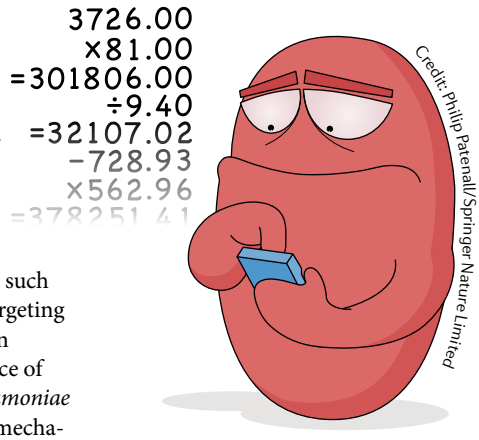
ANTIMICROBIAL RESISTANCE

The cost of resistance



Klebsiella pneumoniae is a common cause of hospital-acquired infections and a serious public health concern owing to the spread of multidrug-resistant *K. pneumoniae* strains. The emergence of these strains has led to the increased use of last-resort antibiotics, such as the lipopolysaccharide-targeting polymyxin colistin, which, in turn, promotes the emergence of polymyxin-resistant *K. pneumoniae* strains. The most common mechanism underlying colistin resistance involves lipid A modifications that arise from the loss-of-function mutation of a small regulatory protein, MgrB. Inactivation of MgrB leads to increased activity of the two-component system PhoPQ and thus an increase in the lipid A modifications. Data suggest that antibiotic resistance is associated with a biological cost for the bacterial cell, but results have been conflicting. Bray et al. report that although colistin resistance in *K. pneumoniae* is associated with a fitness defect in gut colonization, it increases bacterial survival outside the host, thus enabling efficient host-to-host transmission.

The authors first showed that the deletion of *mgrB* did not affect the growth rate compared with wild-type *K. pneumoniae* in vitro, which suggests that MgrB-dependent colistin resistance does not have an impact on growth. Next, they tested whether colistin resistance could have an effect on the initial stage of infection. To this end, they used a mouse model of *K. pneumoniae* gastrointestinal colonization and tested the ability of the MgrB-deletion strain to colonize mice with an intact microbiota. Over the course of 15 days post inoculation the authors found that the mutant strain was shed less in faeces than the wild-type strain as well as an MgrB complemented strain, which indicates that the lack of MgrB function causes a colonization defect. However, this effect could be alleviated by antibiotic treatment, which promoted a temporary 'super-shedder' phenotype in the wild-type and the MgrB-deletion strains. Furthermore, the MgrB-deletion strain had decreased levels of capsular polysaccharide, which suggests that the reduced amount of capsule leads to increased clearance from the gastrointestinal tract. The capsule also promotes environmental survival; thus, the authors hypothesized that the MgrB-deletion strain has decreased survivability outside the host. However, the mutant had a significantly higher survival rate than the wild-type and the complemented strain. Moreover, increased environmental survival correlated with higher transmission efficiency. The authors were able to show that enhanced survival was due to the dysregulated PhoPQ two-component system as well as accumulation of the stress response master regulator RpoS. Thus, both lipid A modifications and a constitutive stress response have a role in increased survival and subsequent transmission.

In sum, the study shows that the fitness cost of colistin resistance negatively affects colonization; however, this fitness cost is mitigated by enhanced survival outside the host and thus increased transmissibility.

Andrea Du Toit

ORIGINAL ARTICLE Bray, A. S. MgrB-dependent colistin resistance in *Klebsiella pneumoniae* is associated with an increase in host-to-host transmission. *mBio* https://doi.org/10.1128/mbio.03595-21 (2022)

IN BRIEF

MICROBIOME

Mobilizing resistance genes in the human gut

Antibiotic resistance genes (ARGs) in commensal bacteria in the gut can function as a reservoir for horizontal transfer to pathogens; however, the extent and reach of such events are incompletely understood. Forster et al. compared ARGs in 1,354 cultured commensal strains from the human gut with those from 45,403 pathogens, and found 64,188 shared ARGs and assigned them to 5,931 mobile genetic elements (MGEs). Worryingly, 15 of those MGEs showed a broad host range, occurring in several different bacterial phyla, which indicates absent or weak barriers to their spread. In vitro experiments confirmed that the tested examples could spread between bacterial isolates from different phyla and transfer ARGs between commensals and pathogens. Furthermore, some of these MGEs were also found in microbiome data from other body sites, ruminant guts and soil.

ORIGINAL ARTICLE Forster, S. C. et al. Strain-level characterization of broad host range mobile genetic elements transferring antibiotic resistance from the human microbiome. *Nat. Commun.* **13**, 1445 (2022)
RELATED ARTICLE Brito, I. L. Examining horizontal gene transfer in microbial communities. *Nat. Rev. Microbiol.* **19**, 442–453 (2021)

VIRAL INFECTION

Clotting and SARS-CoV-2 entry

Besides the cellular attachment receptor ACE2, SARS-CoV-2 also requires host proteases, such as TMPRSS2, for entry. These proteases cleave spike, thereby activating it. In a screen to identify entry inhibitors, Kastenhuber et al. noticed that some anticoagulants reduced spike-pseudotyped virus entry, leading the authors to speculate that coagulation factors might also process spike. Indeed, thrombin and factor Xa cleaved SARS-CoV-2 spike similarly to TMPRSS2 and increased infection of cell lines with spike-pseudotyped virus as well as of lung organoids with authentic SARS-CoV-2. Finally, the authors tested a range of protease inhibitors and anticoagulants and found variable reduction of spike cleavage, with nafamostat, a serine protease inhibitor in clinical use as an anticoagulant, having the broadest inhibitory effect. The authors speculate that activation of coagulation during infection might further increase SARS-CoV-2 entry and that early treatment with anticoagulants might prevent this feedback loop.

ORIGINAL ARTICLE Kastenhuber, E. R. et al. Coagulation factors directly cleave SARS-CoV-2 spike and enhance viral entry. *eLife* **11**, e77444 (2022)

BACTERIAL PATHOGENESIS

Novel *C. difficile* toxin receptor

Clostridioides difficile expresses up to three different toxins and expression patterns can explain virulence phenotypes; for example, the hypervirulent clade 2 exclusively expresses the TcdB2 and TcdB4 toxin variants. Whereas the cellular receptor for other TcdB variants was known, the receptor for TcdB2 and TcdB4 was unknown. Luo, Yang, Zhang, Zhang, Wan et al. performed a genome-wide CRISPR–Cas screen for TcdB4 binding and identified tissue factor pathway inhibitor (TFPI), which is expressed in intestinal crypts, as its receptor. Structural analysis showed that variation in the common receptor-binding domain of TcdB was responsible for variant-specific receptor binding, with TcdB4 and TcdB2 sharing the same specificity for TFPI. Finally, treatment with recombinant TFPI protected mice from TcdB2 toxicity.

ORIGINAL ARTICLE Luo, J. et al. TFPI is a colonic crypt receptor for TcdB from hypervirulent clade 2 *C. difficile*. *Cell* **185**, 980–994.e15 (2022)
RELATED ARTICLE Kordus, S. L., Thomas, A. K. & Lacy, D. B. *Clostridioides difficile* toxins: mechanisms of action and antitoxin therapeutics. *Nat. Rev. Microbiol.* https://doi.org/10.1038/s41579-021-00660-2 (2021)