DENDRITIC CELLS CONTRIBUTE TO REDUCTION IN MICE NEUROINFLAMMATION CAUSED BY BCG INTRACEREBRAL INFECTION

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Background
Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is an approved vaccine against tuberculosis that rarely causes BCG disease. BCG disseminated disease mimics tuberculosis. Central nervous system (CNS) tuberculosis (TB) is a severe form of tuberculosis that results in inflammation of the CNS and constitutes about 5-10% of extra-pulmonary tuberculosis cases. Primarily occurrence of CNS-TB is in children and immune compressed adults and it's associated with high morbidity and more than 50% mortality. CNS-TB is initiated as a secondary infection during haematogenous dissemination of pulmonary infection to the brain parenchyma and meninges. The mechanisms associated with CNS-TB infection and cells targeted for invasion are mostly unknown. The regulatory role of dendritic cells (DCs) in CNS-TB has been neglected due to their absence in homeostatic conditions. This study investigated the role of DCs in neuroinflammation caused by BCG.

Methods
C57BL/6 mice were intracerebrally infected with BCG, then sacrificed and organs harvested for processing. Bacterial burdens of isolated brains, spleens and lungs were determined using homogenates plated on nutrient agar plates. Relative recruitment and phenotype of DCs and T cells from brains and cervical lymph nodes were determined using flow cytometry. Histological analysis of samples was also performed.

Results
Infection was established at the site of the intracerebral infection. Brian bacterial loads were highest at week two then decreased significantly by week 6 post infection and BCG dissemination to the spleen and lungs occurred. There was a significant influx of DCs, especially four weeks after BCG infection. There was recruitment of CD4 and CD8 T cells to the brain following BCG infection associated with Th1 polarization. CNS inflammation was significantly reduced after six weeks and corresponded to bacterial clearance.

Conclusion
This study shows that conventional DCs were preferentially recruited to the brain and that maturation of inflammatory DCs contributed to presentation and activation of T cells. Dendritic cells contributed to directing the T cells towards Th1 polarization, indicative of the protective role of DCs play in the clearance of CNS bacterial inflammation. DCs are also targeted for invasion by tuberculosis and this study suggests the potential of targeting DC maturation stages to produce cells with specific polarizing ability for therapeutic intervention strategies. Overall, CNS inflammation caused by BCG is a highly regulated process that limits potential pathology damage.