Tracking Destiny of Anergic B cells Compromised by Autoimmunity Risk Alleles. Andrew Getahun, Janie Akerlund and John C. Cambier, Department of Immunology and Microbiology, University of Colorado School of Medicine, Denver, Colorado, USA

B cells are central participants in the development of many autoimmune diseases, functioning as producers of pathogenic autoantibodies as well as in antigen presentation to pathogenic T cells. B cell promotion of autoimmunity reflects a failure of mechanisms that normally operate to silence autoreactive cells. Most potentially dangerous autoreactive B cells are silenced by a mechanism called anergy wherein chronic stimulation by autoantigen leads to changes in signals emanating from the antigen receptor to favor activation of negative feedback circuitry. This circuitry renders anergic cells unresponsive to a number of activating stimuli.

GWAS and candidate studies have revealed that the protein products of a surprising proportion of autoimmunity risk alleles appear to function in the negative regulatory feedback circuitry that maintains B cell anergy. These proteins, including PTPn22, CSK, LYN, FcgRIIB, BLK, BANK1 and possibly PXK, act in regulation or mediation of signal relay by the Lyn tyrosine. Lyn functions proximally in BCR signaling, initiating the activation of both positive and opposing regulatory circuitry, the balance of which determines cell activation versus unresponsiveness, i.e. anergy. The downstream effectors of this regulatory circuitry include the tyrosine and inositol lipid phosphatases, SHP-1 and SHIP-1, respectively. In an effort to examine the roles of these effectors and, by inference, their upstream lupus risk alleles, in autoimmunity, we have constructed genetic models in which we can acutely express/delete/alter SHIP-1, SHP-1, PTPn22 and products of other risk alleles *in vivo* in anergic B cells and examine the consequences in terms of effects on component events in development of autoimmunity, i.e. BCR signaling, activation marker expression, antigen presentation to T cells, proliferation, differentiation and antibody secretion. It is our hope that such studies will identify novel targets for therapeutic intervention in patients who carry specific risk alleles.

This presentation will focus on the life and times of autoreactive B cell clones whose anergy is compromised by autoimmunity risk alleles and their effectors. Results to be discussed demonstrate that B cell-intrinsic expression of both SHIP-1 and SHP-1 are critical for maintenance of the anergy of chromatin reactive cells. Each acts to limit the initial activation of autoreactive cells, and mediates their effects by targeting different BCR signaling pathways. Interestingly, our studies further indicate that clonal expansion and differentiation of genetically compromised, anergic chromatin reactive B cells requires T cell help and TLRs.

Recommended reading:
B-cell anergy: from transgenic models to naturally occurring anergic B cells?
Cambier JC, **Gauld** SB, Merrell KT, Vilen BJ.Nat Rev Immunol. 2007 Aug;7(8):633-43.

Monophosphorylation of CD79a and CD79b ITAM motifs initiates a SHIP-1 phosphatase-mediated inhibitory signaling cascade required for B cell anergy. O'Neill SK, Getahun A, **Gauld** SB, Merrell KT, Tamir I, Smith MJ, Dal Porto JM, Li QZ, **Cambier JC**. Immunity. 2011 Nov 23;35(5):746-56.

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