Tumor microenvironment analysis provides insights into the activity of CD8 T-cells and their impact on survival

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Key findings

- ❖ **OncoPept*TUME* identifies cancers in which CD8 T-cell infiltration differentially affects patient survival**
- ❖ **Differentially expressed genes in these two groups identify pathways that interact with CD8 T-cells to impact outcome**
- ❖ **Poor prognosis group shows enrichment of ECM and immunosuppressive pathways absent from the good prognosis group**

Introduction

The tumor microenvironment regulates the behavior of malignant cells through a variety of heterotypic cell-cell and cell-matrix interactions. Tumor growth is promoted by the failure of the immune-surveillance mechanisms to keep the tumor growth in check, and is further augmented by soluble factors produced by the stromal cells, including the immune cells. In this study, we analyzed TCGA data to investigate the impact of CD8 T-cell infiltration on the disease outcome. Our analysis indicates that CD8 T-cell infiltration predicts favorable survival in certain cancers, whereas in other cancers survival was unaffected. By comparing tumors from these two groups, we show that multiple cell-intrinsic and extrinsic pathways modulate the anti-tumorigenic effects of CD8 T-cells. The group favored by CD8 T-cell infiltration lacked extracellular matrix remodeling and other immune suppressive pathways that were both enriched in tumors lacking benefit of CD8 T-cell infiltration.

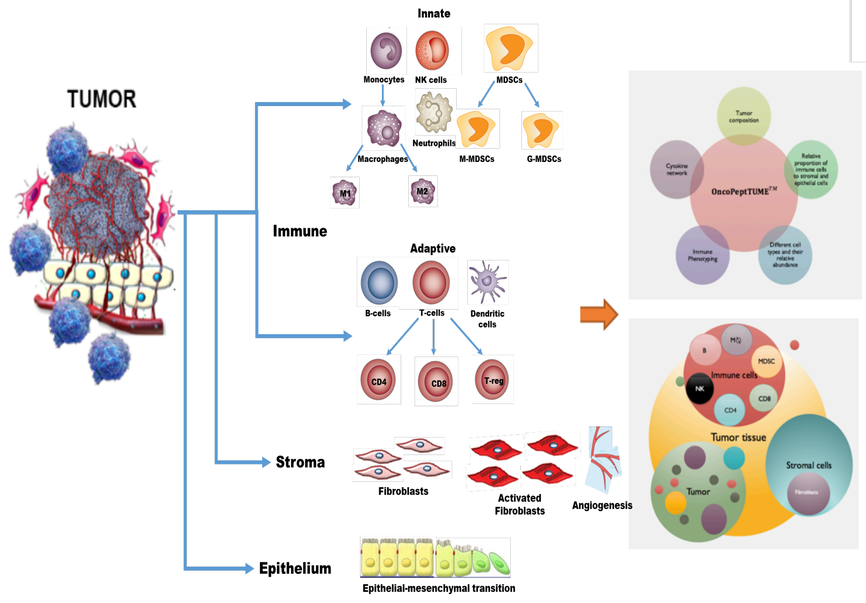
Objectives

1. Investigate the tumor microenvironment features using the OncoPept*TUME* solution.
2. Evaluate infiltration of CD8 T-cells in 9345 TCGA tumor samples from 33 cancers.
3. Analyze cell-intrinsic and extrinsic mechanisms that impact survival in the presence of CD8 T-cells.

Methods

- The TCGA data was analyzed using MedGenome's proprietary OncoPept*TUME* solution. The solution employs curated gene expression signatures to dissect components of the tumor microenvironment. The abundance of cells in the tumors is calculated from the expression of genes contained in each signature.
- www.medgenome.com/oncopept

Figure 1. OncoPept*TUME* workflow



Results

Figure 2. Creation of gene signatures

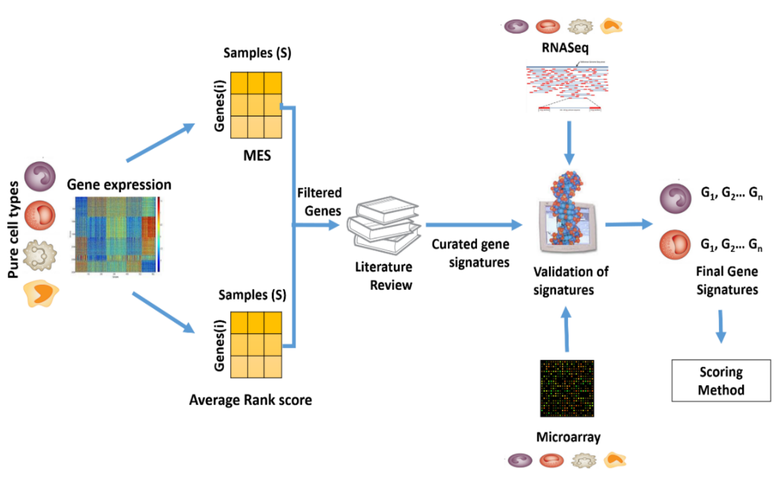


Figure 3. CD8 T-cell infiltration in 33 cancers

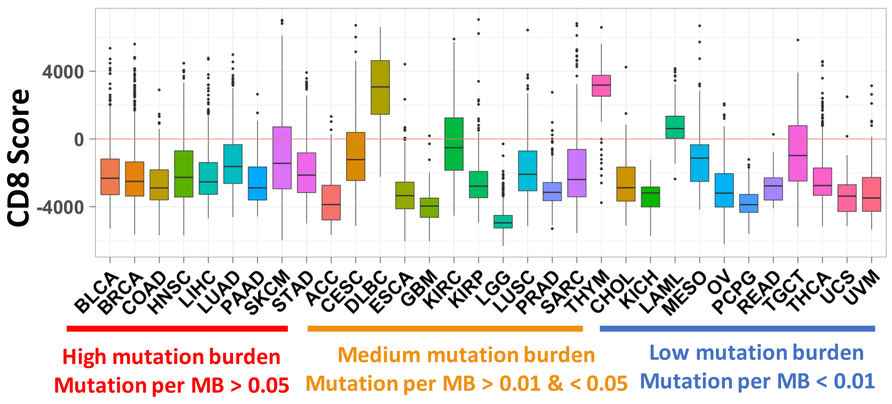


Figure 4. Infiltration of CD8 T-cells and immune reactivity of the tumors.

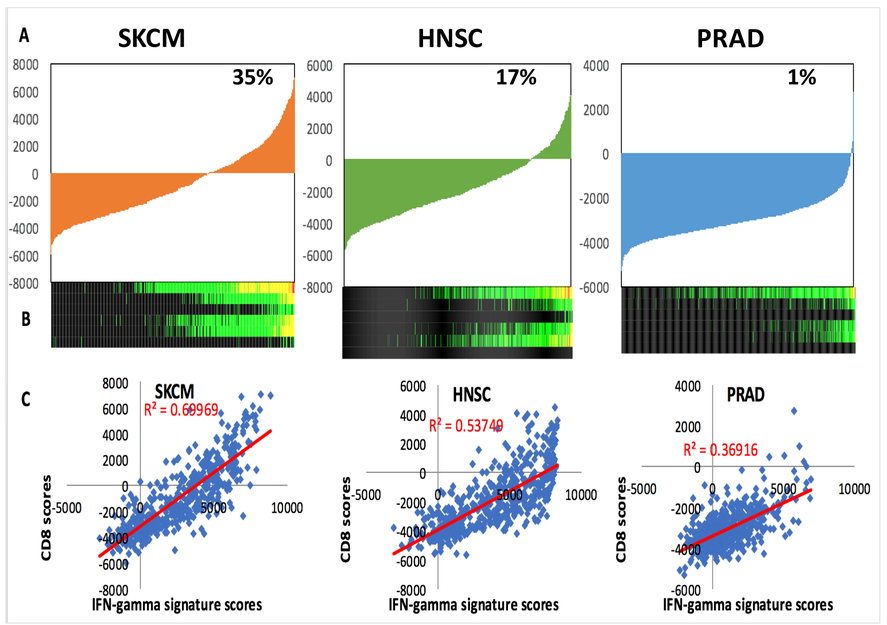


Figure 5. Expression checkpoint regulators

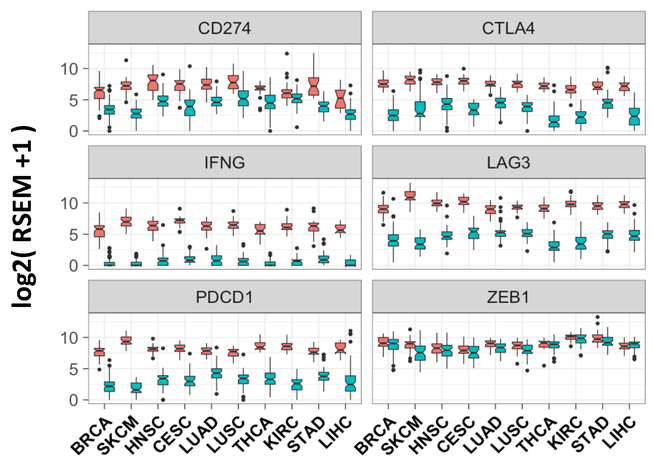


Figure 6. CD8 infiltration and survival outcome

Survival Benefit	No Benefit
SKCM	LUAD
BRCA	LUSC
HNSC	THCA
CESC	LIHC
	KIRC
	STAD

CD8=high CD8=low

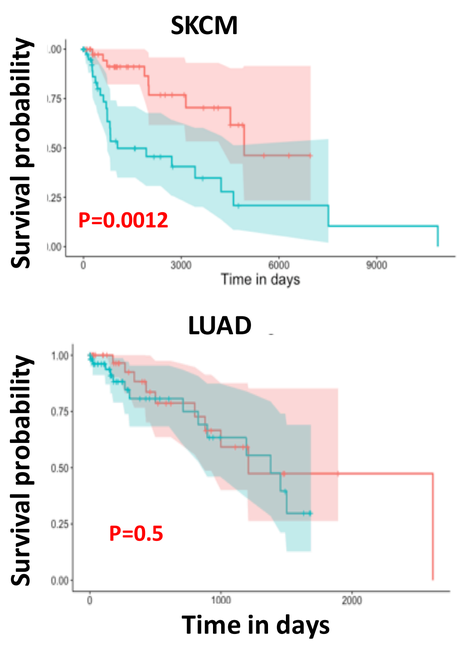


Figure 7. Stromal, Immune and Epithelial content

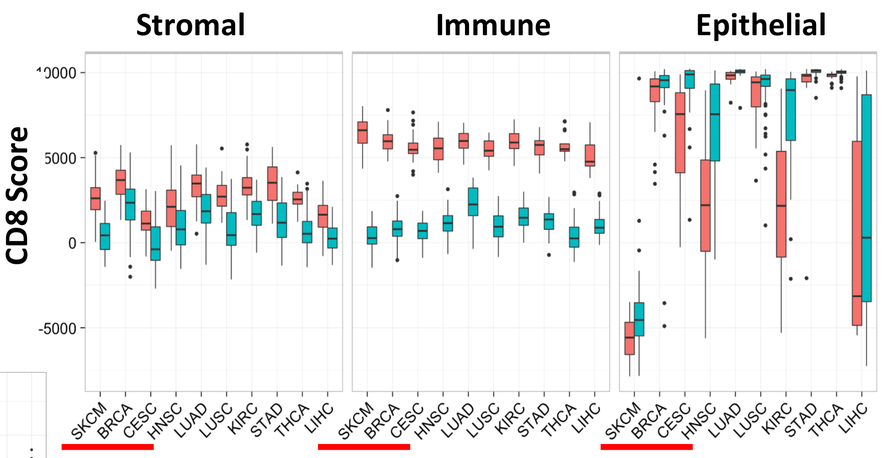
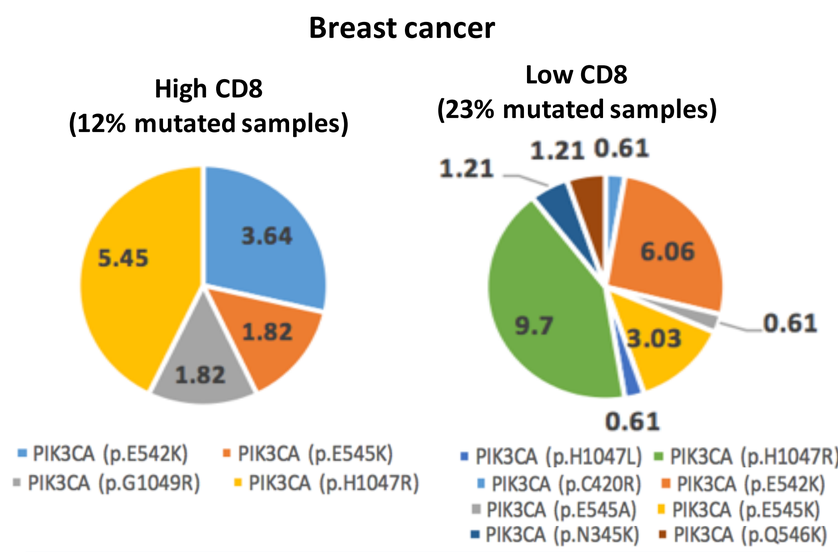


Figure 8. Enrichment of PIK3CA mutations in Low CD8 tumors from breast cancer



Conclusions

- Analysis of the CD8 T-cell content in 9345 tumors from 33 cancers indicate that T-cell infiltration varies significantly across tumors: 35% in melanoma and 1% in prostate cancer.
- High T-cell infiltrated tumors are rich in T-cell-specific markers and IFN-[redacted]expression although survival benefit is not seen in all cancers
- Activation of multiple oncogenic and tumor suppressive pathways correlate with CD8 T-cell exclusion opening up opportunities for target discovery.
- Our study identifies multiple pathways that can be targeted to increase the sensitivity of tumors to checkpoint blockade.