## **IN BRIEF**

### INNATE IMMUNITY

## p38 $\delta$ -PKD1-PTEN signalling promotes neutrophil chemotaxis

A new study shows that expression of the p38  $\delta$ -isoform (a member of the mitogen-activated protein kinase family) in neutrophils is essential for neutrophil chemotaxis. p38 $\delta$ -deficient neutrophils had an impaired migratory capacity in vitro and failed to infiltrate the lungs in a mouse model of acute lung injury. The effect of p38 $\delta$  on neutrophil extravasation and chemotaxis involved the inactivation of protein kinase D1 (PKD1). PKD1 was shown to phosphorylate the phosphoinositide 3-kinase (P13K) regulatory subunit p85 $\alpha$ , which in turn enhanced the activity of the lipid phosphatase PTEN. Thus, inactivation of PKD1 and PTEN downstream of p38 $\delta$  appear to maintain the gradient of phosphatidylinositides (lipid targets of P13K and PTEN) that is required for neutrophil chemotaxis.

**ORIGINAL RESEARCH PAPER** lttner, A. *et al.* Regulation of PTEN activity by p388-PKD1 signaling in neutrophils confers inflammatory responses in the lung. *J. Exp. Med.* 5 Nov 2012 (doi:10.1084/jem.20120677)

#### T CELLS

#### The MALT1 switch in autoimmunity

MALT1 is a dual regulator of nuclear factor-κB (NF-κB) signalling: it functions as a scaffold to promote lκB kinase (IKK)-dependent activation of the canonical NF-κB pathway and proteolytically degrades several NF-κB-related factors, including the non-canonical NF-κB subunit RELB. Now, Brüstle et al. report a central role for MALT1 in the effector function of Thelper 17 (T, 17) cells. MALT1-deficient mice were resistant to the induction of experimental autoimmune encephalomyelitis, despite infiltration of the brain by activated T cells after immunization. Moreover, MALT1-deficient T<sub>11</sub>17 cells lacked pathogenicity and failed to produce the cytokines IL-17 and GM-CSF. Further analyses suggested that IKK activation and RELB degradation by MALT1 are two independent events that are required for the differentiation of  $T_{\rm H}17$  but not  $T_{\rm H}1$  cells. This function of MALT1 in Thelper cell plasticity could be therapeutically targeted in autoimmune disorders.

ORIGINAL RESEARCH PAPER Brüstle, A. et al. The NF-κB regulator MALT1 determines the encephalitogenic potential of Th17 cells. J. Clin. Invest. 1 Nov 2012 (doi:10.1172/IC163578)

### INFLAMMATION

# The GEF way to MYD88-dependent vascular permeabilization

The integrity of the vasculature is compromised under inflammatory conditions, partly as a result of low surface levels of the cell–cell adhesion molecule VE-cadherin. Now Zhu et al. delineate the signalling events that lead to vascular permeabilization following the stimulation of human endothelial cells with interleukin-1 $\beta$  (IL-1 $\beta$ ). IL-1 $\beta$  induced NF-kB-independent activation of the GTPase ARF6, which promoted the endocytosis of VE-cadherin. The guanine nucleotide-exchange factor (GEF) ARNO was required for ARF6 activation and co-immunoprecipitated with the IL-1 $\beta$  signalling adaptor molecule MYD88. As the GEF inhibitor SecinH3 reduced vascular permeabilization and tissue inflammation in two models of inflammatory disease, specific targeting of this GEF-dependent arm of IL-1 $\beta$  signalling may be of therapeutic value.

**ORIGINAL RESEARCH PAPER** Zhu, W. *et al.* Interleukin receptor activates a MYD88–ARNO–ARF6 cascade to disrupt vascular stability. *Nature* 11 Nov 2012 (doi:10.1038/nature11603)