NEUROIMMUNOLOGY

Souring microglia

Cell Metab. **33**, 2260–2276 (2021)

Gut microbiota produce metabolites that influence immune cells in distal sites throughout the body. In *Cell Metabolism*, Erny et al. examine the influence of gut microorganisms on microglia. Several lines of genomic and metabolic profiling reveal altered mitochondrial function in microglia obtained from germ-free (GF) mice as compared with conventionally housed mice. Although microglia from GF mice have increased mitochondrial content, their membrane potential is reduced. The authors trace these defects to a selective impairment of the activity of microglial mitochondrial complex II, which could be rectified by oral supplementation of acetate to the GF mice. Using the 5xFAD mouse model of Alzheimer's disease, gut-derived acetate is shown to influence microglial functional activity, including phagocytosis of amyloid-β plaques and the expression of inflammatory cytokines. *LAD*

https://doi.org/10.1038/s41590-021-01106-w

B CELLS

Signaling metabolites

Nature https://doi.org/10.1038/s41586-021-04082-1 (2021)

GABA (γ-aminobutyric acid) is considered an inhibitory neurotransmitter. In *Nature*, Fagarasan and colleagues show that resting and activated B cells in mice and humans synthesize and secrete GABA and express GAD67, one of two enzymes that convert glutamate to GABA. In culture, GABA signaling inhibits the activation of $CD8^+$ T cells and promotes the differentiation of macrophages with anti-inflammatory properties. In a model of colon carcinoma in mice, B cell-specific deletion of GAD67 results in reduced tumor growth and increased infiltration of $CD8^+$ T cells compared with wild-type mice, whereas GABA supplementation in B cell-deficient mice increases tumor growth. These observations may explain the poor prognosis of specific cancers with high infiltration of B cells. *IV*

https://doi.org/10.1038/s41590-021-01107-9

NEUROIMMUNOLOGY

An immunological engram

Cell https://doi.org/10.1016/j.cell.2021.10.013 (2021)

In *Cell*, Rolls and colleagues investigate whether immune-related information can be stored in and retrieved from the brain. Using two distinct models of inflammation — dextran sulfate sodium (DSS)-induced colitis and zymosan-induced peritonitis — the authors show that there is activation of neurons in a discrete region of the brain: the insular cortex (InsCtx). Using mice that had recovered from colitis or peritonitis that then underwent chemogenetic stimulation of the InsCtx, the authors find that many inflammatory features could be recapitulated, and importantly that the inflammation was constrained solely to either the colon or the peritoneum. These findings suggest that the brain can store long term a representation of a peripheral immune response. *ZF*

https://doi.org/10.1038/s41590-021-01108-8

COVID-19

Vaccine thrombosis

Science https://doi.org/10.1126/sciadv.abl8213 (2021)

Blood https://doi.org/10.1182/blood.2021013231 (2021)

The occurrence of unusual blood clots has been associated with the adenoviral vector-based COVID-19 vaccines. Research published in *Science* and *Blood* supports a cause for this thrombosis is an antibody-mediated response to complexes formed between the adenovirus and platelet factor 4 (PF4). In the *Science* paper, the researchers used cryo-electron microscopy to show the highest resolution capsid structure so far of the viral vector ChAdOx1 and then used computational models and surface plasmon resonance to show a binding mechanism between PF4 and the adenoviral vectors used in COVID-19 vaccines. Meanwhile, the *Blood* paper shows that antibodies bind to this complex, and this results in platelet activation. These findings might enable tweaks to the viral vector vaccines to avoid such adverse events in the future. *NJB*

https://doi.org/10.1038/s41590-021-01111-z

IMMUNOMETABOLISM

Controlling T_H17 cells

Immunity https://doi.org/10.1016/j.immuni.2021.10.011 (2021)

Metabolic cues can control T cell differentiation and function including the important balance between effector and regulatory states. In *Immunity* Sugirua et al. identified the enzymatic function of methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) as a controller of these cues. CD4-specific *Mthfd2* deficiency or a MTHFD2 inhibitor resulted in reduced purine biosynthesis, with a consequent drop in mTORC1 activity and a switch from glycolysis towards oxidative phosphorylation in T helper (T_H) cells. Under T_H1 and T_H17 culture conditions, this effect resulted in reduced expression of the inflammatory T cell transcription factors Tbet and RORγt and the cytokines IL-17 and IFN-γ, but increased expression of FOXP3 as well as suppressive functionality. MTHFD2 deficiency also reduced inflammation and pathology in a variety of mouse models, including EAE, IBD and allergic airway disease, with the implication being that these T regulatory-like switched T_H17 cells might contribute to the effect and that MTHFD2 could be a viable therapeutic target. *NJB*

https://doi.org/10.1038/s41590-021-01112-y

VACCINE RESPONSES

Mellower with age

eLife https://doi.org/10.7554/eLife.70554 (2021)

In *eLife*, Linterman and colleagues investigate the response to trivalent seasonal influenza vaccination in both young and older individuals (18–36 and over 65 years old, respectively). Vaccination triggered the generation of circulating T follicular helper (cT_{FH}) cells from pre-existing memory $CD4^+$ T cells. Irrespective of age, influenza-specific IgG levels correlate closely with cT_{FH} cell frequency; however, older individuals show impaired IgG. cT_{FH} cells from older individuals show increased inflammation and IL-2 signatures that might underpin the defective generation of cT_{FH} cells and consequent weaker vaccine response. *ZF*

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