NTM MUCOSAL-INDUCED IMMUNE RESPONSE ENHANCES THE PROTECTIVE EFFECT OF BCG AGAINST MYCOBACTERIUM TUBERCULOSIS INFECTION

Dr. Marcela Henao-Tamayo, Associate Professor, Department of Microbiology, Immunology, and Pathology. Co-Director Mycobacteria Research Laboratories.
BCG vaccine

Protection variability

Why?

Genetic divergence of BCG strains used for vaccination

Host-related factors, such as nutritional status, other infections, and genetic diversity

Exposure to environmental Non-tuberculous Mycobacteria (NTM)
In our study we used *Mycobacterium avium* subsp. *avium* (TMC 724) from ATCC.

Experimental plan

- Saline or BCG
- No NTM
- NTM 100 CFUs/ml
- NTM 10^5 CFUs/ml

C3H/HeOuJ

Day-1
LDA Mtb HN878
Day 30 Post Infection
Day 60 Post Infection
Day 120 Post Infection

90 days
Mtb aerosol infection
Live NTM water feeding
End
Day -1 → NTM exposed mice have increased numbers of B cells and CD4 T cells in Peyer’s patches.
Day -1 → NTM exposed mice have increased numbers of B cells in the lungs
Day -1 → Increased BALF and Serum anti-Mtb antibodies
Mycobacterial burden in the lungs decreased significantly in mice vaccinated with BCG exposed to NTMs in the drinking water.
Increased B and NK cells numbers in the lungs of mice vaccinated with BCG exposed to NTMs

Increased B and NK cells numbers correlated with lower CFUs in the lungs.

- **Correlation between Total B cells and lung CFUs**
  - Total number of cells vs. CFUs
  - Correlation coefficient: $R = -0.56$, $p = 0.0017$

- **Correlation between perforin/granzyme releasing Natural Killer cells and lung CFUs**
  - Total number of cells vs. CFUs
  - Correlation coefficient: $R = -0.47$, $p = 0.015$
Day 120 - Presence of lymphoid-like follicles in the lungs of mice vaccinated with BCG exposed to NTMs

Spatial transcriptomics

Area of follicular structure had
- Higher number of B-cells
- Higher transcriptional signatures of:
  - Immunoglobulin heavy chain alpha (Igha)
  - B-cell lymphoma-6 (Bcl-6)
  - Lymphotoxin-alpha (Lta)
  - Lymphotoxin beta (Ltb)
  - Stromal cells
  - Upregulated genes involved in B-cell activation/GC pathway (not shown)

Indicative of the presence of ectopic Germinal Centers

Dr. Taru Dutt
Increased IgA and IgG antibodies against Mtb whole cell lysate in BALF of NTM exposed mice (at 120 days post Mtb infection)
Summary: NTM provide additional protection than BCG by B cell and antibody mediated mechanism

NTM exposure elicits B cells in PPs

Mice infected with Mtb via aerosol

NTM-activated B cells travel to lungs (site of infection)

B cells will be activated by T-cell dependent mechanism

1. B-cell receptor signaling
2. CD40-40L interaction along with co-stimulatory signals
3. T-cell secrete cytokines to initiate B-cell activation