TITLE: STRUCTURAL CHANGE AND GENE EXPRESSION IN *Pseudomonas aeruginosa* EXPOSED TO MEROPENEM

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ABSTRACT:

Pseudomonas aeruginosa is major nosocomial pathogens worldwide. A new approach to understanding the mechanisms of resistance, usually presented by *P. aeruginosa*, can contribute to the knowledge of antimicrobial interaction and bacterial target. The present study evaluated and quantified structural changes and differential gene expression in a multidrug-resistant clinical isolate and a susceptible standard strain of *P. aeruginosa*, after exposure to subinhibitory concentration of meropenem. Scanning (SEM) and Transmission Electron Microscopy (TEM) were used to structural changes evaluation. The differential gene expression was obtained by Representational Difference Analysis technique (RDA), and quantified by Real-Time PCR (qPCR). Additionally, *amp*C, *mex*A, *opr*D resistance genes and *lex*A gene were included. Structural changes observed by TEM showed rounded bacilli and disruption of cell wall due to exposure to meropenem. The cell rounding was also observed in SEM, as well as central bulge cells. The resistant bacterial strain (1071-MRPA) showed higher percentage of morphological change, especially an internal accumulation of cell wall, which may suggest an attempt to bacterial adaptation to the antimicrobial action. Differential gene expression was found after 1h exposure to 0,5 X MIC respective concentration to meropenem in a resistant clinical isolate as the standard strain ATCC 27853. Gene products related to the maintenance of cell morphology and wall, as well as a gene related to glutamate-aspartate transporter system were differentially expressed in both samples but quantitatively overexpressed in resistant clinical isolate. Resistance genes *amp*C showed also overexpression in 1071-MRPA. Significant difference between the samples was not observed in quantifying the expression of efflux pumps of the MexA type. Exposure to meropenem also indicated the bacterial SOS response mechanisms were less activated in multidrug-resistant clinical isolate. These findings suggest that *P. aeruginosa* clinical isolates may be resistant to meropenem for more efficiently activate genes responsible for maintaining the cell wall, morphology, and inherent antimicrobial resistance.

Keywords: *Pseudomonas aeruginosa*, structural changes, gene expression, meropenem