

## REVIEW

# Priming of T follicular helper cells by dendritic cells

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**T follicular helper cells (Tfh) are required to generate long-lived antibody responses, which confer long-term protection to pathogens following vaccination or infection. Despite significant advances in the field, however, little is known about the early steps that drive Tfh cell differentiation. In this review, we will discuss the mechanisms by which dendritic cells promote the initial commitment of activated CD4<sup>+</sup> T cells to the Tfh cell differentiation pathway.**

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The recent characterization of T follicular helper cells (Tfh) as a distinct subset of CD4<sup>+</sup> T cells has significantly advanced our understanding of T cell-dependent B-cell responses. Tfh cells are a unique subset of CD4<sup>+</sup> T cells that express high levels of the transcription factor, Bcl6, and promote the differentiation of activated, antigen-specific B cells into memory B cells as well as long-lived plasma cells.<sup>1–3</sup> The chemokine receptor, CXCR5, is a characteristic marker of Tfh cells and promotes their homing to the B-cell follicles and germinal centers, where they provide differentiation and survival signals (T-cell help) to B cells—hence, the name Tfh cells. Numerous studies over the last few years contribute to our understanding of the essential role played by this specialized subset of CD4<sup>+</sup> T cells in the generation and maintenance of long-term humoral immunity.<sup>1</sup> In fact, without Tfh cells, germinal centers do not develop, long-lived plasma cells are not generated and long-term antibody responses are impaired.<sup>4–7</sup> However, the molecular mechanisms and the cellular interactions that regulate Tfh cell fate commitment are still unclear.

Recent advances in Tfh cell biology reveal that antigen presentation by dendritic cells (DCs) is necessary and sufficient to initiate Tfh cell commitment,<sup>8–11</sup> despite the fact that in most cases, antigen presentation by B cells is ultimately responsible for promoting the full differentiation program of Tfh cells. Thus, by determining the cellular and molecular mechanisms used by DCs to initiate Tfh cell commitment, we may be able to target antigens specifically to those DCs that induce Tfh cells or develop adjuvants that preferentially activate DCs to promote Tfh cell priming. In this review, we will discuss recent findings regarding how DCs promote Tfh cell differentiation and whether T effector and Tfh cell responses may be differentially controlled by DCs.

## EVIDENCE FOR A ROLE OF DCs IN PRIMING TFH CELL RESPONSES

The commitment of naive CD4<sup>+</sup> T cells into the Tfh cell differentiation pathway depends on the expression of the transcription factor,

Bcl6, which represses the expression of other T-cell subset-specific transcription factors and promotes the sustained expression of CXCR5.<sup>5–7</sup> Early studies show that priming of Bcl6-expressing Tfh cells requires the interaction of naive CD4<sup>+</sup> T cell with antigen-presenting B cells.<sup>5,6,12,13</sup> These observations suggest a binary model in which primed CD4<sup>+</sup> T cells either encounter activated B cells at the border of the B-cell follicle, where they are instructed to differentiate into Tfh cells, or they encounter DCs within the T-cell area and differentiate into effector CD4<sup>+</sup> T cells.<sup>1</sup> However, recent data challenge this view and indicate that although antigen presentation by activated B cells is important for the maintenance of Tfh cell responses, antigen presentation by DCs is necessary and sufficient to induce the initial expression of Bcl6, CXCR5 and the inducible T-cell co-stimulator (ICOS) and to launch the Tfh cell differentiation program.<sup>8–11,14</sup>

In fact, the upregulation of Bcl6 and commitment to the Tfh differentiation pathway occurs rapidly after immunization or infection<sup>8,11,14,15</sup> and takes place outside the B-cell follicle in the absence of B cells.<sup>14,15</sup> For example, Bcl6 and CXCR5 expression on CD4<sup>+</sup> T cells occurs as early as the second cell division following viral infection and does not require the presence of B cells.<sup>8</sup> Moreover, SAP-deficient CD4<sup>+</sup> T cells, which fail to establish sustained interactions with cognate B cells, but interact normally with antigen-presenting DCs,<sup>16</sup> upregulate Bcl6 and CXCR5 following activation<sup>8,10</sup> and migrate into the B-cell follicles<sup>10</sup>—both traits of Tfh cells. Together, these results suggest that some aspects of Tfh differentiation are initiated before contact with B cells, most likely following interaction with DCs. However, the most compelling evidence in favor of a role for DCs in Tfh cell priming comes from a recent study using mice in which MHC class II expression is restricted to conventional DCs and is absent from B cells.<sup>9</sup> In this study, the authors elegantly demonstrate that cognate-interactions with antigen-presenting DCs are necessary and sufficient to trigger the initial steps of Tfh differentiation, including turning on the expression

of Bcl6, CXCR5 and ICOS and promoting the physical homing of responding CD4<sup>+</sup> T cells to the B-cell follicle.

Importantly, even though the ability of CD4<sup>+</sup> T cells to upregulate Bcl6 and CXCR5 and to home to B-cell follicles does not necessarily require cognate-interactions with B cells, the full differentiation of Tfh cells and their long-term maintenance are typically impaired in the absence of B cells,<sup>5,9,12,15,17</sup> or when B cells do not express MHC class II molecules.<sup>9,10</sup> Based on these results, some authors suggest that naive CD4 T cells first contact DCs outside the B-cell follicle,<sup>15,18</sup> where they are primed, begin to proliferate and some of them acquire low levels of CXCR5 and Bcl6.<sup>8,9</sup> These early pre-Tfh cells subsequently migrate to the border between the B-cell follicle and T-cell zone, where they encounter antigen-activated B cells<sup>8</sup> and receive additional and unique survival and differentiation signals that are required to complete the Tfh cell differentiation program and to sustain prolonged Tfh cell responses.<sup>5,12,13,19</sup> Supporting this model, the expansion of the Tfh cell response is impaired when B cells do not express certain co-stimulatory molecules, such as ICOS ligand<sup>8</sup> or PD-1 ligand.<sup>20</sup>

Although cognate interactions with activated B cells are typically required to sustain DC-primed Tfh cells, late B cell-mediated antigen presentation is not required when antigen is in excess.<sup>9,10</sup> In fact, DCs can substitute for B cells as antigen-presenting cells and support prolonged Tfh cell responses when mice receive an antigen boost.<sup>9,10</sup> These studies indicate that B cells are not required to provide a unique signal that promotes (or sustains) Tfh cell differentiation later on in the immune response. Instead, antigen-specific B cells only become the principal antigen-presenting cells when antigen availability is limited.<sup>9,10</sup> This model is consistent with recent findings showing that maintenance of the Tfh cell phenotype requires sustained antigenic stimulation<sup>19,21</sup> and with previous data demonstrating that, compared with DCs, B cells are particularly efficient antigen-presenting cells when antigen is limited because of their capacity to capture antigen through their high-affinity antigen-B cell receptor.<sup>22</sup> Collectively, these data suggest that antigen availability dictates the transition from DC-dominated Tfh cell priming to B cell-dominated Tfh cell expansion and maintenance.

## THE ROLE OF DCs IN THE SPATIAL COMPARTMENTALIZATION OF EFFECTOR AND TFH CELL DIFFERENTIATION

Naive CCR7-expressing CD4<sup>+</sup> T cells are thought to encounter recently activated, CCR7-expressing, antigen-bearing DCs within the T-cell area of secondary lymphoid organs,<sup>23</sup> where they subsequently differentiate into effector T cells following exposure to polarizing cytokines secreted by the DCs.<sup>24,25</sup> In this model, the cytokines made the DCs are the main driving force behind the subsequent differentiation of T cells toward a polarized effector phenotype. However, several lines of evidence indicate that, in addition to the

polarizing cytokines secreted by DCs, the spatial location of the responding T cells within the secondary lymphoid organ is also an important factor in their subsequent differentiation.<sup>26–29</sup> For example, a recent study<sup>15</sup> indicates that Tfh cells are initially primed within the interfollicular zone—the narrow strip between B-cell follicles that, despite being on the edge of the B-cell area, is also not in the T-cell zone.

The idea that the interfollicular zone is important for Tfh differentiation represents a paradigm shift from the original idea that pre-Tfh cells upregulate CXCR5, downregulate CCR7 and migrate to the T-B border, where they interact with B cells.<sup>12,30,31</sup> Instead, the new studies suggest that pre-Tfh cells turn on CXCR5, migrate to the interfollicular zone and upregulate Bcl6 expression independently of any cognate interactions with B cells<sup>15,32</sup>—implying that other antigen-presenting cells, such as DCs, are promoting the expression of both CXCR5 and Bcl6.<sup>9,10,15,33</sup> Although DCs predominate in the T zone, conventional DCs are also found in the B-cell follicle and in the interfollicular areas,<sup>28,34,35</sup> where they may transfer antigen to B cells and help primary antibody responses.<sup>36</sup> Importantly, DCs found near the B cell follicles also express high levels CXCR5, low levels of CCR7 and migrate in response to CXCL13.<sup>28,35,36</sup> Thus, the expression of CXCR5 by DCs is likely to be instrumental in their placement near the B follicles and their ability to promote Tfh cell responses.

Despite the potential role of CXCR5-expressing DCs in the priming of Tfh responses, it is not clear whether Tfh cell priming is conducted by a specific subset of CXCR5-expressing DCs that are specialized in priming Tfh cells or whether any DC that receives the appropriate activating signals will upregulate CXCR5, but not CCR7, migrate to the interfollicular zone and promote the differentiation of Tfh cells. In favor of the DC subset hypothesis, myeloid DCs in secondary lymphoid organs can be broadly separated into two major categories, resident DCs (rDCs) and migratory DCs (mDCs), based on their anatomic origin.<sup>37–42</sup> Whereas rDCs reside constitutively in secondary lymphoid organs and capture and present antigen that access the lymphoid organs directly through the blood or lymph, mDCs differentiate in the peripheral tissues and, upon activation, migrate into draining lymph nodes via afferent lymphatic vessels (Table 1). Importantly, mDCs characteristically express high levels of CCR7, whereas rDCs display low levels of this chemokine receptor,<sup>43</sup> suggesting that if rDCs were to also upregulate CCR5, they could migrate to the interfollicular zone and prime Tfh cells. In contrast, the high levels of CCR7 found on most mDCs would promote their homing to the T zone and preclude their priming of Tfh cells.<sup>23,28,44–47</sup>

Interestingly, numerous studies indicate that mDCs can carry antigens from peripheral tissues into draining lymph nodes and subsequently transfer those antigens to rDCs.<sup>48–51</sup> Therefore, one could envision a scenario in which CCR7<sup>+</sup> mDCs may hand off antigen to CCR7<sup>–</sup> rDCs, which then turn on CXCR5, migrate into

**Table 1** Phenotype and anatomical origin of the DC subpopulations in the mediastinal lymph nodes after pulmonary challenge

| DC subset                  | Origin         | Phenotype   |
|----------------------------|----------------|---|
| CD8a <sup>+</sup> rDCs     | LN resident    | MHCII <sup>int</sup> CD11c <sup>hi</sup> B220 <sup>–</sup> CD103 <sup>hi</sup> CD8α <sup>+</sup> CD11b <sup>–</sup> Ly6C <sup>–</sup> CD64 <sup>–</sup> Mar1 <sup>–</sup> CCR7 <sup>–</sup>         |
| CD4 <sup>+</sup> rDCs      | LN resident    | MHCII <sup>int</sup> CD11c <sup>hi</sup> B220 <sup>–</sup> CD4 <sup>+</sup> CD8α <sup>–</sup> CD11b <sup>hi</sup> Ly6C <sup>–</sup> CD64 <sup>–</sup> Mar1 <sup>–</sup> CCR7 <sup>–</sup>           |
| CD4/8α <sup>–</sup> rDCs   | LN resident    | MHCII <sup>int</sup> CD11c <sup>hi</sup> B220 <sup>–</sup> CD4 <sup>–</sup> CD8α <sup>–</sup> CD11b <sup>hi</sup> Ly6C <sup>–</sup> CD64 <sup>–</sup> Mar1 <sup>–</sup> CCR7 <sup>–</sup>           |
| CD103 <sup>+</sup> mDCs    | Lung-migratory | MHCM <sup>hi</sup> CD11c <sup>int</sup> B220 <sup>–</sup> CD103 <sup>hi</sup> Lang <sup>+</sup> CD11b <sup>lo</sup> Ly6C <sup>lo</sup> CD64 <sup>lo</sup> Mar1 <sup>lo</sup> CCR7 <sup>hi</sup>     |
| conCD11b <sup>+</sup> mDCs | Lung-migratory | MHCII <sup>hi</sup> CD11c <sup>int</sup> B220 <sup>–</sup> CD103 <sup>int</sup> Lang <sup>–</sup> CD11b <sup>hi</sup> Ly6C <sup>hi</sup> CD64 <sup>lo</sup> Mar1 <sup>int</sup> CCR7 <sup>int</sup> |
| moCD11b <sup>+</sup> mDCs  | Lung-migratory | MHCII <sup>hi</sup> CD11c <sup>int</sup> B220 <sup>–</sup> CD103 <sup>lo</sup> Lang <sup>–</sup> CD11b <sup>hi</sup> Ly6C <sup>hi</sup> CD64 <sup>hi</sup> Mar1 <sup>hi</sup> CCR7 <sup>lo</sup>    |
| Plasmacytoid DCs           | Bone marrow    | MHCII <sup>lo</sup> CD11c <sup>int</sup> B220 <sup>+</sup> CD8α <sup>+</sup> CD11b <sup>–</sup> Ly6C <sup>+</sup>   |

Abbreviations: DC, dendritic cell; mDC, migratory DC; rDC, resident DC.

the interfollicular area and promote Tfh differentiation. Alternatively, although activation through pathogen recognition receptors often triggers CCR7 expression on mDCs, mDCs can also upregulate CXCR5 (without upregulating CCR7) in response to some pathogens, and as a consequence, preferentially home into the interfollicular area after reaching the draining lymph node.<sup>28</sup> These data suggest that, at least in some circumstances, mDCs might upregulate CXCR5 and home into the interfollicular zone to directly prime Tfh cell responses. In a third scenario, some mDC populations may migrate from the infected tissues to the draining lymph node by a CXCR3-dependent mechanism<sup>52</sup> and, following a stromal cell-derived CXCL9 gradient,<sup>27</sup> access the interfollicular area and promote Tfh cell responses.<sup>52</sup> In each of these scenarios, a specific subset of DCs or activation state of DCs is required to prime Tfh responses in the interfollicular zone, suggesting that a specific subset of Tfh-activating DCs should be able to be identified and targeted during vaccination.

An important remaining question is why encounters between activated T cells and DCs within the interfollicular zone facilitate Bcl6 upregulation and Tfh cell differentiation. Interestingly, in addition to regulating lymphocyte trafficking, chemokine–chemokine receptor interactions also modulate the activation and maturation of monocytes and DCs.<sup>53</sup> Indeed, DCs upregulate costimulatory molecules and secrete pro-inflammatory cytokines in response to CCL19 and CCL21 and preferentially prime Th1 responses after CCR7 stimulation.<sup>54,55</sup> On the basis of these findings, one could speculate that, in addition to orchestrating encounters between DCs and T cells, chemokine–chemokine receptor interactions also condition the capacity of DCs to prime Tfh cell responses by regulating the expression of co-stimulatory molecules and inflammatory cytokines required for Tfh cell development (Figure 1). For example, whereas the engagement of CCR7 on DCs could program them to preferentially prime polarized Th1 responses, the engagement of CXCR5 on DCs may preferentially condition them to initiate Tfh cell responses. Alternatively, the positioning of DCs within the particular microenvironment of the interfollicular area may allow them to receive conditioning signals from nearby B cells or stromal cells that ultimately instruct them to induce Tfh cell differentiation. Consistent with this last possibility, the

differentiation of interleukin (IL)-4-producing Tfh cells requires interactions with lymphotoxin-conditioned stromal cells in the interfollicular zone.<sup>28</sup> Thus, environmental triggers may be as important as cytokines in promoting Tfh differentiation.

## INFLUENCE OF DC-DERIVED CYTOKINES IN TFH CELL DEVELOPMENT

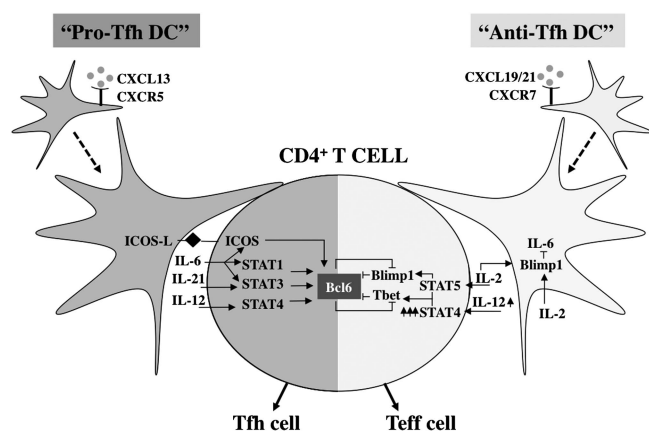
The differentiation of activated CD4<sup>+</sup> T cells into Tfh or polarized effector T cells is fine-tuned by the balance of cytokines that promote Tfh differentiation and those that prevent Tfh cell differentiation.<sup>56,57</sup> For example, whereas IL-6<sup>58–60</sup> and IL-21<sup>60,61</sup> cooperate to induce Tfh cell formation by activating STAT3, which in turn promotes Bcl6 and CXCR5 expression, IL-2 signaling prevents Tfh cell development via STAT5 activation.<sup>4,62,63</sup> The differential activation of DCs by pathogens or adjuvants enhances their production of a wide range of cytokines that work cooperatively to guide the responding T cells down the various pathways of differentiation.<sup>24,25</sup> In a similar way, DCs may have important roles in controlling induction of Tfh cell responses by regulating the balance between the cytokines required for Tfh differentiation and those required for effector T-cell polarization.

### DC-derived IL-6

Despite abundant evidence suggesting an important role for IL-6 in Tfh cell development,<sup>58–60,64</sup> the relevant cellular source of IL-6 *in vivo* remains unclear. Recent studies suggest that early IL-6 signaling is required to initiate the Tfh differentiation program following acute viral infection.<sup>58</sup> Activated conventional DCs secrete large amounts of IL-6, particularly in response to CD40 stimulation.<sup>65,66</sup> Interestingly, type I interferon is required to license CD40-dependent IL-6 secretion by DCs and, as a result, *Ifnar1*<sup>−/−</sup> DCs fail to produce IL-6 in response to LPS and CD40 stimulation.<sup>66</sup> Although *Ifnar1*<sup>−/−</sup> CD8<sup>+</sup> T cells fail to differentiate into fully functional cytolytic effector cells following viral infections *in vivo*, *Ifnar1*<sup>−/−</sup> CD4<sup>+</sup> T cells differentiate normally into Tfh cells. However, Tfh cell responses are impaired in mice in which *Ifnar1* deficiency is restricted to DCs. Based on these results, one could argue that DCs stimulated by CD40 in the presence of type I interferon would preferentially trigger Tfh cell differentiation by promoting Bcl6 upregulation via STAT3 and STAT1 activation following IL-6 signaling.<sup>58</sup>

Plasmacytoid DCs (pDCs) also secrete IL-6 upon activation by microbial products<sup>67–69</sup> and may have a role in promoting Tfh cell differentiation. For example, ICOS expression, which is required for Tfh cell differentiation,<sup>8</sup> is induced on T cells in response to pDC-derived IL-6.<sup>70</sup> Moreover, pDCs also upregulate ICOS-ligand in response to influenza,<sup>70–73</sup> suggesting that pDCs could contribute to the Tfh cell pathway by promoting interactions between ICOS and its ligand.<sup>70</sup> Consistent with this idea, a recent study shows that the antibody response to influenza is impaired in pDC-depleted mice.<sup>74</sup> Thus, the production of IL-6 by both conventional DCs and pDCs may promote Tfh differentiation.

IL-6 production by DCs is triggered by exposure to microbial products and by interactions with T cells via CD40. However, the production of IL-6 by DCs can also be repressed under some circumstances. For example, recent studies suggest that BLIMP-1-1 negatively regulates the capacity of activated DCs to secrete IL-6.<sup>18,75,76</sup> In fact, BLIMP-1-deficient DCs preferentially induce Tfh cell differentiation *in vitro*<sup>19</sup> and mice lacking BLIMP-1 in the DC compartment produce high levels of IL-6 and exhibit spontaneous germinal center formation and autoantibody production. Thus, in addition to directly inhibiting Tfh cell differentiation by preventing Bcl6 expression in T cells,<sup>5</sup> Blimp-1 may also prevent Tfh cell



**Figure 1** Priming of effector and Tfh cell responses by conditioned DCs. Tfh cell development is regulated by the cross-talk between cytokines that promote Bcl6 expression and the cytokines that prevent it. DCs conditioned to secrete 'pro-Tfh cells' cytokines preferentially induce Tfh cell expansion, whereas DCs secreting large amounts of 'anti-Tfh cell' cytokines promote effector T-cell differentiation.

responses by regulating the capacity of conventional and pDCs to produce IL-6 and thereby instruct Tfh cell priming.

### DC-derived IL-2

IL-2 is often thought of as the canonical growth factor for both CD4<sup>+</sup> and CD8<sup>+</sup> T cells. However, despite its potent effects on T-cell proliferation and the differentiation of effector T cells, IL-2 signaling through the IL-2R expressed on T cells actually prevents Tfh cell differentiation.<sup>4</sup> IL-2 likely disrupts the differentiation of Tfh by promoting BLIMP-1 expression via STAT5,<sup>62,63</sup> or by inducing the expression of T-bet, which forms complexes with Bcl6 that mask the DNA-binding domain of Bcl6 and prevent Bcl6 from repressing the expression of BLIMP-1.<sup>77</sup> Although activated CD4<sup>+</sup> T cells are often considered the principal source of IL-2 during the course of an immune response, DCs also produce significant amounts of IL-2 in response to various microbial stimuli.<sup>78,79</sup> Indeed, DCs engaged in cognate interactions with T cells secrete IL-2 in a directed manner toward the T cell–DC interface,<sup>79</sup> a process that may help expand both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell effectors. Moreover, some viruses infect DCs and actively prevent them from secreting IL-2,<sup>80</sup> thus limiting the capacity of DCs to expand responding T cells and highlighting the importance DC-derived IL-2 in promoting T-cell responses against viruses. Therefore, given that IL-2 signaling is required for effector T-cell differentiation,<sup>81,82</sup> but precludes Tfh cell formation,<sup>13–15,21</sup> contact of naive CD4 T cells with IL-2-producing DCs may favor effector T-cell development at expense of Tfh cell formation.<sup>4,62,63,77</sup>

Although IL-2 clearly acts directly on T cells via CD25 to impair the differentiation of Tfh cells, IL-2 may act on more than just T cells to prevent Tfh differentiation. For example, CD25 expression is not restricted to T cells, and is also found on human<sup>83,84</sup> and mouse DCs.<sup>85</sup> Given that IL-2 signaling drives BLIMP-1 expression in T cells, it may also promote BLIMP-1 expression in DCs. In turn, BLIMP-1-expressing DCs should produce less IL-6, leading to a bias in CD4<sup>+</sup> T-cell differentiation away from the production of Tfh cells. Consistent with this idea, BLIMP-1-deficient DCs promote the expansion of germinal centers and the production of autoantibodies in mice.<sup>75,76</sup> Thus, is possible that IL-2 signaling induces Blimp-1 expression in DCs just like it does in T cells and thereby inhibits their capacity to promote Tfh cell responses by limiting IL-6 production.

### DC-derived IL-12

Activation of DCs by certain pathogen-recognition receptors, such as TLR4 or TLR7, results in the robust secretion of IL-12, which conditions responding T cells to secrete Th1 cytokines.<sup>24,25</sup> However, IL-12 has been also implicated in Tfh cell development via STAT4 activation, which seems to be required for early upregulation of Bcl6 and IL-21 genes, in both human and mice.<sup>86,87</sup> In fact, the induction of IL-21-secreting Tfh-like cells by human DCs is dependent on IL-12,<sup>88</sup> suggesting that early contacts of naive CD4<sup>+</sup> T cells with IL-12-secreting DCs may be required to initiate the Tfh cell program. Intriguingly, using the same STAT4-dependent mechanism,<sup>89,90</sup> IL-12 signaling also induces the upregulation of T-bet,<sup>11,12</sup> which prevents Bcl6 activity and Tfh cell development.<sup>77,86</sup> Thus, whereas IL-12 may induce early expression of Tfh cell markers, prolonged IL-12 receptor signaling may prevent Tfh cell responses by inducing T-bet expression. Based on this model, it is not just the presence or absence of a particular cytokine-signaling pathway that alters Tfh cell differentiation, but that the duration and intensity of some signaling pathways may control the cell fate commitment of Tfh cells. Importantly, which DC subsets produce IL-12, as well as the

amount of IL-12 secreted by a particular population, depends on the kind of the microbial challenge encountered.<sup>39,91–93</sup> Thus, the nature of the activation signal could determine, at least to some degree, the capacity of the different DCs subsets to prime Tfh cells responses by conditioning their ability to secrete IL-12 upon activation.

### CONCLUDING REMARKS

Given that Tfh cells are required for the generation of germinal centers and the establishment of long-lived antibody responses, it is essential that we understand how to manipulate Tfh responses in order to improve the efficacy of vaccines and intervene in the case of antibody-dependent autoimmunity. Importantly, by characterizing the cellular and molecular mechanisms by which DCs control Tfh priming, we will be able to define adjuvants that boost Tfh cell responses and promote long-term antibody responses to vaccination. On the other hand, knowing the mechanisms by which DCs promote unregulated Tfh cell responses will lead to the design of new therapeutic approaches to inhibit the development of self-reactive Tfh cell responses, which would ultimately help to prevent effector auto-reactive B-cell responses and immunopathology.

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