A gut vascular barrier

The blood-brain barrier is the best-characterized vascular 'firewall' in the body. In *Science*, Rescigno and colleagues identify a vascular barrier in the gut that is analogous to that in the brain and is present in both mice and humans. They identify a distinct gut vascular barrier (GVB) composed of closely interacting endothelial cells, glial cells and pericytes. This GVB prevents the translocation of large molecules from the gut lumen. However, oral infection of mice with *Salmonella typhimurium* disrupts the GVB and allows the translocation of much larger molecules, as well as dissemination of the bacterium itself. The ability of *S. typhimurium* to cross the GVB depends on its ability to impair Wnt signaling in the endothelium. Therefore, in addition to the epithelium, the GVB presents a second, independent barrier that regulates the translocation of luminal bacteria and their ligands, as well as innocuous food antigens. ***ZF***

Science **(13 November 2015) doi:10.1126/science.aad0135**

T_{reg} cell wiring

Regulatory T cells (T_{reg} cells) are known to have intracellular signaling patterns different from those of their conventional T cell counterparts. In the *Proceedings of the National Academy of Sciences USA*, Benoist and colleagues investigate the basis of this altered signaling. They confirm that signaling via various pathways emanating from the T cell antigen receptor (TCR) on T_{reg} cells is considerably diminished compared with that of conventional T cells. This impairment is not explained by increased expression of signal modulators such as CD5, PD-1, or CTLA4 in T_{reg} cells nor indeed by differences in expression of the TCR itself. However, diminished phosphorylation is not a global characteristic of T_{reg} cells, because signaling via certain cytokines, such as type I interferons, IL-2 and (in part) IL-6, is instead enhanced. T_{reg} cells are therefore 'wired' to be relatively unresponsive via the TCR but more sensitive to particular cytokines. *ZF*

Proc. Natl. Acad. Sci. USA (20 October 2015) doi:10.1073/pnas.1520393112

Pathogenicity control

Distinct subsets of the T_H17 subset of helper T cells have been identified on the basis of their cytokine profiles and pathogenicity. In *Cell*, Regev and colleagues use single-cell RNA sequencing to profile T_H17 cells isolated from the central nervous system of mice with experimental autoimmune encephalomyelitis or differentiated *in vitro* in various conditions to identify four previously unknown genes encoding products that control the pathogenic phenotype of T_H17 cells: *Gpr65*, *Plzp*, *Toso* and *Cd5*l. Kuchroo and colleagues show that CD5L is expressed in non-pathogenic T_H17 cells but not in pathogenic T_H17 cells that infiltrate the central nervous system or were differentiated with IL-23. CD5L deficiency increases the amount of saturated fatty acids and lowers the amount of polyunsaturated fatty acids in T_H17 cells. The former enrich binding of the transcription factor RORγt to the *Il17* and *Il23r* loci, while the latter increase its binding to the *Il10* locus. Thus, CD5L regulates the transcriptional activity of RORγt and the cytokine profile of T_H17 cells by controlling the fatty acid composition of the lipidome. ***IV***

Cell **(19 November 2015) doi:10.1016/j.cell.2015.11.009 & doi:10.1016/j.cell.2015.10.068**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Insulin resistance: old or obese?

While macrophage-dependent inflammation is the driver of obesity-associated insulin resistance, the mechanisms of age-associated insulin resistance remain unclear. In *Nature*, Zheng and colleagues show that fat resident T_{reg} cells modulate age-associated insulin resistance in mice. Although the macrophage subsets remain unchanged, the T_{reg} cell population expands substantially with age in the visceral adipose tissue (VAT). Selective depletion of T_{reg} cells in the fat of aged mice leads to improved insulin sensitivity, remodeling of VAT, less hepatic steatosis, lower body mass, greater oxygen consumption and higher core body temperature, without systemic inflammation. VAT T_{reg} cells have higher expression of *Pparg*, *Gata3*, *Irf4, Ctla4, Il2ra* and *Il10* and of the IL-33 receptor ST2 than that of splenic T_{reg} cells and maintain considerable suppressive ability in aged mice. Partial depletion of fat T_{reg} cells by targeting ST2 enhances the insulin sensitivity of VAT without signs of systemic T_{reg} cell dysfunction, which would suggest therapeutic potential. *IV*

Nature (18 November 2015) doi:10.1038/nature16151

ADAR1 regulates Mda5-MAVS

Mutations in the gene encoding the RNA-editing enzyme ADAR1 lead to Aicardi-Goutières syndrome, an autoinflammatory disease. Similarly, ADAR1 deficiency in mice results in embryonic death characterized by exuberant expression of type I interferon. In *Immunity*, Pestal *et al.* show that ADAR1 suppresses activation of the intracellular RNA sensor pathway mediated by Mda5 and MAVS. *Adar*-null embryos are 'rescued' by loss of expression of either Mda5 or MAVS. RNA sequencing analyses reveal that only 20% of the genes dysregulated in $Adar^{-/-}$ embryos are MAVS-dependent interferon-stimulated genes, whereas additional defects in organ development, intestinal homeostasis and hematopoiesis are apparent in $Adar^{-/-}Mavs^{-/-}$ neonates. *Adar* encodes two isoforms, p150 and p110, which have non-redundant functions, as mice lacking p150 are 'rescued' by MAVS deficiency but still show loss of B cell development and intestinal abnormalities. The p150 isoform might edit long duplex RNAs that serve as Mda5 ligands, in addition to editing other RNA targets. ***LAD***

Immunity **43, 933–944 (2015)**

TAMs in border security

Receptor tyrosine kinases of the TAM family recognize the phosphatidylserine-binding proteins Gas6 and protein S and contribute to tissue homeostasis. In *Nature Medicine*, Miner *et al.* show that two TAM receptors, Axl and Mertk, also contribute to blood-brain barrier function after encephalitic viral infection. Loss of either Axl or Mertk, but not loss of the TAM receptor Tyro3, leads to diminished barrier integrity at baseline and fails to sufficiently tighten junctions between brain microvascular endothelial cells after subcutaneous infection with West Nile virus or La Crosse virus, which are enveloped viruses that can bind Gas6. Mutant mice have higher viral loads in brain and spinal cord tissues than those of similarly infected wild-type mice. TAM signaling acts in synergy with interferon-β to reduce blood-brain barrier permeability via a mechanism that involves activation of the Rho-family GTPase Rac1 and increased colocalization of the junction proteins claudin-5 and ZO-1. Whether direct interaction occurs between the TAM receptors and the signaling receptor IFNAR1 remains unknown. *LAD*

Nat. Med. (2 November 2015) doi:10.1038/nm.3974