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M. bovis BCG vaccination induces mycobacteria-specific immune responses but lacks protection from infection of human alveolar macrophages from tuberculosis

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Background: To eliminate tuberculosis (TB) by 2035, a new vaccine is urgently needed to effectively prevent infection and disease in *M. tuberculosis* exposed individuals. *M. bovis* BCG- vaccination, one of the most commonly used vaccines worldwide, reduces TB morbidity and mortality but does not have a substantial influence on TB incidence. A key obstacle for the identification and development of novel TB vaccines, is the lack of surrogate markers for immune protection against *M. tuberculosis*.

We investigated growth rates of *M. tuberculosis* in the Mycobacterial Growth Inhibition Assay (MGIA) as a potential biomarker for antimycobacterial control of human alveolar macrophages before and after BCG-vaccination.

Material/methods: Seventeen healthy BCG-vaccine naive subjects underwent blood sampling and bronchoscopy before and 59 days after *M. bovis* BCG-vaccination. At both time-points bronchoalveolar lavage cells (BALC) and peripheral blood mononuclear cells (PBMC) were *ex vivo* infected with *M. tuberculosis* (H37Rv) and cultured for 96 hours. Mycobacterial growth rate was detected as time to culture positivity (TTP) in Mycobacterium Growth Indicator Tube (MGIT) and also counted as Colony Forming Units (CFU) on solid culture (Middlebrook agar plates). The MGIA was performed with and without the *in-vitro* supplementation of Vitamin D. BALC and PBMC were characterized by flow cytometry for CD3, CD4, CD8, Granulysin, Granzym B and Perforin expression. Vaccine-induced immune response of peripheral blood T-cells was evaluated by ELISPOT-Interferon-γ-release assay (IGRA).

Results: TTP in the MGIA was significantly longer in PBMC in comparison to BALC ($p<0.0001$). Phenotypical characterization of BALC and PBMC revealed significant differences between expression of Granzym B (higher in BALC; $p=0.016$) and Perforin (higher in PBMC; $p<0.001$).

BCG vaccination induced a positive PPD-response in 10/17 of the vaccinated candidates (59%). Intra-individual evaluation of the MGIA growth rates before and after BCG-vaccination revealed no significant difference in TTP before and after vaccine application in BALC ($p=0.604$) and PBMC ($p=0.199$). The magnitude of PPD response induced by BCG-vaccination did not correlate with growth control in BALC and PBMC. The *in-vitro* supplementation of Vitamin D to the MGIA significantly improved growth control with an increase of the TTP of 17.2 hours ($p<0.001$) in BALC and 20.6 hours ($p<0.001$) PBMC.

Conclusions: The MGIA with BALCs is a novel promising method to ascertain correlates of growth control after *M. tuberculosis* infection in humans. As *M. bovis* BCG vaccination does not lead to functional immune control against *M. tuberculosis* by BALCs, despite the development of mycobacteria-specific IGRA-responses, the development of novel vaccines against TB remain a research priority.