IN BRIEF

ANTIMICROBIALS

A class of its own

The spread of multidrug-resistant (MDR) bacteria poses a great risk to global health, and despite considerable efforts, no new class of antibiotic has been approved for Gram-negative pathogens in recent years. Arylomycins are a class of natural products that exhibit low antibacterial activity. By chemically modifying arylomycin, the authors discovered a synthetic derivative, termed G0775, with potent in vitro and in vivo antibacterial activity against multiple clinically relevant MDR Gram-negative pathogens. G0775 binds to the bacterial signal peptidase LepB, a new antibiotic target, with high affinity and kills bacteria by inhibiting this peptidase. Moreover, G0775 has improved ability to cross the outer membrane through a porin-independent mechanism, and de novo resistance to G0775 occurred at a low frequency. Thus, optimized arylomycin analogues may represent a new class of Gram-negative antibiotics.

ORIGINAL ARTICLE Smith, P. A., Koehler, M. F. T. et al. Optimized arylomycins are a new class of Gram-negative antibiotics. *Nature* https://doi.org/10.1038/s41586-018-0483-6 (2018)

BACTERIAL PHYSIOLOGY

Increasing virulence factors

A previous transcriptome study revealed an increase in antisense transcription and gene expression changes in the absence of the transcription termination factor Rho in *Staphylococcus aureus*. This study assessed the physiological importance of Rho-dependent transcription termination by comparing the *S. aureus* HG001 strain and its isogenic *rho*-deletion mutant. Proteome analysis revealed an increase in the levels of secreted virulence factors that are controlled by the SaeRS two-component system in the absence of Rho in vitro. In addition, inhibition of Rho by the antibiotic bicyclomycin led to increased levels of SaeRS-dependent virulence factors, similar to those observed in the *rho*-deletion mutant. Finally, a *rho*-deletion strain exhibited increased virulence in mice compared to the wild type. These findings identify a link between Rho-dependent transcription termination and virulence regulation in *S. aureus* and suggest that antibiotic treatment can modulate the expression of virulence factors.

ORIGINAL ARTICLE Nagel, A. et al. Inhibition of Rho activity increases expression of saers-dependent virulence factor genes in *Staphylococcus aureus*, showing a link between transcription termination, antibiotic action, and virulence. *mBio* https://doi.org/10.1128/mBio.01332-18 (2018)

VIRAL EVOLUTION

Folding unstable proteins

Adaptive mutations enable influenza viruses to evade host immune responses; however, these adaptive amino acid substitutions are often biophysically deleterious and can affect either protein folding or stability. For example, adaptive mutations in influenza virus nucleoprotein (NP) enables escape from human restriction factors but might render the protein unstable. Thus, viruses must balance the costs of NP folding defects with the benefits of escaping host immunity. The authors tested the hypothesis that viruses hijack host chaperones to promote folding of biophysically defective NP escape variants. A destabilized Pro283 NP variant, which enables evasion of the restriction factor Myxovirus resistance protein A, is not tolerated in chaperone-depleted host cells. This suggests that host chaperones rescue biophysically defective viral protein variants and thus influence the fitness cost of destabilized protein variants.

ORIGINAL ARTICLE Phillips, A. M., Ponomarenko, A. I. et al. Destabilized adaptive influenza variants critical for innate immune system escape are potentiated by host chaperones. *PLOS Biol.* https://doi.org/10.1371/journal.pbio.3000008 (2018)

VIRAL EVOLUTION

HIV-1's fingerprint

Only few people that are infected with HIV-1 develop broadly neutralizing antibodies (bnAbs), which target conserved viral antigens and thus can neutralize diverse viral variants. The factors that determine whether someone will develop bnAbs are not entirely clear; in particular, the contribution of virus characteristics is unknown. Identifying viral determinants of a broadly neutralizing immune response would be very helpful for vaccine development. Kouyos et al. investigated the antibody responses in a large cohort of HIV-1 transmission pairs within the Swiss HIV Cohort Study and found that the HIV-1 strain that someone is infected with determines part of the breadth and strength of the antibody response.

The authors hypothesized that if viral factors determine the quality of the antibody response, individuals with closely related viral strains would have similar neutralization responses. To test this hypothesis, they identified 303 transmission pairs based on the sequence similarity of their HIV-1 polymerase gene. They then tested the ability of the antibody response in these individuals to neutralize 14 different virus strains and to bind 13 antigens, determining what the authors call the 'antibody fingerprint' of the infecting virus. Indeed, transmission pairs had a more similar antibody fingerprint than pairs that were randomly assigned. Specifically, the infecting virus determined 13.2% in the variability of neutralization responses and 7–19% of the IgG reactivity (depending on the IgG class), which confirms that the infecting virus can imprint the neutralization capacity of the ensuing antibody response. Even when taking into account factors that are known to influence bnAb development, such as duration of infection and HIV-1 subtype, the correlation between infecting virus

BACTERIAL PHYSIOLOGY

Surf's up!

Surfing motility is an accelerated form of active surface motility that is dependent on the presence of the glycoprotein mucin. This form of motility was first described when *Pseudomonas aeruginosa* was cultured in cystic fibrosis medium, which is formulated with mucin to mimic cystic fibrosis lung sputum. In *P. aeruginosa* several characteristics of surfing motility have been observed, including rapid surface spread, adaptability to various media viscosities, a dependence on flagella and quorum-sensing systems, and conferring broad-spectrum antibiotic resistance; however, it was unknown whether other mucosa-associated bacteria use this form of motility. Now, Sun et al. report that surfing motility is a conserved yet diverse form of motility in bacteria.

To determine whether other motile bacteria can surf, the authors cultured

Credit: Phillip Patenall/Springer Nature Limited

Credit: Ikon Images / Alamy Stock Photo

and the neutralization fingerprint remained in a similar range.

Although this association between virus genetics and neutralization was highly statistically significant, the average effect size was moderate, similar to the effect size of virus genetics on $CD4^+$ T cell loss. HIV-1 is a hugely variable virus and some viral variants might be much stronger 'imprinters'. Remarkably, the authors found one transmission pair of so-called elite neutralizers; that is, the pair had neutralization levels in the top 1% of the original cohort in which the transmission pairs were identified. The authors confirmed that this pair had developed a broadly neutralizing response by testing 42 different HIV-1 strains and they determined that the probability of finding a pair with such a strong and similar bnAb response by chance is low at 0.017.

In summary, Kouyos et al. found that differences in HIV-1 genetics influence the development of antibody responses and that some viral variants can elicit bnAbs across individuals. Although such strong bnAb imprinting is likely to be rare, the viral strains and antigens that underlie this effect are prime candidates for vaccine development.

Ursula Hofer

ORIGINAL ARTICLE Kouyos, R. D. et al. Tracing HIV-1 strains that imprint broadly neutralizing antibody responses. *Nature* https://doi.org/10.1038/s41586-018-0517-0 (2018)

Gram-negative *Enterobacter cloacae*, *Proteus mirabilis*, *Salmonella enterica*, *Escherichia coli* and *Vibrio harveyi* in cystic fibrosis medium containing mucin on semi-solid agar plates. They observed the same basic physical characteristics of surfing motility in all species and that mucin was the only wetting agent (a substance that lowers the surface tension of a liquid) that was able to consistently induce surfing.

Next, the authors investigated the surfing motility of the different species in various medium viscosities. Compared to swarming and swimming motility, which occur in limited ranges of medium viscosities, surfing motility occurred over a broader range of viscosities and generally at a higher viscosity.

As *P. aeruginosa* exhibits increased resistance to antibiotics during surfing motility, the authors tested whether surfing cells of the other species were similarly resistant to antibiotics. All tested species exhibited broad-spectrum antibiotic resistance during surfing motility, but there was substantial variation in resistance to specific classes of antibiotics.

Surfing was first reported to be dependent on flagella but not pili in *P. aeruginosa*. This finding was corroborated for the other species as only flagella mutants, but not pili or fimbriae mutants, exhibited surfing defects. The authors also tested the importance of quorum sensing, which was reported to be required for *P. aeruginosa* surfing; however, this aspect was not conserved in the other tested species, including *V. harveyi* and *S. enterica*, as demonstrated by assaying quorum-sensing mutants. This finding suggests that the regulation of surfing is distinct among motile bacteria.

In summary, Sun et al. found that the physical characteristics of surfing motility are conserved among motile mucosa-associated pathogens and that this phenotype is associated with broad-spectrum antibiotic resistance.

Ashley York

ORIGINAL ARTICLE Sun, E., Liu, S. & Hancock, R. E. W. Surfing motility: a conserved yet diverse adaptation among motile bacteria. *J. Bacteriol.* https://doi.org/10.1128/JB.00394-18 (2018)

IN BRIEF

FUNGAL PATHOGENESIS

Making matters worse

Gut microbiota can have a distant effect on immune function in the lung through the gut–lung axis. This study observed that the specific expansion of the commensal fungus *Wallemia mellicola* in the gut (that is, without overgrowth of the total fungal community in the gut) enhances the severity of allergic airway disease in mice. Whereas mice with a healthy gut microbiota were able to resist a population expansion when gavaged with live spores of *W. mellicola*, mice that had been treated with antibiotics did not. Mice that had increased levels of *W. melliola* in the gut experienced alterations in a number of pulmonary immune responses to inhalation of the house dust mite antigen (an aeroallergen). Colonization of fungus-free altered Schaedler Flora mice with *W. mellicola* enhanced the severity of allergic airways disease, suggesting that any changes in bacterial community composition do not have a role in this phenomenon.

ORIGINAL ARTICLE Skalski, J. H. et al. Expansion of commensal fungus *Wallemia mellicola* in the gastrointestinal mycobiota enhances the severity of allergic airway disease in mice. *PLOS Pathog.* **14**, e1007260 (2018)

FURTHER READING Budden, K. F. et al. Emerging pathogenic links between microbiota and the gut–lung axis. *Nat. Rev. Microbiol.* **15**, 55–63 (2017)

VIRAL INFECTION

Exploiting peroxisomes

Peroxisomes perform important metabolic functions, including lipid metabolism. This study finds that human cytomegalovirus (HCMV) and herpes simplex virus 1 (HSV1) induce peroxisome biogenesis and changes to peroxisome morphology that support viral infection. Using proteomics, the authors observed a global increase in the abundance of peroxisomal proteins during HCMV and HSV1 infections. Microscopy analysis and mathematical modelling showed that infection caused peroxisome growth and fission, leading to an increase in the number of peroxisomes. On average, peroxisomes became larger in size and more elongated, which causes an increase in the peroxisome membrane-to-lumen ratio. HCMV-induced peroxisome biogenesis also enhanced the synthesis of the phospholipid plasmalogen, increasing virus production. Altogether, this suggests that these viruses exploit peroxisome lipid metabolism to enhance viral replication.

ORIGINAL ARTICLE Jean Beltran, P. M. et al. Infection-induced peroxisome biogenesis is a metabolic strategy for herpesvirus replication. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2018.09.002 (2018)

BACTERIAL PATHOGENESIS

Stronger together

Uropathogenic *Escherichia coli* (UPEC) is a major cause of urinary tract infections. These infections are initiated by adhesion to the bladder epithelium, after which UPEC colonizes and persists in the bladder niche. Hollenbeck et al. find that the *E. coli* curli amyloid fibres promote bladder epithelial cell adhesion and that phosphoethanolamine (pEtN) cellulose enhances this interaction. The authors used a custom-built live cell monolayer rheometer to directly measure individual and combined contributions of type 1 pili, curli and pEtN cellulose to bladder cell adhesion during high-shear conditions. Using the UPEC strain UTI89, isogenic mutants and conditions that result in the production of the cell surface structures, curli-mediated adhesion was found to be stronger than type 1 pili and this was enhanced by pEtN cellulose, which the authors posit functions as a mortar, increasing the strength of the interaction.

ORIGINAL ARTICLE Hollenbeck, E. C. et al. Phosphoethanolamine cellulose enhances curli-mediated adhesion of uropathogenic *Escherichia coli* to bladder epithelial cells. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1801564115 (2018)