Cancer Immunology and Immunotherapy

---- The battle between immune system and cancers

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Basic knowledge of cancer

- What is Cancer?
- How does cancer occur?
- How many types of cancers?
- Current therapeutic strategies for cancers
Definitions of Cancer

• Cancer consists of single clones or several clones of cells that are capable of independent growth in the host.

• Cancer cells arise from host cells via neoplastic transformation or carcinogenesis.

• Physical, chemical and biological agents may cause cancer. -- carcinogens
Carcinogens

- **Radiation**: Ultraviolet light, sunshine; X-rays, radioactive elements induce DNA damage and chromosome brakes.
- **Chemical**: smoke and tar, countless chemicals that damage DNA (mutagens).
- **Oncogenic viruses**: insert DNA or cDNA copies of viral oncogenes into the genome of host target cells.
- **Hereditary**: certain oncogenes are inheritable.
Neoplastic Transformation -- Carcinogenesis

• Activate growth regulatory genes: Growth factor receptors (erbA, -B, fims, neu); molecules of signal transduction (src, abl, ras); transcription factors (jun, fos, myc)- referred to as oncogenes.

• Genes that inhibit growth: (p53 controls DNA repair and cell proliferation; Rb)-suppressor oncogenes.

• Genes that regulate apoptosis: bcl-2, Bax, Bid.
Classification of cancer

- **Carcinoma**: epithelial origin involving the skin, mucous membranes, epithelial cells in glands
- **Sarcoma**: cancer of connective tissue, i.e. liposarcoma, fibrosarcoma
- **Lymphoma**: T-cell, B-cell, Hodgkin’s, Burkitt’s lymphomas; - *solid tumors*
- **Leukemia**: *disseminated tumors* - lymphoid, myeloid, acute and chronic
Current strategies to combat cancers

- Mechanics -- surgery, 1600 BC
- Physics -- radiotherapy, 1896
- Chemistry -- chemotherapy, 1942
- Biology -- immunotherapy, 1976
Advantages of Immunotherapy for cancer

- Cancer cells are immunogenic
- Single cell kill
- Migrate to tissue
- Memory
- Specific
- Life-long protection
Cancer Immunology and Immunotherapy
• How does the immune system eliminate cancer cells?
• How do cancer cells escape from Immunosurveillance?
• How can we help to win the battle between immune system and cancers? – Cancer immunotherapy
• Examples
Cancer Immunosurveillance

- The hypothesis was first proposed by Ehrlich in 1909, and modified by Thomas and Burnet in 1957.
- Immunosurveillance: the immunological resistance of the host against the development of cancer.
- Now referred to “cancer immunoediting” encompassing 3 phases: elimination, equilibrium and escape.
Cells of the Immune System

- Bone graft
- Macrophage
- Erythrocytes
- Eosinophil
- Mast cell
- Basophil
- Megakaryocyte
- Neutrophil
- Lymphoid progenitor cell
- T lymphocyte
- Natural killer cell
- B lymphocyte
- Dendritic cell
- Bone
- Hematopoietic stem cell
- Marrow
- Multipotential stem cell
- Myeloid progenitor cell
- Platelets
- Myeloid progenitor cell
- Erythrocytes
- Monocyte
- Megakaryocyte
- Neutrophil
- Lymphoid progenitor cell
- T lymphocyte
- Natural killer cell
- B lymphocyte
- Dendritic cell
Army of the host to fight cancers

- Antibody
- Macrophage
- Cancer cell
- Helper T cell
- NK cell
- Cytotoxic T cell
- Dendritic cell
- Cytokine
- Chemokine

Cytotoxic T cells (CTLs)

CD8+ T cells: attaching to class I MHC - peptide complex, they destroy cancer cells by perforating the membrane with enzymes or by triggering an apoptotic pathway.
Helper T cells

CD4+ T cells: reacting to class II MHC-peptide complex, they secrete cytokines.

cytotoxic T cell response (Th1 helper T cells)

antibody response (Th2 helper T cells)
Dendritic Cells

The professional antigen-presenting cells in the final common pathway for activating naïve T cells.

A novel subset of dendritic cells [IFN-producing killer DC] (IKDC): TRAIL & perforin- tumor cell lysis; via T cell; IFNγ-angiogenesis
Other cells

NK cells: after activation, directly killing tumor cell

NKT cells: TRAIL/perforin- tumor cell lysis;

IFN$\gamma$-angiogenesis

Macrophages: antigen presenting
Cytokines

- Regulating the innate immune system: NK cells, macrophages, and neutrophils; and the adaptive immune system: T and B cells
- IFN-α -- upregulating MHC class I, tumor antigens, and adhesion molecules; promoting activity of B and T cells, macrophages, and dendritic cells.
- IL-2 -- T cell growth factor that binds to a specific tripartite receptor on T cells.
- IL-12 – promoting NK and T cell activity, and a growth factor for B cells
- GM-CSF (Granulocyte-monocyte colony stimulating factor) -- reconstituting antigen-presenting cells.
Antibody - produced by B cells

- **Direct attack**: blocking growth factor receptors, arresting proliferation of tumor cells, or inducing apoptosis.
  - is not usually sufficient to completely protect the body.
- **Indirect attack**: major protective efforts
  1. **ADCC** (antibody-dependent cell mediated cytotoxicity)
     - recruiting cells that have cytotoxicity, such as monocytes and macrophages.
  2. **CDC** (complement dependent cytotoxicity)
     - binding to receptor, initiating the complement system, 'complement cascade', resulting in a membrane attack complex, causing cell lysis and death.
Tumor elimination
How does cancer progress?
Cancer Immunology/Immunotherapy

• How does the immune system eliminate cancer cells?
• How do cancer cells escape from Immunosurveillance?
• How can we help to win the battle between immune system and cancers? – Cancer immunotherapy
• Examples
Mechanisms of cancer escape from the Immunosurveillance

1. **Altering Their Characteristics**:
   - Loss/downregulation of MHC class I
   - Down-regulation, mutation, or loss of tumor antigens
   - Loss of costimulation

2. **Suppressing the Immune Response**:
   - Ineffective signals to CTL
   - Alteration in cell death receptor signaling
   - Immunosuppressive cytokine

3. **Outpacing the Immune Response**: Tumour cells can simply proliferate so quickly that the immune response is not fast enough to keep their growth in check
How cancer cells avoid immunosurveillance

1. **Weapons from tumors**

2. **Defects of immune system**
(1) Loss/down-regulation of HLA class I (MHC I)

- Total loss: β2 microglobulin mutation, alteration in antigen processing machinery
- Haplotype loss: LOH in chromosome 6
- HLA allelic loss: mutations of HLA class I genes
- HLA-A, B, C locus down-regulation: alteration of transcriptional factors
- Compound phenotype: 2 or more independent mechanisms
(2) Down-regulation, mutation or loss of tumor antigens

Tumor antigens (TA)
Tumor associated antigen (TAA)

- Complete loss
- Down-modulation
Tumor Antigens

- **Altered self:** K-ras, products of normally unexpressed genes (MAGE, BAGE, GAGE), proteins of alternative reading frame, - of post-translational modification, - different orders of glycosylation (mucin-CA125, MUC1).
- **Viral antigens:** EBNA, E-6,E-7, papilloma virus antigens of cervical carcinomas.
- **Oncofetal antigens:** alpha-fetoprotein (AFP), Carcinoembryonic antigen (CEA)
- **Autoantigens:** overexpression - c-myc in lymphomas, leukemias; HER-2/neu epidermal growth factor receptor-breast cancer (Herceptin).
(3) Loss of costimulation

Costimulatory molecules recognized:

- B7.1(CD80)
- B7.2(CD86)
- CD40 L
- CD27, CD30
- 4-1BB
- OX40
- ICAM-1
T cell Activation

Co-stimulation

No Activation

Loss of costimulation
The initiation of T cell responses requires two distinct signals.

The role of signals 1 and 2 in T-cell activation.

No signal 2 or costimulation because of lack of B7.
(4) Alterations in cell death receptor signalling

- Defects in Fas/FasL signaling system: resistance to apoptosis
- Apoptosis resistance: overexpression of Bcl-2
(5) Immunosuppressive cytokines

- a number of immunosuppressive cytokines.
- IL-10 inhibits antigen presentation and IL-12 production.
- TGF-beta induces overproduction of IL-10.
- VEGF (vascular endothelial growth factor), avoid immune recognition, inhibit the effector function, prevent T cell activation, cytokine production.
Inhibition of antitumour response by TGF-β. a | Production of transforming growth factor-β (TGF-β) will inhibit maturation and antigen presentation by dendritic cells, thereby diminishing their T-cell-stimulating capacity. b | Apoptotic cell death of tumour cells can contribute to TGF-β production at the tumour site as well as inhibition of function of dendritic cells that process those cells. Once APCs bring the tumour antigen to the lymphoid organ to present it to T cells, activation of T cells can be inhibited by TGF-β produced by the tumour cells (c) or the immune cells in response to the tumour antigens (d). e | Even if some precursor cytotoxic T lymphocytes (pCTLs) are activated under such inhibitory conditions, TGF-β would still inhibit their differentiation into effector CTLs. PSR, phosphatidylserine receptor; TReg, T-regulatory cell.
(6) Induction of Immunosuppressive cells

- CD4+CD25+ T cells (constitute 5-10% of CD4+ T cells): immunological tolerance to self-antigens, inhibition of T cell proliferation.

- Gr1+CD11b+ myeloid cells:
  -- Expressing the granulocyte-monocyte markers Gr1+CD11b+, accumulate in spleens, lymph nodes and blood of tumor-bearing mice.
  -- Inhibiting antibody production, CTL generation, T cell function, lymphocytic proliferation, CD3 ζ chain expression.
Regulatory T Cells

T cells compete for same antigen

Cytotoxic T cell
Mature dendritic cell
Regulatory T cell
STOP
STOP
STOP

T cells compete for cytokine signals

Regulatory T cells
Proliferation
Potential sources for regulatory T cells
Possible suppressive mechanisms regulatory T cells

(a) APC → Induction of B7-H4 expression → T-cell cycle arrest

(b) APC → Activated regulatory T cell → Perforin and Granzyme B → APC and T-cell apoptosis

(c) IDO → Metabolized tryptophan → Decreased expression of:
- MHC molecules
- CD80 and CD86
- IL-10

(d) IL-10, TGFβ → APC dysfunction → T-cell anergy
(7) Production of other suppressive factors

- **IDO (Indoleamine 2, 3-dioxygenase):** expressed in most human tumour tissues and splenic DC subsets, leading to blockage of proliferation of T cells
- **ganglioside** (sialic acid containing glycosphingolipids)
- **Prostaglandins**
Summary: Main defences of the tumors against immunity

1) Alteration of MHC class I and tumor antigen expression

2) Dysregulated expression of adhesion / costimulatory molecules by tumor and/or antigen-presenting cells

3) Changes in T-cell signal transduction molecules, i.e. cell death receptor signalling

4) Induction of immune suppressive cytokines

5) Induction of immunosuppressive cells

6) Secretion of suppressive factors
1. Weapons from the tumors

2. Defects of immune system
• Immune defects in T cells

• Malfunction of dendritic cell system
Immune defects in T cells in cancer

- Alterations in the expression of signal transduction molecules in immune cells.
- Loss of CD $3\zeta$ chain. TCR-CD3 complex. It functions as a single transducer upon antigen binding.
- Receptor-mediated apoptosis of T cells contributes to T cell dysfunction.
Receptor-mediated apoptosis of lymphocytes
Malfunction of dendritic cell system

- Tumor-mediated inhibition of DC generation, differentiation and maturation
- Functional impairment of DCs: lack of expression of costimulatory molecules
- Induction of DC apoptosis by tumors
<table>
<thead>
<tr>
<th>Tumor-derived factors</th>
<th>Effect on DCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>tumor infiltration and generation</td>
</tr>
<tr>
<td>TGF-beta</td>
<td>CD80 and CD86 expression</td>
</tr>
<tr>
<td>Gangliosides</td>
<td>inhibition of dendropoiesis from hematopoietic precursor cells</td>
</tr>
<tr>
<td>IL-6</td>
<td>differentiation</td>
</tr>
<tr>
<td>IL-10</td>
<td>differentiation, CD80/CD86/CD40 expression, IL-12 production</td>
</tr>
<tr>
<td>Prostanoids, prostaglandins</td>
<td>differentiation</td>
</tr>
<tr>
<td>PgE2</td>
<td>generation</td>
</tr>
<tr>
<td>NO</td>
<td>induction of apoptosis</td>
</tr>
</tbody>
</table>
Summary

How do tumors progress?
a. Tumour-cell precursor
   Peptide–MHC class I molecule
   Immunoselection
   Loss of tumour antigens and IFNγR or signalling components
   Tumour-cell precursor
   CD8⁺ T cell

b. Tumour
   NOS2 and ARG1
   Tumour-specific T cell
   Recruitment
   Maturation of DCs in lymph nodes
   Suppression of tumour-cell lysis directly by inhibition of CTLs or indirectly by inhibition of DCs

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c. CD80 or CD86
   IFNγ
   IDO
   Tryptophan
   Kynurenines
   Inhibition of CD8⁺ T-cell proliferation; promotion of CD4⁺ T-cell apoptosis

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e. Immature DC
   CD8⁺ T cell
   Regulatory T cell
   IL-10
   CD8⁺ T cell
   T-cell anergy

---

g. Invariant TCR
   CD1d
   Antigen uptake
   IL-13
   IL-13R
   STAT6
   TGFβ
   MSC
   Apoptosis

h. Recruitment to tumour
   Tumour cell
   Inflammation
   DC
   Angiogenesis
Activation versus suppression of immunity during tumor progression
The fortune of tumor cells depends on the battle between immune system and tumor cells.
The defense of tumor overweighs the anti-tumor immunity

Cytotoxic CD8 cells
Dendritic cells
Macrophages
Cytokines
Antibodies

Antigen/MHC loss
T-cell dysfunction
Suppressive cytokine
Suppressive T cells
Overweighing effector cells

Balance
Cancer Immunology/Immunotherapy

- How does the immune system eliminate cancer cells?
- How do cancer cells escape from Immunosurveillance?
- How can we help to win the battle between immune system and cancers? – Cancer immunotherapy
- Examples
Tumor Immunotherapy

Strategies to improve the tumor-associated immune response by either boosting components of the immune system that produce an effective immune response or by inhibiting components that suppress the immune response.
Immunotherapy --- Reverse the imbalance
# Strategies to supplement the missing or insufficient immune elements

<table>
<thead>
<tr>
<th>Immune elements</th>
<th>Enhancing ‘the enhancer’</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells</td>
<td>Injection of cytotoxic T cells</td>
</tr>
<tr>
<td>Dendritic Cells</td>
<td>DC vaccination</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>Injection of activated NK cells</td>
</tr>
<tr>
<td>TAA</td>
<td>Peptide, TAA-vector vaccination</td>
</tr>
<tr>
<td>Effector cytokines</td>
<td>IL-2, IL-12</td>
</tr>
</tbody>
</table>
## Strategies to block the suppressive mechanisms

<table>
<thead>
<tr>
<th>Suppressive elements</th>
<th>Inhibiting ‘the inhibitors’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory T cells</td>
<td>Blocking their function</td>
</tr>
<tr>
<td>dysfunctional DCs</td>
<td>Blocking the pathway</td>
</tr>
<tr>
<td>Suppressive cytokines</td>
<td>Blocking potential common cytokine signalling</td>
</tr>
<tr>
<td>Suppressive factors</td>
<td>Blocking their function</td>
</tr>
</tbody>
</table>
Main Mechanisms of Immunotherapy

• Stimulating the antitumor response, either by increasing the number of effector cells or by producing soluble mediators.

• Decreasing suppressor mechanisms.

• Altering tumor cells to increase their immunogenicity and make them more susceptible to immunologic defences.

• Improving tolerance to cytotoxic drugs or radiotherapy, such as stimulating bone marrow function with GM-CSF.
History: Non-specific approach

- 1892 - WB Coley observed tumour regression after bacterial infections
- BCG vaccine to treat bladder carcinoma
- 1970-80’s – cytokines
  - includes interferons, interleukins and tumor necrosis factor (TNF)
  - Limited success
Current Immunotherapeutic strategies in clinic or clinical trials

- Antibody Therapy
- Cytokine Therapy
- Adoptive Therapy
- Vaccination
- Combinational therapy
Examples
Antibody Therapy

Rituximab: The first approved antibody by FDA in clinical trial. Targeting CD20. low-grade non-Hodgkin lymphoma

Figure 4. Rituximab for Initial Treatment of LGNHL: Duration of Response

## Cytokine therapy -- IL-2

<table>
<thead>
<tr>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery of IL-2</td>
<td>Morgan et al. (1976)</td>
</tr>
<tr>
<td>Mitogenic IL-2 signal and long-term cultures of tumor-specific CTL</td>
<td>Gillis and Smith (1977)</td>
</tr>
<tr>
<td>Activating IL-2 signal (LAK cells)</td>
<td>Grimm et al. (1982)</td>
</tr>
<tr>
<td>Local administration of IL-2 inhibits tumour growth in preclinical</td>
<td>Bubeník et al. (1983)</td>
</tr>
<tr>
<td>models</td>
<td></td>
</tr>
<tr>
<td>Local administration of IL-2 inhibits growth of human tumors</td>
<td>Pizza et al. (1984)</td>
</tr>
<tr>
<td>Systemic administration of IL-2 inhibits growth of metastatic</td>
<td>Rosenberg et al. (1985a)</td>
</tr>
<tr>
<td>experimental tumours</td>
<td></td>
</tr>
<tr>
<td>Utilization of recombinant IL-2 for clinical trials in patients with</td>
<td>Rosenberg et al. (1985b)</td>
</tr>
<tr>
<td>generalized tumours</td>
<td></td>
</tr>
<tr>
<td>Local IL-2 gene therapy inhibits tumour growth in preclinical models</td>
<td>Bubeník et al. (1988)</td>
</tr>
<tr>
<td>Utilization of TIL or tumour cells carrying an inserted IL-2 gene</td>
<td>Anderson (1992); Foa et al. (1992)</td>
</tr>
</tbody>
</table>
## Local and regional IL-2 administration in cancer patients - selected examples from the early trials

<table>
<thead>
<tr>
<th>Interleukin-2</th>
<th>Dose (units/patient)</th>
<th>Tumour</th>
<th>Response (%) Complete/partial</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>gibbon lymphoid</td>
<td>1.5 x 10⁻² – 4.0 x 10⁻³</td>
<td>urinary bladder carcinomas</td>
<td>30/30</td>
<td>Pizza (1984)</td>
</tr>
<tr>
<td>human recombinant</td>
<td>1.0 x 10⁻⁴ – 2.8 x 10⁻⁴</td>
<td>lung carcinomas</td>
<td>0/82</td>
<td>Yasumoto (1987)</td>
</tr>
<tr>
<td>human recombinant</td>
<td>8.0 x 10⁻² – 5.4 x 10⁻³</td>
<td>malignant gliomas</td>
<td>13/13</td>
<td>Yoshida (1988)</td>
</tr>
<tr>
<td>human lymphoid</td>
<td>2.0 x 10⁻³</td>
<td>squamous cell carcinomas</td>
<td>29/29</td>
<td>Forni (1988)</td>
</tr>
<tr>
<td>human lymphoid</td>
<td>2.0 x 10⁻³</td>
<td>squamous cell carcinomas</td>
<td>30/30</td>
<td>Cortesina (1988)</td>
</tr>
<tr>
<td>human lymphoid</td>
<td>1.5 x 10⁻⁶/week</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*n.v.*, not verified because of incomplete transurethral resection
Adoptive immunotherapy

- Stimulating immune cells by exposing them to tumour cells or antigens in the laboratory and then injecting expanded populations of the treated cells into patients.
- Patient is both donor and recipient.
(1) Tumor cells that produce TGFβ that exert inhibitory effects on the immune system. Specific CTL can be genetically modified to become resistant to the TGFβ inhibitory effect through transgene expression of a mutant dominant-negative TGFβ type II receptor (DNR).

(2) Specific T cells genetically modified to produce IL-12 can overcome IL-10 inhibitory effect.

(3) Tumors express FasL and induce apoptosis of effector T cells. Small interfering RNA (siRNA) can be used to knock-down Fas receptor in specific CTL, allowing a significant reduction of their susceptibility to Fas/FasL-mediated apoptosis.
Adoptive immunotherapy

The Journal of Clinical Investigation Vol 113 Number 11 June 2004 pp 1515

Generation of dendritic cell vaccines from peripheral blood monocytes:
1) Monocytes cultures with GM-CSF + IL-4 to produce DCs
2) Matured with CD40 ligand
3) Pulsed with peptide or tumour lysate
4) Re-injected as vaccine to induce T-cell immune response against tumour
Antitumor Vaccines

Administration of some form of antigen to induce a specific antitumour immune response.
# Antitumor Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole tumor cell</td>
<td>1. Studied extensively</td>
<td>1. Requires availability of autologous tumor or an allogeneic cell line sharing the relevant tumor antigens;</td>
</tr>
<tr>
<td></td>
<td>2. Can be processed to enhance antigen presentation (e.g., irradiated tumor cells or tumor lysates);</td>
<td>2. Poor ability to stimulate immune responses;</td>
</tr>
<tr>
<td></td>
<td>3. Can be administered with adjuvants (e.g., BCG, KLH, viruses, etc.);</td>
<td>3. Few responses and little benefit reported when used adjuvantly in randomized clinical trials;</td>
</tr>
<tr>
<td></td>
<td>4. Likely to express the relevant tumor antigens;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Antigens need not be defined</td>
<td></td>
</tr>
<tr>
<td>Gene-modified tumor cells</td>
<td>1. Likely to express the relevant tumor antigens;</td>
<td>1. Requires availability of autologous tumor or an allogeneic cell line expressing the relevant tumor antigens;</td>
</tr>
<tr>
<td></td>
<td>2. Antigens need not be defined</td>
<td>2. Weak antigen presentation by many tumors;</td>
</tr>
<tr>
<td></td>
<td>3. Often engineered to coexpress immunostimulatory molecules and cytokines (e.g., GM-CSF, IL-2);</td>
<td>3. Long manufacturing time;</td>
</tr>
<tr>
<td></td>
<td>4. Use of allogeneic tumor cell lines and fibroblasts are under investigation as an approach to accelerate vaccine production;</td>
<td>4. Need for ex vivo cell culture;</td>
</tr>
<tr>
<td></td>
<td>5. Some immunological and clinical responses reported</td>
<td>5. Cost, time, and labor intensive</td>
</tr>
<tr>
<td>Plasmid (naked) DNA</td>
<td>1. Constructed to express the relevant tumor antigen;</td>
<td>1. Requires detailed knowledge of the antigen DNA sequence;</td>
</tr>
<tr>
<td></td>
<td>2. Easy to produce and stable;</td>
<td>2. Low immunological potency for self (tumor) antigens;</td>
</tr>
<tr>
<td></td>
<td>3. Can be administered as a direct injection or biologically (“gene gun”)</td>
<td>3. Response may be Th2 skewed;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. High doses of plasmid DNA are required to generate immune responses</td>
</tr>
</tbody>
</table>
# Antitumor Vaccines

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Viral gene transfer vectors</th>
<th>Antigen-modified DCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Can limit immune response to epitopes distinct from the wild type (e.g., point mutations or breakpoint-fusion genes);</td>
<td>1. Engineered to express the relevant tumor antigen;</td>
<td>1. Need for ex vivo cell culture;</td>
</tr>
<tr>
<td>2. Epitopes can be enhanced;</td>
<td>2. Can be engineered to coexpress immunostimulatory molecules and cytokines;</td>
<td>2. Cost, time, and labor intensive;</td>
</tr>
<tr>
<td>3. Easy to produce and stable;</td>
<td>3. Wide variety of available vectors (e.g., adenovirus, pox viruses, lentiviruses, etc.);</td>
<td>3. Optimal technique for antigen loading remains undefined;</td>
</tr>
<tr>
<td>4. Can be combined as cocktails of peptides;</td>
<td>4. Some cellular immune responses reported</td>
<td>4. Possibility of tolerization by immature DCs;</td>
</tr>
<tr>
<td>5. Some immunological and clinical responses reported</td>
<td></td>
<td>5. Lack of criteria for standardization of final product</td>
</tr>
<tr>
<td></td>
<td>1. Requires knowledge of the specific epitope;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Immunogenicity restricted to a limited number of MHC molecules;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Usually requires the addition of an adjuvant for immunogenicity</td>
<td></td>
</tr>
</tbody>
</table>
Approaches to antitumor vaccination

APC – antigen presenting cell
DC – dendritic cell
TAA – tumour associated antigen
MHC – major histocompatibility complex
Dendritic Cells That Attack Cancer

- **Complex binds to dendritic cell precursor**
- **Dendritic cell matures and is infused back into patient**
- **Tumor antigen**
- **T cell**
- **Cancer cell**

- **Tumor antigen is linked to a cytokine**
- **Complex is taken in by dendritic cell precursor**
- **T cells attack cancer cell**

Combinational Therapy
-- a three-stranded cord is not easily broken

• Combination of different immunotherapies
  ACT+IL-2 + costimulation

• Combining immunotherapy with other therapeutic strategies
Examples from my research work
Cancer immunotherapy using tumor cells transfected with the gene encoding B7 costimulatory molecule.
The immune system can be harnessed as a potent weapon to combat cancer, but only if immunotherapy is combined with treatment strategies that target a tumour’s weapons of survival, defence, and attack. If cancer cells are prevented from growing they will be unable to generate immune escape variants.
Gene transfer of antisense hypoxia inducible factor-1α enhances the therapeutic efficacy of cancer immunotherapy

Potential mechanisms for synergy displayed by combined blocking hypoxia pathway and B7.1-mediated immunotherapy:

- **B7.1+AS-HIF**
  - Activates NK cells
  - Anti-angiogenesis
  - Heat-shock driven anti-tumor immunity

- **Glycolysis**
  - Cell vitality
  - Immune suppressive elements

- **Apoptosis**
  - Necrosis
  - Tumor cell

- **NK**
  - B7.1

- **Tumor cell**
  - Apoptosis
  - Necrosis

- **Antigen** + hsp70- tumor

- **APC**
  - B7.1
  - MHCI
  - CD28

- **CD28**
  - MHCI
  - MHCII

- **T cell**
  - Proliferation & CTL-mediated killing
  - Tumor Cell
  - Apoptosis
B7H3-mediated Cancer Immunotherapy

Arsenic trioxide synergizes with B7H3-mediated immunotherapy to eradicate hepatocellular carcinomas


Complete eradication of hepatocellular carcinomas by combined vasostatin gene therapy and B7H3-mediated immunotherapy.

*Journal of Hepatology* 2007;46: 98-106
Novel co-stimulatory molecule- B7H3

Molecular Structure

SS                      IgV-like                         IgC-like                                Cytoplasmic
[Image of Molecular Structure]

Signal peptide
MLRGWGGGPSVGVLCRTALGVLCLCLTGAVEVQVSEDVPVALVDTDATLRC
SFSPEPGLSLQLNLIWQLTDKQLVHSFTEGRDQGSAYSNRTALFPDLLVQ
GNASLRLQVRVTDEGSYTCFVSIOQDFDSAASVLQVAAPYSKPSMTLEPNK
DLRPGNMVTITCSSYQGYPÆAEVFWKDQQGVPVTLGNVTTSQMANERGLFD
VHSVLRVVLGANGTYSCILVRNPVLQQDAHGSGVTITGGQPLTPPEALWVTVG
LVSVCLVVVLLVALAFRCWRKIKQŚCEDENAGÆEDQGDGEGSKTÁLRTLPKPS
ENKEDDGQEIA

Gene transfer results in expression of B7H3 on the surface of tumor cells.

pcDNA3.1
Flag-B7H3

→ Flag-B7H3
→ Tubulin
Combinational therapy led to eradication of large tumors and generation of memorized anti-tumor immunity.
Production of anti-tumor cytokine and CTLs by immunotherapy

- **Sera**
  - Level of IFN-γ (pg/ml)
  - B7H3+: 300, 400, 500
  - B7H3: 300, 400, 500
  - As2O3: 300, 400, 500
  - pcDNA3.1: 300, 400, 500
  - PBS: 300, 400, 500

- **Supernatants**
  - Level of IFN-γ (ng/ml)
  - B7H3+: 100, 200, 300
  - B7H3: 100, 200, 300
  - As2O3: 100, 200, 300
  - pcDNA3.1: 100, 200, 300
  - PBS: 100, 200, 300

- **Cytotoxicity (%)**
  - E:T Ratio: 20:1, 100:1
  - B7H3+: CD4+, CD8+, NK
  - B7H3: CD4+, CD8+, NK
  - As2O3: CD4+, CD8+, NK
  - pcDNA3.1: CD4+, CD8+, NK
  - PBS: CD4+, CD8+, NK
Treatment of single tumor eradicates multiple distant tumors

- Tumor-1, treated
- Tumor-2, untreated
- Tumor-3, untreated
- Tumor-4, untreated
- Tumor-5, untreated

Tumor Size (cm, diameter) vs. Weeks after therapy
Conclusion

• Immunotherapy may be the next great hope for cancer treatment.
• While antibodies, cytokines, and vaccines have individually shown some promise, it is likely that the best strategy to combat cancer will be to attack on all fronts.
• The effect of immunotherapy in combination with traditional cancer therapies is another avenue.
Thank you!

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