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Impact of the L421P mutation in the ponA gene, encoding Penicillin-Binding Protein 1, on fitness and antibiotic resistance in Neisseria gonorrhoeae

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Author(s)

Gabriella L. Gentile, n/a

Graduate Research Assistant

University of North Carolina - Chapel hill

Background

Chromosomally mediated resistance to beta-lactam antibiotics in Neisseria gonorrhoeae is driven primarily by 4 mutated alleles: penA, mtrR, penB, and ponA1. The roles of penA, mtrR, and penB in facilitating resistance to beta-lactams are more clearly defined than that of ponA1. ponA1 introduces an L421P mutation into Penicillin-Binding Protein 1 (PBP1), a bifunctional transglycosylase (TGase)/transpeptidase (TPase) enzyme involved in peptidoglycan synthesis. The L421P variant, which is present in a large majority of penicillin-resistant strains, has a 3-fold lower acylation rate for penicillin G (PenG). Surprisingly, while reversion of ponA1 back to wild-type in penicillin-resistant isolates decreased the MIC of PenG twofold, replacement of the wild-type ponA allele with ponA1 in a third-step transformant did not increase the MIC of PenG. Thus, despite the high prevalence of ponA1 in penicillin-resistant isolates, the role of ponA1 in facilitating resistance to beta-lactam antibiotics is unclear.

Aim/Methods

To assess to role of ponA1 in antibiotic resistance in N. gonorrhoeae, we investigated the biochemical and phenotypic effects on the gonococcal cell incurred through acquisition of the L421P mutation.

Results

Phylogenetic analysis of sequenced N. gonorrhoeae isolates revealed that, in addition to penicillin-resistant strains, ponA1 is also present in a large majority of ceftriaxone-resistant strains harboring a mosaic penA allele, which encodes highly mutated variants of PBP2, but rarely in antibiotic-susceptible strains. The L421P mutation, unlike resistance-conferring mutations in PBP2, is located far from the active site on the hinge region between the OB domain and the penicillin-binding domain, and introduction of a proline could alter interactions between the TPase domain and the other domains of PBP1. Transformation studies with active-site mutants in either the TGase or TPase domains indicate that these mutants are not viable, indicating both activities are essential for cell viability.

Conclusions

These data suggest that ponA1 is involved in beta-lactam resistance in some capacity, but the extent and nature of the role ponA1 plays in resistance is not completely understood. The essentiality of both the TGase and TPase domains and lack of PBP1-specific beta-lactam antibiotics suggest that PBP1 could be a heretofore untapped target for drug development.