

Two B's or Not To B: Mechanisms of B-Cell Delivered Tolerance for Autoimmune Diseases

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During the past decade, we developed a gene therapy model based on the use of immunoglobulin carriers and B-cell antigen presentation to achieve specific T-cell tolerance. Thus, recipients of activated splenic B cells transduced with a retroviral vector encoding peptide-IgG fusion proteins are rendered specifically tolerant to the encoded peptides in multiple animal models for autoimmune diseases, as well as in a murine model for hemophilia inhibitor formation. Importantly, this system is effective in immunized recipients to reverse an ongoing immune response. Tolerance induction requires the expression of B7 and MHC class II by the B cells and is enhanced by the presence of the IgH chain. Further data suggest that tolerogenic B cells recruit antigen-specific regulatory T cells. Recently, we noted that the mode of activation of the B cells was critical for tolerance induction. In collaboration with the Cahalan lab, we have followed the interaction of tolerogenic *versus* non-tolerogenic B cells and specific T cells *in vivo* by two photon microscopy. Surprisingly tolerogenic B cells formed long-lived contacts with antigen-specific T cells that lasted more than twice as long as contact with non-tolerogenic B cells, due in part to the expression of higher levels of integrins, B7, and MHC class II/peptide complexes. These contacts were also CTLA-4 dependent in that blocking antibody treatment reduced average contact duration by slightly more than half, yielding similar contact times as non-tolerogenic B cells and antigen specific T cells. These data suggest that B7/CTLA-4 interactions are critical for tolerance induction, which is consistent with the observation that tolerance is mediated by inducing or activating Tregs. Expansion of specific Tregs by B cell-delivery of tolerogenic fusion proteins will be presented. Additional data suggest that different subsets of B cells may be more effective as tolerogenic APC. Finally, we will present results demonstrating the efficacy of this system to induce "tolerance" *in vitro* with human T clones from hemophilia patients. (Supported by US Public Health Service [NIH] grants AI035622, DK068343, HL061883, GM-48071 and GM41514)

References:

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