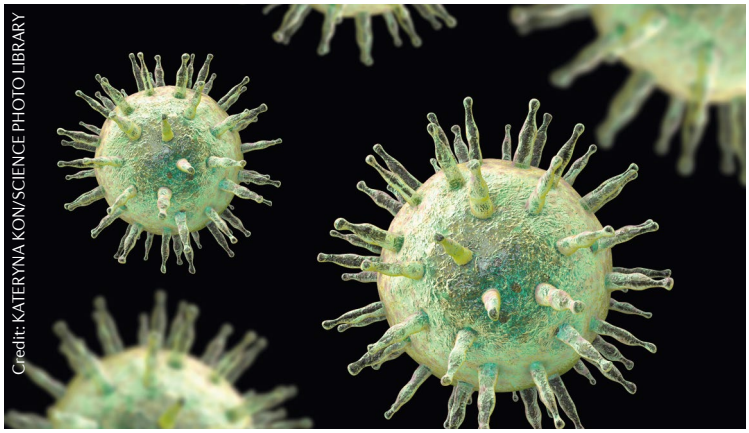

VIRAL PATHOGENESIS

EBV linked to multiple sclerosis

Multiple sclerosis is an inflammatory, demyelinating and neurodegenerative disease of the central nervous system. The causes are still not known but several risk factors have been implicated, including Epstein–Barr virus (EBV) infection. Two recent papers implicate EBV as a trigger for the development of multiple sclerosis and provide mechanistic insights into EBV-mediated development of the disease.

In the first paper, Bjornevik, Cortese et al. report their findings from a longitudinal study analysing the incident of multiple sclerosis in a cohort comprising more than 10 million young adults. Nine hundred and fifty-five individuals developed multiple sclerosis and the authors assessed the EBV infection status in collected blood samples. Importantly, they showed that EBV seroconversion correlated with the time of disease onset in the diagnosed individuals, and, only in one case, the individual was EBV seronegative. These findings suggest that EBV infection greatly increases the risk of subsequent multiple sclerosis. By contrast, the authors did not find increased risk for disease following cytomegalovirus infection.

Moreover, the authors did not find any signs of neuroaxonal degeneration before EBV seroconversion in individuals who later developed multiple sclerosis, indicating that EBV infection precedes symptom onset. Finally, the authors also report that the overall antibody response to peptides of several viruses known to infect humans was similar in individuals with multiple sclerosis and controls, but they detected higher titres of antibodies to EBV in individuals with multiple sclerosis than in controls, further strengthening the causal link between virus infection and multiple sclerosis.

In a second paper, Lanz et al. identified a B cell-encoded antibody in the cerebrospinal fluid of patients with multiple sclerosis that binds to EBV. Specifically, the antibody binds to the viral transcription factor EBNA1. The authors then discovered that the antibody also binds to glial cell adhesion molecule (GlialCAM). Phoshorylation of GlialCAM at residues surrounding the central epitope region further enhanced binding affinity and enables cross-reactivity.

Testing plasma samples from patients with multiple sclerosis and healthy individuals the authors found that most healthy individuals exhibited plasma reactivity to only EBNA1, whereas activity to EBNA1 and to GlialCAM was significantly increased in patient samples.

Finally, immunization of mice with the EBNA1 epitope exacerbates autoimmune demyelination.

In sum, both studies provide convincing data for a mechanistic link between multiple sclerosis and EBV.

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ORIGINAL ARTICLES Bjornevik, K. et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* **375**, 296–301 (2022) | Lanz, T. V. et al. Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. *Nature* https://doi.org/10.1038/s41586-022-04432-7 (2022)

IN BRIEF

ENVIRONMENTAL MICROBIOLOGY

Pesticides and soil viruses

Pesticides, in particular organochlorine pesticides (OCPs), can contaminate soils and have toxic effects on the soil microbiome. Zheng et al. studied the soil microbiome at the site of a former OCP factory in the Yangtze River Delta in China and found that contaminated soil had a lower bacterial diversity but higher viral diversity than clean soil. Furthermore, the viral metagenomes contained auxiliary metabolic genes (AMGs) linked to pesticide degradation and AMG levels correlated with OCP levels. Experimental validation of one of these AMGs showed that the encoded enzyme indeed can protect bacteria from pesticide toxicity, supporting the hypothesis that viral AMGs help bacteria survive in contaminated soils. Furthermore, the authors suggest that such viruses and the AMGs that they carry might be useful for the bioremediation of contaminated soils.

ORIGINAL ARTICLE Zheng, X. et al. Organochlorine contamination enriches virus-encoded metabolism and pesticide degradation associated auxiliary genes in soil microbiomes. *ISME J.* https://doi.org/10.1038/s41396-022-01188-w (2022)

MICROBIOME

Infant respiratory infections disturb microbiota

The respiratory tract microbiota is important for immune homeostasis and its disturbance has been linked to disease. As in other mucosal sites, early-life host–microbiota interactions are important and can be easily disturbed. A cohort study following 114 infants during the first year of their life now shows that niche colonization in the first days of life activates mucosal pattern recognition and inflammasome signalling. Infants that experienced early viral infections had stronger interferon signalling than those without infection. Furthermore, their microbiota showed an enrichment of *Moraxella* and *Haemophilus* spp., and this microbial signature was associated with more frequent subsequent viral respiratory tract infections, which suggests that early infections predispose to further infections, although causality and potential mechanisms still need to be established.

ORIGINAL ARTICLE de Steenhuijsen Piters, W. A. A. et al. Early-life viral infections are associated with disadvantageous immune and microbiota profiles and recurrent respiratory infections. *Nat. Microbiol.* https://doi.org/10.1038/s41564-021-01043-2 (2022)

VIRAL INFECTION

SARS-CoV-2 'super-permissive' cells

The cellular replication dynamics of SARS-CoV-2 are incompletely understood, in particular on a quantitative single-cell and single-molecule level. Lee et al. used single-molecule fluorescence in situ hybridization (smFISH) in three different cell lines to investigate where and when SARS-CoV-2 RNA is produced in cells. They found that initially mainly subgenomic RNA is produced in viral factories and genomic RNA is mostly produced later on. Furthermore, only a fraction of cells (~5–10%) produce substantial amounts of viral RNA, leading the authors to call these cells 'super-permissive'. The mechanism is unclear at the moment but smFISH analysis of infected hamsters also showed patchy RNA levels. In the cell lines, the authors noted that the SARS-CoV-2 genomic RNA is long lived, which suggests that it evades degradation by nucleases. Interestingly, experiments with the Alpha variant showed slower replication kinetics in the cells than the ancestral variant, which led the authors to speculate that it might trigger the innate immune response less, potentially thereby contributing to its higher transmissibility.

ORIGINAL ARTICLE Lee, J. Y. et al. Absolute quantitation of individual SARS-CoV-2 RNA molecules provides a new paradigm for infection dynamics and variant differences. *eLife* **11**, e74153 (2022)