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Metabolic Responses to Polymyxin Treatment in *Acinetobacter baumannii* ATCC 19606: Integrating Transcriptomics and Metabolomics with Genome-Scale Metabolic Modeling

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Abstract

Multidrug-resistant (MDR) *Acinetobacter baumannii* has emerged as a very problematic pathogen over the past decades, with a high incidence in nosocomial infections. Discovered in the late 1940s but abandoned in the 1970s, polymyxins (i.e., polymyxin B and colistin) have been revived as the last-line therapy against Gram-negative "superbugs," including MDR *A. baumannii*. Worryingly, resistance to polymyxins in *A. baumannii* has been increasingly reported, urging the development of novel antimicrobial therapies to rescue this last-line class of antibiotics. In the present study, we integrated genome-scale metabolic modeling with multiomics data to elucidate the mechanisms of cellular responses to colistin treatment in *A. baumannii*. A genome-scale metabolic model, iATCC19606, was constructed for strain ATCC 19606 based on the literature and genome annotation, containing 897 genes, 1,270 reactions, and 1,180 metabolites. After extensive curation, prediction of growth on 190 carbon sources using iATCC19606 achieved an overall accuracy of 84.3% compared to Biolog experimental results. Prediction of gene essentiality reached a high accuracy of 86.1% and 82.7% compared to two transposon mutant libraries of AB5075 and ATCC 17978, respectively. Further integrative modeling with our correlative transcriptomics and metabolomics data deciphered the complex regulation on metabolic responses to colistin treatment, including (i) upregulated fluxes through gluconeogenesis, the pentose phosphate pathway, and amino acid and nucleotide biosynthesis; (ii) downregulated TCA cycle and peptidoglycan and lipopolysaccharide biogenesis; and (iii) altered fluxes over respiratory chain. Our results elucidated the interplay of multiple metabolic pathways under colistin treatment in *A. baumannii* and provide key mechanistic insights into optimizing polymyxin combination therapy.

IMPORTANCE Combating antimicrobial resistance has been highlighted as a critical global health priority. Due to the drying drug discovery pipeline, polymyxins have been employed as the last-line therapy against Gram-negative "superbugs"; however, the detailed mechanisms of antibacterial killing remain largely unclear, hampering the improvement of polymyxin therapy. Our integrative modeling using the constructed genome-scale metabolic model iATCC19606 and the correlative multiomics data provide the fundamental understanding of the complex metabolic responses to polymyxin treatment in *A. baumannii* at the systems level. The model iATCC19606 may have a significant potential in antimicrobial systems pharmacology research in *A. baumannii*.

Keywords

Author Keywords: *Acinetobacter baumannii*; genome-scale metabolic modeling; metabolomics; transcriptomics; polymyxins

KeyWords Plus: COLISTIN RESISTANCE; EXPRESSION; GENES; IDENTIFICATION; PHARMACOLOGY; COMBINATION; MUTATIONS; PATHWAYS; IMPACT; KEGG

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