Presenter Disclosure

Information

Richard C. Wu

The following relationships exist related to this presentation:

No relationship to disclose
Identification of a Novel CD8^+CD57^+ T-cell Subset in Melanoma Exhibiting An Incompletely Differentiated CTL Phenotype

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Introduction

- CD8⁺ cytotoxic T lymphocytes (CTL) play a critical role in anti-tumor immunity. They are an essential component of TILs.

- Composition of CD8⁺ TILs is not homogeneous, but rather represents varying contributions from different subsets.

- Understanding the phenotypic and functional characteristics of different subsets of anti-tumor CD8⁺ T cells is important in understanding the mechanism of action of cancer vaccines and adoptive T-cell therapy.
A working model for CD3+CD8+ antigen-specific T-cell differentiation

Naïve

CD45RA+CCR7+
CD28+CD27+
GB− Perforin−CD57−

Effector Memory (TEM)

CD28+ CD27+ CD57−CD56−
GB+ Perforin−

? CD28+ CD27+ CD57−CD56−
GB+ Perforin+/−

? CD28− CD27+ CD57−CD56−
GB+ Perforin+/−

Early

CD28− CD27−CD57−
GB++ Perforin++

Late/terminal

CD28− CD27−CD57−
GB++ Perforin++

CD28− CD27−CD57+ 
GB++ Perforin++
Key Questions

• What are the phenotypic and functional characteristics of different CD8⁺ T-lymphocyte subsets in TILs?

• How do these characteristics of CD8⁺ TILs fit in with current models of CD8⁺ CTL differentiation?

• Which subsets of CD8⁺ TILs have the most potent killing activity against cancer cells?
Freshly-isolated melanoma CD8+ TILs mainly reside in the early effector-memory ($T_{EM}$) subset.
A working model for CD3⁺CD8⁺ antigen-specific T-cell differentiation

**Naïve**
- CD45RA⁺CCR7⁺
- CD28⁺CD27⁺
- GB⁺ Perforin⁻CD57⁻

**Effector Memory (TEM)**
- CD28⁺CD27⁺ CD57⁻CD56⁻
- GB⁺ Perforin⁻
- CD28⁺CD27⁺ CD57⁻CD56⁻
- GB⁺ Perforin⁺⁻/
- CD28⁻CD27⁺ CD57⁻CD56⁻
- GB⁺ Perforin⁺⁻/

**Effector**
- CD28⁻CD27⁻CD57⁻
- GB⁺ Perforin⁺⁺
- CD28⁻CD27⁻CD57⁻
- GB⁺ Perforin⁺⁺
- CD28⁻CD27⁻CD57⁻
- GB⁺ Perforin⁺⁺
Working Hypothesis

Block in terminal CD8+ CTL differentiation in the tumor?

Appearance of “abnormal” CD8+ T-cell phenotypes

Early $T_{EM}$

CD28+CD27+ CD57-/CD56- GB+ perforin^-/lo

CD56+ GB++ perforin++

CD28- CD27- CD57+ GB++ perforin++
Presence of CD8+ CD27+CD28+ lymphocytes co-expressing CD57 in metastatic melanomas
Presence of CD8+ CD27+CD28+ lymphocytes co-expressing CD57 in metastatic melanomas

\[
\begin{align*}
\text{CD8+ and CD27+} & \quad P=0.0007 \\
\text{CD8+ and CD28+} & \quad P=0.0006
\end{align*}
\]
CD8⁺CD57⁺ TILs are less differentiated compared to CD8⁺CD57⁺ lymphocytes in peripheral blood.
Abnormal CD8+ T cell differentiation to end-stage CTL in tumor microenvironment

TN
CD27+, CD28+, GB-, Perf-

TEM
CD27+, CD28+, GB++, Perf-/lo

Differentiated CTL
CD27-, CD28-, CD57+, GBhi, Perfhi

Senescent? Anergic?

Atypical TEM
CD27+, CD28+, CD57+, GB+, Perf-/lo
CD8⁺CD27⁺CD57⁺ subset is not senescent or anergic
CD8⁺CD27⁺CD57⁺ subset is not senescent or anergic
CD8^+CD57^+ can differentiate further into CD27^-CD57^+, perforin^+ cells ex vivo

A

Fresh TIL 2276

Culture with IL-2

B

Gated on CD3^+CD8^+CD57^+ subset

<table>
<thead>
<tr>
<th>Condition</th>
<th>Perf-high cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh TIL</td>
<td>20</td>
</tr>
<tr>
<td>Culture with IL-2</td>
<td>40</td>
</tr>
<tr>
<td>CD3 restim.</td>
<td>80</td>
</tr>
<tr>
<td>CD3+CD28 restim.</td>
<td>80</td>
</tr>
</tbody>
</table>
Abnormal CD8+ T cell differentiation to end-stage CTL in tumor microenvironment

\( T_N \)
- \( CD27^+, CD28^+ \)
- \( GB^-, Perf^- \)

\( T_{EM} \)
- \( CD27^+, CD28^+ \)
- \( GB^{+/+}, Perf^{-/lo} \)

\( \text{Atypical } T_{EM} \)
- \( CD27^+, CD28^+, CD57^+ \)
- \( GB^+, Perf^{-/lo} \)

\text{Differentiation}
- \text{ex vivo expansion with IL-2}
- \text{ex vivo expansion with IL-2}

- \( CD8^+CD56^+CD57^-, GB^+, \text{ and Perf}^{++} \) (the best anti-tumor effector cells?)
- \( CD8^+CD57^+, GB^+, \text{ and Perf}^{++} \) (better anti-tumor effector cells?)
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