IN BRIEF

COVID-19

Transient IgA, steady IgG?

Successful vaccine design requires an assessment of antibody responses and their protectivity over time. In this preprint, Sterlin et al. characterize the early humoral immune response to SARS-CoV-2 in 38 patients. Longitudinal serum analysis revealed that IgA and IgG differ in potency and prevalence over time. At onset of disease, mucosal-homing IgA-secreting plasmablasts predominate; these appear to arise in a germinal centre-independent fashion. Most SARS-CoV-2-targeted antibodies bound to the receptor-binding domain region and IgA provided more efficient neutralization than IgG. However, as infection progressed, IgA serum levels declined whereas IgG levels increased. Therefore, testing for virus-specific IgA should be suitable for early diagnosis, whereas testing for IgG is more relevant post-infection. However, bronchoalveolar lavage of patients with severe infection revealed a predominance of IgG, highlighting differences in mucosal and systemic responses to SARS-CoV-2.

ORIGINAL ARTICLE Sterlin, D. et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.10.20126532 (2020)

COVID-19

SARS-CoV-2: too infectious to handle?

In this preprint, Andersson et al. assessed whether blood samples obtained from patients with COVID-19 carry active infectious SARS-CoV-2 RNA. A systematic review of 22 recently published preprints combined with the authors' own patient data (424 individuals) showed that 10% of blood samples taken within 28 days of symptom onset contain SARS-CoV-2 RNA at low copy number, but no sample exceeded the threshold for viral infectivity. Incubation of VeroE6 cells with SARS-CoV-2-RNA-positive serum samples from patients did not reveal any cytopathic effects or lead to viral replication. Further studies will be required to determine the safety of blood samples to inform changes to biosafety policies.

ORIGINAL ARTICLE Andersson, M. et al. SARS-CoV-2 RNA detected in blood samples from patients with COVID-19 is not associated with infectious virus. Preprint at *medRxiv* https://doi.org/10.1101/2020.05.21.20105486 (2020)

COVID-19

Caught by NETs

In this preprint, Veras et al. report a cohort study of 32 patients with critical and severe COVID-19. The authors found increased concentrations of neutrophil extracellular traps (NETs) in plasma, tracheal aspirates and lung tissue of patients and show that neutrophils from patients spontaneously released higher levels of NETs than their counterparts from healthy controls. Interestingly, in vitro experiments showed that SARS-CoV-2 can induce NET formation in neutrophils from healthy controls, with viral antigens being detected inside the cells. In co-culture experiments, these NETs induced apoptosis of lung epithelial cells. The authors suggest that inhibitors of NET synthesis or promoters of NET fragmentation may be beneficial in patients with COVID-19.

ORIGINAL ARTICLE Veras, F. P. et al. SARS-CoV-2 triggered neutrophil extracellular traps (NETs) mediate COVID-19 pathology. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.08.20125823 (2020)

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The authors declare no competing interests.

NEUROIMMUNOLOGY

Liver–brain–gut reflex tones T_{reg} cells

Regulatory T (T_{reg}) cells in the gut are controlled by environmental signals, from cytokines, the diet and microbiota, and also by neuronal signals. A new study in *Nature* identifies a neural arc between the liver, brain and gut that ensures proper differentiation and maintenance of T_{reg} cells in the gut and protects against inflammatory bowel disease.

To investigate how neural signals influence gut homeostasis, the authors first performed a vagotomy in wild-type mice. Vagotomized mice showed a significant reduction in the number of FOXP3$^+$ T_{reg} cells in the colon compared with sham-operated mice. This coincided with a decrease in levels of retinoic acid-synthesizing enzymes (aldehyde dehydrogenases) in colonic antigen-presenting cells (APCs), which are known to support the development of T_{reg} cells in the gut. RNA sequencing analysis revealed higher expression of muscarinic acetylcholine receptor (mAChR) in colonic APCs than in splenic APCs, suggesting enhanced responsiveness to neurotransmitters.

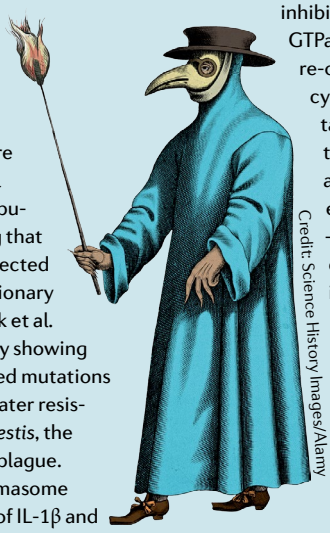
Vagotomized mice also had increased susceptibility to chemically induced colitis. Development of acute colitis led to the activation of hepatic sensory afferents, which was prevented by selectively removing the common hepatic branch of the vagal nerve (a surgical procedure referred to as HVx). Compared with sham-operated mice, mice subjected to HVx showed marked reduction of colonic T_{reg} cells, likely due to altered methylation status at key T_{reg} cell-specific demethylation regions. By tracing neural connections, the authors saw that the liver senses the gut environment via hepatic sensory afferents of the vagus nerve and transmits signals to the brain via the left nodose ganglion. This lateralized ascending pathway

INFLAMMATION

Pyrin variants can burn out the plague

The autoinflammatory disease familial Mediterranean fever (FMF) is caused by gain-of-function mutations in the *MEFV* gene, which encodes the pyrin component of the pyrin inflammasome. These *MEFV* mutations are common in several Mediterranean populations, suggesting that they have been selected for through evolutionary pressure. Now, Park et al. confirm this idea by showing that FMF-associated mutations in pyrin confer greater resistance to *Yersinia pestis*, the bacterial cause of plague.

The pyrin inflammasome drives the release of IL-1β and IL-18 and induces pyroptosis, an inflammatory form of cell death. Its activation is induced by the inhibition of RhoA, a small GTPase that is essential for re-organization of the leukocyte cytoskeleton. RhoA is targeted by many bacterial toxins, but *Yersinia* species are unique in that they encode a virulence factor — YopM — that specifically inhibits the pyrin inflammasome. The authors thus examined whether *Y. pestis* may have driven the selection of *MEFV* mutations that lead to FMF. Evaluation of 2,313 individuals from the Turkish population (where ~10%



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