IN BRIEF

SYMBIOSIS

Finding the difference

The microbial gut communities of social bees comprise only a few bacterial groups and are an emerging model system to study host-associated microbial communities. In this study, Engel and colleagues used comparative metagenomics to analyse the gut microbiota of two closely related honey bee species, *Apis mellifera* and *Apis cerana*. Although they are colonized mostly by the same 16S rRNA phylotypes, the authors found that at genomic resolution, each host species harbours a highly distinct bacterial community. Compared with *A. cerana*, *A. mellifera* displayed a much higher diversity of strains and functional gene content in the microbiota, encoding more diverse enzymes for polysaccharide degradation, which may provide more metabolic flexibility. Studies are now needed to understand the mechanisms and functional consequences of strain-level diversity among related host-associated communities.

ORIGINAL ARTICLE Ellegaard, K. M. et al. Vast differences in strain-level diversity in the gut microbiota of two closely related honey bee species. *Curr. Biol.* https://doi.org/10.1016/j.cub.2020.04.070 (2020)

MICROBIOME

Reducing cholesterol levels

The human microbiome encodes a vast metabolic repertoire, but how microorganisms influence human metabolic health is incompletely understood. Xavier and colleagues combined bioinformatic and biochemical approaches and identified cholesterol dehydrogenases from gut microbiomes that contribute to the metabolism of cholesterol to coprostanol. The cholesterol dehydrogenases are encoded by intestinal sterol metabolism A (*ismA*) genes in uncultured members of cluster IV *Clostridium* and were shown to be prevalent across geographically diverse human cohorts. The presence of coprostanol-forming bacteria correlated with lower levels of faecal and serum cholesterol, which may suggest that these bacteria decrease host cholesterol levels in the intestine and serum. Cholesterol-metabolizing gut bacteria could be exploited as a strategy to lower serum cholesterol and thus decrease the risk of cardiovascular disease.

ORIGINAL ARTICLE Kenny, D. J. et al. Cholesterol metabolism by uncultured human gut bacteria influences host cholesterol level. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2020.05.013 (2020)

STRUCTURAL BIOLOGY

Catching the mode of action

The cell wall is a key drug target in *Mycobacterium tuberculosis*. The arabinosyltransferases EmbA, EmbB and EmbC are involved in the synthesis of the complex mycobacterial cell wall, and they are regarded as a target of the anti-tuberculosis drug ethambutol, as mutations in these proteins result in clinically resistant strains. The enzyme structures, their mechanism of action as well as the mode of action of ethambutol remained unknown. Zhang et al. determined the cryo–electron microscopy structures of heterodimeric EmbA–EmbB and homodimeric EmbC complexes, showing how the donor and acceptor substrates bind in the active site, providing insights into how arabinose is transferred. Ethambutol binds to the same site as the substrates in the EmbB and EmbC subunits, which suggests that the drug inhibits the enzymes by competing for binding. Finally, ethambutol-resistance mutations are located close to the ethambutol-binding site.

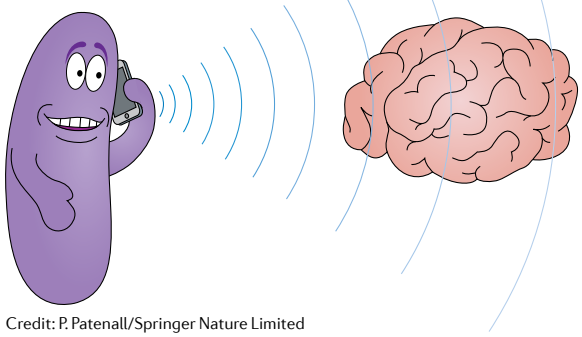
ORIGINAL ARTICLE Zhang, L. et al. Structures of cell wall arabinosyltransferases with the anti-tuberculosis drug ethambutol. *Science* **368**, 1211–1219 (2020)

MICROBIOME

Let the gut do the guiding

Growing evidence suggests that the microbiome of animals not only affects host health but also their behaviour. However, the mechanisms involved in the gut–brain axis are not well understood. In a recent study, O'Donnell, Sengupta and colleagues report that gut-colonizing commensal bacteria produce a neurotransmitter that modulates the sensory behaviour of their host.

The authors used chemotaxis assays to test the influence of various non-pathogenic bacteria on olfactory responses of the nematode *Caenorhabditis elegans*. They found that co-culturing of the worms with multiple species of the Gram-negative bacterium *Providencia*, particularly *Providencia alcalifaciens* strain JUb39, decreased avoidance of the volatile repellent odorant octanol, an effect that they refer to as octanol modulation. Moreover, JUb39 is ingested by *C. elegans*, colonizes the posterior intestine of the worms and, interestingly, the extent of colonization correlated with the level



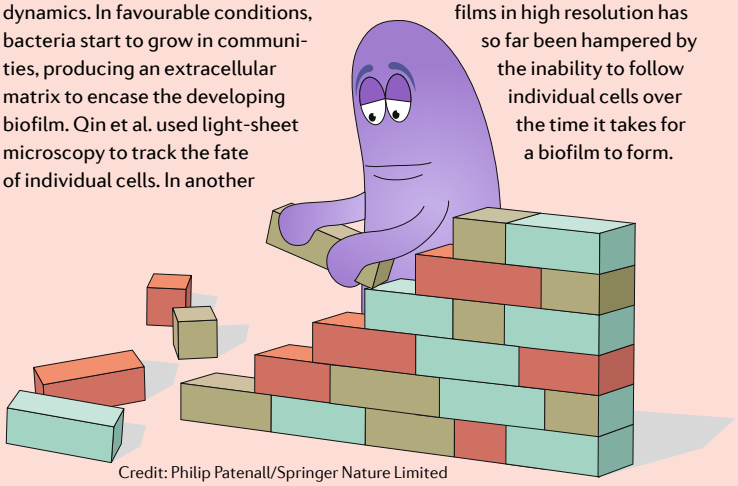
Credit: P. Patenall/Springer Nature Limited

BIOFILMS

How to build a biofilm

Biofilms are complex structures, and the ever increasing capacity to image them is providing new insights into their formation and dynamics. In favourable conditions, bacteria start to grow in communities, producing an extracellular matrix to encase the developing biofilm. Qin et al. used light-sheet microscopy to track the fate of individual cells. In another study, Rooney et al. imaged channels in mature biofilms that transport nutrients to the inside of biofilms.

Studying the development of biofilms in high resolution has so far been hampered by the inability to follow individual cells over the time it takes for a biofilm to form.



Credit: Philip Patenall/Springer Nature Limited

of octanol aversion. The findings indicate that JUb39 mediates octanol modulation in the animals.

C. elegans carrying mutations in the biosynthetic pathway for the neurotransmitter tyramine are defective in octanol modulation, and co-culturing with JUb39 restored some of this modulation. Furthermore, the authors were able to show that JUb39-produced tyramine functionally compensates for the loss of host-derived tyramine. They identified two bacterial genes that encode decarboxylases with the potential to generate tyramine, and those enzymes were necessary and sufficient for octanol modulation.

But how does JUb39-derived tyramine modulate octanol avoidance in worms? Further investigations revealed that host enzymes are likely to be involved in the conversion of bacterially derived tyramine to the neurotransmitter octopamine, which binds to the OCTR-1 receptor on sensory neurons of the host, which have previously been shown to affect aversive behaviour.

The findings led the authors to propose a model whereby JUb39 is ingested by *C. elegans* and successfully colonizes the host. These gut bacteria produce tyramine, which acts to reduce aversion to bacterially generated volatiles, such as those produced by JUb39. This in turn affects the feeding decisions of *C. elegans*, positively selecting for the increased consumption of JUb39. The bacteria present a rich food source for *C. elegans*, which suggest that the described mechanism promotes both host and microorganism fitness — thus, the relationship between the host and the commensal might be mutually beneficial.

In sum, this study provides important mechanistic insights into the gut–brain axis and opens avenues for further studies on how gut microbiome may modulate host behaviours.

Akila Sridhar

ORIGINAL ARTICLE O'Donnell, M. P. et al. A neurotransmitter produced by gut bacteria modulates host sensory behaviour. *Nature* https://doi.org/10.1038/s41586-020-2395-5 (2020)

Qin et al. used dual-view light-sheet microscopy and labelled *Vibrio cholerae* cells with fluorescent cytoplasmic puncta. This enabled the researchers to track the trajectories of individual cells over 16 hours. In the first few hours as cells divided, cells showed Brownian, mostly random motion and the biofilm grew laterally. After ~7 hours, cells showed ballistic motion, and the biofilm started to also expand vertically. Interestingly, some of the cells, in particularly those formed early, became trapped near the substrate and did not move much, whereas others contributed to the expansion of the biofilm through a 'fountain-like' flow, spilling new cells up and to the side.

Interestingly, this fountain-like motion was dependent on the matrix protein RbmA because mutant cells without this protein showed highly irregular movement, suggesting that RbmA keeps dividing cells on the 'right' track and supports coherent biofilm growth.

In the second study, Rooney et al. looked at mature *Escherichia coli* biofilms with a Mesolens. They observed 15 μm-wide channels that link the biofilm centre with the edge. After mixing and disruption of the biofilm, channels formed again, suggesting a functional role. Indeed, when the authors added fluorescent microspheres to the medium, they observed transport of the microspheres along the channels into the biofilm. Furthermore, biofilms of a strain with an arabinose-inducible fluorescent marker showed that cells growing along the channels had the strongest marker induction, as a consequence of arabinose in the medium being transported in.

Both studies exemplify the strength of imaging to study emergent properties of biofilms.

Ursula Hofer

ORIGINAL ARTICLES Qin, B. et al. Cell position fates and collective fountain flow in bacterial biofilms revealed by light-sheet microscopy. *Science* **369**, 71–77 (2020) | Rooney, L. M. et al. Intra-colony channels in *E. coli* function as a nutrient uptake system. *ISME J.* https://doi.org/10.1038/s41396-020-0700-9 (2020)
RELATED ARTICLE Flemming, H.-C. et al. Biofilms: an emergent form of bacterial life. *Nat. Rev. Microbiol.* **14**, 563–575 (2016)

IN BRIEF

BACTERIAL PHYSIOLOGY

Isolation of manganese oxidizers

Chemolithoautotrophic microorganisms obtain energy by oxidizing inorganic compounds such as hydrogen, ferrous iron and ammonia. Manganese is one of the most abundant metals on Earth, but whether oxidation of manganese drives the growth of chemolithotrophs has remained unknown. Now, Yu and Leadbetter report the cultivation of a co-culture of two manganese oxidizers — '*Candidatus* Manganitrophus noduliformans' and *Ramlibacter lithotrophicus* — that are dependent on manganese for CO_2 fixation and exponential growth. Transcriptomics of manganese-dependent growth revealed candidate metabolic pathways for coupling extracellular manganese oxidation to aerobic energy conservation and autotrophic CO_2 fixation. The findings of this study have important implications for the manganese biogeochemical cycle.

ORIGINAL ARTICLE Yu, H. & Leadbetter, J. R. Bacterial chemolithoautotrophy via manganese oxidation. *Nature* **583**, 453–458 (2020)

HOST RESPONSE

Can COVID-19 strike twice?

Millions of cases of coronavirus disease 19 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been reported worldwide, but whether convalescing individuals can be re-infected with SARS-CoV-2 is unclear. Deng et al. generated a non-human primate model of SARS-CoV-2 infection in which rhesus macaques develop pneumonia and exhibit systemic viral dissemination. Once the macaques were in the early phases of recovery, they were rechallenged with the identical SARS-CoV-2 strain. Notably, these animals did not exhibit detectable viral dissemination, clinical symptoms and histopathological changes associated with COVID-19. The authors compared the humoral and cellular immune responses after primary infection and rechallenge and found enhanced neutralizing antibody and immune responses in the rechallenged macaques, which suggests that primary SARS-CoV-2 exposure may protect against reinfection.

ORIGINAL ARTICLE Deng, W. et al. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science* https://doi.org/10.1126/science.abc5343 (2020)

VIRAL INFECTION

Snatching from the host

The first step of transcription for many negative-strand RNA viruses like influenza viruses and arenaviruses is a process known as 'cap snatching', whereby the viral RNA-dependent RNA polymerase cleaves 5′ capped host mRNAs to prime viral RNA synthesis. Ho et al. found that start codons within cap-snatched host mRNAs lead to a novel mechanism of gene origination that they call 'start snatching'. Depending on the frame of the snatched start codon, start-snatching allows the translation of host–virus chimeric proteins that are either amino-terminus-extended viral proteins, or completely novel proteins that are out of frame with canonical viral open reading frames. The authors found that both chimeric forms are produced in influenza A virus-infected cells, that chimeric proteins contribute to virulence in vivo and that epitopes within the chimeric proteins are recognized by the adaptive immune system, which suggests that start snatching has a role in host–virus interactions.

ORIGINAL ARTICLE Ho, J. S. Y. et al. Hybrid gene origination creates human-virus chimeric proteins during infection. *Cell* **181**, 1502–1517 (2020)