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OncoPeptVAC: A robust TCR binding algorithm to prioritize neoepitope using tumor mutation (DNAseq) and gene expression (RNAseq) data

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Abstract

Neoepitopes are tumor-derived immunogenic peptides that arise from intracellular proteolytic processing of somatic mutation in protein coding genes. These peptides bind HLA Class I proteins and are presented on the surface by antigen presenting cells. Productive engagement of HLA Class I-bound peptide with T-cell receptor (TCR) activates CD8+ T-cells to generate cytotoxic T cells, which mediate lysis of the neoantigen-expressing tumor cells. Neoepitopes can be used as cancer vaccines to prime $CD8^+$ T-cells against tumor cells. As tumors accumulate hundreds of mutations during cancer development and only a small subset of these are immunogenic, identifying the neoepitopes requires accurate modeling of the steps involved in peptide production, presentation as well as TCR binding. Most current pipelines prioritize neoepitopes based on the expression of mutant proteins and their HLA binding affinity. However, presentation of peptides on the surface is not sufficient to activate T-cells. To improve the predictive power of our neoepitope prioritization pipeline and to circumvent selection biases that are inherent with using HLA binding as a proxy for neoepitope prediction, we developed a novel algorithm that prioritizes peptide interactions with the TCR.

OncoPept*VAC* algorithm uses features selected by analyzing crystal structures of TCR and HLA-peptide complex present in the Protein Data Bank. A neural network model was built to derive a composite score that includes, besides TCR binding, other features associated with the peptide, such as level of expression of the mutant allele, affinity of HLA binding, affinity of TAP binding and sensitivity to proteasomal processing. We validated our neural network prediction model on known immunogenic and non-immunogenic peptides and achieved superior accuracy, sensitivity and specificity of prediction compared to using the standard HLA binding affinity of ≤500 nM. By applying OncoPept*VAC* neoepitope prioritization solution to 2.2 million unique somatic mutations, we identified ~700 immunogenic peptides derived from recurrent somatic mutations in all cancers. Several of these peptides were validated on a $CD8^+$ T cell-activation assay. Our *in silico* prioritization platform combined with the cell-based validation method is a powerful tool to identify therapeutic vaccines for personalized cancer immunotherapy applications.

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