IN BRIEF

ANTIMICROBIAL RESISTANCE

Outgrowing antibiotic action

Bacterial cells can show reduced susceptibility to antibiotics owing to phenotypic variability as, for example, observed for slow-growing antibiotic persister cells. Łapińska et al. now find that fast-growing bacteria can also evade antibiotic action without developing resistance mutations owing to phenotypic reduced drug accumulation. The authors used fluorescent antibiotic probes and microfluidics to analyse the antibiotic susceptibility of single cells. Depending on the specific antibiotic and bacterial species studied, they found that individual cells showed delayed or reduced accumulation of the antibiotics. Further mechanistic work focusing on *Escherichia coli* and a macrolide antibiotic confirmed that reduced accumulation indeed led to increased cell survival and that this phenomenon affected fast-growing cells, which had more ribosomes (the target of the antibiotic) and efflux pumps than slower-growing cells. Further work is needed to determine whether similar mechanisms apply to other antibiotics and other bacterial species.

ORIGINAL ARTICLE Łapińska, U. et al. Fast bacterial growth reduces antibiotic accumulation and efficacy. *eLife* **11**, e74062 (2022)

VIRAL PATHOGENESIS

Animal model of long COVID?

A subset of individuals has prolonged disease after COVID-19, which is known as long COVID or post-acute sequelae of COVID-19 (PASC). The underlying mechanisms are poorly understood, in part owing to a lack of experimental models. Frere et al. followed hamsters for up to a month after SARS-CoV-2 infection, looking at changes in different tissues, and compared the data with influenza A virus (IAV) infection. Both viruses triggered a similar host response dominated by type I interferon and pathology mostly of the lung with limited involvement of other organs. However, at 31 days post infection, SARS-CoV-2 showed stronger peribronchiolar metaplasia in the lung and tubular atrophy in the kidney. Furthermore, SARS-CoV-2 caused persistent inflammation in the olfactory bulb and epithelium, which was not seen in IAV-infected hamsters. Similar transcriptomic changes were seen in olfactory tissues from human autopsy samples of people recovered from COVID-19. The authors conclude that hamsters could potentially be used for further mechanistic and interventional studies of long COVID.

ORIGINAL ARTICLE Frere, J. J. et al. SARS-CoV-2 infection in hamsters and humans results in lasting and unique systemic perturbations post recovery. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.abq3059 (2022)

MICROBIOME

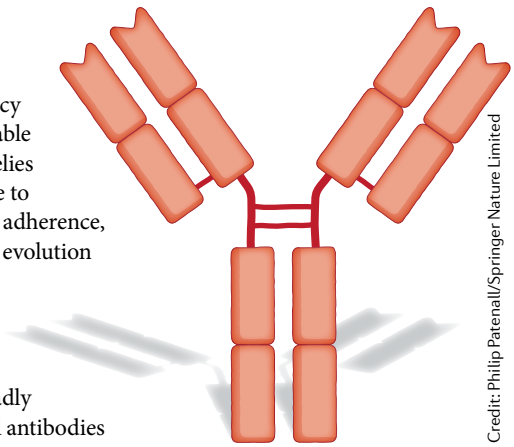
Gut–brain axis in ageing

The microbiota is known to affect brain development and function through the gut–brain axis, and has been linked to several neurological conditions. A study in mice now links the gut microbiota to age-related neurodegeneration through the microbial metabolite isoamylamine (IAA). The authors used comparative metabolomics to identify microbial metabolites that are increased in aged mice compared with young mice or germ-free mice. Further analysis confirmed that one of the identified metabolites, IAA, correlated with the expression of S100A8, which is increased in aged mouse brains and which triggers microglia death. Furthermore, Ruminococcaceae, which produce IAA, were increased in aged mice, whereas phages targeting this bacterial family were decreased; these changes were also seen in aged human participants.

ORIGINAL ARTICLE Teng, Y. et al. Gut bacterial isoamylamine promotes age-related cognitive dysfunction by promoting microglial cell death. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2022.05.005 (2022)

VIRAL INFECTION

Long-term control of HIV



Credit: Philip Patenall/Springer Nature Limited

Modern antiretroviral therapy (ART) is highly effective at suppressing human immunodeficiency virus (HIV) to undetectable levels, but suppression relies upon life-long adherence to medications. Issues with adherence, drug side effects and the evolution of ART resistance have prompted the development of alternative therapies aimed at suppressing HIV. Broadly neutralizing monoclonal antibodies (bNAbs) that target the HIV envelope glycoprotein (Env) offer a new approach for virological suppression. Regular infusions of two bNAbs (3BNC117 and 10-1074) can suppress viraemia, but the long-term feasibility of this approach is not well explored.

Chun and colleagues report the findings of a two-component clinical trial using 3BNC117 and 10-1074 and provide evidence that infusion of these bNAbs provides sustained virological suppression for up to 43 weeks after analytical treatment interruption (ATI). The first component was a randomized, double-blind, placebo-controlled trial that enrolled 14 individuals who started ART during the acute/early phase of infection and who then underwent ATI 3 days after receiving the first infusion of bNAbs or placebo. The second component was an open-label study involving five individuals who had controlled viraemia but had not received ART.

Whereas individuals in group 1 who received placebo experienced plasma viral rebound within 8 weeks of ATI, individuals who received bNAbs suppressed viraemia for up to 43 weeks. Two out of the five individuals in group 2 who had baseline sensitivity to both antibodies suppressed viraemia for an average of 41.7 weeks. Importantly, individuals in both groups who were infected with viruses that are resistant to either 3BNC117 or 10-1074 did not achieve virological suppression. The study demonstrates that combination therapy with 3BNC117 and 10-1074 can suppress viraemia in the absence of ART for extended periods, as long as antibody-resistant virus is not present.

In a separate study, Barzel and colleagues performed in vivo engineering of B cells in mice to address some of the challenges that are associated with bNAb-based therapies for HIV. For instance, bNAbs have a half-life of a few weeks, necessitating regular infusions, and improper glycosylation or maturation can arise when bNAbs are not produced in B cells. In their proof-of-concept study, the authors engineered B cells in vivo to secrete 3BNC117.

After intravenously injecting two adeno-associated viral (AAV) vectors (one encoding *Staphylococcus aureus* Cas9 (saCas9) and the other encoding 3BNC117) into mice, the authors observed editing of B cells. The engineered B cells underwent antigen-induced activation, leading to memory retention, clonal selection and differentiation into plasma cells that secrete neutralizing titres of 3BNC117. Further studies are needed to confirm antiviral efficacy in vivo, but this proof-of-concept study suggests the possibility of in vivo B cell engineering for the long-term control of HIV in the absence of ART.

Ashley York

ORIGINAL ARTICLE Sneller, M. C. et al. Combination anti-HIV antibodies provide sustained virological suppression. *Nature* https://doi.org/10.1038/s41586-022-04797-9 (2022) | Nahmad, A. D. et al. In vivo engineered B cells secrete high titers of broadly neutralizing anti-HIV antibodies in mice. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-022-01328-9 (2022)