HHS Public Access

Author manuscript

Trends Microbiol. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Trends Microbiol. 2016 May ; 24(5): 338–344. doi:10.1016/j.tim.2016.02.006.

T_{FH} in HIV Latency and as Sources of Replication Competent Virus

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Abstract

During untreated disease, HIV replication is concentrated within T follicular helper cells (T_{FH}). Heightened permissiveness, the presence of highly infectious virions on follicular dendritic cells (FDC), low frequencies of virus-specific cytotoxic T lymphocytes (CTL) in B cell follicles, expansions in T_{FH}, and T_{FH} dysfunction all likely promote replication in T_{FH}. Limited data suggest that memory T_{FH} play a role in the latent or subclinical reservoir of HIV during antiretroviral therapy (ART), potentially for many of the same reasons. A better understanding of the role of memory T_{FH} and FDC-bound virions in promoting recrudescent viremia in the setting of ART cessation is essential. Studies that target follicular virus reservoirs are needed to determine their role in HIV latency and to suggest successful cure strategies.

Keywords

HIV-1; T follicular helper cells; follicular dendritic cell; latency

Role of T_{FH} in HIV Replication in Untreated Disease

T follicular helper cells (T_{FH}) are a specialized subset of CD4+ helper T cells that express CXCR5, migrate into B cell follicles, and promote B cell maturation and antibody production during infections (reviewed in [1]). In untreated, asymptomatic HIV infection, T_{FH} serve as the major site of HIV infection and replication (Figure 1) [2–5]. A median of 60–75% of HIV-producing cells are located within B cell follicles in lymph nodes from untreated, asymptomatically infected individuals [2, 4], and a CD4+ T cell located within a B cell follicle is 40 times more likely to be productively infected than a CD4+ T cell located outside of the follicle [4]. Similarly, in chronically SIV-infected rhesus macaques without simian AIDS (SAIDS), the majority of SIV-producing cells are located within follicles [6, 7]. Even after normalizing for differences in memory cells between the follicular and extrafollicular compartments, follicular CD4+ T cells are a median of 6.5 times more likely to be producing SIV RNA than extrafollicular CD4+ T cells [6]. Interestingly, in non-pathogenic SIV-infection in sooty mangabeys, a follicular concentration of virus replication

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is not observed [7], suggesting that productive T_{FH} infection may be a critical driver of HIV and SIV immunopathogenesis.

Mechanisms that promote HIV replication within T_{FH} are not fully understood. T_{FH} from human tonsils are highly permissive to both CCR5- and CXCR4-tropic HIV compared to other CD4+ T cell subsets *ex vivo* [8, 9]. The heightened permissivity of tonsillar T_{FH} cannot be fully explained by differences in memory subsets, cellular activation, or chemokine co-receptor expression [9]. Importantly, in an HIV-model system using humanized mice, T_{FH} rapidly accumulate in gut and female reproductive tract mucosal tissues and are the most permissive CD4+ T cell subset to HIV [10], suggesting that gut and vaginal T_{FH} may play a key role in establishment of HIV infection as well as ongoing virus replication.

The presence of a follicular dendritic cell (FDC) network and large amounts of FDC-associated HIV virions adjacent to T_{FH} within germinal centers (GC) [11–13] is one contributing factor predisposing T_{FH} to high levels of HIV infection and replication. This extracellular burden of virions is bound to FDC via antibody through complement and FC receptors [14] and appears shortly after infection [15]. In chronic disease, the amount of viral RNA (vRNA) associated with FDC is 10- to 40-fold more than is found in lymphoid mononuclear cells [12]. FDC harbour archived virus from the host [16], and these virions are potently infectious to CD4+ T cells, even in the presence of neutralizing antibodies [13]. FDC further promote HIV replication within T_{FH} by upregulating virus transcription through release of tumor necrosis factor-α (TNF-α) [8].

High concentrations of virus replication within T_{FH} are further promoted by a paucity of virus-specific cytotoxic T lymphocytes (CTL) within B cell follicles in both HIV [4] and SIV infection [6, 17]. Few SIV-specific CTL express the follicular homing molecule CXCR5 in the absence of the extrafollicular retention molecule CCR7, which restricts most from entering the follicle [6]. SIV replication is widespread throughout lymphoid tissues and viral replication is not concentrated in the follicle during acute infection, prior to when the CTL response has evolved to control the virus [6]. Similarly, compartmentalization of virus replication in T_{FH} is attenuated during AIDS, when the virus-specific CTL response is known to wane [6], and ablated following CD8 depletion in rhesus macaques [18]. Thus, other lymphoid cells besides T_{FH} are capable of replicating HIV-1, but largely restricted from doing so during asymptomatic disease by the presence of CTL.

Remarkably, despite the fact that T_{FH} are the major virus-producing cells in asymptomatic disease, they increase in number during early and mid-stages of chronic HIV [3, 19] and SIV infection [20]. It was shown in rhesus macaques that acute SIV infection results in the rapid formation of GC and an accumulation of T_{FH} coinciding with high levels of p27 expression in the follicle [21]. Furthermore, in lymph nodes from chronically HIV-infected individuals, virus-specific T_{FH}, particularly HIV Gag-specific T_{FH}, are expanded [19]. Thus, at least part of T_{FH} expansion is due to HIV antigen, as CD4+ T cells require antigen exposure for most cell division [22] and antigen persistence in the GC is required to sustain T_{FH} phenotypes [23]. Within the GC, T_{FH} are chronically exposed to HIV virions and antigens through interactions with B cells [24] and FDCs [11, 12]. Circulating T_{FH} are decreased in untreated

chronically-HIV infected individuals [25], suggesting that the GC offers a unique environment allowing for T_{FH} expansion. It should be noted that in advanced infection, T_{FH} expansions and GC morphology are lost and this is associated with the onset of SAIDS in rhesus macaques [26] and AIDS in humans [27].

Non-antigen-specific influences may promote expansion and persistence of T_{FH} in HIV and SIV infection in early stages of disease as well. Alterations of cytokine production observed during HIV and SIV infection, such as decreased interleukin-2 (IL-2) [28] and increased IL-6 [20, 29] and interferon-γ (IFN-γ) [30] promote T_{FH} expansions [1]. T follicular regulatory cells (T_{FR}) are a subset of follicular cells that directly regulate numbers and function of T_{FH} during HIV and SIV infection [31–34]. Two studies linked relative decreases of T_{FR} to expansions of T_{FH} in the SIV-infected rhesus macaque model [31, 32]. Increased cell survival may contribute to the persistence of T_{FH} as well. CXCR5+ cells in healthy human tonsils express elevated levels of the anti-apoptotic protein Bcl-2, and in the context of *ex vivo* R5 infection, Bcl-2 is upregulated in productively infected cells [35]. Interestingly, the depletion of CD8 T cells in untreated SIV infection leads to similar levels of replication in lymphoid memory T_{FH} and memory non-T_{FH}, however the memory T_{FH} contain higher levels of RNA and DNA copies up to 135 days after depletion and after CD8 recovery [18], suggesting possible preferential survival of T_{FH}.

HIV infection not only leads to alterations in T_{FH} numbers, but also changes in T_{FH} function. T_{FH} from lymph nodes of untreated individuals demonstrate expansions of HIV-specific IL-21+, INF-γ+, and TNF-α+ T_{FH} compared to treated individuals [19]. Furthermore, B cells from untreated individuals demonstrate a skewed phenotype [19]. Hypergammaglobulinemia is a well described phenomenon in untreated HIV-infected individuals, and Bcl6 expression in T_{FH} correlates with immunoglobulin G (IgG) levels [19]. Nevertheless, T_{FH} from untreated HIV patients are unable to stimulate robust IgG production *in vitro* [36], suggesting significant impairments in T_{FH} in the context of untreated infection, which is consistent with known clinical impairments in responses to vaccines. *In vitro*, impairments in the ability of T_{FH} to stimulate IgG are reversed by supplementation with IL-21 or blockade of PD-1 ligation on T_{FH} [36]. Circulating IL-21+ CD4+ T cells were shown to be transcriptionally equivalent to T_{FH} in seronegative individuals and peripheral HIV-specific IL-21+ T_{FH} in untreated HIV+ subjects were able to stimulate autologous CD8+ T cell activation and B cell class switching [37]. Expansions in T_{FR} occur in the context of both HIV and SIV infection, and these cells impair the ability of T_{FH} to secrete IL-21 and IL-4 [33], suggesting another potential mechanism for T_{FH} dysfunction.

Follicular HIV Reservoirs During Treated Disease

A stable and inducible latent viral reservoir within memory CD4+ T cells is maintained in HIV-infected individuals despite years of antiretroviral therapy (ART) that renders plasma viremia undetectable [38–40]. Furthermore, low frequencies of vRNA+ lymphocytes persist in peripheral blood [41] and lymph nodes of treated individuals [42] undergoing successful long-term ART. Virus replication rebounds from multiple foci in secondary lymphoid tissues once ART is stopped in both HIV-infected humans and SIV-infected rhesus macaques [43,

44]. Characteristics of the viral reservoir that is the source of recrudescent viremia are incompletely understood, and this is a major barrier to the development of an HIV cure. Furthermore, whether virus replication is ongoing in the context of ART is a matter of controversy. The presence of vRNA+ cells during ART could be due to reactivation of latently infected cells or alternatively ongoing rounds of virus replication. Although drug concentrations have been reported to be suboptimal in the lymph node [45], curiously little evidence for virus evolution has been found in most studies in patients whose viral loads remained well suppressed [46–48]. Furthermore, ART-related resistance mutations do not develop after long term virologic suppression [47, 49], which one would expect to occur if indeed drug concentrations in lymph nodes were suboptimal. Indeed, founder variants are the main HIV strains that emerge from lymphatic tissues during treatment interruption [44], and increasing data suggest that homeostatic proliferation of viral DNA+ cells is the major factor underlying persistent viral DNA levels [48, 50].

The fact that T_{FH} display anti-apoptotic properties, as discussed above, despite being the major virus-producing cell subset in untreated, asymptomatic HIV, suggests that they could harbour a significant amount of the latent viral DNA (vDNA) during treated disease. Indeed, in ART-suppressed SIV-infected rhesus macaques, the major vRNA+ cells in lymphoid tissues are T_{FH}, as determined by cell sorting studies [18], although vDNA was not concentrated in this subset. Virus replication in these cells could represent reactivation of latently infected memory T_{FH}. The existence of memory T_{FH} in humans has only recently been recognized [1, 51], and they have not been extensively studied in the context of HIV or SIV infection. T_{FH} transcription factors may promote establishment of HIV latency. The HIV long terminal repeat (LTR) contains binding sites for the master T_{FH} transcription factor Bcl6 that allows Bcl6 to repress HIV transcription [52] and it has been speculated that Bcl6 supports HIV latency [53]. Memory T_{FH} can be long-lived and primarily have a central memory phenotype, similar to the resting CD4+ T cell reservoir that harbors the majority of HIV DNA in treated individuals [50]. One recent study reported that the majority of HIV-1 DNA in peripheral blood was harboured by central memory T_{FH} in subjects with sustained virologic suppression on ART [54]. Nevertheless, the precise phenotype of peripheral T_{FH} is somewhat controversial [55] and until an accurate phenotype is determined, identifying the role of T_{FH} in the latent HIV reservoir using peripheral blood will be challenging.

During ART treatment T_{FH} numbers decrease relative to untreated disease, but remain elevated compared to healthy individuals [19]. Phenotypically, lymph node T_{FH} from treated HIV+ subjects have lower activation rates as evidenced by decreased Bcl6 expression and fewer HIV-specific IL-21+ T_{FH}, INF-γ+ T_{FH}, and TNF-α+ T_{FH} [19]. The expansion of T_{FH} in both HIV+ untreated and treated subjects, compared to healthy controls, is also associated with an increased transitional B cell phenotype and lower memory B cell formation [19]. The number of functional circulating T_{FH} is decreased in untreated HIV+ subjects, and T_{FH} numbers and function slightly recover in treated HIV+ subjects [25]. However, T_{FH} function is still incomplete and HIV+ subjects still have functional impairments [19] and poor vaccine responses [56, 57]. T_{FH} function has also been found to be crucial for subsequent vaccine responses in treated HIV+ subjects, as responses to flu vaccination were directly dependent on the ability of T_{FH} to proliferate, express ICOS, and produce IL-21 [58].

An alternative or additional explanation for the presence of HIV RNA+ cells in T_{FH} in the context of suppressive ART is that they represent new infection from virus archived on FDC. Following 6 months of ART, FDC-bound virions decrease but are nonetheless detectable; the residual number of copies of HIV RNA present on FDC was estimated to be nearly 10^8 virions in an average individual [59]. How long FDC bound virions remain infectious is unknown. In a non-permissive mouse model, FDC-bound HIV remained infectious for the maximum period studied, which was 9 months [60]. Although antiretroviral drugs that block entry, reverse transcription, and integration prevent most infections, these may not be fully effective resulting in occasional virus integration and replication. Thus, FDC-bound HIV could potentially provide a low level of new infections that manifest as founder virus, due to the archived nature of FDC bound virions [16].

Eliminating Follicular HIV Reservoirs

To date only one person has been successfully cured of HIV infection after receiving a bone marrow transplant with donor cells that were genetically resistant to HIV infection [61]. Multiple other attempts to achieve a cure or reduce the HIV proviral load have not achieved success. Knowledge of the follicular reservoirs outlined here and the hurdles that they pose to achieving a cure could provide some insights into these failures, as well as redirect efforts to more successful approaches.

Early attempts to activate and purge the viral reservoir were conducted using IL-2 [62] or CD3 activation [63], with the assumption that the viral reservoir would be purged from latently infected cells through HIV cytopathic effects or immune clearance. Patients receiving IL-2 in addition to ART had lower levels of replication competent HIV in peripheral blood CD4+ T cells [62] but upon interruption of ART plasma HIV levels quickly rebounded [64]. Thus, broad immune activation and treatment cessation proved unsuccessful in purging the HIV reservoir. More recent approaches to activate and purge the HIV reservoir have been directed at activating latent gene expression through the use of inhibitors of histone deacetylases (HDAC). This approach activates viral transcription without activating the cells. Clinical trials of several HDAC inhibitors have demonstrated increases in HIV RNA expression [65–67], however, none of these studies have revealed significant decreases in the latent resting CD4+ T cell reservoir [65–68]. One reason for this failure has been hypothesized to be a lack of an effector CTL response, as *in vitro* virus-specific CTL have been shown to reduce latently infected cells upon activation [69]. An alternative explanation is that virus-specific CTL are present, but do not enter follicles, as has been reported in untreated disease [4, 6]. Thus, strategies to boost numbers of CTL in B cell follicles, such as by transduction of the follicular homing molecule CXCR5 into HIV-specific CTL [70], could be an important component of HIV cure in combination with latency reversing agents. Although it is unknown if this approach would have deleterious effects, such as disruption of the GC reaction or alteration of antibody production, directing HIV-specific CTL into the follicles could eliminate HIV-infected cells within follicles.

The use of broadly neutralizing antibodies prophylactically after HIV exposure led to decreased establishment of HIV reservoirs in humanized mice and was effective in decreasing established reservoirs when combined with a combination of viral inducers [71].

Although the humanized mouse models are useful to study many aspects of HIV immunopathogenesis, most do not recapitulate key aspects of human lymphoid tissues. Specifically, they lack FDC and GC, and fail to develop IgG responses [72]. As noted above, FDC-bound virions are potently infectious to T_{FH}, even in the presence of neutralizing antibodies [13]. Thus, it would be important to carefully examine this strategy in a more physiologically relevant model, such as the SIV-infected rhesus macaques, before proceeding to test it in humans.

Despite the successful bone marrow transplant of the “Berlin patient” [61], subsequent transplants have proven unsuccessful in preventing HIV rebound [73, 74], although HIV DNA was not detected in these individuals peripheral blood mononuclear cells (PBMC) prior to interruption of therapy. Viral reservoirs also persist in simian-human immunodeficiency virus (SHIV)-infected rhesus macaques following transplantation [75]. Although some have concluded that this failure is due to residual infection of host CD4+ T cells, it is difficult to imagine that any purging strategy will more effectively eliminate infected CD4+ T cells than a bone marrow transplant, particularly in cases of graft versus host disease, which occurred in some of these transplants. An alternative explanation is that the transplantation regimens failed to eliminate cell-free infectious virus on FDC. It would be important to evaluate this possibility particularly in animal models, and develop approaches that are more effective against FDC in the transplant setting. Furthermore, strategies to displace virions bound to FDC outside of the transplant setting should be evaluated to determine if they diminish the reservoir. Previous work has shown the effectiveness of complement and CD21 antibody-mediated displacement of virions from the surface of B cells from HIV-infected patients *ex vivo* [24]. An immunotoxin-conjugated agent might be effective against FDC-bound virions as well [76].

Concluding Remarks

T_{FH} expand in number and are a major site of virus infection and replication in untreated, asymptomatic HIV infection as well as in treated disease. Multiple factors likely contribute to the concentration of virus replication in T_{FH} including heightened permissiveness, the presence of highly infectious virions on FDC, low frequencies of virus-specific CTL in B cell follicles, expansions in numbers and impairments in function. Emerging data suggest that memory T_{FH} constitute a significant fraction of the latent reservoir in treated disease, and this is an important area for future research (see Outstanding Questions). Whether interactions between FDC harbouring infectious virions and T_{FH} further contribute to the latent HIV reservoir remains to be determined. Strategies aimed at targeting follicular reservoirs of HIV could provide important insights into these questions, and potentially a cure for HIV infection. It should be noted that although T_{FH} may be a major cellular reservoir, other reservoirs have been described including the nasopharynx, lung, male and female genital tracts, as well as the brain [77, 78]. The relationship between follicular reservoirs and these sites, specifically whether additional therapies may be necessary to achieve a cure, remains to be determined and is an important question for future research.

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Outstanding Questions

- What fraction of latently infected CD4+ T cells are memory T_{FH}?
- How long do infectious virions persist on FDC in the setting of ART?
- Can removal of infectious complexes from FDC reduce the HIV reservoir and prevent viral rebound?
- Will expression of CXCR5 by virus-specific CTL induce them to home to follicles and suppress virus replication and ultimately clear the latent HIV reservoir?
- What is the relationship between follicular HIV reservoirs and other HIV reservoirs throughout the body?

Trends

- T follicular helper cells (T_{FH}) are the major HIV-producing cells in untreated disease.
- Heightened T_{FH} permissivity, follicular dendritic cells (FDC) virion retention, cytotoxic T lymphocytes (CTL) exclusion from the follicle, expansion of the T_{FH} subset, and T_{FH} dysfunction all contribute to HIV replication in T_{FH}.
- Limited data suggest that follicular reservoirs of HIV, including latently infected memory T_{FH} and FDC-bound virions, exist in treated disease.
- Strategies that target follicular reservoirs of HIV could be used to dissect out their role in the latent reservoir and HIV persistence.

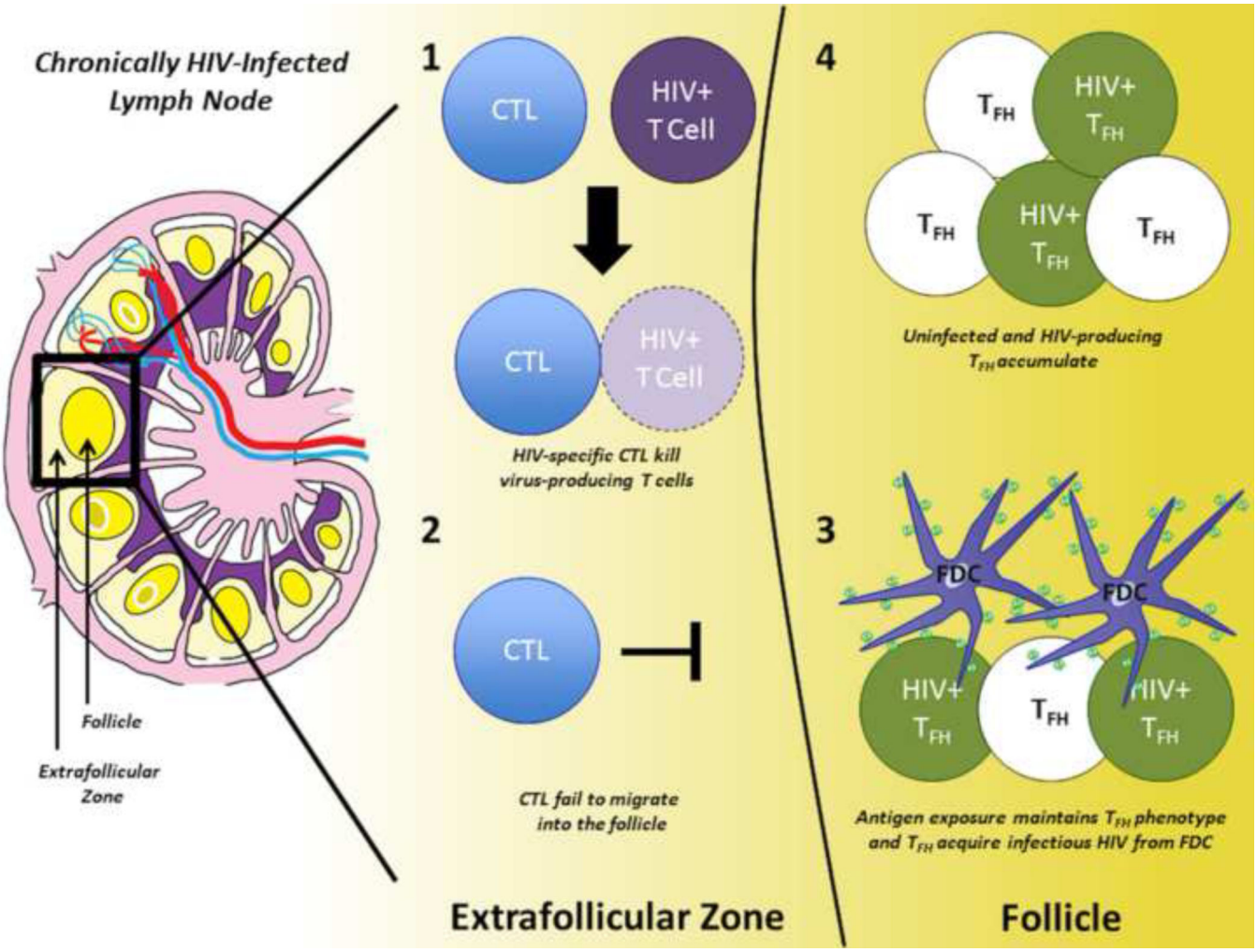

Figure 1. Model of T_{FH} Accumulation in Chronic, Untreated HIV Infection

HIV-specific CTL recognize and kill virus producing T cells (HIV+ T cell) in the extrafollicular zone (1), but are found in low numbers within the follicle due to low CXCR5 expression (2). Within the follicle, T follicular helper cells (T_{FH}) receive both activation signals and infectious HIV from interactions with follicular dendritic cells (FDC) (3). T_{FH}, including HIV-producing T_{FH} (HIV+), accumulate within the follicle (4).