**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.

**Related Article**

Bray, A. S. Microbial resistance genes in *Klebsiella pneumoniae*. *In Brief* 2022, 317.

**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 anti-coagulants 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 anti-coagulants and found variable reduction of spike cleavage, with nafamostat, a serine protease inhibitor in clinical use as an anti-coagulant, 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 anti-coagulants might prevent this feedback loop.

**Bacterial Pathogenesis**

**Novel *Clostridium difficile* toxin receptor**

*Clostridium 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.

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Bray, A. S. Microbial resistance genes in *Klebsiella pneumoniae*. *In Brief* 2022, 317.

**VIRal INFECTION**

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Kastenhuber, E. R. et al. Coagulation factors directly cleave SARS-CoV-2 spike and enhance viral entry. *eLife* 11, e7444 (2022).