(1) Submission ID#1521255

Transcriptome-guided metabolic network analysis reveals rearrangements of carbon flux distribution in Neisseria gonorrhoeae during neutrophil co-culture

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Background

Metabolic adaptation to the host is a potent driver of bacterial pathogenesis, enabling both colonization and invasive disease, particularly for Neisseria species which do not encode a large repertoire of virulence factors or toxins. Infection with Neisseria gonorrhoeae (Gc), the causative agent of gonorrhea, is characterized by the rapid influx of neutrophils (PMNs) that not only fail to clear the infection, but are also thought to exacerbate disease through the induction of excessive inflammation. The inability of the human host to clear Gc infection is particularly concerning in light of the emergence of superbug strains, resistant to all clinically recommended antibiotics. Bacterial metabolism therefore represents a promising target for the development of new therapeutics.

Aim/Methods

To investigate metabolic drivers of Gc pathogenesis, we undertook an interdisciplinary investigation integrating transcriptomics, systems biology approaches, and classical molecular microbiology. We generated a curated genome-scale metabolic network reconstruction of Neisseria gonorrhoeae, which links genetic information to metabolic fluxes, and predicts Gc growth yield and energy consumption. We validated this model against published transposon library and metabolomics datasets. We then contextualized this model by integrating transcriptomics data of Gc exposed to PMNs.

Results

This work revealed substantial rearrangements of Gc central metabolism and the induction of Gc nutrient acquisition strategies in response to PMNs. This work further revealed that PMNs, which do not clear Gc,

become a source of nutrition for Gc during infection. Mechanistically, we found that PMNs supply lactate and pyruvate to Gc which relieves the Gc requirement for pyruvate kinase for glycolysis during co-culture.

Conclusions

The metabolic interplay between Gc and PMNs is thus a major driver of Gc-PMN interactions. Together, our work reveals new mechanisms by which Gc persists in the presence of PMNs and uncover the unique aspects of metabolism in this fastidious bacterium. These metabolic Achilles' heels could be targeted to block infection and reduce the burden of gonorrhea in the human population.