Basic Principles of Cancer Immunotherapy

Eric Bartee
Assistant Professor
Medical University of South Carolina

Disclosures

No relevant financial relationships to disclose
I will be discussing non-FDA approved indications during my presentation.

The fundamental Question

Why does the immune system fail to eliminate cancer?

Cancer cells grow progressively in immunocompetent hosts without evidence of systemic T cell exhaustion or anergy.
The 3 Es of cancer immunoediting
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- Tumors insulate themselves with layers of different immunosuppression
- Overcoming these multiple layers represents a daunting challenge for tumor-specific T cells
- The goal of Immunotherapy is to overcome these layers restoring the capacity of T cells to eradicate the tumor

Multi-layered immunosuppression

Fundamental types of immunotherapy

<table>
<thead>
<tr>
<th>Positive</th>
<th>‘Negative’</th>
<th>Targeting</th>
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<tbody>
<tr>
<td>Turning the immune system on so it can punch through the inhibitory layers better</td>
<td>Making the existing immune response more effective by removing layers of inhibition</td>
<td>Keeping the immune response specific to tumor tissue</td>
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T cell checkpoint modulation/blockade

- T cell function is modulated by a large number of pathways in both **positive** and **negative** directions

- These pathways can be altered by addition of inhibitory or agonistic antibodies

- Checkpoint blockade typically works by taking the brakes off existing immune responses

- PD-1 signaling promotes T cell ligation by inhibiting downstream activation signals
  - PD-1 expression is upregulated by activated and exhausted T cell populations
  - T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
  - Many cells within the tumor microenvironment express PD-L1/PD-L2 allowing for the suppression of T cell activation

- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. TLR activation of PD-L1
  2. Oncoprotein signaling pathways

- Transgenic cancer models
  - TCR engineering
  - TCR transduction
  - T cell adoptive transfer

- Checkpoint modulation/blockade therapies
  - Inhibitory antibodies
  - Agonistic antibodies
  - Synergistic immunotherapies

- Examples of checkpoint blockade therapies
  - PD-L1/PD-1
  - CTLA-4
  - TIM-3

- Clinical successes with checkpoint blockade
  - Melanoma
  - Lung cancer
  - Renal cancer
Anti-PD1 antibodies were approved for metastatic melanoma in 2014

Ipilimumab (anti-CTLA-4) was approved for metastatic melanoma in 2010
• Not all tumors have existing anti-tumor immune responses

• In these immunologically silent tumors, 'negative' immunotherapeutic methods typically fail

• The goal of therapeutic cancer vaccines is to induce new anti-tumor immunity

Oncolytic HSV was approved for late stage melanoma in 2015

- Corrales L and Gajewski TF

- Rivas et al. Cell 2017
T cell Adoptive Transfer Therapy (ACT)

- ACT takes T cells from a patient, expands them to large numbers ex vivo, and then reinfuses them back into the patient to elicit anti-tumor effects.
- The goal of ACT is to win the numbers game and overwhelm the tumor with massive numbers of T cells.

ACT can involve engineered (CAR, TCAR) or patient-derived (TIL, PBMC) T cells.
TIL based T cell adoptive transfer

Effective treatment of relapsed B-cell ALL with CD19 CAR T cell therapy

Antibody
Specific to tumor-associated antigen

Radiolabeled or Cytotoxic agent
Designed to kill target cells when internalized and released or activated

Linker
Attaches cytotoxic agent to the antibody
• **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity

• **Internalization:** The target tumor surface protein must internalize to deliver the toxin - it should do so frequently and to a suitable endosomal compartment.

• **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.

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**Rituximab maintenance improves survival of NHL following therapy**

![Graph showing progression-free survival over time for Rituximab maintenance and observation groups.]

- Patients at Risk: 150
- 5 Year Event-Free Survival: 82%
- P = .0005

**The Abscopal effect (Hidden Immunotherapy)**

- Localized treatment of a tumor causes/evokes reduction of distant ones

- Caused by tumor cells killed by initial treatment priming secondary anti-tumor responses

- Effectively acting as positive immunotherapy
Radiation induced immune responses

Radiotherapy synergizes with blockade of CTLA-4 and PD-1

Combination Immunotherapy
Not all combinations work

• More isn’t always better
• Combination of checkpoint therapies is often associated with increased auto-immune like toxicities

If you get the right combination, however, the results can be powerful

The fields future directions

• Identifying new immune inhibitory pathways and discovering ways to overcome them
• Rationally designing new immunotherapy combinations and predicting patient responsiveness
• Identifying methods to preventing autoimmune like complications
Questions?