HHS Public Access

Author manuscript

Curr Opin Organ Transplant. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Curr Opin Organ Transplant. 2016 February ; 21(1): 1–6. doi:10.1097/MOT.0000000000000260.

T Follicular Helper Cells in the Generation of Alloantibody and Graft Rejection

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Abstract

Purpose of Review—T follicular helper (Tfh) cells are an increasingly relevant $CD4^+$ T cell subset responsible for the provision of help to B cells for the generation of an effective humoral immune response. Here we review recent studies that have provided critical insights into the mechanisms of Tfh cell differentiation and function, and introduce newly identified roles for Tfh cells in human disease.

Recent findings—Novel molecular regulators of the Tfh cell differentiation program along with newfound roles for the costimulatory and coinhibitory ICOS, PD-1 and CTLA-4 pathways on Tfh cell function have been appreciated. While circulating Tfh and Tfh-like subset signatures have been linked to numerous immune conditions, extrapolation of these findings to organ transplantation is just beginning.

Summary—The combination of recent progress with regard to Tfh cell biology at the basic science and clinical levels is guiding the elucidation of the role of Tfh cells in the alloimmune response. Application of this knowledge towards the development of novel therapeutic strategies for use in transplantation is imminent.

Keywords

T follicular helper cells; donor-specific antibodies; germinal centers; costimulation

Introduction

The discovery that T follicular helper (Tfh) cells likely constitute a distinct lineage of $CD4^+$ T cells [1] has spurred a wealth of investigation into this area over the last decade. The importance of Tfh cells in the provision of T cell help to B cells, germinal center (GC) formation, affinity maturation and the generation of memory B cells and long-lived plasma cells is widely accepted in the context of salutary immune responses to pathogens and vaccination, and pathologically in autoimmunity [2, 3*]. However, a considerable knowledge gap exists regarding the role of Tfh cells in alloimmunity. Here we review the recent discovery of novel molecular and cellular mechanisms of Tfh cell regulation along with newly identified roles of Tfh cells in human disease that will help elucidate the role of

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Conflicts of interest

None

Tfh cells in donor-specific humoral immune responses and guide therapeutic strategies aimed at targeting Tfh cells to improve outcomes in organ transplantation.

Basic Tfh Biology

Tfh cells frequently encounter antigen during their multistage differentiation process, thus it makes teleological sense for them to have a very fine-tuned and sensitive TCR signaling response with great capacity for stimulatory and inhibitory control of their differentiation and activity. Novel molecular insights into the factors that regulate the Tfh cell differentiation program, including the increasing levels of ICOS, PD-1 and CTLA-4 expression on Tfh cells as they differentiate into more polarized forms, present an opportunity for tight regulation and therapeutic manipulation of Tfh cell function.

Molecular regulation of Tfh cell differentiation

A critical knowledge deficit remains in our understanding of Tfh cell differentiation. The transcription factors LEF-1 and TCF-1 have just recently been implicated in orchestrating early Tfh cell differentiation by establishing responsiveness of naïve $CD4^+$ T cells to Tfh cell signals, sustaining expression of the IL-6 cytokine receptor, enhancing expression of the costimulatory receptor ICOS, and promoting expression of the transcription factor Bcl6 [4*]. Later in the differentiation process, ICOS co-stimulation and its downstream signals have been shown to maintain the Tfh cell phenotype and control Tfh cell localization in the B cell follicle by regulating the novel transcription factor Klf2 via Foxo1 [5]. Additionally, sphingosine-1-phosphate receptor 2 is highly expressed in GC Tfh cells and, along with CXCR5, cooperatively regulates localization and retention of Tfh cells in GCs [6]. These novel insights provide a better understanding of Tfh cell development and offer molecular targets for Tfh-directed treatment strategies.

Expanded roles for ICOS:ICOSL interactions

Because B cells represent the major APC type for follicle-homing T cells at later stages of Tfh cell differentiation, recent studies have shown that the amount of antigen dictates the Tfh cell and GC B cell response, and that persistent antigen and GC B cells sustain the Tfh phenotype [7]. Importantly, ICOS:ICOSL and CD40:CD154 interactions were required for the maintenance of mature Tfh cells in response to antigen, and prolonged stimulation of Tfh cells led to an exaggerated humoral immune response.

Not only does ICOS on Tfh cells mediate positive costimulatory signaling for Tfh cell differentiation via binding of ICOSL on cognate antigen-specific B cells, the ICOS:ICOSL axis plays a newly discovered role in the follicular recruitment of activated T cells by inducing directional migration of $CD4^+$ T cells [8]. This is a costimulation-independent process where non-cognate, follicular bystander B cells express ICOSL to collectively form an ICOS-engaging field that results in ICOS-driven motility and recruitment into the B cell follicle. Once the GC reaction is underway, ICOSL induces a dynamic state of cognate T-B cell entanglement with B cell acquisition of CD40 signals that promotes outer-zone co-localization of GC B cells and Tfh cells [9**]. This ICOSL-mediated, contact-dependent positive feedback interaction gives high affinity GC B cells more access to Tfh help and

provides individual B cells the ability to competitively participate in the GC reaction and develop into high affinity plasma cells.

These results demonstrate both costimulation-dependent and -independent functions for ICOS expression on Tfh cells, and uncover key aspects of ICOS:ICOSL-mediated Tfh cell development, maturation, maintenance, and control of the quality of long-lived humoral immunity. Thus therapies aimed at disrupting the ICOS-ICOSL and Tfh cell-GC B cell interactions may be useful in the treatment of T cell-dependent antibody-mediated conditions.

Inhibition and regulation of Tfh cells through PD-1 and CTLA-4

This review period includes major key developments in the regulation of Tfh cells via the classic coinhibitors PD-1 and CTLA-4. First, it is now known that PD-1 exerts a coinhibitory effect on Tfh cells. Evidence for this includes work from Butler et al., who used a murine model of malarial infection to show that in vivo blockade of PD-L1 restored $CD4^+$ T cell function, amplified the number of Tfh and GC B cells, enhanced protective antibodies, and rapidly cleared blood-stage malaria [10]. In humans, higher frequencies of PD-L1-expressing GC B cells exist in lymph nodes from HIV-infected individuals [11]. Importantly, in vitro analysis of lymph nodes from uninfected and infected persons showed that engagement of PD-1 on Tfh cells led to a reduction in ICOS expression and IL-21 secretion, and PD-1 blockade enhanced HIV-specific immunoglobulin production.

CTLA-4 has long been implicated in controlling humoral responses, but the mechanisms by which CTLA-4 regulates antibody production are not known. Several groups have recently provided significant contributions to our current understanding of the role of CTLA-4 on Tfh cell-mediated immunity. Sage et al. observed that Tfh and T follicular regulatory (Tfr) cells express increased levels of CTLA-4, and that genetic deletion of CTLA-4 increased both Tfh and Tfr cell numbers and augmented B cell responses [12**]. In the effector phase following immunization, loss of CTLA-4 on Tfh cells resulted in improved B cell responses, whereas loss of CTLA-4 on Tfr cells resulted in defective suppression of antigen-specific antibody responses. Similarly, Wing et al. demonstrated that Treg control of antigen-specific Tfh cells and humoral responses is also accomplished via CTLA-4 [13**]. Furthermore, it has been reported that CTLA-4 controls Tfh cell differentiation by regulating the strength of CD28 engagement by its ligands in a graded fashion, and that the magnitude of CD28 engagement as regulated by CTLA-4 determines the degree of Tfh cell differentiation [14**].

In total, these studies have identified various novel inhibitory and regulatory mechanisms by which PD-1 and CTLA-4 limit Tfh cell function. The suppressive potential of PD-1 and CTLA-4 on the humoral immune response is ripe for future investigations aimed at exploiting these axes to combat antibody-mediated rejection (AMR) following transplantation.

Cytokine signaling in Tfh differentiation

Targeting cytokines critical for Tfh cell function represent another strategy to suppress antigen-specific humoral responses. IL-6 is required for early stage Tfh cell differentiation

[15, 16] and may mediate peripheral differentiation of human Tfh cells by circulating plasmablasts [17]. Anti-IL-6R treatment in mice sensitized with skin allografts successfully attenuated both *de novo* and secondary donor-specific antibody (DSA) responses [18, 19] by modulating a number of regulatory and effector cells, including a reduction of Tfh cells. Targeting of the IL-6/IL-6R axis may present a readily translational strategy to prevent primary DSA formation and control Tfh cell-mediated recall antibody responses in previously sensitized transplant recipients, as the humanized anti-IL-6R mAb tocilizumab is clinically available and approved by the FDA for the treatment of rheumatoid arthritis.

In contrast to IL-6, IL-7 has not been widely recognized as a critical cytokine for Tfh differentiation. Nonetheless, Sung and colleagues have recently demonstrated that IL-7 plays a pivotal role in Tfh generation and GC formation in vivo [20]. Treatment with anti-IL-7 neutralizing antibody markedly impaired the development of Tfh cells and IgG responses, while co-delivery of Fc-fused IL-7 significantly increased influenza virus vaccine-induced antibody responses, accompanied by robust expansion of Tfh cells and GC B cells. Furthermore, IL-7-mFc induced earlier and cross-reactive IgG responses, leading to striking protection against heterologous influenza virus challenge. These results suggest that while an IL-7 agonist could be used for inducing strong and cross-protective humoral immunity against highly mutable viruses, antagonism of the IL-7 axis may suppress DSA formation and the generation of heterologous alloantibodies in the setting of organ transplantation.

Finally, emerging evidence exists to suggest that the IL-12/23 pathway may play a role in Tfh differentiation and/or survival. In a clinical report, subjects lacking functional IL-12R1 (a receptor for IL-12 and IL-23) displayed substantially less circulating memory Tfh and memory B cells, along with impaired GC formation than control subjects [21].

Clinical studies of Tfh cells: Circulating subsets

Defined subsets of $CD4^+CXCR5^+$ T cells that have experienced some aspects of Tfh differentiation and exhibit distinct effector and memory functions are continuously being defined in response to vaccination and in autoimmune conditions [2]. Contrary to previous dogma that GC Tfh cells were terminally differentiated and could not leave GCs, recent studies have clearly demonstrated Tfh cell memory in mice [22–24] and now humans [25–27]. In one study, the induction of a subpopulation of circulating $ICOS^+CXCR3^+CXCR5^+CD4^+$ memory Tfh cells correlated with the development of protective antibody responses generated by memory B cells following influenza vaccination [25]. He et al. identified a $CCR7^{lo}PD\text{-}1^{hi}$ subset of circulating $CXCR5^+CD4^+$ Tfh cells in humans and mice with a partial Tfh effector phenotype that was indicative of active Tfh differentiation in lymphoid organs and correlated with clinical indices of autoimmune disease [26]. Another subpopulation of circulating $PD1^+CXCR5^+CD4^+$ memory T cells was identified in normal individuals; these resting memory cells most related to GC Tfh cells by gene expression, cytokine profiles and functional properties, and their frequencies correlated with beneficial broadly neutralizing HIV antibody responses [27]. Thus, because access to lymphoid tissue is limited in humans, it is beneficial to study circulating Tfh and Tfh-related cells that comprise a small subset of lymphocytes [28, 29] in order to identify the best

correlates of B cell help in the context of human immunity and disease. Frequencies of circulating $CD4^+CXCR5^+$ T cells or subsets thereof could serve as biomarkers to monitor for protective antibody responses during infection or after vaccination, disease activity in cases of autoimmunity, or possibly in transplant rejection.

Tfh cells in Transplantation

Thus far the recent developments in Tfh biology presented in this review collectively highlight the potential for targeting Tfh cells through novel transcription factors, costimulatory and coinhibitory molecules, and cytokines that control their development to help B cells in mounting the humoral immune response. Coupled with the correlation of traceable circulating Tfh and Tfh-like cells, these novel findings are poised to guide investigational strategies aimed at understanding Tfh cell biology in response to alloantigen in the transplantation setting.

Costimulation Blockade

CD28/CD80/86 and CD40/CD154 costimulatory interactions are essential for effective Tfh cell development and T-dependent antibody responses. Rabant et al. reported that donor-specific memory $CD4^+$ T cells deliver help to CD40-deficient B cells and induce DSA in CD40 knockout heart recipient mice in a CD40-independent manner [30]. However, this process was not accompanied by GC formation and failed to maintain stable levels of DSA and induce long-lived plasma and memory B cells, emphasizing that targeting the T:B cell interaction is critical to any attempt at curbing the development of durable humoral alloimmunity. In a related follow up study, short-term neutralization of BAFF alone or BAFF plus APRIL synergized with anti-CD154 mAb to prolong heart allograft survival in recipients containing donor-reactive memory $CD4^+$ T cells [31*]. The prolongation was associated with a reduction in anti-donor antibody responses, and inhibition of reactivation and helper functions of memory $CD4^+$ T cells. Further, the discovery that IFN-γ production by memory helper T cells is required for CD40-independent alloantibody responses in the same murine heart allograft model offers another alternative target to help combat costimulation blockade-resistant T cell-dependent antibody responses in transplantation [32]. While Tfh cells were not specifically described in these studies, the authors' conclusions are relevant to Tfh cells as approximately 20% of all human central memory $CD4^+$ T cells are $CXCR5^+$ [33].

Costimulation blockade of the CD28 pathway in the form of CTLA-4Ig is known to attenuate DSA, but whether this effect is mediated through Tfh cells is yet to be determined. The data reviewed here implicating CTLA-4 as a critical mediator of Tfh regulation and inhibition supports that Tfh suppression may be enhanced by selective CD28 blockade rather than CTLA-4Ig, which indiscriminately blocks both CD28 and the co-inhibitor CTLA-4 [34]. Based on this hypothesis our group showed that Tfh cells express high levels of CTLA-4, and that selective CD28 blockade led to a greater reduction in donor-specific Tfh cells, prolonged murine skin allograft survival, and exhibited superior suppression of DSAs when compared to CTLA-4Ig [35*]. These observations suggest that selective CD28 blockade in the presence of intact inhibitory CTLA-4 signaling facilitates improved suppression of Tfh cells and T cell dependent alloantibody responses, and should serve to

guide the preclinical development of agents aimed at targeting the CD28 costimulation pathway for use in transplantation.

Antibody-mediated rejection

In a murine model of chronic graft versus host disease (cGVHD) caused in part by alloantibody secretion, blockade of GC formation suppressed cGVHD [36]. Definition of the cellular components of this cGVHD model showed that increased Tfh and GC B cells were required, and that IL-21, ICOS and CD40 blockade hindered GC formation and alloantibody-mediated cGVHD [37]. Likewise, in a nonhuman primate (NHP) kidney transplant model of AMR, the use of belatacept (second generation CTLA-4Ig) or anti-CD40 each prevented *de novo* DSA formation [38*]. Belatacept and anti-CD40 treatment were associated with the maintenance of immature circulating IgM^+ B cell phenotypes and reduced B cell clonal expansion, GC Tfh cells and IL-21 production. DSA prevention using these methods of costimulation blockade are well documented at the small and large animal level [39, 40], including human studies [41], but the mechanism of DSA suppression has not been elucidated. These data are the first in large animals to implicate the Tfh and GC axis in pathologic alloantibody formation, supporting blockade of these pathways to prevent *de novo* DSA formation in transplant recipients. Using the same NHP model of T cell depletion and AMR, treatment with atacicept to achieve BAFF blockade led to decreased levels of DSA and shifted the histologic character of rejection from humoral to cellular [42], suggesting that BAFF/APRIL blockade with atacicept may reduce humoral rejection in the setting of clinical T cell depletion.

Tfh in human kidney transplantation

The identification of circulating Tfh cells and their ability to mediate humoral alloreactivity in transplantation is just beginning to be explored. In a small number of renal transplant recipients, peripheral Tfh cells were identified before and after transplant [43*]. These Tfh cells had diminished ability to make IL-21 *ex vivo*, but retained their ability to induce IL-21-mediated B cell differentiation and immunoglobulin production despite immunosuppression. Interestingly, the authors identified Tfh cells co-localized with B cells and immunoglobulins in kidney biopsies taken during rejection, suggesting the presence of follicular-like structures in the rejecting kidney. The authors speculate that functional Tfh cells circulate in kidney transplant patients on immunosuppression with the potential to contribute to the humoral immune response, possibly through ectopic lymph node-like structures in the allograft. This hypothesis is supported by the well documented increase in Tfh and Tfh-like cells in patients with autoimmune diseases [2] and the recent identification of functional Tfh cells in inflamed human renal tissue in the setting of *in situ* inflammation [44**]. Based on these observations and what is known about Tfh cells and clinical disease, Baan et al. propose that the problems of DSA and AMR in transplantation are mediated by Tfh cell production of IL-21 in secondary and ectopic lymphoid organs, and that targeting the IL-21 axis has great therapeutic potential [45].

Conclusion

Despite great strides in understanding the molecular and cellular mechanisms of Tfh cells and their roles in human disease, much more remains to be learned regarding the balance of costimulatory and coinhibitory signaling on activated $CD4^+$ T cells committed to Tfh differentiation, and their regulation by cellular mechanisms that determine their ultimate function, particularly in the setting of transplantation. While it is now generally accepted that circulating $CD4^+CXCR5^+$ cells and their subsets are related to bona fide Tfh cells and have been linked to the state of the humoral immune response, further examination of these cells in the context of transplantation is imminent and heavily warranted.

Acknowledgements

None.

Financial support and sponsorship

The authors are supported by the following sources: R01 AI073707 (M.L.F.), R01 AI104699 (M.L.F.), and an ASTS Fellowship in Transplantation Grant (I.R.B.)

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Key Points

- ICOS has critical costimulation-dependent and –independent roles in Tfh cell differentiation and function.
- PD-1 and CTLA-4 limit Tfh cell function through novel inhibitory and regulatory mechanisms.
- Circulating Tfh cell subsets that correlate with clinical indices of human immunity and disease are being increasingly recognized.
- New knowledge of Tfh cell biology is readily being applied to guide costimulation blockade-based strategies to prevent DSA formation and combat AMR in transplantation.