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Systems pharmacology of interactions among Acinetobacter baumannii, human lung epithelial cells and polymyxin B

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Background: *Acinetobacter baumannii* is one of the six 'superbugs' currently presenting a major global health concern. This highly antibiotic-resistant bacterium can cause life-threatening pneumonia in critically-ill patients. Understanding the interaction of this pathogen with respiratory epithelial cells during antibiotic treatment is valuable for the prevention and treatment of pneumonia caused by this pathogen. In this study, we investigated how *A. baumannii* and human lung epithelial cells interact at the molecular level when concomitantly exposed to polymyxin B.

Material/methods: *A. baumannii* ATCC 19606 was co-cultured with A549 cells for 2 h with or without 2 mg/L polymyxin B. Non-infecting/adhering bacteria were removed and both bacterial and eukaryotic RNA extracted; bacterial mRNA was enriched with a MICROBEnrich kit. Affymetrix microarray was used for quantifying eukaryotic mRNA, while Illumina HiSeq1500 was used for sequencing bacterial mRNA. R limma package was employed to analyse the transcriptomic data. DAVID, KEGG and Biocyc were used for GO terms and pathways analysis. *A. baumannii* AB5075 transposon insertion mutant library was employed for the evaluation of significant differentially expressed genes (DEGs) and enriched pathways. Genes related to polymyxin resistance were examined with population analysis profiles (PAPs) and potential virulence genes were investigated using FACS.

Results: In A549 cells infected with *A. baumannii*, upregulated DEGs were enriched for inflammatory responses, specifically TNF signaling pathway. Addition of polymyxin B to this infection did not significantly alter the overall gene expression. Moreover, 2 mg/L polymyxin B alone did not cause significant changes in the gene expression of A549 cells.

Interestingly, infection of A549 cells caused upregulated DEGs enriched for arginine and tyrosine degradation pathways in *A. baumannii*. Genes encoding outer membrane protein (Omp) A and W were significantly upregulated. When *A. baumannii* was exposed to polymyxin B alone, upregulated DEGs highly enriched for the histidine degradation pathway were evident. Upregulated lipoprotein transporter activity (e.g. *lolB*) was identified in *A. baumannii* during exposure to A549 cells with polymyxin B compared to *A. baumannii* and A549 cells alone.

Using the mutant library, *ompA* was identified to involve in biofilm production. The *ompA* mutant showed similar killing of A549 cells compared to the wildtype using FACS. With the PAPs, we screened *hutU*, *hutH* and *hutI* mutants lacking key enzymes for the histidine degradation pathway and identified *hutU* and *hutI* mutants had a >100-fold less polymyxin-resistant subpopulation compared to the wildtype AB5075

Conclusions: A systems approach for the host-pathogen-drug interactions provides a better understanding of the progression of bacterial infection in the presence of antibiotics. We are the first to show that arginine and tyrosine degradation in *A. baumannii* are major pathways involved in its infection, and histidine degradation is a potential pathway involved in polymyxin resistance in *A. baumannii*.