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A zinc regulated metalloprotein Ngo1049 contributes to metal homeostasis in Neisseria gonorrhoeae

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Background

Neisseria gonorrhoeae (Ngo) is a human-specific bacterial pathogen that colonizes mucosal surfaces and activates an innate immune response characterized by the robust recruitment of neutrophils to the site of infection. Neutrophils deploy metal sequestering proteins to restrict the availability of essential metals from microbes in an active process termed nutritional immunity. Ngo subverts host metal restriction mechanisms by producing outer membrane transporters to pirate metals from human metal-sequestering proteins such as iron from lactoferrin and transferrin, and zinc from calprotectin and psoriasin. However, the repertoire of Ngo gene products that maintain metal homeostasis in distinct niches within the host have not been fully identified.

Aim/Methods

A gene product of interest encoded by ngo1049 is conserved and functionally uncharacterized. ngo1049 is expressed in Ngo grown under zinc-limiting conditions, including during infection of human ectocervical cells

and neutrophils, indicating a potential role for Ngo1049 in Ngo pathogenesis. To characterize the function of Ngo1049, we are evaluating the subcellular localization and regulation of Ngo1049, the role of Ngo1049 in zinc acquisition in metal-limiting conditions, and the contribution of Ngo1049 to the survival of Ngo in physiologically relevant human epithelial cell and primary immune cell infection models.

Results

Subcellular fractionation and immunofluorescence imaging experiments revealed that Ngo1049 localizes to the periplasm. Expression of ngo1049 transcripts and production of Ngo1049 protein were regulated in a zinc dependent manner by the zinc uptake repressor Zur. Inactivation of Ngo1049 resulted in decreased growth of Ngo in zinc-limiting media. Preliminary structural analysis of Ngo1049 revealed Ngo1049 is a homodimer with one metal binding site per monomer, consisting of residues H29, H31, and H142. Mutation of these residues in Ngo1049 significantly reduced the growth of Ngo compared with bacteria making the WT protein, suggesting the zinc-binding capacity of Ngo1049 is vital for its function.

Conclusions

Ongoing experiments are testing the potential for Ngo1049 to serve as a periplasmic metallochaperone under extreme zinc limitation. Understanding how Ngo responds to host-mediated zinc limitation using Ngo1049 can point to new therapies that interfere with bacterial zinc acquisition as treatments for this drug-resistant bacterium, thereby helping to combat this major public health concern.