Presenter disclosure information

• David H. Munn, MD

The following relationships exist related to this presentation:

*NewLink Genetics, Inc. (Consultant, stock, SAB)*
IDO and immune suppression

David H. Munn
Cancer Center
Georgia Health Sciences University
Tumor-induced immune suppression

- Tumors suppress immune responses to their own antigens
- This immune suppression is active, specific and acquired
- Suppression thus resembles natural acquired tolerance
- Hypothesis: tumors exploit the natural, endogenous mechanisms of acquired tolerance used by the immune system
Indoleamine 2,3-dioxygenase (IDO)

- IDO is a natural endogenous molecular mechanism of immune suppression
- IDO can create acquired peripheral tolerance *de novo*
- IDO is counter-regulatory (i.e., induced by inflammation but suppressive for immune responses)
- IDO regulates both innate and adaptive responses
  - control of local inflammation, IL-6, etc
  - suppresses effector T cells, activates Tregs
IDO helps maintain tolerance to the fetus
IDO helps maintain tolerance to self antigens derived from apoptotic cells

IDO induced in marginal-zone macrophages by apoptotic cell challenge

IDO-KO mice develop lupus when challenged with apoptotic cells

From Tracy McGaha lab
Ravishankar B et al. PNAS 2012;109:3909-3914
IDO as a single transgene can create acquired tolerance:

Haplo-mismatched allografts transfected with IDO are tolerated without additional immunosuppression

figure adapted from KA Swanson, David S. Wilkes et al

© 2004 [American Thoracic Society](https://www.thoracic.org)
IDO and malignancy:

• IDO can be expressed by the cancer cells themselves in a range of tumor types

• High IDO expression appears correlate with poor outcome in a number of cancers
  • ovarian cancer
  • AML
  • endometrial carcinoma
  • colon cancer
  • melanoma
Prognostic significance of IDO in colorectal carcinoma

From Ferdinande et al. *Clinicopathological significance of indoleamine 2,3-dioxygenase 1 expression in colorectal cancer*

IDO in cells of the host immune system
(tumor-draining lymph node of human melanoma)
Predictive value of abnormal IDO expression in human tumor-draining lymph nodes

- 40 patients with cutaneous malignant melanoma, no metastases
- sentinel lymph node obtained at time of initial diagnosis

- in collaboration with Scott Antonia at Moffitt Cancer Center

IDO is expressed by tolerogenic DCs in tumor-draining LNs

B16F10 mouse melanoma tumor (day 11-14)
Self-amplifying tolerogenic milieu in the TDLN

IDO $\rightarrow$ CTLA4 loop
How does IDO get turned on?
DCs in prostate tumors express FOXO3, which induces IDO expression and a suppressive DC phenotype


<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold change tumor/non-tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASLG</td>
<td>5.2</td>
</tr>
<tr>
<td>IDO1</td>
<td>7.3</td>
</tr>
<tr>
<td>CD274</td>
<td>3.1</td>
</tr>
<tr>
<td>STAT3</td>
<td>5.1</td>
</tr>
<tr>
<td>FOXO3</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Table 2
Human TADCs have elevated expression of genes associated with tolerance

RNA was isolated and hybridized to Affymetrix Human Gene 1.0 ST arrays. Fold change values have corresponding *P* values of less than 0.00001 (ANOVA). Data are representative of 5 independent microarrays for tumor and non-tumor biopsies.
Tregs are highly pre-activated in TDLNs

IDO-inhibitor (D-1MT) is synergistic with vaccine against established tumors.

Naïve, resting $T_{EFF}$ must be activated in vivo in the tumor-bearing host.
IDO blockade produces effects similar to CTLA4 blockade
IDO and Tregs form a self-amplifying suppressive loop

... once established, this positive-feedback loop is highly stable and very difficult to disrupt.
How can we interrupt this suppressive loop?

Hypothesis: CD4+ helper T cells can disrupt the suppressive loop via an opposing inflammatory loop based on CD40L and IL-6
CD40L $\rightarrow$ IL-6 loop

(drives immunogenic state)
When also exposed to activated **effector cells**, this becomes a self-amplifying inflammatory loop

**CD40L → IL-6 loop**

*(drives immunogenic state)*
“Tipping-point” model

• each loop is self-amplifying and stable

• one or the other will be dominant

• intervening at only a single point will not be effective
IDO blockade is **synergistic** with CD40-agonist mAb
IDO-activated Tregs drive upregulation of PD-ligands on DCs

**Resting DCs**

- **Start of assay**
  - CD11c+ PD-L1
    - 19%
  - CD11c+ PD-L2
    - 5%

**After Tregs**

- **no Tregs**
  - CD11c+ PD-L1
    - 3%
  - CD11c+ PD-L2
    - 4%

- **αCD3 activated Tregs**
  - CD11c+ PD-L1
    - 4%
  - CD11c+ PD-L2
    - 9%

- **IDO-activated Tregs**
  - CD11c+ PD-L1
    - 99%
  - CD11c+ PD-L2
    - 95%
IDO blockade enhances PD-1/PD-L blockade
Chemo-immunotherapy in mouse melanoma (B16F10 model)

Phase I Trial of 1-methyl-D-tryptophan

PI: Scott Antonia MD PhD
Co PI: Hatem Soliman MD
Dan Sullivan MD

Moffitt Cancer Center/Southeast Phase II Consortium

Chuck Link MD
Nick Vanahanian MD
William Ramsey MD PhD

NewLink Genetics Inc
• Hypophysitis in 3 patients
  • this was a recall toxicity associated with prior ipilimumab therapy (anti-CTLA4 mAb)

• recall hypophysitis occurred at very low dose of D-1MT (200 mg/day p.o.)

• otherwise 1MT was well tolerated

From Antonia et al ASCO Abstract #3004, 2009
D-1MT bypasses mTOR block

Inhibition of mTOR by TRP starvation

Bypass of mTOR inhibition by 200 nM D-1MT

Cells were Starved of Tryp for 18 hours and then stimulated for 2 hours with Varying amounts of D-1MT

From Metz et al, Oncoimmunology (in press 2012)
Clinical strategy: IDO-inhibitor drugs

Combination with chemotherapy

- inhibiting IDO in the post-chemotherapy window allows anti–tumor immune responses to occur that would otherwise be suppressed

Combination with immunotherapy

- Blocking IDO allows enhanced response to vaccines
- reduces Treg-mediated suppression
- IDO pathway and CTLA-4 pathway are closely linked
- IDO blockade may be synergystic / enhancing in combination with CD40-agonist antibody or PD-1/PD-L blockade
Acknowledgements

- Madhav Sharma
- Andrew Mellor lab
- Ted Johnson lab
- Tracy McGaha lab

Medical College of GA, Ga. Health Sciences Univ.
- Bruce Blazar
- University of Minnesota

- Scott Antonia
- Hatem Soliman
- Moffitt Cancer Center

- George Prendergast
- Rick Metz
- Lankenau Institute
High expression of IDO and Foxp3 at baseline may be associated with clinical response to ipilimumab

1MT + chemotherapy: effect on tumor growth (autochthonous breast cancer model, DL-1MT)

from Prendergast and colleagues
Cancer Res. 2007; 67: (2) 793
1MT stereo-isomers

4T1 Tumor model

mmtv-neu Tumor model

From Prendergast and colleagues
Cancer Res. 2007; 67: (2) 793
INDO expression by microarray and by qPCR correlated to clinical outcome in patients with adult AML
