Better late than never

Surface membrane proteins of the semaphorin family are required for proper T cell function. However, ascribing specific functions to individual semaphorins is problematic, as redundancy in receptor-ligand interactions confound unambiguous interpretations. In the *Proceedings of the National Academy of Science*, O'Connor *et al.* show that semaphorin 6D (Sema6D) is required for late proliferative responses in CD4$^+$ T cells. Dendritic cells (DCs) presenting cognate peptide induce Sema6D expression; however, surface expression is delayed until late time points. Blocking the interaction of Sema6D with plexin A1 expressed on DCs results in less T cell proliferation. Such inhibition disrupts phosphorylation of the LAT signalling adaptor protein, which suggests crosstalk between the semaphorin proteins and T cell receptor (TCR) signaling. Future work should identify whether memory responses are likewise disrupted. ***LAD***

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Generating controlled variability

How stochastic protein expression results in phenotypic variability in a clonal cell population without compromising response reliability is not clear. In *Science*, Altan-Bonnet and colleagues use a computer model of T cell activation to analyze the consequences of stochastic protein expression. Initial modeling predicts that TCR signaling components are in three expression categories: noncritical, whose variation does not measurably affect TCR responses; analog, whose variation 'fine-tunes' responses; and digital, whose variation leads to 'all or none' responses. These categories are exemplified by the Erk1 kinase, CD8 coreceptor and SHP-1 phosphatase, respectively. Multiparameter flow cytometry of T cells for endogenous protein expression and TCR signal responses shows variations in the expression of Erk1, CD8 and SHP-1, consistent with the model predictions. Coregulation of the expression of CD8 (analog) and SHP-1 (digital) through gene locus colocalization or shared transcription factors limits the hyper-responsiveness and diversity of T cell responses. These observations provide insight into how cells generate controlled variability from stochastic gene expression. *DCB*

Science **321**, 1081–1084 (2008)

Spliceosomes aid AID

Somatic hypermutation and class-switch recombination increase the affinity and diversify the effector function of immunoglobulins synthesized by antigen-activated B cells. In *Molecular Cell*, Neuberger and colleagues identify an RNA-splicing factor, CTNNBL1, that interacts specifically with activation-induced cytidine deaminase (AID) and contributes to the efficiency of both somatic hypermutation and class-switch recombination. CTNNBL1 recognizes a 'patch' on AID encompassing amino acids 39–42, as chimeric AID proteins in which this region is replaced with that from APOBEC2 fail to interact with CTNNBL1 and show less recombination despite having deaminase activity similar to that of intact AID. These data add to evidence linking RNA splicing to AID-mediated antibody diversification, but the details of this reaction remain elusive. ***LAD***

***Mol. Cell* 31, 474–484 (2008)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Chemokine citrullination

Amino-terminal truncation and binding to glycosaminoglycans enhances the chemotactic activity of CXCL8, which promotes neutrophil recruitment via the receptors CXCR1 and CXCR2. In the *Journal of Experimental Medicine*, Van Damme and colleagues add citrullination, in which peptidylarginine deiminase (PAD) enzymes deiminate an arginine to form citrulline, to the list of post-translational modifications affecting CXCL8 activity. Approximately 14% of the full-length CXCL8 released from human peripheral blood mononuclear cells contains citrulline in place of arginine at position 5. Citrullinated CXCL8 binds less efficiently to glycosaminoglycans, is resistant to thrombin- and plasmin-mediated amino-terminal proteolysis, elicits less calcium flux and phosphorylation of the kinase Erk through CXCR2 and fails to induce neutrophil recruitment when injected into mice. A polymorphism in the gene encoding PAD has been associated with greater susceptibility to rheumatoid arthritis, but whether CXCL8 or another PAD enzyme substrate contributes to this susceptibility is not yet clear. *CB*

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Negative regulation by Trex1

Toll-like receptors and cytosolic sensors account for nearly all interferon-stimulated, nucleic acid–induced antiviral immunity. In *Cell*, Stetson and Medzhitov find that 3′ repair exonuclease 1 (Trex1) is a negative regulator of the interferon-stimulatory response mediated by DNA (ISD). Trex1 substrates are essential ligands of the ISD pathway accumulation of which stimulates interferon production dependent on interferon-response factor 3. Mice lacking Trex1 die from inflammatory myocarditis caused by interferon-dependent recruitment of lymphocytes, which is reversed in Trex1-deficient mice also lacking interferon-response factor 3 or the type I interferon receptor. Substrates of Trex1 consist of two types of single-stranded DNA fragments, from genes expressed in heart tissue and from endogenous L1 retrotransposons and endogenous retroviruses, consistent with Trex1's being a single-stranded DNA exonuclease. These data suggest that the ISD pathway may be a previously unknown, cell-intrinsic detection system of retroviruses that is negatively regulated by Trex1. ***DCB***

***Cell* 134, 587–598 (2008)**

Tolerizing autophagy

By presenting peptides derived from tissue-specific proteins in the context of MHC class II molecules, thymic epithelial cells (TECs) direct the positive and negative selection of developing thymocytes. In *Nature*, Klein and colleagues find that TECs use macroautophagy to generate MHC class II–bound peptides that shape the CD4$^+$ TCR repertoire. When transplanted under the kidney capsules of wild-type mice, embryonic thymi lacking Atg5—a protein essential for macroautophagy—contain fewer thymocytes and fail to positively select thymocytes expressing some MHC class II–restricted TCR transgenes; selection of MHC class I–restricted TCRs is not impaired. Wild-type TECs contain abundant autophagosomes, and *Atg5*$^{-/-}$ TECs show quantitative alterations in surface expression of a particular MHC class II–bound peptide. Athymic recipients of *Atg5*$^{-/-}$ embryonic thymi manifest CD4$^+$ T cell–driven multiorgan inflammation. Whether this inflammation results from defective positive selection of regulatory T cells and/or impaired negative selection of conventional T cells remains to be determined. *CB*

Nature (13 August 2008) doi:10.1038/nature07208