
CORBIS

ANTIMICROBIALS

Disruption of quorum sensing meets resistance

The use of drugs that specifically target mechanisms associated with virulence rather than cell growth has been suggested as a strategy to reduce the selective pressure that leads to antibiotic resistance in bacteria. However, Maeda *et al.* now show that such approaches do not necessarily prevent the development of bacterial resistance.

The seaweed *Delisea pulchra* prevents the formation of bacterial biofilms on its surface by secreting brominated furanones that interfere with bacterial quorum sensing. The best characterized synthetic furanone is C-30, which interacts with the bacterial transcriptional regulator LasR to decrease acyl-homoserine lactone-based signalling and *Pseudomonas aeruginosa* virulence in a mouse pulmonary model of infection. Although C-30 has no effect on bacterial growth in rich media, the authors set out to investigate whether the compound affects bacterial growth, and therefore selects for resistance, under the more restrictive growth conditions that might be experienced in a clinical setting.

They grew *P. aeruginosa* str. PA14 on minimal medium using adenosine as the sole carbon source and observed that the presence of C-30 decreased cell growth about five-fold after 48 hours and inhibited the phenotypes associated with quorum sensing, including swarming and pyocyanin production. Using a random transposon mutagenesis approach to screen for mutants that grew faster in the presence of C-30, they identified strains containing mutations in the *mexR* and *nalC* genes, both of which encode negative regulators of the MexAB–OprM multidrug resistance efflux pump. Growth inhibition by C-30 was reduced in both of these strains, and there was no apparent inhibition of quorum sensing phenotypes, owing to the increased efflux of C-30 from the cells by MexAB–OprM. Importantly, in a *Caenorhabditis elegans* infection model, C-30 had little effect on the *mexR*-mutant strain, whereas it substantially reduced the virulence of wild-type *P. aeruginosa*. Finally, the authors found that several isolates from patients with cystic fibrosis and chronic *P. aeruginosa* infections contained mutations in *mexR* and *nalC* and exhibited no growth defect in the presence of C-30, indicating that clinical isolates that are resistant to synthetic furanones already exist.

These findings suggest that bacteria readily develop resistance to antivirulence drugs and that this approach may therefore prove not to be such a powerful tool in targeting bacterial pathogens.

Andrew Jermy

> “bacteria may readily develop resistance to antivirulence drugs.”

ORIGINAL RESEARCH PAPER Maeda, T. *et al.* Quorum quenching quandary: resistance to antivirulence compunds. *ISME J.* 15 Sep 2011 (doi:10.1038/ismej.2011.122)
FURTHER READING Rasko, D. A. & Sperandio, V. Anti-virulence strategies to combat bacteria-mediated disease. *Nature Rev. Drug Discov.* **9**, 117–128 (2010) | Cegekski, L. The biology and future prospects of antivirulence therapies. *Nature Rev. Microbiol.* **6**, 17–27 (2008)