Immunity
Review

T Follicular Helper Cell Differentiation, Function, and Roles in Disease

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Follicular helper T (Tfh) cells are specialized providers of T cell help to B cells, and are essential for germinal center formation, affinity maturation, and the development of most high-affinity antibodies and memory B cells. Tfh cell differentiation is a multistage, multifactorial process involving B cell lymphoma 6 (Bcl6) and other transcription factors. This article reviews understanding of Tfh cell biology, including their differentiation, migration, transcriptional regulation, and B cell help functions. Tfh cells are critical components of many protective immune responses against pathogens. As such, there is strong interest in harnessing Tfh cells to improve vaccination strategies. Tfh cells also have roles in a range of other diseases, particularly autoimmune diseases. Overall, there have been dramatic advances in this young field, but there is much to be learned about Tfh cell biology in the interest of applying that knowledge to biomedical needs.

Introduction

There has been a great deal of recent activity in the study of T follicular helper (Tfh) cells. While the first evidence of Tfh cells was reported in human lymphoid tissue more than a decade ago, much of the interest in Tfh cells traces its origins to the identification of Bcl6 as an essential transcription factor in $CD4^+$ T cells for Tfh cell differentiation and the development of germinal centers (GCs) (Johnston et al., 2009; Nurieva et al., 2009; Yu et al., 2009). The field of Tfh cell biology has now exploded with activity, examining everything from the biochemistry of transcription factors involved in programming Tfh cell differentiation to the cellular biology of Tfh cell-mediated selection of germinal center B cells, and examining important roles of Tfh cells in biological processes as diverse as vaccine-elicited immune responses, chronic autoimmune diseases, and even roles of Tfh cells in protective immunity in human cancers. This article reviews our understanding of Tfh cell differentiation, molecular biology, and function and discusses the most recent advances in these areas, as well as the complexities of Tfh cell biology. In addition, a new conceptual model is introduced to explain the relationship between Tfh cell and other $CD4^+$ T cell differentiation programs. For an oral presentation of the review, see Movie S1 available online.

Stages of Tfh Cell Differentiation

Tfh cell differentiation is a multistage, multifactorial process. There is no single event that defines Tfh cell differentiation, unlike T helper 1 (Th1) cell differentiation, for instance, which can be fully induced by interleukin-12 (IL-12) exposure in vitro or in vivo. Instead, Tfh cell differentiation is a multistep, multisignal process that also accommodates a significant amount of heterogeneity. The canonical Tfh cell differentiation process starts at initial dendritic cell (DC) priming of a naive $CD4^+$ T cell (Goenka et al., 2011) (Figure 1A). The $CD4^+$ T cell undergoes a cell-fate decision within the first few rounds of cell division (Choi et al., 2011; 2013b). If the chemokine receptor CXCR5 is expressed, the early Tfh cell will migrate to the border of the B cell follicle and undergo further Tfh cell differentiation. If the cell instead receives Th1, Th2, or Th17 signals (Figure 1), then the $CD4^+$ T cell follows a Th1, Th2, or Th17 cell differentiation program, including upregulation of chemokine receptors for inflammatory chemokines that will drive the effector cell to exit the lymphoid tissue and traffic to the site of infection or inflammation.

Early Tfh cell differentiation (the DC priming phase) is regulated by IL-6, inducible costimulator (ICOS), IL-2, and T cell receptor (TCR) signal strength in mouse models. TCR signal strength can bias T cell differentiation in vivo (Tubo et al., 2013), but a single naive mature T cell can give rise to multiple different differentiated effector cell types upon stimulation and proliferation, demonstrating that non-TCR and TCR signals combine to determine T cell differentiation fates. $CD4^+$ T cells possessing TCRs with high affinity preferentially differentiated into Tfh cells in a pigeon cytochrome C (PCC) model (Fazilleau et al., 2009), but not a Friend virus infection (Ploquin et al., 2011). Utilizing a range of systems, it was found that TCR: major histocompatibility complex-II (MHCII) dwell time is a more accurate predictor of cell-fate preference, with a nonlinear relationship (Tubo et al., 2013), such that there was no simple relationship between TCR signal strength and Tfh cell differentiation. IL-6 is the earliest non-TCR signal involved in initiation of Tfh cell differentiation. IL-6 signaling through IL-6 receptor (IL-6R/gp130) transiently induces Bcl6 expression by newly activated $CD4^+$ T cells (Nurieva et al., 2009). Bcl6 is necessary for early CXCR5 expression in multiple models (Choi et al., 2011; 2013a; Pepper et al., 2011). In the absence of IL-6 an early defect in Tfh cell differentiation is observed (Choi et al., 2013a). The DC type responsible for initiating Tfh cell differentiation is unknown. Most likely, there are multiple Tfh cell differentiation pathways and there is no single DC type responsible. Instead, multiple DC and monocyte types can prime Tfh cell differentiation in different conditions (Ballesteros-Tato and Randall, 2014). Many DC types are robust producers of IL-6. *Prdm1*$^{-/-}$ DCs are hyperactive producers of IL-6, resulting in spontaneous Tfh cell and GC development in vivo (Kim et al., 2011). IL-6 can also be a signal for Th17 cell differentiation, and therefore it is assumed that IL-6, in

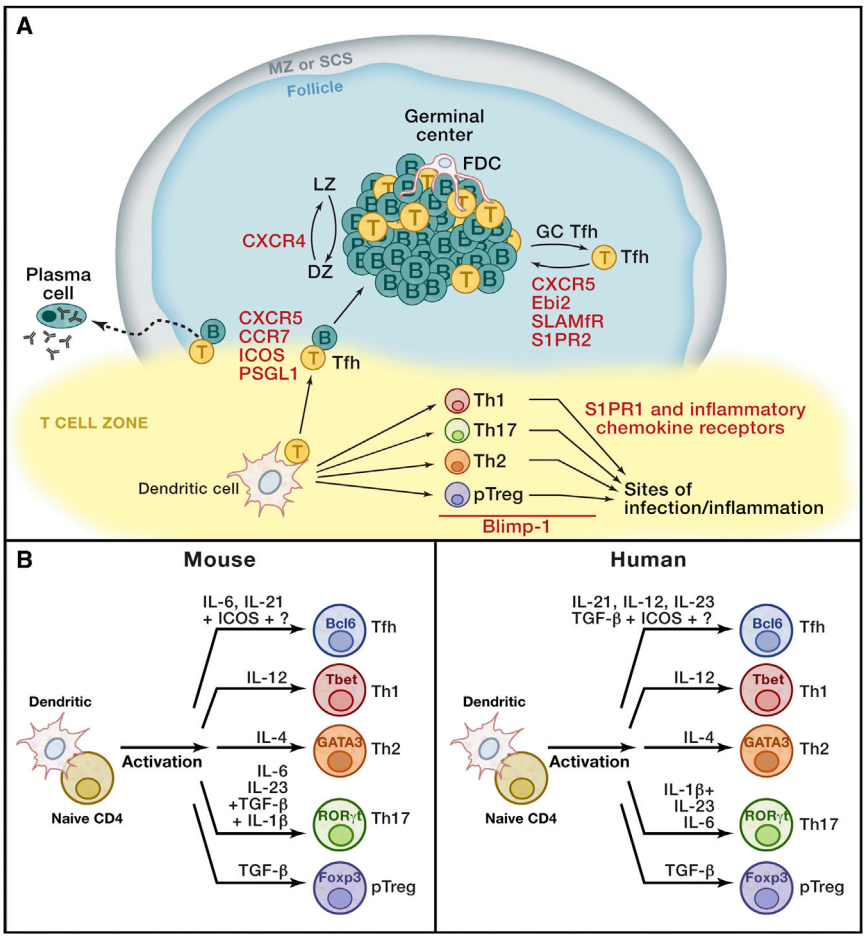

Figure 1. Overview of Tfh Cell Differentiation

(A) Stages of Tfh cell differentiation, highlighting roles of migration-associated molecules.

(B) Signals in CD4 T cell differentiation. A simplified model of CD4 T cell differentiation pathways, showing transcription factors and inducing factors, highlighting apparent differences between human and mouse Tfh cell differentiation.

combination with different signals, is involved in Tfh cell versus Th17 cell differentiation. Interestingly, no increase in Th17 cells was seen in hyper-IL-6-producing mice, in contrast to the increase in Tfh cells. IL-1 is an important driver of Th17 differentiation, whereas ICOS is important for Tfh differentiation (Choi et al., 2011; Nurieva et al., 2008). ICOS has roles in both Tfh cell differentiation and migration, and there are data supporting a synergistic role of ICOS and IL-6. The importance of ICOS is highlighted by the multiple ways in which ICOS signaling is regulated. Roquin inhibits ICOS, and combined loss of Roquin1 and Roquin2 results in spontaneous Tfh cell and GC development (Pratama et al., 2013; Vogel et al., 2013). In addition, the miR-19∼72 complex is necessary for Tfh cell differentiation, and it works, in part, via dampening the PI(3)K inactivating phosphatases PHLPP2 and PTEN, which are inhibitors of ICOS signaling (Baumjohann et al., 2013; Kang et al., 2013). IL-2 signaling is another major regulator of Tfh cell differentiation. IL-2 is a potent inhibitor of Tfh cell differentiation (Ballesteros-Tato et al., 2012; Johnston et al., 2012) and can act very early during T cell priming (Johnston et al., 2012). Thus, the interplay between IL-6, ICOS, IL-2, and TCR signaling orchestrates early induction of mouse Tfh cell differentiation during DC priming via control of CXCR5, Bcl6, and other targets.

The second stage of Tfh cell differentiation occurs when the T cell interacts with antigen-specific B cells in the follicle, interfollicular zone, or the T-B border. Much of Tfh cell differentiation and function is tightly interconnected with the microanatomical geography of the T and B zones of the lymph node (LN) and spleen. The early Tfh cells colocalize with B cells because they express CXCR5, downregulate C-C chemokine receptor type 7 (CCR7) (the primary chemotactic receptor for the T zone), and downregulate P-selectin glycoprotein ligand 1 (PSGL1), which is thought to anchor T cells to CCL19 and CCL21 decorating the T zone extracellular matrix (Figure 1A). Tfh cells have a highly symbiotic relationship with B cells, and B cells are required for Tfh cell development under almost all conditions (Crotty, 2011). ICOS is a costimulatory molecule, but it has been recently demonstrated that ICOS-ICOS ligand (ICOSL) binding also induces directional migration of $CD4^+$ T cells, which can play an important role in proper localization of the early Tfh cells to the B cell follicle (Xu et al., 2013). B cells serve both as antigen-presenting cells (APCs) and as a source of ICOSL (Choi et al., 2011; Haynes et al., 2007; Nurieva et al., 2008). B cells rapidly become the primary APCs available in a LN during an acute infection or immunization because mature DCs last for only a few days before dying, whereas the antigen-specific B cells undergo geometric replication. Antigen presentation is critical, because unlike effector CD8 T cells, antigen-specific CD4 T cells require antigen recognition for virtually every cell division (Choi et al., 2013b; Obst et al., 2005; Yarke et al., 2008).

The third stage of Tfh cell differentiation involves the GC (Figure 1A). The GC is a distinct structure consisting of GC Tfh cells, GC B cells, follicular dendritic cells (FDCs), macrophages, and stroma. The majority of GC Tfh cells can be observed to possess a canonical Tfh cell differentiation program. The majority of GC Tfh cells are $CXCR5^{hi}PD1^{hi}Bcl6^{hi}Maf^{hi}SAP^{hi}$. They are also $PSGL1^{lo}CD200^{+}BTLA^{hi}CCR7^{lo}$. The canonical secreted Tfh cell molecules are C-X-C motif chemokine 13 (CXCL13), IL-21, and IL-4 (Crotty, 2011; Kroenke et al., 2012; Liang et al., 2012; Linterman et al., 2011). These GC Tfh cell surface proteins, transcription factors, and secreted molecules are well conserved across in vivo conditions and species. GC Tfh cells can be readily identified in mice, humans, and nonhuman primates as $CXCR5^{hi}PD1^{hi}Bcl6^{hi}$ CD4 T cells. The biology of GC Tfh cells is strongly associated with changes in several