NEUROIMMUNOLOGY

Brain hematopoiesis

Science https://doi.org/10.1126/science.abf9277 (2021)
Science https://doi.org/10.1126/science.abf7844 (2021)

Conventional knowledge suggests that adult hematopoiesis occurs in the marrow of long bones, giving rise to mature cells that then circulate in blood throughout the body. In *Science*, Brioschi et al. and Cugurra et al. show that specialized niches in skull bone marrow support B cell development and myelopoiesis, yielding distinct populations of cells that enter the bordering meninges and patrol tissues of the central nervous system. Using parabiotic pairs of mice, irradiation experiments that involved differential body shielding and skull bone tissue transplantation, the authors confirmed that de novo hematopoiesis occurs in calvaria bone regions. Cells derived from this niche enter meningeal borders via ossified vascular channels that connect the skull to the meninges. Single-cell transcriptomic analyses revealed that all stages of B cell lymphopoiesis are present within the meningeal B cell population, whereas circulating blood only contains mature B cells. Similarly, the meningeal-derived myeloid cells are distinct from their bloodstream counterparts. The findings point to potentially distinct roles played by these local meningeal immune cells in the central nervous system. *LAD*

https://doi.org/10.1038/s41590-021-00988-0

INFECTIOUS DISEASE

Immunology at a distance

Biol. Lett. https://doi.org/10.1098/rsbl.2021.0125 (2021)

The avoidance of diseased members of the same species (conspecifics) is an effective behavioral mechanism for preventing infection and is exhibited widely across the animal kingdom. In *Biology Letters*, Love et al. investigate whether perception of diseased individuals alone is sufficient to evoke immunological changes in the perceiver. Domestic canaries infected with the avian pathogen *Mycoplasma gallisepticum* have visually apparent symptoms, including conjunctivitis and classic sickness behaviors. *M. gallisepticum*–infected birds were separated from a second group of healthy birds by a transparent divider that prevented pathogen transmission but allowed visual cues, whereas the control *M. gallisepticum*–infected group was separated by an opaque divider. This setup allowed the effects of visual as opposed to olfactory or auditory cues to be studied separately. Birds perceiving infection showed elevated complement activity that coincided with peak symptoms in the infected group. Heterophils (the avian functional equivalent of neutrophils) also transiently spiked after sick birds were perceived. These findings suggest that the mere perception of sickness can prime the immune system and may allow it to act in an anticipatory manner. *ZF*

https://doi.org/10.1038/s41590-021-00989-z

COVID-19

An infectious link to the brain

Nature https://doi.org/10.1038/s41586-021-03710-0 (2021)

Respiratory epithelium is the primary target of SARS-CoV-2; however, sporadic reports of neurological symptoms associated with COVID-19 suggest that the virus may either directly or indirectly target the central nervous system. In *Nature*, Wyss-Coray and colleagues use single-cell analysis to compare post mortem brain samples from individuals who had COVID-19 with samples from a patient with terminal influenza or from non-infected brain tissue. Immunohistochemistry revealed SARS-CoV-2 infection of the barrier vasculature—specifically, the choroid plexus (CP)—in some of the patients with COVID-19, but no overt infection of brain parenchyma. However, transcriptomic analysis found signs of inflammation and activation of antiviral pathways not only in the CP itself but also within the frontal cortex. These characteristic expression changes were not observed in influenza infection. Many gene expression changes in the COVID-19 cohort are shared with neurodegenerative disease, especially those in astrocytes and excitatory neurons. These data suggest that inflammatory signals may 'ripple out' from infected CP into the brain parenchyma and thereby mediate the psychiatric manifestations occasionally seen in COVID-19. *ZF*

https://doi.org/10.1038/s41590-021-00990-6

MICROBIOME

Bacteria guide development of the fetal immune system

Cell https://doi.org/10.1016/j.cell.2021.04.039 (2021)

Bacteria have been detected in fetal tissues, indicating that they are able to cross the placental barrier, but whether these bacteria are viable and how they affect the developing immune system in utero is a matter of debate. Research published in *Cell* addresses this controversy with paired microbiome and T cell mass cytometry data from multiple human organs. The researchers isolated blood and tissue from lung, skin, intestines, thymus, liver and lymph nodes to compare adults with the second-trimester fetus. 16S ribosomal RNA sequencing data show low levels of *Flavobacteria*, *Staphylococci*, *Prevotella* and *Lactobacilli* (and others) in many of the fetal tissues and inside the intestinal lumen, a finding supported by microscopy imaging showing bacterial cocci localized primarily within meconium-associated mucin-like structures from week 14 of gestation. Importantly, many bacterial strains were isolated and cultured, indicating bacteria are viable within these tissues. CyTOF/UMAP (cytometry time of flight/uniform manifold approximation and projection) cluster analysis then shows that during the second trimester there are abundant regulatory T cell populations in the fetal tissues, as well as a sizeable pool of cytotoxic T cells and effector memory T cells. Furthermore, T cells from mesenteric lymph nodes could mount memory responses to bacterial stimulation ex vivo. All of these results suggest that development of the human fetal immune system is guided by the microbiome from as early as the second trimester. *NJB*

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COVID-19

Long COVID

Nat. Med. https://doi.org/10.1038/s41591-021-01433-3 (2021)

Chronic fatigue occurs after SARS and a spectrum of other viral infections. In *Nature Medicine*, Blomberg et al. report that 81% of 65 hospitalized and 55% of 247 non-hospitalized patients in Bergen, Norway, had persistent symptoms 6 months after infection with SARS-CoV-2. Among the non-hospitalized patients, 83% had

symptoms during acute disease; 37% had comorbidities like asthma or COPD (10%), hypertension (8%) and rheumatic disease (4%); and 55% experienced persistent symptoms at 6 months after infection (13% of 0–15 year olds, 50% of 15–30 and 60% of 31–45, 45–60 and over 60). The most frequent lasting symptoms in non-hospitalized patients aged 31–45 and 45–60 were disturbed taste and smell (34 and 28%, respectively), fatigue (31 and 33%), dyspnea (17 and 18%), concentration problems (19 and 21%) and memory problems (16 and 22%). Of non-hospitalized patients over 30, 7% experienced severe fatigue as compared to 24% of hospitalized patients. In non-hospitalized patients, antibody titers at 2 months were associated with the severity of the initial illness, while persistent fatigue was associated with the severity of the initial illness, fever during the initial illness and female gender. *IV*

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