Physiological and transcriptional response of *P. aeruginosa* PAO1 cells lacking six major RND pumps

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Resistance-Nodulation-Division (RND) superfamily of transporters are responsible for the intrinsic antibiotic resistance of Gram-negative bacteria. Widespread nosocomial pathogen *Pseudomonas aeruginosa* PAO1 strain possesses twelve RND pumps, which are connected with development of clinical multidrug resistance and contribute to virulence, quorum sensing and many other physiological functions. However, the consequences of efflux inhibition on bacterial physiology and how cells might counteract the loss of activities of RND pumps remain unclear. In this study, we use PΔ6 cells carrying deletions in genes encoding the six major RND efflux pumps (*mexAB-oprM*, *mexCD-oprJ*, *mexJK*, *mexEF-oprN*, *mexXY* and *triABC*) in both exponential and stationary phases to analyze how *P. aeruginosa* changes its physiology in response to the lack of efflux pumps. We compared the transcriptomes of the exponentially growing and stationary PΔ6 and its parent PAO1 cells and identified the functions stressed by the lack of active efflux. This study shows that the mutational inactivation of six major RND pumps elicits a specific transcriptome response, but do not affect the central metabolism. Loss of active efflux generates dramatic changes in transport activities across the cell envelope, cell-to-cell communication and environmental responses, such as iron acquisition, production of pyocyanin, motility or biofilm formation.

Antimicrobial resistance; RND efflux pumps, Pseudomonas aeruginosa