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Driving innovation from discovery to access

Characterising lung mucosal and systematic immune response in an aerosol BCG human challenge model using single cell sequencing

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Background: The development of tuberculosis (TB) vaccines is hampered by a limited understanding of the human host-pathogen interactions, the uncertain predictive value of animal models, and the absence of validated immune correlates of protection. The aerosol BCG human challenge model enables the investigation of immune responses to mycobacterial infection at defined timepoints.

Methods: Healthy, BCG-naive UK adults received a 1x107 CFU BCG Danish 1331 or saline aerosol infectious challenge. Bronchoalveolar lavage (BAL) samples were collected from volunteers in five groups on Days 2, 7, 14, 28, and 56, respectively. Peripheral blood mononuclear cells (PBMC) were collected at various times from the same volunteers. Samples underwent single-cell RNA sequencing. T-cell receptor (TCR) repertoires were profiled in PBMCs. The trial was registered at ClinicalTrials.gov, NCT04777721.

Results:

- The activation of monocytes in PBMC post aerosol BCG challenge was more transient compared to macrophage activation in BAL.
- T cell diversity in BAL decreased after aerosol BCG challenge, accompanied by activation of BCG-specific T cells.
- Pre-existing BCG-specific T cells were more likely to be activated CD4+ T cells and enriched in BAL compared to BCG-specific T cells detected exclusively post BCG challenge.
- BCG-specific activated CD4+ T cells in PBMC were more likely to enrich in BAL compared with BCG-specific regulatory CD4+ T cells.

Conclusions: The aerosol BCG challenge rapidly triggered lung mucosal immune responses, marked by an early surge of T-cells and activation of myeloid cells. This is followed by activation of BCG-specific T-cells. The immune response in monocytes was more transient compared to macrophages in BAL. BCG-specific T-cells that existed before the challenge showed different transcription profiles and were more likely to enrich in BAL compared to those appearing after the challenge.

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Conflicts of Interest
None