NEUROIMMUNOLOGY

Brain lymphatic (dys)function

Nature https://doi.org/10.1038/s41586-018-0368-8 (2018)

The discovery of brain lymphatics has challenged the concept that the healthy brain is an immunoprivileged organ; however, the function of these lymphatics in disease states has been unclear. In *Nature*, Kipnis and colleagues investigate the potential homeostatic and pathophysiological roles of brain lymphatics. Genetic and pharmacological disruption of brain lymphatics results in less drainage of the cerebrospinal and interstitial fluids to the cervical lymph nodes. Such disruption also results in select cognitive impairment and behavioral alterations. Increasing the diameter of brain lymphatics via administration of recombinant growth factor VEGF improves the drainage of macromolecules to the cervical lymph nodes of aged mice. Finally, disruption of brain lymphatics worsens mouse models of Alzheimer's disease. Collectively, these findings suggest that dysfunction of brain lymphatics might provide an important contribution to age-related cognitive decline and neurodegenerative disease. *ZF*

https://doi.org/10.1038/s41590-018-0194-z

REPORTER SYSTEMS

All about timing

EMBO J. https://doi.org/10.15252/embj.201899013 (2018) & *J. Cell Biol.* https://doi.org/10.1083/jcb.201711048 (2018)

Studying the real-time kinetics of gene expression quantitatively in vivo is technically very challenging but could offer genuine insight into fundamental biological processes. In two related papers in the *Journal of Cell Biology* and *EMBO Journal*, Ono and colleagues describe the novel reporter mouse Tocky ('timer of cell kinetics and activity'; the homonym 'toki' means 'time' in Japanese). The Tocky model uses a fluorescent timer protein that spontaneously shifts its emission from blue to red with a distinct half-life. Through appropriate pairing of the timer protein and quantitative modeling, it is potentially possible to monitor transcriptional activity in vivo for any gene of interest. The authors use Tocky mice to investigate the kinetics of gene expression in regulatory T cells during differentiation and under inflammatory conditions. *ZF*

https://doi.org/10.1038/s41590-018-0195-y

MACROPHAGES

Keeper of specificity

Immunity https://doi.org/10.1016/j.immuni.2018.07.004 (2018)

Macrophages adopt tissue-specific identities. In *Immunity*, Scott et al. report that the transcription factor Zeb2 controls the tissue identity of macrophages from the liver, lungs, brain, colon and spleen. Kupffer cells and alveolar macrophages with conditional deletion of Zeb2 gradually disappear from the tissue (by 20 days in the liver and >48 days in the lungs) and show differences in the expression of 60% and 72%, respectively, of their core tissue-specific genes. Spleen, brain and colon macrophages with conditional deletion of Zeb2 also show alterations in the expression of 60–75% of their core tissue-specific genes, with Zeb2-deficient spleen macrophages gradually disappearing from the tissue (microglia and colon macrophages were not assessed). Loss of Zeb2 results in mostly tissue-specific changes, with only 32 genes that are expressed differentially being shared by all tissues. *IV*

https://doi.org/10.1038/s41590-018-0196-x

PHASE TRANSITIONS

cGAS liquid droplets

Science https://doi.org/10.1126/science.aat1022 (2018)

The cyclic GMP-AMP synthase cGAS is an intracellular sensor that detects cytosolic double-stranded DNA. Binding to DNA activates the enzymatic activity of cGAS and leads to accumulation of the cyclic dinucleotide GAMP, which in turn activates a signaling cascade dependent on the adaptor STING that results in the production of type I interferons. In *Science*, Du and Chen report that cGAS undergoes a liquid-like phase transition after binding to DNA but not after binding to duplex RNA. This liquid-droplet formation is dependent on zinc ions. Long DNA duplexes are more efficient than short DNA duplexes in promoting the formation of cGAS puncta in vivo. The phase transition of cGAS to liquid droplets results in greater enzymatic specific activity and thus more efficient activation of type I interferon responses. *LAD*

https://doi.org/10.1038/s41590-018-0199-7

IMMUNOMETABOLISM

Starved NK cells

Cell Metab. https://doi.org/10.1016/j.cmet.2018/06.021 (2018)

Dysfunction of natural killer (NK) cells is linked to tumor progression. In *Cell Metabolism*, Wei and colleagues use a Kras-driven model of lung cancer in mice to show that induction of the glycolysis-inhibiting enzyme FBP1 in NK cells impairs their viability and gradually induces a dysfunctional state. NK cells potently prevent tumor initiation (stage 1) but fail to control the promotion or progression (stages 2 and 3) of lung cancer. Stage 2 and stage 3 NK cells have attenuated cytotoxicity and proliferation, increased expression of intracellular ROS and FBP1 and decreased glycolysis, relative to that of spleen NK cells, but stage 1 NK cells do not. Inhibition of FBP1 'rescues' the cytotoxicity, viability and proliferation of stage 2 NK cells, but not that of stage 3 NK cells, and, after transfer of stage 2 NK cells into these mice, slows tumor growth. *IV*

https://doi.org/10.1038/s41590-018-0197-9

INNATE IMMUNITY

ICAM-1 in ILC2s

J. Exp. Med. https://doi.org/10.1084/jem.20172359 (2018)

Group 2 innate lymphoid cells (ILC2s) are dependent on the transcription factor GATA-3 and produce the cytokines IL-5 and IL-13 after being activated. In *The Journal of Experimental Medicine*, Lei et al. show that signaling via the adhesion molecule ICAM-1 regulates ILC2 development and function. *Icam1*$^{-/-}$ mice generate fewer ILC2s and develop less-severe allergic responses than those of wild-type mice. *Icam1*$^{-/-}$ ILC2s produce less IL-5 and IL-13 in vitro, suggestive of a cell-intrinsic defect. Ligation of ICAM-1 by the integrin LFA-1 triggers activation of the kinase Erk, which stabilizes GATA-3 protein. Loss of ICAM-1 thus results in destabilization of GATA-3 and diminished GATA-3-dependent transcriptional responses. These findings suggest that interfering with ICAM-1–LFA-1 might ameliorate allergic responses. *LAD*

https://doi.org/10.1038/s41590-018-0198-8

Laurie A. Dempsey, Zoltan Fehervari and Ioana Visan