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Authors: Cubas R, Perreau M

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The dysfunction of T follicular helper cells

Rafael Cubas[1] and **Matthieu Perreau**[2]

[1]Vaccine and Gene Therapy Institute of Florida, Port St. Lucie, FL, USA [2]Divisions of Immunology and Allergy, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

Abstract

Purpose of review—T follicular helper (Tfh) cells play a critical role as providers of B-cell help and dysfunction in Tfh/B-cell interactions can lead to autoimmunity or immunodeficiency. These observations have generated a great deal of interest in understanding how these cells are affected during HIV infection and how their functional changes might affect antibody responses.

Recent findings—Recent studies have shown that HIV/SIV infection affects both Tfh-cell frequency and function and suggest that Tfh-cell perturbations might contribute to the relative inefficiency of HIV-infected individuals to generate broadly neutralizing antibodies (bNAbs).

Summary—The present review will highlight these recent findings addressing the role of Tfh cells in HIV infection as well as the impact HIV infection has on Tfh and circulating memory Tfh (cTfh) cell frequency and function.

Keywords

Tfh cells; HIV; B cells and dysfunction

Introduction

T follicular helper (Tfh) cells are a specialized subset of CD4 T cells that provides help to B cells in germinal centers (GCs) [1]. These cells are necessary for GC formation, immunoglobulin (Ig) class-switch recombination (CSR), somatic hypermutation (SHM) and differentiation of B cells into long-lived memory B cells and plasma cells [2–10]. GCs are specialized structures within B-cell follicles where B cells undergo SHM of their Ig variable (V) region genes to achieve higher affinity against a corresponding antigen conferring greater protective efficacy and CSR of their constant Ig domain (Fc) which provides different effector potentials [11–20]. Due to their critical role as providers of B-cell help, there has been a great deal of interest in understanding how these cells are affected during HIV infection and how their functional changes alter antibody responses.

Correspondence should be sent to: Dr. Matthieu Perreau, Division of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland, Matthieu.Perreau@chuv.ch, Phone: +41213141073.

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Tfh-cell differentiation is driven by the transcription factor Bcl-6 [21, 22], although IRF4, BATF, MAF and the recently described Ascl2 are also involved in Tfh-cell differentiation and function [1, 23–26]. Tfh cells are characterized by their high level of CXCR5, ICOS and PD-1 [6–9] (described tissue resident Tfh cell subsets are summarized in Table 1) expression and produce a variety of cytokines including IL-4, IL-10 and IL-21 that are critical for the survival and differentiation of GC B cells into long-lived memory B cells and plasma cells [2–10]. Tfh/B-cell interactions are therefore essential for the generation of efficient neutralizing and non-neutralizing antibody responses [9, 10, 15, 20, 21, 41, 42] and have attracted a lot of recent interest.

The frequency and function of Tfh cells are tightly controlled under physiological conditions and their dysregulation can lead to various immune perturbations such as autoimmunity and immunodeficiency [1, 43–46]. In particular, recent studies have shown that HIV/SIV infection affects both Tfh-cell frequency and function [34–36, 40] and suggest that Tfh-cell perturbations might contribute to the relative inefficiency of HIV-infected individuals to generate bNAbs [32, 40]. Finally, the recently described population of blood circulating memory Tfh cells (cTfh) might mirror at least in part GC Tfh-cell perturbations [32]. In this review, we will highlight the recent findings that addressed the role of Tfh cells in HIV infection as well as the impact HIV infection has on Tfh and cTfh-cell frequency and function.

Role of Tfh cells in HIV infection

Lymphoid organs are the primary anatomic compartments for HIV/SIV replication and spreading [47–51] and *in situ* hybridization clearly indicated that HIV/SIV RNA was associated with GCs [37, 50, 52,]. In viremic HIV-1 infected individuals, Tfh cells were shown to contain the highest percentage of CD4 T cells harboring HIV DNA and were the most efficient in supporting productive infection *in vitro* [34]. Replication competent HIV was also readily isolated from Tfh cells in subjects with high and low viremia (<2000 HIV RNA copies) [34]. In addition, the frequency of Tfh cells was found to correlate with plasma viremia suggesting that Tfh cells might also be one of the primary sources of circulating virus or the primary target for HIV infection [34].

Interestingly, recent studies have also shown a relative expansion of Tfh cells during the viremic phase of both HIV and SIV infection [34–37]. These observations are not surprising as Tfh cells likely expand in response to cognate antigen, but this is in contrast with their increased susceptibility to SIV [36, 38] and HIV [34] infection. Indeed, HIV-infected CD4 T cells can be killed by either direct viral cytopathic effects or by HIV-specific CD8 T cells [53, 54]. Although the precise mechanism by which Tfh cells could withstand HIV-mediated depletion is unknown, HIV and SIV-specific CD8 T cells appeared to locate outside GCs [37, 55], which may in turn facilitate HIV/SIV-infected Tfh-cell accumulation in the follicles. Recently, a population of regulatory Qa-1-restricted CD8 T cells has been shown to localize in GCs and dampen Tfh cell development in mice [39]. However, their presence in human GCs and their role in targeting Tfh cells have not been investigated.

HIV-1 infected activated CD4 T cells escaping cytotoxic CD8 T cells as well as viral cytopathic effects can enter a quiescent state and thereby represent a major source of latently infected cells [56, 57] and a major obstacle for HIV eradication [56–59]. Indeed, estimates for the half-life of the HIV latent reservoir in the blood indicated that it might take as long as 70 years to completely eradicate the latent reservoir in the presence of fully suppressive ART [60]. Pioneer studies demonstrated that latently infected cells are relatively rare with a frequency of about 1 in 10^6 resting CD4 T cells with no significant difference observed between blood and lymph nodes [56, 61]. These observations led to the conclusion that cells from peripheral blood could be appropriately used to study the HIV latent reservoir. Using this strategy, Chomont *et al.* have identified central memory (CM; defined by the $CD45RA^{-}CCR7^{+}CD27^{+}$) and transitional memory (TM; $CD45RA^{-}CCR7^{-}CD27^{+}$) CD4 T cells as major cellular compartments of the latent HIV-1 reservoir in blood [62]. However, lymphoid organs contain about 98% of the total body lymphocytes [56] which are phenotypically and functionally distinct from CD4 T-cell populations circulating in the blood [6]. Therefore, studying HIV-1 latently infected LN memory CD4 T-cell populations might enable the identification of new cellular compartments that may contribute to the latent reservoir and help in the discovery of new targets for HIV-1 eradication. In this context, Yukl *et al*., are currently investigating the cellular subtype distribution of HIV-1 DNA contained in blood and lymphoid tissues collected from ART treated HIV-infected individuals and showed that effector memory (EM; $CD45RO^{+}CCR7^{-}CD27^{-}$) CD4 T cells generally contained a higher level of HIV DNA than other CD4 T-cell populations in LNs (CROI 2014, #137). While Tfh cells might be enriched in this EM compartment [6, 8], further investigation and use of additional markers will be required to highlight the specific role of Tfh cells in the HIV latent reservoir.

Taken together, while recent studies have clearly demonstrated the preponderant role of Tfh cells during the viremic phase of HIV/SIV [34, 36] infection, the identification of latently infected CD4 T-cell reservoirs in the blood and lymph nodes (LNs) and their relationship to each other remain to be established and will contribute to efforts in finding targets for a potential cure.

Tfh cell functional alterations during HIV infection

While, HIV-1 infection elicits robust antibody responses to envelope proteins (gp120 and gp41) [63, 64], only 10–30% of HIV-infected individuals generate potent bNAbs [65–69]. This relative inefficiency to generate bNAbs is partially attributed to HIV-1 structure, which harbors numerous mechanisms of humoral evasion like sequence variable loops [70], glycosylation [71] and conformational masking of receptor-binding sites [72]) and by the fact that HIV-infected individuals develop lymphadenopathies associated with damages to follicular structures likely affecting B-cell differentiation and affinity maturation [73, 74]. Notably, the aforementioned morphological modifications have also been associated with Ig and B-cell abnormalities during the course of HIV infection [73]. Numerous B-cell perturbations appear during HIV infection and although many of these defects are improved by ART, B-cell responses to HIV specific antigens are diminished [75–81].

Due to their critical requirement in GC B-cell responses, several groups have investigated the impact of HIV/SIV infection on Tfh-cell frequency and function [34–37]. These studies have shown an expansion of Tfh cells in HIV/SIV-infected individuals that correlated positively with the frequency of GC B-cells and antibody production [34–37]. However, despite an increase in the frequency of these cells, we have recently shown that Tfh cells from HIV-infected individuals are functionally impaired and cannot provide adequate B-cell help [40]. This appeared to be partly due to increased PD-L1 expression by GC B cells leading to PD-1 triggering on Tfh cells which can affect Tfh cell proliferation, activation, ICOS expression and IL-21 cytokine secretion. Indeed blocking PD-1 signaling enhanced antibody production and exogenous IL-21 could rescue antibody responses and plasma cell generation *in vitro* [40]. It therefore appears that Tfh-cell function is affected in HIV infected LNs and might arise due to microenvironmental signals leading to an aberrant expression of inhibitory molecules.

The recent identification of follicular regulatory T (Tfr) cells that can migrate into follicles and restrain Tfh-cell differentiation represents another level of regulation in lymphoid tissues which could affect Tfh-cell function and B-cell responses during HIV infection [82–86]. Their mechanism of action is unknown but studies in mice indicated that in the absence of PD-1 and PD-L1 these cells expanded and inhibited Tfh-cell function [87]. In a PD-1/PD-L1 deregulated environment such as the one in HIV-infected LNs, the function of these cells might be reduced leading to an expansion of Tfh cells.

A better understanding of Tfh/GC B-cell interactions will have important implications for the generation of robust HIV-specific B cell responses and for the generation of *de novo* humoral responses to infections or vaccination. Clearly, the amount of data currently available is very limited and further investigation on the impact of HIV infection on Tfh-mediated B-cell help is required. A better understanding of the mechanisms that are affected by HIV infection leading to defective Tfh-cell signaling and B-cell responses could provide a critical framework for the development of novel therapeutics and vaccines and could also shed some light on the mechanisms responsible for the failure in the majority of HIV-infected individuals to produce bNAbs and their diminished responses to immunization [88–90].

Circulating memory Tfh cells

The fate and commitment of Tfh cells is still incompletely understood [91–95]. Indeed, using a mouse model of acute lymphocytic choriomeningitis virus (LCMV) infection, Hale *et al.*, showed that both LCMV-specific memory CD4 T cells with Tfh and Th1 commitment were generated [91]. By using an IL-21 reporter mouse system, Lüthje *et al.*, showed that Tfh cells gave rise to Tfh-like memory cells that could differentiate into conventional effector T helper cells or Tfh cells upon antigen recall [93]. Additional studies showed that Tfh cells could revert in long-lived memory Tfh cells expressing low levels of Bcl6, CXCR5 and PD-1 expression in the absence of antigen [92, 95]. Choi *et al*. also confirmed the capacity of Tfh cells to form memory and showed that Tfh cells shared phenotypic characteristics with memory precursor CD8 T cells [96]. Overall, these studies demonstrated that at least in mice, a fraction of Tfh cells have the capacity to become memory cells and

can promote GC formation and antibody production more effectively than non-Tfh cells upon antigenic challenge [91–95].

Initial evidence for memory cTfh cells in humans came from studies of human malignancies [27, 28, 97]. A more comprehensive study by Morita *et al.* further defined a population of memory Tfh-like cells with an enhanced capacity to provide naïve and memory B-cell help [29]. This study subdivided circulating Tfh-like cells into three subsets (Th1, Th2 and Th17-like) based on their expression or the lack of CXCR3 and CCR6 and demonstrated that both the Th2 and Th17-like cells ($CXCR3^{-}CCR6^{-}$ and $CXCR3^{-}CCR6^{+}$ respectively) efficiently helped naïve B cells and differentially modulated isotype switching while Th1-like subset ($CXCR3^{+}$) did not provide adequate help to naïve B cells (described circulating Tfh-like cell subsets are summarized in Table 1). The presence of blood central memory CD4 T cells expressing CXCR5 and CXCL13 and efficiently induced plasma cell differentiation and antibody secretion further supported the existence of cTfh cells [30].

Studies of memory cTfh cells in the context of HIV infection have been scarce but they have suggested that the capacity of these cells to provide B-cell help might be compromised [31–33, 98]. Indeed, Pallikkuth *et al.* assessed H1N1/09 influenza responses induced following vaccination in HIV-uninfected and HIV infected individuals under ART and showed that half of HIV-infected vaccinees did not respond to the immunization. Based on this observation, the authors assessed cTfh-cell capacity to produce IL-21, CXCL-13 and express ICOS, and concluded that cTfh cells from non-responders were functionally impaired (reduced IL-21 secretion and ICOS expression) [31].

A more recent study identified a population of memory $CD4^{+}CXCR5^{+}$ T cells ($CCR6^{hi}PD\text{-}1^{hi}$) that produced IL-21 and supported B cell differentiation [33]. This study found that the frequency of these cells was decreased in treatment naïve HIV infected individuals but was recovered after antiretroviral therapy. Additionally, this study also found decreased antibody production and a reduced frequency of IL-2, IL-17 and IL-21 producing $CD4^{+}CXCR5^{+}CCR6^{hi}PD\text{-}1^{hi}$ cells in HIV infected when compared to uninfected controls. The relationship between these circulating Tfh-like cells and those previously described by other studies [29, 30, 32,] is unknown. However, analysis of Tfh-associated genes showed that these cells more closely resembled non-Tfh memory cells as opposed to GC Tfh cells [33].

In addition, Locci *et al.* showed that memory $CXCR5^{+}CXCR3^{-}PD\text{-}1^{+}$ $CD4^{+}$ T cells were closely related to GC Tfh cells based on gene expression and cytokine profiles and their capacity to provide B-cell help [32]. Interestingly, the frequency of these cells positively correlated with the development of bNAbs in HIV-infected subjects [32], suggesting that the frequency of cTfh cells could be indicative of enhanced and probably efficient GC responses. In contrast, Boswell *et al.* showed that the frequencies of cTfh cells (defined by $CXCR5^{+}CCR6^{hi}PD\text{-}1^{hi}$ expression) in untreated HIV infected did not correlate with the frequencies of memory B cells or with Ig neutralizing activity [33]. This lack of concordance between the two studies likely arises from differences in the patient samples studied as well as the markers of cTfh used.

Taken together, the use of cTfh-cell frequency and function as an indirect marker of GC Tfh cells or ongoing GC reactions represents a very interesting tool, but will require additional investigation in order to improve their definition and harmonize their assessment.

Conclusion

The past few years have witnessed considerable findings with regards to Tfh cells and HIV pathogenesis. However, it is clear that intense investigation will be needed in order to better understand the mechanisms in charge of both Tfh and cTfh cell dysfunctions during the course of HIV infection and to determine the role of these cells during HIV infection. The progressive characterization of Tfh and cTfh cells will also be highly useful to elucidate the impact of HIV infection on the generation of efficient HIV-specific B-cell responses. Interestingly, as recently suggested [32], cTfh cells might be valuable indicators of vaccine-induced B-cell responses [31, 32, 98, 99].

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- Tfh cells serve as the major CD4 compartment for HIV-1 infection, replication and production. Yet, their role in establishing and forming part of the latent reservoir remains to be elucidated.
- While Tfh-cell frequencies are increased during the viremic phase of HIV infection, Tfh cells are functionally impaired and cannot provide adequate B-cell help.
- The presence of blood circulating memory Tfh-like cells has recently been described. Their actual relationship to GC Tfh cells still requires further investigation but a population of these cells has been shown to be closely related phenotypically and functionally to GC Tfh cells and their frequency correlated with the development of potent bNAbs in HIV-infected individuals.
- Recent studies have suggested that the function of circulating memory Tfh cells might be impaired in HIV infected subjects but this requires further investigation.

Table 1

Described phenotypes of circulating Tfh-like cells subsets and tissue resident Tfh cell subsets.

Phenotype	Model	Tissue	References
Circulating Tfh-like cell subsets			
$CD45RO^{+}CXCR5^{+}$	Human	Blood	[27] Bossaller *et al.*
$CXCR5^{+}$ with increased ICOS/PD-1 expression in SLE patients	Human	Blood	[28] Simpson *et al.*
$CD45RA^{-}CXCR5^{+}$ subdivided into $CXCR3^{-}CCR6^{+}$, $CXCR3^{-}CCR6^{-}$ and $CXCR3^{+}CCR6^{-}$ cells	Human	Blood	[29] Morita *et al.*
$CD45RA^{-}CCR7^{+}CXCR5^{+}$	Human	Blood	[30] Chevalier *et al.*
$CD45RA^{-}CXCR5^{+}$	Human	Blood	[31] Pallikkuth *et al.*
$CD45RO^{+}CXCR5^{+}CXCR3^{-}PD\text{-}1^{+}$	Human	Blood	[32] Locci *et al.*
$CD27^{hi}CD45RO^{hi}CCR7^{hi}CXCR5^{hi}CCR6^{hi}PD\text{-}1^{hi}$	Human	Blood	[33] Boswell *et al.*
Tissue resident Tfh cell subsets			
$CD45RA^{-}CXCR5^{+}PD\text{-}1^{hi}$	Human	LN	[34] Perreau *et al.*
$CXCR5^{+}PD\text{-}1^{hi}$	Human	LN	[35] Linqvist *et al.*
$CCR7^{low}PD\text{-}1^{hi}ICOS^{hi}$	Macaques	LN	[36] Petrovas *et al.*
$CD3^{+}PD\text{-}1^{hi}$ (*in situ*)	Macaques	LN	[37] Hong *et al.*
$CD45RA^{-}PD\text{-}1^{hi}CD127^{low}$	Macaques	Spleen and LN	[38] Xu *et al.*
$CD45RA^{-}CXCR5^{+}CD57^{+}$	Human	Tonsils	[39] Kim *et al.*
$CXCR5^{+}ICOS^{+}$	Human	Tonsils	[8] Breitfeld *et al.*
$CD45RA^{-}CXCR5^{hi}$	Human	Tonsils and LN	[40] Cubas *et al.*