Fasting fights leukemia

Dietary restriction delays aging. In *Nature Medicine*, Zhang and colleagues report that fasting alone inhibits the initiation and reverses the progression of B cell and T cell acute lymphoblastic leukemia (ALL), but not that of acute myeloid leukemia (AML), in mouse models. Various regimens of fasting cycles lower the frequency of malignant lymphocytes in the blood and lymphoid organs and enhance survival, if initiated early or late after the transfer of leukemic cells. In ALL cells, but not in non-transformed cells or AML, fasting induces a transcriptional program characterized by activation of the JAK-STAT signaling pathway, lower expression of the oncoprotein n-Myc and the upregulation of cytokine receptors, including the leptin receptor (LEPR). Leptin–LEPR signaling inhibits ALL development through upregulation of the transcription factor Blimp-1, which is important for the terminal differentiation of B cells and T cells. The expression of genes associated with LEPR signaling positively correlates with patient survival in pediatric ALL but not in AML samples. ***IV***

***Nat. Med.* (12 December 2016) doi:10.1038/nm.4252**

The interferon signature

In cancer, interferon-γ (IFN-γ) signaling can induce expression of the checkpoint ligand PD-L1. In *Cell*, Benci *et al.* investigate whether interferons can induce tumor resistance beyond upregulation of PD-L1. In a melanoma model, prolonged IFN-γ signaling *in vitro* and *in vivo* induces adaptive resistance to immunotherapy, which is maintained by both type I interferons and type II interferons. Persistent IFN-γ stimulation increases the expression and genome occupancy of the transcription factor STAT1 in melanoma cell lines and induces an epigenetic profile similar to that of resistant tumors, characterized by high expression of inhibitory receptors, such as PD-L1, TIM3, LAG3 and galectin-9, and of cancer-associated products of interferon-stimulated genes, such as IFIT1 and Mx1. Blocking interferon signaling or deletion of receptors for type I and type II interferons 'rescues' the tumor response to PD-1- or CTLA-4-blockade therapy. In patients, high expression of IFIT3 and Mx1 correlates with progression after PD-1-blockade therapy. *IV*

Cell **167**, 1540–1554 (2016)

Keeping IgE$^+$ B cells under wraps

Immunoglobulin E (IgE) is central to triggering allergy; therefore, IgE$^+$ B cells must be tightly controlled and their numbers must be kept in check. In *eLife*, Allen and colleagues study the IgE B cell antigen receptor (BCR) to gain insight into how it regulates the fate and frequency of IgE$^+$ B cells. They find that the IgE BCR is weakly active even in the absence of cognate ligand and drives a pathway that involves the signaling molecules Syk, BLNK and Btk. This signaling promotes the differentiation of B cells into low-affinity plasma cells, but the authors find no evidence that it triggers apoptosis. This characteristic signaling activity of the IgE BCR is dependent in part on a short and distinctive membrane-proximal segment called the 'migis'. The unique properties of the IgE BCR are therefore hardwired to avoid the generation of large numbers of potentially harmful high-affinity IgE molecules. ***ZF***

***eLife* (9 December 2016) http://dx.doi.org/10.7554/eLife.21238**

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

Keeping your T cells

Age-related changes in human T cells throughout a person's lifespan have been observed only in analyses of blood; however, such studies capture only a tiny proportion of the overall T cell population and repertoire. In *Science Immunology*, Farber and colleagues study T cells in primary and secondary lymphoid tissue from organ donors of a wide age range. Thymopoiesis does not diminish gradually, as expected; instead, it seems to be generally stable until around 40 years of age, at which time it undergoes a precipitous decrease. Naive T cells (which are essential for responses to antigens not previously encountered) are most numerous in the young yet still persist even in the elderly and maintain naive functionality, as assessed by production of interleukin 2. Naive T cells occupy lymphoid tissues at varying frequencies and with largely distinct non-overlapping repertoires of T cell antigen receptors. Collectively, these findings indicate that throughout life, secondary lymphoid organs serve as important reservoirs of functional naive T cells. *ZF*

Sci. Immunol. (2 December 2016) http://dx.doi.org/10.1126/sciimmunol.aah6506

Neurologic Mtb-HIV complications

Mycobacterium tuberculosis* infection is frequently found in patients infected with human immunodeficiency virus and commonly involves meningeal infection. Such patients can develop potentially lethal complications arising from the excessive cytokine production that can ensue after the initiation of antiretroviral therapy (ART), a scenario known as 'immune-reconstitution inflammatory syndrome' (IRIS). In the *Journal of Infectious Diseases*, Marais *et al.* monitor patients infected with human immunodeficiency virus who have *M. tuberculosis* meningitis (TBM), before and after they receive ART. At time of diagnosis, those patients who developed TBM–IRIS have higher neutrophil counts in their cerebrospinal fluid (CSF) and higher expression of neutrophil effector molecules in both blood and CSF than do those patients with TBM who did not develop IRIS after ART. Transcripts associated with NLRP3 inflammasomes increase over time in those patients who developed TBM-IRIS. These findings suggest that innate immunity involving neutrophil and inflammasome activation in the CSF contribute to the complications of TBM–IRIS.** ***LAD

***J. Infect. Dis.* (8 December 2016) http://dx.doi.org/10.1093/infdis/jiw561**

Neurophils aid successful pregnancy

The establishment of maternal immunotolerance is essential for the survival of allogeneic fetuses. In the *Proceedings of the National Academy of Science*, Nadkarni *et al.* report a role for neutrophils exposed to maternal hormones that help establish a 'tolerant' environment within the developing placenta. These 'tolerogenic' neutrophils upregulate expression of the transcription factor Foxo1 and annexin-A1 and release apoptotic bodies that then promote the generation of fetal-antigen-specific regulatory T cells that express IL-10 and IL-17. IL-17 enhances pro-angiogenic activities necessary for placental growth and decidualization. Depletion of neutrophils in pregnant mice leads to defective placental development and decreases the number of viable fetuses. Similarly, neutrophils from women with pre-eclampsia fail to induce regulatory T cells and express less Foxo1 than do neutrophils from healthy expectant mothers. These findings indicate a role for the neutrophil-mediated transfer of Foxo1 to CD4$^+$ T cells to induce Foxp3 expression within the uterine environment. *LAD*

Proc. Natl. Acad. Sci. USA (12 December 2016) http://dx.doi.org/10.1073/pnas.1611944114