BIOCHEMISTRY SEMINAR

How do B cells sense and respond to virus-like antigen display?

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Abstract: Our lab is interested in mechanisms of immune tolerance that enable lymphocytes (T cell and B cells) to discriminate “self” from “foreign”. Viruses are the prototypical “foreign” stimulus that B cells have evolved to recognize. Viruses exhibit a unique biophysical structure (small size with repeating array of antigenic epitopes displayed on their surface) and can be sensed directly by B cells through antigen receptors. Multivalent viral epitope display has long been recognized to induce rapid, robust, and T cell-independent antibody responses by B cells, but the biochemical basis for such potency remains incompletely understood. Indeed, the prevailing assumption has been that epitope valency and B cell receptor cross-linking account for this biology. To understand how B cells sense and respond to antigens with different biophysical structures (e.g. monomeric "self-like" antigen vs. multivalent "foreign" viral-like antigen display), we have taken advantage of a set of liposomes of viral size engineered to display affinity mutants of the model antigen (Ag) hen egg lysozyme. Particulate Ag induces exquisitely potent 'all-or-none' digital B cell responses that are epitope density-dependent but affinity independent and may be sensitive enough for single particle activation of B cells. Unlike soluble protein Ag, particulate Ag induces signal amplification downstream of the B cell receptor by selectively evading inhibitory pathways. As a result, particulate but not soluble Ag maximally activates NF-κB in a manner that mimics T cell help. Unexpectedly we also discover divergent nuclear translocation of the NFAT transcription factor by soluble and particulate Ag. Together, these differences result in distinct B cell fates that toggle between tolerance and robust effector responses. We describe a molecular basis for highly sensitive B cell responses to virus-like antigen display that is independent of encapsulated nucleic acids and is not merely accounted for by avidity and B cell receptor cross-linking.

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