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Cell division principles and mechanisms of ceftriaxone resistance in Neisseria gonorrhoeae

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Background

The Gram-negative diplococcus Neisseria gonorrhoeae is an urgent public health threat, as extensive and increasing antibiotic resistance has resulted in only one remaining drug, the 3rd generation cephalosporin ceftriaxone, recommended for treatment of N. gonorrhoeae infections. Ceftriaxone resistance (CROR) is primarily mediated by target-site variants in penA, which codes for Penicillin-Binding Protein 2 (PBP2), a peptidoglycan transpeptidase that functions during cell division. With the emergence and international spread of CROR strains, it is critical to understand the mechanisms of resistance and how N. gonorrhoeae mitigates the fitness costs incurred by resistance mutations, which in turn requires detailed characterization of cell division.

Aim/Methods

In this study, we probed the mechanisms of N. gonorrhoeae division and used high-resolution time-lapse microscopy to determine the impact of CROR on cellular morphology and of a mutation in the TCA cycle enzyme, aconitase hydratase (acnB) that compensates for resistance-promoted fitness costs.

Results

Live cell imaging revealed that successive division planes were oriented perpendicularly and were overlapped in timing, such that assembly of a second division plane began before the first resolved. CROR mutants harboring resistance-conferring penA alleles were less fit compared to susceptible counterparts in in vitro competition experiments and showed abnormalities in cell size, septal peptidoglycan thickness, and interdivision time. The introduction of a compensatory mutation in the acnB gene (acnBG348D), previously

identified as a compensatory mutation alleviating the fitness costs incurred by the penA41 allele in a mouse model of gonorrhea, restored single cell growth metrics, including cell size and interdivision time as compared to strains with the resistance-conferring penA alleles alone.

Conclusions

This work helps create a framework for detailing the molecular and cellular consequences of ceftriaxone resistance and how N. gonorrhoeae maintains fitness in the face of antibiotic pressure through acquisition of both resistance and compensatory mutations.