# IN BRIEF

## VIRAL INFECTION

### How flaviviruses infect both humans and insects

Mosquito-borne flaviviruses, such as Zika virus (ZIKV), are adapted to two very different hosts and must replicate in both mosquito and human cells. By contrast, some closely related flaviviruses are insect-specific but it is unclear which barriers prohibit their spillover to humans. Zhang et al. speculated that host receptor differences might explain the lack of human infection by these viruses. However, pseudoviruses expressing the structural proteins of such insect-specific flaviviruses could infect human cells, indicating that the block is post-entry. Furthermore, they showed that Donggang virus (DONV), one of the insect-specific flaviviruses, reached the endosomes in human cells but could not replicate. Replacement of the untranslated regions (UTRs) of DONV with those from ZIKV rescued replication. The reverse experiment, adding the DONV UTRs to ZIKV, abrogated replication in human cells but had little effect in insect cells, confirming that the UTRs, which are important for binding host factors, provide host specificity.

**ORIGINAL ARTICLE** Zhang, Y. et al. Replication is the key barrier during the dual-host adaptation of mosquito-borne flaviviruses. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.2110491119 (2022)

## BIOFILMS

### *Fusobacterium* orchestrates oral biofilms

Dysbiosis and growth of pathogens in oral biofilms can cause periodontitis. These polymicrobial communities have complex metabolic interactions. The commensal *Fusobacterium nucleatum* is one of the key species in oral biofilms, although its role in pathogenesis is incompletely understood. Sakanaka et al. now show that *F. nucleatum* is at the centre of a cross-feeding network with other commensals, such as *Streptococcus gordonii* and *Veillonella parvula*. Consortia of these bacteria secrete and then use amino acids to produce polyamines, including butyrate and putrescine. Putrescine then accelerates the biofilm life cycle of *Porphyromonas gingivalis*, a periodontal pathogen. Indeed, plaque from human subjects showed the co-occurrence of *P. gingivalis* and the putrescine genetic modules in the commensals. These results suggest that *F. nucleatum* and its metabolic networks might promote the development of periodontitis.

**ORIGINAL ARTICLE** Sakanaka, A. et al. *Fusobacterium nucleatum* metabolically integrates commensals and pathogens in oral biofilms. *mSystems* https://doi.org/10.1128/msystems.00170-22 (2022)

## VIRAL PATHOGENESIS

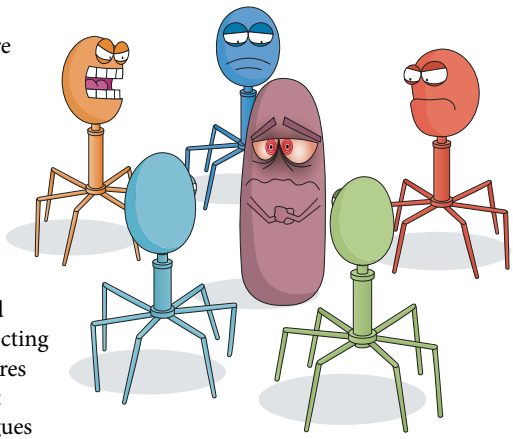
### SARS-CoV-2 tunnels to new cells

SARS-CoV-2 can cause neurological complications such as loss of smell or other central nervous system symptoms. It is unclear whether and to what extent the virus infects the brain, in particular as neuronal cells show low expression of ACE2, the cellular entry receptor of SARS-CoV-2. Pepe et al. find that SARS-CoV-2 can spread in vitro from Vero E6 cells, an epithelial cell line readily infected by SARS-CoV-2, to SH-SY5Y, a neuronal cell line, which is not permissive to the virus on its own. The authors show that tunnelling nanotubes (TNTs), thin membrane conduits, form between infected and uninfected cells and transport SARS-CoV-2 to the neuronal cells even though these receiving cells lack ACE2. This finding led the authors to suggest that spread through TNTs might contribute to central nervous system manifestations of COVID-19. It remains to be tested, however, whether TNTs also form and transport the virus in more physiologically relevant conditions and whether this form of spread indeed contributes to pathogenesis.

**ORIGINAL ARTICLE** Pepe, A. et al. Tunneling nanotubes provide a route for SARS-CoV-2 spreading. *Sci. Adv.* https://doi.org/10.1126/sciadv.abo0171 (2022)

## MICROBIOME

# A phage cocktail for IBD?



Credit: Philip Patenall/Springer Nature Limited

Gut pathobionts such as *Klebsiella pneumoniae* are thought to contribute to uncontrolled inflammation in the intestinal tissues of individuals with inflammatory bowel disease (IBD). However, the feasibility of specifically targeting IBD-associated pathobionts without affecting the gut microbiota requires investigation. In a recent study, Elinav and colleagues report that a cocktail of five phages successfully targets a *K. pneumoniae* strain associated with inflammation in IBD, suppressing inflammation and disease in IBD models.

The authors analysed the stool microbiome of 537 individuals from France, Israel, the USA and Germany with either ulcerative colitis or Crohn's disease and discovered a clade of antibiotic-resistant *K. pneumoniae* strains (Kp2 clade) that was significantly enriched during an IBD flare, compared with a remission state. The authors isolated 598 *K. pneumoniae* strains from the stool of individuals with IBD, and 10 Kp2 and 9 non-Kp2 strains were selected for further experiments in colitis-prone germ-free mice. Oral administration of the Kp2 isolates elicited a significant pro-inflammatory response, leading to tissue damage in mice compared with non-Kp2 strains, which suggests that members of this clade have a role in IBD immunopathogenesis.

Next, the authors developed a phage cocktail that specifically targeted the pathogenic Kp2 clade. Phages targeting Kp2 strains were isolated and tested in an iterative process involving 41 phages that target Kp2 strains, 8 of which were chosen for 18 three-, four- and five-phage combinations. The authors identified a cocktail of five phages (MCoc5c, 8M-7, 1.2-3 s, KP2-5-1 and PKP-55) that consistently reduced bacterial burden in specific pathogen-free mice colonized with different Kp2 strains.

Next, the authors assessed the capacity of the five-phage cocktail to reduce Kp2 strain-induced intestinal inflammation in mouse models of IBD, and found that phage combination therapy significantly reduced *K. pneumoniae* levels as well as colonic inflammation and tissue damage with no evidence of the evolution of anti-phage resistance to the cocktail.

Last, the authors investigated the feasibility of phage combination therapy in humans by assessing Kp2-targeting phages in a simulator of the human intestinal microbial ecosystem (SHIME) as well as in human volunteers in a randomized, single blind, placebo-controlled phase I clinical trial. Together, the data from these investigations suggest that the tested phages can be safely consumed by humans, retain viability after passing through the low-pH environment of the stomach and accumulate in the lower gut. Importantly, no off-target effects were observed in the faecal microbiome of participants, suggesting that the approach is precise and targeted as expected.

In sum, the authors demonstrate the feasibility of combination phage therapy for reducing the inflammation seen in IBD, potentially paving the way for the development of further phage therapies for other pathobionts involved in the pathogenesis of human diseases.

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**ORIGINAL ARTICLE** Federici, S. et al. Targeted suppression of human IBD-associated gut microbiota commensals by phage consortia for treatment of intestinal inflammation. *Cell* **185**, 2879–2898 (2022)