Secondary Immunotherapeutic Targets In Inflamed Tumors.

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Introduction

Immune checkpoint inhibitors are now used to treat many different types of cancer, with some patients demonstrating durable clinical responses. As expected, a significant number of responders express high levels of primary cancer immune biomarkers such as PD-1/PD-L1, MSI, or mutational burden. Here we present immune-related expression signatures for patients with an immune activated phenotype that overexpress several pro- and anti-inflammatory genes with or without primary biomarker detection. These immune signatures were identified as part of Immune Report Card™ (IRC), a comprehensive molecular and immunological assay that uses five testing modes to detect several known markers of the host anticancer immune response.

Methods

167 formalin-fixed, paraffin-embedded (FFPE) cancer samples of diverse histologies were evaluated by IRC to measure transcript levels of genes related to T-cell receptor signaling and tumor infiltrating lymphocytes (RNA-seq) and mutational burden (DNA-seq).

Resultant data was QC filtered, normalized and ranked based on an assorted reference population of various tumor types. Gene signatures and mutational burden were determined using these ranked values with a rank value > 85th percentile considered high. Tumors are also defined as inflamed or non-inflamed based upon RNA-seq analysis of CD8. Tumors ≥ 75th percentile of rank for CD8 are considered inflamed, while those ≤ 25th percentile are considered non-inflamed (>25th to <75th percentile are considered borderline). RNA-seq analysis of CD8 had been previously calibrated against quantitative image analysis using the Aperio platform.

Immune GEX Landscape

Supervised hierarchical clustering based on CD8 gene expression. Stratification of 167 samples (rows) across 395 genes (columns) measured as part of the RNA-seq component of IRC. Black box denotes the ≥ 75th percentile of tumors with high CD8+ expression representing the inflamed phenotype used to interrogate immunotherapeutic targets.

Response Markers

Interrogation of response biomarkers (tumor mutational burden upper panel, PD-L1 IHC lower panel) versus CD8 gene expression status. TMB High as measured by DNA-seq did not correlate with any specific CD8 phenotype. PD-L1 status was highest (72% of samples) within the inflamed phenotype and lowest in Immune Desert (29% of samples).

Immunotherapeutic Targets

Identification of immunotherapeutic targets in the inflamed phenotype as defined by CD8 expression. These immune biomarkers are potential checkpoint inhibitor therapy targets.

Conclusions

Immune Report Card profiles the tumor immune microenvironment to outline the immune biology of tumor samples. IRC is not only able to identify samples with highly expressed immune response biomarkers such as PD-L1, MSI, or mutational burden, but using RNA-seq can also identify immunotherapeutic targets in many samples. These secondary biomarkers shed light on the underlying biological immune-state of the tumor microenvironment, potentially identifying additional mono or combination immunotherapies in PD-L1 negative inflamed tumors. With the ever-increasing numbers of FDA-approved therapies and clinical trials, IRC offers a robust tool to identify patients that might benefit from these options.