Stem-like CD8$^+$ T cells in the response to checkpoint blockade immunotherapy

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T Cell Dysfunction, Co-inhibitory Receptors, and Immunotherapy

- Dysfunctional T cell express co-inhibitory or immune checkpoint receptors, eg. CTLA-4, PD-1, Tim-3
- Debate about whether checkpoint blockade therapies can modulate dysfunctional T cells
- Many patients still fail to respond to checkpoint blockade
- Important to achieve a better understanding of how checkpoint blockade alters CD8+ TILs response and what constitutes response to therapy
Expression of T cell dysfunction signature in CD8\(^+\) TILs

**Checkpoint Receptor Positive**

**Checkpoint Receptor Negative**

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**Kurtulus, Madi et al. Immunity 2019**
ICB induces greater transcriptional change in checkpoint receptor negative CD8+ TILs

MC38-Ova

Day post implant

Tumor size (mm²)

Tim-3+PD-1+ ▲ Tim-3−PD-1−

Isotype

ICB

Kurtulus, Madi et al. Immunity 2019
Transcriptional changes upon ICB correspond to acquisition of effector T cell function

Kurtulus, Madi et al. Immunity 2019
Checkpoint blockade gene signature highlights two groups of cells within PD-1− CD8+ TILs

Kurtulus, Madi et al. Immunity 2019
Novel subpopulations within PD-1− CD8+ TILs

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>GSEA</th>
<th>Naive</th>
<th>Memory-Precursor</th>
<th>Effector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>-</td>
<td>Ki-67+</td>
<td>Ki-67+</td>
<td>Ki-67+</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>-</td>
<td>GZMB, CD107a</td>
<td>GZMB, CD107a</td>
<td></td>
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<tr>
<td>Cytokine</td>
<td>-</td>
<td>IL-2, IFNg, TNFa</td>
<td>IFNg</td>
<td></td>
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<tr>
<td>Ag specificity</td>
<td>-</td>
<td>Ova+</td>
<td>Ova+</td>
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</tr>
</tbody>
</table>

Kurtulus, Madi et al. Immunity 2019
Shifts in PD-1⁻ CD8⁺ TILs subsets across tumor types and upon different checkpoint blockade therapies

Kurtulus, Madi et al. Immunity 2019
Effector-like and memory-precursor like PD-1⁻ CD8⁺ TILs share features with T cells from patients treated with ICB
Tcf7 (TCF1) is a regulator of memory-precursor CD8+ PD-1- TILs

Kurtulus, Madi et al. Immunity 2019
Loss of *Tcf7* in CD8⁺ T Cells limits response to ICB and other immunotherapies

**MC38-OVA Tumor**

- WT
- Tcf7KO
- WT + ICB
- Tcf7KO + ICB

**B16-OVA Tumor**

- WT + Isotype
- WT + PDL1/Tim3
- KO + Isotype
- KO + PDL1/Tim3

**TLR9 Agonist**

*E8i-Cre⁻ Tcf7⁻/⁻ TLR9*

![Graphs showing tumor area and percent tumor burden change over time for different conditions and treatments.](image)

*Kurtulus, Madi et al. Immunity 2019*
PD-1⁻ CD8⁺ TILs respond to ICB-induced inflammation

Isotype / PD1-Tim3-blockade

Similar results for IL-6 and IL1b
Summary

- Discovered previously unappreciated changes in PD-1<sup>-</sup> CD8<sup>+</sup> TILs upon ICB

- Discovered a stem-like memory-precursor subset regulated by Tcf7 (TCF-1) that shares features with a stem-like PD-1<sup>+</sup>T cells as well as T cells associated with response to ICB in patients

- Loss of Tcf7 (TCF-1) limits the response to ICB and other immunotherapies

- ICB may work through both direct and indirect mechanisms to harness the CD8<sup>+</sup> T cell response
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