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Phenotypic models of T cell activation (IRC5P.627)

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Abstract

T cell activation is a crucial checkpoint in adaptive immunity, and this activation depends on the binding parameters between the T cell receptor (TCR) and peptide-MHC (pMHC) complexes as well as the dose at which the pMHC is presented. Despite extensive experimental studies, it still remains controversial as to how these parameters govern the resultant activation. We present the development of a model that captures the phenotype of T cell activation. This model is influenced by existing models in the literature as well as a quantitative dataset we have generated that probes T cell activation over wide range of pMHC binding parameters and doses. The dataset was generated by stimulating jurkats and primary cells transduced with a therapeutic high affinity T cell receptor with a panel of plate bound pMHC that are mutations of the HLA-A2 NYESO pMHC. These ligands have a 10^5-fold range in binding time for the TCR. Activation was quantified by measuring IL8 (jurkats) and IFN-ϒ (primary). We have observed from the data that there is an optimal ligand binding time that gives the most potent activation. Of further interest is the observation of an inhibition in T cell activation at high doses of pMHC presentation. Our analysis indicates that a kinetic proofreading with limited signalling mechanism combined with a negative signalling motif can produce this observed phenotype of optimal ligand binding time and optimal ligand dose.