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Characterizing the Role of CpsA in Mycobacterial Pathogenesis

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Mycobacterium tuberculosis

What is M. tuberculosis?
- Causative agent of tuberculosis
- Infects 1/3 of the world’s population
- 1.5 million deaths worldwide in 2014
- M. tuberculosis survives in macrophages by arresting phagosome maturation and altering cellular trafficking.

What is CpsA?
- Virulence factor secreted by M. tuberculosis
- Member of the LytR-CpsA-Psr (LCP) family of proteins
- M. tuberculosis uses CpsA to alter cellular trafficking and disrupt host immunity mechanisms (see Dr. Sandeep Upadhyay Poster).

CpsA promotes virulence in M. tuberculosis

ΔcpsA M. tuberculosis grows poorly in human and murine macrophages.
- It is also required for virulence in mice (data not shown).

ΔcpsA M. tuberculosis does not grow in vitro compared to wild type.

CpsA binds to Ndp52

What is Ndp52?
- Adaptor protein that acts as an autophagy receptor for ubiquitin-coated pathogens
- CpsA was shown to interact with full-length Ndp52 using a yeast two hybrid assay.
- We hypothesize that the interaction with Ndp52 is important for the ability of CpsA to promote virulence.

Research Question

Is CpsA sufficient to promote enhanced virulence in M. smegmatis, a non-pathogenic relative of M. tuberculosis?

Methods
- Electroporate shuttle plasmids expressing cpsA and vector alone into M. smegmatis competent cells
- 0.1% Triton X-100
- CFU plating

Results
- 24 hpi
- CpsA Confirmed by Western Blot
- ΔcpsA, ΔkatG
- 72 hpi
- CpsA Confirmed by Western Blot
- ΔcpsA, ΔkatG

Conclusions
- When introduced into M. smegmatis, M. tuberculosis CpsA confers enhanced intracellular survival to M. smegmatis, such that 5-fold more bacteria are found 72 hours after infection.
- This data demonstrates that CpsA is an important virulence factor in M. tuberculosis.

References
- Center for Disease Control and Prevention, TB Data and Statistics, Sept. 2015.

Future Steps
- Determine if the LytR domain is sufficient for CpsA binding to Ndp52.
- Determine if the LytR domain is important for virulence in M. tuberculosis, using CpsA deletion constructs.
- Investigate the mechanism by which CpsA confers enhanced intracellular survival to M. smegmatis.

Future Steps

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