Differential gene expression and tumor mutanome analysis reveal significantly enriched pathways associated with higher tumor burden of M1 and M2 macrophages.

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Introduction

Many attributes of the tumor microenvironment, such as the level of CD8 T-cells in the tumor, higher levels of pro-inflammatory cytokines dominated by interferon signaling, antigen processing and presentation correlate with superior efficacy of checkpoint control inhibitors. Tumors lacking CD8 T-cells are less responsive to checkpoint control blockade, and therefore other therapeutic modalities for treating these tumors need to be explored. In this study, we setout to identify a set of core pathways associated with macrophage infiltration in tumors. These core pathways can be modulated to alter the immune profile of these unresponsive tumors and sensitize them to checkpoint control blockade.

Objectives

- Evaluate the infiltration of M1 and M2 macrophages in 9345 TCGA tumor samples from 33 cancers using OncoPept*TUME*
- Identify enriched pathways associated with high M1 and M2 macrophage infiltration
- Effect of tumor mutational burden on macrophage infiltration

Methods

- Curated gene expression signatures were used to assess tumor infiltration of macrophages
- TCGA gene expression data was analyzed to identify tumors with varying levels of macrophage infiltration

Figure 1. Creation of gene signatures

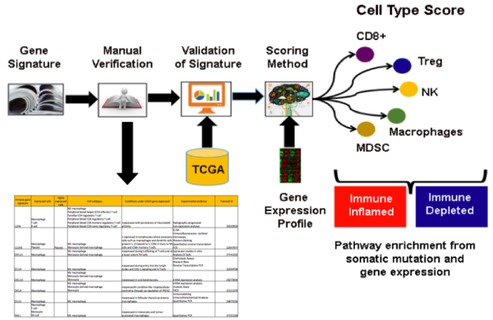
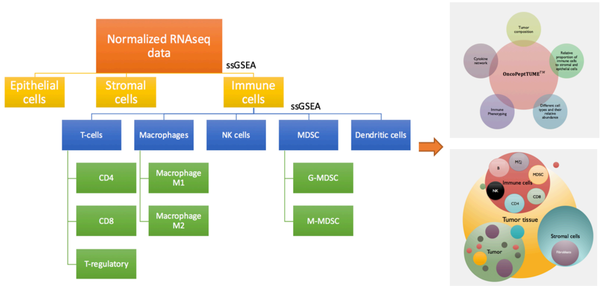


Figure 2. OncoPept*TUME* workflow



Results

Figure 3. Macrophage infiltration in 33 cancers

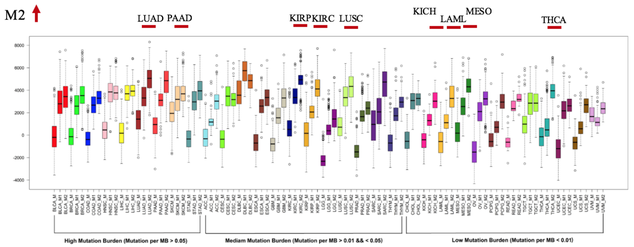


Figure 4. Mutation burden and proliferative index of M1+M2 high tumors vs M1+M2 low tumors

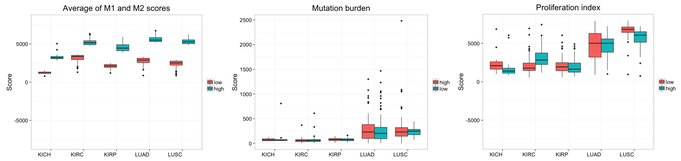


Figure 4. Abundance of M1 and M2 macrophages in tumors

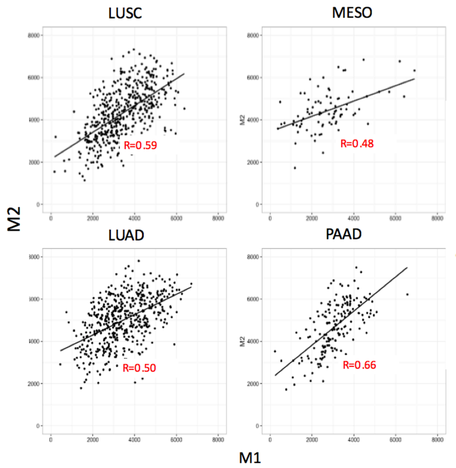


Figure 5. Common up- and down-regulated genes in M1+M2 high tumors vs M1+M2 low tumors

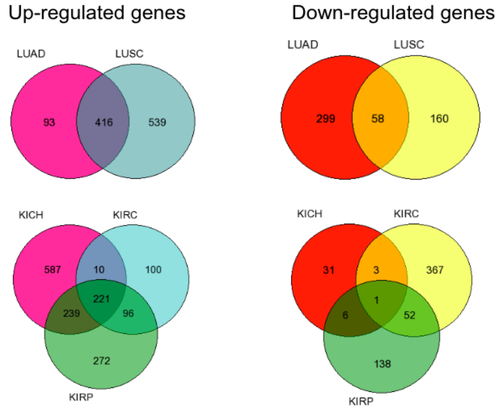
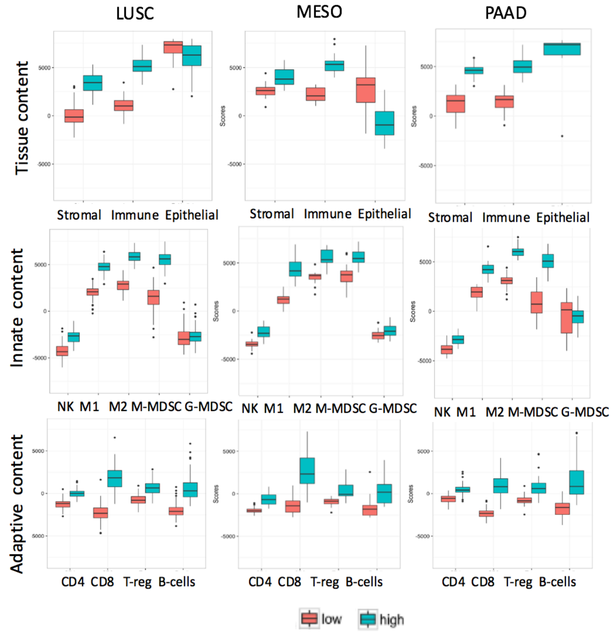


Figure 6. Immune phenotyping of tumors containing high M1 and M2 macrophages



Conclusion

- Most cancers have infiltration of M1 and M2 macrophages
- Tumors with higher abundance of M1+M2 macrophages have higher stromal content and higher infiltration of innate and adaptive immune cells
- Differential gene expression analysis indicate that high M1+M2 infiltrated tumors have higher TCR signaling, IFN-[redacted] expression and activated T-cells suggesting potential anti-tumor activity
- PI3K signaling is enriched in high M1+M2 infiltrated tumors from all cancers