Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms & Their Application to Clinical Trials of Vaccines

Part 1: The Basics

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Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms

**Definition of IMMUNE SYSTEM**

-the bodily system that protects the body from foreign substances, cells, and tissues

-by producing the immune response which includes the...

(1) thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract and bone marrow),

(2) macrophages, lymphocytes including the B cells and T cells, and

(3) antibodies and cytokines
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Basic immunologic mechanisms

II. Application to prevention & treatment of cancer

1. Antibodies: as drugs

2. Vaccines: general principles & your vaccine trials & more…

   I) Vaccines to prevent cancers caused by infectious agents

   II) Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
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Context: Premalignant Progression to Cancer

What is Carcinogenesis?

Breast Cancer
Cervical Cancer
Colorectal Cancer
Prostate Cancer

Normal

Initiated

Precancer/Premalignancy

Cancer

Genetic changes cumulative
Context: Premalignant Progression to Cancer

What is Carcinogenesis?

Cancer is a “genetic disease”
- not so simple!

Microenvironment (includes the immune system)

See Mukherjee New Yorker article – “seed versus soil”
Context: Premalignant Progression to Cancer

What is Carcinogenesis?

Cancer is a “genetic disease”

preventive intervention

Microenvironment (immune system)

Genetic changes cumulative

See Mukherjee New Yorker article – “seed versus soil”

- Drugs
- Immune therapies
Microenvironment: immune system

Intact immune system \(\rightarrow\) immunoediting

![Immune System Diagram](Adapted from Zitvogel, Nature Reviews Immuno1ology 6 October 2006 Figure 1)
As carcinogenesis progresses, the immune system gets suppressed = **immunoediting**: “Good” immune cells go away & “bad” cells emerge & dominate.
Hematopoiesis

Physical components of the immune system:

**Cells** of the immune system: macrophages, lymphocytes (B cells, T cells), etc.

**Molecules** of the immune system: Antibodies, cytokines, etc.
Hematopoiesis

Two main lineages

Cells of the immune system: macrophages, lymphocytes (B cells, T cells), etc.

Molecules of the immune system: Antibodies, cytokines, etc.
Basic Immunological Mechanisms:

**Innate versus Adaptive Immunity**

I. Basic immunologic mechanisms

**hierarchy of the immune system**

II. Application to prevention & treatment of cancer

1. Antibodies: as drugs

   a. **Innate versus Adaptive Immunity** – 2 compartments

   b. Focus on Adaptive Immunity – 2 cell types:

      B cells and T cells

      (1) B cells = humoral immunity (antibodies)

      (2) T cells = cellular immunity (cells do the work)

         (a) Cytolytic T cells/CTLs (CD8)

         (b) T helper cells (CD4)

2. Vaccines: general principles & your vaccine trials & more…

I) Vaccines to prevent cancers caused by infectious agents

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1- Type 1 response

2- Type 2 response
## Basic Immunological Mechanisms: Innate versus Adaptive Immunity

### 2 Compartments of Immunity

<table>
<thead>
<tr>
<th>Innate</th>
<th>versus</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No specific molecule/antigen needed to induce innate response</strong></td>
<td></td>
<td><strong>Specific molecule/antigen needed to induce adaptive response</strong></td>
</tr>
<tr>
<td>Nonspecific immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quick response to generalized “inducer” (0-4 hours)</strong></td>
<td></td>
<td><strong>Response takes time/slow (&gt;96 hours)</strong></td>
</tr>
<tr>
<td>Short-lived response</td>
<td></td>
<td><strong>Lasts long time (lifelong)</strong></td>
</tr>
<tr>
<td>Macrophages, dendritic cells, natural killer cells, neutrophils</td>
<td></td>
<td><strong>T cells, B cells, dendritic cells</strong></td>
</tr>
<tr>
<td><strong>- memory</strong></td>
<td></td>
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</tr>
</tbody>
</table>
Innate immunity: CELLS OF THE INNATE IMMUNE SYSTEM

- Skin
- Epithelial barriers
- Phagocytes
- Dendritic cells
- Plasma proteins
- NK cells

- Neutrophil
- Dendritic cell
- Macrophage
- Natural Killer

Antigen Presenting Cell (Adaptive immunity)

Myeloid lineage

http://missinglink.ucsf.edu/lm/immunology_module/prologue_objectives/obj02.html
Adaptive Immunity

Humoral versus Cellular immunity

B cells

T cells

The cell does the work

B cell receptors

Humoral immunity in cancer: important in fighting viruses (including those causing cancer) e.g. HPV vaccines, Covid-19 vaccines
Adaptive Immunity: B cells

- Humoral v Cellular Immunity

B cells

- Antibodies

Immunoglobulin (Ig)

Humoral immunity in cancer: important in fighting viruses (including those causing cancer) e.g. HPV vaccines, Covid-19 vaccines
Adaptive Immunity: T cells = cellular immunity (cells do the work)

CD4 subtypes

CD=cluster of differentiation
Adaptive Immunity: T cells = cellular immunity (cells do the work)

In cancer:
We want T\textsubscript{H}1 cells - to kill cancer cells
We do not want Treg & T\textsubscript{H}2 cells
Adaptive Immunity: T cells = cellular immunity (cells do the work)

In cancer:
- We want $T_{H1}$ cells - to kill cancer cells
- We do not want Treg & $T_{H2}$ cells

In normal cells:
- We want Treg cells - to protect these normal cells

Distinguish Self from Non-self: save the self!

Immune Tolerance
Adaptive Immunity: Cellular Immunity (T cells)

Antigen Presentation & T Cell Activation

Specific part of T cell activation

Infection (virus)
Cancer
Bad Antigen

APC/
antigen presenting cell

Processed Bad Antigen (epitope)

TCR

MHC/HLA

T cell

Signal 1 specific

IFN-γ
IL-17

T cell activation

MHC = Major Histocompatibility Antigen
TCR = T cell receptor
HLA = Human Leukocyte Antigen
Adaptive Immunity: Cellular Immunity (T cells)

Antigen Presentation & T Cell Activation

Generalized part of T cell activation

Infection (virus)  
Cancer  
Bad Antigen

Signal 2  
Nonspecific  
(CD80,86)  
B7

Signal 1  
specific

APC/antigen presenting cell

Processed Bad Antigen (epitope)

MHC/HLA  
Co-stimulatory molecule

TCR

IFN-\(\gamma\)  
IL-17

T cell

MHC = Major Histocompatibility Antigen  
TCR = T cell receptor  
HLA = Human Leukocyte Antigen
Adaptive Immunity: Cellular Immunity

Antigen Presentation & T Cell Activation

Antagonizing T cell activation

Infection (virus)
Cancer

Bad Antigen

Processed Bad Antigen (epitope)

APC/ antigen presenting cell

MHC/HLA

B7 or PD-L1

CD80,86

CD28

TCR

B7

CTLA-4 or PD-1

T cell

T cell inactivation

= immune suppression

CTLA-4 = cytotoxic T-lymphocyte-associated protein
PD-1 = programmed cell death protein-1
Adaptive Immunity: Cellular Immunity

**CD4/helper** versus **CD8/cytotoxic** T cells

- **Infection**
- **Cancer**
- **Bad Antigen**
- **Processed Bad Antigen**
- **APC/antigen presenting cell**

**CD4 / Helper T cell**
- **MHC class II** restricted
- **Presented antigen = Epitope**
- **Signal 1 specific**

**CD8 / cytotoxic T cell / CTLS (cytotoxic T lymphocytes)**
- **MHC class I** restricted

**MHC = Major Histocompatibility Antigen**
**TCR = T cell receptor**
**HLA = Human Leukocyte Antigen**
Adaptive Immunity: Cellular Immunity:
-Antigen Presentation, T Cell Activation: What are APCs?
-CD4 vs CD8 and CD4: T_{H1} vs T_{H2}

**Professional APCs**
- Dendritic cells
- Macrophages
- Certain B-cells
- Certain activated epithelial cells
- Fibroblasts (skin)
- Thymic epithelial cells
- Thyroid epithelial cells
- Glial cells (brain)
- Beta cells (pancreas)
- Vascular endothelial cells

**Non-Professional APCs**

**Mature helper CD4+ T cell** (T_{H1} or T_{H2})
- IL-2, IFNγ

**Mature cytotoxic CD8+ T cell** (CTL)
- IL-4

**Humeral immune response** = B cells

**Cellular immune response**
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II. Application to prevention & treatment of cancer

1. Antibodies: as drugs “passive immunity”

2. Vaccines: general principles & your vaccine trials & more…

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1. Antibodies: as drugs “passive immunity”

Examples:
Herceptin (trastuzumab) – binds Her2 receptor on breast cancer cells
Rituxan (rituximab) – binds CD20 on B cells in non-Hodgkin’s lymphoma, chronic lymphocytic leukemia

------used as drugs “off-the-shelf”
CONVALESCENT SERUM LINES UP AS FIRST-CHOICE TREATMENT FOR CORONAVIRUS

ANTIBODIES FROM BLOOD DONATED BY PEOPLE WHO RECOVERED FROM THE ILLNESS AND HYPER-IMMUNOGLOBULINS ARE BECOMING TREATMENTS OF CHOICE FOR COVID-19, WITH RECOMBINANT POLYCLONAL ANTIBODY APPROACHES
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SUCCESS OF VACCINES against infectious diseases

Successful immune response: B cell -> antibodies

**Graphs showing the reduction in reported cases of Diphtheria, Polio, and Measles from 1940 to 1990.**
<table>
<thead>
<tr>
<th>Date</th>
<th>Trial</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAY2013-01-01</td>
<td>MUC 1/COlon</td>
<td>Non-infection associated cancer</td>
</tr>
<tr>
<td>MAY2013-02-01</td>
<td>VACCINE/HCV LIVER</td>
<td>Infection associated cancer</td>
</tr>
<tr>
<td>MAY2016-08-01</td>
<td>MUC-1/LUNG</td>
<td>Non-infection associated cancer</td>
</tr>
<tr>
<td>MDA2014-04-02</td>
<td>VADIS/BREAST</td>
<td>Non-infection associated cancer</td>
</tr>
<tr>
<td>NWU2015-06-02</td>
<td>HPV 9-VALENT/TRANSPLANT</td>
<td>Infection associated cancer</td>
</tr>
<tr>
<td>UAZ2014-03-01</td>
<td>PROSTVAC/PROSTATE</td>
<td>Non-infection associated cancer</td>
</tr>
<tr>
<td>UAZ2015-05-01</td>
<td>HPV-9-VALENT/PEDIATRICS</td>
<td>Infection associated cancer</td>
</tr>
<tr>
<td>UWI2014-03-01</td>
<td>WOKVAC/BREAST</td>
<td>Non-infection associated cancer</td>
</tr>
</tbody>
</table>
**KEY COMPONENTS OF VACCINES**

**the specific component:**
- **the Antigen**
  - Peptide-long vs short
  - Genetic vaccines:
    - DNA (encodes a protein)
    - RNA vaccines
    - Viral vector
  - Pentamer of a protein

**the nonspecific component:**
- **the Adjuvant**
  - Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens *in vivo*

**Adjuvants** = agents added to vaccine formulations that enhance the immunogenicity of antigens *in vivo*
KEY COMPONENTS OF VACCINES

The specific component:

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**Vaccines**

- Genetic vaccines:
  - DNA (encodes a protein)
  - RNA vaccines
  
- Viral vector
- Pentamer of a protein

**Cell-based vaccines**
Vaccines - “active immunity”
Adaptive Immune System

KEY COMPONENTS OF VACCINES

Antigen comes from the thing you want to destroy: cancer cell, pathogen

the **specific** component: **the Antigen**

- Peptide - long vs short

the **nonspecific** component: **the Adjuvant**

Epitope (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells); main immunogenic part of the vaccine

VLP

Pentamer of a protein

- Viral vector

Cell-based vaccines

**Adjuvants** = agents added to vaccine formulations that enhance the immunogenicity of antigens *in vivo*
Vaccines - “active immunity”
Adaptive Immune System

**KEY COMPONENTS OF VACCINES**

the specific component:

the Antigen

- Peptide-long vs short
- Pentamer of a protein

Epitope (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells)

How do we pick the antigen/epitope to target?

the nonspecific component:

the Adjuvant

Adjuvant non-specific stimulation to immune system = INNATE

- Non-specific Immuno-Modulators = INNATE only
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

Elicits a specific response from the body’s own immune system: **Focus on the Antigen!**

I. Overview: Context of immunologic mechanisms: carcinogenesis

II. Structure/physical components and hierarchy of the immune system

I. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs “passive immunity”

2. Vaccines: general principles & your vaccine trials
   
   I) Vaccines to prevent cancers caused by infectious agents
   
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20% of cancers worldwide are attributable to infectious agents (estimated 30% in developing & 15% in developed countries).

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Agent (group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Schistosoma haematobium (blood fluke)</td>
</tr>
<tr>
<td>Cervix</td>
<td>HPV (papillomavirus)</td>
</tr>
<tr>
<td>Liver</td>
<td>HBV (hepadnavirus)</td>
</tr>
<tr>
<td>Bile duct</td>
<td>HCV (flavivirus)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>EBV (herpes virus)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Helicobacter pylori (bacterium)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell</td>
<td>HTLV-I (retrovirus)</td>
</tr>
<tr>
<td>Burkitt</td>
<td>EBV (herpesvirus)</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>EBV (herpesvirus)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
</tr>
<tr>
<td>Kaposi</td>
<td>HHV8 (herpesvirus)</td>
</tr>
</tbody>
</table>

Viral Pathogens Associated With Cancer

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cancer Site</th>
<th>Attributable Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>Cervix</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Anus</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Vulva, vagina</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Penis</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Mouth</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Oropharynx</td>
<td>12</td>
</tr>
<tr>
<td>HBV</td>
<td>Liver</td>
<td>54</td>
</tr>
<tr>
<td>HCV</td>
<td>Liver</td>
<td>31</td>
</tr>
<tr>
<td>EBV</td>
<td>Burkitt’s lymphoma</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s lymphoma</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal carcinoma</td>
<td>98</td>
</tr>
<tr>
<td>KSHV</td>
<td>Kaposi’s sarcoma</td>
<td>100</td>
</tr>
<tr>
<td>HTLV</td>
<td>Adult T cell leukemia/lymphoma</td>
<td>2</td>
</tr>
</tbody>
</table>
Vaccines to prevent cancers caused by infectious agents

Pathogenesis of Virus-Associated Cancer

Viral exposure → Viral infection → Chronic Viral infection → Precancer conditions → Cancer
Vaccines to prevent cancers caused by infectious agents

Pathogenesis of Virus-Associated Cancer

*Therapeutic* from an infectious disease standpoint; actually *prophylactic* from a cancer standpoint
Vaccines to prevent cancers caused by infectious agents

Targets a specific antigen = ADAPTIVE

How do we pick the antigen/epitope to target?

The infectious agent is FOREIGN/NON-SELF

→ pick the antigen from this!
I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

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WHAT DOES THE IMMUNE SYSTEM SEE IN CANCER?

Immune Tolerance:
Host’s defense system: distinguish Self from Non-self

T tolerance signals

Activated TH1/CD4 & CTL/CD8 cells:
Promote immune response

Attack signals

T regulatory cells (Tregs): Suppress immune response

Prevents autoimmune responses

But also prevents anti-cancer responses
Vaccines to prevent cancers not caused by infectious agents

Targets a specific antigen = **ADAPTIVE**

**How do we pick the antigen/epitope to target?**

The antigen is from ALTERED SELF cells → tolerance = self vs non-self!

**Selection of appropriate antigen** in non-infection-associated cancers, the antigens are **modified normal antigens**, taken from cancer cells.

Concern is:

We do not want the immune system to attack the normal cells (don’t want toxicity),

We only want the immune system to attack the cancer cells, which have modified normal antigens.

- **Self Antigen**
- **Nonself/Foreign, Unwanted Antigen**

**Prevent autoimmune responses**

*Tolerance signals*

**But want anti-cancer responses**

*Attack signals*
Vaccines to prevent non-infection associated cancer: the Antigen Mechanism of Tumor Antigen:

- **Tumor Associated Antigens (TAAs)/ neoantigens**
  - “self”- antigens or normal cellular proteins that become immunogenic during the malignant process

- **Mechanisms** by which normal cell protein becomes aberrant in cancer (“abnormal-self”)

  1- **acquisition of mutations** (melanoma antigen MAGE1)

  2- **overexpression** of cancer associated proteins (breast cancer HER2/NEU)

  3- **post-translational modifications** (abnormal glycosylation (colon cancer antigen MUC-1))
Keep Tuned

More to come...

August 3, 2020