رقم البحث: (٨)

عنوان البحث باللغة الانجليزية:

Penicillin-Binding Protein 5/6 Acting as a Decoy Target in *Pseudomonas aeruginosa* Identified by Whole-Cell Receptor Binding and Quantitative Systems Pharmacology

إسم المجلة – سنة النشر:

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الملخص باللغة الإنجليزية:

ABSTRACT

The β-lactam antibiotics have been successfully used for decades to combat susceptible *Pseudomonas aeruginosa*, which has a notoriously difficult to penetrate outer membrane (OM). However, there is a dearth of data on target site penetration and covalent binding of penicillin-binding proteins (PBP) for β-lactams and β-lactamase inhibitors in intact bacteria. We aimed to determine the time course of PBP binding in intact and lysed cells and estimate the target site penetration and PBP access for 15 compounds in *P. aeruginosa* PAO1. All β-lactams (at 2 × MIC) considerably bound PBPs 1 to 4 in lysed bacteria. However, PBP binding in intact bacteria was substantially attenuated for slow but not for rapid penetrating β-lactams. Imipenem yielded 1.5 ± 0.11 $\log_{10}$ killing at 1h compared to <0.5 $\log_{10}$ killing for all other drugs. Relative to imipenem, the rate of net influx and PBP access was ~ 2-fold slower for doripenem and meropenem, 7.6-fold for avibactam, 14-fold for ceftazidime, 45-fold for cefepime, 50-fold for sulbactam, 72-fold for ertapenem, ~ 249-fold for piperacillin and aztreonam, 358-fold for tazobactam, ~547-fold for carbenicillin and ticarcillin, and 1,019-fold for cefoxitin. At 2 × MIC, the extent of PBP5/6 binding was highly correlated (r^2 = 0.96) with the rate of net influx and PBP access, suggesting that PBP5/6 acted as a decoy target that should be avoided by slowly penetrating, future β-lactams. This first comprehensive assessment of the time course of PBP binding in intact and lysed *P. aeruginosa* explained why only imipenem killed rapidly. The developed novel covalent binding assay in intact bacteria accounts for all expressed resistance mechanisms.