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Elucidation of Molecular Mechanisms Underlying Successful Adaptation to Carbapenem Antimicrobials in High Risk Carbapenem Resistant Escherichia coli Lineages

Escherichia coli is a leading cause of human infection and a major contributor to the epidemic of antimicrobial resistant (AMR) bacteria. Thus, there is an urgent need to understand how certain *E. coli* populations successfully adapt to antibiotic treatments in clinical settings. One of the most challenging AMR *E. coli* infections are those that are resistant to carbapenems, which are considered as last-resort antibiotic treatments. While there has been extensive research on carbapenem resistant *E. coli*, there remains a knowledge gap of how particular high-risk *E. coli* lineages are able to adapt to initial antibiotic exposure, which can be conceptualized as a 'pre-resistant' phase. One of the most prolific high-risk *E. coli* lineages is sequence type 131 (ST131), which include certain sub-populations that readily develop carbapenem resistance. We used a combination of multiple experimental evolution platforms and computational biology techniques to analyze the early adaptive response of ST131 *E. coli* to carbapenems. We identified evidence of early phenotypic changes predicted to reduce carbapenem entrance into the *E. coli* cell prior to a fully carbapenem resistant phenotype. Moreover, we found that at the same time ST131 *E. coli* also rapidly responds to carbapenem exposure by increasing the copy number of antimicrobial resistant genes, which in combination with reduced carbapenem entrance could allow for cell survival in the presence of a carbapenem. Importantly, these changes occur prior to fixed genetic mutations that are ultimately found in fully carbapenem resistant strains. The long-term goals of our holistic investigation of the central tenets of these pre-resistant isolates are to identify which ST131 *E. coli* strains have the capacity to develop carbapenem resistance following carbapenem exposure and to fully understand the adaptive strategies of these high-risk bacteria to assist with the development of novel preventative approaches.