
Credit: Cleaning / Alamy Stock Photo

a range of T6SS toxins. Here, the authors used strains that could only secrete one toxin each, either Tae1, an amidase that targets the cell wall and leads to rapid lysis, or Tse2, which kills cells without inducing rapid lysis. The Tae1 attackers could rapidly clear the competing *E. coli* cells, whereas the Tse2 attackers were unable to eliminate the competitors owing to a barrier of dead cells. Interestingly, a similar protective barrier formed when the Tae1 attack happened in the presence of an osmoprotectant, which inhibits cell lysis. Together, these in vitro experiments confirmed that T6SS attack is most beneficial in segregated, competing populations, if it uses a toxin that quickly lyses targets.

In support of the benefit of T6SS attack with a lytic toxin, the authors found in an analysis of the genomes of 466 bacterial species that >80% of the identified T6SS effectors were lytic toxins. In summary, the study shows that effective use of the T6SS as a competitive weapon not only requires killing but also clearing dead cells.

Ursula Hofer

ORIGINAL ARTICLE Smith, W. P. J. & Vettiger, A. et al. The evolution of the type VI secretion system as a disintegration weapon. *PLoS Biol.* **18**, e3000720 (2020)

in vitro. Remarkably, no resistant clones emerged, despite using sub-lethal concentrations over 5–30 passages, indicating sustained action that is not species specific.

To investigate the MoA, the authors turned to image-based bacterial cytological profiling and compared cell death phenotypes between SCH-79797 and established antibiotics with known MoAs. Their analysis showed that the MoA of SCH-79797 was distinct from any other tested antibiotic. Using high-throughput thermal proteome profiling followed by a screen with a *Bacillus subtilis* CRISPRi knockdown library, the authors identified a dihydrofolate reductase (DHFR; an *Escherichia coli* FolA homologue) as the target of SCH-79797. In vitro enzyme assays showed that SCH-79797 directly inhibits DHFR activity. SCH-79797 was also found to be distinct from other FolA inhibitors like trimethoprim, in that it also affects bacterial cell membrane integrity, conferring a dual MoA. The authors also observed that a single treatment with SCH-79797 was more potent than a combination of two antibiotics — trimethoprim and nisin, or polymyxin B and daptomycin.

Delving into the chemistry behind the dual MoA, the authors found that the pyrroloquinazolinediamine core of SCH-79797 contributes to DHFR inhibition while the hydrophobic isopropylbenzene targets membrane integrity. To further demonstrate this, they synthesized a derivative, Irresistin-16 (IRS-16), that is more hydrophobic than SCH-79797. IRS-16 recapitulated the dual MoA on bacteria both in culture and in vivo, reducing the vaginal burden of *Neisseria gonorrhoeae* in a mouse infection model for gonorrhoea.

In sum, this study presents a promising candidate for a novel broad-spectrum antibiotic and highlights the potential in combining multiple MoAs into a single chemical for the treatment of diverse bacterial pathogens.

Akila Sridhar

ORIGINAL ARTICLE Martin, J. K. II., Sheehan, J. P. & Bratton, B. P. et al. A dual-mechanism antibiotic kills Gram-negative bacteria and avoids drug resistance. *Cell* https://doi.org/10.1016/j.cell.2020.05.005 (2020)

IN BRIEF

BACTERIAL PATHOGENESIS

Host serotonin signals to enteric pathogens

The majority of the neurotransmitter serotonin is made in the gut, and studies have suggested that it has major effects on the gut microbiota. Now, Kumar, Russell et al. find that serotonin modulates the virulence of enterohemorrhagic *Escherichia coli* (EHEC) and *Citrobacter rodentium*, a mouse model of EHEC infection. Serotonin was found to bind to the histidine sensor kinase CpxA, leading to its dephosphorylation and the activation of the transcription factor CpxR, which regulates the expression of EHEC virulence genes, particularly those within the locus of enterocyte effacement (LEE). Increasing the level of serotonin in the mouse gut decreased LEE expression and reduced *C. rodentium* loads. By contrast, inhibiting serotonin synthesis enhanced pathogenesis and decreased host survival. As other bacterial pathogens also encode CpxA, it represents a promising broad-spectrum antibiotic target.

ORIGINAL ARTICLE Kumar, A. & Russell, R. M. et al. The serotonin neurotransmitter modulates virulence of enteric pathogens. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2020.05.004 (2020)

FUNGAL GENOMICS

When two fungi become one

Interspecific hybridization between two species is an important driver of evolution and can produce new species that are genetically and phenotypically distinct from the parents (for example, in pathogenic traits). Hybrids of human pathogenic yeasts and plant-pathogen filamentous fungi have been observed, but not human-pathogenic filamentous fungi. Now, Steenwyk, Lind et al. report the discovery of *Aspergillus latus* allodiploid hybrids isolated from patients with aspergillosis that were formed by the fusion of two species in the *Aspergillus* section *Nidulantes* — *Aspergillus spinulosporus* and an unknown, but close relative of *Aspergillus quadrilineatus*. Genomic analyses and studies in the invertebrate *Galleria mellonella* animal model revealed that the isolates exhibit heterogeneity for various pathogenic traits and are phenotypically distinct from the parental and related species.

ORIGINAL ARTICLE Steenwyk, J. L. & Lind, A. L. et al. Pathogenic allodiploid hybrids of *Aspergillus* fungi. *Curr. Biol.* https://doi.org/10.1016/j.cub.2020.04.071 (2020)

MICROBIOME

Tumour-specific microbiomes

Bacteria are known to inhabit malignant tumours, but a detailed characterization of the tumour microbiome has been challenging because tumours have a very low bacterial biomass, hampering our understanding of the role of intratumour bacteria in cancer. Now, Nejman, Livyatan, Fuks et al. report the most comprehensive analysis of the tumour microbiome to date. The authors analysed the microbiome of 1,526 tumours (and adjacent normal tissue) from individuals with breast, lung, ovary, pancreas, melanoma, bone or brain cancer. Using a novel five-region 16S ribosomal RNA gene sequencing method, microscopy and cell culture, the authors found that all types of tumour harbour bacteria and that each had distinct microbial compositions. The breast tumour microbiome was found to be richer and more diverse than that of other tumour types. Unexpectedly, intratumour bacteria were found to be intracellular and present within both cancer and immune cells. The authors reported associations between the metabolic functions of the microbiomes and clinical features of tumour subtypes, smoking status and responses to immunotherapy.

ORIGINAL ARTICLE Nejman, D., Livyatan, I. & Fuks, G. et al. The human tumor microbiome is composed of tumor type–specific intracellular bacteria. *Science* **368**, 973–980 (2020)