**Repeatability of antibiotic resistance evolution of Enterococcus faecium in vivo and in vitro**

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1Evolution is the root of the antibiotic resistance crisis. Clarifying the evolutionary processes leading to resistance, in particular the determinants of chance and repeatability, are thus pivotal to understanding how pathogens adapt to drugs and identifying alternative treatment strategies that are informed by evolution and favor continued treatment efficacy whilst minimizing the likelihood of adaptation. Two important open questions are how reproducible antibiotic resistance evolution is within human hosts and to what extent those evolutionary paths seen in vivo can be recapitulated in vitro. To address these two questions, we retrospectively identify changes in resistance against daptomycin and linezolid when these drugs are used as the main treatment in patients with blood stream infections with Enterococcus faecium. E. faecium isolates from blood cultures of hospitalized patients are routinely stored in our lab. Twelve patients were identified with in vivo resistance evolution of E. faecium to daptomycin and six to linezolid, each obtained from independent patients. We fully sequenced and assembled the genomes of 18 initially sensitive isolates. We then performed whole genome sequencing of the subsequent isolates showing an increase in resistance against the corresponding drug within the same patient to identify the repeatability of genomic changes associated with resistance. Additionally, each of the 18 initially sensitive isolates was used to found 20 independent biological replicates for in vitro evolution against increasing concentrations of the corresponding drug in order to determine whether the same mechanisms identified in vivo emerge in vitro. This study casts light on the role of determinism and contingency in evolution, with potential implications for medical treatment.

1. What is your pathogen? Multiple options possible (e.g. if working on coinfections)

Bacteria : Enterococcus faecium

2. On a scale of 1-5 is your work mostly eco/epidemiological or evolutionary? 4

3. On a scale of 1-5 is your work mostly theoretical or experimental/empirical? 4

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