identify the protein ELKS as a component of the IKK complex that acts as a bridging molecule to couple IKK to its target IκBα. ELKS constitutively interacts with IKK1, IKK2 and NEMO. ELKS also binds IκBα. Downregulation of ELKS by RNA interference blocked activation of NF-κB in response to tumor necrosis factor (TNF), due to diminished IKK activity. However, an ELKS N-terminal deletion mutant showed enhanced IKK activity and NF-κB activation in the absence of cytokine stimulation. Hence, ELKS is a cytokine-responsive regulator of IKK. *LAD*

***Science* 304, 1963–1967 (2004)**

Tolling out the genes

A recently identified IκB protein, IκB-ζ, is induced by interleukin 1 (IL-1) and the Toll-like receptor 4 (TLR-4) ligand lipopolysaccharide (LPS). In *Nature*, Akira and colleagues analyzed the physiological function of IκB-ζ in TLR–IL-1R–mediated immune responses. IκB-ζ-deficient macrophages have defective IL-6 production in response to TLR ligands and IL-1 but not TNF stimulation. Microarray analysis showed that IκB-ζ controls not only *Il6* expression but also the expression of other LPS-induced genes such as *Il12b*. Functionally, IκB-ζ associates with the NF-κB subunit p50 and can bind the NF-κB site of the *Il6* promoter. Because LPS-induced IκB-ζ mRNA upregulation precedes expression of *Il6* and other LPS-induced genes, these data suggest TLR–IL-1R–mediated responses are regulated in at least a 'two-step' process. *JDKW*

Nature **430**, 218–222 (2004)

Accessibility issues

V(D)J recombination at the immunoglobulin and T cell receptor genes is regulated. Rearrangements that result in the production of surface receptors exclude further rearrangement by the process of 'allelic exclusion'. In *Cell*, Liang *et al.* show (V to J) rearrangement of the *Igk* locus is consistent with rare stochastic monoallelic transcriptional activation of the *Igk* locus. Single-cell analysis with cells from green fluorescent protein 'knock-in' reporter mice indicated that only 5% of pre-B cells expressed germline κ transcripts, but expression was monoallelic. The highly transcribed allele was preferentially targeted by the recombinase. However, additional constraints must exist, because both alleles produced κ transcripts in mature B cells. The DNA CpG methylation status of the early transcribed allele seems to have such a function. *LAD*

Cell **118**, 19–29 (2004)

Escaping innate immunity

Virus mutants that escape the adaptive immune response are well documented for RNA viruses. In *Immunity*, Yokoyama and colleagues show that the double-stranded DNA virus MCMV can also generate escape mutants. C57BL/6-SCID mice, which lack an adaptive immune response, initially controlled MCMV infection, but succumbed to disease at a later stage. SCID-MCMV isolates derived from these later time points induced early mortality in both immunodeficient and C57BL/6 mice. Specifically, the SCID-MCMV isolates contained mutations in *m157*, which encodes the ligand of Ly49H, an activation receptor on natural killer cells that mediates MCMV control during acute infection. Deliberate mutation of *m157* mimicked the phenotype observed with SCID-MCMV isolates. Pathogens causing severe disease in immunocompromised patients may therefore represent mutants escaping innate immunity. *JDKW*

Immunity **20**, 747–756 (2004)

Fine-tuning T cell activation

Although mitogen-activated protein kinases (MAPKs) are important in regulating T cell functions, how these kinases affect T cell activation is unclear. By developing a screening method to identify molecules that are phosphorylated by MAPK family members, Matsuda *et al.* report in the *EMBO Journal* that the T cell adaptor molecule LAT is a substrate for MAPKs. Both ERK and JNK but not p38 phosphorylate threonine at position 155 (T155) of LAT. Phosphorylation of T155 decreases calcium mobilization, activation of the transcription factor NFAT and further activation of ERK. This negative feedback loop is a result of decreased association of ERK with molecules in the T cell activation cascade, PLCγ1 and SLP-76. Thus, productive T cell activation is carefully controlled to avoid a damaging outcome. *PTL*

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