Quantitative contribution of efflux to multi-drug resistance of clinical Escherichia coli and Pseudomonas aeruginosa strains

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Efflux pumps mediate antimicrobial resistance in several WHO critical priority bacterial pathogens. However, most available data come from laboratory strains. The quantitative relevance of efflux in more relevant clinical isolates remains largely unknown.; We developed a versatile method for genetic engineering in multi-drug resistant (MDR) bacteria, and used this method to delete tolC and specific antibiotic-resistance genes in 18 representative MDR clinical E. coli isolates. We determined efflux activity and minimal inhibitory concentrations for a diverse set of clinically relevant antibiotics in these mutants. We also deleted oprM in MDR P. aeruginosa strains and determined the impact on antibiotic susceptibility.; tolC deletion abolished detectable efflux activity in 15 out of 18 tested E. coli strains, and modulated antibiotic susceptibility in many strains. However, all mutant strains retained MDR status, primarily because of other, antibiotic-specific resistance genes. Deletion of oprM altered antibiotic susceptibility in a fraction of clinical P. aeruginosa isolates.; Efflux modulates antibiotic resistance in clinical MDR isolates of E. coli and P. aeruginosa. However, when other antimicrobial-resistance mechanisms are present, inhibition of MDR efflux pumps alone is often not sufficient to restore full susceptibility even for antibiotics with a dramatic impact of efflux in laboratory strains. We propose that development of novel antibiotics should include target validation in clinical MDR isolates. FUND: Innovative Medicines Initiative of European Union and EFPIA, Schweizerischer Nationalfonds, Swiss National Research Program 72, EU Marie Skłodowska-Curie program. The funders played no role in design, data collection, data analysis, interpretation, writing of the report, and in the decision to submit the paper for publication.
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