Development of the Immune System

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nk

CD8+

CD4+

TH1

TH2

CTL

CD8+

CD4+

CTL

TH1

TH2

CD8+

CD4+
The Immune System

Innate
- physical barriers
- natural killer cells
- macrophages

Toll-like receptors
Complement

Cell-mediated
- T & B cells

Humoral
- antibody-mediated

Acquired
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 IMMUNITY

Physical Barriers

- skin
- hair
- mucous
INNATE IMMUNITY

Chemical Barriers

- sweat
- tears
- saliva
- stomach acid
- urine
Fallagrin 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

**Alternative**
- Microbes
  - C3(H$_2$O), Bb
- Recurrent pyogenic infections (*Strep. pneumonia*)
- Glomerulonephritis, SLE
- Anaphylotoxin
  - C3a
  - C3b, Bb, P
  - Opsonin
- Factor I
- Factor H

**Membrane Attack Complex**
- Bactericidal Activity

- Recurrent *Neisserial* infections
- Familial HUS
- Age-related Macular Degeneration
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
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)
The Human Toll-like Receptor Family

TLRs

TLR4  TLR5  TLR1  TLR2  TLR6  TLR10

LPS  Flagellin  Various Membrane/Wall Components

TLR3  TLR7  TLR8  TLR9

dsRNA  ssRNA  ssRNA  dsDNA

Viral and Bacterial Nucleic Acids

ENDOSOME

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.
Bursa of Fabricus
**B CELL CLONAL EXPANSION**

1. **B cells**
   - **a**
   - **b**
   - **c**
   - **d**
   - **e**
   - **f**

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**

5. **Cardiovascular system**
   - **Antibodies**
   - **Plasma cells secrete antibodies into circulation.**

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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
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
GALT = Gut Associated Lymphoid Tissue
BALT = Bronchial Associated Lymphoid Tissue
GENITAL TRACT

• **no** associated lymphoid tissue
• **no** clear site of immunologic priming
Antigen Processing

- Macrophage
- T cell
- B cell

Bacteria
Remember the 5 Classes of Antibodies

- Ig = Immunoglobulin

  **G** - **A** - **M** - **E** - **D**

- Ig\textsubscript{G} = “**G**ood” major antibody class
- Ig\textsubscript{A} = “**A**ppetite” to “**A**” hole, orifices
- Ig\textsubscript{M} = **M**acroglobulin, first one out
- Ig\textsubscript{E} = “**E**vil”, causes allergies
- Ig\textsubscript{D} = “**D**umb class”, does nothing
Antibody Structure

- **Two Heavy Chains**
  - IgA = $\alpha$ Alpha
  - IgD = $\delta$ Delta
  - IgM = $\mu$ Mu
  - IgE = $\varepsilon$ Epsilon
  - IgG = $\gamma$ Gamma

- **Two Light Chains**
  - Kappa $\kappa$
  - Lambda $\lambda$
Antibody Drawing

Antigen
Antigen-binding fragment

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

Digestion in lysosome:

Digestion by macrophage:

Opsonization:
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
CD4 CELLS with HIV

The diagram shows the changes in CD4 cell count over time for different progressors of HIV infection. The y-axis represents the CD4 count with values ranging from 200 to 1500. The x-axis represents time in years from primary infection (approx. 6 months) to 10 years.

- **Fast Progressor**: The CD4 count drops rapidly and remains low. Treatment with ARV (抗病毒药物) is indicated after 2-3 years.
- **Average Progressor**: The CD4 count drops significantly in the early years but recovers slightly. Treatment with ARV is indicated after 7-8 years.
- **Slow Progressor**: The CD4 count remains relatively stable, with a gradual decline over time. No immediate treatment with ARV is indicated.

The graph illustrates the importance of early detection and treatment to prevent rapid decline in CD4 cell counts, which can lead to AIDS.
ALLERGIES?
Pathophysiology of Allergic Inflammation: Sensitization

Phase 1: Sensitization

- Allergens
- Antigen-presenting cell
- Processed allergens
- CD4 T cell
- B cell
- IgE antibodies
- Plasma cell

Sensitization Phase 1:
- Antigen-presenting cell presents processed allergens to CD4 T cells and B cells.
- B cells produce IgE antibodies.
- Plasma cells produce IgE antibodies.

IgE antibodies bind to mast cells and basophils, leading to allergic reactions upon re-exposure to allergens.
Pathophysiology of Allergic Inflammation: Clinical Disease

Phase 2: Clinical Disease

Early Inflammation

Allergens

IgE antibodies

Mast cell

Mediator release

Blood vessels

Sneezing

Rhinorrhea

Congestion

Late Inflammation

Cellular infiltration

Eosinophils

Basophils

Monocytes

Lymphocytes

Late-phase reaction

Priming

Hyper-responsiveness

Resolution

Complications

Irreversible disease (?)
In the midst of final exams, Noreen developed an allergic reaction to algebra.
ST  DOB: 04-09-1995
Skin Tests 12-28-2001  Weeds, Trees, Mixed Grass, Cat Pelt
Three Legged Stool of Allergy Treatment

1. Avoidance
2. Medications
3. Immunotherapy
Medications
Immunotherapy
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

IL-18

activated T-Cells

draining Lymphnode

naïve T-Cells
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
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).

- ~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
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.

![Normal pancreas](image1)
![Diabetic pancreas](image2)
I am only half my mom!
How does mom’s immune system tolerate me?
TH1 and TH2 Balance

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 MESSOW AND KIM KOLARK, THE C-J
What is in the Air Now?

Tree Pollen
Pollen Forecast

<table>
<thead>
<tr>
<th>Trees</th>
<th>Absent</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeds</td>
<td></td>
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</tbody>
</table>

Kraig W. Jacobson, M.D. and Robert F. Jones, M.D., Allergy & Asthma Research Group
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?