OncoPept*TUME* identifies pathways enriched in T-cell inflamed tumors

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Key findings

- A robust scoring method quantifies tumor infiltrated immune cells in different cancers
- Prostate cancer has poor T-cell infiltration compared to melanoma or Head & Neck cancer
- T-cell inflamed tumors show different patterns of mutations in different cancers
- Differential gene expression analysis identifies upregulation of pro-inflammatory pathways in T-cell inflamed tumors predicting sensitivity to checkpoint control inhibitors

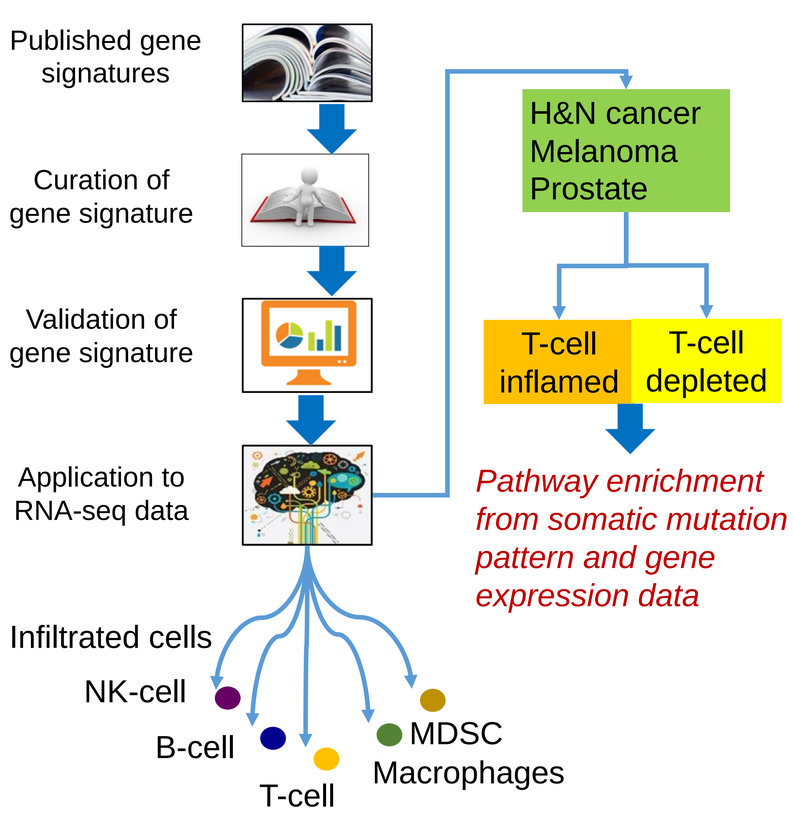
Introduction

The efficacy of checkpoint control inhibitors is dependent on the presence of CD8+ T-cells in the tumor microenvironment. Tumor cells employ a variety of immune-evasive mechanisms to protect themselves from immune attach, such as creating an immune suppressive microenvironment, where T-cells are rendered inactive, avoiding T-cell-mediated recognition by downregulating Class-I presentation and preventing infiltration of T-cells within the tumor. Mechanisms blocking T-cell infiltration within the tumor is poorly characterized. Most studies have focused on tumor extrinsic factors produced by stromal cells and tumor associated macrophages that suppress T-cell activity. However, tumor intrinsic activation of oncogenes and tumor suppressor genes has the potential to upregulate signaling pathways that can impact T-cell migration into the tumor. A robust method to identify T-cell inflamed from T-cell depleted tumors will enable molecular dissection of tumor intrinsic, and tumor extrinsic factors regulating T-cell infiltration in the tumors. The approach can lead to the discovery of novel drug targets to enhance T-cell infiltration in cancer

Methods

The RNA-seq and somatic mutation data were downloaded from TCGA. The CD8+ T-cell signature was used from published papers and applied to the RNA-seq data An unique scoring method was developed that assigns a score based on the expression of T-cell signature genes. The method was applied to three cancer types from TCGA - Head & Neck, Prostate and Melanoma. Samples showing high and low T-cell score were analyzed to identify unique genetic alterations associated with T-cell infiltration. Additionally, differential gene expression analysis identified pathways highly enriched in T-cell inflamed tumors

Figure 1. Workflow of building gene signatures and their application to TCGA data



Results

Figure 2. Expression of CD8+ T-cell gene signature in 26 cancer types from TCGA

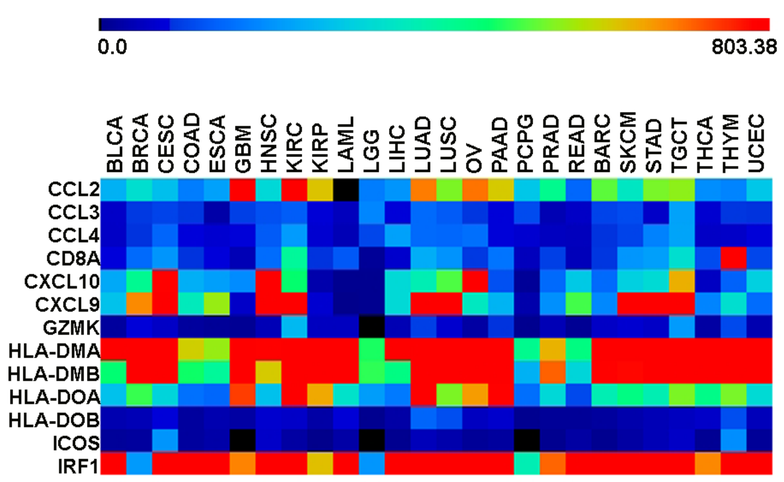


Figure 3. Clustering of tumors containing differential infiltration of CD8+ T-cells

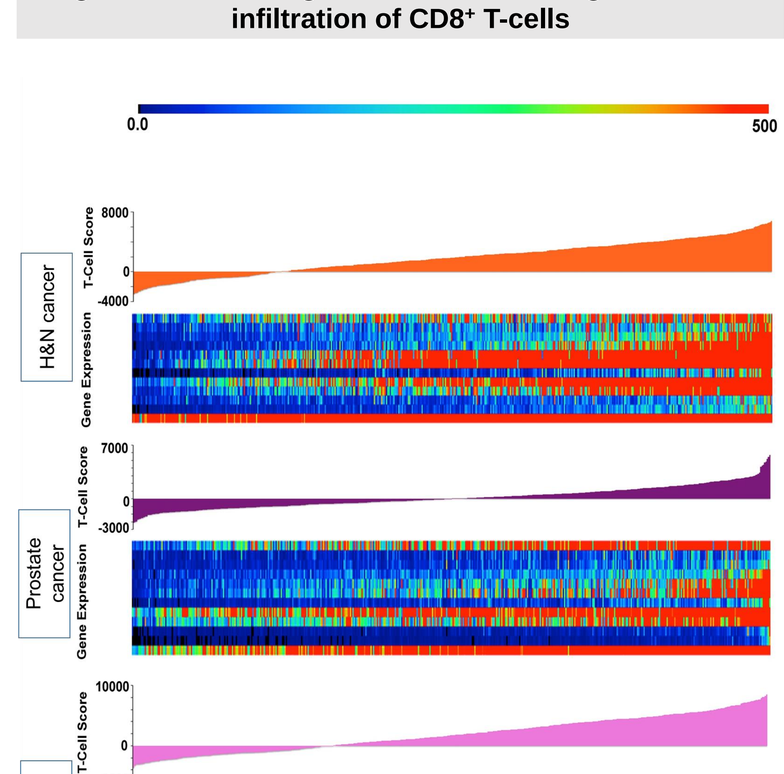


Figure 4. Different pattern of mutations in T-cell inflamed and depleted tumors

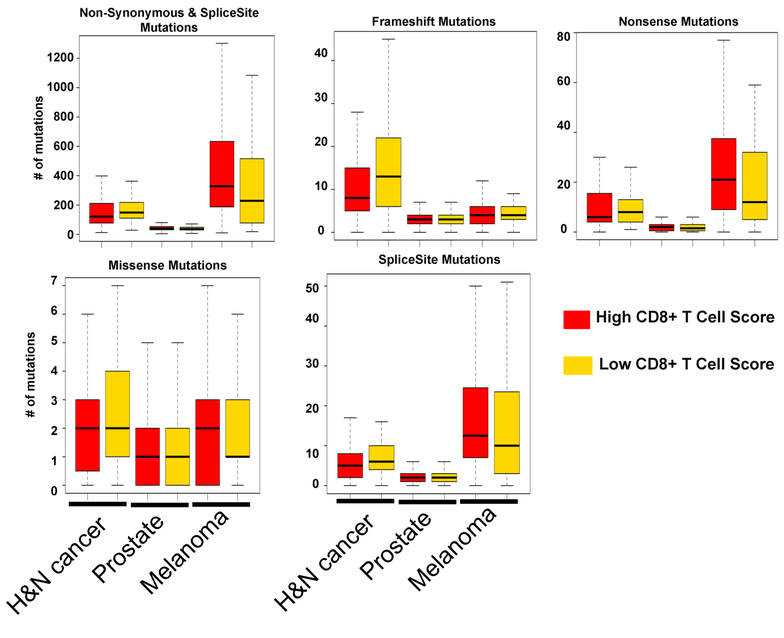


Figure 5. Comparison of genes carrying non-synonymous mutations in top 100 samples in high and low CD8+ T-cells. All genes with p<0.01 (Fisher test) are shown. (a) Head & Neck, (b) Melanoma. No significantly mutated genes found in prostate cancer because of low T-cell infiltration in this cancer type

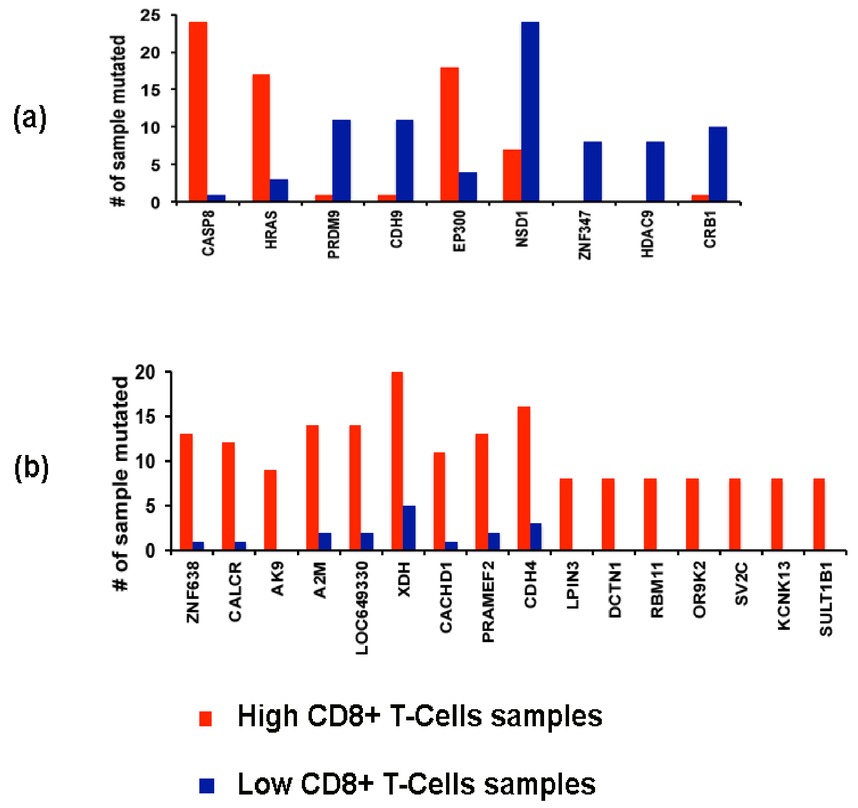


Figure 6. Differentially expressed genes in T-cell inflamed and depleted tumors

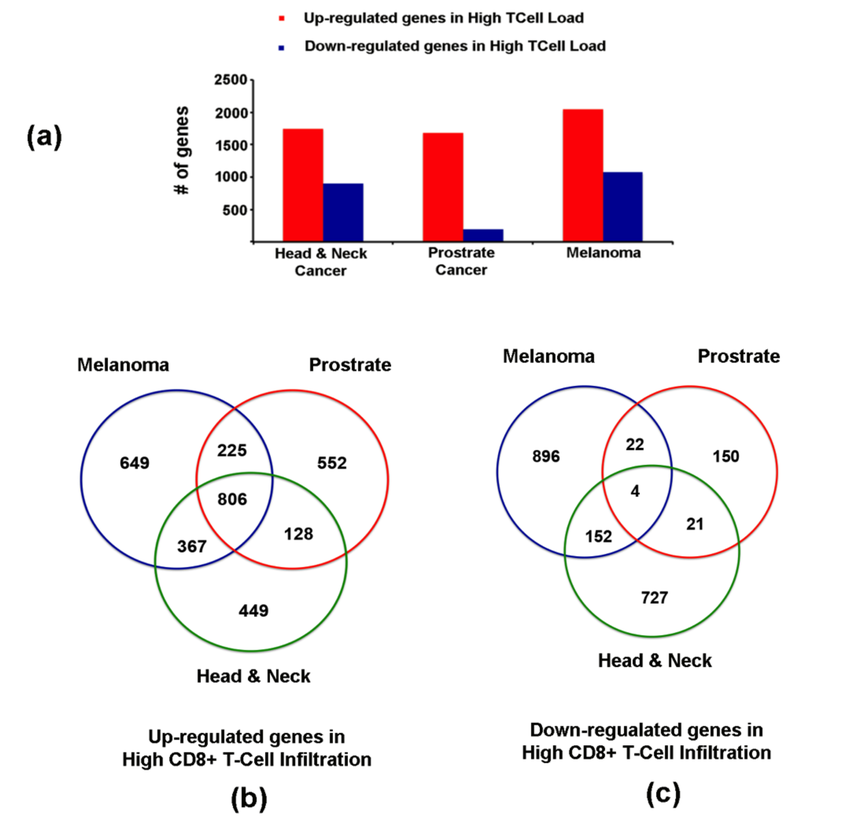


Figure 7. List of significant pathways (Reactome) in T-cell inflamed tumors using 806 differentially upregulated genes in H&N cancer and Melanoma (FDR < 0.01, FDR=0.001)

PATHWAY from up-regualted genes in High CD8+ T-cell infiltration	FDR
Endosomal/Vacuolar pathway	9.66E-15
Translocation of ZAP-70 to Immunological synapse	9.66E-15
Interferon alpha/beta signaling	9.66E-15
PD-1 signaling	9.66E-15
Interferon gamma signaling	9.66E-15
Interferon Signaling	9.66E-15
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	9.66E-15
Chemokine receptors bind chemokines	9.66E-15
Antigen Presentation: Folding, assembly and peptide loading of class I MHC	9.66E-15
Class I MHC mediated antigen processing & presentation	9.66E-15
Antigen processing-Cross presentation	9.66E-15
ER-Phagosome pathway	9.66E-15
Adaptive Immune System	9.66E-15
Immune System	9.66E-15
Cytokine Signaling in Immune system	9.66E-15
Phosphorylation of CD3 and TCR zeta chains	1.00E-13
Peptide ligand-binding receptors	3.96E-12
Class A/1 (Rhodopsin-like receptors)	4.83E-09
Generation of second messenger molecules	9.98E-09
Costimulation by the CD28 family	4.76E-08
Downstream TCR signaling	9.56E-05
GPCR ligand binding	1.63E-04
MHC class II antigen presentation	3.89E-04
G alpha (i) signalling events	4.40E-04
TCR signaling	0.00128