

Systems biology of rBCG-LTAK63 immunization highlights correlation between circadian rhythm, immune response, and protection against tuberculosis

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Introduction: Tuberculosis (TB) causes 1.5 million fatalities with 10 million new cases each year worldwide. The BCG vaccine, currently the only vaccine available, shows variable effectiveness in preventing adult pulmonary tuberculosis. Immunization with rBCG-LTAK63 (recombinant BCG expressing a detoxified form of the E. coli Heat Labile Toxin - LTAK63) induced strong Th1/Th17 immune responses, increased numbers of memory T cells, and improved protection for up to 180 days, as compared to BCG.

Objective: Perform an extensive systems biology analysis of the effects of immunization with rBCG-LTAK63 at different time intervals before and after the Mtb challenge, aiming to identify genes and pathways associated with protection. Methods: Lungs of immunized BALB/c mice were collected at 7- and 90-days post-immunization (dpi), 7- and 30-days post-challenge (dpc). Transcriptome was evaluated by RNA-seq followed by Ingenuity Pathways and CEMiTool for co-expression analysis. The immune response was analyzed by flow cytometry and CBA. The protection was evaluated by lung bacillary load quantification and H&E histopathology analysis, after the Mtb H37Rv challenge.

Results: We show that rBCG-LTAK63 boosts Th1/Th17 immune responses and improves protection as compared to BCG (30 dpc). Immediately after the challenge (7 dpc), rBCG-LTAK63 reduces bacterial burden and inflammation. Genes and pathways associated with circadian rhythm were induced in all timepoints, decreasing at 30 dpc. Expression of these genes show strong negative correlation with protective and inflammatory immune responses.

Conclusion: This study suggests that rBCG-LTAK63 immunization can orchestrate an association between circadian rhythm, inflammatory response, and tuberculosis protection. The data may explain how rBCG-LTAK63 can regulate the immune responses and improve its protection.

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A1: Mechanisms of biomarkers and protection

Conflicts of Interest

LL has a patent application on the use of rBCG-LTAK63 as a vaccine against Mtb. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

