Allergy and Immunology

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Contact Dermatitis
Contact Dermatitis
Contact Dermatitis
Vasculitis
Subacute Cutaneous Lupus
Immune System Theme

• It is all about ME!!
Primary Function of the Adaptive Immune System

• Protect self from non-self;

and ... 

• Remember it!
Why do you need immunity?
Development of the Immune System

ereny, pl, neu, mφ, nk, thy, CD8+, CD4+, CTL, TH1, TH2
The Immune System

Innate
- physical barriers
- natural killer cells
- macrophages
- Toll-like receptors
- Complement

Acquired
- Cell-mediated
  - T & B cells
- Humoral
  - antibody-mediated
Innate Immune System

**INNATE IMMUNE SYSTEM**

- Lysozyme in tears kills Gram-positive bacteria
- Removal of particles by turbinates and humidification
- Mucus and cilia capture organisms and remove them
- Skin: physical barrier
- Stomach acid kills ingested pathogens
- Fatty acids inhibit growth of many bacteria
- Competition and toxic products from intestinal flora
- Flushing action of urinary flow removes organisms
- Low vaginal pH from lactobacilli prevents colonization by pathogens

**Whole body:**
- Molecular and cellular defence
- Pattern recognition molecule e.g. TLRs
- Neutrophiles
- Macrophages

**NORMAL FLORA**

**NASOPHARYNX**
- Streptococci
- Haemophilus
- Neisseria
- Mixed anaerobes
- Candida
- Actinomyces

**SKIN**
- Staphylococci
- Streptococci
- Corynebacteria
- Propionibacteria
- Yeasts

**UPPER BOWEL**
- Enterobacteriaceae
- Enterococci
- Candida

**LOWER BOWEL**
- Bacteroides
- Bifidobacteria
- Clostridium
- Peptostreptococci

**VAGINA**
- Lactobacilli
- Streptococci
- Corynebacteria
- Candida
- Actinomyces
- Mycoplasma hominis
**Except for IgE allergic reactions**
Model of Immune Responses: Speed and Specificity

- Innate immune responses
- Adaptive responses

response vs. time after infection
INNATE IMMUNITY

Physical Barriers

- skin
- hair
- mucous
INNATE IMMUNITY

Chemical Barriers

- sweat
- tears
- saliva
- stomach acid
- urine
Filaggrin null mutation
4 Compartments of the Immune System

**Innate Immunity**
- Complement: "Land Mines"
- Phagocytes: "The Marines"
- Neutrophils
- Macrophages

**Adaptive Immunity**
- B Cells: "Air Force – Make & Deploy Cruise Missiles"
- T Cells: "The Generals" "The Assassins" "The Psychologists"

Host Defense

Cytokines & Chemokines
Complement

Classical

Immune Complex

- C1
- C2
- C4
- C4b, 2a

Microbes

- C3(H₂O), Bb
- Recurrent pyogenic infections (Strep. pneumoniae)
- Glomerulonephritis, SLE

Alternative

- C3b, Bb, P
- Factor I
- Factor H

Anaphylotoxin

C3a

- Recurrent Neisserial infections
- Familial HUS
- Age-related Macular Degeneration

C3b

Opsonin

C5

- C5a
- C5b, 6, 7, 8, 9

Membrane Attack Complex

Bactericidal Activity
Immune System — Garbage Disposal is Important
Complement and Phagocytes Aid in Clearance of Cell Debris

Autoimmunity

DNA, HMGB1
ANA
Type I IFN
Complement Deficiency

- **C1q/r/s Deficiency** – ~90% of homozygotes develop SLE or GN, usually <20 y/o.
- **C4 Deficiency** - ~75% of homozygotes develop SLE or GN.
- **C2 Deficiency** – Most common homozygous complement deficiency. ~40% of homozygotes develop SLE or GN.

Successful plasma infusion treatment of a patient with C2 deficiency and systemic lupus erythematosus: clinical experience over forty-five months.
Steinsson K1, Erlendsson K, Valdimarsson H.
45 cycles, 22 infusions 6-8 weeks apart
TLRs in Treatment

Imiquimod (Aldara) activates immune cells through the toll-like receptor 7 (TLR7), commonly involved in pathogen recognition. Cells activated by imiquimod via TLR-7 secrete cytokines (primarily interferon-α (INF-α), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). There is evidence that imiquimod, when applied to skin, can lead to the activation of Langerhans cells, which subsequently migrate to local lymph nodes to activate the adaptive immune system. Other cell types activated by imiquimod include natural killer cells, macrophages and B-lymphocytes.
4 Compartments of the Immune System

**Innate Immunity**

- **Complement**
  - "Land Mines"

- **Phagocytes**
  - "The Marines"
  - Neutrophils
  - Macrophages

**Adaptive Immunity**

- **B Cells**
  - "Air Force – Make & Deploy Cruise Missiles"

- **T Cells**
  - "The Generals"
  - "The Assassins"
  - "The Psychologists"

**Host Defense**

**Cytokines & Chemokines**
<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen independent</td>
<td>Antigen dependent</td>
</tr>
<tr>
<td>No time lag</td>
<td>A lag period</td>
</tr>
<tr>
<td>Not antigen specific</td>
<td>Antigen specific</td>
</tr>
<tr>
<td>No Immunologic memory</td>
<td>Development of memory</td>
</tr>
</tbody>
</table>

(except IgE)
Primary Function of the Adaptive Immune System

- Protect self from non-self;

and ...  
- Remember it!
T and B Lymphocytes

- **T** cells originate from the **Thymus** and may be Helper (CD4), Suppressor (CD8) or Cytotoxic.

- **B** cells originate from the “**Bursa**”. Their major function is to produce antibodies in response to foreign proteins including bacteria, viruses, and tumor cells.
1. B cells encounter and bind to antigen.

2. B cell c responds to antigen by proliferating.

3. Some B cells differentiate into long-lived memory cells.

4. Other B cells differentiate into plasma cells.

5. Plasma cells secrete antibodies into circulation.

B CELL CLONAL EXPANSION

Cardiovascular system
Function of the Immune System (Self / Non-self Discrimination)

• To protect from pathogens
  • Intracellular (e.g. viruses and some bacteria and parasites)
  • Extracellular (e.g. most bacteria, fungi and parasites)

• To eliminate modified or altered self
Hypersensitivity

There are four different responses of the immune system:

**Type I: Immediate hypersensitivity**
- onset within minutes of antigen challenge
- examples are allergies to molds, insect bites

**Type II: Cytotoxic hypersensitivity**
- onset within minutes or a few hours of antigen challenge
- examples are adult hemolytic anemia and drug allergies

**Type III: Immune complex-mediated hypersensitivity**
- onset usually within 2 - 6 hours
- examples include serum sickness and systemic lupus erythematosus

**Type IV: Delayed hypersensitivity**
- inflammation by 2-6 hours; peaks by 24 - 48 hours
- examples include poison ivy and chronic asthma
Two Sides of the Adaptive Immune System

Humoral = Immediate sensitivity Antibodies (Type I, II, III)
Two Sides of the Adaptive Immune System

Cellular = Delayed sensitivity (Type IV)

24 - 48 hours after exposure
CONTACT DERMATITIS
HUMBOLT 420
HUMORAL (ANTIBODY-MEDIATED) IMMUNE SYSTEM
Control of freely circulating pathogens

1. A B cell binds to the antigen for which it is specific. Usually requires cooperation from helper T cell.

2. The B cell, often with stimulation from a helper T cell, differentiates into a plasma cell.

3. Plasma cells proliferate and produce antibodies against the antigen.

CELL-MEDIATED IMMUNE SYSTEM
Control of intracellular pathogens

Intracellular antigens expressed on the surface of a cell infected by a virus, bacterium, or parasite. (Also may be expressed on surface of an APC).

1. A T cell binds to MHC-antigen complexes on the surface of the infected cell, activating the T cell (with its cytokine receptors).

2. A helper T cell produces cytokines that cause the activated T cell to differentiate into a cytotoxic T cell. These cytokines also influence the formation of plasma cells and activated macrophages.

3. The infected target cell is lysed by the cytotoxic T cell.
GALT = Gut Associated Lymphoid Tissue
BALT = Bronchial Associated Lymphoid Tissue
GENITAL TRACT

- no associated lymphoid tissue
- no clear site of immunologic priming
Why Doesn’t the Genital Tract have Lymphoid Tissue?

Self or non-self for the woman?
Remember the 5 Classes of Antibodies

- Ig = Immunoglobulin

G — A — M — E — D

- IgG = "Good" major antibody class
- IgA = "Appetite" to "A" hole, orifices
- IgM = Macroglobulin, first one out
- IgE = "Evil", causes allergies
- IgD = "Dumb class", does nothing
Antibody Structure

• Two Heavy Chains
  - IgA = α Alpha
  - IgD = δ Delta
  - IgM = μ Mu
  - IgE = ε Epsilon
  - IgG = γ Gamma

• Two Light Chains
  - Kappa κ
  - Lambda λ
Extracellular bacteria

Macrophage

Opsonization

Ingestion by macrophage

Digestion in lysosome
BACTERIAL CAPSULE: The slippery capsule of *Streptococcus pneumoniae* enables these bacteria to avoid being eaten by neutrophils.
HIV

An infection of T Helper or CD4 Cells

Figure 4
Virus attaches to healthy T-cell

Figure 6
The viral RNA and the reverse transcriptase change the T-cell, giving it a new set of codes/info
ALLERGIES?
Pathophysiology of Allergic Inflammation: Sensitization

Phase 1: Sensitization

- Allergens
- Antigen-presenting cell
- Processed allergens
- CD4 T cell
- B cell
- IgE antibodies
- Plasma cell
Pathophysiology of Allergic Inflammation: Clinical Disease

Phase 2: Clinical Disease

Early Inflammation
- Allergens
- IgE antibodies
- Mast cell
- Mediator release
- Blood vessels
- Nerves
- Glands
- Sneezing
- Rhinorrhea
- Congestion

Late Inflammation
- Cellular infiltration
  - Eosinophils
  - Basophils
  - Monocytes
  - Lymphocytes

Late-phase reaction

Hyperresponsiveness

Priming

Resolution

Complications

Irreversible disease (?)
In the midst of final exams, Noreen developed an allergic reaction to algebra.
Three Legged Stool of Allergy Treatment

1. Avoidance
2. Medications
3. Immunotherapy
Avoidance
Medications
Immunotherapy
Type IV Hypersensitivity - A Delayed Reaction

CONTACT DERMATITIS

Antigen (red dots) are processed by local APCs

T cells (blue cells) that recognize antigen are activated and release cytokines

Inflammatory response causes tissue injury

Antigen is presented by APC’s to antigen-specific memory T cells.

They become activated and produce chemicals that cause inflammatory cells to move into the area, leading to tissue injury.

Inflammation by 2 - 6 hours with peak in 24 - 48 hours.
ALLERGIC CONTACT DERMATITIS

Sensitization

Allergen

Stratum Corneum

Epidermis

95% Keratinocytes

Dermis

Elicitation

Langerhans Cells

Inflammation

activated T-Cells

draining Lymphnode

naïve T-Cells

IL-18
STEVEN'S-JOHNSON SYNDROME

TOXIC EPIDERMAL NECROLYSIS (TEN)
What Makes us Sick?

- “Enemies” in the environment like microbes and chemicals are constantly attacking our bodies, disrupting **homeostasis**.
- Sometimes immune system homeostasis is disrupted on its own.

- It may **over-react** to antigens such as with allergies.
- It may **under-react** as with human immunodeficiency virus infection (HIV).
- It may **react to self proteins** as with autoimmune disease.
Auto-Immune Diseases

The immune system sees “self” antigens as “non-self”.

• The autoimmune response results in tissue damage;
  – Some damage occurs in only one or a few organs;
  – In other cases it may be body-wide (systemic).

• \( \sim 3.5 \% \) of people have autoimmune diseases;
  On average, women are 2.7 times more likely to develop these diseases than men.

• The cause may be due to genetic factors, infectious agents, gender, and age.

Most auto-immune diseases have no known cause or cure - treatment is aimed at controlling symptoms.
Why Does the Immune System Attack What it’s Supposed to Protect?

• Failure to recognize some cells as “self”
  – In rheumatic fever, the streptococcus antigen is very similar to a protein in heart tissue, so the body mistakenly identifies heart tissues as foreign.

• Cells seen as foreign are attacked and destroyed
  – May be organ-specific, targeting a few select cells or organs;
  – May be systemic.
Auto-Immune Diseases

- **Organ-Specific**
  - Multiple Sclerosis
  - Juvenile Diabetes

- **Systemic**
  - Systemic Lupus Erythematous
  - Rheumatoid Arthritis
BECHETS DISEASE
Systemic Lupus Erythematousus (SLE)

- A chronic systemic autoimmune disease.
  - Complexes of anti-self antibodies and antigen deposit in, and cause tissue damage.
- 1 million sufferers in the U.S.
  - SLE strikes women nine times more often than men.
- Symptoms may include a butterfly-shaped rash on face, fatigue, and headaches.
- Triggered by environmental effects in persons who are genetically susceptible.

Lupus “butterfly” rash

Damaged kidney (left) caused by immunoglobulin deposits (right)
Rheumatoid Arthritis (RA)

- A chronic systemic autoimmune disease.
  - Anti-self antibodies that react with the constant regions of other antibodies (rheumatoid factor).
- Disease onset occurs most often between the ages of 25 – 55.
  - Women are 3 times more likely to develop this than men.
- Symptoms include weakness, fatigue, and joint pain.
- Infections, hormones and genetic factors may be involved.

X-ray shows severe arthritis affecting the joints and limiting mobility.
Multiple Sclerosis (MS)

- A chronic organ-specific disease - may be mild or severe.
  - MS involves the destruction of the myelin sheath that covers cells of the spinal cord and brain.
- Affects ~ 1 in 1,600 people.
  - 60% of the cases occur in women.
- Symptoms include weakness, tremors or paralysis of one or more extremities, numbness, decreased memory and attention span and may disappear and recur over time.
- Infections, hormones and genetic factors may be involved.
Juvenile Diabetes

- Also known as Type - I diabetes or insulin-dependent.
  - Beta-cells in the pancreas produce little or no insulin.
- Usually occurs before the age of 30.
  - Occurs in 1 in 7,000 children each year.
  - The incidence decreases after the age of 20.
- Symptoms include increased thirst and urination, weight loss, nausea, and fatigue.
- Cause is linked to genetic, viral, and autoimmune factors.
I am only half my mom!

How does mom’s immune system tolerate me?
TH1 and TH2 Balance

Delayed-type hypersensitivity (DTH), cytotoxicity

Influence of immunological factors including cytokines

Humoral immunity

Allergy, antibody-mediated autoimmune diseases, tolerance

T-cell-mediated autoimmunity, graft rejection

Th1 cell

Th2 cell

A model to illustrate the complex balance between T helper 1 (Th1) and Th2 cells

Expert Reviews in Molecular Medicine ©2000 Cambridge University Press
WHERE IS THE WORST?

This map shows the four cities with the highest measured one-day readings for seasonal allergens (plus Louisville’s highest readings) in the year 2000, as reported by the National Allergy Board.

For comparative readings from other cities, see the chart on Page 2. (Note: Readings are not taken in all cities, and monitoring methods vary.)

Source: National Allergy Board of the American Academy of Allergy, Asthma and Immunology (aaaai.org).
Used by permission.

BY JOANNE WEISHEW AND KIM KOLARK, THE C-T

WHAT POLLEN COUNTS MEAN
Numbers are grains of pollen or mold spores per cubic meter

<table>
<thead>
<tr>
<th></th>
<th>Weeds</th>
<th>Grasses</th>
<th>Trees</th>
<th>Molds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-10</td>
<td>0-6</td>
<td>0-15</td>
<td>0-6,500</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-50</td>
<td>5-20</td>
<td>15-90</td>
<td>6,500-13,000</td>
</tr>
<tr>
<td>High</td>
<td>50-500</td>
<td>20-200</td>
<td>90-1,500</td>
<td>13,000-60,000</td>
</tr>
<tr>
<td>Very high</td>
<td>500+</td>
<td>200+</td>
<td>1,500+</td>
<td>50,000+</td>
</tr>
</tbody>
</table>

Symptoms

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Only individuals extremely sensitive to these pollens and molds will experience symptoms.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Many individuals sensitive to these pollens and molds will experience symptoms.</td>
</tr>
<tr>
<td>High</td>
<td>Most individuals with any sensitivity to these pollens and molds will experience symptoms.</td>
</tr>
<tr>
<td>Very high</td>
<td>Almost all individuals with any sensitivity to these pollens and molds will experience symptoms.</td>
</tr>
</tbody>
</table>
What is in the Air Now?

Tree Pollen
Corylus = Hazelnut
Alnus = Alder
Betula = Birch
Ambrosia = Ragweed
Gramineae / Poaceae = Grass
Ulmus americana (Ulmaceae) 30um
American Elm
Quercus spp. (Fagaceae) 27-45um
Oak
Celtis occidentalis (Ulmaceae) 28-30um
Hackberry
Acer saccharum (Aceraceae)  28-38um  
Sugar Maple
Fraxinus spp. (Oleaceae) 19-34um Ash
Morus alba (Moraceae) 20-22ug
White Mulberry
Pinus strobus (Pinaceae) 68-81um
White Pine
What Makes The Willamette Valley Unique?
Pollen Particles

Release of small particles from hydrated grass pollen
(a detailed explanation of the figure appears on page 5A)
At the Coburg Fire Station
Questions?