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HIGHLIGHTS

Basic

REVIEW

# Antigen-dependent multistep differentiation of T-follicular helper cells and its role in SARS-CoV-2 infection and vaccination

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**T-follicular helper (Tfh) cells play an essential role in regulating the GC reaction and, consequently, the generation of high-affinity antibodies and memory B cells. Therefore, Tfh cells are critical for potent humoral immune responses against various pathogens and their dysregulation has been linked to autoimmunity and cancer. Tfh cell differentiation is a multistep process, in which cognate interactions with different APC types, costimulatory and coinhibitory pathways, as well as cytokines are involved. However, it is still not fully understood how a subset of activated CD4$^+$ T cells begins to express the Tfh-defining chemokine receptor CXCR5 during the early stage of the immune response, how some CXCR5$^+$ pre-Tfh cells enter the B-cell follicles and mature further into GC Tfh cells, and how Tfh cells are maintained in the memory compartment. In this review, we discuss recent advances on how cognate interactions and antigen are important for Tfh cell differentiation and long-term persistence of Tfh cell memory, and how this is relevant to the current understanding of COVID-19 pathogenesis and the development of potent SARS-CoV-2 vaccines.**

**Keywords:** Antigen · Antibody formation · Differentiation · Memory · T cells

## Introduction

Upon activation, naïve CD4$^+$ T cells can differentiate into distinct subsets of effector Th with varied functions. T-follicular helper (Tfh) cells form a unique subset of CD4$^+$ T cells that provides help to B cells and is essential for GC formation and regulation [1–5]. The differentiation and function of Tfh cells have been shown to determine the kinetics and magnitude of GC B-cell responses and the generation of high-affinity antibodies. Tfh cell differentiation is commonly regarded as a multistage process (Fig. 1). During the early stages of CD4$^+$ T-cell responses, antigen presentation by DCs activates naïve CD4$^+$ T cells and initiates Tfh cell differentiation including the induction of the chemokine receptor CXCR5 and the transcription factor Bcl6. Besides TCR signaling, costimulation and the local cytokine milieu are also critical for Tfh cell fate decision. After initial interactions with DCs, terminal Tfh cell differentiation requires interactions with B cells. In the past decade, great progress has been made in our understanding of Tfh cell differentiation and function. Here, we will discuss these findings and highlight some important questions regarding how cognate interactions with APCs at the different stages of Tfh cell differentiation play a central role in this process and

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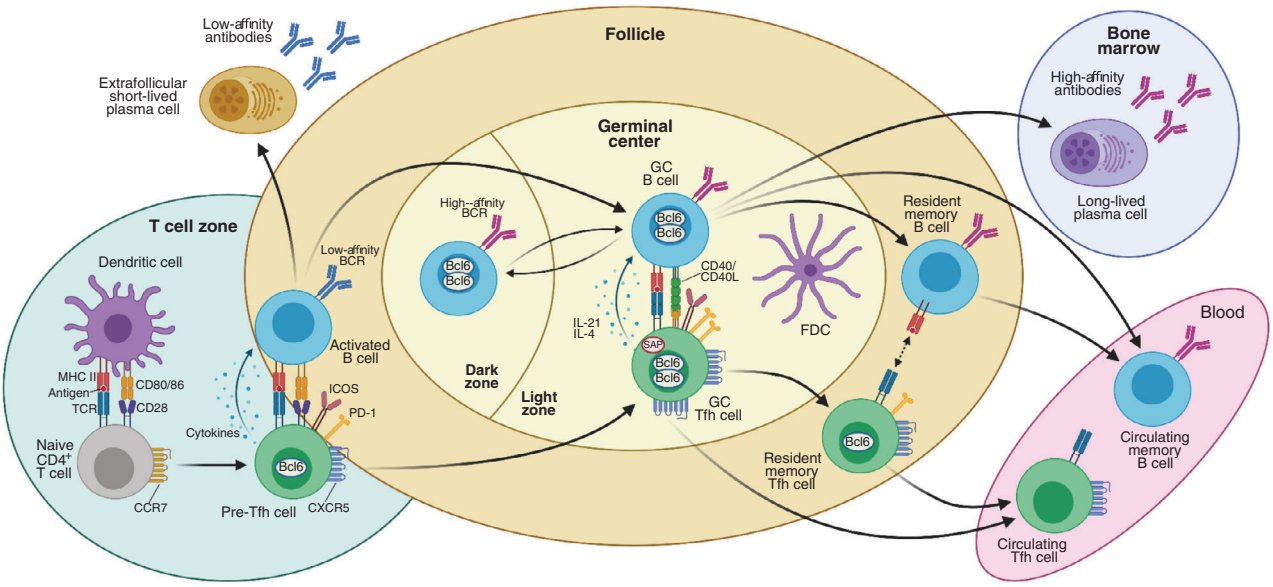


**Figure 1.** Antigen-dependent multistep differentiation of T follicular helper (Tfh) cells. Naïve CD4$^+$ T cells are primed by DCs in the T-cell zones of secondary lymphoid organs such as the spleen or LNs. This antigen-specific interaction is mediated by presentation of processed peptides by MHC-II molecules that are recognized by the cognate TCR. Together with the expression of costimulatory molecules and production of cytokines, these signals induce the Tfh cell differentiation program that is characterized by upregulation of the chemokine receptor CXCR5 and downregulation of CCR7, which allows these cells to migrate to the T/B border where they interact with activated B cells. This second interaction with an APC type coincides with the expression of characteristic costimulatory (ICOS) and coinhibitory receptors (PD-1) by the Tfh cells, which may be called "pre-Tfh" cells at this stage. Some of the interacting T and B cells relocate to the follicle to form germinal centers (GCs). In these highly specialized microanatomical structures that consist of dark (DZ) and light (LZ) zones, GC Tfh and B cells continue to interact in an antigen-specific manner. GC Tfh cells are more polarized and express higher levels of PD-1, Bcl6, and CXCR5 than "pre-Tfh" cells. In addition, they produce IL-21 and IL-4 that act on the B cells. While GC B cells mutate their immunoglobulin genes and proliferate in the DZ, GC Tfh cells provide essential signals to B cells in the LZ of the GC, where they cooperate with follicular dendritic cells (FDCs) in the selection of high-affinity B-cell clones and in the generation of memory B cells and long-lived plasma cells that maintain serological memory. Once the GC reaction is resolved, some memory CXCR5$^+$ CD4$^+$ T cells reside in close proximity with memory B cells in lymphoid organs, while others are released from the draining lymphoid organs and circulate in the blood. Both memory Tfh cell subsets express lower levels of Bcl6 and CXCR5 as compared to their effector counterparts. Upon antigen rechallenge, these cells rapidly acquire the effector functions of Tfh cells and strongly support secondary immune response.

how this knowledge can contribute to a better understanding of COVID-19.

## DC priming for initial Tfh cell differentiation

DCs are the most important APCs for naïve CD4$^+$ T-cell activation and differentiation. During the initiation of the CD4$^+$ T-cell response, DCs are sufficient to prime naïve CD4$^+$ T cells and generate CXCR5$^+$ Tfh cells [6, 7]. However, further differentiation into GC-Tfh cells still requires B-cell interactions [8]. DCs can be subdivided into conventional DC (cDC) and plasmacytoid DC. Among the cDCs, further subdivision can be observed based on their division of labor. Using Batf3-deficient mice (lacking cDC1) and Dock8-deficient mice (lacking cDC2), it was shown that the migratory cDC2, but not cDC1, uniquely induced Tfh cell responses at the T-B border [9]. Further, it was demonstrated that monocyte-derived DCs were able to promote Tfh cell differentiation in specific inflammatory contexts [10]. It was also demonstrated that Tfh cell differentiation of EBI2-deficient CD4$^+$ T cells was compromised in a B-cell independent manner [11]. More precisely, most of the activated CD4$^+$ T cells colocalized with cDC2s in the outer T zone. In contrast, in the absence of EBI2, activated CD4$^+$ T cells were dispersed, with only some colocalizing in proximity of cDC2s. Further, the authors revealed a novel mechanism underlying DC-T-cell interaction at the interfollicular region with cDC2s expressing membrane-bound CD25 (IL-2R) and releasing soluble IL-2R to absorb the surrounding IL-2, thereby reducing IL-2-mediated suppression of Tfh cell differentiation as previously reported [12–14].

During CD4$^+$ T-cell priming, increased doses of antigen favored the differentiation of Tfh and GC-Tfh cells [15]. It was also shown that in the absence of DCs, high doses of antigen were able to overcome the defective Tfh cell differentiation [16]. In the context of viral infection, it was demonstrated that mice in which DCs are constitutively ablated did not show marked alterations of Tfh cell differentiation and response after systemic low-dose infection of mice with lymphocytic choriomeningitis virus [17]. In addition to antigen dose and nature, it has been shown that antigen size also has an impact on Tfh cell differentiation, in which an antigen size of 200 nm induced a stronger Tfh cell and antibody response, despite a similar activated T-cell response [18]. This suggested that increasing antigen size could

 

lead to sustained antigen presentation by DCs, resulting in enhanced Tfh cell differentiation.

## TCR affinity, TCR signal strength, and TCR tonic signaling in Tfh cell differentiation

Using two distinct TCR-transgenic mouse strains with different TCR affinities for the exact same peptide-MHC class II (pMHCII) complex, it was shown that high-affinity T cells developed significantly more into Tfh cells, suggesting that a high-affinity TCR at the surface of naïve T cells preferentially induces the Tfh cell program [19]. The link between TCR affinity and Tfh cell differentiation was further studied by monitoring the progeny of naïve $CD4^+$ T cells after pathogen infection [20]. The authors showed that naïve $CD4^+$ T cells specific for a certain pMHCII underwent distinct effector fates based on their unique TCR, thus, each naïve T cell is poised to generate certain types of effector cells. The authors demonstrated that when the dwell time of TCR/pMHCII interaction increased, Tfh cell differentiation also increased and reached a plateau. As stated above, studies in viral infection models have shown that the IL-2/STAT5 pathway suppresses Tfh cell differentiation [13–15]. Using IL-2 reporter mouse strains, it was shown that newly activated $CD4^+$ T cells could be subdivided into IL-$2^+$ cells enriched for *Bcl6* mRNA expression and IL-$2^-$ T cells expressing higher mRNA levels of *Prdm1* [21]. It was further demonstrated that IL-2 reporter expression was restricted to $CXCR5^+$ $CD4^+$ T cells and that specific depletion of IL-2-producing cells inhibited Tfh cell differentiation, suggesting that Tfh cells derived from IL-2-producing cells. The authors also demonstrated that IL-2 production and Tfh cell differentiation correlated with TCR signal strength and that higher TCR signaling favored Tfh cell differentiation. Interestingly, it has been reported that low-affinity antigen did not impact Tfh cell differentiation [22].

How TCR signaling induces downstream transcriptional regulation that influences T-cell differentiation has recently been described. It was shown that the TCR signal-induced transcription factor IRF4, which was essential for the differentiation of Bcl6-expressing Tfh cells [23]. It was further found that the amount of IRF4 was increased proportionately to TCR signal strength [24]. Strikingly, the authors also showed that in specific conditions of increased TCR signaling, high amount of antigen or overexpression of IRF4, reduced Tfh cell differentiation. Mechanistically, the authors demonstrated that greater IRF4 levels allowed binding to low-affinity binding sites that were enriched in non-Tfh effector genes, a process that was independent of IL-2 signaling. Another layer of difficulty was recently added to this field of investigation. It was questioned whether another TCR-dependent factor could contribute to Tfh cell fate determination, namely peripheral TCR signaling in response to self-pMHCII, also called tonic signaling [25]. It was revealed that tonic signaling instructed Tfh cell fate, where strong tonic signaling inhibited Tfh cell differentiation and weak tonic signaling promoted it. Overall, stronger TCR signaling favored Tfh cell differentiation either through increased tonic signaling strength and/or through TCR activation induced by increased dose of antigen.

While the above studies investigated the role of TCR signaling in Tfh cell differentiation, it still remains elusive when the divergence between $CXCR5^-$ and $CXCR5^+$ cells occurs upon activation of naïve $CD4^+$ T cells. Using single-cell RNA sequencing to cartography effector $CD4^+$ T-cell differentiation, the developmental trajectories of Th1 and Tfh cells were recently reconstructed during blood-stage Plasmodium infection in mice [26]. The authors demonstrated that both cell subsets diverged after the initial cycle of cell proliferation associated with an upregulation of aerobic glycolysis and accelerated cell cycling. This is consistent with the finding that CXCR5 expression was particularly upregulated in activated $CD4^+$ T cells that had proliferated the most and which coexpressed high levels of Bcl6 [7].

## Cognate T/B interactions in Tfh cell differentiation and maintenance

After priming by APCs, activated $CD4^+$ T cells proliferate and those cells upregulating CXCR5 and concomitantly downregulating CCR7 migrate to the B-cell follicle [27, 28]. First, these cells localized to the T/B border where they interacted with antigen-primed B cells in a cognate fashion. Eventually, some of them enter deeper into the B-cell follicles and contribute to the formation of GC, their terminal differentiation into GC Tfh cells being dependent on B cells [8, 29-31]. Indeed, interaction with cognate B cells allows stable Bcl6 and, in turn, CXCR5 expression. Thus, efficient T- and B-cell interactions are important as seen by the absence of GC Tfh cell differentiation in SAP-deficient mice [32–35]. Moreover, other costimulatory signals are critical for terminal Tfh cell differentiation. ICOS/ICOS-L signaling was demonstrated to be crucial [36–38]. ICOS overexpression in mice that carry a mutation in the roquin gene led to extensive Tfh cell differentiation and lupus-like syndrome [39]. Moreover, BCR stimulation inversely correlated with ICOS-L expression, which consequently decreased Tfh cell differentiation [40]. Thus, the decision between the extrafollicular versus the GC pathway relies on affinity for the antigen of the BCR expressed by naïve B cells [41] and the impact of BCR affinity on the quality of T/B interaction.

One important characteristic of GC reactions is affinity maturation. It was shown that increased propensity to present antigen to Tfh cells and to interact with GC-Tfh cells led to a decrease in the number of high-affinity B cells since GC B cells were in less competition with each other [42]. These observations provided evidence for a model in which Tfh cells are the limiting factor that shape the GC response and affinity selection therein. Using similar technologies, another study showed that Tfh cells were able to recirculate between different GCs, thus, maximizing the diversification of T cell help during GC responses [43]. Notably, Tfh-GC B-cell interaction impacts the outcome of GC B cells with stronger interaction promoting formation of plasma cell precursors versus recycling GC cell fate [44]. Continued T-cell-specific Bcl6

 

expression in $CD4^+$ T cells is required for the maintenance of established Tfh cells and GCs and prevents the transdifferentiation of Tfh cells into Th1 cells during acute viral infection [45]. Similarly, global miRNA expression is not only required for the induction of Tfh cells [46], but also for their maintenance [47], further highlighting the fragile nature of the Tfh cell program that is dependent on continued presentation of antigen as well as costimulation [8, 15, 36, 37, 48].

## Tfh memory

Initially, Tfh cells were thought to be effector cells that would die once the GC reaction had ended [49, 50]. Nevertheless, it was also reported that $CXCR5^+$ $CD4^+$ memory T cells form in mice after protein vaccination and viral infection [51–54] and their existence in humans was also demonstrated [55–59]. While it was further shown that Bcl6 was essential for the formation of memory $CD4^+$ T cells [60], intrinsic Bcl6 expression was lower in memory cells as compared to GC Tfh cells [61–63], which correlated with a less differentiated phenotype than their effector counterparts [54, 64, 65]. Finally, it was demonstrated that memory $Bcl6^+$ $CXCR5^+$ T cells were memory Tfh cells, since they were shown to preferentially give rise to GC Tfh cells upon reactivation [61]. Interestingly, the Tfh cell compartment can be subdivided into resident cells remaining in draining lymphoid organs and circulating cells. Both cell subsets had the capacity to support secondary humoral immune responses, but they displayed different locations, resident cells being in B-cell follicles and circulating ones in T-cell areas or in the blood [66]. Further, this cell subdivision was demonstrated to rely on cognate interactions between resident memory B and T cells, from which the circulating T-cell pool emerged, emphasizing the role of antigen presentation even in the memory phase. In this context, it was observed that after antigen reactivation, memory B cells induced rapid Bcl6 expression and effector function by memory Tfh cells, thereby highlighting the close functional relationship between memory B cells and Tfh cells [67]. In *Listeria monocytogenes* infection, it was shown that $CXCR5^+$ memory $CD4^+$ T cells were multipotent as they generated secondary Tfh and Th1 cell responses and these cells behaved more like central memory T cells as they expressed CCR7 and were mainly located in T-cell areas [68]. More recently, it was reported that long-lived Tfh cells are susceptible to cell death induced by NAD-mediated ribosylation of P2RX7 [69]. Blocking this process during tissue isolation yielded many additional live cells that were used to confirm by single-cell RNA sequencing that memory Tfh cells retained plasticity. Whether the memory T cell multipotency depends on the plasticity of these cells or whether these cells represent a heterogenous population of cells still remains unclear.

In humans, circulating Tfh (cTfh) cells found in the blood stream represent a relatively easily accessible Tfh cell population that shares characteristics with bona fide Tfh cells found in secondary lymphoid organs [56]. It was shown that these cTfh cells originate from GCs in LNs [70] and they may serve as circulating memory cells that can be rapidly recruited to secondary immune responses. Due to their lower expression of costimulatory molecules, such as ICOS and PD-1, which might be a consequence of missing antigenic interactions in the blood, they display a resting state, and increased activated cTfh cells can be detected after infections and vaccinations [58, 71]. Another interesting connection that still needs to be resolved is the appearance of peripheral Tfh-like (pTfh) cells that have been described in seropositive rheumatoid arthritis patients [72] and in breast cancer patients [73]. These cells express many characteristics of Tfh cells, including expression of PD-1 and ICOS and colocalization with B cells, yet they lack expression of CXCR5. In the context of Influenza infection, lung-resident memory T cells were described to promote protective B-cell responses in a Bcl6-dependent fashion in nonlymphoid organs in mice [74, 75]. These T cells are CXCR5-negative and exhibit mixed features of Tfh cells and resident memory T cells. They were named resident helper T cells (TRH). It will be important to study the function of pTfh and TRH cells and their relationship to cTfh and bona fide Tfh cells in the future.

## Tfh cells in SARS-CoV-2 infection and vaccination

Given the importance of humoral immunity for fighting infectious pathogens, such as SARS-CoV-2, the current COVID-19 pandemic has sparked great interest into the role of Tfh cells in the immune response to SARS-CoV-2 as well as their function in newly developed vaccines (Fig. 2). Elevated frequencies of activated Tfh cells were detected in the blood of nonsevere COVID-19 patients [76] and in the LNs of SARS-CoV-2-infected rhesus macaques [77]. High frequencies of activated cTfh cells correlated with low disease severity in COVID-19 patients [78].

The Th1-polarizing conditions of a viral infection usually result in the predominant generation of type-1 cTfh cells, such as in influenza vaccination [58, 79], following the live-attenuated yellow fever vaccine [71], and in Hepatitis C Virus infection [80, 81]. A similar type-1 polarization with increased ICOS expression levels has also been observed during SARS-CoV-2 infection in humans [82–86] and in rhesus macaques [77]. Importantly, functional spike-specific memory CXCR5-positive cTfh and CXCR5-negative T cells persisted for at least 6 months after symptom onset [87, 88]. Even though Tfh cells were not analyzed, a recent report suggested antigen-persistence in the gut driving the evolution of anti-SARS-CoV-2 memory B cell and antibody responses, which might involve Tfh cells as well [89].

Single-cell RNAseq analysis of COVID-19 patients identified increased frequencies of cytotoxic Tfh cells and decreased frequencies of Treg among SARS-CoV-2-reactive $CD4^+$ T cells of hospitalized patients [90]. Cytotoxic Tfh cells were particularly increased early on in hospitalized versus nonhospitalized patients and their presence inversely correlated with levels of SARS-CoV-2 spike protein-specific antibodies. Since cytotoxic Tfh cells have been described to directly kill B cells and their frequency correlated with disease severity in recurrent group A *Streptococcus*

 

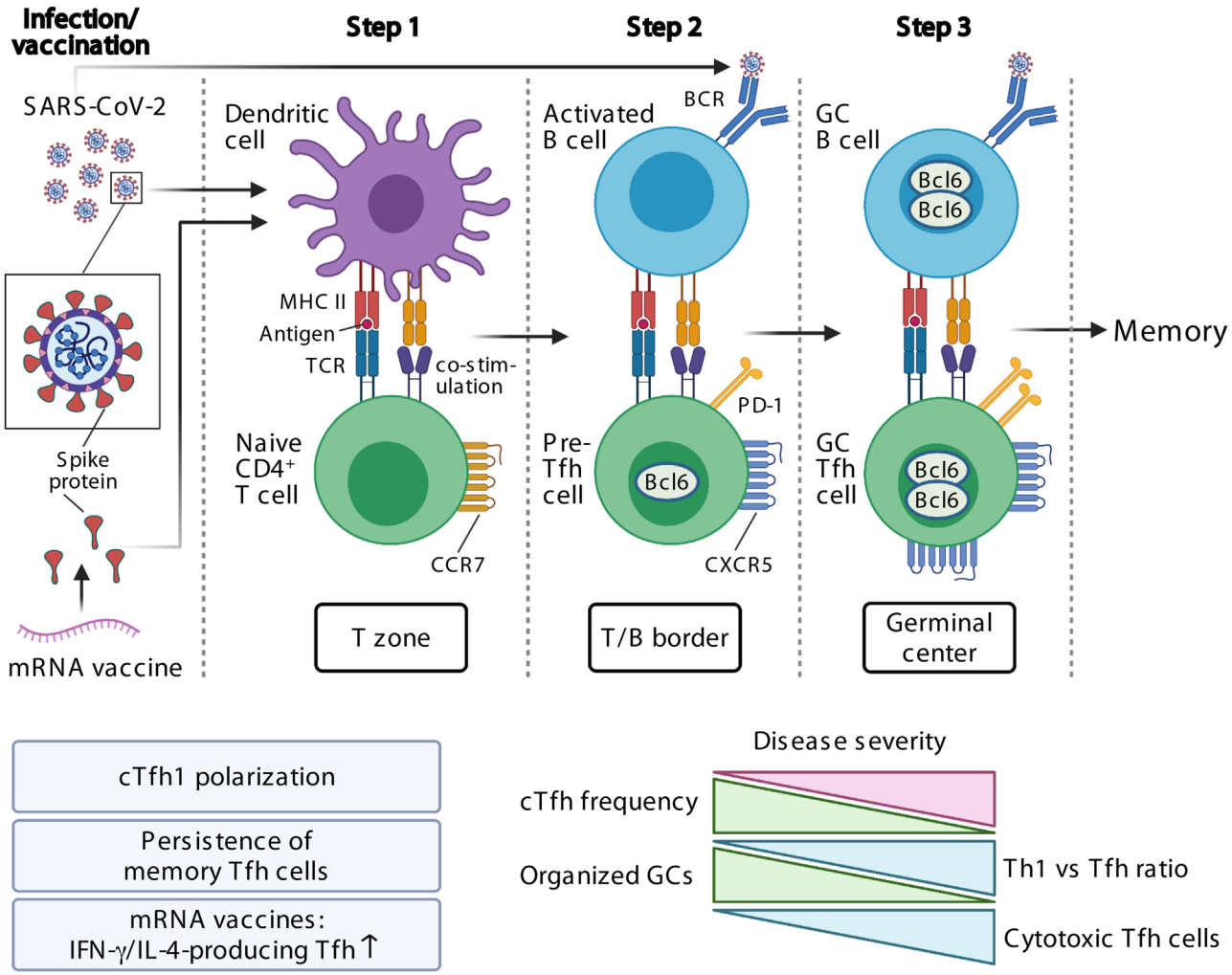


**Figure 2.** Impact of SARS-CoV-2 infection and vaccination on Tfh cell differentiation and function. Upon infection of the host with SARS-CoV-2, virus antigens are taken up by DCs, which process and present them on MHC-II to naïve $CD4^+$ T cells and induces Tfh cell differentiation toward type 1 polarization. The stronger this Tfh1 cell polarization is, the lower COVID-19 severity is. After encounter of activated B cells at the T/B border, some Tfh cells express higher levels of Bcl6, CXCR5, and PD-1 and form GCs with B cells. Absence of GC structures is observed in symptomatic patients with severe COVID-19. Interestingly, months after natural infection, persistence of SARS-CoV-2-specific memory Tfh cells was demonstrated. Eventually, mRNA vaccines encoding full-length SARS-CoV-2 spike protein allow efficient Tfh cell differentiation, GC formation, and protective humoral response.

tonsillitis [91], it is plausible, that cytotoxic Tfh cells also contribute to lower humoral activity in severe COVID-19 patients. In this regard, it is interesting to note that GCs were largely absent in postmortem spleen and LNs in acute SARS-CoV-2 infection, with a block in $Bcl6^+$ Tfh cells and a converse increase in Th1 cells [92]. Furthermore, reduced CXCR5 expression by B and T cells was observed in moderate and severe COVID-19 patients, further indicating that impaired T/B crosstalk may precipitate dysregulated humoral immune responses [85, 93].

By comparing a SARS-CoV-2 mRNA vaccine that encoded the receptor-binding domain (RBD) and the full-length spike protein of SARS-CoV-2 with a recombinant SARS-CoV-2 RBD (rRBD) protein that was formulated with the MF59-like AddaVax adjuvant, it was recently shown in mice, that the mRNA vaccine induced more potent Tfh cell and GC responses characterized by stronger CXCR5 and ICOS levels on Tfh cells. In addition, the mRNA vaccine led to robust coproduction of IFN-γ and IL-4, resembling a combined Th1/Th2 polarization, which, in contrast to the Th2-polarized Tfh cell response elicited by the rRBD protein vaccine, translated to higher neutralizing antibody titers [94]. These data further support the efficacy of the first FDA-approved SARS-CoV-2 vaccines in humans that were also based on mRNA vaccine technology.

## Conclusions

Future studies will provide additional important insights into this unique population of $CD4^+$ T cells that can be leveraged for improved vaccine design and the treatment of various diseases including autoimmunity.

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*Abbreviations:* **cDC**: conventional DC · **cTfh**: circulating Tfh · **pMHCII**: peptide-MHC class II · **pTfh**: peripheral Tfh-like · **RBD**: receptor-binding domain · **rRBD**: recombinant SARS-CoV-2 RBD · **Tfh**: T-follicular helper · **TRH**: resident helper T cells

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