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T cells as a self-referential, sensory organ

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We are interested in the molecular requirements for T cell activation and subsequent signaling. To this end we have developed a imaging methodology to precisely quantitate the number of agonist peptide ligands that an αβ T cell needs to "see" in order to initiate and sustain T cell activation. Remarkably, four out of four T cells can begin activation when in contact with even a single peptide-MHC complex on the surface of another cell. This shows that agonist dimers could not be the "trigger" for activation and thus we have proposed a model (the "psuedodimer hypothesis") in which particular endogenous peptide-MHC complexes ("co-agonists") can synergize with individual agonist ligands to initiate a signaling cascade. We have obtained substantial support for this model with recent experiments and further hypothesize (and find experimental support for) the notion that dimers of these co-agonist ligands are responsible for positive selection in the thymus. This quantitative approach is also useful with respect to the requirements for negative selection in thymus and for understanding the relationship between immunological synapse formation and cytokine secretition or killing in mature T cells. Together these data and the work of others suggests that T lymphocytes in the aggregate are a type of sensory 'organ' that systematically uses the repertoire of 'self' ligands to both shape and bolster immune responsiveness. We have also used a variety of electron microscopic techniques to obtain high resolution pictures of synapses and to gain insight into the structure of the plasma membrane. A surprising outcome of these EM studies is that all or most membrane proteins are clustered into "islands" occupying 20-40% of the plasma membrane. These protein islands have abundant actin underneath, suggesting a strong connection to the cytoskeleton. This leads us to propose a new model for plasma membrane structure.

References:

1. Irvine, D.J., M.A. Purbhoo, M. Krogsgaard and M.M. Davis. Direct observation of ligand recognition by T lymphocytes. *Nature*, 419:845-849, 2002.
2. Purbhoo, M.C., D.J. Irvine, J.B. Huppa and M.M. Davis. T cell killing does not require formation of a stable mature immunological synapse. *Nature Immunol*., 5:524-530, 2004.
3. Krogsgaard, M., Q.-J. Li, C. Sumen, J.B. Huppa, M. Huse and M.M. Davis. Agonist/endogenous peptide-MHC heterodimers drive T cell activation and sensitivity. *Nature*, 434:238-243, 2005.
4. Lillemeier, B.F., J.R. Pfeiffer, Z. Surviladze, B.S. Wilson and M.M. Davis. Plasma membrane-associated proteins are clustered into 'islands' attached to the cytoskeleton. (Manuscript submitted)