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Physics of building an immunological synapse

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The adaptive immune response depends upon interaction of T cell antigen receptor (TCR) and peptide-MHC complexes in the nanometer scale (15 nm) gap between the T cell and antigen presenting cells. This immunological synapse is built on a foundation of cell adhesion molecules (CAMs). Short CAM pairs (15 nm) and long CAM pairs (∼30 nm) work in parallel to form immunological synapses under control of antigen receptor signaling. The engaged antigen receptor recruits tyrosine kinases to initiate formation of multicomponent signaling complexes that also incorporate F-actin foci. The physical process by which ligand binding to the TCR ligand in the context of the immunological synapse triggers the kinase cascade is not clear. Self-assembly of CAMs to form terraced junctions- with 15 nm and larger spacing between membranes in different positions, may contribute to triggering. We demonstrated segregation of the short and long CAMs in a model synapse in 1998, which was complementary to results from Kupfer demonstrating a bull's eye organization of TCR in the center surrounded by a ring of long CAMs- described as supramolecular activation clusters (SMACs), but corresponding to the predicted terraces. We can directly observe tyrosine kinase recruitment to the TCR complex and the dependence of this recruitment on the strength of interaction of TCR and peptide-MHC. Experimental manipulation of CAM length can predictably alter the effective 2D affinity, lateral mobility and the organization of other associated elements in a size dependent manner. We have developed a general model and will discuss supporting experimental data and implications for immunological synapse assembly in this talk and a related poster.

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