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Characterizing the Role of CpsA in Mycobacterial Pathogenesis

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Characterizing the Role of CpsA in Mycobacterial Pathogenesis

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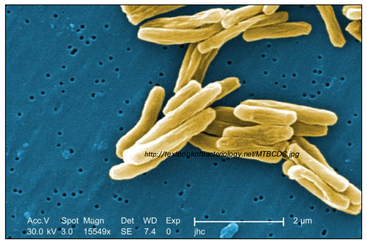
Introduction

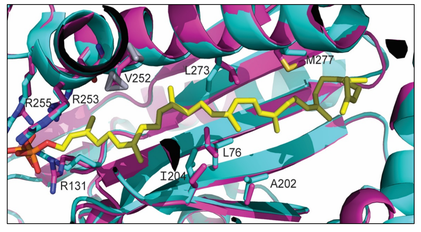
Mycobacterium tuberculosis



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.

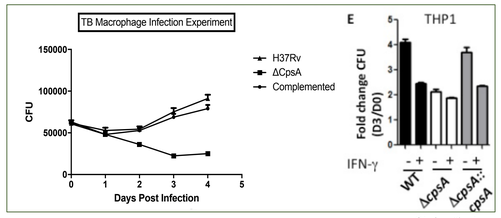
CpsA



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*



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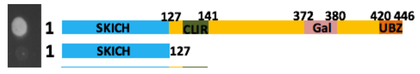
- Δ*cpsA M. tuberculosis* grows poorly in human and murine macrophages.
- It is also required for virulence in mice (data not shown).

CpsA binds to Ndp52



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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.

Project Goals

Goal 1

- Determine whether *M. tuberculosis* CpsA is sufficient to promote enhanced virulence in *Mycobacterium smegmatis*.

Goal 2

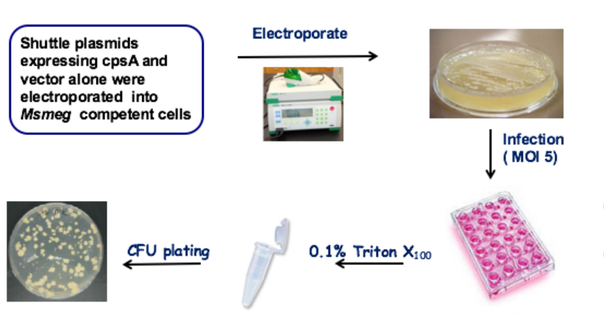
- Define which regions of the CpsA protein are required for interacting with host protein Ndp52.

Goal 1

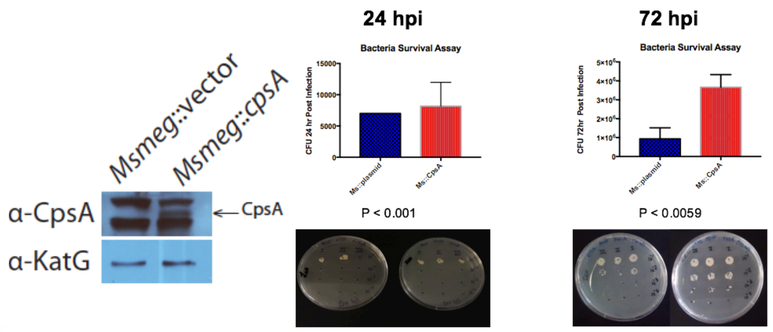
Research Question

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

Methods



Results



Conclusions

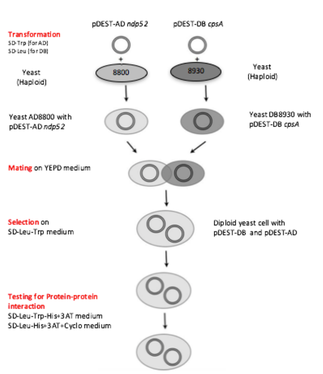
- When introduced into *M. smegmatis*, *M. tuberculosis* CpsA confers enhanced intracellular survival to *M. smegmatis*, such that 5-fold more bacteria are found 72 hours after infection.
- This data demonstrates that CpsA is an important virulence factor in *M. tuberculosis*.

Goal 2

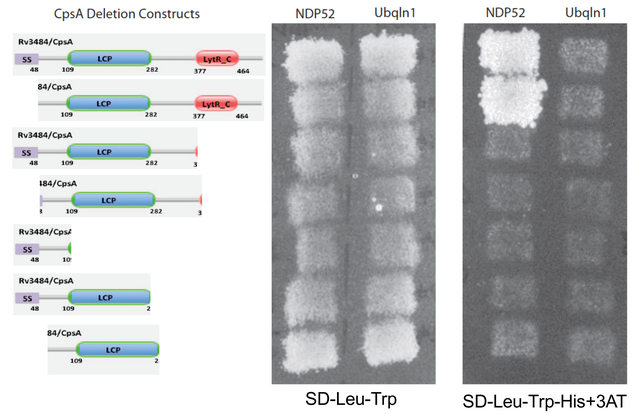
Research Question

Which regions of the CpsA protein are required for interaction with host protein Ndp52?

Methods



Results



Conclusions

The LytR domain of *cpsA* is required for CpsA binding to host protein Ndp52.

References

- Center for Disease Control and Prevention, TB Data and Statistics, Sept. 2015.
- Wang Q, Zhu L, Jones V, et al. CpsA, a LytR-CpsA-Psr Family Protein in Mycobacterium marinum, Is Required for Cell Wall Integrity and Virulence. Ehrt S, ed. *Infection and Immunity*. 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*.

Acknowledgements

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