Published in final edited form as:
Curr HIV Res. 2013 December ; 11(8): 595–600.

Expansion or Depletion of T Follicular Helper cells During HIV Infection: Consequences for B cell Responses

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Abstract

HIV infection is characterized by aberrant B cell responses and B cell dysfunction. These dysfunctional responses have been extensively documented in peripheral blood and organized lymphoid tissues such as the lymph nodes. Though the loss of CD4 T cell help has been thought to play a key role in dysfunctional B cell responses, recent studies have implicated a subset of CD4 T helper cells called the T follicular helper (Tfh) cells in this process. Tfh cells interact with B cells and play a key role in mediating the germinal center reaction, and driving the differentiation and maturation of B cells. Why Tfh expand in some HIV infected individuals as compared to their loss in others is still not clear. Here we review some of the recent developments in the field and discuss the implications of Tfh cell dysregulation on B cell responses during HIV infection.

Keywords

simian; HIV; SIV; IL-21; Tfh; B cells

Introduction

Naïve CD4 T cells can differentiate into, distinct lineages that can be identified based on their unique cytokine signature and expression of transcription factors that drive their differentiation; T-helper-1 (Th1) cells express IFNγ and Tbet, while T-helper-2 (Th2) cells express IL-4 and Gata3, and T-helper-17 (Th17) cells that express IL-17 and RORγt[1]. Recent studies have identified a novel class of CD4 T helper cells called the T-follicular helper cells (Tfh) that preferentially express IL-21 and the transcription factor Bcl6. Tfh cells have also been shown to secrete other cytokines such as IFNγ, IL-4 and IL-17[1,2].

Initial evidence for the existence of Tfh cells came from studies that characterized the expression of CXCR5 on memory CD4+ T cells that that were found to be associated with B cells in the Germinal Center (GC) follicles[3–6]. Tfh cells are a primary source of IL-21 in the GC and provide critical help to GC B cells. Mice lacking IL-21 or IL-21R have low numbers of IgG switched B cells[7] suggesting that IL-21 plays a crucial role in Ig class switching in the LN follicles[8,9]. Likewise, IL-21 has been shown to play an important role in B cell

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The authors declare no financial conflict of interest.

differentiation to plasma cells[10,11], and essential for the survival of memory B cells in the GC[10,12]. Paradoxically, IL-21 can have a proapoptotic effect on B cells[13] under certain conditions such as when they receive co-stimulatory signals via Toll like receptors TLR)-4 and -9[14]. This effect appears to be caspase dependent[10].

Tfh cells, unlike other T helper lineages, express high levels of Bcl6, a transcriptional repressor initially discovered in B cell lymphomas[15] and a negative regulator of transcription for a number of proteins which plays a critical role in Tfh differentiation[16,17]. Additionally, Tfh cells have been shown to express a number of co-stimulatory molecules such as ICOS, PD-1, CD40L that interact with their cognate ligands on B cells in the GC (Fig. 1) and a number of other proteins such as SAP, OX40, CD30L and BTLA[2,18]. The exact role some of these proteins may play in Tfh mediated help is still under investigation. Interestingly, Tfh cells display reduced expression of CCR7 (the receptor for CCL19 and CCL21 in T cell zones) that likely allows these cells to home to the border of the T and B cell zones where they mediate their function[19].

A number of recent studies have identified a class of CD4 T cells in blood, based on high CXCR5 expression, that exhibit functions similar to Tfh cells found in the lymph nodes. They secrete high levels of IL-21 and are specialized for providing help to B cells[20]. Locci et al[21] described a subset of PD-1^{+} CXCR3^{-} CXCR5^{+} CD4^{+} memory T Cells in the periphery that had a transcriptional profile similar to Tfh cells in the LN and Boswell et al[22] reported that CCR7^{hi} CXCR5^{hi} CCR6^{hi} PD-1^{hi} CD4 T cells in peripheral blood were highly specialized in secreting IL-21 and providing help to B cells. Pallikkuth et al[23] showed that peripheral Tfh cells expressed CXCR5 and displayed a central memory phenotype and play a critical helper function in generating vaccine responses.

Tfh Differentiation and Bcl-6 Expression

Early events in Tfh differentiation begin with recognition of antigen on DC by CD4 T cells leading to upregulation of Bcl6 by mechanisms that are not fully understood[24]. Some studies have localized this process to the LN interfollicular zone where B cell and T cell zones are in close proximity[25] with IL-21 and IL-6 playing an important role during this initial differentiation[26]. CD4 T cells stimulated by IL-6 *in vitro* upregulate a number of markers such as Bcl-6 that are unique to Tfh cells[17] and recent studies have shown that IL-6 knockout mice were significantly delayed in their ability to generate Tfh cells during LCMV infection. This IL-6 dependent induction of Tfh cells required STAT1 activation[27].

The upregulation of Bcl6 appears to be critical for the development of a Tfh phenotype as it is thought to drive the expression of CXCR5 on Tfh cells. Bcl6 has been shown to upregulate the expression of other co-receptors thought to be essential for Tfh cells function such as CD40L, CXCR4, PD-1, ICOS, IL-21R and IL-6R, and down regulate the expression of CCR7[16,17,28–30]. In addition to promoting the development of Tfh cells, Bcl6 has been shown to inhibit T-bet mediated differentiation of Th1 cells, block Stat6 signaling that is essential for Th2 differentiation, and limit the RORγ driven differentiation of Th17 cells[2,17,30,31].

Tfh cells have been shown to express additional co-receptors such as SAP (signaling lymphocytic activating molecule (SLAM)-associated protein) and OX40 that are upregulated by Bcl6 and thought to play a role in Tfh cell and cognate B cell interactions in the lymph nodes. These interactions appear to be critical for B cells to form GC in T cell dependent reactions and thought to be essential for maintaining Bcl6 expression in Tfh cells[28,32]. Disruption of these interactions have been shown to rapidly downregulate Bcl6 expression[33,34].

Tfh cells and B cell differentiation

B cells undergo class switch and differentiation in the GC. BCL6 is required for germinal center formation and maintenance[35] and its expression is dependent on interactions between Tfh and B cells. Bcl6 expression is essential for the survival of germinal center B cells undergoing clonal selection and somatic hypermuation by making the B cells more tolerant to DNA damage[36,37]. Bcl6 represses human programmed cell death-2 (PDCD2) gene which is involved in apoptosis[38]. Bcl6 has also been shown to control the expression of B7-1/CD80, a co-stimulatory factor involved in B cell - T cell interactions in the germinal centers[39].

Bcl6 represses BLIMP1 and IRF4, two transcription factors in B cells required for the development of plasma cells[40,41]. Bcl6 targets the transcription of PD-L1, a ligand for PD-1 on Tfh cells[42]. The interaction of PD-L1 and PD-1 has been shown to be important for plasma cell formation[43].

The expression of BLIMP1 appears to be essential for the generation of plasma cells[44–46]. BLIMP1 is also a transcriptional repressor that generally promotes antibody secretion by silencing the transcriptional programs that define mature B cells. BLIMP1 represses Bcl6 and AID (Activation-induced deaminase)[47–49] and targets Pax5 (paired box protein 5) that is required for the commitment of lymphocyte progenitors to the B cell pathway[50,51]. Pax5 also represses a number of genes that are involved in antibody secretion and plasma cell development[52,53]. BLIMP1 has been shown to regulate the processing of heavy chain of immunoglobulin (Ig) mRNA by altering the 3' end to encode a secreted variant of Ig, and upregulates the expression of integrin α4 which potentially permits the homing of plasma cells to anatomical niches[45,48]. IL-21 is capable of inducing BLIMP-1 expression in B cells[8,10]. Tfh cells are a major source of IL-21 in the germinal centers (Fig. 1) and a number of studies have highlighted the importance of IL-21 in plasma cell differentiation[8,10,54]. Paradoxically IL-21 is also capable of upregulating Bcl6 on GC B cells[12].

The mechanisms regulating memory B cell formation versus plasma cell differentiation are unclear. Interferon regulatory factor 4 (IRF4) is essential for plasma cell formation and it is believed to regulate BLIMP1 expression[55]. It has been shown that graded expression of IRF4 may help coordinate plasma cell differentiation by targeting PRDM1, the gene that encodes BLIMP1. Indeed higher levels of IRF4 lead to significantly higher levels of BLIMP1[56] and IRF4 has been shown to be required for IL-21 dependent regulation of PRDM1 during plasma cell development via phosphorylation of STAT3[57]. Interestingly IRF4 is targeted by IL-21 during the differentiation of Th17 and Tfh cells[57] suggesting that

IL-21 produced by Tfh cells could potentially play a role in regulating IRF4 in GC B cells and in determining the fate of plasma cell versus memory B cell formation.

Studies have shown that Tfh cells are highly specialized in providing help to B cells and in driving B cell differentiation from naïve B cells to memory B cells and antibody secreting cells *in vitro*[20,54,58]. Others have shown that co-culture of GC B cells with autologous T cell populations that were enriched from the GC generated memory B cells[59]. Good-Jacobson et al[43] showed that the interactions between PD-1 on Tfh cells and PD-L1 and PD-L2 on GC B cells were critical for formation of plasma cells.

HIV Infection and Tfh cells

HIV infection is characterized by a progressive loss of CD4 T cells, and immune dysfunction that contribute to immunodeficiency and AIDS. Tfh cells have a central memory phenotype and express CCR5 that makes them potentially susceptible to infection by HIV[60,61]. Our studies have shown that rhesus macaque Tfh cells like human Tfh cells express a predominantly memory phenotype[62]. Recent studies have demonstrated that infected Tfh cells constitute a major HIV reservoir within the GC niche of the LN where they are shielded from effector CD8 T cell responses allowing them to persist in this microenvironment even when viral loads are completely suppressed with therapy[63]. Others have shown that FDC were a major source of HIV virions in the GC[64] and these FDC's likely constitute a potential source of infection for Tfh cells during their interaction in the LN[65]. A number of studies have reported that CD8 T cells are rarely present in the GC[66,67] and if they do, they appear to be less cytotoxic than CD8 T cells in the periphery[68]. This may explain why Tfh cells within the GC environment harbor significantly higher levels of HIV when compared to CD4 T cells in other compartments[63].

A number of recent studies have examined the dynamics of Tfh cells during HIV infection. Hong et al[69] using Immunohistochemical analysis showed that GC from chronically SIV infected macaques harbored 4-fold higher frequencies of PD-1^{+}CD4^{+} Tfh cells compared to uninfected controls. Kaufmann et al[70] demonstrated that PD-1 expression was increased on HIV infected CD4 T cells. Others have shown that both chronic HIV and SIV infections were characterized by a significant expansion of Tfh in lymph nodes though not all patients or SIV infected animals show a dramatic expansion of Tfh cells during infection suggesting that the host microenvironment likely contributes to the differential levels of Tfh cells during infection. Interestingly, recent studies have reported that circulating Tfh-like populations in peripheral blood were significantly depleted during HIV infection[22]. On the other hand Pallikkuth et al[23] showed that impaired peripheral Tfh function in HIV infected individuals play a role in nonresponsiveness to vaccines such as the 2009 H1N1/09 vaccine.

The exact mechanisms for the expansion of Tfh cells during infection are still under investigation. It is possible that increased levels of IL-6, a Tfh differentiating cytokine, that is increased during HIV infection might play a role in Tfh expansion as some studies have suggested[61]. Tfh cells have been shown to express high levels of IL-6R that correlated with increased IL-6 levels during chronic SIV infection[61]. Recent studies have implicated IFNγ as a potential mechanism for the accumulation of Tfh in the GC[71] and Boyle et al[72] showed

that IFN γ levels were significantly enhanced in the LN of HIV infected patients. Expansion of Tfh cells have been reported in a number of autoimmune diseases such as SLE[73], Sjogren's syndrome[74], Rheumatoid Arthritis[75] and Juvenile Dermatomyositis[20].

Why Tfh cells expand in some HIV and SIV infected subjects as compared to their loss in others is not clear. Tfh cells express significantly higher levels of Ki67, a marker for immune activation, along with CCR5 and other memory T cell markers suggesting that infection associated loss may be a potential mechanism for the depletion of Tfh cells. Perreau et al[63] showed that Tfh cells serve as a major reservoir for HIV infection, replication and production. On the other hand, high levels of PD-1 expressed by Tfh cells during HIV infection may lead to increased PD-1: PD-L1 binding that could induce a negative regulatory effect on Tfh cells[76] potentially leading to apoptosis. PD-L1 is upregulated on pDC's during HIV infection and pDC's play a critical role in Tfh differentiation[24]. Recent studies[76,77] have demonstrated that blocking PD-1 : PD-L1 interaction using antibodies was associated with better GC function and B cell responses. Pallikkuth et al[78] showed that administration of IL-21 to SIV infected macaques significantly improved memory B cell levels, indicating that loss of IL-21 producing cells may be a contributing factor in the generation of defective memory B cell responses. Taken together, a number of potential mechanisms likely contribute to the depletion of Tfh cells in some subjects and further studies are required to address this question in greater detail.

Numerous studies have shown that HIV infection is associated with B cell abnormalities such as hypergammaglobulinemia, polyclonal B cell activation[79,80] and B cell driven lymphadenopathy[81–83]. Recent reports suggest that these processes may be driven by the expansion of Tfh cells. Petrovas et al[61] showed that chronic SIV infection was associated with a significant increase in Tfh cells that correlated with hypergammaglobulinemia whereas Lindqvist et al[60] reported that Tfh levels directly correlated with plasma immunoglobulin levels during chronic HIV infection.

The expansion and correlation of Tfh cells with hypergammaglobulemia provides a likely mechanistic explanation for this phenomenon during HIV infection. It is, however, difficult to reconcile highly functional Tfh cell responses with other B cell defects such as the loss of CD27+ memory B cells in blood, low levels of serological memory antibodies[84–86], and the defective generation and survival of memory B cells[84] seen in HIV infected subjects. It is possible that the loss of Tfh cells plays a critical role in mediating these B cell defects. Cubas et al[76] reported that inadequate Tfh cell help impaired B cell responses during HIV infection. Though loss of Tfh cells likely plays a key role, other mechanisms such as the binding of gp120 to B cells leading to signaling defects in these cells[87] or the damaged fibroblastic reticular network[88,89] likely contribute to the overall B cell defects seen during HIV infection.

Conclusions

The importance of Tfh cells during HIV infection is currently an intense area of research. A number of critical observations have been made during the past 2 years that has significantly enhanced our understanding of the relationship between Tfh cells, HIV infection and B cell

responses. Significant gaps regarding the exact mechanisms that drive Tfh cell expansion in some HIV infected subjects as compared to their depletion in others, however, remain. How Tfh cells can be exploited to develop better HIV vaccines present some exciting opportunities. Additional studies, some of which are currently underway are needed to address these critical questions that may lead to exciting breakthroughs in the field.

Acknowledgments

The described work was supported by DE019397 awarded to JJM by National Institute for Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDCR or the National Institutes of Health.

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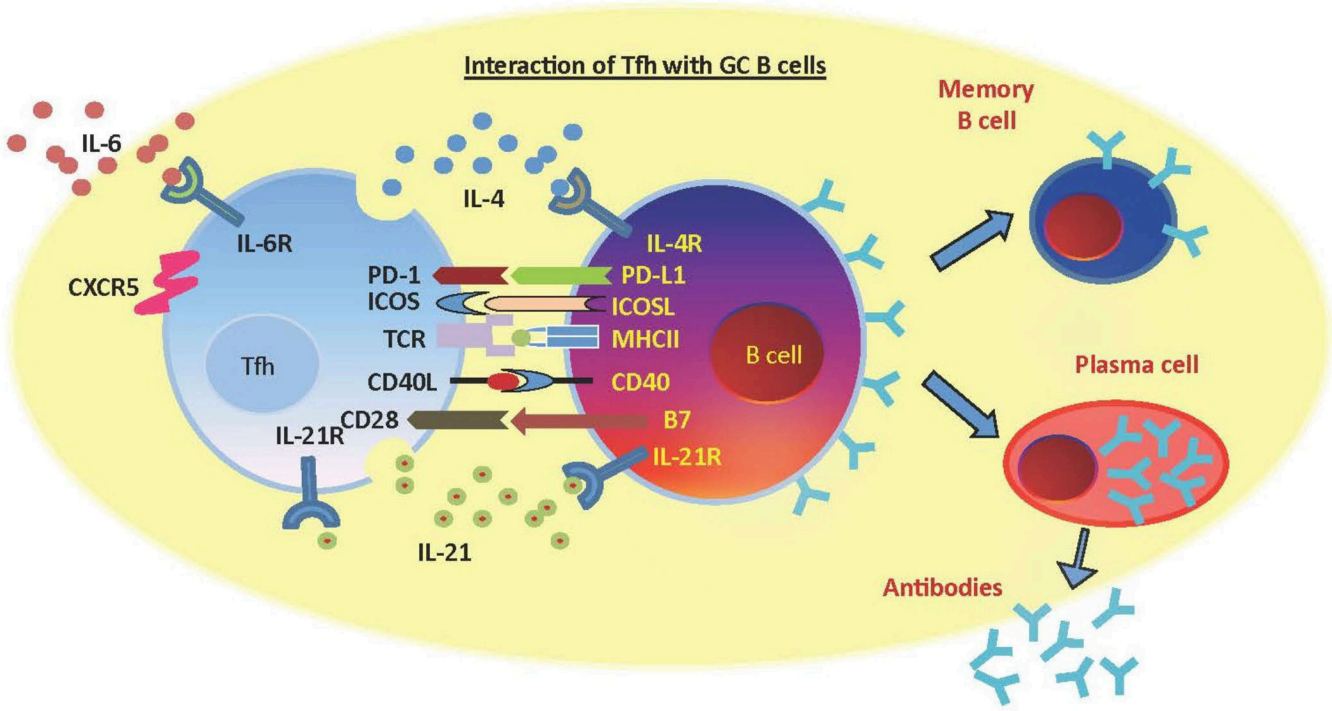

Figure 1.
T follicular helper cell and B cell interaction in the lymph node