Simian immunodeficiency virus confounds T follicular helper T cells and the germinal centre

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Comment on: Yamamoto T, Lynch RM, Gautam R, *et al.* Quality and quantity of TFH cells are critical for broad antibody development in SHIVAD8 infection. Sci Transl Med 2015;7:298ra120.

Abstract: Yamamoto *et al*. have studied T follicular helper (T_{FH}) and germinal centre (GC) responses after infection of rhesus macaques (RM) infected with simian immunodeficiency virus (SIV). In this study the authors examined the behaviour of T_{FH}, reproducing infection-associated T_{FH} accumulation and their association with the quality of antibody responses against cross-clade viral epitopes. The authors correlate T_{FH} *IL4* and *CD154* expression with superior antibody responses. Accumulation of T_{FH} was accompanied by aberrant expression of non-T_{FH} transcriptional regulators such as *BLIMP1* in T_{FH}, suggesting viral induced abnormalities may affect T_{FH} function.

Keywords: T follicular helper cells; germinal centre (GC); human immunodeficiency virus (HIV); simian immunodeficiency virus (SIV); antibody

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In this study, Yamamoto and colleagues (1) examine the association of T follicular helper (T_{FH}) cell characteristics with the production of broadly neutralising antibodies (bNAbs) in rhesus macaques (RM) infected with simian immunodeficiency virus (SIV) AD8 as a model of human immunodeficiency virus (HIV) infection. T_{FH} cells are specialised CD4+ T cells essential to the germinal centre (GC) reaction, promoting affinity maturation and class switching of their cognate GC B cell receptors (2). This process is essential to the generation of long-lived high-quality antibody responses which form the basis of vaccination. The HIV-1 envelope glycoprotein spike that mediates viral entry is the primary epitope of naturally occurring neutralising antibodies against the virus and therefore a central target for HIV vaccine studies (3). However, genes encoding the HIV-1 envelope glycoproteins are also highly mutagenic with subsequent amino acid substitutions, insertions/deletions, and glycan shifting all occurring in the most easily accessible regions (4). The consequence of this is that development of bNAbs in HIV infection typically occurs late in chronic infection.

Yamamoto *et al*. infected eight RM with SIV-AD8 and monitored them for up to 120 weeks with periodic peripheral blood lymphocyte, lymph node and plasma sampling. The total strength and diversity of anti-HIV antibody responses from each RM were summarily scored based on the 50% inhibitory dilution titres of their plasma against 19 simian-human immunodeficiency virus (SHIV) and HIV clade viral isolates. The authors reproduce the observation that higher SIV set point viral load correlate with eventual CD4+ T cell depletion (5), late accumulation of T_{FH} and development of neutralising antibodies (6). T_{FH} accumulation was observed from 20 weeks post-infection, it is not clear if this represents a relative or absolute increase as identified previously (7).

However, it did not appear to have a temporal relationship with generation of neutralising antibody which peaked at around 40 weeks, suggesting elevated T_{FH} numbers were not necessarily responsible for eventual antibody responses. At 44 weeks after infection Env-specific T_{FH}, defined as T_{FH} producing CD154 (CD40L), IL-4 or IFNγ in response to stimulation with HIV Env protein, were found in greater frequency in RM with higher scoring bNAbs. In particular the Env-responsive T_{FH} expressing IL-4 and CD154 correlated with both the number of IgG+ Env-specific GC B cells and stronger antibody responses. These findings are perhaps unsurprising as IL-4 and CD154 are crucial to GC interactions and their absence profoundly impairs GC and antibody responses (8,9), whereas the contribution of IFNγ is less clear. Whilst excess IFNγ can enhance GC responses and contribute to autoimmunity, its deficiency does not substantially impair the GC responses (10) and it is also unclear whether IFNγ has a similar function in primates as reported in mice.

The authors examined the transcriptional profile of these Env-responsive T_{FH}. Although absence of conventional normalisation makes interpretation difficult, several intriguing observations were made. Whilst conventional T_{FH} genes such as *BCL6*, *MYB* and *IL-21* were expressed as expected, surprisingly the transcriptional repressor *PRDM1* was found at equivalent levels between Env-responsive CD4+CD44+CXCR5+PD-1+ T_{FH} and non-T_{FH} CD4+ cells. *BCL6*, as the master transcriptional regulator essential to T_{FH} differentiation, is crucial to both the differentiation and promotion of many important T_{FH} functions (11). *BCL6* and *PRDM1* are mutually repressive in CD4+ T cells for the purpose of directing Th1/Th2 versus T_{FH} CD4+ effector lineage commitment (12). Thus it is perplexing that *PRDM1* expression was equivalent between non-T_{FH} and T_{FH} effector CD4+ T cells; it would be expected that T_{FH} have BCL6-mediated repression of *PRDM1*. Curiously, the transcription factors *TBET* (T_{H1}), *GATA3* (T_{H2}), and *FOXP3* (T_{REG}) were also observed at equivalent levels between the non-T_{FH} and T_{FH} effector CD4+ T cells. Although T_{FH} may potentially arise from other CD4+ effectors, non-*BCL6* transcriptional regulators such as *TBET* are normally only found in subsets of T_{FH} and at lower levels compared with non-T_{FH} effector CD4+ populations (13). Given abnormally high levels of transcriptional regulators and cytokines typically associated with other CD4+ subsets within the Env-responsive T_{FH} raises the possibility of either aberrant CXCR5/PD1 expression amongst effector CD4 sets, contamination of T_{FH} sorted pools, or issues with gene expression data.

Finally, although sequencing of single-cell sorted Env-specific IgG+ B cells heavy chain variable genes (VH4) correlated the degree of mutation with the calibre of late antibody response, the overall rate of mutation was very low suggesting hypofunctional GC responses. Unfortunately, it was not clear whether infected RM developed the hypergammaglobulinemia associated with HIV and SIV infection and which accompanies T_{FH} abnormalities. Thus it is uncertain whether the increase in bNAbs represented a smaller pool containing more higher-quality antibody, or simply a larger pool of antibody with bNAbs representing overwhelming hypergammaglobulinemia, a sign of the quality of the GC and T_{FH} response.

This study reproduces several unusual aspects of the GC biology in HIV/SIV infection. Despite declines in CD4+ T cells, phenotypically bona fide T_{FH} (ICOS+Bcl6+CD40L+PD1+) are known to accumulate in SIV infected RM (14). These T_{FH} are correlated with increased GC B and plasma cells and a reduction in memory B cells as observed by Yamamoto *et al*. This data supports the observation that it is not total numbers of T_{FH}, but rather the quality which may impair their function. It remains elusive as to why T_{FH} do not function normally in HIV infection. The GC is an established reservoir for HIV, particularly follicular dendritic cells (15), and T_{FH} are known to be infected and form sites of viral replication (14,16). Due to PD1-PDL1 interactions between T_{FH} and GC B cells repressing IL-21, T_{FH} in HIV-infected individuals may be unable to induce normal antigen-specific immune responses (17). This impairment in T_{FH} function is also observed with impaired influenza vaccination responses in HIV infected patients (18). The expression of *PRDM1* and other transcription regulators in T_{FH} in this study by Yamamoto *et al*. suggests abnormalities in T_{FH} function, highlighting the need to better understand the effect of HIV/SIV infection on T_{FH} biology. bNAbs may represent high-quality antibody production arising from T_{FH} cell with typical transcriptional responses and GC characteristics, and optimising T_{FH} response may represent novel target for HIV vaccine development.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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