Integrated genomics approach of modeling tumors to assess their sensitivity to immune-mediated elimination

Ravi Gupta, Ashwini Patil, Nitin Mandloi Kiran V. Paul, Priyanka Shah, Malini Manoharan, Rohit Gupta and Amitabha Chaudhuri

E-mail: amitc@medgenome.com

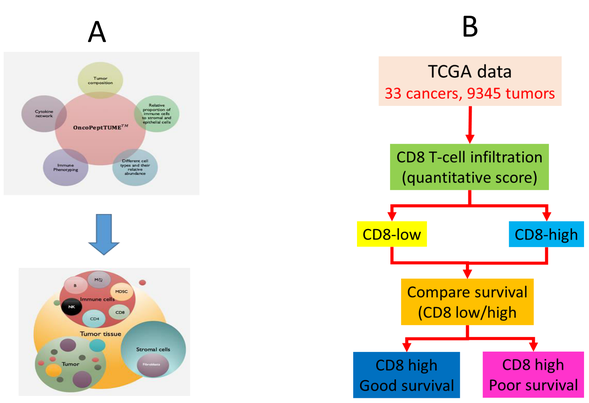
Background and Objectives

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 immunesurveillance mechanisms to keep tumor growth in check, and is further augmented by soluble factors produced by stromal cells, including immune cells. In this study we have analyzed TCGA data to investigate the impact of CD8 T-cell infiltration on disease outcome. Our analysis indicates that CD8 T-cell infiltration predicts favorable survival in certain cancers, whereas in other cancers it has no effect. 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 the benefit of CD8 T-cells.

Methods

The TCGA data was analyzed using MedGenome's proprietary OncoPept*TUME* pipeline. The pipeline applies curated gene expression signatures to dissect components of the tumor microenvironment. Workflow to analyze CD8 T-cell infiltration. The abundance of cells in the tumors is calculated from the expression of genes contained in each signature (www.medgenome.com/oncopept)

Figure 1. Tumor ME analysis work flow



Key findings and Results

- **OncoPept*TUME* identifies cancers in which CD8 T-cell infiltration exhibits differential effects on 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**

Figure 2. CD8 T-cell low (blue) and high (red) tumors in 33 human cancers

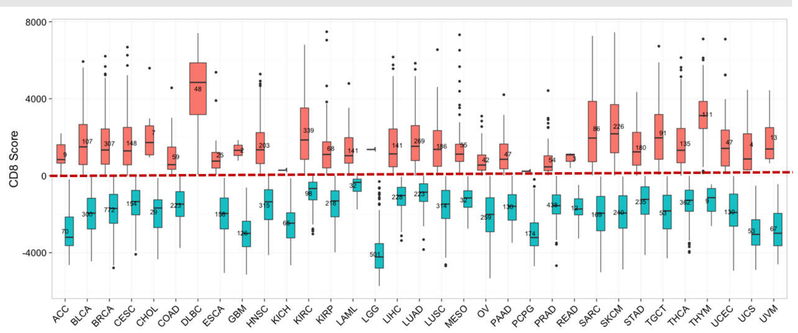
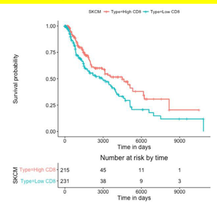


Figure 3. Effect of CD8 infiltration on patient survival. High and low CD8 infiltrated tumors were analyzed for survival. A typical plot of benefit vs lack of benefit is shown.

CD8 high survival benefit	CD8 high lack of survival benefit
Bladder (BLCA)	Adenocortical (ACC)
Cervical (CESC)	Kidney clear cell (KIRC)
Head & Neck (HNSC)	Kidney papillary (KIRP)
Liver (LISC)	Colon (COAD)
Lung squamous (LUSC)	Lung adeno (LUAD)
Mesothelioma (MESO)	Pancreas (PAAD)
Skin (SKCM)	Prostate (PRAD)
	Stomach (STAD)
	Thyroid (THCA)
	Sarcoma (SARC)
	LAML

SKCM (survival benefit)



LUAD (No survival benefit)

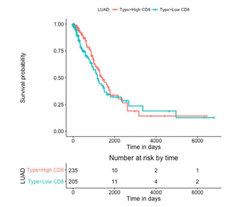
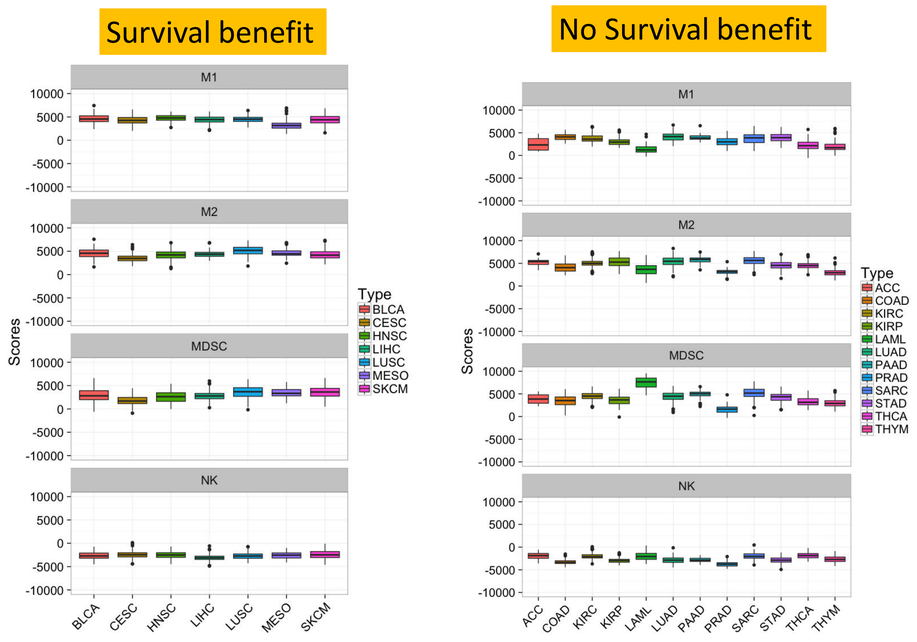


Figure 4. Differential gene expression analysis identifies features of the tumor microenvironment in CD8-high tumors showing favorable, or lack of survival benefit

A. Landscape of innate immune cells in CD8 high tumors.



B. Landscape of adaptive immune cells in CD8 high tumors

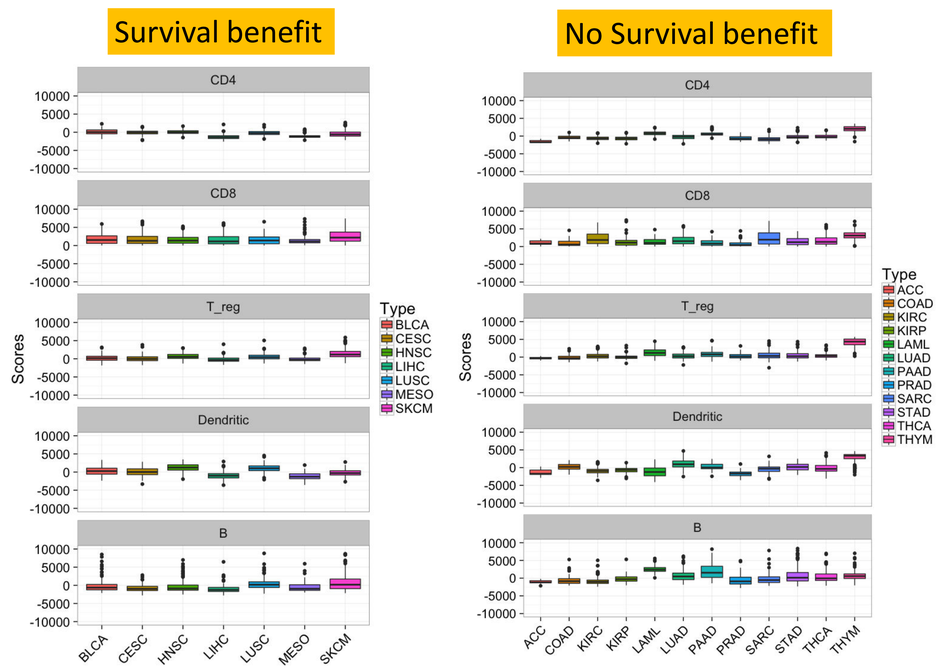
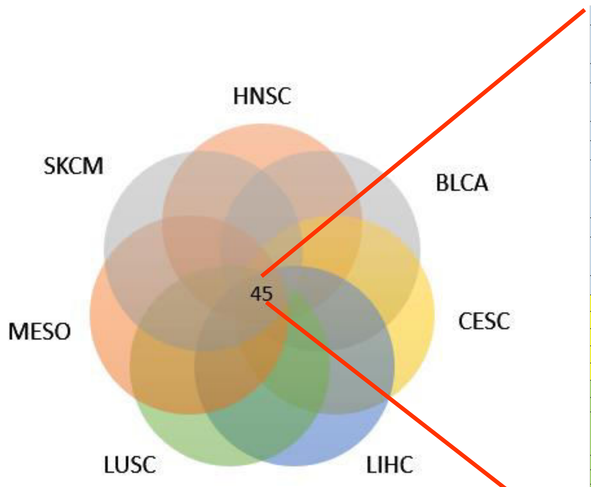


Figure 5. Pathway analysis discriminates tumors showing survival benefit vs tumors with lack of survival benefit

A. TCR signaling is enriched in tumors with survival benefit



T-cell receptor pathways
Phosphorylation of CD3 and TCR zeta chains
Costimulation by the CD28 family
Translocation of ZAP-70 to Immunological synapse
Downstream TCR signaling
TCR signaling
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell
PD-1 signaling
NOTCH2 intracellular domain regulates transcription
Signaling by NOTCH2
Immune-related pathways
Adaptive Immune System
TNFs bind their physiological receptors
Chemokine receptors bind chemokines
Peptide ligand-binding receptors
Other pathways
Class A/1 (Rhodopsin-like receptors)
Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models
Neurodegenerative Diseases
G alpha (i) signalling events
Generation of second messenger molecules
Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG)
Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG)

45 upregulated genes common too all cancers were mapped to pathways

B. TCR signaling is associated with ECM and innate and immunosuppressive pathways in cancers with lack of survival benefit. One common upregulated gene is shared between all cancers. Shared pathways indicated by numbers