The Immune System and Cancer

Transformed cells

Patrolling immune cells

Attacking abnormal cells

Successful tumor suppression

Fatal Melanoma Transferred in a Donated Kidney 16 years after Melanoma Surgery

» 1998: a woman died of a brain aneurysm, two kidneys were donated
» That female donor had a primary melanoma 16 years before sudden death (unrelated to melanoma diagnosis 16 years earlier)
» Melanoma was removed, with no residual tumor, followed in melanoma clinic for 15 years and was discharged, apparently tumor free, in 1997
Incidence of certain cancers is higher in immune-suppressed transplant recipients

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of cases observed</th>
<th>No. of cases expected</th>
<th>Ratio observed/expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell</td>
<td>59</td>
<td>3.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>39</td>
<td>9.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Ovarian</td>
<td>22</td>
<td>1.8</td>
<td>12.0</td>
</tr>
<tr>
<td>Cervical</td>
<td>29</td>
<td>3.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>24</td>
<td>2.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Anal</td>
<td>22</td>
<td>3.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Bladder</td>
<td>26</td>
<td>4.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Colorectal</td>
<td>28</td>
<td>10.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Lung</td>
<td>29</td>
<td>12.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Brain</td>
<td>15</td>
<td>8.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>11</td>
<td>9.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7</td>
<td>4.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Breast</td>
<td>15</td>
<td>12.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>


Generating anti-cancer immunity is a multistep challenge

2013 Cancer Immunotherapy Breakthrough of the Year
Identify key immunologically relevant concepts in the treatment of cancer

» Cytokines
» Checkpoint blockade
» Cells
» Microbes
» Antigens

Rationale for type I Interferon

» Breast cancer, melanoma and GI cancer patients show reduced IFN-α signaling in T and B cells, and reduced IFN-γ signaling in B cells.
» Early and persistent defect, independent from stage and chemotherapy.
IFN-alpha:
- Increases hematopoietic stem cell proliferation, increases pool of cells
- Increased migration of immune cells
- Increased cells in lymph nodes, activation of Dendritic cells to stimulate T cells
- Activated Dendritic cells take up tumor antigen to stimulate T cells, IFN-α also increases MHC on tumor cells

T-Cell Activation and Proliferation
- Cognate T-Cell Receptor and MHC presentation of peptide antigen
- Costimulatory signal
**T-Cell Activation and Proliferation**

**IL-2 Cytokine**

**Growth Factor; T cell expansion**

**Stimulate the immune system**

*Interleukin – 2*

**Response to Ipilimumab 10 mg/kg x 2 doses**

*No progression 5+ years*
T cell Autoregulation blocked

- T-cell activation
- T-cell inhibition
- T-cell remains active

Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)
PD-1 Blockade (nivolumab/pembrolizumab)

Tumor Micronenvironment

Antitumor (cytotoxic, lytic, proliferation, migration to tumor)

I am exhausted

Modified from Blood 2013 121:1485-1486
The intestinal microbiota influences the efficacy of PD-1 blockade

Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting
Cells/molecules that promote vs. inhibit tumor formation

<table>
<thead>
<tr>
<th>Promote Tumor Outgrowth</th>
<th>Inhibit Tumor Outgrowth</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCs, M1 macrophages, N1 neutrophils, NK cells, Th1 cells, CD8+ T cells, killer cells, IFNγ, IL-2, IL-12, STAT1, perforin, NKG2D</td>
<td>M2 macrophages, N2 neutrophils, B cells, T-regulatory cells, Th2 cells, NF-κB, FOXP3, TGF-β, IL-4, IL-10, STAT3, MMPs, CTLA4, PD-1/PD-L1</td>
</tr>
</tbody>
</table>

Mφ polarization: Fine-tuning macrophage function

M1, Classically activated
- Prominently inflammatory
- Promote Th1, Th17
- Antitumor immunity

M2, Alternatively activated
- Regulate wound healing, angiogenesis
- Suppress T cell responses
- Suppress antitumor immunity

Tumor Infiltrating Lymphocytes (TIL) or Adoptive Cell Therapy (ACT)

"Culture"
Talimogene laherparepvec (T-VEC) - An HSV-1 Derived Oncolytic Immunotherapy

- Selective viral replication in tumor tissue
- Accumulation of the virions / lysis of cancer cell = oncolytic effect
- Systemic tumor-specific immune response
- Death of distant cancer cells

‘Final common pathway’ of human cancer immunotherapy: targeting random somatic mutations

Potential strategies for enhancing clinical responses to cancer neoantigens

» Use T cells recognizing neoepitopes for ACT
» Utilize TCRs recognizing neoepitopes in Tg TCR
» Combine above with other immune therapy
» Neoepitope/peptide therapeutic “vaccination”
Controlling the immune system is not as simple as driving a car.

Thank you.