

T-cell recognition in health and disease: The role of self-peptides and high-throughput analysis of the response to a cancer vaccine

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Abstract

We are interested in the molecular requirements for T-cell activation and subsequent signaling, as well as applying this knowledge to understand and manipulate the human response to cancer. To this end, we have been developing single cell imaging methodologies in order to precisely quantitate the number of agonist peptide ligands that $\alpha\beta$ T cells need 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 "pseudodimer 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 secretion 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 defined ligand thresholds for helper and cytotoxic T cells and find that memory cells in the Th lineage have a much lower threshold for IL-2 secretion than blast cells. A number of experimental manipulations, including the ectopic expression of a specific microRNA, can change these thresholds, yielding some clues as to how they are established. Lastly, there is a clear gap between what we have learned about cancer and treatment protocols in mouse models and actual experience in the clinic. This makes it imperative that we learn much more than is current practice about specific immune indicators during clinical trials of immunotherapeutic regimes. To this end, we have developed a high-throughput cell capture and analysis methodology that enables us to get a great deal of information quickly about immune responses. Analysis of a melanoma vaccine trial using this methodology indicates a broad heterogeneity in the responses to the vaccine, which may help to explain why clinical responses are so variable.