Vaccine-Mediated Enhanced Control of Pathogenic SIV infection is Associated With Co-localization of Follicular Anti-viral CD8 T Cells and Tfh cells in the Germinal Centers

Mylvaganam GH, Rios D, Velu V, Amara RR

ABSTRACT:
BACKGROUND: Recent studies have demonstrated lymphoid tissue resident virus-infected T follicular helper cells (Tfh, CXCR5+, PD-1hi) as an important source of virus replication during chronic SIV/HIV infection and harbor significant levels of latent virus under HAART. Thus, therapeutic approaches to achieve a functional cure of HIV/SIV infection must target virus-infected Tfh. CD8 T cells are mostly restricted to T cell zone and it is not clear if anti-viral CD8 T cells can migrate to B cell follicles and play any role in controlling virus in Tfh. Here we studied the fate of Tfh in the rectum and LN during chronic SIV infection in a cohort of unvaccinated and DNA/MVA vaccinated rhesus macaques (RM) and the importance of follicular CD8 T cells at these sites.

METHODOLOGY: Lymphocytes isolated from LN and rectum of SIV-naïve and SIVmac251- infected RM (unvaccinated and DNA/MVA vaccinated) were separated and characterized by multi-color flow cytometry. Sorted cells were used for measuring cell associated viral RNA by qRT-PCR. Cellular localization was determined by immunofluorescence staining. Anti-viral CD8 T cells were characterized using Gag CM9 tetramer staining.

RESULTS: Following a pathogenic SIV infection, despite a global depletion of memory CD4 T cells, Tfh cells increased significantly in animals that failed to control SIV infection (set point >10^4 viral RNA copies/ml of plasma) and supported virus replication. In contrast, vaccine-mediated viral control (plasma viral loads below 10^4 viral RNA copies/ml) was associated with limited Tfh expansion at these lymphoid sites. Interestingly, the vaccinated controllers had a 10-40 fold higher frequencies of functional SIV-specific CD8 T cells with the potential to home to B cell follicles (CD8+ CM9-Tet+ Granzyme B+ CXCR5+) than non-controllers in the LN. Further investigation, using immunofluorescence staining, of both rectal and LN tissues from vaccine controllers revealed co-localization of CD8 T cells with PD-1hi cells in IgD- GC, a phenomena strikingly not observed in the SIV infected non-controlling RM.

CONCLUSIONS: These data reveal a novel mechanism by which infiltration of functional SIV-specific CD8 T cells to GC of lymphoid sites and contribute to lack of aberrant Tfh expansion and enhanced viral control in the vaccinated controllers.