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Driving innovation from discovery to access

A *Mycobacterium tuberculosis* variable antigen vaccine induces infection tolerance

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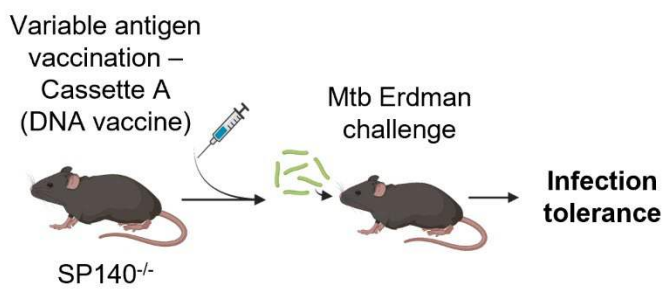
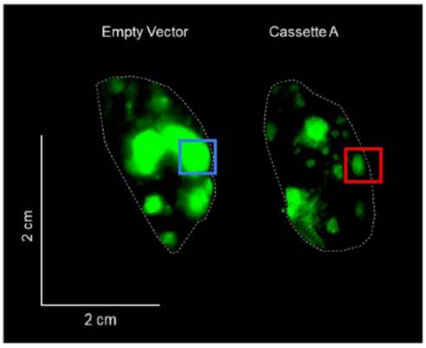
More than 95% of the immunodominant T cell antigens of Mycobacterium tuberculosis (Mtb) are hyperconserved. Lack of antigenic variation suggests insufficient selection pressure from T cell responses to infection. We identified 6 variable-sequence Mtb proteins representing hypothetical antigens that vary due to selective pressure from protective CD4 T cell responses. To investigate the impact of CD4 T cell responses to these variable-sequence antigens, we vaccinated hypersusceptible SP140-/- mice using a DNA vaccine encoding a fusion protein of four variable-sequence antigens (Rv0010c, RimJ, Rv2719c, and Rv0990c). We then assayed bacterial burdens, immune cell populations by flow cytometry, and immunopathology by immunofluorescence microscopy and Sytox Green injection. Vaccination with variable-sequence antigens did not reduce bacterial burdens but caused markedly reduced immunopathology in SP140-/- mice. Vaccination reduced lung necrosis, measured as a reduction in total Sytox Green fluorescence in whole lungs. Vaccination of SP140-/- mice with a DNA vaccine encoding for RimJ alone demonstrated a similar phenotype to vaccination with the fusion construct, which indicates that responses to RimJ are sufficient for the altered immunopathology phenotype. In other fields of biology, reduction in pathology without reduction in pathogen burden is termed infection tolerance, which describes the effect of our vaccine. Vaccination induced increases in RORγt+ CD4 T cells, but further investigation is needed to determine the primary mechanism by which RimJ-specific vaccine responses induce infection tolerance. Most preclinical studies evaluate candidate vaccines for their ability to reduce bacterial burden, while our results demonstrate a distinct phenotype and endpoint for identifying promising candidate vaccines, since reduction of tissue damage can reduce TB morbidity and potentially reduce TB transmission.

Funding Sources
F31AI172360

Conflicts of Interest
None


Variable antigen vaccination – Cassette A (DNA vaccine)
Mtb Erdman challenge
Infection tolerance
SP140-/-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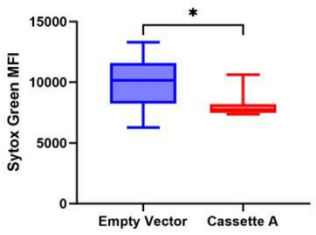
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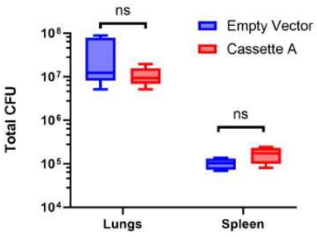
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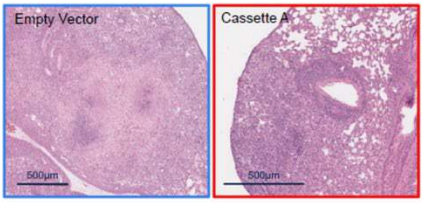
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