Identification of the cognate peptide-MHC target of T cell receptors using molecular modeling and force field scoring

Interactions of T cell receptors (TCR) to peptides in complex with MHC (p:MHC) are key features that mediate cellular immune responses. While MHC binding is required for a peptide to be presented to T cells, not all MHC binders are immunogenic. The interaction of a TCR to the p:MHC complex holds a key, but currently poorly comprehended, component for our understanding of this variation in the immunogenicity of MHC binding peptides. Here, we demonstrate that identification of the cognate target of a TCR from a set of p:MHC complexes to a high degree is achievable using simple force-field energy terms. Building a benchmark of TCR:p:MHC complexes where epitopes and non-epitopes are modelled using state-of-the-art molecular modelling tools, scoring p:MHC to a given TCR using force-fields, optimized in a cross-validation setup to evaluate TCR inter atomic interactions involved with each p:MHC, we demonstrate that this approach can successfully be used to distinguish between epitopes and non-epitopes. A detailed analysis of the performance of this force-field-based approach demonstrate that its predictive performance depend on the ability to both accurately predict the binding of the peptide to the MHC and model the TCR:p:MHC complex structure. In summary, we conclude that it is possible to identify the TCR cognate target among different candidate peptides by using a force-field based model, and believe this works could lay the foundation for future work within prediction of TCR:p:MHC interactions.