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Competing For Help: New Insights into the Function of Follicular Helper T Cells

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The development and function of the CD4 T cell subset that controls B cell responses to protein antigens has lagged behind our knowledge of other effector lineages of CD4 T cells. Two new studies published in *Nature Immunology*^{1, 2} shed light on the requirements for CD4 T cells that are selected for B cell help, and how they mediate that function through the secretion of cytokines.

The knowledge that CD4 T cells are required for B cells to produce high-affinity antibodies and generate long-lived responses to most protein antigens (T-dependent antigens) has been appreciated for many years³. However, CD4 T cells can differentiate into several subsets defined by the specific secretion of cytokines and by the expression of transcription factors that mediate particular functions, suggesting not all CD4 T cells are engaged in B cell help. More recently, a subset of CD4 T cells, termed follicular helper T cells (T_{FH} cells), has been shown to be primarily responsible for B cell help during an immune response; separating this population from other CD4 T cell subsets such as Th1 and Th2. T_{FH} cells have largely been defined by their permanent expression of CXCR5, a chemokine receptor required for their migration to the B cell follicle chemokine CXCL13 and to the germinal center (GC), the main site of B cell selection, and by the production of the cytokine IL-21⁴. The identification of IL-21 secretion by T_{FH} cells suggested this cytokine would be responsible for B cell selection and somatic hypermutation; however, studies in IL-21-deficient mice suggested it was not required for antibody production or GC formation. Moreover, IL-21 appeared to have overlapping roles with IL-4, a cytokine thought to be specific to the Th2 lineage⁵. In addition, the observation by several groups that IL-4 (as well as IFN γ) played a role in shaping the antibody repertoire clouded our understanding of how T_{FH} cells functioned to mediate B cell help, and suggested that Th1 and Th2 cells globally secreted cytokines that could also effect B cell responses. Finally, the requirements for differentiation of T_{FH} cells remained undefined.

New studies by Reinhardt *et al.*¹, and Fazilleau *et al.*² answer many of these questions, suggesting a new model for the development of T_{FH} cells. In the former study, the authors take advantage of a sophisticated IL-4 reporter system that has the benefit of tracking both the IL-4 competent and IL-4 secreting CD4 T cells that develop in the lymph node during an immune response. Interestingly, they find at time points where B cell responses are at their peak that all of the IL-4 secreting CD4 T cells are located within GCs, indicating they are in

fact T_{FH} cells, and not Th2 cells. Furthermore, they describe a population of T_{FH} cells in the GC that can also make IFN γ , suggesting that GC B cells compete for cytokine-producing T_{FH} cells, shaping the B cell selection process and antibody repertoire. By carefully sorting out T-B cell co-conjugates, they show this is indeed the case. Those B cells in contact with IL-4 secreting T_{FH} cells are largely producing IgG1 or IgE, known isotypes associated with IL-4 production, while B cells coupled with IFN γ secreting T_{FH} cells produce IgG2a, an isotype traditionally related to IFN γ sufficiency. This study shows definitively that T_{FH} cells are not limited to IL-21 secretion, and answers the mystery of how Th1 and Th2 associated cytokines can shape the GC-dependent antibody response.

In the second study by Fazilleau and colleagues, the authors explore the role of TCR affinity in the development of T_{FH} cells, extending previous work demonstrating that CD4 T cells with strong affinity for antigen preferentially became a local pool of memory T_{FH} cells. When comparing T_{FH} cells to other effector CD4 T cell subsets, the authors found that CD4 T cells with the highest affinity TCR were more likely to develop into T_{FH} cells than other effector CD4 T cell subsets. This suggested the program that drives T_{FH} cell differentiation required either strong TCR signaling, or long duration with antigen presenting cells in order to fully drive T_{FH} cell development.

Based on these two studies, we can now extend the model of T_{FH} cell development and function (Figure 1). Upon CD4 T cell encounter with antigen presented by DCs in the T cell zone, activation will drive competency for the expression of IL-4 or IFN γ , and upregulate the homing receptor CXCR5. Expression of the latter molecule will allow migration of the T cell toward the B cell follicle, and those CXCR5⁺ CD4 T cells expressing a TCR with high affinity for antigen will interact with B cells and receive additional signals to become a T_{FH} cell, perhaps including maintenance of CXCR5 expression. Those T cells that do not interact with an antigen presenting B cell may leave the lymph node and ultimately become a Th1 or Th2 cell. Other studies have shown already that B cells are required for T_{FH} cell development^{6, 7} and GC formation^{8–10}, specifically via delivery of a ligand signal to ICOS, an inducible costimulatory molecule on T cells. If TCR affinity and ICOS signals are required, and both be derived from DCs or B cells, one question requiring further exploration is how these two signals integrate to drive a T_{FH} cell program. One possibility is that expression of a TCR with high affinity for antigen ensures the T cell will have strong and long lasting interactions with B cells, which may be necessary to deliver other signals, possibly via ICOS, for differentiation into T_{FH} cells.

The presence of T-B co-conjugates *in vivo* is also of particular interest, as studies using methods of tracking live cells in a GC reaction failed to identify many T_{FH} cells that interacted with B cells for any considerable length of time. In fact, T_{FH} cells appeared to move quite quickly in and around the GC, making very few if any contacts with B cells^{11–13}. Although the study by Reinhardt *et al.* demonstrates that IL-4 production has a distinct consequence in shaping B cell responses, the precise mechanism of how and when this occurs remains to be elucidated. Furthermore, the location and timing of affinity maturation and B cell selection within the GC is still not well understood, and the role that cytokine-producing T_{FH} cells play in that process is still unknown. Although these studies significantly increase our understanding of T_{FH} cell development and function, more work is needed to appreciate the mechanisms by which T and B cells drive the antibody response necessary for pathogen elimination and long-lived immune protection.

References

1. Reinhardt RL, Liang HE, Locksley RM. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol.* 2009

2. Fazilleau N, McHeyzer-Williams LJ, Rosen H, McHeyzer-Williams MG. The function of follicular helper T cells is regulated by the strength of T cell antigen receptor binding. *Nat Immunol.* 2009
3. Parker DC. The functions of antigen recognition in T cell-dependent B cell activation. *Semin Immunol.* 1993; 5:413–420. [PubMed: 8123796]
4. King C, Tangye SG, Mackay CR. T follicular helper (TFH) cells in normal and dysregulated immune responses. *Annu Rev Immunol.* 2008; 26:741–766. [PubMed: 18173374]
5. Ozaki K, Spolski R, Feng CG, Qi CF, Cheng J, Sher A, et al. A critical role for IL-21 in regulating immunoglobulin production. *Science.* 2002; 298:1630–1634. [PubMed: 12446913]
6. Haynes NM, Allen CD, Lesley R, Ansel KM, Killeen N, Cyster JG. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1high germinal center-associated subpopulation. *J Immunol.* 2007; 179:5099–5108. [PubMed: 17911595]
7. Nurieva RI, Chung Y, Hwang D, Yang XO, Kang HS, Ma L, et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. *Immunity.* 2008; 29:138–149. [PubMed: 18599325]
8. Bossaller L, Burger J, Draeger R, Grimbacher B, Knoth R, Plebani A, et al. ICOS deficiency is associated with a severe reduction of CXCR5+CD4 germinal center Th cells. *J Immunol.* 2006; 177:4927–4932. [PubMed: 16982935]
9. McAdam AJ, Greenwald RJ, Levin MA, Chernova T, Malenkovich N, Ling V, et al. ICOS is critical for CD40-mediated antibody class switching. *Nature.* 2001; 409:102–105. [PubMed: 11343122]
10. Dong C, Temann UA, Flavell RA. Cutting edge: critical role of inducible costimulator in germinal center reactions. *J Immunol.* 2001; 166:3659–3662. [PubMed: 11238604]
11. Allen CD, Okada T, Tang HL, Cyster JG. Imaging of germinal center selection events during affinity maturation. *Science.* 2007; 315:528–531. [PubMed: 17185562]
12. Schwickert TA, Lindquist RL, Shakhar G, Livshits G, Skokos D, Kosco-Vilbois MH, et al. In vivo imaging of germinal centres reveals a dynamic open structure. *Nature.* 2007; 446:83–87. [PubMed: 17268470]
13. Hauser AE, Junt T, Mempel TR, Sneddon MW, Kleinstein SH, Henrickson SE, et al. Definition of germinal-center B cell migration in vivo reveals predominant intrazonal circulation patterns. *Immunity.* 2007; 26:655–667. [PubMed: 17509908]

Figure 1. Upon recognition of antigen, naïve T cells can differentiate into CD62L^{hi} CCR7^{hi} T lymphoid cells (T_{Iym}) that remain in the T cell zone, CD62L^{lo} CCR7^{lo} T emigrant cells (T_{em}) that home to peripheral tissues, or CXCR5^{hi} CD62L^{lo} CCR7^{lo} T resident follicular helper cells (T_H). The latter, when given the proper signals from B cells, become T follicular helper cells (T_{FH}) that become cytokine competent after activation by DCs and are more likely to have a TCR with high affinity for antigen compared to other T effector subsets. Upregulation of CXCR5 allows for their migration to the T-B cell border for encounter with activated B cells that have in turn migrated there in part via upregulation of CCR7. B cells then provide additional signals to T cells, including via antigen-MHC and ICOS, likely driving a full T_{FH} cell differentiation program and inducing migration into the GC where secretion of cytokines promotes B cell selection and affinity maturation.