27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: EP188 Update on colistin resistance - from lab to hospital

Category: 3d. Resistance mechanisms

25 April 2017, 12:48 - 12:53
EP0921

Deciphering the metabolic response to polymyxin killing using a high-quality genome-scale metabolic model for an opportunistic pathogen Pseudomonas aeruginosa PAO1

Yan Zhu*[1], Tobias Czauderna[2], Matthias Klapperstueck[2], Meiling Han[3], Jing Lu[4], Tony Velkov[3], Trevor Lithgow[5], Jiangning Song[5], Falk Schreiber[6], Jian LI[7]

[1]*Monash University; Biomedicine Discovery Institute*

[2]*Faculty of Information Technology, Monash University*

[3]*Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University*

[4]*School of Psychological Sciences, Faculty of Medicine, Nursing & Health Sciences, Monash University*

[5]*Infection and Immunity Program, Biomedicine Discovery Institute, Faculty of Medicine, Nursing & Health Sciences, Monash University*

[6]*Department of Computer and Information Science, University of Konstanz*

[7]*Monash Biomedicine Discovery Institute; Department of Microbiology; Monash University*

Background: Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has become a major global threat to public health. Polymyxins are increasingly used as a last-line therapy. Alarmingly, the emergence of MDR *P. aeruginosa* strains with MCR plasmid-mediated polymyxin resistance has been reported recently. Polymyxin resistance in *P. aeruginosa* is mainly due to modifications of the phosphate groups of lipid A by addition of aminoarabinose. However, it is largely unknown how *P. aeruginosa* alters its metabolism in response to polymyxins. This study aimed to investigate the global metabolic responses to polymyxin treatment in *P. aeruginosa* using genome-scale metabolic modelling (GSMM).

Material/methods: GSMM *i*PAO1 was constructed by merging two existing basic models and conducting very extensive manual curation, in particular on lipid A modifications. Growth capabilities were predicted using flux balance analysis (FBA) and experimentally validated using Biolog

Phenotypic Microarray. Gene essentiality was analysed by *in silico* single gene deletion and compared to two existing comprehensive transposon mutant libraries. Growth and metabolic changes due to lipid A modifications were simulated by FBA and randomly sampling the solution space.

Results: *i*PAO1 is the first high-quality GSMM for the type strain PAO1 with a comprehensive module on lipid A modifications. It contains 1,458 genes (25.8% from 5,642 genes in the genome), 4,265 reactions and 3,022 metabolites, representing 107 metabolic pathways. *i*PAO1 was extensively validated using BIOLOG Phenotypic Microarray and published experimental data in the literature. The prediction of growth under various conditions achieved an overall accuracy of 89.1% (254 out of 285 carbon and nitrogen nutrient conditions); the prediction of gene essentiality achieved an overall accuracy of 87.9% compared to the reported transposon insertion mutant libraries. The model was then employed to investigate the impact of lipid A modifications in response to polymyxin treatment on cell growth and metabolism. Compositions of different lipid A types in the biomass equation were set according to the relative abundance of lipid A derived from our lipidomics studies. Comparison of the calculated metabolic fluxes showed increased ammonia assimilation, redox turnover, energy generation, and slightly increased biomass production owing to refueling the deacylated (*R*)-3-hydroxydecanoate from lipid A moiety to the fatty acid biosynthesis pathway. Further prediction of growth rates along with randomly varying lipid A compositions suggested that the aminoarabinosylation of lipid A resulted in compromising growth whereas deacylation of lipid A did not. Our GSMM prediction results indicate the ‘cost-free’ resistance caused by lipid A deacylation can be induced by adaptation to polymyxin treatment.

Conclusions: *i*PAO1 represents the best GSMM for *P. aeruginosa* to date. Our study is the first to apply GSMM to antimicrobial pharmacodynamics and provides a powerful systems tool to comprehensively investigate bacterial responses to antibiotics.