Tumor Purity and Immune Cell Infiltration as a Prognostic Risk Predictor for Clear Cell Renal Cell Carcinoma (ccRCC)

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Background
Solid neoplasms consist not only of tumor cells but also of normal stromal and immune cells.

Heightened interest in the relationship between oncogenesis, disease progression and the immune response.

Novel immunotherapeutics have yielded promising results.
Immune cell infiltration

- ccRCC identified as among the most highly infiltrated tumors
- To date these data have not been clinically correlated

ESTIMATE Algorithm

Aims of the study

- To gain a more thorough understanding of the immune microenvironment within ccRCC
  - integrative analysis of ccRCC tumor samples from the TCGA dataset

- Investigate the relationship between extent of tumor purity, immune cell populations and clinical outcomes

- Identify associations between specific mutations to specific immune cell components
Methods
Patients

- TCGA KIRC (ccRCC) RNASeq dataset
  - 519 tumor and 72 normal samples
  - 20,531 genes
Immune cell signatures

- Immune cell-type-specific gene signatures from Bindea et al. (*Cell Immunity*, 2013)

- 505 unique genes; broken down according to **27 immune cell types**

![Number of genes in immune cell signatures](image)
Statistical methods

- Generated ssGSEA scores for individual immune components

- Evaluated overall tumor purity based on the ESTIMATE algorithm to CSS

- Compared ccRCC immune scores to similar immune scores from 10 other TCGA profiled cancer types

- Correlated immune scores with ccRCC risk-stratifying gene sets ccA (good prognosis)/ ccB (poor prognosis)

- Identified significant relationships between mutational status of driver genes (*BAP1, SETD2, PBRM1, KDM5C*) and immune-cell-specific scores
Results
Overall tumor purity based on ESTIMATE score and CSS

Log-rank test p-value: 0.02744
Pan-cancer comparison of tumor microenvironment

Figures courtesy of Yasin Senbabaoglu
Relationship between immune cell type scores and ccA/ccB

- **Cytotoxic cells**, p-value = 5.65e-05

- **NK cells**, p-value = 0.000958

- **Macrophages**, p-value = 3.51e-10

- **TH2 cells**, p-value = 4.25e-08
CSS associated with particular immune cell types

Cytotoxic cells

Log-rank test p-value: 0.05918

Treg cells

Log-rank test p-value: 0.004663

TH2 cells

Log-rank test p-value: 0.0001317

Cancer-specific survival

Days

% Surviving

LOW

HIGH

Memorial Sloan Kettering Cancer Center...
Key mutations associated with immune cell populations

**PBRM1**
- TH1 cells
- B cells
- Macrophages
- Tfh
- PD-1
- NK cells

**BAP1**
- Angiogenesis
- pDC
- Mast Cells
- Neutrophils
- CD8 Cells
- TH17 cells
- NK CD-56 dim cells
- NKCD56 bright

**KDM5C**
- T Helper cells

**SETD2**
- DC

**Treg**
- PD-L1

**PD-L1**
- NKCD56 bright
Conclusions

• Higher degree of tumor impurity and immune cell infiltration is associated with improved clinical outcomes

• RCC is an outlier with respect to angiogenesis and cytotoxic cell infiltration compared to other common cancer types

• Specific immune cell populations, including cytotoxic and NK cells, are associated with the ccA (good risk) gene signature
  – Macrophages and TH2 cells associated with ccB (poor risk) gene signature

• Possible use of the ESTIMATE and immunes scores as a potential prognostic risk predictor
Ongoing efforts and future direction

• External validation of our current findings with Sato et al. dataset (Nature Genetics, 2013)

• Immune cell associations with PD-L1 (CD274) gene expression

• Collaboration with Immunology colleagues
  – prospectively perform cell-sorting and RNAseq on tumor specimens to further refine our immune signatures
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