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Ribosomal protein paralogs and zinc homeostasis in Neisseria gonorrhoeae

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Background

Treatment of Neisseria gonorrhoeae (Gc) is complicated by evolving antibiotic resistance and the lack of a protective vaccine. One potential target for future therapeutics is Gc subversion of human nutritional immunity. Availability of free essential metals, such as zinc, varies in the human host, and Gc has evolved exquisite mechanisms to acquire metals via interactions with human zinc sequestration proteins. However, it is unknown how Gc maintains internal zinc homeostasis when zinc availability varies. In other bacteria, non-zinc-binding ribosomal proteins replace their zinc binding paralogs on the ribosome in low zinc conditions; the zinc-binding paralogs are degraded and intracellular zinc increases. Gc encodes two sets of paralogous ribosomal proteins that may participate in this process, rpmE/E2 and rpmJ/J2. RpmE and RpmJ have a CxxC motif and are predicted to bind zinc; RpmE2 and RpmJ2 do not and are predicted to be zinc-independent.

Aim/Methods

The aim of this work is to characterize regulation of paralogous ribosomal proteins RpmE/E2 and RpmJ/J2 in Gc. We hypothesized that in Gc, like other bacteria, RpmE2 and RpmJ2 are induced in zinc-limited conditions and RpmE and RpmJ are displaced and degraded, increasing available intracellular zinc to resist starvation. We investigated the regulation of rpmE/E2 and rpmJ/J2 at the transcript level and corresponding RpmE2 protein production via RT-qPCR and western blot in zinc-limited and zinc-replete conditions. We also used co-transcription to detect the rpmE2rpmJ2 operon.

Results

We found that expression of rpmE2 and rpmJ2 is induced in zinc-limited conditions; this derepression is mediated by the transcription factor Zur, which represses transcription of zinc uptake genes in the presence of excess zinc. We also found that rpmE2 and rpmJ2 are expressed as a co-transcript, and RpmE2 production is induced under zinc-limited conditions and repressed in rich media.

Conclusions

Our work demonstrates that non-zinc-binding ribosomal proteins are induced in response to zinc limitation in

Gc, indicating a role for ribosomal protein turnover in this physiologically relevant environment. Future directions of this work will explore the role of zinc-dependent ribosomal protein turnover in maintaining intracellular zinc availability and enabling Gc persistence in zinc-limited environments.