Modulating extracellular TCR-CD3 interaction to identify new immunotherapy targets

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T cell recognition of antigen and resulting proximal signaling are key steps in the initiation of the adaptive immune response. Recently, we identified the specific extracellular contacts between the T cell receptor (TCR) and CD3 subunits through NMR, cryo-EM and photo-crosslinking techniques gives more precise guidance for immunotherapeutic strategies that modulate T-cell immunity by targeting signaling through the TCR-CD3 complex. Further, biomolecular force probe (BFP) measurements allowed us to determine how 2D affinity and force-modulated TCR-pMHC kinetics depend on TCR-CD3 interaction sites and affect transduction of extracellular pMHC-TCR ligation into T cell function. This places us in a unique position to translate our findings towards novel and improved immunotherapy strategies. Our hypothesis is that by modulating TCR-CD3 interactions in specific ways, immune-mediated cytotoxicity can be increased without losing specificity for the cancer antigen. We created TCR mutants through two different methods – 1) library creation using degenerate primers at specific CD3 interaction sites and 2) in-silico mutational analysis, each of which were tested for increased CD3 tetramer binding, force-mediated kinetics and T cell functionality. In the near future, tumor antigen-specific TCRs with reengineered CD3 binding regions will be analyzed for in tumor rejection in pre-clinical mouse melanoma models to develop more effective T cell therapies for human patients.