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A human infection/antigenic challenge model using pulmonary delivery of live BCG and PPD to gain insights into TB immunopathogenesis

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Background: Controlled human infection models (CHIMs) have facilitated vaccine development for several diseases but safety issues have precluded its use in TB. We have previously established the safety and feasibility of a mycobacterial CHIM, using pulmonary administration of BCG and PPD, in a high burden setting. We have now leveraged this model to investigate TB immunopathogenesis at the site of disease.

Methods: BCG (10^4 CFU) and PPD (0.5 TU) was bronchoscopically administered to healthy participants (n=74) with different TB susceptibility profiles ("protective": close contacts of TB index cases who did not develop TB; "susceptible": persons ≥1 previous TB episode). Bronchoalveolar lavage (BAL) and blood were collected pre- and 3-days post-administration. Flow cytometry-based cellular immunophenotyping, RNAseq-based transcriptomic analysis and LC-MS-based proteomic profiling were performed.

Results and Discussion: Lung-administered BCG induced innate (neutrophil, NK, complement) and adaptive (Th1, Th7, γδ, B-cell, Ig) immune pathways. Several mechanisms linked to TB susceptibility (Type I IFN, MMPs, VEGF and TGFβ) were upregulated in the susceptible group whereas neuroimmune pathways were upregulated in the protective group. Similar but more robust immune responses to PPD were observed, likely due to differences in antigen (protein vs. whole bacteria). Lung-specific upregulated pathways to BCG (γδ-, B- and NK cell-mediated pathways, MHC I & II presentation) were concomitantly reduced in blood indicating inter-compartment migration of specific cell populations.

Conclusion: These data indicate a complex host-pathogen interaction involving multiple immune pathways, with distinct differences in immune responses between groups with differing TB susceptibility profiles. This a model can provide a better understanding of host-pathogen interactions at the site of disease and identify immune correlates of protection to evaluate vaccine candidates

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Conflicts of Interest
None

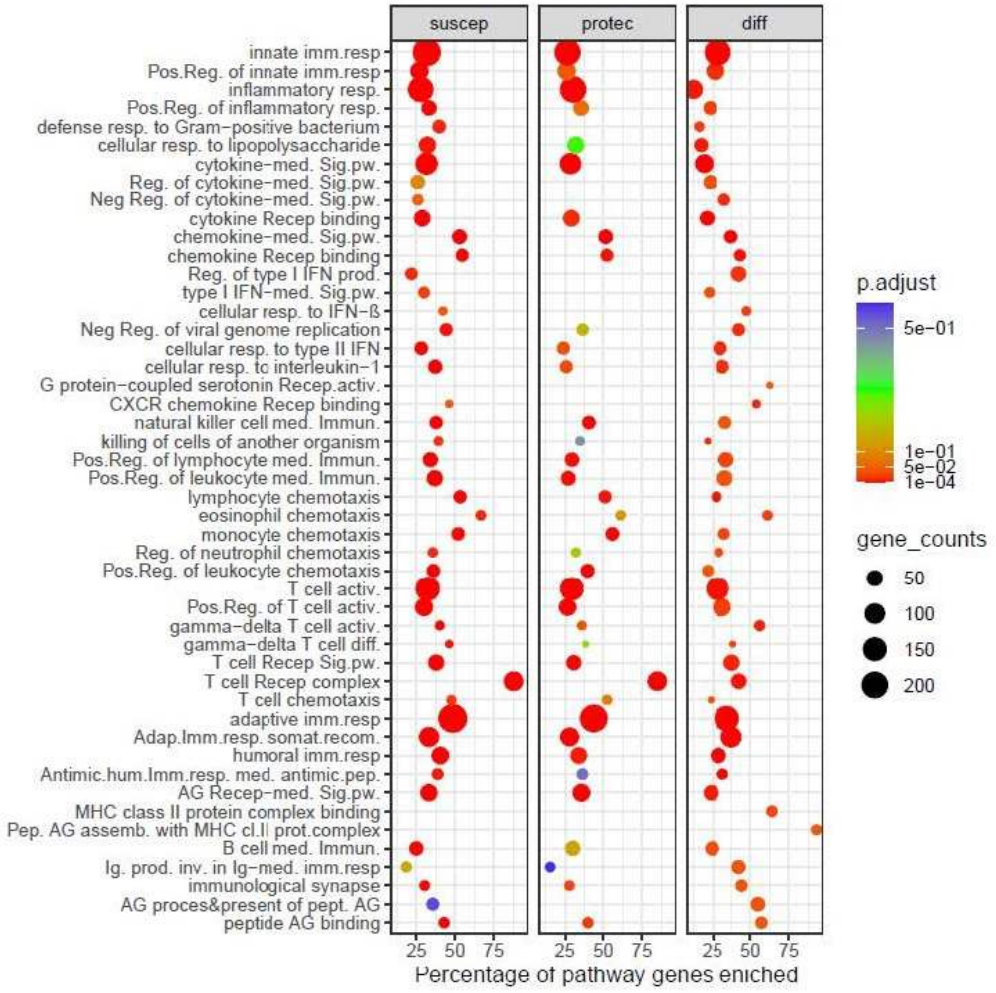

Figure: Transcriptomic analysis of bronchoalveolar lavage (BAL) cells in the different susceptibility groups following pulmonary BCG administration. A gene set enrichment analysis showing specific immune pathways that are up/downregulated in the protective and susceptible groups and the difference between the two groups (susceptible vs protective). Responses are normalised to the pre-challenge BAL