RESEARCH HIGHLIGHTS

IN BRIEF

One to neutralize all

A strategy to mitigate outbreaks of emerging coronaviruses with pandemic potential is the development of pan-coronavirus vaccines and broadly neutralizing antibodies (bnAbs). The SARS-CoV-2 spike glycoprotein, in particular the receptor-binding site, is the primary target of bnAbs; but, owing to selection pressure, neutralization escape variants emerge. Previously it was shown that a bnAb, CC40.8, from a COVID-19-convalescent donor exhibits broad reactivity with human betacoronaviruses. This study reports that CC40.8 targets an S2 stem-helix epitope, which is part of the fusion machinery. The contact residues between the peptide–antibody complex were largely conserved between betacoronaviruses, and CC40.8 neutralized diverse betacoronaviruses and SARS-CoV-2 variants of concern in vitro. Finally, CC40.8 reduced weight loss and SARS-CoV-2 titres in animal models. The findings might guide pan-coronavirus vaccine development and antibody-based intervention strategies.

ORIGINAL ARTICLE Zhou, P. et al. A human antibody reveals a conserved site on beta-coronavirus spike proteins and confers protection against SARS-CoV-2 infection. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.abo215 (2022)

MICROBIOME

Busy symbionts during hibernation

Hibernation is an adaptive strategy of mammals such as the thirteen-lined ground squirrel to seasonal food scarcity, enabling long-term fasting. However, fasting deprives the squirrel of dietary nitrogen, which is crucial for protein and nucleotide synthesis. Regan et al. report the mechanism whereby the gut microbiome of squirrels recycles nitrogen from urea (urea nitrogen salvage) to facilitate host tissue protein synthesis during hibernation. Testing three seasonal squirrel groups they showed that although plasma urea concentrations in early and late winter squirrels were lower than those in summer squirrels, the former two groups might have enhanced urea transport into the gut. Metagenomics revealed that hibernating squirrels have increased expression of urease in their gut microbiome, which hydrolyses urea into NH₃ and CO₂. NH₃ is absorbed by the host and converted into amino acids by both the host and members of the microbiota, thus providing a mechanism to maintain protein synthesis when dietary nitrogen is absent.

ORIGINAL ARTICLE Regan, M. D. et al. Nitrogen recycling via gut symbionts increases in ground squirrels over the hibernation season. Science 375, 460–463 (2022)

MICROBIOME

Gut microbiota and depression

Testosterone deficiency has been associated with depressive symptoms in humans; however, the causes of this deficiency in patients with depression are not entirely clear. Li et al. show that an enzyme expressed by a member of the gut microbiota degrades testosterone and might thus be linked to depressive symptoms. The authors isolated Mycobacterium neoaurum from testosterone-deficient patients with depression and showed that the strain expresses ββ-Hydroxysteroid dehydrogenase (ββ-HSD), which degrades testosterone. Gavaging rats with M. neoaurum or a ββ-HSD-producing Escherichia coli strain led to depression-like behaviours in the animals as well as decreased testosterone levels in the brain and serum, thus providing a potential link between the metabolic capacity of a member of the gut microbiota and depression.

ORIGINAL ARTICLE Li, D. et al. ββ-Hydroxysteroid dehydrogenase expressed by gut microbes degrades testosterone and is linked to depression in males. Cell Host Microbe https://doi.org/10.1016/j.chom.2022.01.001 (2022)

VIRAL PATHOGENESIS

SARS-CoV-2 sensory loss

Anosmia (loss of the sense of smell) is a common symptom of COVID-19, yet the underlying mechanisms leading to olfactory dysfunction are poorly understood. Olfactory sensory neurons (OSNs) do not express SARS-CoV-2 entry receptors, suggesting non-cell-autonomous effects of infection on the olfactory system. Indeed, in a recent study, Zazhytska, Kodra et al. provide evidence that SARS-CoV-2 infection causes non-cell-autonomous disruption of OSN nuclear architecture and the down-regulation of olfactory receptors (ORs) and OR signalling genes.

To investigate COVID-19-associated anosmia, the authors first studied the effects of SARS-CoV-2 infection in golden hamster autopsies of the olfactory epithelium (OE). Single-cell RNA sequencing (scRNA-seq) of hamster OE cells revealed that infection of OSNs was rare; however, antiviral genes were upregulated and various immune cells were recruited to the OE. Sustentacular (SUS) cells, a structural epithelial cell type, were found to be the primary target cell in the OE, leading to a substantial but transient depletion of these cells. Although OSNs were rarely infected, regardless of whether they were infected or not, the authors observed non-cell-autonomous transcriptional changes in this cell type, for instance, in antiviral genes. Importantly, infection caused widespread and significant down-regulation of OR and OR signalling genes and key genes required for the sense of smell, including Adcy3. Remarkably, significant downregulation of OR genes and genes required for olfaction persisted at day 10 post infection, whereas SUS cell and other OSN markers were fully restored to pre-infection levels at this time point.

Next, to investigate the mechanisms leading to the downregulation of olfactory genes, the authors examined OSN nuclear architecture, a known regulator of OR expression. In situ Hi-C analyses (which quantify interactions between chromosomal regions) of OEs from mock or infected hamsters revealed that SARS-CoV-2 infection leads to a marked reorganization of the OSN nuclear architecture and the disruption of genomic compartments containing OR genes, which the authors suggest leads to downregulation of OR genes. Previous studies suggest that systemic cytokines and antiviral responses lead to OR downregulation and olfactory dysfunction. The authors hypothesized that the reorganization of OSN nuclear architecture could be elicited by mimicking the systemic effects of infection in the absence of infectious SARS-CoV-2. Indeed, exposure of OEs to UV-irradiated sera of infected or mock infected hamsters led to significant differences in OSN nuclear architecture and OR downregulation. Importantly, by analysing OE tissue obtained from human autopsies, the authors confirmed that SARS-CoV-2 infection also induces the downregulation of OR and OR signalling genes as well as changes in the nuclear architecture of human OSNs.

In sum, the authors provide a potential mechanism of anosmia caused by a virus that lacks tropism for neurons. This mechanism suggests that SARS-CoV-2 may have systemic effects on other cells that it cannot infect.

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ORIGINAL ARTICLE Zazhytska, M. et al. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19 induced anosmia. Cell https://doi.org/10.1016/j.cell.2022.01.024 (2022)