A novel genome editing platform for drug resistant Acinetobacter baumannii revealed an AdeR-unrelated tigecycline resistance mechanism

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Infections with the Gram-negative coccobacillus Acinetobacter baumannii are a major threat in hospital settings. The progressing emergence of multidrug resistant clinical strains significantly reduces the treatment options for clinicians to fight A. baumannii infections. The current lack of robust methods to genetically manipulate drug resistant A. baumannii isolates impedes research on resistance and virulence mechanisms in clinically relevant strains. In this study we developed a highly efficient and versatile genome editing platform enabling the markerless modification of the genome of A. baumannii clinical and laboratory strains, regardless of their resistance profile.We applied this method for the deletion of AdeR, a transcription factor that regulates the expression of the AdeABC efflux pump in tigecycline resistant A. baumannii, to evaluate its function as a putative drug target. Loss of adeR reduced the MIC90 of tigecycline from 25 μg/ml in the parental strains to 3.1 μg/ml in the ΔadeR mutants indicating its importance in the drug resistant phenotype. However, 60% of the clinical isolates remained non-susceptible to tigecycline after adeR deletion. Evolution of artificial tigecycline resistance in two strains followed by whole genome sequencing revealed loss of function mutations in trm, suggesting its role in an alternative AdeABC-independent tigecycline resistance mechanism. This finding was strengthened by the confirmation of trm disruption in the majority of the tigecycline resistant clinical isolates. This study highlights the development and application of a powerful genome editing platform for A. baumannii enabling future research on drug resistance and virulence pathways in clinical relevant strains.
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