Allergy and Immunology

Kraig W. Jacobson
M.D., CPI

Feb. 6, 2018
Contact Dermatitis
Contact Dermatitis
Contact Dermatitis
Vasculitis
Subacute Cutaneous Lupus
Guttate Psoriasis
What is the Immune System 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

- ery
- pl
- neu
- mφ
- nk
- thy
- CD8+
- CD4+
- TH1
- TH2
- CTL
- mye
- lym
The Immune System

Innate
- physical barriers
- natural killer cells
- macrophages

Toll-like receptors
Complement

Cell-mediated
- T & B cells

Acquired
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

** 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

** Whole Body **

- Molecular and cellular defence
- Pattern recognition molecule e.g. TLRs
- Neutrophils
- Macrophages
Except for IgE allergic reactions
Model of Immune Responses: Speed and Specificity

- Innate immune responses
- Adaptive responses

(time after infection vs. response)
INNATE IMMUNITY
Physical Barriers

- skin
- hair
- mucous
prurigo nodularis
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
  - C3
  - C4
  - C4b, 2a

**Alternative**
- Microbes
  - C3(H₂O), Bb
  - Recurrent pyogenic infections (Strep. pneumonia)
  - Glomerulonephritis, SLE

**Membrane Attack Complex**
- Bactericidal Activity

- C5
  - C5a
  - C5b, 6, 7, 8, 9

- Factor H
  - Familial HUS
  - Age-related Macular Degeneration

- Anaphylotoxin
  - C3a
Immune System – Garbage Disposal is Important
Complement and Phagocytes Aid in Clearance of Cell Debris

Autoimmunity

DNA, HMGB1 → Type I IFN

ANA →
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
The Human Toll-like Receptor Family

TLRs

LPS  Flagellin  Various Membrane/Wall Components

TLR4  TLR5  TLR1  TLR2  TLR6  TLR10

ENDOSOME

dsRNA  ssRNA  Viral and Bacterial Nucleic Acids

dsDNA

INNATE IMMUNE RESPONSE
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.[9] 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.
**B CELL CLONAL EXPANSION**

1. **B cells**
   - **B cells encounter and bind to antigen.**

2. **Antigens**
   - **B cell c responds to antigen by proliferating.**
   - **Clone of B cells**
   - **Some B cells differentiate into long-lived memory cells.**
   - **Other B cells differentiate into plasma cells.**

3. **Memory cells**

4. **Plasma cells**
   - **Plasma cells secrete antibodies into circulation.**

---

**Cardiovascular system**

Copyright © 2001 Benjamin Cummings, an imprint of Addison Wesley Longman, Inc.
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
**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

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
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 = Macro globulin, 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
Antibody Drawing
Extracellular bacteria

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
Pathophysiology of Allergic Inflammation: Sensitization

Phase 1: Sensitization

1. Allergens
2. Antigen-presenting cell
3. Processed allergens
4. CD4 T cell
5. B cell
6. IgE antibodies
7. Plasma cell

Sensitization Phase 1: Sensitization
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**

**Hyper-responsiveness**

**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
Oralair 300 IR
(sweet vernal, orchard, perennial rye, timothy, and kentucky blue grass mixed pollens allergen extract) TABLET FOR SUBLINGUAL USE
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.
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 Erythematosus
  - Rheumatoid Arthritis
BECHETS DISEASE
Systemic Lupus Erythematosus (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.

Magnetic resonance image of brain of patient with chronic form of multiple sclerosis, showing characteristic lesions of MS (white spots)
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.
Questions?