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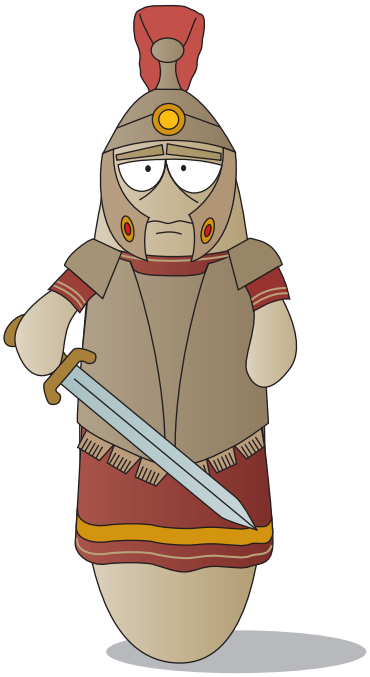
BACTERIAL EVOLUTION

Historical influences on antibiotic resistance



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Bacterial pathogens that are multidrug resistant to almost all available antibiotics are continuing to spread worldwide and are therefore a major public health concern. Adaptation to a single antibiotic during treatment can result in bacteria becoming more resistant or more susceptible to other antibiotics; however, how adaptation to one drug can influence resistance to other antibiotics remains unclear.

In a recent study, Yen and Papin investigated how the history of adaptation to a single antibiotic influences the trajectory of evolutionary dynamics during subsequent treatments with different antibiotics. First, the authors serially passaged *Pseudomonas aeruginosa* in increasing concentrations of three clinically relevant antibiotics (piperacillin, tobramycin and ciprofloxacin) with different mechanisms of action for 20 days, followed by 20 further days of passage in a different antibiotic while measuring levels of antibiotic resistance. They observed differences in resistance levels to the drugs that were dependent on the history of past treatments and that sensitivity to the first drug could be restored after exposure to a second drug, confirming that the history of antibiotic exposure affects the rate at which antibiotic resistance is acquired or lost. Interestingly, the authors observed unique outcomes for different pairings of sequential antibiotic treatment; for example, no drug-order-specific effects were observed for *P. aeruginosa* that was initially passaged in piperacillin and then passaged in tobramycin compared with passaging in antibiotic-free media, whereas after passaging the cultures in ciprofloxacin, the cultures became sensitive to piperacillin again, which suggests that specific treatment with ciprofloxacin has an active role in piperacillin resensitization. Similarly, passage in tobramycin followed by ciprofloxacin, or vice versa, led to differences in piperacillin and ciprofloxacin resistance, depending on the order of treatment, highlighting that the sequential treatment of an infection with a series of antibiotics can result in differences in drug resistance that are dependent on the order that is used.

> “history of antibiotic exposure affects the rate at which antibiotic resistance is acquired or lost”

The authors hypothesized that mutations in the *P. aeruginosa* genome during adaptation were responsible for the drug-order-specific effects. They sequenced the genomes of the untreated *P. aeruginosa* at day 0 and the antibiotic-treated *P. aeruginosa* at 20 days and 40 days post-treatment and found 201 unique mutations, the majority of which were homogenous in the resistant populations. Many of these mutations were found in genes that relate to the mechanism of antibiotic action; for example, the ribosomal genes in the case of the ribosome-targeting antibiotic tobramycin. Next, the authors looked for patterns in the mutated genes and found that some of the mutations could explain the observed drug-specific-order effects. For example, a 400 kb deletion was found when *P. aeruginosa* was passaged in piperacillin, resulting in the loss of homogentisate 1,2-dioxygenase (*hmgA*) and the hyperproduction of pyomelanin (a brown pigment that has been associated with persistent infections). However, *P. aeruginosa* that had been exposed to tobramycin or ciprofloxacin prior to piperacillin did not have this phenotype, which suggests that the hyperproduction of pyomelanin during piperacillin adaptation is dependent on previous antibiotic exposures.

In summary, these findings demonstrate the importance of previous antibiotic exposures in determining the trajectory of the evolution of multidrug resistance during subsequent antibiotic treatments and highlights the need for considering past drug exposures when combating bacterial infections.

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