

Dendritic cells and B cells in effector T cells decisions

Promotion of antibody induction in lymphoid tissue or gut homing

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg, Fredagen den 1 Juni , klockan 09.00

av Samuel Alsén

Fakultetsopponent:

Professor **Kai-Michael Toellner**

Institute of Immunology and Immunotherapy

University of Birmingham

Avhandlingen baseras på följande delarbeten

- I. T Follicular Helper, but Not Th1, Cell Differentiation in the Absence of Conventional Dendritic cells.
Dahlgren M. W, Gustafsson-Hedberg T, Livingston M, Cucak H, **Alsén S**, Yrlid U and Johansson-Lindbom B.

The Journal of Immunology, 2015 June 1; 194(11); 5187-5199*
- II. IL-4 secretion following a Th1 skewing immunization is restricted to T follicular helper cells that also downregulate IL4R α .
Alsén S, Wenzel A. U, Dahlgren M.W, Erlandsson E, Gustafsson-Hedberg T, Bryder D, Johansson-Lindbom B and Yrlid U.
Manuscript
- III. B cells regulate lymph node exit of tissue tropic T helper cells following immunization.
Alsén S, Cervin J, Cucak H, Livingston M, Johansson-Lindbom B and Yrlid U.
Manuscript

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Abstract

CD4⁺ T cells are principal cells of the adaptive immune system, equipped with the ability to boost innate immune cells and aid B cells in the germinal centers. Every T cell clone carries a variable and unique T cell receptor that recognizes a protein-derived peptide presented on MHC molecules by antigen presenting cells (APC) in secondary lymphoid organs. Dendritic cells (DC) are the most prominent APC due to their unmatched ability to internalize foreign protein antigens, degrade them into peptides, load peptides onto MHC molecules and migrate to lymph nodes and present the antigen to T cells. Recognition of its cognate antigen leads to activation and proliferation of T cells while additional co-stimulatory signals dictate the differentiation and fate of T cells. Although T effector cell differentiation can be induced during the first encounter with an APC, the differentiation of B cell supporting T follicular helper (Tfh) cells require continuous antigen presentation by B cells. These two differentiation pathways of T cells occur in parallel and are guided by reciprocal antagonistic transcription factors. Herein, we have studied how APCs, with a focus on DCs and B cells, influence T cell differentiation.

By adoptively transferring CD4⁺ T cells with a known antigen specificity into recipient transgenic mice in which DCs can be depleted we show Tfh differentiation in the absence of DCs as long as a sufficient amount of antigen is administered together with the adjuvant. However, depletion of DCs lead to a loss of Th1 effector T cells that had downstream consequences on B cells by preventing class-switching into the Th1-associated antibody isotype. Excluding the altered class-switch, germinal center B cells showed normal affinity maturation and memory formation. This shows that Tfh cells generated in the absence of DCs are fully functional and that DCs therefore do not provide unique accessory signals required for Tfh differentiation.

T cells that differentiate to develop into Tfh cells become programmed to do so already during the primary encounter with an APC. To fulfill the Tfh differentiation program pre-Tfh cells must then interact with antigen presenting B cells to fully adopt Tfh functionality. This step-wise process has been extensively studied but it still remains unclear precisely how B cells enforce the Tfh program. In the second and third study, we exploited mixed bone marrow chimeras to generate mice in which B cells cannot present antigens to T cell thus terminating the Tfh program at the stage of T-B interactions.

In these studies, we reveal a role of B cells in regulating T cell expression of IL-4, its receptor IL4R α and a H2-Q2, a gene previously not described in T cell biology. We also show that B cells affect the output of T effector cells from the lymph node. In lymph, we identify T cells that exhibit phenotypic characteristics of Tfh cells, show a history of IL-4 secretion and are dependent on cognate B cell interactions. Some of these migratory ex-Tfh cells show gut tropism and can be tracked to small intestinal lamina propria. This suggests that Tfh cells not selected for germinal center entry can convert into tissue-tropic effector T cells.

Keywords: T cells, T follicular helper cells, dendritic cells, B cells, germinal center, small intestinal lamina propria, differentiation, adaptive immunity

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