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Molecular Mechanisms Underlying B cell Anergy

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Although nearly two decades have passed since it was discovered that immunologic tolerance can be maintained by the B cell compartment despite the continued presence of antigen binding cells, the basis of unresponsiveness of these cells remains obscure. Studies using the MD4 anti-HEL transgenic and various lymphoma models have taught that anergic cells exhibit high based intracellular free calcium levels and phosphorylation of Erk. Antigen receptor signal transduction is impaired in these cells as indicated by the reduction in even the most receptor proximal signaling events.

We have begun to explore the basis of impaired BCR signaling in a new □/□immunoglobulin "transgenic" anergy model, Ars/A1 (Benschop, et al, 2001 *Immunity*, 14:33-43). In this model receptors are specific for the hapten arsonate, but exhibit low affinity crossreactivity with DNA. Hapten specificity provides a unique opportunity to explore the role of receptor occupancy in induction and maintenance of anergy in this model.

Like the MD4/ML5 model, anergic Ars/A1 B cells exhibit high basal [Ca^{2+}]; and elevated Erk phosphorylation with impaired BCR signaling. New studies in the Ars/A1 model indicate that anergy requires continued receptor occupancy, as cells revert to the naïve phenotype within minutes of exposure to monovalent hapten. At least two molecular mechanisms appear to contribute to unresponsiveness in this model. Receptors are destabilized resulting in inefficient signal transduction through the receptor. Cells exhibit constitutive activation of the inhibitory signaling effectors; SHIP, an inositol 5-phosphatase, and Dok, a rasGAP adaptor. Activation of this loop may result from selective anergen induction of Ig-□ and Ig-□ monophosphorylation. This presentation will focus on these molecular mechanisms, and their role in maintaining the anergic state.

References

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