Nicole Baumgarth

The Regulation of Antiviral B Cell Responses – More Than Just Waiting for T Cell-Help

Nicole Baumgarth, Center for Comparative Medicine, University of California, Davis, CA 95616

The two-signal model of lymphocyte activation has developed from the premise that antigen recognition alone is insufficient to stimulate naïve B cells, as this could potentially induce autoreactive responses, and that cognate T-B interaction is necessary to induce a full B cell response. Recent evidence suggests, however, that T cell-independent B cell activation is part of the humoral immune response to viruses and other pathogens, and therefore that antigen alone, or antigen plus signals provided by cells other than T cells, can provide all necessary signals to induce a B cell response.

Several features of antiviral humoral responses exist that cannot easily be reconciled with the existing view of how B cell responses develop. The rapid kinetics of antiviral serum-IgG responses seem at odds with a proposed absolute requirement of B cells for a "second" signal provided by the simultaneously developing T helper cell response. Furthermore, there is a poor correlation between time after infection and the overall affinity of the developing antiviral antibodies. This correlation would be expected if competition for antigen is the main driving force that shapes the developing humoral response. Instead antiviral responses, such as those to influenza virus, contain complex sets of distinct antibody-idiotypes that dominate the response at different times after infection. Finally, early secretion of IgM produced either as "natural" IgM by $CD5^+$ B-1 cells, or as antigen-induced IgM by conventional (B-2) cells, is necessary for immune protection and for the development of a maximal antiviral IgG response. This suggests not only that virus-binding IgM plays an important, previously unrecognized, role in immune protection, but also that its production is regulated significantly differently from the production of IgG.

An overwhelming number of studies, using model antigens such as the hapten NP and pathogens such as influenza virus, have demonstrated a crucial role for cognate T-B interaction in the development of high affinity antibody responses and for B cell memory. Thus, the question that needs to be addressed to understand the regulation of pathogen-induced B cell responses is not whether T cells *are* important for B cell responses, but rather *at what phase* during the developing B cell response T cells become necessary. Most importantly, studies are required that address the question of what other regulatory mechanisms exist that shape B cell responses to pathogens, particularly early in infection, and how those signals affect B cell differentiation.

To reconcile the existing data on antiviral B cell responses with our current understanding of B cell activation, I will propose a new "two-phase model" of B cell activation. I will discuss recent data from our studies on a murine model of influenza virus infection that have opened up the possibility that intrinsic differences in the types of responding B cell populations might contribute to the regulation of antiviral B cell responses.

Innate immune mechanisms dominate the early immune responses to pathogens. It is likely that signals provided by these innate defense mechanisms shape humoral responses in ways not previously recognized. The benefits from uncovering these regulatory mechanisms are potentially enormous, since they are likely to be broadly reactive against a class of pathogens and can thus strengthen our efforts in the development of better vaccines and therapies.