

## **Molecular underpinning of B cell Anergy**

John C. Cambier Ph.D.

University of Colorado and National Jewish Medical and Research Center, Denver, Colorado, USA

Recently published findings indicate that in certain genetic contexts autoreactive B cells can function as initiators of autoimmunity. These findings underscore the importance of silencing the approximately 70% of newly produced B cells that are autoreactive. We recently reported that a large proportion of these cells are silenced by anergy, a condition wherein cells that encounter their antigen in the absence of second signals are rendered unresponsive to subsequent antigen exposure despite continued availability of receptors. This presentation will focus on studies that seek to define how, in molecular terms, the antigen unresponsiveness of anergic B cells is normally maintained but in some cases lost. Salient conclusions are as follows:

- Anergy can be reversed rapidly by dissociation of (auto-) antigen from BCR, indicating that continuous receptor occupancy and signaling are necessary to maintain unresponsiveness.

- In anergic B cells there is chronic transduction of “altered” signals from mIgM to CD79a/b (Ig- $\alpha/\beta$ ) components of the BCR.

- These altered BCR signals lead to biased activation of inhibitory feedback signaling circuitry; selectively stimulating BCR ITAM tyrosine monophosphorylation and consequent activation of the Lyn/ SHIP-1/Dok-1 pathway.

- Function of the Lyn/SHIP-1/Dok-1 circuit is necessary for prevention of autoimmunity. This circuit acts by inhibiting transduction of signals that require phosphatidylinositol3,4,5P3 and are important in B cell survival and positioning, e.g. BCR, CXCL12, BAFFR, sphingosine-1-phosphate.

Citations:

Gauld SB, Benschop R, Merrell K and Cambier JC. 2005. Maintenance of B Cell Anergy Requires Constant Antigen Receptor Occupancy and Signaling. *Nat Immunol.* Nov;6(11):1160-7

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Brauweiler A, Merrell K, Gauld SB and Cambier JC. 2007. Cutting Edge: Acute and chronic exposure of immature B cells to antigen leads to impaired homing and SHIP1-dependent reduction in stromal cell-derived factor-1 responsiveness. *J Immunol* Mar 15 178(6):3353-7.