

Título: UPREGULATION OF GENES ASSOCIATED WITH EFFLUX PUMPS AND CELL DIVISION PROTEINS IN ANTIMICROBIAL REFRACTORY CELLS OF *STREPTOCOCCUS PYOGENES*

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Resumo:

Streptococcus pyogenes is re-emerging as a pathogen associated with increasing incidence of invasive diseases and post-infectious sequelae. Despite the fact that these bacteria remain universally susceptible to penicillin, cases of therapeutic failure have been reported. Previously, we observed that high cell density population (HCDP) displays an antimicrobial drug refractory behavior, which was paralleled by an overexpression of efflux activity. In addition, proteomic assays of HCDP showed increased number of proteins associated with transport and multidrug efflux pumps in comparison with low cell density population (LCDP). Thus, in this study, to better comprehend the phenomenon, real time qRT-PCR was carried out to evaluate the expression of some genes associated with transport and efflux pump proteins (*acrA*, *mdr*, *proP*, *mefE*, *cycD*, *norM*, *norA*, *tptB*). In fact, from this screening we found a gene (*tptB*), belonging to the RND family of efflux pump, whose expression was significantly increased (> 4-fold) in HCDP, and in HCDP treated with clindamycin or penicillin. To evaluate if persistence mechanisms would be involved in the drug--refractory bacteria induced by HCDP, we analyzed the expression of *ftsA* (associated with cell division) and *guaA* (associated with acid nucleic metabolism). Our results showed a significant reduction (more than 2-fold) for both genes, indicating impairment in cell division in these refractory bacteria; similarly to what is observed for persisters. Concluding, from these data, one might envisage that this mechanism of persistence induced by HCDP might occur in vivo in infections with high bacterial load. More attention should be given to the role of intrinsic multi-drug efflux pumps on clinical drug resistance, focusing on the mechanisms and development of novel therapeutic countermeasures against drug-refractory infections.

Palavras-chave: Efflux pumps, resistance, *Streptococcus pyogenes*

Agências de fomento: CNPq, FAPERJ, PRONEX