Shedding Light In Drug Discovery With Antimicrobial Resistance

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Abstract
The rise of antimicrobial resistance poses a serious threat to public health on a global scale. A recent report estimated that based on the current rate of emerging resistance, by the year 2050 antimicrobial resistance will take 10 million lives annually and cost $100 trillion globally. Understanding the genetic basis of antimicrobial resistance is paramount for the molecular epidemiology of drug resistance, treatment and drug discovery.

Here, we explore how chemical genetics are used to select for drug resistant mutants and identify the mechanisms of resistance through whole genomic sequencing and reverse genetics. Previous work examining resistance to selected drugs in tuberculosis and malaria has emphasized the value of understanding underlying mechanism and the role that this comprehension may have in the clinic and drug discovery. By observing for infectious diseases that have become resistant to a source of stress, such as an experimental compound or know antimicrobials, the mutation prevention concentration (MPC) as well as mutation frequency can be determined and the compound’s target in addition to the mutation type can be elucidated. Such information has implications in treatment regimes, synergistic combinations, and public health policy and drug development. For example, mutation types can guide drug discovery away from compounds associated with high fitness mutations, which should therefore be avoided, while simultaneously highlighting compounds that target critical residues, which should thus be favored. In summary, understanding mechanisms of antimicrobial resistance and experimental compounds is fundamental for the molecular epidemiology of drug resistance, treatment and future drug development.

Selected Publications for Reference


