OncoPept*TUME*™ identifies tumor intrinsic and extrinsic factors promoting infiltration of granulocytic myeloid-derived suppressor cells (G-MDSCs) in human cancers

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Key findings

- 28 of the 33 cancers show undetectable G-MDSC, but exhibited high infiltration of M-MDSCs.
- 5 cancers – colon adenocarcinoma (COAD), acute myeloid leukemia (LAML), rectum adenocarcinoma (READ), cholangiocarcinoma (CHOL) and stomach adenocarcinoma (STAD) - G-MDSCs were present at significantly higher levels, similar to the level of M-MDSCs.
- Tumors infiltrated by both G- and M-MDSCs are more immune suppressive than tumors infiltrated by M-MDSCs alone.

Introduction

Myeloid-derived suppressor cells are a heterogeneous mixture of functionally immature myeloid cells with impaired ability to develop into mature myeloid cells, such as macrophages and dendritic cells. They exhibit both antigen-specific and non-specific immune suppressive activities by producing cytokines, growth factors and reactive oxygen and nitrogen species. The two MDSC subtypes, granulocytic G-MDSCs, or monocytic M-MDSCs are distinguished by their morphology and surface marker expression and differ functionally in their mechanism of immune suppression. Whereas, G-MDSCs induce suppression by cell-cell contact with antigen-specific T-cells, M-MDSCs drive T-cell tolerance in an antigen-independent manner. Few studies have analyzed the functional cross-talk between G- and M-MDSCs in human cancers and investigated their immune suppressive effect on the tumor microenvironment.

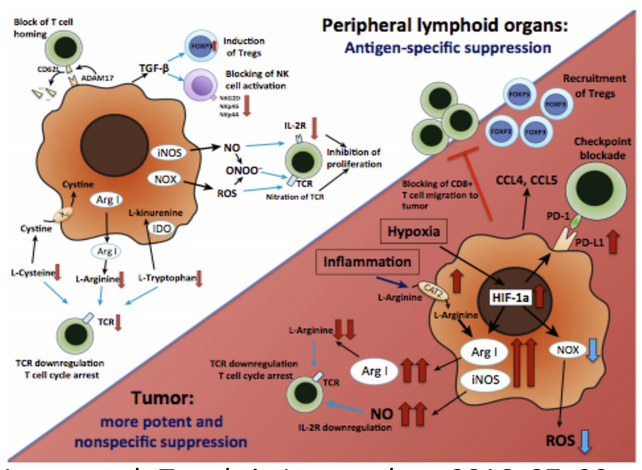
Objectives

1. Investigate the tumor microenvironment using the OncoPept*TUME* solution.
2. Evaluate the infiltration of M-MDSCs and G-MDSCs in 9345 TCGA tumor samples from 33 cancers.

Methods

- To identify tumors carrying different burden of G- and M-MDSCs, we used OncoPept*TUME* solution to quantitate the infiltration of the two subtypes of MDSCs in human cancers from whole tumor RNA-seq data.
- We used proprietary gene expression signatures that discriminated G- from M- MDSCs in all TCGA tumors. The combined expression of genes present in a signature was used to calculate an expression score that captured the relative content of a specific cell type within the tumor.
- We calculated the epithelial, stromal and the immune content for each tumor in a given cancer type and estimated the level of G- and M-MDSC infiltration.

Figure 1. Function of MDSCs in cancer



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Results

Figure 2. OncoPept*TUME* workflow

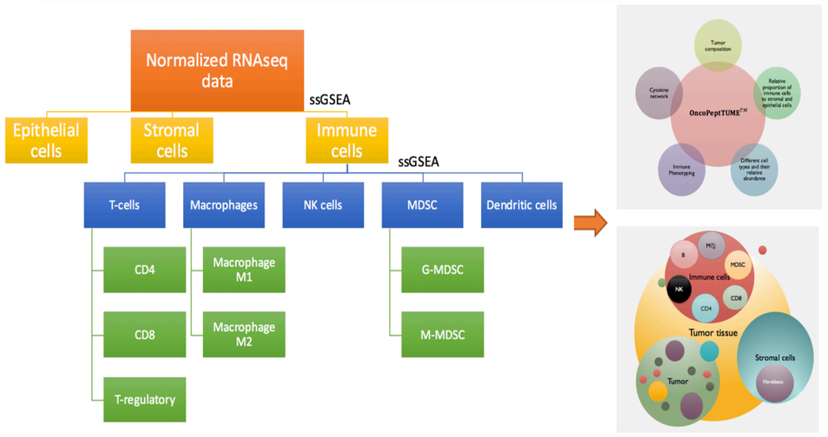


Figure 3. Creation of gene signatures

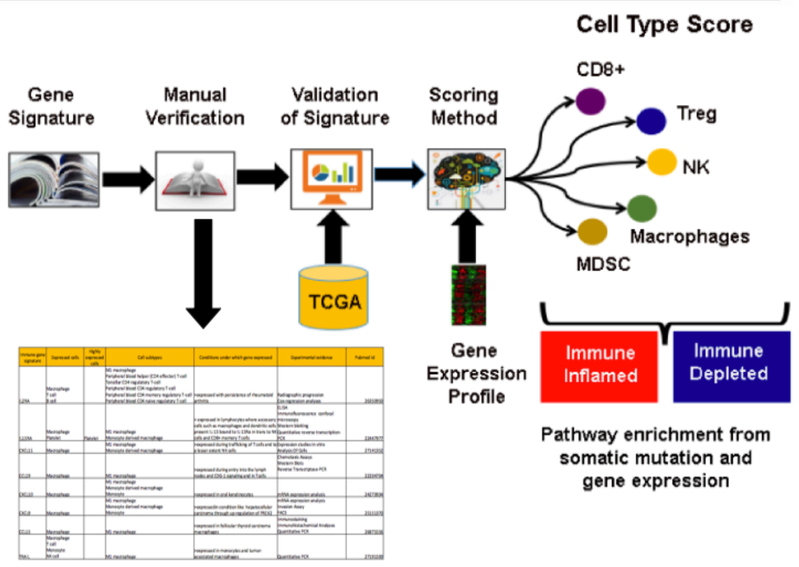


Figure 4. Epithelial, Stromal and Immune content of 33 cancers from TCGA

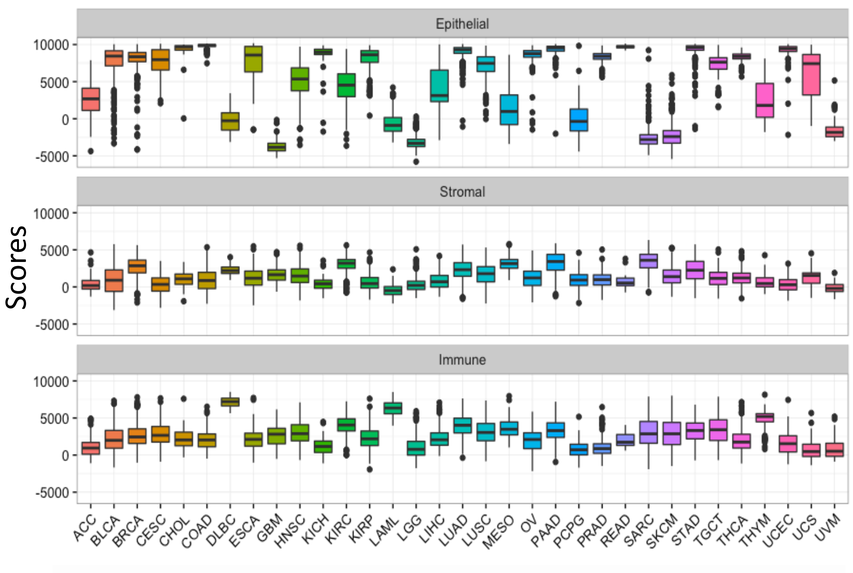


Figure 5. MDSC infiltration in 33 cancers

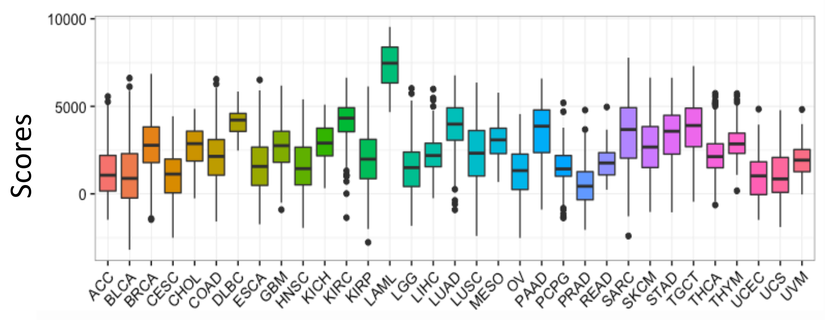


Figure 6. G-MDSC and M-MDSC levels in 33 cancers

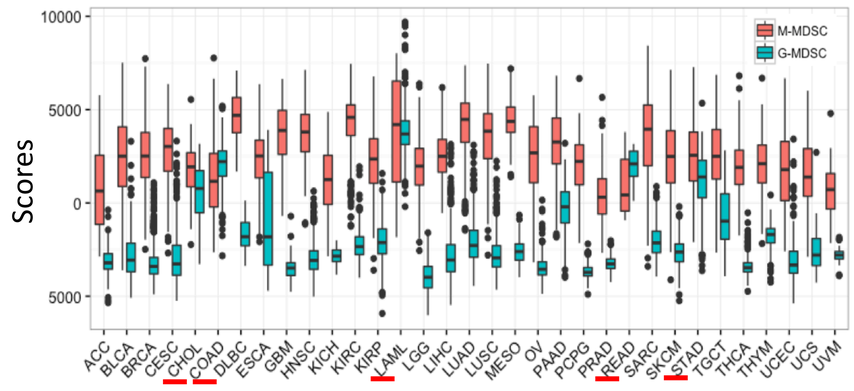
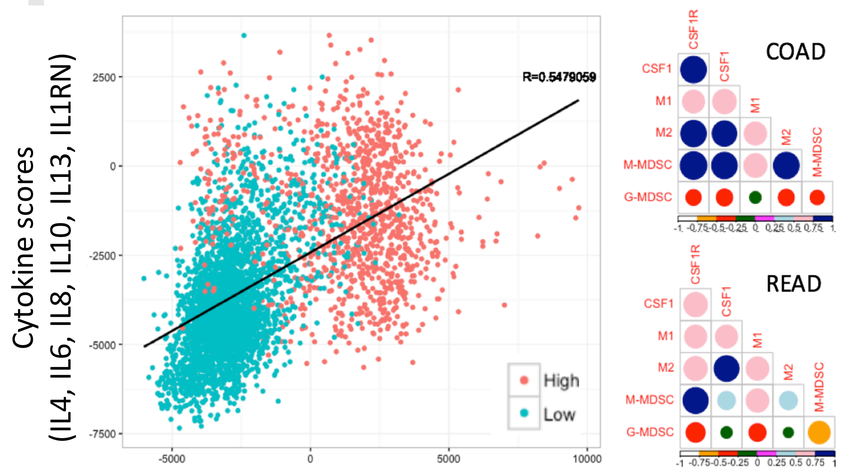


Figure 7. Samples in G-MDSC^{hi}/M-MDSC^{hi} group and G-MDSC^{low}/M-MDSC^{hi} group



G-MDSC^{hi}/M-MDSC^{hi} samples: 926
G-MDSC^{low}/M-MDSC^{hi} samples: 3078

Table 1. Enriched genes/signatures in G-MDSC^{hi}/M-MDSC^{hi} group vs G-MDSC^{low}/M-MDSC^{hi} group

Genes/ signatures	t	p-value	df
M-MDSC	-5.29	1.46E-07	1333.7
G-MDSC	74.74	0.00E+00	1309.37
M1	1.41	0.159304416	1742.31
M2	3.17	0.001568955	2036.07
VEGF	3.82	0.000141514	1445.78
TGFB	5.57	3.10E-08	1389.71
CCL2	-11.43	6.14E-29	1385.4
CSF1R	-10.68	1.31E-25	1348.75
CSF1	-14.83	3.40E-46	1360.79
CSF2	20.03	8.62E-78	1280.36
ARG1	10.83	4.87E-26	1098.11
NOS1	-7.47	1.27E-13	1874.38
NOS2	17	3.50E-57	1015.19
PTGS2	24.6	8.74E-111	1359.71
Cytokines	31.74	8.98E-170	1508.82

Conclusion

- All cancers are infiltrated by myeloid-derived suppressor cells.
- Few cancers show significant infiltration of granulocytic myeloid-derived suppressor cells (G-MDSCs) along with monocytic myeloid-derived suppressor cells (M-MDSCs).
- G- and M-MDSC infiltrated tumors are more immunosuppressive than those infiltrated by M-MDSCs alone.
- High up-regulation of CCL2 is associated with higher M-MDSC levels in tumors and lack of G-MDSC cells.
- NOS2, PTGS2 and CSF2 are associated with double infiltration by G- and M-MDSCs.
- CSF1R expression is highly correlated in tumors infiltrated by G- and M-MDSCs.
- CSF2, ligand of CSF1R is associated with M2 macrophage infiltration in G- and M-MDSC infiltrated colorectal cancer.