Foundations of Public Health Immunology

Autoimmunity, Transplants & Tumors

Transplant surgeons bring donor organ to operating room.

T cells (orange) have an important role in the fight against cancer cells (pink).
Objectives

• Define autoimmunity, tolerance, & ignorance
• Identify the mechanism involved in development of autoimmunity
• Identify the mechanism involved in the control of autoimmunity (central vs. peripheral)
• Identify selected disorder of autoimmunity
• Identify and explain the types, mechanisms of donor organ rejection
• Identify drug therapies to prevent graft rejection
• Describe how the immune system can recognize * kill tumor cells
• Identify the mechanisms tumor cells use to evade the immune response
• Identify novel approaches for cancer vaccines
Autoimmunity

• **Definition:** an immune response against self antigens

• Between 1-2% of people suffer from autoimmune diseases worldwide (up to 8% in US)

• 2 major factors contribute to autoimmunity developing in a person:
  - Inheritance of **susceptibility genes**
  - **Environmental triggers** (i.e. infections)
  - These factors can lead to reactivation of lymphocytes that recognize self
**Tolerance**

- Lack of immune cell response to an antigen that is induced after exposure to that particular antigen.
Central T-cell Tolerance

- Thymus is the site of central T-cell tolerance
- Involves **negative selection** of immature T-cells that react strongly to self-antigens
- Defective central tolerance may predispose to autoimmunity
Central Tolerance: Apoptosis & Treg cells

- Occurs in thymus
- Apoptosis (Deletion) happens if T cells strongly recognize self antigens [negative selection]
- T cells that recognize ag in the thymus can develop into regulatory T cells
  - Induced by repeated activation of immature T-cells by self-antigen and/or repeated recognition of self-antigens without second signals
  - Play a critical role in preventing autoimmune reactions
Peripheral T-cell Tolerance

• Occurs when mature T-cells recognize self-antigens in peripheral tissues or in secondary lymphoid organs

• Two possible outcomes:
  • Anergy or death
  • Regulatory T cell suppression
**Anergy**

- **Functional inactivation** of T-cells due to recognition of antigens without adequate levels of costimulators
  - Despite ag recognition, need these second signals for full T-cell activation
- **T cells become anergic without ag+ costimulators**
Suppression

• Suppression by Treg cells
• Exposure to self-antigens induces some self-reactive T-cells to become regulatory cells
• Most regulatory cells are CD4+ & express high levels of CD25
• Inhibit T cells & effector functions in tissues
• Critical to downplay inflammatory response, prevent autoimmunity & immunopathology

CD4+CD25+ T reg cell

Source: http://www.mcgill.ca/microimm/department/professors/piccirillo/
Central B-cell Tolerance

- B-cell central tolerance may occur by:
  - Negative selection
  - Receptor editing
    - Self-reactive B cells may **reactivate** their immunoglobulin recombination genes
    - Express **new Ig light chain** which binds the previous Ig heavy chain
    - Produces **new antigen receptor** that is not self-reactive
Peripheral B-cell Tolerance

- Mature B-cells exposed to high levels of self-antigen in secondary lymphoid organs become anergic to self-antigens.
Autoimmunity

- Situation in which the immune system exhibits reactivity to self-antigens
- May or may not always be accompanied by detectable disease
- May be antibody or cell-mediated
- Development of autoimmunity is affected by genetic and environment factors
Autoimmunity

- **Infections** may induce the development of autoimmunity
- **Induction of costimulators** on APCs by microbes
  - Presentation of self-antigens by these altered APCs to T-cells results in T-cell activation against self-antigens
- **Molecular mimicry**
  - Some microbial antigens may cross-react with self-antigens
  - Immune reactions to the microbial antigens result in attacks against the self-antigens
Autoimmunity continued

• Insulin-dependent diabetes mellitus
  • Autoimmune destruction of the beta cells in the Islets of Langerhans in the pancreas
  • Results in little to no insulin being produced by the body

• Malaria
  • Four species of malarial protozoa exist worldwide
  • The species, Plasmodium malarie, can induce glomerulonephritis in the kidneys
Periodontal diseases

- Widely prevalent chronic inflammatory disorders induced by a bacterial biofilm found on teeth
- Periodontitis
  - Most destructive form of periodontal disease
  - Affects approximately 30% of the U.S. population, one of the most significant causes of tooth loss in adults
  - Characterized by irreversible destruction of soft tissue and bone
    - Results from a complex interplay between the host response and specific plaque microorganisms, such as Porphyromonas gingivalis
    - Both innate and acquired immunity are involved in the host response
Multiple Sclerosis (MS)

- MS is an **autoimmune disease** that primarily affects whites in North America & Europe.
- MS affects proper functioning of the central nervous system, leading to systemic loss of motor, sensory, and bladder control.
- Primarily causes by **T cell mediated attacks on nerve tissue** and subsequent demyelination of axons.
Organ Transplants & Immune Rejection

• Transplant nearly any solid organ (heart, lung, liver, skin, etc)
  • Allograft: transplanted organ or tissue with a different genetic makeup (non-identical twins) from same species
  • Xenograft: transplanted organ or tissue between 2 different species
• Donor to recipient matching not as critical due to immunosuppressive drugs
Ag Recognition of Organ Transplants

- Transplanted organs express **donor MHC molecules** that can be recognized by the recipient immune system.
- Two pathways of antigen recognition (allorecognition) by the recipient’s T cells:
  - **Direct** – recipient T cells recognize intact donor MHC molecules combined with peptide and expressed on donor cells
    - Responsible for acute rejection
  - **Indirect** – recipient APCs process the donor-MHC antigen then present it to recipient T cells
    - Responsible for **chronic** rejection
Antigen Recognition of Organ Transplants

• Both donor and recipient factors contribute to the immune response to transplanted tissue
  • Major **donor** factor – expression of MHC antigens on the donor tissue and the presence of APCs within the transplanted graft
  • Major **recipient** factor – previous sensitization against ABO and HLA antigens expressed on the graft or other foreign antigens
Types of Rejection

- Hyperacute
  - Accelerated
- Acute
- Chronic

- Type of rejection is determined by the time frame & histopathologic characteristics of the transplanted organ
Hyperacute Rejection

- Occurs **immediately** (within minutes to hours of the vascularization of the transplanted graft)
- Caused by **humoral immune response** against ABO blood group antigens, vascular endothelial antigens, and histocompatibility (HLA) antigens
- Hyperacute rejection results in:
  - Complement activation
  - Massive intravascular coagulation
  - Decreased tissue perfusion
  - Eventual graft necrosis and death
**Accelerated Acute Rejection**

- Variation of hyperacute rejection
  - However, it is a cellular immune response (not humoral)
- Can occur if the recipient has been previously exposed to low levels of donor tissue antigens
  - Creates a rapid memory response after the transplantation
- Accelerated acute rejection occurs within a few days to few weeks following transplantation
- Leads to graft death
Acute Graft Rejection

• Due to a **cellular** immune response involving mononuclear, cytotoxic and Th cells, monokines, and lymphokines

• May occur within a week to approximately 4 months after transplantation
  • Greatest risk during the first 6 months after transplantation
  • Aggressive treatment prevents graft loss
  • Acute graft rejection is the greatest predictor of chronic rejection

• Produces nonspecific signs that need definitive diagnosis through biopsy
Chronic Rejection

- Cause of chronic rejection is unclear
  - Both T cells and B cells contribute to the damage
- Hallmarks of chronic rejection:
  - Slowly developing graft fibrosis
  - Widespread arterial disease (arteriopathy)
  - Eventual graft malfunction and loss
- Probably begins at the time of transplantation, but may take months or years to be clinically detectable
- Prevention is the best method to limit chronic rejection although retransplantation is possible
Drug Therapy

- Need **lifetime of immunosuppressive drugs** to prevent graft rejection
  - Most organ transplants are successful now because of drugs
- New experimental therapies are being developed to decrease side effects & toxicity of steroidal drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>Cyclosporine and FK506</td>
<td>Blocks T cell cytokine production by inhibiting activation of the NFAT transcription factor</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Blocks lymphocyte proliferation by inhibiting IL-2 signaling</td>
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<tr>
<td>Corticosteroids</td>
<td>Reduce inflammation by inhibiting macrophage cytokine secretion</td>
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<tr>
<td>Anti-CD3 monoclonal antibody</td>
<td>Depletes T cells by binding to CD3 and promoting phagocytosis or complement-mediated lysis (Used to treat acute rejection)</td>
</tr>
<tr>
<td>Anti-IL-2 receptor antibody</td>
<td>Inhibits T cell proliferation by blocking IL-2 binding. May also opsonize and help eliminate activated IL-2R-expressing T cells</td>
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<tr>
<td>CTLA4-Ig</td>
<td>Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28; used to induce tolerance (experimental)</td>
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<tr>
<td>Anti-CD40 ligand</td>
<td>Inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40 (experimental)</td>
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Blood Types & Immunopathology

- Antigens on blood cells also can lead to recipient rejection (and death) from incorrect transfusions
  - Sugar ags (no T cell response)
- Blood transfusion reactions
  - ABO systems (See next slide)
  - Reaction involves IgM & complement
**ABO System**

Human blood cells can be groups according to the presence or absence of surface antigens. For example, an individual with A-type blood has A antigens on their erythrocytes and anti-B antibodies in their serum. However, individuals with O-type blood have no A or B antigens on their erythrocyte surfaces and have both anti-A and anti-B antibodies in their serum. This lack of surface antigens allows Type O blood to be transfused into individuals with other blood types.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Blood–group phenotype</th>
<th>Antigens on erythrocytes (agglutinins)</th>
<th>Serum antibodies (isoheamagglutinins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA or AO</td>
<td>A</td>
<td>A</td>
<td>Anti–B</td>
</tr>
<tr>
<td>BB or BO</td>
<td>B</td>
<td>B</td>
<td>Anti–A</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>A and B</td>
<td>None</td>
</tr>
<tr>
<td>OO</td>
<td>O</td>
<td>None</td>
<td>Anti–A and anti–B</td>
</tr>
</tbody>
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**Universal Acceptor**

**Universal Donor**
Cancer

• Definition: group of more than 100 disease characterized by uncontrolled growth, spread of abnormal cells
  • Cancer cells ignore signals to specialize, stop dividing, or to die
• Cells divide in a haphazard manner & usually form a non-structured mass or tumor
  • Benign tumors generally stay in one place
  • Malignant tumors can metastasize & spread to other parts of the body
• Cancers have been associated with genetic, dietary, & environmental factors, as well as smoking & infectious agents
Tumor Rules

- Tumor cells are normal host cells that have mutated or changed.
- They can be characterized by their location in the body, or by what triggered the changes.
  - Altered surface proteins (ags) may appear from radiation.
  - Oncogenes can be triggered to make mutated products inside the cell.
  - Too many self proteins can be expressed on some melanoma cells.
  - Oncogenic viruses can also generate mutated proteins in certain cancers.
- These tumor cells can be recognized by CD8+ T cells.
CD8+ T cell Response to Tumors

Cytolytic T cells (grey) show attacking a tumor.
Tumor Evasion Strategies

- Tumors are difficult to contain – grow extremely rapidly
- Tumor antigens also **closely resemble “self”** as they were at one time normal host cells
- Also have evolved several **evasion strategies** to beat the immune response
  - Lose expression of tumor antigens
  - Down-regulate production of MHC I molecules (prevent CD8+ cells from knowing that the normal cell is now cancerous, no ag presentation)
    - **NK cells** provide redundancy in immune response to prevent this strategy
  - Secrete cytokines that inhibit the cellular immune response
Cancer Vaccines

• Only 2 vaccines currently available that prevent cancers (both due to infectious causes)

• Need for vaccines that can treat (& prevent) oncogenic cancers

• Personalized tumor vaccines – inject own tumor cells with modifications to induce stronger immune response
Good News: Cancer Therapies

• Until the last several years, successful cancer therapies included radiation, chemotherapy, and surgery (or a combo of all 3) to remove or diminish the cancerous cells
  • However, these therapies have significant side effects, including immunosuppression of the good guys while killing off the cancer (bad cells)

• Watch the brief videos listed this module in Canvas that describe significant breakthroughs in cancer treatment & vaccines that attempt to minimize damage to the normal cells
**In Summary**

- Understand the principles of T & B cell tolerance (central & peripheral) to control autoimmunity
- Identify mechanisms that lead to autoimmunity
- Define & identify examples of autoimmune diseases
- Describe each of the 3 types of organ rejection
- Identify the mechanisms of organ rejection
- Identify how tumor cells are not “normal”
- Identify immune evasion strategies employed by cancer cells
- Identify types of cancer vaccines
Self-Test Questions

• Define autoimmunity. What 2 factors influence the development of autoimmune diseases?
• What is central T cell tolerance? How does it differ from peripheral tolerance?
• What do regulatory T cells do? What is receptor editing in B cells? How do these functions prevent autoimmunity?
• What is molecular mimicry?
• Describe allore cognition (textbook). How does this influence organ rejection?
• What are the 3 types of rejection? How is the type of rejection characterized?
• Name 2 classes of drugs that limit immune rejection of transplants. How do they work?
• What is the ABO system?
• How are tumor cells different from normal cells?
• How do CD8+ T cells kill tumor cells? What provides the second signals, if they are targeting self (cancerous) cells?
• How do tumor cells evade the immune response?
• Describe 2 types of cancer vaccines.