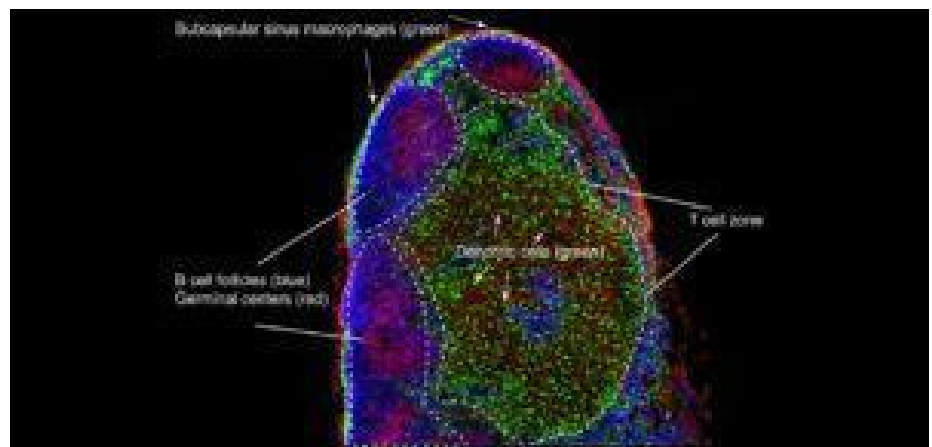
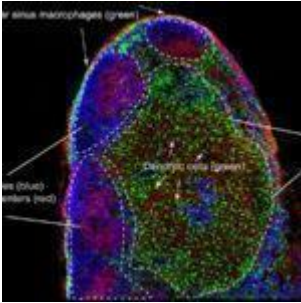


How do $\gamma\delta$ T cells control humoral immunity ?



A mouse lymph node section showing B cell follicles (anti-B220, blue) containing germinal centers (peanut agglutinin (PNA), red), in which B cells are selected for high affinity antibody specificity. CD11b+ dendritic cells CX3CR1-GFP, green) are located in the T cell zone, as well as and subcapsular sinus macrophages (CX3CR1-GFP, green) are present above prominent B cell follicles (empty areas).

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$\gamma\delta$ T cells are well known for their wide range of functional properties that play a role in immunity against pathogens and

tumours. $\gamma\delta$ T cells have also been shown to participate in induction of humoral immune responses by helping B cells. Whether $\gamma\delta$ T cells directly interact with B cells or indirectly affect humoral immunity is not known. Additional studies have shown that $\gamma\delta$ T cells promote B cell hypermutation by expressing follicular T helper cells (Tfh)-like properties such as expression of CXCR5 (allowing migration of the B cell follicle), CD40 ligand (crucial for B cell activation) and IL-4 and IL10 cytokine secretion (facilitating IgG class switching). However, it is not known whether $\gamma\delta$ "Tfh-like" cells truly exist.

Rezende and colleagues, aimed to determine mechanisms by which $\gamma\delta$ T cells control and/or contribute to induction of humoral immunity. Rezende et al., used murine models of immunization with complete Freund's adjuvant (CFA) or alum, or pristane-induced lupus to study $\gamma\delta$ T cell responses. Researchers, observed that immunizing TCR $\gamma\delta$ knockout mice resulted in reduced antibody serum levels, as well lower frequencies of Tfh cells that also had low expression of CD40L. This suggests that in the absence of $\gamma\delta$ T cells, the Tfh compartment is dysfunctional in providing help to B cells. Additionally, researchers observed that though $\gamma\delta$ T cells expressed CXCR5, PD-1 and ICOS, but have limited expression of CD40L and do not express Bcl6 (Tfh transcriptional factor) nor produce IL-21. This suggests that these $\gamma\delta$ T cells are not "Tfh-like" cells.

Studies by others have shown that induction of Bcl6 is mediated by upregulation of Ascl2 (transcription factor) via the β -catenin pathway. Induction of Ascl2 via β -catenin activation molecules (Wnt agonist) initiates commitment to the Tfh lineage by preventing differentiation into other T helper subsets. Finally, researchers showed that CXCR5+ $\gamma\delta$ T cells express high transcriptional levels of the Wnt ligands, *Wnt8a* and *Wnt8b*, which results in upregulation of CXCR5 in CD4 T cells.

In summary, this study demonstrates how $\gamma\delta$ T cells participate

in humoral immunity. Briefly, activation $\gamma\delta$ T cells by antigens induces expression of CXCR5, which facilitates migration towards the follicle. Where $\gamma\delta$ T cells present antigen to CD4 T cells, as well as release Wnt ligands which induce AScl2, initiating Tfh programming, with assistance from dendritic cells. These induced Tfh cells then interact with B cells and provide signal necessary for differentiation.

Journal Article: Rezende *et al.*, 2018. [\$\gamma\delta\$ T cells control humoral immune response by inducing T follicular helper cell differentiation.](#) Nature Communication

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