Cancer Immunotherapy: Harnessing the immune system to treat cancer

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Disclosure

- I serve on a scientific advisory board for Luminary Therapeutics
- I hold patents in cell therapy reagents
What is cancer immunotherapy?

- Stimulating a patient’s own immune system to attack cancer
  - Immune Checkpoint Blockade

- Giving a patient synthetic (man-made) components to specifically target cancer
  - Chimeric Antigen Receptor (CAR) T cell therapy
Why immunotherapy?

- Immune cells have evolved over millions of years to specifically recognize and kill abnormal and/or infected cells
Immunology 101:
The Immune System Maintains Balance/Equilibrium/Homeostasis

● The immune system is activated when the body experiences injury, infection, or disease.
● The end result of immune system activation (and subsequent deactivation) is a return to a healthy state.
  ◦ The wound is healed.
  ◦ The infection is resolved.
  ◦ The disease is eradicated.
The Immune System Works via Cells and Secreted Molecules (Proteins)

- Cells
  - White blood cells (leukocytes)
White Blood Cells are Immune Cells

Blood Sample

Plasma

Antibodies (Secreted Proteins)

Immune Cells (White Blood Cells)

Red Blood Cells

http://www.chemistryland.com/CHM130FieldLab/Lab5/Lab5.html
Many Immune Cell Types

<table>
<thead>
<tr>
<th></th>
<th>Basophils and mast cells</th>
<th>Neutrophils</th>
<th>Eosinophils</th>
<th>Monocytes and macrophages</th>
<th>Lymphocytes and plasma cells</th>
<th>Dendritic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary function(s)</td>
<td>Release chemicals that mediate inflammation and allergic responses</td>
<td>Ingest and destroy invaders</td>
<td>Destroy invaders, particularly antibody-coated parasites</td>
<td>Ingest and destroy invaders, including antigen presentation</td>
<td>Specific responses to invaders, including antibody production</td>
<td>Recognize pathogens and activate other immune cells by antigen presentation</td>
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Masonic Cancer Center
University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute
Immune System Continuum

Cell Types

- Leukocytes (WBCs)
  - Neutrophil
  - Macrophage
  - DC
  - NK
  - B cell
  - T cell
  - Lymphocytes

Function

- Innate: Rapid, No Memory
- Adaptive: Delayed, Memory

Recognition

- Innate: General
- Adaptive: Very Specific
Expression of Receptors Involved in Immune Activation

Innate
- General
- All cells express same pathogen-recognition receptors

Adaptive
- Diverse
- Very Specific
- Each cell expresses a unique receptor

B cells
T cells
Time Course of an \textit{Innate} Immune Response

![Graph showing the time course of an innate immune response.](image-url)
Time Course of a Primary Adaptive Immune Response

-Time (days)

Years

-Subclinical infection

#Pathogens

-Adaptive Immune cells

-Innate Immune Cells

#Adaptive Immune cells

# Innate Immune Cells

≈ 96 hr delay

Memory
Time Course of a Secondary Adaptive Immune Response

Subclinical infection

# Adaptive Immune cells
# Innate Immune Cells

# Pathogens

Memory
The Immune System Works via Cells and Secreted Molecules (Proteins)

- **Cells**
  - White blood cells (leukocytes)

- **Molecules**
  - Cell-cell communication
  - Locally and at a Distance
  - Target pathogens and kill infected cells
Antibodies are proteins
• Produced by B cells
• Fight infection
• Bind specifically to Antigens
Antigen

- Any molecule that stimulates an immune response
- Typically a protein expressed by a pathogen
- But can be anything
- Antibodies Bind Antigens
How Antibodies Work

- Antibodies are specific
- Antibodies are secreted by adaptive immune cells
- Antibodies can be drugs

Mark cells for destruction by immune cells
Monoclonal Antibodies are Essentially Chemically Defined (Identical) Molecules
The Immune System Maintains Balance/Equilibrium/Homeostasis

- The immune system is activated when the body experiences injury, infection, or disease.
- The end result of immune system activation (and subsequent deactivation) is a return to a healthy state.
  - The wound is healed.
  - The infection is resolved.
  - The disease is eradicated = immune surveillance
Cytotoxic T lymphocytes (T cells)

- Major immune cell type that mediates tumor cell killing
- Specific recognition
- Release **cytotoxic** molecules into cell
- Spare neighboring cells

T cell killing a cancer cell
The HPV vaccine is effective for cervical cancer so why don’t we have vaccines for other cancers?

- HPV is virus (foreign pathogen)
- HPV infection causes cervical cancer
- Vaccine is to HPV (not cervical cancer)
Why don’t we have vaccines for other cancers?

- Most cancers are not caused by foreign pathogens (viruses)
- Most cancers arise from spontaneous/random mutations in DNA in normal self tissues
- There is no way to predict what “proteins” to vaccinate against to prevent cancer in any individual
- Vaccines tend to only work if administered in a preventative setting
What is the evidence that the immune system plays a role in cancer control?

- Tumors that contain more T cells (TILs) favor a better prognosis
- Increase risk for cancer as we age, and immune system becomes less functional as we age
- Patients with HIV infection with low T cell numbers are at much greater risk for developing some cancers

T cells proliferate in response to infection

- Millions of T cells in the body!
- Each T cell expresses a unique T cell receptor
- Only those T cells that are specific to the particular infection will proliferate
T cells must be tightly controlled or they will cause autoimmunity and pathology

- Most T cells that are reactive to self proteins die during development
- T cells in the body should express receptors that are “tolerant” to self proteins but not to foreign proteins
- Organ transplant – need a ”Match”, e.g., similar immune proteins between transplant and recipient or T cells will see another individual's immune proteins as foreign and attack the transplant
How are tumors detected by the immune system?

- Mutations in DNA can create a novel (non-self) protein
- Mutated protein (neoantigen) can be recognized as foreign by T cells

Cancers differ greatly in mutational burden

- Formation of neoantigens
  - Frequently
  - Regularly
  - Rarely

Mutation Prevalence
Activated T cells express an inhibitory protein PD-1 that binds PD-L1 expressed on tumor cells.

- PD-1 binding to PD-L1 shuts down T cells
- “Immune Checkpoint”
Drugs that interfere with PD-1:PD-L1 are now FDA approved cancer immunotherapies

- Blocking PD-1:PD-L1 releases the brakes on T cells
- Drugs that block PD:PD-L1 are antibodies
Tumor cells often highly express PD-L1
Which cancer types respond to PD-1/PD-L1 blockade?

Mutation Prevalence

- Pilocytic astrocytoma
- AML
- ALL
- Thyroid
- Kidney chromophobe
- CIL
- Medulloblastoma
- Neuroblastoma
- Glioma low grade
- Glioblastoma
- Prostate
- Ovary
- Myeloma
- Pancreas
- Breast
- Kidney papillary
- Lymphoma B-cell
- Kidney clear cell
- Head and neck
- Liver
- Cervix
- Uterus
- Bladder
- Colon rectum
- Lung small cell
- Esophagus
- Stomach
- Lung adenocarcinoma
- Melanoma

Formation of neoantigens

- Frequently
- Regularly
- Rarely
Which cancer types respond to PD-1/PD-L1 blockade?

- In general, those cancers with a lot of mutations
- Greater # mutations = Greater immunogenicity (more foreign)
2018 Nobel Prize in Physiology & Medicine:

- Decades of **basic immunology research** using mouse models led to the discovery of a new way to treat cancer

Tasuku Honjo, MD, PhD  James P. Allison, PhD,
Entered a New Era of Cancer Therapy
Immune checkpoints inhibitors have benefit in only a subset of cancer patients

- Response rates are high (45-60%) in melanoma or subset of tumors with many of mutations!
- Response rates are more typically ~15-30% (but can be dismally low in some cancer types)
- Why?
Heterogeneity (diversity) in T cell infiltrate in pancreatic cancer

Few T cells “Cold”  Many T cells “Hot”

Tumor cells

Stromnes I, et al., CIR, 2017
Activation of self-reactive T cells leading to “off-tumor” toxicity

- Tumor-specific T cell
  - PD-1+
  - Attack Tumor

- Auto-reactive (self-specific) T cell
  - PD-1+
  - Attack Normal cells

Antibody to PD-1
Immune-related adverse events (irAE) can correlate with clinical efficacy

Freeman-Keller et al., CCR, 2016
What are the current challenges?

- **Immune checkpoint inhibition + drug X,Y,Z…**
  - Critical to model the human disease faithfully
  - Directly test for safety in cancer patients that have not responded to standard of care in early phase, small clinical trials

- **Identify patients more likely to respond**
  - High mutational burden
  - High PD-L1

- **Identify mechanisms of resistance**

- **Identify new immune checkpoints**
  - CD200, Tigit, Tim-3, NKG2A, Lag3…..

- **Identify when to stop treatment**
  - Expensive
  - Durable control yet not cancer elimination
Preclinical research in Minnesota: novel combinations to enhance immunotherapy

Cell Reports
Combination PD-1 and PD-L1 Blockade Promotes Durable Neoantigen-Specific T Cell-Mediated Immunity in Pancreatic Ductal Adenocarcinoma

Authors
Adam L. Burack, Ellen J. Spartz, Jackson F. Raynor, Iris Wang, Margaret Olson, Ingram M. Stromnes

Reprogramming responsiveness to checkpoint blockade in dysfunctional CD8 T cells
Christine E. Nelson, Lauren J. Mills, Jennifer L. Curtan, Emily A. Thompson, Davis M. Seelig, Siddheshwar Bhela, Clare F. Quarnstrom, Brian T. Fife, and Vaiva Vezys

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How can the immune system be manipulated to target tumors that don’t have many mutations?
Genetically engineered T cell therapies

- **Chimeric antigen receptor (CAR) T cells**
  - Synthetic receptor expressed in a patient's own T cells
  - CAR binds an extracellular protein expressed on cancer cells

- **T cell receptor (TCR) T cells**
  - T cells are modified to express a tumor-specific TCR
  - TCRs can recognize intracellular proteins
What is a Chimeric Antigen Receptor (CAR)?

Adapted from Robert Mazjner & Crystal Mackall, *Nature Medicine*, 2019
CARs are further modified to enhance T cell activation

Adapted from Robert Mazjner & Crystal Mackall, *Nature Medicine*, 2019
CAR T cells are infused into a cancer patient: Living therapy

Patients are enrolled who have not responded to many other aggressive treatments (chemotherapy, radiation, bone marrow transplantation)

Adapted from Robert Mazjner & Crystal Mackall, *Nature Medicine*, 2019
CAR-T cell therapy is FDA approved for B cell malignancies

- CAR T cells are specific to a molecule expressed on malignant B cells, CD19
- CD19 is also expressed on normal B cells
- CD19 CAR T cells proliferate robustly, kill tumor and also kill normal B cells in patients
CD19 CART cell therapy has toxicity

- Cytokine Release Syndrome
- Neurological Toxicity
- Toxicity can be fatal if not managed
- Toxicity can be a sign that the therapy is working
- Currently no way to predict who will respond and how
- Toxicity is highly unpredictable among individuals
Large B cell Lymphoma → Manufacturing Failure → Primary Resistance → Complete Response → Relapse → Sustained Response

- CD19 CART cell therapy outcomes

- Antigen+
- Antigen-
Immune Editing and Tumor escape

-Antigen-loss variants- relapsed malignant B cells no longer express CD19
Loss of T cell function: Exhaustion

Relapse

Complete response

Antigen$^+$

Primary Resistance

T cell infusion

Antigen$^-$

Tumor

Dysfunctional T Cells

Fibroblast

Tumor cell

Myeloid

Regulatory cytokines
Can CAR T cells work in other types of malignancies?

- Identifying a protein that is unique to cancer and is also reproducibly expressed among cancers is challenging.

- T cell receptor engineering (alternative approach to target mutations that are expressed inside the cell)
Gene Editing T cells for Cancer Therapy

Immune cells (brown) attack a cancer cell. Using CRISPR could make the immune cells more potent.

STEVE GSCHMEISSNER/SCIENCE SOURCE
Final thoughts:

- Cancer is not a single disease
- Immunotherapy is changing the standard of care
- Challenging to separate efficacy from toxicity
- Toxicities are hard to predict (not like chemotherapy)
- Field is moving so fast, technologies are unprecedented, how can good quality science keep up?
- Funding basic research is critical
- Interdisciplinary Team Science (U of M!)
- Since most drugs fail in clinic, we need better preclinical models
Stromnes Lab
Dr. Adam Burrack
Anna Panek
Jackson Raynor
Meagan Rollins
Ellen Spartz
Iris Wang
Advancing Knowledge, Enhancing Care