Foundations of Public Health
Immunology

Hypersensitivity

Type I hypersensitivity reactions can be caused by a variety of allergens

Objectives
• Describe the hypersensitivity reaction to antigen exposure
• Identify and explain the similarities and differences in the mechanism of the four types of hypersensitivity reactions
• Identify selected disorders for each type of hypersensitivity reaction (selected disorders of autoimmunity)
• Identify and explain the mechanisms of sepsis

Hypersensitivity

• Normally beneficial immune responses that occur in an exaggerated or inappropriate form
  • Results in inflammation, tissue damage or other problems known as immunopathology
  • Hypersensitivity reaction only occur on the second or subsequent exposure to an allergen
  • The host must first be sensitized to the allergen!!

Characteristics of Hypersensitivity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>IgE</td>
<td>IgG, IgA, IgM</td>
<td>IgG, IgA, IgM</td>
<td>None</td>
</tr>
<tr>
<td>Antigen</td>
<td>Exogenous</td>
<td>Cell surface</td>
<td>Soluble</td>
<td>Tissue &amp; organs</td>
</tr>
<tr>
<td>Response time</td>
<td>15-30 minutes, minutes-hours</td>
<td>24 hours</td>
<td>48-72 hours</td>
<td>3-10 days</td>
</tr>
<tr>
<td>Appearance</td>
<td>Wheal &amp; flare, erythema</td>
<td>Quiescent</td>
<td>Erythema and edema, necrosis</td>
<td>Quiescent and induration</td>
</tr>
<tr>
<td>Histology</td>
<td>Basophil and eosinophil</td>
<td>Antibody and complement, macrophages</td>
<td>Complement and neutrophils</td>
<td>Macrophages and lymphocytes</td>
</tr>
<tr>
<td>Transmitted with</td>
<td>Antibody</td>
<td>Antibody</td>
<td>Antibody</td>
<td>T cells</td>
</tr>
<tr>
<td>Examples</td>
<td>Allergic asthma, hay fever, chronic urticaria</td>
<td>Sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, chronic granulomatous disease</td>
<td>Serum sickness, thrombocytopenia purpura, and hemolytic transfusion reaction</td>
<td>Tissue damage, organ damage, and cell-mediated reactions</td>
</tr>
</tbody>
</table>

Table Source: http://pathmics.med.sc.edu/greve/hypertype0.htm

Hypersensitivity

• Four types of hypersensitivity diseases
  • Mechanism of immune injury is different in each type

Type I: Immediate Hypersensitivity

• Also know as:
  • Allergy
  • Atopy
  • Anaphylaxis
  • Most severe form of Type I reaction

• Examples of Type I reactions
  • Asthma
  • Hay fever
  • Some food and drug allergies
Type I Hypersensitivity

**Reaction**
- IgE is produced in 1st exposure to an antigen
- IgE proteins bind to Fc receptors on mast cells (on both the connective tissue and in the mucosa) and basophils
- Repeat exposure to the antigen then cross-links the IgE molecules

**Type I Reaction cont’d**
- Cross-linking induces degranulation of the involved mast cells and basophils—on 2nd & later exposures
- Mediators are released during degranulation
- Trigger the symptoms of Type I hypersensitivity
  - One mediator released during this reaction is histamine
  - Anaphylatoxins, C3a & C5a, also released in complement cascade triggered by released mediators.

**Process of Sensitization To An Antigen**

Notice the production of the IgE and its binding to the sensitized mast cells

**Process of the cross-linking of IgE with the antigen**

**Type I: Immediate Hypersensitivity**

- Th2 cytokines promote Type I hypersensitivity
- Genetic predisposition for allergen which appears to be Human Leukocyte Antigen (HLA)-linked
- Environmental pollutants can promote allergies
  - These pollutants can act as IgE adjuvants
Type I: Immediate Hypersensitivity
- Allergies can be diagnosed by the Skin Prick Test
  - "Wheal & Flare" is characteristic of an allergic reaction
  - Common allergens include pollen, foods, dander
- A variety of medication and treatments are used to control allergies
  - Hyposensitization (Desensitization) therapy
  - Person is exposed in increasing levels of the antigen until tolerance develops

Type 1: Latex Allergy
- Occurs when the immune system reacts to proteins in natural rubber latex
- An estimated 1 – 6% of general population has been sensitized to latex
  - 5 – 10% of healthcare workers are sensitized!
- Should substitute synthetic gloves for latex
- Products that commonly cause reactions included gloves, balloons & condoms
- May also react to rubber bands, erasers, rubber parts of toys, pacifiers, etc.

Ascaris (Roundworm)
- Strong immune response to larval stage Ascaris lumbricoides infestation
  - Ascaris allergen is the most potent of all allergens or parasitic origin
- Bronchial asthma, urticaria (hives), angioedema (diffuse swelling and hives) frequently occur with the larval stage parasite
- However, the immune system is frequently tolerant of adult Ascaris intestinal infestation
**Dracunuliasis**
- Also known as Guinea Worm disease
- The female worm forms a painful blister on the skin (usually the feet) and when the foot is placed in water, the female worm releases numerous eggs
- The worm can be removed by winding it slowly around a stick over many days (see photo w/ match stick)
- If worm ruptures during removal, it will release numerous antigens & produce a severe allergic reaction.

**Type 2: Cytotoxic Hypersensitivity**
- With Type 2 reactions, the reaction is against an antigen located on a cell surface
- The antigen being attacked is an integral part of the cell!!
- IgM and IgG antibodies bind to the cell surface or tissue antigens in conjunction with complement activation
- The complement activation results in:
  - Chemotaxis
  - Inflammation
  - Opsonization
  - Cellular activation

**Type 2 Mediated Immunopathology**

**Type 2: Blood Immunopathologies**
- Blood transfusion reactions
- Hemolytic Disease of the Newborn
  - RhD factor
  - Reaction involves IgG
  - Also called erythorblastosis fetalis

**Erythroblastosis fetalis**

**Rhesus prophylaxis**
Type 2: Autoimmune Blood Reactions

- Spontaneous reactions that destroy erythrocytes
  - Warm antibody hemolytic anemia involve autoantibodies that attach to and destroy erythrocytes at temperatures above normal body temperature
  - Cold antibody hemolytic anemia involve autoantibodies that attach to and destroy erythrocytes at temperatures below normal body temperature
- Thrombocytopenia (low platelet count)

Type 2: Adverse Drug Reactions

- Drug-induced reactions involving drug-Ab immune complex and erythrocyte antigens
- Steven-Johnson Syndrome (SJS)
  - Affects people of all ages, but more child cases
  - If untreated, can result in death
- Toxic Epidermal Necrolysis Syndrome
  - Another form of SJS

Type 2: Autoimmune Diseases

- Goodpasture’s syndrome
  - Involves IgG and complement
  - Lungs & kidneys are effected
  - Results in kidney basement membrane damage
  - May be triggered by viral respiratory infections or inhaling hydrocarbon solvents
  - Treat with immunosuppressive drugs and plasmapheresis (to remove harmful autoantibodies from the blood)

Type 2: Autoimmune Diseases

- Pemphigus vulgaris
  - Involves antibodies against chromosome proteins, skin and mucous membranes
  - Results in blistering
  - Exact cause is unknown
  - Disease is uncommon, occurs mostly in middle-aged (or older) patients
Type 2: Autoimmune Diseases
- Myasthenia Gravis
  - Involves IgG and complement against acetylcholine receptors on muscle cell membranes
  - Results in muscle weakness and fatigue
- Thymus abnormalities often present
  - Thymic tumors found in 10% of patients
  - Changes in germinal centers found in 70% of patients

Type 3: Immune Complex Hypersensitivity
- With type 3 hypersensitivity, damage occurs to tissues at sites of immune complex deposition
- Antigens involved in Type 3 reactions are insoluble, small immune complexes which have not been removed by phagocytes, the liver, or the spleen
- Involves the deposited antigen, antibodies (IgG), complement deposition & effector cells
  - The antigen-antibody complexes induce complement activation & result in inflammation mediated by neutrophils

Factors Contributing to Deposition of Immune Complexes
- Complement deficiencies
- Low affinity antibodies
- Antibody isotype
- Ineffective phagocytosis
- Abnormal carbohydrate on antibody molecules
- Size of immune complex and the antibody isotype
- Increased vascular permeability (due to vasoactive amines)
- High blood pressure and turbulence (for example in the glomerular capillaries of the kidneys)
- Affinity of the antigen for specific tissues

Type 3 Hypersensitivity
- Three General Groups:
  - **Persistent infection** involving microbial antigens and the kidneys
  - Autoimmune disease against **self antigen**
    - Damage can occur to the kidneys, joints, & arteries etc.
  - **Extrinsic** antigens
    - Inhaled antigen – (mold) lung
    - Serum Sickness
    - Arthus Reaction

Symptoms of serum sickness

**Immune complexes**

**Serum levels**

**Time after BSA injection, days**

**Free Ag**

**Free Ab**

**Serum sickness**

**Arthus Reaction**
**Type 3: Autoimmune Disease**

- Systemic Lupus Erythematosus (SLE)
  - Formation of immune complexes cause inflammation & tissue injury
  - Affects many parts of the body (joints, skin, kidneys, heart, lungs, brain, blood vessels)
  - Characterized by periods of illness (flares) & times of health (remission)
  - More common in young women

**Autoimmune Diseases: Autoantibodies**

- Not always a direct hypersensitivity link, but formation of autoantibodies can cause autoimmunity
- Graves disease & Hashimoto’s thyroiditis are 2 disease where autoantibodies target a single organ – the thyroid
- Rheumatoid arthritis is a systemic autoimmune disorder – high levels of circulating autoantibodies target multiple organs but most commonly affect the joints

**Autoantibody Tests**

- Antinuclear antibody (ANA): may be found in autoimmune disorders (especially lupus, scleroderma, Sjogren’s syndrome, polymyositis, certain types of chronic active hepatitis)
- Anti-DNA antibody: may be present in lupus
- Titers will decrease when treatment is successful
- Usually not found in other autoimmune diseases
- Antiphospholipid antibody: may be found in lupus and certain other conditions
- Associated with miscarriages and clots
- Rheumatoid factor: often found in blood and joint synovial fluid in rheumatoid arthritis patients

**Type 4: Delayed Hypersensitivity**

- Type 4 reactions are regulated by cell-mediated reactions
- Type 4 reactions usually take longer than 12 hours to develop due to mediation via T-cells
- Protective immunity does not always occur with Type 4 reactions
- Three varieties of Type IV Hypersensitivity:
  - Contact hypersensitivity
  - Tuberculin type hypersensitivity
  - Granulomatous hypersensitivity

**T Cell Mediated Hypersensitivity**

- Granuloma formation around a schistosome egg (center) destroys the liver tissue.
- Wristwatches may stimulate contact hypersensitivity reactions.
Contact Hypersensitivity

- With contact hypersensitivity, haptens penetrate the epidermis and conjugate with protein (which acts as a carrier for the hapten)
  - Examples of possible haptens include nickel, poison ivy, chromate, DNBC, etc.
  - CD4+ T-cells and macrophages are involved in contact hypersensitivity reaction
  - There is down regulation of the reaction by cytokines

Contact Hypersensitivity

- The reaction involves both sensitization and elicitation phases
- Maximal reaction occurs at 48 to 72 hours
- The reaction produces an eczematous reaction of the skin

Type 4 Contact Hypersensitivity

- Examples of tuberculin type hypersensitivity reactions include the tuberculin skin test and the intradermal tuberculin injection
- CD4+ T-cells and macrophages are involved in tuberculin type hypersensitivity
- With previous exposure to the antigen, a localized induration occurs at the site of the injection
- A maximal reaction occurs at 48 to 72 hours
- The induration usually resolved within 5 to 7 days
Granulomatous Hypersensitivity

- Persistent antigen and can be considered “Pathologic CMI”
- Chronic inflammation can produce these reactions
- Reactions result from secretory epithelioid and giant cells, macrophages, and lymphocytes
- Granulomatous hypersensitivity produces hardening or fibrosis of tissue
- These reactions may take 21 to 28 days or longer to develop
- Diseases that may exhibit granulomatous hypersensitivity include Tuberculosis, Leprosy, Schistosomiasis, Sarcoidosis

Enlarged liver and spleen occurs in schistosomiasis due to granuloma formation, blocking abdominal circulation.

Summary of Delayed Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical</th>
<th>Histology</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Eczema</td>
<td>Lymphocytes</td>
<td>Epidermal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>macrophages edema</td>
<td>nickel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>poison</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>Local Induration</td>
<td>Lymphocytes</td>
<td>Intradermal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>macrophages</td>
<td>tuberculin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monocytes</td>
<td></td>
</tr>
<tr>
<td>Granuloma</td>
<td>Hardened skin &amp; lung</td>
<td>Fibrosis</td>
<td>Persistent Ag or Ag/Ab complexes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelioid</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Giant Cell</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Macrophage</td>
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</tr>
</tbody>
</table>

Innate Hypersensitivity: Systemic Inflammatory Response Syndrome (SIRS)

- Effects of a systemic activation of the innate immune response without regard to the cause
  - The body produces an exaggerated response to the stimulus
- Everyone is potentially at risk for SIRS
  - However, certain individuals are at greater risk including critically ill patients and immunocompromised patients
  - Factors contributing to increased mortality from sepsis
    - underlying disease
    - older age

SIRS

- SIRS represents a continuum of disease:
  - Bacteremia – bacteria in the bloodstream
  - Sepsis – SIRS due to an infection regardless of infecting organism (bacterial, viral, fungal)
  - Severe sepsis – Sepsis associated with at least one acute organ dysfunction, poor perfusion, or low blood pressure (hypotension)
  - Septic shock – Sepsis-induced hypotension persists despite adequate fluid replacement
  - MODS (Multiple organ dysfunction syndrome) – Presence of altered function in two or more organs in an acutely ill patient
  - Death
**In Summary**

- Hypersensitivity
  - Mechanisms of Types I – IV hypersensitivity
  - Examples of each type
  - Associated autoimmune diseases
  - Autoantibodies
  - Sepsis

**Self-Test Questions**

- Describe the 4 types of hypersensitivity. How do the cells, mechanisms of action, and times for each reaction differ?
- Name 2 examples of autoimmune diseases associated with each type of hypersensitivity.
- What are autoantibodies? What are some tests that can be used to identify these antibodies?
- Name 4 factors that contribute to immune complex diseases.
- What is the fundamental difference between Type 4 hypersensitivity & the other 3 types?
- What are the 3 types of delayed hypersensitivity reactions? Name an allergen or example of each type.
- What is SIRS? Why is SIRS like adaptive hypersensitivity diseases? Who is at risk? Is there a specific stimulus that causes it?