Ubiquitinating class II

Two hallmarks of activated dendritic cells (DCs) are increased surface expression of major histocompatibility complex (MHC) class II and reduced endocytosis. In *Nature*, Mellman and colleagues demonstrate that both processes are controlled by the ubiquitination of MHC class II β-chains. Immunoblot for MHC class II in cell lysates from bone marrow–derived or splenic DCs demonstrates a characteristic 'ladder' of ubiquitinated β-chain proteins. Substitution of a β-chain lysine required for ubiquitination results in cell surface expression of MHC class II in immature DCs, whereas wild-type ubiquitinated MHC class II is found in late endosomes. Moreover, only wild-type ubiquitinated MHC class II molecules efficiently endocytose bound antibody. In mature DCs, in contrast, ubiquitination of MHC class II β-chains is not found and correlates with low MHC class II endocytosis, yet expression of constitutively ubiquitinated MHC class II restores endocytosis. Thus, DC maturation abrogates ubiquitination of MHC class II β-chains, resulting in increased cell surface expression of MHC class II and reduced endocytosis. ***DCB***

***Nature* 444, 115–118 (2006)**

1918 flu immunization

The highly pathogenic H1N1 influenza virus caused considerable mortality, even in previously healthy people, during the 1918 pandemic. In the *Proceedings of the National Academy of Science*, Nabel and coworkers show that DNA immunization with altered H1 hemagglutinin–encoding cDNA produces protective immunity in mice. Somewhat unexpectedly, T cell depletion after immunization does not alter the survival of mice subsequently challenged with live 1918 virus. Passive immunization of naive mice with sera from immunized mice confers substantial protection, suggesting humoral antibody responses are important in stemming viral replication and the ensuing pathogenesis. Serum titers of protective H1-specific antibodies can be detected by a new 'pseudotyped lentivirus' neutralization assay, providing a rapid and safe means for testing vaccine candidates for potential new pandemic influenza strains. *LAD*

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Dicer in T_{reg} cells

Endogenous microRNAs (miRNAs) regulate post-transcriptional mRNA abundance and stability by a Dicer-dependent pathway. In the *Journal of Experimental Medicine*, Merkenschlager and colleagues report Dicer ablation in $CD4^+$ T cells leads to 'preferential' loss of regulatory T cells (T_{reg} cells). T_{reg} cells and resting naive $CD4^+$ T cells have distinct miRNA profiles, but after being activated, $CD4^+$ effector cells transiently express miRNAs common to T_{reg} cells, suggesting that T_{reg} cells have a partially activated miRNA 'fingerprint'. Transfection of the transcription factor Foxp3 or induction of endogenous Foxp3 with transforming growth factor-β triggers the T_{reg} cell miRNA expression profile. Loss of Dicer in T_{reg} cells leads to immune pathologies, suggesting reciprocal regulation of Foxp3- and T_{reg} cell–specific miRNA, although molecular characterization of this regulation remains to be determined. ***LAD***

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Tracking IEL precursors

Agonist stimulation drives some but not all $CD4^+CD8^+$ thymocytes into the 'unconventional' $CD8\alpha\alpha^+$ intestinal epithelial lymphocyte (IEL) lineage. In *Immunity*, Cheroutre and colleagues ask if this heterogeneity stems from the existence of precommitted IEL precursors. Subsets of adult and fetal $CD4^+CD8^+$ thymocytes express CD8αα. These 'triple-positive' (TP) thymocytes lack surface CD69 and CD5 and are found (albeit with low surface expression of T cell receptor-β (TCRβ)) in *Tcra*$^{-/-}$ mice, suggesting that positive selection is required for the maturation but not for the appearance of TP thymocytes. However, *Tcrb*$^{-/-}$ mice are devoid of TP precursors, indicating that pre-TCR signaling is required for TP differentiation. A larger fraction of TP thymocytes than $CD4^+CD8^+$ thymocytes survives agonist stimulation and gives rise to $CD8\alpha\alpha^+$ IELs after injection into the thymus, but not the blood, of recipient mice. These data confirm the thymic origin of $CD8\alpha\alpha^+$ IELs and emphasize a potential dichotomy with unconventional T cell lineages such as natural killer T cells, for which precommitted precursors have not been identified. *CB*

Immunity **25**, 631–641 (2006)

Essential IFN kinases

The kinases TBK1 and IKK-i are required for some interferon responses. In the *Journal of Immunology*, Matsui *et al.* demonstrate that TBK1 and IKK-i are required for interferon-α/β (IFN-α/β) production by conventional DCs and macrophages after infection with RNA viruses, whereas TBK1 alone is required for IFN-β production after stimulation with lipopolysaccharide. Gene microarray analysis of Newcastle disease virus–infected conventional DCs lacking TBK1 and IKK-i indicates that both kinases are required for activation of the transcription factor IRF-3 and expression of IFN-α genes; in contrast, plasmacytoid DC–induced IFN-α requires neither TBK1 nor IKK-i. These data suggest that lipopolysaccharide-mediated stimulation of TBK1 activates the IRF-3–IFN-β pathway, whereas RNA virus–mediated stimulation of TBK1 activates both the IRF-3–IFN-β and the IRF-7–IFN-α pathways. These data also show that plasmacytoid DCs produce IFN-α independently of both TBK1 and IKK-i. Targeting these kinases may thus lead to selective modulation of interferon responses. ***DCB***

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Peptide 'editor'

In endosomes, HLA-DM 'edits' the repertoire of peptides that bind to MHC class II molecules. A similar editor of peptides that bind to MHC class I in the endoplasmic reticulum has not been identified. In *Cell*, Ahn and colleagues show that cells lacking peptide disulfide isomerase (PDI) or expressing PDI mutants with defective catalytic or peptide chaperone activity have reduced disulfide bonds in MHC class I and impaired peptide loading onto MHC class I. PDI associates with the peptide-loading complex and MHC class I and oxidizes MHC class I disulfide bonds in the presence of peptides that bind MHC class I with high but not low affinity. The human cytomegalovirus protein US3, known to inhibit peptide loading onto MHC class I, binds to and triggers the degradation of PDI, ultimately resulting in reduction of MHC class I disulfide bonds. These results suggest that PDI, by regulating the redox state of MHC class I, edits peptide presentation. *CB*

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