Neoantigen Homology and Predicting Response to Immune Checkpoint Blockade in Cancer

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Summary

Immune checkpoint inhibitors are promising cancer treatments for a variety of malignancies, but accurate prediction of clinical response remains an active area of research.

Recent work [1, 2] has revealed that nonsynonymous mutation burden and candidate neoantigen burden significantly correlate with durable clinical benefit to anti-CTLA-4 treated melanomas and anti-PD-1 treated lung cancers.

Using cancer exome and RNAseq data obtained from [1], we further investigated covariates with immune checkpoint inhibitor response.

Methods

- Patients
  - The study in [1] consisted of 64 patients treated with an anti-CTLA-4 (ipilimumab or 4-1BB) regimen.
  - 44/64 patients were classified as cutaneous melanoma.
  - 34/64 samples were taken prior to treatment.

- DNA
  - DNA samples were obtained for all patients.
  - Alignment and post-processing was performed as described in [1], while variants were called using 4 SNV callers (Strelka, MuTect, VarScan, SomaticSniper).
  - Indel calling was performed using Strelka.

- RNA
  - RNASeq was obtained for 24 patients.
  - Indel calling was performed using Strelka.
  - HLA typing from RNA-Seq sequence reads.

- Mutant Epitope Prediction
  - Mutant protein sequences were predicted using Varcode (unpublished).
  - MHC binding prediction was done using NetMHC (unpublished).
  - HLA typing from RNA-Seq sequence reads.

- Pathogen Homology
  - Predicted neoantigens were aligned with T-cell positive peptides from IEDB of the same length, considering positions 3 through n-1 (n = length).
  - Peptide alignment was scored with the PMBEC matrix [3] and a gap penalty of min(PMBEC).
  - For example, the following entry had a score of 1.4:
    - TP WRAPA-KIE L
    - QP HAPBRIP T

- Expression of Immune Activity?
  - We found HLA expression to be higher in responding samples, including those sampled before treatment.

  However, unlike other covariates mentioned, HLA expression in these samples was not associated with mutation load.

Conclusions

- Mutational burden is correlated with benefit.
- A higher percentage of UV mutations is correlated with mutational burden.
- Predicted neoantigen burden is correlated with benefit.
- Mutational burden increases the number of organisms matched in IEDB.
- Higher HLA expression was correlated with benefit in both pre- and post-treatment samples, independent of mutational burden.

References