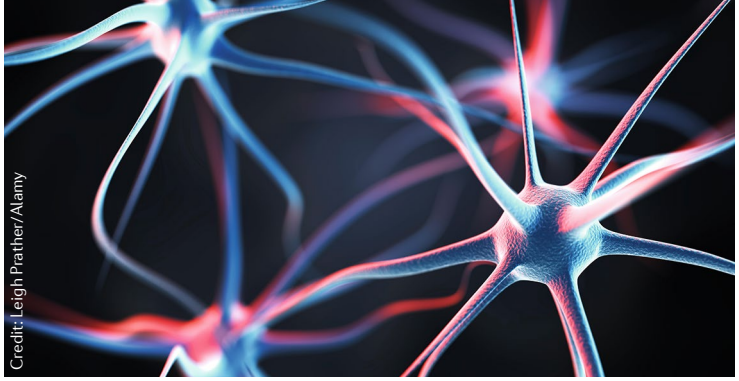
Credit: Leigh Prather/Alamy

was confirmed by selective perturbation of the hepatic sensory afferents to the left nodose ganglion not the dorsal root ganglion. Accordingly, left but not right vagal stimulation was essential for maintaining intestinal T_{reg} cells and aldehyde dehydrogenase activity in APCs.

Genetic ablation of mAChR signalling by the parasympathetic neurotransmitter acetylcholine, but not abrogation of signalling by the sympathetic neurotransmitter noradrenaline, in intestinal APCs also reduced T_{reg} cells in the colon. Accordingly, treatment with a mAChR agonist restored aldehyde dehydrogenase expression by APCs and colonic T_{reg} cell frequency in HVx mice, which suggests that the liver–brain–gut reflex, independent of the sympathetic system, creates the intestinal T_{reg} cell niche.

Finally, although HVx did not cause notable changes in gut microbiome diversity or composition, tonic microbial signals were required for functioning of the liver–brain–gut neural arc, as antibiotic-treated mice and *Myd88*-knockout mice did not develop worse colitis after HVx.

In summary, the liver–brain–gut neural arc — connecting the hepatic vagal sensory afferents, the brainstem, vagal efferents and enteric neurons to mAChR$^+$ APCs — serves as a feedback loop to protect the intestine from excessive inflammation.

Lucy Bird

ORIGINAL ARTICLE Teratani, T. et al. The liver–brain–gut neural arc maintains the T_{reg} cell niche in the gut. *Nature* https://doi.org/10.1038/s41586-020-2425-3 (2020)

of individuals carry FMF mutations) confirmed that two of the major *MEFV* mutations linked to FMF have undergone recent positive selection rather than accumulating in the population owing to genetic drift. The mutations were shown to have arisen independently more than 1,800 years ago.

YopM forms complexes with pyrin and with members of the PKN and RSK protein kinase families; these interactions result in phosphorylation of pyrin and the inhibition of the pyrin inflammasome. The authors found that the binding of YopM to pyrin and the phosphorylation of pyrin were reduced in *Y. pestis*-infected monocytes from patients with FMF. In keeping with this, patient peripheral blood mononuclear cells (PBMCs) released more IL-1β than control PBMCs upon in vitro infection with *Y. pestis*. By contrast, both sets of PBMCs showed comparable IL-1β production when infected with YopM-deficient *Y. pestis*. Therefore, the mutant forms of pyrin found in patients with FMF show reduced interaction with YopM, which attenuates the ability of YopM to suppress the pyrin inflammasome.

To confirm these findings in vivo, the authors used various FMF knock-in mice. Mice lack the B30.2 domain of human pyrin that contains the FMF mutations (including *MEFV*_p.M680I). Therefore, the authors compared systemic *Y. pestis* infection in *Mefv*$^{B30.2/B30.2}$ and *Mefv*$^{M680I/M680I}$ knock-in mice — they found that the latter showed significantly increased survival. By contrast, IL-1 receptor-deficient *Mefv*$^{M680I/M680I}$ mice were highly susceptible to *Y. pestis* infection. This indicates that FMF-associated mutant pyrin provides a survival advantage during *Y. pestis* infection that is mediated by the IL-1β signalling pathway.

Of note, the two major plague pandemics of 541 CE and 1347 CE were rooted in the Middle East and Mediterranean basin, which may explain why FMF-associated pyrin variants are so common among these populations.

Yvonne Bordon

ORIGINAL ARTICLE Park, Y. H. et al. Ancient familial Mediterranean fever mutations in human pyrin and resistance to *Yersinia pestis*. *Nat. Immunol.* https://doi.org/10.1038/s41590-020-0705-6 (2020)

IN BRIEF

COVID-19

COVID-19 and influenza: preparing for the storm

The basis of the varied immune responses seen to SARS-CoV-2 and other respiratory infections remains unclear. This preprint by Mudd et al. used single-cell RNA sequencing of PBMCs from patients with COVID-19 or influenza to ascertain disease-specific signatures. The authors identified two select cytokine modules (namely, IL-1RA and IL-6) that correlated with COVID-19 disease severity and were predictive of poor outcomes. By contrast, patients with influenza exhibited higher generalized inflammation. Compared with patients with influenza, patients with COVID-19 had reduced monocyte subsets, as well as lymphopenia, and exhibited a suppressed type I interferon response across multiple immune cell types. Interestingly, these cells, and especially the monocytes, showed enriched glucocorticoid and metabolic stress signalling. These data provide key insights that may guide the design of disease-specific therapies before the start of a new flu season.

ORIGINAL ARTICLE Mudd, P. A. et al. Targeted immunosuppression distinguishes COVID-19 from influenza in moderate and severe disease. Preprint at *medRxiv* https://doi.org/10.1101/2020.05.28.20115667 (2020)

COVID-19

SARS-CoV-2-specific T cells without antibodies

In this preprint, Gallais et al. investigated humoral and cellular immune responses to SARS-CoV-2 in 9 index and 8 contact patients from 7 households. All index patients developed SARS-CoV-2-specific antibodies and T cells, with the responses directed against multiple structural and accessory proteins. However, none of the contact patients had detectable antibodies to SARS-CoV-2. Despite the lack of seroconversion, SARS-CoV-2-specific T cells were detected in 6 contact patients at similar frequencies to in index patients. This suggests that testing for SARS-CoV-2-specific T cells may be better than serological tests for assessing prior infection and immunity to SARS-CoV-2. However, further study is warranted to rule out cross-reactivity with prior coronavirus infections.

ORIGINAL ARTICLE Gallais, F. et al. Intrafamilial exposure to SARS-CoV-2 induces cellular immune response without seroconversion. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.21.20132449 (2020)

COVID-19

Dexamethasone to the rescue

In this preprint study of the RECOVERY clinical trial involving 6,425 hospitalized patients with COVID-19, Horby et al. report that patients receiving a 6 mg daily dose of the corticosteroid dexamethasone had a reduced 28-day mortality compared with those receiving standard of care. Importantly, dexamethasone reduced death by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients requiring oxygen only but showed no benefit in patients who did not require respiratory support. Overall, the results of this study suggest that dexamethasone, an inexpensive and widely available anti-inflammatory drug, is a valuable treatment for severe cases of COVID-19.

ORIGINAL ARTICLE Horby, P. et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.22.20137273 (2020)

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The authors declare no competing interests.