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The regulation of T follicular helper responses during infection

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Abstract

Following infection, naïve CD4 T cells can differentiate into various functionally distinct effector and memory subsets, including T follicular helper (T_{FH}) cells that orchestrate germinal center (GC) reactions necessary for high-affinity, pathogen-specific antibody responses. The origins and function of this cell type have been extensively examined in response to subunit immunization with model antigens. More recently, we are beginning to also appreciate the extent to which microbial infections shape the generation, function and maintenance of T_{FH} cells. Here we review recent advances and highlight additional knowledge gaps in our understanding of how microbial infections influence priming, differentiation, localization and activity of T_{FH} cells following acute and chronic infections.

Introduction

Resolution of infections often depends on the generation of pathogen-specific antibodies. T follicular helper cells (T_{FH}) are key orchestrators of germinal center (GC) reactions, the products of which are plasma cells that secrete high-affinity antibodies that function to resolve primary infection and long-lived memory B cells that afford heightened protection against pathogen re-infection [1*]. Our understanding of the molecular regulation of T_{FH} cell development, function and maintenance is ever expanding and includes well-defined effects of specific cytokines (reviewed in this issue), transcription factors [2], microRNAs [3] and MHCII/TCR interactions [4,5]. By extension, understanding how various microbial infections regulate T_{FH} cell activity remains an important goal. Here, we review recent work that has shaped our current understanding of how T_{FH} responses are regulated during infection. Defining the cellular and molecular processes that govern the activation, function and maintenance of infection-induced T_{FH} cells will ultimately lead to novel strategies to modulate these cells to limit pathogen burden or truncate infection-induced pathologic responses.

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Infection-induced modulation of T_{FH} priming and differentiation

Distinct APC may differentially prime T_{FH} responses following infection—

Canonical T_{FH} priming is driven by cognate interaction between naïve $CD4^+$ T cells and conventional dendritic cells (cDC) expressing key cytokines (IL-6 in mice and IL-12 in humans) that induce Bcl-6, a transcriptional repressor that promotes expression of CXCR5. CXCR5 endows lymphocytes with the capacity to home to B cell follicles rich in CXCL13. Emerging data highlight how specific infections shape the activation of distinct subsets of APC that may preferentially induce T_{FH} development (**Figure 1**). During experimental cutaneous *Leishmania* infection, Langerhans cells facilitate T_{FH}-GC B cell interactions in skin draining lymph nodes, and ablation of Langerin+ cells markedly reduced the number of GC reactions and limited parasite-specific humoral immunity [6]. Recently, targeting antigen to splenic $CD169^+$ marginal zone macrophages triggered long-lived high affinity antibody responses and expanded T_{FH} cells [7], and $CD169^+$ macrophages may be preferentially targeted by some pathogens [8,9]. Notably, in models of systemic LCMV infection, T_{FH} cells are observed by day 2 post-infection, suggesting cDCs are driving this response [10]. In contrast, following IAV infection, a distinct population of $CD45^+$ mononuclear cells undergo CXCR3-dependent migration from the infected lung to the draining lymph nodes with markedly delayed kinetics [11], which coincides with the activation and differentiation of IAV-specific T_{FH}. Adoptive transfer of this APC population was sufficient to accelerate viral clearance, confirming their in vivo relevance to T_{FH} priming. In addition to the initial interactions with DC, or macrophages, new data show that B cells can participate in initial T_{FH} priming [12]. Strikingly, the capacity for B cells to prime T_{FH} differentiation is only apparent after infection, and not protein immunization. Moreover, the requirement of B cells for T_{FH} maintenance may only occur following infection by acute pathogens, because as the infection is resolved antigen becomes limiting. Indeed, when antigen is in excess, B cells can be dispensable for T_{FH} differentiation [13,14]. Finally, the extent to which an infection impacts the biology or activity of antigen presenting cells is also relevant for pathogen re-exposure, as recent work shows that circulating memory T_{FH} cells require interactions with DC in order to potentiate secondary immune responses in vivo [15**]. Thus, modulation of the survival or activity of unique APCs following infection may alter the induction of T_{FH} immunity and pathogen-specific humoral immune responses.

Infection-induced cytokines can promote and constrain T_{FH} development and activity—

Infectious organisms encode and release specific pathogen-associated molecular patterns (PAMPs) that engage pattern recognition receptors (PRRs) on APCs, triggering the release of distinct profiles of cytokines (**Figure 1**). While PAMPs are widely known to regulate extra-follicular B cell responses following infection or vaccination [16], recent data show that TLR9 signaling in DC and GC B cell numbers and the quantity and quality of secreted antibody [17]. Indeed, the ligand for TLR9 is unmethylated CpG DNA, which is relatively common in bacterial and viral DNA genomes, and TLR9 signaling can lead to the activation and secretion of IL-12 or type I IFN (IFNα/β) which are each known to regulate the priming and activity of T_{FH} cells (discussed below). While this study was limited to an examination of how various PAMPS modulate humoral immunity against model antigens, these data highlight that the nature of the infectious agent may influence priming of T_{FH}

responses. Consistent with this, engagement of retinoic acid-inducible gene I (RIG-I), a key PRR for RNA viruses, was recently shown to enhance vaccine-induced humoral immunity [18].

Cytokines play key roles in all phases of T_{FH} cell biology (**Figure 1**) and several recent studies show specific infections regulate the formation and activity of T_{FH} cells through modulation of cytokine release. IL-6 is key signal for the induction and initial differentiation of T_{FH}, mainly acting through either STAT1 or STAT3 to transactivate Bcl-6 [19,20]. Indeed, STAT3 signaling in T cells is necessary for antiviral humoral immunity and control of chronic LCMV infection [21]. Notably, in that model, STAT3 was dispensable for IFN-γ expressing effector T cell activity, but numbers and frequency of virus-specific Bcl-6$^+$CXCR5$^+$ T_{FH} cells were reduced by 50%. Although IL-6-mediated STAT3 activation and down regulation of CD25 expression (IL-2 signaling) are important for initial T_{FH} differentiation by [19], genetic deficiency of IL-6 does not prevent the eventual development of either T_{FH} or GC responses following acute LCMV infection [22], suggesting that other factors can compensate. IL-21 (or IL-27 discussed below) may serve this compensatory role, as the loss of both IL-6 and IL-21 wholly abrogates T_{FH} and GC B cell responses [23]. SIV infection of macaques is also linked to IL-6 production and expansion of T_{FH} cells [24], although humoral antiviral immunity was not directly examined in those studies. In contrast to the aforementioned studies, IL-6-deficiency in the setting of chronic helminthic infection results in enhanced parasite-specific IgE responses [25], although other aspects of humoral immunity, including T_{FH} responses, were not examined in that study. Collectively, these data highlight the context-specific role of IL-6 in regulating T_{FH} development and activity.

As noted, a related cytokine, IL-27, may also substitute for IL-6 as it can both promote T_{FH} differentiation and trigger STAT3-dependent IL-21 expression by T_{FH} cells during viral infection [26,27]. IL-27 also appears to limit IL-2 expression in effector CD4 T cells [28], which may indirectly promote T_{FH} differentiation because IL-2 and STAT5 signaling are potent negative regulators of T_{FH} development [29,30]. Paradoxically, IL-27 signaling can also activate STAT5. Thus, a critical balance of STAT3 and STAT5 activation likely impacts T_{FH} differentiation. Because IL-2 potently limits T_{FH} development [30], systemic infections associated with relatively high IL-2 expression are therefore likely to sharply dampen T_{FH} responses. Notably, following experimental IAV infection, T regulatory (T_{REG}) cells indirectly promote the formation of GC reactions by consuming excess IL-2 [31**]. It will be of interest to determine whether the ability of T_{REG} to promote T_{FH} differentiation via the consumption of IL-2 is more important for particular types of infection (i.e. localized vs. systemic), or compared to subunit vaccination.

Type I IFN (IFNα/β) are induced by many pathogens and this family of cytokines has varying effects on T_{FH} development. Type I IFN were recently shown to induce Bcl-6, CXCR5 and PD-1, but not IL-21, in CD4 T cells [32], suggesting that type I IFN may promote CD4 T cells to adopt a T_{FH} phenotype. On the other hand, following LCMV infection, IFNα/β signaling directly represses T_{FH} development [33]. In that model, T_{FH} differentiation required STAT3 signaling and in CD4 T cells lacking STAT3, blockade of type I IFN signaling restores the defective T_{FH} response [33]. Adding to the complexity, the timing of either T cell priming or type I IFN signaling following infection may profoundly

impact T_{FH} differentiation. CD4 T cells primed during an established persistent infection are less likely to become T_H1 cells and almost exclusively develop into T_{FH} cells, a process that requires type I IFN signaling [34*]. Clearly the context of type I IFN signaling determines whether it promotes or constrains T_{FH} development. Type II IFN (IFN-γ) has also been linked to regulating T_{FH} development and activity. Excessive IFN-γ is reported to drive pathologically large T_{FH} responses that contribute to autoimmunity [35]. Conversely, IFN-γ is known to transiently down regulate the expression of CXCL13 and disrupt trafficking of DC and lymphocytes in reactive lymphoid tissue [36]. Moreover, IFN-γ can function in a STAT1-dependent feed-forward loop to activate T-bet [37], which can directly interact with and limit the activity of Bcl-6 [38]. Thus, while promoting T_{FH} development in a genetic model, IFN-γ may restrict the formation or maintenance of T_{FH} during infection. Consistent with the latter, we have observed that IFN-γ can limit T_{FH} and GC B cell responses during blood stage *Plasmodium* infection (Butler and Zander et al., submitted). Collectively, these reports underscore that distinct APC subsets and specific cytokines shape whether pathogen-specific CD4 T cells adopt a T_{FH} fate and that developing strategies to manipulate these pathways could improve outcomes following infection.

Modulation of T_{FH} trafficking and localization during infection

Following priming by DC, CXCR5-dependent anatomic repositioning of T_{FH} cells into B cell follicles is essential for orchestration of the GC reaction. In addition to CXCL13, T_{FH} motility is regulated by ICOS-ICOSL interactions between T_{FH} and non-cognate B cells at the T-B boarder, which potentiates T_{FH} migration into the follicle [39]. Once in the follicle, T_{FH} activity depends on cognate interactions with B cells, which further reinforces T_{FH} differentiation and function [40,41]. Each step of T_{FH} activation and differentiation critically depends on cell-cell interactions within discreet anatomic structures of lymphoid tissue. Thus, infections that disrupt the organization of lymphoid tissues can negatively impact humoral immunity. *Toxoplasma* infection dysregulates expression of cytokines that position cells in lymphoid tissue (e.g. LTα and LTβ delays the kinetics of the anti-parasitic antibody response [42]. Experimental malaria models also reveal profound disruption of splenic architecture with impacts on the quality of the parasite-specific antibody response [43]. LPS and associated gram negative bacterial infections also markedly alter cellular organization in lymphoid tissues; infection with *Salmonella* disrupts lymphoid architecture via dysregulation of chemokine gradients [44]. These observations are notable as trafficking and localization of T_{FH} cells may also determine their relative B cell helping capacity [45], as has been observed following IAV infection [46]. Together, these data underscore that infections that disrupt the organization and homing of cell to lymphoid tissue can directly impact the formation of T_{FH}-regulated antibody responses.

Alteration of T_{FH}-GC B cell conjugates and helper function during infection

T_{FH} engage in bi-directional communication with GC B cells via secreted factors (e.g. IL-21 and IL-4) and cell surface expressed co-stimulatory and co-inhibitory receptors. CD28 is essential for naïve CD4 T cell priming and activation, but new data show that CD28 is also critical for the differentiation and maintenance of T_{FH} cells responding to viral infection [47]. Another costimulatory receptor, OX40, is required for antiviral humoral immunity [48]; however, administration of OX40 agonists early after viral infection halts T_{FH}

differentiation [49], suggesting that either the timing or context of OX40 signaling critically regulates T_{FH} differentiation (**Figure 1**). The co-inhibitory receptor PD-1 is widely used to identify T_{FH} cells, but it also regulates T_{FH} activity. Following vaccination, the absence of PD-1 signaling diminishes the quantity of antigen-specific antibody but enhances the affinity [50]. In contrast, following infection with either helminthes [51] or protozoan parasites [52], disrupting association of PD-1 with its major ligand PD-L1 markedly enhances pathogen-specific antibody responses. Consistent with this, Cubas et al [53**] recently reported higher frequencies of PD-L1 expressing B cells in lymph nodes of HIV-infected individuals and that engagement of PD-1 on T_{FH} suppressed proliferation and expression of ICOS and IL-21. Of note, following vaccinia virus infection, the loss of CD80, but not CD86, on follicular B cells profoundly inhibited T_{FH} and neutralizing antibody responses [54]. It is worth noting that CD80 is an alternative ligand for the PD-L1. Thus, whether the PD-1:PD-L1:CD80 axis differentially regulates T_{FH} function following infection by distinct microbes remains an important question. Finally, inducible deletion of the co-inhibitory receptor CTLA-4 in T cells resulted in T_{FH} expansion and enhancement of antigen-specific B cell and secreted Ab responses [55,56**]. Although this work was restricted to subunit vaccination, these data further support that co-inhibitory molecules can profoundly regulate T_{FH} cell activity in the GC. These data also argue that compared to vaccination, infection may change the relative role of molecules that regulate T_{FH}-GC B cell interactions. This is in line with observations showing Bcl-$6^{-/-}$ mice fail to form sizable and stable $CXCR5^{+}$ T_{FH} populations following acute *Listeria monocytogenes* infection [57], but $CXCR5^{+}$ CD4 T cells develop normally in Bcl-$6^{-/-}$ mice following peptide vaccination [58]. Thus, the contribution of known regulators of T_{FH} activity may depend on the nature of the infection and it will be of particular interest to understand how various infections alter circuits of communication between T_{FH} and GC B cells.

Modulation of T_{FH} plasticity and ‘memory’ formation during infection

A large body of work supports that T_{FH} development is not solely driven by the activity of a single “master” transcription factor (i.e. Bcl-6) and the differentiation of T_{FH} cells is shaped by the composite of cooperative and antagonistic factors (reviewed in [1]). From this perspective, infections may differentially impact both T_{FH} plasticity and the capacity of T_{FH} to form memory subsets. Indeed, T_{FH} cells retain chromatin marks consistent with their ability to revert to T_H1, T_H2 and T_H17 cell differentiation patterns [59] and schistosome-specific T_{FH} cells differentiate from IL-4^{+}GATA-3^{+} T_H2 cells [60], suggesting that T_{FH} cells retain a relatively high degree of plasticity and functional diversity. In contrast, other data show that CD4 T cells “remember” their previous lineage pathway, exhibit evidence of having committed to either T_H1 or T_{FH} lineage differentiation and assume their original phenotype and function during secondary immune responses [61**]. Indeed, whether T_{FH} form functional memory populations following infection is an area of intense focus. One of the first reports that show formation of T_{FH} memory cells following infection utilized an IL-21 reporter mouse. In that study, IL-21^{+} T_{FH} cells formed long-lived populations that could adopt either conventional T_H1 effector activity or retain T_{FH} activity during recall responses [62], further supporting the relative plasticity of memory T_{FH}. Circulating memory T_{FH} have been identified and have been shown to be more potent inducers of secondary immune responses compared to primary effector T_{FH} cells [15**]. In some HIV

infected individuals, circulating populations of memory-like T_{FH} cells exhibit high functional activity *ex vivo* and their numbers strongly correlate with broadly neutralizing antibody responses [63]. Of note, cells purported to be T_{FH} precursors, which exhibit a $CCR7^{lo}PD\text{-}1^{hi}$ phenotype, were recently identified [64**]. Strikingly, these cells appear in the circulation prior to the formation of GC reactions and it was argued these T_{FH} precursors might circulate to non-draining lymph nodes positioning them to rapidly mount humoral immunity should an infection become systemic. The formation, stability and participation of infection-induced circulating memory T_{FH} cells warrant further investigation.

Chronic infections shape TFH development and activity

Chronic HIV, parasitic and bacterial infections significantly impact human health and understanding the extent to which chronic infections regulate T_{FH} cell activity is of interest. In general, data support that persistent infections direct CD4 T cells towards a T_{FH} developmental pathway [65*]. Late expression of IL-6 appears to instruct this developmental redirection during chronic LCMV infection [20]. Moreover, the persistence/density of antigen [41,66,67], DC-T cell dwell time [66] and overall APC-T cell interaction affinity [4] have each been implicated in regulating T_{FH} differentiation or function. Despite data showing that sustained antigenic stimulation promotes T_{FH} development, chronic HIV infection is associated with impaired T_{FH} responses [68]. Moreover, a study in *Leishmania*-infected macaques showed that as infection transitions from acute to chronic T_{FH} responses undergo contraction and parasite-specific antibody titers wane rapidly [69], arguing that the lack of T_{FH} cell maintenance may underlie inefficient humoral immunity during chronic visceral leishmaniasis. Chronic *Litomosoides sigmodontis* infection also causes long-term disruption of T-dependent antibody responses linked to reduced frequencies and numbers of T_{FH} cells [70]. Although the exact cellular and molecular mechanisms were not established in the *L. sigmodontis* model, the induction of regulatory cells was postulated to constrain the induction of humoral immunity. Chronic bacterial infections are also linked to reduced T_{FH} activity. *Borrelia bergdorferi* infection is associated with dysfunctional GC reactions [71], and recent data show that although *B. bergdorferi*-specific T_{FH} cells are induced, they only support short-lived antibody responses [72]. While there are conflicting data regarding whether antibody responses are critical for limiting *Mycobacterium tuberculosis* (*Mtb*) infection, in murine models, $CD4^{+}CXCR5^{+}$ T cells accumulate in the *Mtb*-infected lung and exhibit features of both T_{FH} and T_H1 cells [73]. These cells respond to CXCL13, localize within the lung parenchyma and orchestrate the formation of lymphoid follicles within the granuloma to provide optimal control of *Mtb*. Consistent with this, $CXCR5^{+}$ B cells and plasma cells secreting *MtB*-specific antibody are found within granulomas in infected macaques [74]. Finally, emerging evidence suggests that co-infection may also profoundly influence the activity of T_{FH} cells and subsequent pathogen-specific antibody responses [75]. The extent to which medically important chronic infections shape the formation and function of effector and memory T_{FH} cells is only beginning to be understood.

Conclusions

T_{FH} cells are essential for helping B cells produce antibodies that limit microbial infection. APC activity, cytokines, cell trafficking and communication with GC B cells regulate the

differentiation, function and formation of effector and memory T_{FH} cells. Recent studies are beginning to reveal how acute and chronic infections impact each facet of T_{FH} development, as well as their plasticity and their capacity to form stable memory populations. However, numerous questions remain. For example, the full extent to which major human pathogens (e.g. *Plasmodium* and HIV) limit T_{FH} development and function is of significant interest. Indeed, these and other infections that fail to induce long-lived memory B cells and efficacious antibody responses may be linked to direct impacts on T_{FH} biology. Moreover, the relative role and contribution of $Foxp3^+$ T follicular regulatory (T_{FR}) cells [76] during infection warrants investigation. A thorough understanding of the molecular and cellular circuits that regulate T_{FH} activity during infection will help identify opportunities for the treatment of infectious disease.

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Highlights

- Infections impact multiple phases of T_{FH} differentiation
- Distinct populations of APC may differentially prime pathogen-specific T_{FH} cells
- T_{FH} localization and function are influenced by infection
- Chronic infections differentially impact T_{FH} -mediated immunity

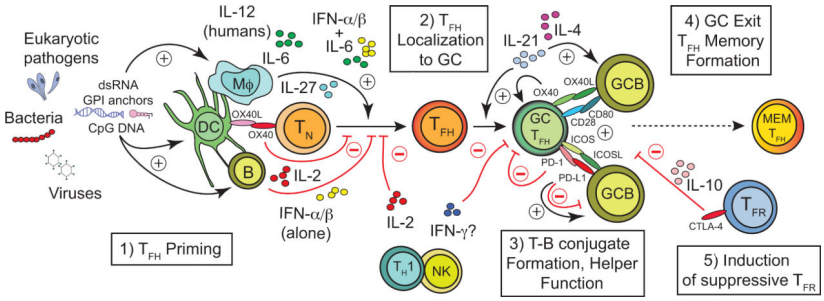

Figure 1.

Acute and chronic infections can impact five key processes that regulate the formation, function and persistence of pathogen-specific T follicular helper (T_{FH}) cells. **1**) Infections may induce or limit the activity or survival of unique subsets of antigen presenting cells (APC) bearing capacity to prime T_{FH} responses. T_{FH} priming may also be impacted by specific pathogen-associated molecular patterns (e.g. dsRNA, CpG DNA, glycophosphatidylinositol (GPI) anchors) that may elicit distinct cytokine profiles. APC-secreted cytokines can either promote (IL-12 in humans; IL-27, IL-6 or IL-6 + IFNα/β in mice) or constrain (IL-2 or IFNα/βalone) the differentiation of T_{FH} cells from naïve $CD4^+$ T cell precursors (T_N). **2**) Many infections cause dysregulation of chemokine expression that coordinates lymphocyte trafficking to or away from follicles (e.g. CXCL13 and CXCL12, CCL19, CCL21, respectively) or controls the architecture of lymphoid tissue (e.g. LTα/β, TNF), thereby limiting the magnitude or quality of T_{FH}-orchestrated germinal center (GC) reactions. The capacity for T_{FH} cells to traffic between GC reactions within a lymph node may also be impacted, although the relative contribution of inter-GC trafficking by T_{FH} cells is less clear. **3**) The capacity of T_{FH} to form stable conjugates with antigen-presenting GC B cells (GCB) is necessary to sustain the GC reaction. Infections may alter the secretion of critical cytokines (IL-21, IL-4, IL-2, IFN-γ) or expression of cell surface receptors (ICOS, PD-1, CD80, OX40) and ligands (ICOSL, PD-L1, CD28, OX40L) that mediate these interactions and coordinate the bi-directional communication between T_{FH} and GC B cells. **4**) Infections likely impact the formation and stability of memory (MEM) T_{FH} subsets, although the factors that regulate this are not yet clear. **5**) Infections also likely trigger the expansion or enhance the suppressive capacity of $Foxp3^+$ follicular regulatory (T_{FR}) cells that impede the development of long-lived memory B cell and secreted antibody responses through specific cytokines (e.g. IL-10) or cell surface receptors and ligands (e.g. CTLA-4). Black arrows and red “T” lines represent factors that either promote or limit T_{FH} and GC B cell responses, respectively.