IN BRIEF

MICROBIOME

Sublethal antibiotics and a sticky situation

Antibiotic treatment affects commensal bacteria of the gut microbiota, even at sublethal concentrations. Schlomann, Wiles et al. examined the effect of sublethal doses of ciprofloxacin on the dynamics of gut bacterial populations using live imaging of larval zebrafish. They focused on two native zebrafish isolates: fast-growing, planktonic *Vibrio cholerae* ZWU0020 and slow-growing *Enterobacter cloacae* ZOR0014, which forms dense bacterial aggregates. Germ-free fish were colonized with either bacterial strain before ciprofloxacin treatment. The antibiotic enhanced aggregation of bacterial cells, which resulted in their increased expulsion from the gut by the mechanical activity of the intestine. Moreover, the effect was more pronounced for slow-growing bacteria. As low concentrations of the antibiotic are often found in the environment, the findings of this study highlight the possibility of gut microbiota perturbations due to environmental antibiotic contaminants.

ORIGINAL ARTICLE Schlomann, B. H. et al. Sublethal antibiotics collapse gut bacterial populations by enhancing aggregation and expulsion. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1907567116 (2019)

CLINICAL MICROBIOLOGY

Human trial of vaginal microbiome transplantation

Bacterial vaginosis is characterized by changes in the vaginal microbial community, and therapeutic options are limited for persistent or recurrent bacterial vaginosis. Lev-Sagie, Goldman-Wohl, Cohen et al. report the feasibility of vaginal microbiome transplantation (VMT) from healthy donors as treatment for patients suffering from symptomatic, intractable and recurrent bacterial vaginosis. Four of the five treated patients showed full long-term remission and one patient incomplete remission after VMT, which suggests that VMT might be beneficial in treating the condition. Samples from donors and VMT recipients were analysed using shotgun metagenomic sequencing, which revealed that four of five recipients exhibited substantial changes in the microbiome composition, which were more similar to that of the collective donor vaginal microbiome. Randomized, placebo-controlled trials are needed to determine efficacy of VMT and the possible associated risk factors.

ORIGINAL ARTICLE Lev-Sagie, A. et al. Vaginal microbiome transplantation in women with intractable bacterial vaginosis. *Nat. Med.* https://doi.org/10.1038/s41591-019-0600-6 (2019)

ANTIMICROBIALS

Designing phagebodies

Phage therapy is a promising treatment option for multi-drug-resistant infections; however, successful development of phage-based therapies is hampered by the possible acquisition of resistance by bacteria. Lu and colleagues identified regions in the tail fibre of the T3 phage that dictate phage host range, termed host-range-determining regions. They genetically engineered these regions through site-directed mutagenesis in a high-throughput manner. This approach, which is analogous to antibody specificity engineering, led to the generation of synthetic 'phagebodies' with a broadened host range that were able to target naturally occurring phage-resistant bacterial mutants. Bacterial resistance to phagebodies was not observed. Finally, an engineered phagebody cocktail eliminated sensitive bacterial strains in a mouse skin infection model. The findings will enhance the development of phage-based antimicrobials.

ORIGINAL ARTICLE Yehl, K. et al. Engineering phage host-range and suppressing bacterial resistance through phage tail fibre mutagenesis. *Cell* **179**, 459–469 (2019)

MICROBIOME

An apple a day helps *Bacteroides* to stay

Previous studies have shown that the gut microbiota can have a role in protection from obesity, in particular certain *Bacteroides* spp. However, the relationship is complex and involves interactions between different members of the microbiota and dietary components such as fibre. It has been difficult to determine the underlying mechanisms, molecules and pathways and thus to target them specifically. In a new study, Gordon and colleagues use germ-free mice, colonized with defined consortia of gut bacteria, and artificial food particles coated with different fibres to better understand these interactions.

The authors colonized germ-free mice with bacteria isolated from a lean donor and fed them a human diet high in fat and low in fruits and vegetables supplemented with 34 different fibres, including fibres from apples, citrus, peas and other plants. The different fibres had specific effects on the composition of the gut bacterial community; for example, fibre from pea skins increased the abundance of *Bacteroides thetaiotaomicron*, whereas fibres from orange peels increased *Bacteroides cellulosilyticus*.

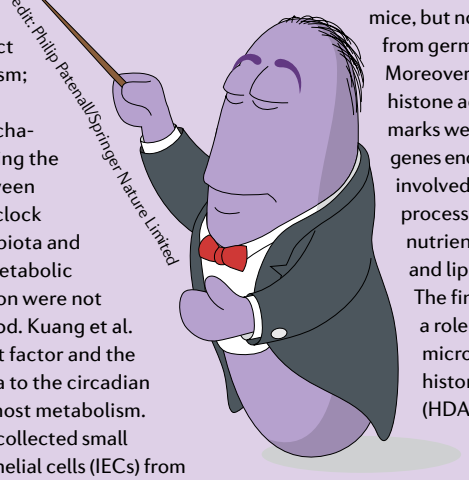
The next step was to identify the bioactive fibre components and how they were used by community members. Biochemical analyses showed that the fibres contained complex mixtures of different molecular components. The authors used proteomic analysis to demonstrate that *Bacteroides* spp. responding to different types of fibres upregulated enzymes encoded in polysaccharide utilization loci linked to

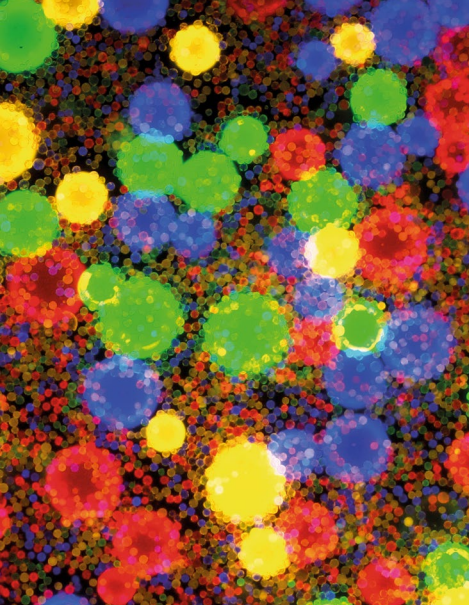
MICROBIOME

Microbial conductors

The mammalian circadian clock synchronizes physiological processes, such as cellular metabolism, with day–night cycles by controlling rhythmic oscillations in gene expression. Emerging evidence suggests that diurnal host–microbiota interactions also affect host metabolism; however, the molecular mechanisms underlying the crosstalk between the circadian clock and the microbiota and its effect on metabolic gene expression were not well understood. Kuang et al. now link a host factor and the gut microbiota to the circadian regulation of host metabolism.

The authors collected small intestinal epithelial cells (IECs) from wild-type and germ-free mice in a 24-hour period and assessed two acetylation marks associated with transcriptional activity: histone H3 lysine 9 acetylation (H3K9ac) and H3K27ac. Both acetylation marks showed synchronized diurnal oscillations in IECs from wild-type mice, but not in IECs from germ-free mice. Moreover, oscillating histone acetylation marks were enriched at genes encoding proteins involved in metabolic processes, such as nutrient transport and lipid metabolism. The findings suggest a role for both the microbiota and a histone deacetylase (HDAC), and indeed compared to the wild type,





Artificial food particles. Courtesy of M. L. Patnode, Washington University School of Medicine St. Louis, USA.

metabolism of specific carbohydrate structures.

The authors then used multi-taxon insertion sequencing of four *Bacteroides* spp. to further define pathways required for the responses to fibres. Indeed, mutants that had defects in the same polysaccharide utilization loci identified in the proteomics datasets lost the capacity for the fibre-specific increases in abundance. Interestingly, some of the *Bacteroides* strains competed for the same fibre component, whereas others deferred to their neighbours.

Finally, the authors constructed artificial food particles that functioned as biosensors of microbial fibre digestion in vivo. Particles coated with different fibre polysaccharides were fed to mice colonized with combinations of *Bacteroides* spp. Indeed, beads recovered from the faeces had less polysaccharide on their surface in a manner that was dependent on community composition.

In summary, responses of the gut microbiota to fibre are specific to both the fibre components and the species present. The new biosensors are a promising tool to characterize the nutrient processing capacities of microbial communities and develop next-generation microbiota-directed foods.

Ursula Hofer

ORIGINAL ARTICLE Patnode, M. L. et al. Interspecies competition impacts targeted manipulation of human gut bacteria by fiber-derived glycans. *Cell* **179**, 1–15 (2019)
RELATED ARTICLE Kolodziejczyk, A. A., Zheng, D. & Elinav, E. Diet–microbiota interactions and personalized nutrition. *Nat. Rev. Microbiol.* https://doi.org/10.1038/s41579-019-0256-8 (2019)

germ-free mice had lower levels of HDAC3. The authors showed that the deacetylase was recruited to histones in a diurnally rhythmic manner. Moreover, IECs in which HDAC3 had been depleted showed increased target gene expression and exhibited dampened diurnal expression rhythms. In addition, the recruitment of HDAC3 was dependent on the microbiota, as the expression of target genes was higher in IECs from germ-free mice than in those from wild-type mice. Thus, the microbiota is required for the recruitment of HDAC3 to chromatin, where it functions as a co-repressor owing to its deacetylase activity.

Interestingly, mutant IECs also showed decreased expression of some genes involved in lipid absorption, including *Cd36* (encoding a fatty acid transporter), which is in agreement with the observed lower uptake of lipids into these cells. Moreover, mice lacking HDAC3 in IECs seemed to be protected from high-fat-diet-induced obesity, and depletion of the microbiota in wild-type mice led to the same phenotype (lowered body weight and body fat percentages). On the basis of these results, the authors proposed that epithelial HDAC3 is required for the microbiota to promote diet-induced obesity.

Finally, the finding that the expression of some of the genes involved in lipid absorption was decreased when HDAC3 was absent indicated that the enzyme can also affect gene expression through a nonconventional mechanism. Indeed, the authors showed that HDAC3 functions as a co-activator for oestrogen-related receptor-α, which leads to the rhythmic transcription of *Cd36*, in a manner dependent on the microbiota. Thus, the data support the notion that the microbiota promotes *Cd36* expression and lipid absorption through HDAC3.

In sum, the study identifies HDAC3 as a key factor that integrates microbial and circadian cues to regulate diurnal metabolic rhythms.

Andrea Du Toit

ORIGINAL ARTICLE Kuang, Z. et al. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. *Science* **365**, 1428–1434 (2019)

IN BRIEF

MICROBIOME

Providing resistance to rotavirus

Rotavirus is a contagious enteric pathogen and the leading cause of diarrhoea in infants and children. After ingestion, rotavirus infects the intestinal epithelium, which is colonized by diverse members of the gut microbiota. Shi et al. report that gut segmented filamentous bacteria (SFB) prevent and cure rotavirus infection in immunodeficient mice. The authors unintentionally developed a mouse breeding colony that was highly resistant to rotavirus infection and hypothesized that the gut microbiota conferred resistance. Accordingly, resistance was transferred by co-housing and faecal microbiota transplantation. The authors used filtration, heating, antibiotics and limiting dilution to identify SFB as the protective component of the microbiota. Protection was independent of previously observed rotavirus-restricting immunological factors. Instead, SFB caused changes in host gene expression and enhanced gut epithelial turnover, and SFB-containing faeces reduced rotavirus infectivity in vitro, suggesting that SFB could be used to combat rotavirus infections.

ORIGINAL ARTICLE Shi, Z. et al. Segmented filamentous bacteria prevent and cure rotavirus infection. *Cell* https://doi.org/10.1016/j.cell.2019.09.028 (2019)

FUNGAL PATHOGENESIS

A probiotic for candidiasis?

Non-*albicans Candida* (NAC) species infections are of increasing concern owing to rises in complications associated with antifungal resistance, necessitating novel approaches for combating these fungal pathogens. Now, Kunyeit et al. report probiotic yeasts that inhibit virulence of several NAC species, including multidrug-resistant *Candida auris*, an important emerging pathogen. The authors tested the ability of two food-derived yeasts — *Saccharomyces cerevisiae* (strain KTP) and *Issatchenkia occidentalis* (strain ApC) — to inhibit traits such as adhesion, filamentation and biofilm formation in several NAC species. Probiotic treatment prevented adhesion to abiotic surfaces and cultured gut epithelial cells, and inhibited the formation of mixed-culture biofilms as well as biofilms of NAC species and *Candida albicans* in vitro. Furthermore, experiments in *Caenorhabditis elegans* suggest that exposure to the probiotic yeasts attenuates NAC species infection in vivo, highlighting a potential new strategy to prevent or treat candidiasis.

ORIGINAL ARTICLE Kunyeit, L. et al. Probiotic yeasts inhibit virulence of non-*albicans Candida* species. *mBio* https://doi.org/10.1128/mBio.02307-19 (2019)

ENVIRONMENTAL MICROBIOLOGY

Distinct drivers of functional diversity

Soil microbiomes have a central role in biogeochemical cycles, so it is important to understand the impact of global change on community function. Zhang et al. found that the functional diversity of core and accessory genes (genes required for living in a specific environment) are governed by distinct processes. The authors performed a longitudinal 5 year nitrogen and water addition experiment in the Eurasian steppe and surveyed the microbial gene diversity using metagenomics. Rises in nitrogen led to an increase in the abundance of ammonia-oxidizing bacteria, which in turn increased the relative abundance of core genes. Water addition stimulated microbial respiration such that carbon sources became limited, leading to a decrease in the diversity of accessory community genes. These findings highlight that the functional diversity of soil microbiomes is affected differently by distinct environmental change processes.

ORIGINAL ARTICLE Zhang, X. et al. Distinct drivers of core and accessory components of soil microbial community functional diversity under environmental changes. *mSystems* https://doi.org/10.1128/mSystems.00374-19 (2019)