Presenter Disclosure Information

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The following relationships exist related to this presentation:

No Relationships to Disclose
CD47 limits cooperation between adaptive tumor immunity and radiation therapy

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High CD47 expression in human cancers correlates with poor prognosis

Zhao PNAS 2011; Majeti Cell 2009; Willingham PNAS 2012; Baccelli Oncotarget 2014
Role of CD47 in cancer: signaling versus immune modulation?

CD47

Thrombospondin-1

Macrophages

SIRPα

“Don’t eat me”

VEGF/NO/cGMP signaling

Angiogenesis/ tumor perfusion/immunity

Self-renewal/stem cell reprogramming

Stress resistance (Apoptosis vs. autophagy)
CD47 limits cell and tissue radioresistance

- Mice lacking CD47 or its ligand thrombospondin-1 are radioresistant.
- Therapeutic blockade of CD47 using an antisense morpholino protects mice from local and total body irradiation.
- CD47 blockade protects bone marrow hematopoietic function.
- Circulating lymphocytes are preserved.
- Radioprotection is cell-autonomous and mediated by a protective autophagy response.

Suppression of CD47 enhances the radiation-induced delay in B16 melanoma growth in C57Bl/6 mice
Synergism between CD47 blockade and radiation therapy requires T cells

Enhancement by CD47 blockade of radiation growth delay for 15-12RM fibrosarcoma in BALB/c mice requires CD8$^+$ T cells
Synergism between CD47 blockade, adoptive CD8 T cell immunotherapy, and irradiation

15-12 RM Fibrosarcoma Tumor Growth in athymic nu/nu BALB/c mice

Soto-Pantoja, *Cancer Res* 2014
CD47 blockade increases CD8 CTL activity in vitro

301: murine CD47 blocking antibody

Soto-Pantoja, Cancer Res 2014
Eliminating CD47 in the tumor microenvironment is sufficient to enhance tumor radiation response.

**B16 melanoma in WT versus CD47-null C57Bl/6 mice**

![Graph showing tumor volume over time for WT and CD47-null mice with and without irradiation.](image)

**Weight (g)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>WT + IR</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>CD47-/-</td>
<td>6.0 ± 0.7</td>
</tr>
<tr>
<td>CD47-/- + IR</td>
<td>3.5 ± 0.6</td>
</tr>
</tbody>
</table>

**CD8+ Cells (% per field)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CD8+ Cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>CD47-/-</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>IR</td>
<td>10 ± 0.5</td>
</tr>
<tr>
<td>CD47-/- + IR</td>
<td>35 ± 3</td>
</tr>
</tbody>
</table>

*Soto-Pantoja, Cancer Res 2014*
CD47 signaling limits T cell activation

CD47 blockade synergizes with radiation to increase granzyme B expression

15-12RM Fibrosarcoma adoptive transfer model
15-12RM Fibrosarcoma in immune-competent mice
B16 melanoma model

Soto-Pantoja, Cancer Res 2014
CD8⁺ T cell infiltration inversely correlates with CD47 expression in human melanomas

Soto-Pantoja, Cancer Res 2014
Differential effects of CD47 signaling blockade on tumor vs. stromal cells

Healthy tissues and tumor stroma:

CD47 blockade increases stromal cell survival via:

- Nitric oxide and VEGF signaling
- Enhanced autophagy
- Inducing c-Myc and other stem cell factors

Tumor cells:

CD47 blockade increases tumor cell death via:

- Decreasing protective autophagy
- Resistance to c-Myc regulation
- Decreased resistance to innate immunity
- Enhanced CTL killing of tumor cells
Lessons and Take Home Messages

• Key points
  - Suppression of CD47 in the tumor microenvironment enhances radiation growth delay in syngeneic fibrosarcoma and melanoma models.
  - Synergism between CD47 blockade and radiation to delay tumor growth requires CD8^+ T cells.
  - Blockade of CD47 on either target or effector cells enhances antigen-dependent CD8^+ CTL-mediated killing of tumor cells in vitro and the efficacy of adoptive CD8^+ T cell transfer in vivo.
  - Enhanced T cell mediated killing following CD47 blockade is associated with increased granzyme B expression.

• Potential impact on the field
  - Therapeutics targeting CD47 could improve the efficacy of radiation therapy alone and in combination with adoptive T cell immunotherapy

• Lessons learned
  - CD47 is an immune checkpoint inhibitor for T cells