

Follicular helper CD4 T cell (T_{FH}) differentiation and their role in protective immunity

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CD4⁺ T cell help is critical for both the generation and maintenance of germinal centers, and long term antibody responses. It has been thought that a distinct CD4⁺ effector T cell subset, called T follicular helper cells (T_{FH}), provides this help; however the molecular requirements for T_{FH} differentiation are unknown. We have now shown that expression of the transcription factor Bcl6 in CD4⁺ T cells is both necessary and sufficient for *in vivo* T_{FH} differentiation and T cell help to B cells in mice. In contrast, the transcription factor Blimp-1, an antagonist of Bcl6, inhibits T_{FH} differentiation and help, thereby preventing B cell germinal center and antibody responses. These findings demonstrate T_{FH} are required for proper B cell responses *in vivo* and Bcl6 and Blimp-1 play central yet opposing roles in T_{FH} differentiation (Science 2009).

SAP (SH2D1A) expression in CD4 T cells is essential for germinal center development. However, SAP-deficient mice have only a moderate defect in T_{FH} differentiation as defined by common T_{FH} surface markers. CXCR5⁺ T_{FH} cells are found within the germinal center as well as along the boundary regions of T/B cell zones. We have now shown that germinal center associated T cells (GC T_{FH}) can be identified by their co-expression of CXCR5 and GL7, allowing for phenotypic and functional analysis of T_{FH} and GC T_{FH} populations. We show GC T_{FH} are a functionally discrete subset of T_{FH} cells, with enhanced B cell help capacity and a specialized ability to produce IL-4 in a T_H2-independent manner. Strikingly, SAP-deficient mice have an absence of the GC T_{FH} subset and SAP⁻ T_{FH} are defective in IL-4 and IL-21 production. We further demonstrated that SLAM (Slamf1, CD150), a surface receptor that utilizes SAP signaling, is specifically required for IL-4 production by GC T_{FH}. GC T_{FH} cells require IL-4 and IL-21 production for optimal help to B cells. These data illustrate complexities of SAP-dependent SLAM family receptor signaling, revealing a prominent role for SLAM receptor ligation in IL-4 production by germinal center CD4 T cells but not in T_{FH} and GC T_{FH} differentiation, whereas SAP mediated signaling in T_{FH} cells is essential for GC T_{FH} differentiation.

References:

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