7. Summary

Despite its poor efficacy, Bacillus Calmette-Guérin (BCG) has been used as a tuberculosis (TB) vaccine since its inception in 1921. BCG induces robust T helper 1 (Th1) immune responses, but this is not sufficient for host resistance against Mycobacterium tuberculosis (M. tb) infection. Here we show that early secreted antigenic target protein 6 (ESAT-6), expressed by the virulent M. tb strain H37Rv but not by BCG, promotes vaccine-enhancing Th17 cell responses. These activities of ESAT-6 were dependent on TLR-2/MyD88 signalling and involved IL-6 and TGF-β production by dendritic cells. Thus, animals that were previously infected with H37Rv or recombinant BCG containing the RD1 region (BCG::RD1) exhibited improved protection upon re-challenge with virulent H37Rv compared with mice previously infected with BCG or RD1-deficient H37Rv (H37RvΔRD1). However, TLR-2 knockout (TLR-2-/-) animals neither showed Th17 responses nor exhibited improved protection in response to immunization with H37Rv. Furthermore, dendritic cells (DCs) infected with H37Rv or BCG::RD1 failed to upregulate microRNA-146a (miR146a), which controls expression of the Th17-promoting cytokine IL-6, whereas BCG and H37RvΔRD1 upregulated miR146a. Consistent with these findings, ESAT-6 had no effect on miR146a expression in uninfected DCs, but dramatically inhibited its upregulation in BCG-infected or LPS-treated DCs. Collectively, our findings indicate that, in addition to Th1 immunity induced by BCG, RD1/ESAT-6-induced Th17 immune responses are essential for optimal vaccine efficacy.