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Human T Follicular Helper Cells in Primary Immunodeficiency: Quality Just as Important as Quantity

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Abstract T follicular helper (Tfh) cells are a subset of effector $CD4^+$ T cells specialised to induce Ab production by B cells. This review highlights some of the recent advances in the field of human Tfh cells that have come from the study of primary immunodeficiencies. In particular it is increasingly evident that the quality of the Tfh cells that are generated, is just as important as the quantity.

Keywords Human T follicular helper (Tfh) cells · primary immunodeficiency · B-cell help · humoral immunity

Introduction

When faced with infection, successful elimination of the invading pathogen is dependent on the generation of an appropriate class of immune response. Thus, upon activation, naïve $CD4^+$ T cells have the potential to differentiate into distinct effector subsets that have evolved to protect the host against infection by specific pathogens. For instance, Th1 cells secrete IFNγ and protect against viruses and intracellular pathogens, IL-4-secreting Th2 cells are crucial for immunity against extracellular pathogens and parasites, and Th17 cells are required for immunity against mucocutaneous infections caused by *Candida* spp. [1, 2]. Importantly, T follicular helper (Tfh) cells are specialised to support the differentiation of B cells into memory and plasma cells, thus underpinning intact long-lived humoral immune responses. In light of their essential role in mediating Ab responses, in recent years a great deal has been invested into determining the factors that regulate the development and function of Tfh cells. In particular a wealth of knowledge has come from the study of these cells in human primary immunodeficiency due to monogenic mutations in key genes; this will be the focus of this review.

Tfh cells were first described in human tonsils as $CD4^+$ T cells that resided in B cell areas of secondary lymphoid organs [3, 4]. This positioning is facilitated by acquiring expression of CXCR5, the B cell zone homing chemokine receptor, and the concurrent down-regulation of CCR7, the T cell zone homing chemokine receptor [3, 4]. This localisation, in conjunction with the expression of B cell tropic molecules such as CD40L and ICOS, and cytokines such as IL-21 and IL-10, equip Tfh cells with the ability to induce B cell activation, expansion and differentiation [3–6]. Thus, it has been shown that $CD4^+CXCR5^+$ T cells are more efficient than $CD4^+CXCR5^-$ T cells at inducing Ab production by co-cultured B cells [3, 4, 7–9]. In terms of their differentiation from a naïve $CD4^+$ T cell, Tfh cells require the transcription factor *BCL6*, although other transcription factors such as BATF, IRF4, cMAF, STAT3, and Ascl2 also play a role [10, 11]. Human Tfh cells develop largely under the influence of IL-12 as well as the STAT3-activating cytokines IL-6, IL-21, IL-23 and IL-27 [12–15].

Types of Human Tfh Cells

While the original characterisation of Tfh cells was based on their anatomical localisation in secondary lymphoid organs, the ability to access these cells and study their developmental requirements in the human setting is challenging. In more

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recent years, this issue has been resolved with the discovery that some $CD4^+CXCR5^+$ T cells in the peripheral blood (PB) correspond to bona fide Tfh cells that can be found in secondary lymphoid organs. Thus, activated PB $CD4^+CXCR5^+$ were found to express more IL-21, IL-10, CXCL13, CD40L, ICOS, PD-1, and BCL-6 and were better at providing B-cell help than their $CD4^+CXCR5^-$ T cell counterparts [16–19]. However, compared to Tfh cells in secondary lymphoid organs, PB Tfh cells express much lower levels of CXCR5, BCL-6, ICOS and PD-1 [6, 16–20]. These differences between Tfh cells in secondary lymphoid organs and PB are likely to reflect different stages of differentiation. Indeed, even within the $CD4^+CXCR5^+$ PB T cell compartment there is substantial heterogeneity suggesting Tfh cells have the potential to receive different signals that alter their differentiation towards a particular subset. One of the earliest studies to establish this revealed that PB $CD4^+CXCR5^+$ Tfh cells could be further divided into Th1-like, Th2-like and Th17-like Tfh cells based on differential expression of the chemokine receptors CXCR3 and CCR6 [16]. Accordingly, in addition to IL-21, $CXCR3^+CCR6^-$ Th1-like Tfh cells also express *TBX21* and IFNγ, $CXCR3^-CCR6^-$ Th2-like Tfh cells express *GATA3*, IL-4, IL-5 and IL-13, and $CXCR3^-CCR6^+$ Th17-like Tfh cells express *RORC*, IL-17A and IL-22 [16]. The significance of this finding was highlighted by the further observation that Th2- and Th17-like Tfh cells secreted higher amounts of IL-21 than Th1-like Tfh cells, and were consequently better able to support B-cell differentiation [16]. More recent studies have confirmed these findings by revealing the most potent induces of B-cell help are $CCR6^+$ or $PD1^+CXCR3^-$ cells within the $CD4^+CXCR5^+$ T cell population [18, 21]. Furthermore, gene expression profiling revealed $CD4^+CXCR5^+PD1^+CXCR3^-$ T cells resembled tonsillar GC Tfh cells (94 of the top 100 genes were equivalently expressed by these two populations), and could be classified as "memory" cells inasmuch that they contained Ag-experienced cells [18]. Interestingly, $CD4^+CXCR5^+PD1^+CXCR3^-$ T cells in the PB were also found to express low levels of CCR7 and thus likely to correspond to the $CD4^+CXCR5^+CCR7^{lo}PD1^{hi}$ T cell population that was described by He et al. [19]. Again, similar to bona fide Tfh cells in secondary lymphoid tissues, $CD4^+CXCR5^+CCR7^{lo}PD1^{hi}$ T cells were the highest expressers of IL-21, the most potent B-cell helpers, and were increased transiently post-vaccination and in patients with systemic lupus erythematous (SLE) and rheumatoid arthritis (RA) [19]. Taken together, these studies unequivocally showed that circulating PB $CD4^+CXCR5^+$ cells correspond to bona fide Tfh cells located in secondary lymphoid organs. These seminal studies have justified the validity of studying circulating PB Tfh cells in humans, particularly in disease settings. As such, the study of Tfh cells in primary immunodeficiency will be the focus of the reminder of this review (Table 1).

Costimulatory Molecules

CD40 or CD40LG

The interaction between CD40 on Ag presenting cells and CD40L on $CD4^+$ T cells results in the activation of signalling pathways downstream of these molecules in both cell types. Accordingly, inactivating mutations in either *CD40* or *CD40LG* result in the primary immunodeficiency hyper IgM (HIGM) syndrome [22]. As the name suggests, HIGM patients have normal to elevated serum IgM and reduced serum IgG, IgA, and IgE levels, thereby revealing that CD40L-CD40 signalling on B cells is required for Ig isotype switching [23, 24]. Consistent with this, a decrease in memory B cells and Ig isotype switched B cells have been observed in CD40L-deficient patients [21, 25]. While initial emphasis was on the role of CD40-CD40L signalling in B cells, subsequent work showed that CD40L-deficient patients have a reduction in circulating $CD4^+CXCR5^+$ Tfh cells [26]. We have recently extended these initial observations to show a decrease in $CD4^+CXCR5^+$ T cells in CD40L-deficient patients but no alterations in Th1-, Th2- and Th17-like Tfh subsets (Table 1) [21]. Regardless, CD40-CD40L signalling is required for intact Tfh cell formation.

ICOS

Inducible costimulator (ICOS) is a member of the CD28 superfamily of costimulatory molecules and is expressed on activated T cells [27]. Defects in *ICOS* were found in a subset of patients that presented with common variable immunodeficiency (CVID) [28]. These initial reports detailed numerous B cell defects that accounted for the humoral defect in ICOS-deficient patients. This included a decrease in total B cells, memory B cells and germinal centres and low serum Ig [26, 28, 29]. However, a decrease in PB $CD4^+CXCR5^+$ Tfh cells was also revealed indicating both B and T cell defects contribute to humoral defects in ICOS-deficient patients [21, 26]. Interestingly, the initial studies of ICOS deficiency revealed a reduction in production of IL-17 by $CD4^+$ T cells. We have recently established that this also reflects a defect in Th17-like Tfh cells, which were found to be the main providers of B-cell help (Table 1) [21]. Interestingly, when ICOS-deficient T cells were activated in vitro, they were unable to upregulate and maintain CXCR5 expression to the same extent as normal T cells, thereby suggesting an important role for ICOS in generating Tfh cells [26]. Indeed, this has been observed in mouse models of Tfh cell differentiation. Taken together these results indicate a role for ICOS in the maintenance and differentiation of human Tfh cells.

Table 1 Tfh cells in primary immunodeficiency

Affected Gene	Disease manifestations	Tfh cell phenotype	Reference
Costimulatory receptors			
CD40 or CD40LG	HIGM	Decrease in CXCR5$^+$ Tfh cells; normal distribution of Th1, Th2 and Th17 Tfh cells	[21, 26]
ICOS	CVID	Decrease in CXCR5$^+$ Tfh cells; decrease in Th17 Tfh cells	[21] [26]
OX40	Kaposi sarcoma in childhood	Normal frequency of CXCR5$^+$ T cells	[32]
Cytokine/cytokine receptors			
IFNGR1/2	MSMD	Normal frequency of CXCR5$^+$ Tfh cells and Th1, Th2, and Th17 Tfh subsets	[21]
IL12RB1	MSMD	Normal frequency of CXCR5$^+$ Tfh cells and Th1, Th2, and Th17 Tfh subsets	[13, 21]
IL10R	Early-onset IBD	Decrease in CXCR5$^+$ Tfh cells; normal distribution of Th1, Th2 and Th17 Tfh cells	[21]
IL21R or IL21	IL-21R: Susceptibility to cryptosporidiosis IL-21: Early-onset IBD and CVID	Normal frequency of CXCR5$^+$ Tfh cells; decrease in Th17 Tfh cells; increase in PD-1 expression on Tfh cells.	[21, 43]
Transcription factors			
STAT1lof	MSMD +/− viral	Normal frequency of CXCR5$^+$ Tfh cells and Th1, Th2, and Th17 Tfh subsets	[13, 21]
STAT1gof	CMC	Normal frequency of CXCR5$^+$ Tfh cells; increase in Th1 and decrease in Th17 Tfh cells; increase in PD-1 expression on Tfh cells.	[21]
STAT3lof	AD-HIES	Decrease in CXCR5$^+$ Tfh cells; increase in Th1 and decrease in Th17 Tfh cells; increase in PD-1 expression on Tfh cells.	[13, 21, 51]
Intracellular signalling molecules			
BTK	XLA	Decrease in CXCR5$^+$ Tfh cells; normal distribution of Th1, Th2 and Th17 Tfh cells	[21, 55]
E2A	agammaglobulinemia	Decrease in CXCR5$^+$ Tfh cells	[54]
SH2D1A	XLP	Normal frequency of CXCR5$^+$ Tfh cells; defective function	[19, 59, 60]
NEMO	IP, HED, XR-MSMD	Decrease in CXCR5$^+$ Tfh cells; decrease in Th17 Tfh cells	[21]
TYK2	MSMD +/−susceptibility to viral infections/AR-HIES	Normal frequency of CXCR5$^+$ Tfh cells and Th1, Th2, and Th17 Tfh subsets	[13, 21, 66]

AD autosomal dominant, *AR* autosomal recessive, *CMC* chronic mucocutaneous candidiasis, *CVID* common variable immunodeficiency, *HED* hypohidrotic ectodermal dysplasia, *HIES* hyper IgE syndrome, *HIGM* hyper IgM syndrome, *IBD* inflammatory bowel disease, *IP* incontinentia pigmenti, *MSMD* mendelian susceptibility to mycobacterial disease, *XLA* X-linked agammaglobulinemia, *XLP* X-linked lymphoproliferative disease, *XR* X-linked recessive

OX40

OX40 is co-stimulatory molecule expressed on activated T cells and has been recently implicated in promoting human Tfh cell differentiation [30]. Specifically, triggering of OX40 on human naive and memory CD4$^+$ T cells induced a Tfh gene signature as indicated by an up-regulation of *CXCR5*, *BCL6*, *IL21*, *CXCL13* and *PDCD1* (encodes for PD-1) and down-regulation of PRDM1 [30], which encodes for the transcription factor Blimp-1 that repressors Tfh cell differentiation [31]. Furthermore, CD4$^+$ T cells activated in the presence of OX40L became sufficient B cell helpers and there was an increase in OX40L by myeloid APCs and ICOS$^+$ Tfh in the circulation of patients with active SLE [30]. In contrast to these findings, human OX40 deficiency did not alter the proportions of CXCR5$^+$ Tfh cells in PB, nor antibody responses in this individual (Table 1). Instead, this patient presented with early onset Kaposi sarcoma, but was otherwise relatively healthy [32], suggesting a redundant role for OX40 in the differentiation of human Tfh cells. Thus, it is likely that OX40 is redundant for the generation and maintenance of human Tfh cells under normal conditions, but plays a role in the pathogenesis of autoimmune diseases such as SLE.

Cytokine/Cytokine Receptors

IFNγR1/2 and IL12Rβ1

The IFNγ receptor is made up of a heterodimer complex of the IFNγR1 and IFNγR2 chains, while IL-12Rβ1 is a component of the receptors for both IL-12 and IL-23. Loss-of-function mutations in *IFNGR1*, *IFNGR2* or *IL12RB1* result in Mendelian susceptibility to mycobacterial disease (MSMD) [33]. Patients with MSMD display extreme susceptibility to poorly virulent mycobacteria and Salmonella strains, but are otherwise relatively healthy (Filipe-Santos et al. 2006). In addition to this, Ab immune responses are intact as patients can generate Ag-specific Abs following natural infection or vaccination [34–36]. In fact, a substantial proportion of patients with mutations in *IFNGR1/2* or *IL12RB1* are

hypergammaglobulinemic, due to the role of IFNγ in impeding B cell Ab production [21]. Consistent with intact humoral immune responses in *IFNGR1/2* and *IL12RB1*-deficient patients, we found a normal frequency of $CXCR5^+$ and normal distribution of Th1-, Th2- and Th17-like Tfh cells in the circulation of these patients (Table 1) [13, 21]. Thus, while IL-12 has been shown to play an essential role in human Tfh cell differentiation in vitro [12, 37], mechanisms exist that can compensate for a lack of intact IL-12/IL-12Rβ1 signalling. Not surprisingly, in addition to IL-12, other cytokines such as IL-6, IL-21, IL-23 and IL-27 can give rise to human Tfh cells [13, 14]. It is therefore likely that these cytokines compensate for a lack of IL-12 in the setting of *IL12RB1* deficiency.

IL10R

Patients with defects in IL-10R signalling present with early onset inflammatory bowel disease (IBD), indicating an important anti-inflammatory role for IL-10 in the gut [38]. Interestingly when the frequency of circulating memory B cells and Tfh cells in IL-10R-deficient patients was recently investigated, a decrease in both memory B cell and $CXCR5^+$ Tfh cells was found, but the distribution of Tfh cells into Th1-, Th2- and Th17-like Tfh cells was intact (Table 1) [21]. This reveals a role for IL-10 in the differentiation of PB $CXCR5^+$ Tfh cells, but not in the modulation of Th1, Th2 and Th17 subsets of Tfh cells.

IL21 or IL21R

The IL-21 signalling pathway is essential to humoral immunity as IL-21 can induce B cell activation and differentiation into Ab secreting cells [9, 39, 40] as well as human Tfh cell formation and function [12, 13]. Patients with mutations in *IL21R* [41–43] and *IL21* [44] have been described and affected individuals present with susceptibility to cryptosporidial infections, associated with liver disease and early onset IBD and CVID, respectively. IL-21-deficient patients have reduced B cells, and altered B cell differentiation as revealed by an increase in transitional and a decrease in memory B cells, including those that have undergone switching to IgG and IgA [21, 44]. Similarly patients with loss-of-function mutations in IL-21R have a block in B cell differentiation including an increase in naïve B cells and a decrease in total and IgG^+ memory B cells [21, 41]. In regards to Tfh cell formation in IL-21/R deficient patients, a normal frequency of PB $CXCR5^+$ Tfh cells was observed, but there was a decrease in B-cell helper Th17-like Tfh cells (Table 1) [21]. Furthermore, there was an increase in PD-1 expression on these non-B cell helper Tfh cells revealing that PD-1 is not always a good marker for Tfh cells that provide B cell help [21].

Transcription Factors

STAT1

STAT1 is a transcription factor that is downstream of numerous cytokines including interferon and IL-27. Both loss-of-function (lof) [45, 46] as well as gain-of-function (gof) [47] mutations in *STAT1* have ben reported in humans. Autosomal recessive complete lof mutations in *STAT1* result in MSMD with additional viral complications due to abolished IFNα/β and IFNγ signalling [46], while autosomal dominant partial loss of STAT1 function presents with MSMD due to diminished IFNγ but intact IFNα/β signalling [45]. In contrast *STAT1*gof patients usually present with CMC due to enhanced cellular response to STAT1-dependent cytokines such as IFNγ and IL-27 that inhibit Th17 development [47]. Interestingly, when circulating memory B cells and Tfh cells were investigated in STAT1lof and STAT1gof patients distinct phenotypes were observed. STAT1lof patients had a normal frequency of memory B cells and $CXCR5^+$ Tfh cells and a normal distribution of Th1-, Th2-, and Th17-like Tfh cells (Table 1) [13, 21]. However, while STAT1gof also had a normal frequency of PB $CXCR5^+$ cells, there was a significant increase in the non-B cell helper Th1-type and a reduction in B cell helper Th17-like Tfh cells (Table 1). This increase in non-B cell helper Tfh cells was also associated with an increase in PD-1 expression on these Tfh cells and a reduction in memory B cells [21]. Taken together these data indicate that an absence of STAT1 signalling is redundant for human Tfh formation and differentiation, but increased STAT1 signalling skews human Tfh differentiation towards non-B cell helper Tfh cells.

STAT3

STAT3 is a transcription factor that is downstream of multiple cytokine signalling pathways including those for the common gamma chain family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) and the IL-6 and IL-10 families. Lof mutations in *STAT3* were found to cause autosomal dominant hyper IgE syndrome (AD-HIES) [48, 49], a primary immunodeficiency characterised by recurrent *Staphylococcal aureus* and *Candida albicans* infections, recurrent cyst-forming pneumonia as well as elevated levels of serum IgE [50]. Lof mutations in *STAT3* also alter humoral immunity as AD-HIES patients have a severe reduction in memory B cells and fail to generate adequate amounts of Ag-specific Abs [21, 40]. Furthermore, this defect in humoral immunity in AD-HIES is likely to be two-fold as defects in PB Tfh cells have also been reported [13, 21, 51]. Specifically, STAT3lof patients present with a reduction in circulating $CXCR5^+$ Tfh cells and, similar to STAT1gof patients, the Tfh cells that are generated are primarily of a non-B cell helper Th1-like phenotype with a significant reduction in Th17-like Tfh cells and an increase in PD-1

expression (Table 1) [13, 21]. Since multiple STAT3-signalling cytokines (ie IL-6, IL-12, IL-21, IL-23, IL-27) have been implicated in human Tfh cell generation, activation and/or differentiation, further studies will be required to elucidate the contribution of these cytokines to the different stages of Tfh cell development. Along these lines we have shown IL-12 can induce some features of Tfh cells in STAT3-deficient naïve $CD4^+$ T cells such as expression of ICOS, CXCR5, and Bcl-6, but IL-21 expression was defective [13], indicating the IL-12-STAT3 signalling pathway is important for IL-21 expression, but not other aspects of Tfh cell differentiation. Consistent with this, others have shown IL-6 and IL-21 could up-regulate ICOS expression on cord blood $CD4^+$ T cells via a STAT3-dependent pathway [51, 52].

Intracellular Signalling Molecules

BTK or E2A

Bruton's tyrosine kinase (BTK) is a tyrosine kinase involved in BCR signalling that is critical for B cell development. As such, mutations in *BTK* result in the primary immunodeficiency X-linked agammaglobulinemia [53], which is associated with a block in B cell differentiation at the pro-B cell to pre-B cell transition, resulting in an absence of mature B cells in the periphery. More recently, dominant negative mutations in *E2A*, encoding the transcription factor E47, were identified in a subset of individuals with agammaglobulinemia that previously had unidentified mutations [54]. E47-deficient patients have a reduction in circulating B cells, and the few B cells that develop are characterised by a lack of BCR and increased CD19 expression. The block in B cell differentiation was found to be earlier than that of BTK deficiency at the common lymphoid precursor to pro-B cell stage [54]. These primary immunodeficiencies were ideal systems to investigate human Tfh cell development in the absence of B cells. Accordingly, there was a decrease in circulating $CXCR5^+$ Tfh cells in both BTK and E47 deficient patients (Table 1) [21, 54]. At least in BTK deficiency the Tfh cells that do form have a normal distribution of Th1-, Th2-, and Th17-like Tfh cell subsets [21]. These data indicate signals provided by B cells are required for the generation of human Tfh cells [55].

SH2D1A

SH2D1A encodes the small adaptor protein SAP. Mutations in *SH2D1A* result in X-linked lymphoproliferative disease (XLP), a primary immunodeficiency characterised by fulminant infectious mononucleosis, hypogammaglobulinemia, B cell lymphoma and susceptibility to Epstein Barr Virus infections [56]. Consistent with hypogammaglobulinemia, XLP patients have a severe reduction in memory B cells, Ig isotype switching and impaired generation of Ag-specific Abs [57, 58]. Since SAP is unlikely to be expressed in B cells [56], Tfh cells have been investigated for possible explanations for altered B cell development and defective humoral immunity in XLP patients. Accordingly, XLP patients were found to have normal frequencies of PB $CXCR5^+$, $PD1^+$, and $CXCR5^+PD\text{-}1^+$ Tfh cells (Table 1) [19, 59, 60]. However, further investigations into subsets of Tfh in XLP patients has not been performed, suggesting there may be an under representation of Th17-like Tfh cells, which are the most efficient B cell helpers. Consistent with a requirement for intact SAP-signalling for the generation of functional human Tfh cells, $CD4^+$ T cells from XLP deficient patients failed to induce Ig production from co-cultured B cells in vitro [57].

NEMO

NFκB essential modulator (NEMO), also known as IKKγ is required for the activation and translocation of the transcription factor NFκB to the nucleus of the cell. Mutations in *NEMO* result in an X-linked dominant disorder where affect females present with incontinentia pigmenti, which is associated with defects to the skin, hair, nails, teeth, eyes and central nervous system and affected males die in utero [61]. Less severe, hypomorphic mutations in *NEMO* with an X-linked recessive (XR) mode of inheritance have also been described and cause hypohidrotic ectodermal dysplasia with immunodeficiency [62, 63] and XR-MSMD [64]. NEMO-deficient patients were shown to have both reduced circulating memory B cells and $CXCR5^+$ Tfh cells (Table 1) [21, 63]. Furthermore, a reduction in Th17-like Tfh cells was also observed, indicating NEMO is required for the development and differentiation of human Tfh cells.

TYK2

TYK2 is a member of the JAK family of tyrosine kinases and is downstream of multiple signalling pathways, including those of IL-12, IL-23, IFNα/β, IL-10, and IL-6. Mutations in TYK2 were initially shown to cause autosomal recessive HIES (AR-HIES) [65], but this original case may not be representative of TYK2-deficiency as it has been more recently re-classified as susceptibility to mycobacterial and viral infections in the absence of HIES [66]. Consistent with the lack of Ab defects in TYK2-deficient patients, normal frequencies of circulating memory B cells, and $CXCR5^+$ Tfh cells have been detected in these individuals including a normal distribution of Tfh cell subsets (Table 1) [13, 21, 66]. Thus, TYK2 likely plays a redundant role in the differentiation of human Tfh cells.

Concluding Remarks

Primary immunodeficiencies resulting from monogenic mutations have provided valuable insights into the development, differentiation and function of human Tfh cells. Complementary studies also revealed that there is substantial heterogeneity within the circulating Tfh cell pool in humans, and not all Tfh cell subsets are equal in terms of providing "help" for B-cell differentiation. Specifically Th1-like Tfh cells, defined by $CXCR3^{+}CXCR5^{+}$ Tfh cells in the blood, express high amounts of IFNγ and PD-1 and are likely to impede B cell activation and Ab production. Instead, $CCR6^{+}CXCR5^{+}$ Th17-like Tfh cells are the main providers of B cell help. Thus, the quality of the Tfh cells that are generated are just as important as the quantity, and different signalling molecules can differentially affect these parameters of the Tfh cells generated. Furthermore, while the identification of the circulating counterparts to bona fide Tfh cells in secondary lymphoid organs has been a big leap forward for the study of human Tfh cells, there are additional dangers in assessing the function of Tfh cells from patients based purely on the frequency of circulating $CXCR5^{+}$ Tfh cells. This is particularly true when enumeration of PB Tfh cells is used as a biomarker of disease (both immunodeficiency and autoimmunity) or as a measure for vaccine outcomes. Nevertheless, the further study of human Tfh cells in primary immunodeficiency will continue to reveal the mechanisms and pathways involved in the differentiation and function of these cells in health and disease.

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Compliance with Ethical Standards

Conflict of Interest C.S.M has received a speaker honorarium from Baxalta.

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