Exit from the liver

The molecules that control the tissue-specific migration of fetal macrophages remain unknown. In *Nature*, Rantakari *et al.* show that PLVAP, a protein that forms diaphragms in fenestrated endothelial structures, selectively controls the seeding of fetal liver monocyte-derived macrophages to tissues in mice. Yolk-sack-derived and bone-marrow-derived macrophages are present at normal frequencies in adult PLVAP-deficient mice, which corresponds to the normal emergence of primitive progenitors in the yolk sack and AGM region of the embryonic mesoderm. PLVAP is expressed selectively on fetal liver sinusoidal endothelial cells starting at embryonic day 12.5. PLVAP-deficient mice, which completely lack diaphragms in the liver fenestrae during embryogenesis, have normal entry and differentiation of macrophage precursors in the fetal liver, while the exit of mature fetal liver monocytes is impaired. Fenestral diaphragms might assist the emigration of fetal liver monocytes by immobilizing chemotactic molecules or providing a substrate for adhesion. ***IV***
***Nature* 538, 392–396 (2016)**

Human regulatory cells miss their target

T_{reg} cells are essential for 'tuning' appropriate immune responses; however, the extent to which their numerical or functional impairment contributes to allergy in humans is unclear. In *Cell*, Scheffold and colleagues use a technique for isolating and functionally examining minute populations of antigen-reactive human T cells to investigate the role of T_{reg} cells in allergy. In normal volunteers, both conventional T cells and T_{reg} cells are found to react to self, non-self and commensal antigens. People allergic to aeroantigens also show normal T_{reg} cell numbers and functionality but fail to control allergic responses of the T_H2 subset of helper T cells. This relative inability to suppress allergen-specific responses arises because the T_{reg} cells and T_H2 cells target different sets of antigens. The data suggest that rather than there being an inherent wholesale loss of T_{reg} cell functionality, allergy can arise by a failure of the suppressive cells to overlap in time and/or space with the pathogenic T cells. *ZF*
Cell (20 October 2016) doi:10.1016/j.cell.2016.09.050

Spliced-peptide presentation

Protein cleavage by the proteasome supplies peptides that are loaded onto major histocompatibility complex class I molecules and are presented as epitopes to $CD8^+$ T cells. In *Science*, Liepe *et al.* investigate the human 'immunopeptidome' presented by HLA-I and report that proteasome-generated spliced peptides contribute roughly one fourth of the antigenic epitope repertoire displayed on the cell surface. Spliced peptide epitopes are produced by lymphoblastoid cell lines and primary human fibroblasts. Remarkably, some self antigens are presented only as *cis*-spliced epitopes that are derived by deletion of intervening amino acids to obtain the final 9- to 12-residue peptide. Although the rules for how proteasomes generate spliced peptides remain to be delineated, such processing can vastly increase the repertoire of peptides surveyed by $CD8^+$ T cells. Whether infection or inflammation alters this process likewise remains unknown. ***LAD***
***Science* 354, 354–358 (2016)**

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

TLR4 in lung regeneration

Type 2 alveolar epithelial cells (AEC2s) secrete pulmonary surfactant, undergo long-term self-renewal and generate type 1 AECs, which mediate the gas exchange. In *Nature Medicine*, Noble and colleagues show that expression of the innate immunoreceptor TLR4 and the extracellular matrix component hyaluronan (HA) on AEC2s is important for their renewal and lung repair after injury. In mice, TLR4 expression increases in the lung after injury, and *Tlr4*$^{-/-}$ mice are more susceptible to injury and have an enhanced fibrotic response relative to that of wild-type mice. TLR4- and HA-deficient AEC2s proliferate less and have lower colony-forming potential in organoid cultures than do wild-type AEC2s. TLR4- and HA-deficient mice have lower IL-6 expression in the lungs, and recombinant IL-6 increases AEC2 proliferation, lung generation and survival after injury. AEC2s from patients with pulmonary fibrosis have lower colony-forming efficiency and HA expression than do those from healthy donors, whereas their TLR4 expression is normal. *IV*
Nat. Med. (3 October 2016) doi:10.1038/nm.4192

Deworming gives a boost

Helminth infection of humans can perturb immunity and impair vaccine responses. In the *Proceedings of the National Academy of Sciences*, Yazdanbaksh and colleagues investigate the effect of deworming on immunological parameters in a large cohort of volunteers from rural Indonesia. The study group showed a high incidence (~90%) of soil-transmitted helminth infection. Treatment with the anti-helminthic agent albendazole every 3 months over 21 months substantially diminished helminth loads but failed to completely eradicate infection. Immunological parameters such as mitogen responses or those to helminth and unrelated malaria parasites measured at 9 and 21 months after treatment resulted in elevated proinflammatory cytokines, especially TNF. The frequency of regulatory T cells (T_{reg} cells) was not affected by the treatment regimen, but there was a significant decrease in the signature inhibitory molecule CTLA-4. This human study of real-world infection demonstrates the reversal of helminth-triggered immune hyporesponsiveness, with potential implications for prophylactic vaccination and the unmasking of autoinflammatory diseases. ***ZF***
***Proc. Natl. Acad. Sci. USA* (17 October 2016) doi:10.1073/pnas.1604570113**

IFN-α/β-mediated suppression of B cells

Chronic infection by intracellular pathogens commonly fails to elicit neutralizing antibody responses. In *Science Immunology*, three studies by McGavern, Pinschewer and Iannacone and their colleagues report how humoral immunity is blunted during chronic infection with lymphocytic choriomeningitis virus. All three studies invoke early loss of virus-specific B cells dependent on interferon-α and interferon-β (IFN-α/β), which thereby indirectly blunts the generation of neutralizing antibodies. Blockade of the IFN-α/β receptor 'rescues' B cell loss. The studies differ on how IFN-α/β signaling triggers such loss; however, suggested roles include activated $CD8^+$ T cells, nitric-oxide production by $CCR2^+$ inflammatory monocytes, and production of the cytokine TNF by myeloid cells within infected lymph nodes. Curiously, this inhibitory effect wanes within 3–6 d of infection, which suggests a temporal window for boosting the production of neutralizing antibodies by inhibiting IFN-α/β signaling. *LAD*
*Sci. Immunol.***1**, eaah3565, eaah6817 & eaah6789 (21 October 2016)