

## Maintaining barriers

The distal colon is rich in anaerobes whose production of short-chain fatty acids (SCFAs) from dietary fiber has been linked to the control of inflammatory bowel disease. In *Cell Host & Microbe*, Colgan and colleagues demonstrate how SCFAs, in particular butyrate, can regulate gut homeostasis. The addition of butyrate to colonic epithelial cells increases mitochondria-dependent oxygen consumption and contributes to the hypoxic environment of the colonic lumen. Diminished cellular oxygen leads to the stabilization of HIF, a chief transcriptional regulator of inflammation and the response to lower oxygen tension. Accordingly, the addition of butyrate results in the expression of HIF-regulated genes and, most pertinently, those encoding products involved in maintaining epithelial barrier function. These findings demonstrate not only how SCFAs lead to a clement environment for colonic anaerobes but also how SCFAs can maintain epithelial barrier integrity and thereby influence the development of inflammatory bowel disease. **ZF**  
*Cell Host Microbe* 17, 662–671 (2015)

## ILC2 commitment

Group 2 innate lymphoid cells (ILC2 cells) are important in immune responses at barrier surfaces, but the factors that control their development are still being identified. In the *Journal of Experimental Medicine*, two papers by McKenzie and colleagues and Liu and colleagues identify the transcription factor Bcl-11b as being critical for commitment to the ILC2 lineage. The authors find that much like T cells, ILC2 cells have high expression of Bcl-11b in all tissue compartments examined, including in ILC2 progenitors in the bone marrow and mature ILC2 cells in the gut and lungs. Deficiency in Bcl-11b results in an almost total loss of ILC2 cells and, consequently, impaired type II allergic responses and the ability to clear gut helminths. In contrast, the absence of Bcl-11b leads to a greater number of ILC3 cells and intact function. Bcl-11b therefore has an essential cell-intrinsic role in commitment to the ILC2 lineage. **ZF**  
*J. Exp. Med.* (11 May 2015) doi:10.1084/jem.20142224 & doi:10.1084/jem.20142318

## Clonal origin

Central memory T cells ( $T_{CM}$  cells) in the lymph nodes (LNs) and resident memory T cells ( $T_{RM}$  cells) in peripheral tissues have distinct roles in protective immunity. In *Nature Medicine*, Kupper and colleagues use various models of skin immunization in mice and humans and high-throughput sequencing of the gene encoding the T cell antigen receptor  $\beta$ -chain (TCR $\beta$ ) to investigate the clonal origin of  $T_{CM}$  cells and  $T_{RM}$  cells. After immunization,  $T_{CM}$  cells and  $T_{RM}$  cells with identical TCR $\beta$  CDR3 sequences are present with equal abundance in the LNs and skin, respectively. Multiple exposures to the same antigen lead to higher population expansion of skin  $T_{RM}$  cells than of LN  $T_{CM}$  cells. Parabiosis experiments show that  $T_{CM}$  cells are freely migratory between LNs, where they are greatly outnumbered by naive T cells, while skin  $T_{RM}$  cells are sedentary and make up most of the T cells in this location. These data are consistent with the existence of a common naive T cell precursor to  $T_{CM}$  cells and  $T_{RM}$  cells in various anatomic compartments. **IV**  
*Nat. Med.* (11 May 2015) doi:10.1038/nm.3860

## About STATs

Interleukin 6 (IL-6) and IL-27 signal mainly through both of the signal transducers STAT3 and STAT1 but induce distinct effects. In *Immunity*, Hirahara *et al.* evaluate the specificity and redundancy of the transcriptomic changes induced by these two cytokines in CD4<sup>+</sup> T cells. The duration, intensity and dimer composition of the STAT1 and STAT3 response is specific to each cytokine, which activate roughly equal amounts of shared and unique sets of genes. Analysis of the gene-expression profiles and genome-wide compensatory binding of STAT1 and STAT3 in CD4<sup>+</sup> T cells deficient in either STAT3 or STAT1 shows that STAT3 controls the bulk of the transcriptional output of both cytokines either as a homodimer or a STAT1-STAT3 heterodimer, whereas STAT1 provides the specificity of the responses to each cytokine, with STAT1 homodimers regulating genes uniquely induced by IL-27 and genes specifically repressed by IL-6. Thus, combinatorial use of signaling or transcriptional units allows unique responses to signals that share these units. **IV**  
*Immunity* 42, 877–889 (2015)

## Targeting by quartets

Immunoglobulin class-switch recombination (CSR) requires splicing of germline switch transcripts, but the reason for this has remained a puzzle. In *Cell*, Zheng *et al.* show that splicing of switch transcripts in the locus encoding the immunoglobulin heavy chain (*Igh*) generates molecular guide sequences to target CSR to downstream switch regions. RNA 'lariats' formed by splice excision are cleaved by the debranching enzyme DBR1, which allows the formation of guanine quartet (G4) structures from the intronic guanine-rich switch regions. Such G4 RNA is recognized at nanomolar concentrations by AID, the cytidine deaminase that directs CSR. Substitution of the conserved Gly133 residue of AID abolishes recognition of G4 RNA and CSR *in vivo* without altering AID's catalytic activity or transcription and splicing of the *Igh* downstream constant regions. These findings provide a molecular explanation for the requirement for splicing in CSR and show that AID uses G4 RNA to target recombination in a sequence-specific manner. **LAD**  
*Cell* 161, 762–773 (2015)

## Brain lymphatics

The brain and central nervous system (CNS) are thought to be devoid of lymphatic tissues that aid in immunosurveillance. In *Nature*, Kipnis and colleagues identify lymphatic vessels in the brain near the meningeal dural sinuses. These vessels express signature molecules, such as Lyve-1, podoplanin and Prox1, that distinguish lymphatic vessels from endothelial vessels. Both lymphocytes and CD11c<sup>+</sup> cells traffic within these vessels. Cerebrospinal fluid and T cells drain to deep cervical LNs but fail to do so after ligation of the meningeal lymphatic vessels and accumulate instead within the meningeal spaces. These findings support evidence that the CNS is not as 'immunoprivileged' as previously thought. **LAD**  
*Nature* (1 June 2015) doi:10.1038/nature14432