Runx in autoimmunity

Although diverse autoimmune diseases may share common features such as a general breakdown in thymic negative selection, the identification of a more specific molecular etiology has been elusive. In *Nature Genetics*, studies by Helms *et al*. and Tokuhiro *et al*., together with an earlier study by Prokunina *et al*., *Nat. Genet.* **32**, 666–669 (2002), show that diseases with clinical symptoms as distinct as psoriasis, rheumatoid arthritis and systemic lupus erythematosus have single-nucleotide polymorphisms (SNPs) in the binding site for the transcription factor Runx1. The SNPs cause a defect in the binding of Runx1 to its respective gene in all three diseases. Although the precise downstream effects are unclear at present, the Runx1 binding site seems to be a common regulatory pathway. *PTL*

Nat. Genet. 9 Nov 2003 (doi:10.1038/ng1267 & 10.1038/ng1268)

Location, location, location

Protein kinase D (PKD), a serine-threonine kinase, switches from the plasma membrane (mPKD) to the cytosol (cPKD) during T cell activation, but the functional relevance of this is unclear. In *Immunity*, Cantrell and colleagues expressed active cytosol- or membrane-targeted PKD mutants in pre-T cells to address this question. When expressed in Rag-deficient mice, both cPKD and mPKD induced CD25 downregulation and CD2 and CD5 upregulation, events classically associated with β-selection. Both PKD forms also induced thymocyte proliferation. However, only membrane-targeted PKD induced CD4 and CD8 coreceptor expression in Rag-deficient pre-T cells, whereas only cPKD suppressed V_β-to-DJ_β rearrangements in wild-type pre-T cells. Whether PKD functions as a positive or negative regulator of T cells is therefore determined by its intracellular location. *JDKW*

Immunity **19**, 491–501 (2003)

Ungripping neutrophils

Leukocytes subjected to physiological fluid shear stresses rapidly retract their pseudopods. However, how these shear stresses affect membrane adhesion molecules is unclear. In the *Proceedings of the National Academy of Sciences*, Fukuda and Schmidt-Schönbein show that surface CD18 expression on neutrophils is shifted from regions exposed to high shear to regions with lower shear stress even in the presence of activating agents such as fMet-Leu-Phe. This shift in expression is a result of the cleavage of surface CD18 by cysteine proteases, including cathepsin B. Calcium is also required for the removal of CD18, possibly by facilitation of exocytosis of cathepsin-containing granules. Once neutrophils gain a foothold away from fluid shear, the redistribution of CD18 may assist the migration of neutrophils into the tissues. *PTL*

Proc. Natl. Acad. Sci. USA **100**, 13152–13157 (2003)

Paracaspase, the missing link

The IκB kinase (IKK) complex– and caspase-recruitment domain (CARD)–containing proteins CARMA1 and Bcl10 are required for NF-κB activation, but how the CARMA1-Bcl10 complex activates IKK is unclear. The ability of paracaspase to bind and colocalize with Bcl10 *in vitro* indicates this caspase-like protein could link the CARMA1-Bcl10 complex to the IKK complex. In *Science*, Dixit and colleagues addressed the function of paracaspase in NF-κB activation by generating paracaspase-deficient mice. Paracaspase-deficient T and B lymphocytes had impaired antigen receptor-induced NF-κB activation, cytokine production and proliferation. Transfection studies using Bcl10 and paracaspase in embryonic fibroblasts showed paracaspase acts 'downstream' of Bcl10. Whether paracaspase directly associates with the IKK complex or requires other proteins involved in NF-κB activation needs further investigation. *JDKW*

Science 23 October 2003 (doi: 10.1126/science.1090769)

Infectious fat

Macrophages are important in sensing pathogens through Toll-like receptors (TLRs) as well as in controlling atherosclerosis through cholesterol metabolism. Why infection is associated with a higher risk of cardiovascular diseases is still unclear, however. In *Molecular Cell*, Castrillo *et al*. provide a link. The liver X receptor (LXR) pathway, which is essential for moving cholesterol out of macrophages, can be modulated by TLR ligands. TLR3 and TLR4 ligands inhibit LXR-dependent gene expression and thus cholesterol efflux. The MyD88-independent TLR pathway and the transcription factor IRF3 are involved in suppressing LXR transcriptional activity. Thus, the activation of macrophages by bacteria or viruses could directly promote atherosclerosis by supporting the formation of foam cells. *PTL*

Mol. Cell **12**, 805–816 (2003)

HMGB1, an ancient cytokine?

Extracellular deposition of the high-mobility group protein B1 (HMGB1) triggers inflammatory responses and acts as a signal of ongoing cell necrosis. Monocytes and macrophages can amplify this signal by actively exporting nuclear HMGB1 in response to inflammatory stimuli such as lipopolysaccharide (LPS) and interleukin 1. What was unknown was how these cells could regulate secretion of a nuclear protein. In the *EMBO Journal*, Bonaldi *et al.* show HMGB1 is heavily acetylated on multiple lysine residues in response to LPS. Acetylated HMGB1 is prevented from re-entering the nucleus but accumulates in cytoplasmic secretory lysosomes, which are poised for exocytosis after further stimulation. Thus, monocytes use an ancient necrotic signal to prolong inflammatory responses. *LAD*

EMBO J. **22**, 5551–5560 (2003)

Eomes regulates cytolytic functions

Cytolytic $CD8^+$ T effector cells can develop in T-bet-deficient mice. In Science, Reiner and colleagues show that $CD8^+$ T and natural killer cells express a related T-box transcription factor called eomesodermin (Eomes). Expression of Eomes increases after in vivo viral infection and is correlated with increased expression of interferon-γ, perforin and granzyme B. Expression of a dominant negative T-bet or Eomes in T-bet-deficient T cells was sufficient to inhibit acquisition of cytolytic activity in vitro. Thus, Eomes seems to be a specific transcription factor that can specify development of cytolytic effector cells. *LAD*

Science **302**, 1041–1043 (2003)

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