The Basics of Immunotherapy

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Nothing to Disclose
Objectives

- Describe basic components of the immune system
- Review the scientific evidence supporting the role of the immune system in cancer, and the immune response
- Describe several attributes of immunotherapy
- Discuss several types of treatment options for cancer immunotherapy
Immunotherapy

**Definition**

- Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases

**Examples in cancer**

- Monoclonal antibodies
- Cytokines
- Checkpoint inhibitors
- Therapeutic vaccines

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Key Components Involved in the Immune Response

- **Antigens**
  - Molecules produced by microbes or foreign agents that bind to T cells and antibodies

- **Antigen presenting cells (APCs)**
  - Identify and uptake foreign antigens
  - Present them to T cells

- **T cells**
  - Activated by APCs
  - Recognize and destroy cells containing foreign antigen

- **B cells**
  - Produce antibodies specific to foreign antigens

The Cell Cascade
Overview of the Immune Response

- Immune system includes two subsystems.
  - Innate (non-specific) immune system.
  - Adaptive (or acquired or specific) immune system.
History of Cancer Immunotherapy

Key events in the history of cancer Immunotherapy

- 1890s: First cancer vaccine developed (Coley)
- 1960s: Adjuvants (e.g., BCG) shown to eradicate some tumors
- 1986: IFN-α approved as cancer immunotherapy
- 1991: First tumor-associated antigen cloned (MAGE-1)
- 1992: IL-2 approved as cancer immunotherapy
- 1997: Imiquimod approved for external genital warts
- 2004: Imiquimod approved for superficial basal cell carcinoma

Modified from J. Clin. Oncol. 2008. 26: 3445-3455
The six hallmark capabilities originally proposed in 2000.

The past decade has witnessed remarkable progress toward understanding the mechanistic underpinnings of each hallmark.

Hanahan D, Weinberg RA. Cell 2000 100 (1), 57-70
Increased Incidence of Cancer in Immunocompromised Individuals

Malignant tumors develop in individuals with compromised immune systems.

Tumor / cancer risk in transplant patients compared to general population

- Non-melanoma skin cancer
- Non-Hodgkin’s lymphoma
- Kaposi’s sarcoma
- Kidney cancer
- Melanoma
- Vulvovaginal cancer
- Cervical cancer
- Hepatobiliary cancer
- Leukemia
- Bladder cancer
- Testicular cancer
- Breast cancer
- Ovarian cancer
- Pancreatic cancer
- Esophageal cancer
- Stomach cancer
- Prostate cancer
- Lung cancer
- Colon cancer

Fold-increase in tumor/cancer risk:
- 2-fold
- 3-fold
- 5-fold
- 8-fold
- 15-fold
- 20-fold and beyond

Abbas AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.
Immune Cells Within Tumors Predicts Overall Survival

T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers\textsuperscript{1,2}

Kaplan-Meier Curve for OS in Advanced Ovarian Cancer\textsuperscript{1}

\begin{itemize}
  \item Intratumoral T cells (n=102)
    \begin{itemize}
      \item Median OS = 50.3 months
    \end{itemize}
  \item No intratumoral T cells (n=72)
    \begin{itemize}
      \item Median OS = 18 months
    \end{itemize}
\end{itemize}

\textit{P}<0.001

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      (72,5)
      (84,0)
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      (48,10)
      (60,0)
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      (72,0)
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      (48,15)
      (60,5)
      (72,0)
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Dynamics Between Cancer and the Immune System

- In a **dynamic** process, the immune system can either
  - Block tumor growth, development, and survival
  - Allow tumor outgrowth

The Balance

- Elimination
- Equilibrium
- Escape
Figure 4. Evading immune destruction

1. **Cancer immunoediting**
   - Tumor cell

2. **Elimination** (Cancer immunosurveillance)
   - CD8^+ T cell
   - Macrophage
   - NK cell
   - Tumor cell

3. **Equilibrium**
   - CD8^+ T cell
   - Tumor cell
   - NK cell
   - NK cell

4. **Protection**
   - NK cell
   - CD8^+ T cell
   - Tumor cell

5. **Escape** (Cancer progression)
   - NK cell
   - CD8^+ T cell
   - Tumor cell
Features of an Effective Immune Response

- Specificity
- Trafficking
- Adaptability
- Target elimination
- Durability (immune memory)

Cells associated with the Immune System

Cast of characters

MACROPHAGE White blood cells in the bloodstream that gobble up bacteria, viruses or pathogens.

T CELL The human body has about 1 trillion T cells, each with a protective role.

MEMORY T CELL T cells that remember an invader so the body can effectively respond to subsequent attacks.

KILLER T CELL T cells that recognize and kill infected cells. A T cell that homes in on a flu virus will maintain its specificity for that virus each time the T cell divides.

B CELL Immune cells that tag invaders with antibodies so that other immune cells can find and engulf them.

CAR T CELL Genetically engineered T cells with surface receptors (called chimeric antigen receptors or CARs) that bind to a specific antigen on tumor cells.

TREG CELL Peacekeepers that keep the body from attacking its own healthy tissues.

CYTOKINES Chemical messages released by immune cells to orchestrate an attack.
Cell Types Are Defined By Phenotypic Markers
Immunotherapy Proven Effective in Cancer

- Therapies that engage the immune system have been shown to improve patient survival in randomized, phase 3 cancer trials\textsuperscript{1-2}

- Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers\textsuperscript{3}

Immunotherapy: Treatment Considerations

► Standard practice in oncology is the use of combination agents with different mechanisms of action
  ► Chemotherapy and mABs
  ► Radiation and chemotherapy
  ► Multiple chemotherapy regimens

► Immunotherapy offers potential for synergy with other therapies

## Weighing the Treatment Options

### Fighting Cancer: Weighing Treatment Options

<table>
<thead>
<tr>
<th>IMMUNOTHERAPY</th>
<th>CHEMOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROS</strong></td>
<td><strong>PROS</strong></td>
</tr>
<tr>
<td>- Utilizes the body's own immune system to fight disease</td>
<td>- Kills cancer cells directly</td>
</tr>
<tr>
<td>- Can adapt to different cancer cells</td>
<td>- Drugs are available now</td>
</tr>
<tr>
<td>- Immunologic memory can prevent cancer recurrence</td>
<td>-</td>
</tr>
<tr>
<td>- Can have fewer side effects</td>
<td>-</td>
</tr>
<tr>
<td><strong>CONS</strong></td>
<td><strong>CONS</strong></td>
</tr>
<tr>
<td>- Unclear why it works for only some patients</td>
<td>- Impacts healthy cells along with cancer cells</td>
</tr>
<tr>
<td>- Effects can take time</td>
<td>- Suppresses immune system leading to increased risk of infection</td>
</tr>
<tr>
<td>- Possible side-effects from overactivity of the immune system</td>
<td>- Can worsen fatigue</td>
</tr>
<tr>
<td></td>
<td>- Cancer cells can develop resistance</td>
</tr>
</tbody>
</table>

*Source: UC San Francisco*
Checkpoint Inhibitors

• Mechanism of action
  – Block immune checkpoints that regulate T cell activation/function

• Examples
  – CTLA-4 and PD1

• Efficacy
  – Extends overall survival in certain metastatic diseases
  – A significant effect on PFS not consistently observed
Monoclonal Antibodies (mABs)

• **Mechanism of action**¹,²
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death

• **Efficacy**³-⁷
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

Cytokines

• Proteins that are naturally secreted by immune system cells

• Mechanism of action
  – Interleukin-2 (IL-2) stimulates T-cell proliferation

• Examples
  – Interleukins, interferons

• Efficacy
  – High dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma

Preventive vs Therapeutic Vaccines

“Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.”

- NCI (2011)

Therapeutic Cancer Vaccines

• **Mechanism of action**
  − Activation of T cells to seek out and destroy target cancer cells

• **Efficacy**
  − Extended overall survival in certain metastatic diseases without an effect on PFS

Immunotherapy: Future Promise

• Rapid increase in immunotherapy clinical research
  – Doubling of abstracts at major conferences from 2009 to 2012
  – Approximately 800 clinical trials in various phases ongoing
    • eg, breast, colon, head and neck, kidney
• Trials utilize agents alone and in combination with conventional therapies

Summary

- The immune system plays a critical role in controlling cancer

- Key features of an effective immune response include
  - Specificity
  - Adaptability
  - Durability (immune memory)

- Future clinical considerations
  - May elicit better immune system response if used earlier in disease
  - Potential for durable clinical effects and synergy with subsequent therapies

Questions