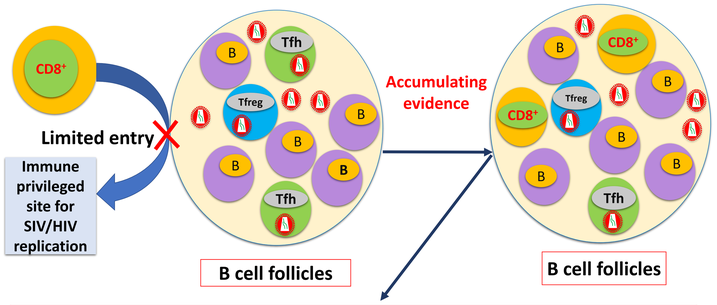
Tfc cells interact with other follicular T cells to control SIV viremia

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Background

In HIV/SIV infection, CD8$^+$ T cells play an important role in control of viral load. Higher concentrations of SIV-producing cells reported to occur in B cell follicles than extrafollicular regions of the secondary lymphoid organs in chronic asymptomatic SIV-infected macaques (Connick, E. et al. *J. Immunol.* 2014). The fact that tetramer-positive CD8$^+$ T cells, although present in extrafollicular areas of lymph nodes of HIV-infected subjects were mostly absent in follicles, provided a rationale for the persistence of HIV/SIV in lymphoid Tfh cells. Accumulating evidence suggested that CD8$^+$ T cells with cytotoxic potential reside in follicular areas.

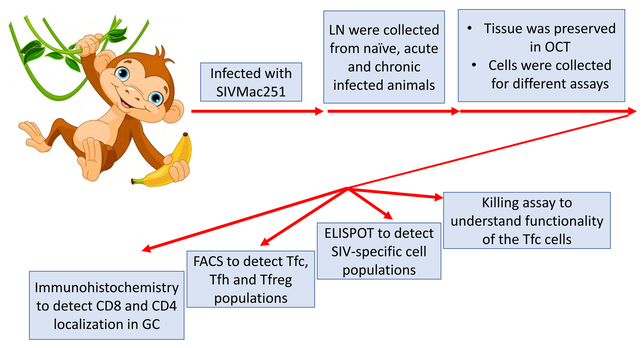


- In healthy humans, a subset of CD8$^+$ T cells was reported to use CXCR5 to enter B cell follicles. Quigley, M.F. et al. *Eur J Immunol* (2007).
- CXCR5$^+$ CD8$^+$ T cells were shown to selectively enter B cell follicles and eradicate LCMV-infected cells in mouse model. Leong, Y.A. *et al. Nat Immunol* (2016).
- In chronic LCMV infection, CXCR5$^+$CD8$^+$ T cells showed more potent cytotoxicity than CXCR5$^-$ subsets. He, R. *et al. Nature* (2016).
- Granzyme B$^+$ CM-9-tetramer$^+$ (SIV Gag-specific) CD8$^+$ T cells were enriched in chronically SIV-infected macaques that controlled infection compared to non-controllers. Mylvaganam, G.H. *et al. Proc Natl Acad Sci U S A* (2017).
- Tfc cells were increased in LN follicles and GC of HIV-infected individuals, and exhibited expression of both granzyme B and perforin. Petrovas, C. *et al.* (2017).
  - ➢ Indicates that follicular CD8+ T cells (Tfc) are located in B cell follicles of secondary lymphoid tissue and might play a key role in the control of viremia.

Objective

The aim of the current study was to clarify the role of SIV-specific Tfc cells in secondary lymphoid tissue over the course of SIV infection in rhesus macaques.

Methods



Results

CD4+ and CD8+ cells localized in Germinal Centers of Naïve and SIV infected animals. A positive correlation between these two kinds of cells was observed in acute and LVL animals.

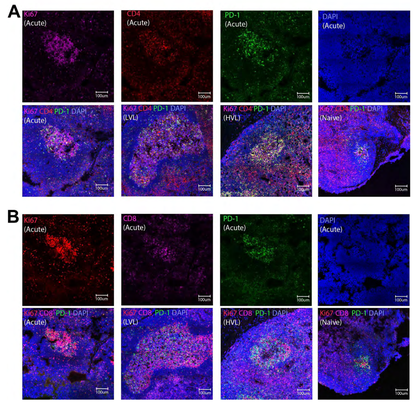


Figure 1. Localization of CD4+ and CD8+ cells in Germinal center of SIV-infected rhesus macaques (A, B).

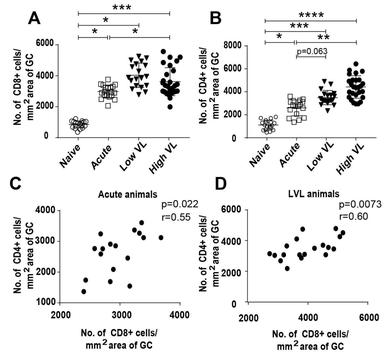


Figure 2. Frequency of CD8$^+$ cells (A) and CD4$^+$ cell (B) in Germinal center. Correlation between the number of CD8+ and CD+ cells in Acute infected and LVL animals, respectively (C, D) .

Frequency of Tfh cells was highest in chronically infected animals. Tfh and Tfc cells positively correlated in LVL animals. IL-21+ Tfh cells negatively correlate with VL in LVL animals.

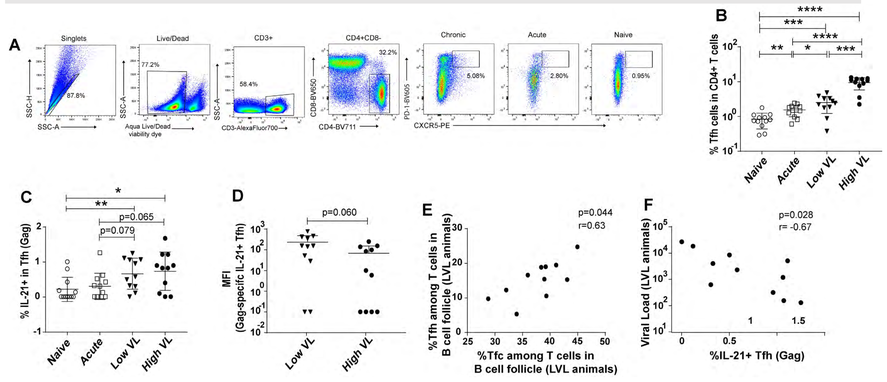


Figure 4. Representative gating of Tfh cells (A). Frequency of Tfh cells (B). Percentage of IL-21$^+$ Tfh cells (C) and IL-21 expression by them (D). Correlation between Tfh and Tfc cell frequencies (E). Correlation between Gag-specific IL-21$^+$ Tfh cells and median chronic viral load (H-I).

Higher frequency of SIV-specific cells in Tfc cells compared to non-Tfc cells. Tfc produce higher frequency of cytokine$^+$ cells and showed higher killing compared to non-Tfc cells.

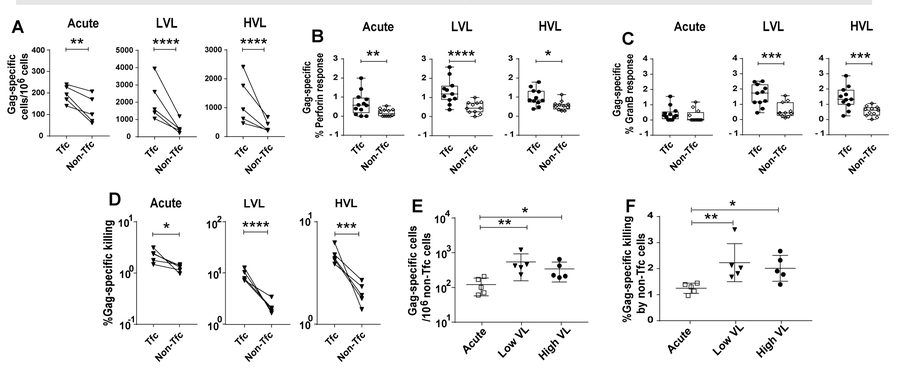


Figure 6. Frequency of SIV-Gag-specific Tfc and non-Tfc cells (A). Percentage of Gag-specific cytokine$^+$ Tfc and non-Tfc cells (B-C). Specific killing by Tfc and non-Tfc cells (D). Frequencies of SIV Gag-specific non-Tfc cells (D-E). Gag-specific killing by non-Tfc cells (F).

Tfc cell frequency was highest in chronically infected animals. Tfc cells showed a negative correlation with VL and a higher killing in LVL animals.

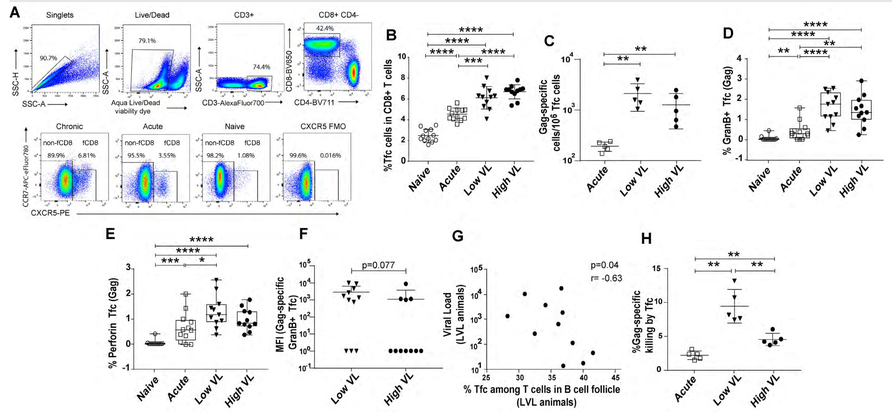


Figure 3. Representative gating of Tfc cells (A). Frequency of Tfc cells (B), SIV Gag-specific (C) and GranB$^+$ and perforin$^+$ Tfc cells (D-E). Gag-specific GranB expression (F). Correlation between median chronic VL and Tfc cells (G). Gag-specific killing by Tfc cells of SIV-infected macaques (H).

High Tfreg frequency in chronically infected animals. Tfregs positively correlate with Tfc cells and negatively correlate with VL in LVL animals, reverse pattern was observed in HVL animals.

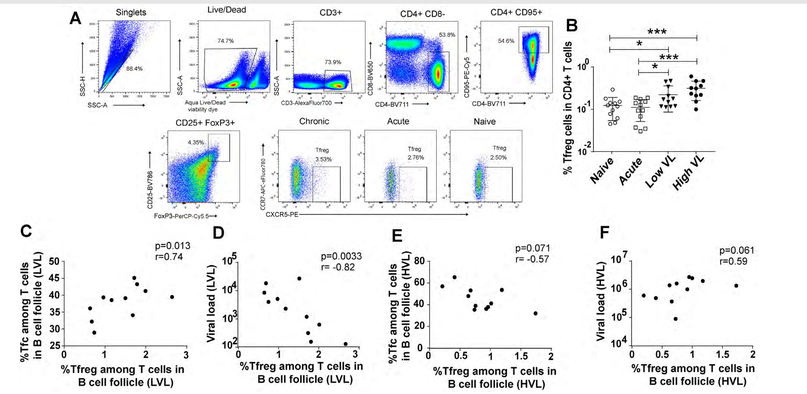
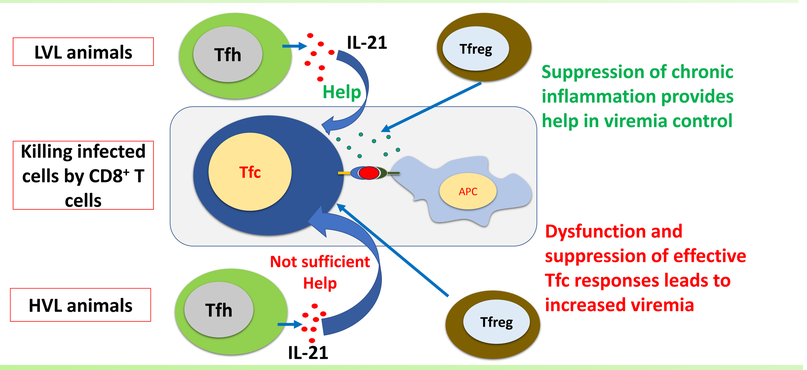


Figure 5. Gating of Tfreg cells (A). Frequency of Tfreg cells among CD4$^+$ cells (B). Correlation between Tfreg and Tfc cells of LVL or HVL animals (C-D). Correlation between the frequencies of Tfreg in LVL or HVL macaques and median chronic viral loads (E-F).

Working model



Conclusion: The elimination of virus-infected cells in the B cell follicle does not only depend on the cytotoxicity of follicular CD8+ T cells (Tfc) but also association of Tfc cells with other T follicular cells including Tfh and Tfreg.

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