

Complex roles of the immunological synapse

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The activation of T lymphocytes (T cells) is stimulated by the binding of the T cell receptor (TCR) to its ligand, short peptides bound to major histocompatibility (MHC) gene products. The amino acid sequence of the peptide determines the stimulatory ability of a given peptide-MHC (pMHC) molecule. Altered peptide ligands (APLs) have been used to investigate the role of antigen quality on T cell activation (1, 2). APLs are generated by mutating residues of the wild-type agonist peptide, and each resulting pMHC complex can then be tested for biological activity. Such an approach allows the identification of peptides that have enhanced or reduced stimulatory ability compared to the WT agonist peptide. In experimental studies using APLs, the stimulatory potency of a peptide is correlated with a variety of parameters that include the dissociation rate characterizing the TCR/pMHC complex, the ability to downregulate TCRs, the ability to form an immunological synapse, and the ability to generate fully phosphorylated TCR- ξ chains. How each of these parameters is linked to stimulatory potency is not known.

We have analyzed how each of these parameters is related to immunological synapse formation using a series of APLs for the AND TCR that recognizes a moth cytochrome C (MCC) peptide presented by I-Ek (3). The immunological synapse is a spatially organized collection of membrane proteins and cytosolic molecules that forms at the junction between a T cell and an APC (4, 5). A distinct feature is the clustering the TCR and pMHC ligands in the center of the contact area (called the central supramolecular activation cluster, cSMAC). The function of the cSMAC is controversial, and diverse functions such as a role in secretion and TCR signaling have been proposed (6). In spite of numerous studies, however, a clear understanding of the function of the cSMAC remains elusive (7). Recently, we combined computational studies with *in vitro* experiments to investigate the relationship between TCR signaling and immunological synapse formation. This investigation suggested that clustering of receptors, ligands and kinases in the cSMAC can enhance TCR signaling which, in turn, promotes receptor downregulation leading to the lack of signaling intermediates in the cSMAC (8). We have recently extended our previous studies to investigate the relationship between antigen quality, synapse formation, and TCR signaling with the goal of understanding how a weak agonist might lead to greater proliferative responses.

Our work suggests that the balance between receptor triggering and degradation upon cSMAC formation is modulated in a complicated way by the half-life of the TCR-pMHC complex. Our experimental and computational results regarding how the balance between receptor triggering and down-regulation in the cSMAC is affected by ligand quality and quantity provide a framework that seems to bring coherence to some apparently conflicting observations regarding signaling in the immunological synapse. Specific experiments that may shed further light on the pertinent issues are also suggested.

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