IN BRIEF

T CELL SIGNALLING

Balancing regulatory and self-reactive T cells

Self-tolerance is maintained by the negative selection of self-reactive T cells in the thymus and the generation of regulatory T (T_{Reg}) cells to control self-reactive T cells in the periphery. How T cell receptor (TCR) signal strength controls these processes has not been clearly defined. In this study, the authors generated mice expressing a signalling-deficient TCR ζ-chain (referred to as 6F). Negative selection of double-positive thymocytes was defective in 6F/6F mice, resulting in a peripheral T cell repertoire skewed towards T cells with an activated memory phenotype, presumably owing to a high affinity for self ligands. However, the mice did not develop spontaneous autoimmune disease, which correlated with the increased generation of thymic T_{Reg} cells. The authors suggest that the attenuation of proximal TCR signalling in 6F/6F mice impairs negative selection but has a compensatory effect on T_{Reg} cell generation by enhancing FOXP3 expression.

ORIGINAL RESEARCH PAPER Hwang, S. *et al.* Reduced TCR signaling potential impairs negative selection but does not result in autoimmune disease. *J. Exp. Med.* 3 Sep 2012 (doi:10.1084/jem.20120058)

TUMOUR IMMUNOLOGY

Splenic myeloid cells tolerize tumour-specific T cells

This study provides evidence of a central role for the spleen in the induction of T cell tolerance in tumour-bearing hosts. In several tumour models, splenectomy fully restored the activation of tumour antigen-specific T cells in tumour-draining lymph nodes. Also, the increased antitumour efficacy of adoptive T cell transfer after chemotherapy with 5-fluorouracil was shown to result from the elimination of $CD11b^{+}GR1^{med}$ myeloid cells in the splenic marginal zone. These immature myeloid cells — which accumulate in the spleen during tumour growth in response to CCL2 — could sample tumour-released exosomes to cross-present tumour antigens and tolerize $CD8^{+}$ T cells. The results suggest that tumour immunotherapy could be enhanced by chemotherapeutic agents that target the highly proliferative myeloid cells in the splenic marginal zone.

ORIGINAL RESEARCH PAPER Ugel, S. *et al.* Immune tolerance to tumor antigens occurs in a specialized environment of the spleen. *Cell Rep.* 6 Sep 2012 (doi:10.1016/j.celrep.2012.08.006)

INFECTIOUS DISEASE

Targeting *M. tuberculosis* for autophagy

In this study, the authors describe a multistep pathway for targeting *Mycobacterium tuberculosis* for autophagy. The *M. tuberculosis* type VII secretion system ESX1 was shown to permeabilize bacterium-containing phagosomes in bone marrow-derived macrophages. This permeabilization allows bacterial DNA to be recognized by the cytosolic sensor STING (stimulator of interferon genes). STING is required for the marking of bacteria with ubiquitin, which initiates the ubiquitin-mediated autophagy pathway through the recruitment of autophagy components, such as LC3, to the bacteria. The targeting of autophagy components to *M. tuberculosis* requires the ubiquitin-binding autophagy receptors p62 (also known as SQSTM1) and NDP52, together with the kinase TBK1, and delivers the bacilli to autophagosomes. Autophagosomes then fuse with lysosomes to create autophagolysosomes, and this results in bacterial killing. Finally, autophagy was shown to be required for effective control of *M. tuberculosis* infection *in vivo*.

ORIGINAL RESEARCH PAPER Watson, R. O., Manzanillo, P. S. & Cox, J. S. Extracellular *M. tuberculosis* DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. *Cell* **150**, 803–815 (2012)