Allergy and Immunity

Presented by: Dr. Dana Aljomah
Introduction

- **Immune system**: composed of a complex set of elements that is designed to distinguish between “self” and “non-self”.
- **self-tolerance**
- **Immune system:**
  1. Innate immunity system.
  2. Adaptive immunity system.
INNATE IMMUNITY

- Non-specific immunity, the organism have no memory of previous contact.
- includes all aspects of the host defense mechanisms that are encoded in the germ-line genes of the host.
- Examples include:
  1. Biologic (skin and surface lining barrier, stomach acid, lysosome)
  2. Antigen-presenting cells APC.
  3. PMN leukocyte and monocyte.
  4. Complement.
  5. Interleukins.
  6. Interferons.
  7. Other cytokines (TNF).
ADAPTIVE IMMUNITY

- Specificity of antigen recognition
- Second line defense.
- Has immunological memory.
- Include: T and B lymphocytes.
- Mediated through antigen-specific receptors on the surface of T and B lymphocytes and through antibodies.
- The two major effector arms of the adaptive immune response are humoral and cellular.
CELLULAR IMMUNE RESPONSES

- Primed T cell through T-cell receptor coming in contact with antigen on an MHC II of an APC.

- Formation of either a CD4+ or a CD8+ T cell.

- Secretion of many cytokines and mediators → activate macrophages for phagocytic and microbicidal activity.
HUMORAL IMMUNE RESPONSE

- mediated by secreted antibodies.

- Primed Th cell comes into contact with specific B cell causing B-cell activation and differentiation into antibody-secreting plasma cells.

- Affect extracellular microbes.
Major Histocompatibility complex

- Important in immune system.
- Regulation of all immune response, including transplantation reactions.
- Principal function: bind fragments of foreign protein, forming complexes that are organized by T cells.
- MHC in humans: HLA, gene found on chr.6
- MHC:
  - **Class I**: present on the surface of most nucleated somatic cells.
  - **Class II**: molecules are expressed primarily on immunocompetent antigen-presenting cells (APC).
cluster of differentiation system (CD)

- A system of classifying lymphocytes according to the collections of antigens on the surface of their cell membranes.

- Each CD has a specific role in cell signaling and communication, guiding cell function and response.

- CDs are critical to the normal function of the Immune system.
Some of the major CDs are

- **CD-1**, which populates B-cell lymphocytes and macrophages and has a role in antigen presentation
- **CD-2**, which populates T-cell lymphocytes and natural killer (NK) cells and activates T-cells
- **CD-3**, which populates T-cell lymphocytes and facilitates antigen binding (the ability of T-cell lymphocytes to receive biochemical messages)
- **CD-4**, which populates T-helper cells (T-cell lymphocytes that direct immune response to infection) and is a key marker for monitoring the progression of HIV/AIDS.
- **CD-5**, which populates B-cell lymphocytes that produce IMMUNOGLOBULIN M (IgM)
- **CD-7**, which populates T-cell lymphocytes in acute lymphocytic leukemia (ALL) and is a marker for STEM CELL leukemias
- **CD-8**, which populates T-suppressor cells (T-cell lymphocytes that end the immune response) and is a key marker for monitoring the progression of HIV/AIDS
T cells

- Leave the marrow; differentiate in the thymus into cytotoxic CD8+ cells or helper CD4+ cells.

- Make up 60-70% of lymphocytes; concentrated in LN and spleen.

- Contribute to cell-mediated immunity.

- CD4+ interacts with MHC-II on APCs; CD8+ interacts with the MHC-I on all cells.
T Cells

- CD4+ develop into two different subsets:
  - Th1 cells secrete IFN-γ, IL-2, TNF-α, and TNF-β, which are important for eliminating intracellular pathogens
  - Th2 cells secrete IL-4, IL-5, IL-6, and IL-13, which are important for the elimination of extracellular organisms

- CD8+ cells secrete cytokines of the Th1 type and function primarily as cytotoxic cells promoting death of cells that are recognized by the immune system as infected.
Macrophage Presents Antigen

Maturation

Thymus

T cell from bone marrow

Lymphokines

T lymphocyte (activated by presenting cell)

Clonal Expansion

MHC antigen complex

Cytotoxic T cell

Memory T cell

Suppressor T cell

Helper T cell

virus-infected cell
B Cells

- Leave the marrow and congregate in lymphoid tissues.
- Constitute approximately 10%-15% of peripheral blood leukocytes.
- B cell mature under the influence of T cell.
- Coordinate humoral response; activated through their surface IgM receptors.
- Once B cells activated differentiate into plasma cells, which are responsible for secreting different classes of immunoglobulins.
1. Immunoglobulin receptors on B cell surface recognize and attach to antigen, which is then internalized and processed. Within the B cell a fragment of the antigen combines with HLA class II.

2. HLA class II–antigen-fragment complex is displayed on B cell surface.

3. Receptor on the T helper cell (TH) recognizes complex of HLA class II and antigen fragment and is activated—producing cytokines, which activate the B cell.

4. B cell is activated by cytokines and begins clonal expansion. Some of the progeny become antibody-producing plasma cells.
Large Granular Lymphocytes

- referred to as *natural killer cells*.
- These cells are usually larger than typical lymphocytes and display less nuclear material and more cytoplasm.
- Provide nonspecific cytotoxic activity toward virally infected cells and tumor cells.
- mediate antibody-dependent cellular cytotoxicity (ADCC) by activation through their IgG Fc receptors.
Myeloid system

- **Neutrophils**
  - AKA PMNs; circulating and marginal pools; involved in acute inflammation; have countless roles, including initial chemotaxis and extravasation
  - Rarely increased with seasonal allergy; role here unknown

- **Eosinophils**
  - Produced in marrow; localize to inflammatory tissue

- **Basophils**
  - Granulocytes with high affinity for IgE receptors
  - Contain histamine; can contribute to anaphylaxis

- **Monocytes**
  - Originate in marrow then released into blood
  - They produce complement components
  - Can mature/differentiate into macrophages, which can then recognize and ingest foreign or damaged material
    - They can produce oxygen and nitrogen radicals
    - They are Ag presenters, T-cell stimulators, and can contribute to eosinophil migration
LYMPHOID ORGANS

Primary lymphoid organs:
1. Thymus.
2. Bone marrow.

Secondary lymphoid organs:
1. Systemic (spleen, LN)
2. Mucosal (tonsils, Peyer’s patches)
ANTIGEN PRESENTATION

- carried out by specialized cells referred to as antigen-presenting cells (APC),

- a diverse group of leukocytes including monocytes, macrophages, dendritic cells, and B cells.

- APC express high levels of class II MHC molecules.
Immunoglobulins

- Are glycoproteins composed of polypeptide (82%–96%) and carbohydrate (4%–18%).
- Produced by activated B cells.
- They account for approximately 20% of the total plasma proteins.
• 4 polypeptide chains connect with disulphate bonds.
  ➢ 2 identical light chains.
  ➢ 2 identical heavy chains.
• Constant region
• Variable region
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Monomer</td>
<td>Pentamer</td>
<td>Dimer (with secretory component)</td>
<td>Monomer</td>
<td>Monomer</td>
</tr>
<tr>
<td>Percentage of total serum antibody</td>
<td>80%</td>
<td>5–10%</td>
<td>10–15%*</td>
<td>0.2%</td>
<td>0.002%</td>
</tr>
<tr>
<td>Location</td>
<td>Blood, lymph, intestine</td>
<td>Blood, lymph, intestine</td>
<td>Secretions (tears, saliva, mucus, intestine, milk), blood lymph</td>
<td>B cell surface, blood, lymph</td>
<td>Bound to mast and basophil cells throughout body, blood</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>150,000</td>
<td>970,000</td>
<td>405,000</td>
<td>175,000</td>
<td>190,000</td>
</tr>
<tr>
<td>Half-life in serum</td>
<td>23 days</td>
<td>5 days</td>
<td>6 days</td>
<td>3 days</td>
<td>2 days</td>
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<tr>
<td>Complement fixation</td>
<td>Yes</td>
<td>Yes</td>
<td>No†</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Placental transfer</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Known functions</td>
<td>Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn</td>
<td>Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection</td>
<td>Localized protection on mucosal surfaces</td>
<td>Serum function not known; presence on B cells functions in initiation of immune response</td>
<td>Allergic reactions; possibly lysis of parasitic worms</td>
</tr>
</tbody>
</table>

*Percentage in serum only; if mucous membranes and body secretions are included, percentage is much higher.
†May be yes via alternate pathway.
Allergic Response

- **Incidence:** 17% to 32% of population is symptomatic.
- **Allergen:** antigen that causes an allergic reaction.
- **Allergic reaction:** an immune response with deleterious effect on the host.

- **Gell and coombs’ classification (1975):**
  - Divided allergic reactions into 4 types.
  - Antibody mediates the first three; T cells and macrophages, the fourth.
I. Mast cells release IgE.
- Active substances such as histamine
- Vasodilatation
- Mucous secretion
- Bronchoconstriction
- Itch
- Related conditions: Allergic rhinitis, Urticaria, Asthma, Anaphylaxis

II. IgG damages by lymphocyte.
- Uptaken by macrophage
- Dissolved by complement
- Related conditions: Autoimmune hemolytic anemia, Idiopathic thrombocytopenic purpura

III. Immune complex formation.
- Immune complex adhesion
- Dissolved by complement
- Related conditions: Hemolytic anemia, Hypersensitivity pneumonia, SLE, RA

IV. Inflammatory cells generate cytokine.
- Cytokine activates T lymphocyte
- Damaged by cytotoxic T lymphocyte
- Related conditions: Contact dermatitis, Liver damage due to drug allergy
- Delayed type hypersensitivity T lymphocyte
Allergy Testing

**In vivo**
- Epicutaneous or percutaneous (SPT)
- Intradermal or intracutaneous (ID)
- Allergen challenge

**In vitro**
- Serum total IgE
- Radioallergosorbent/ImmunoCAP Test
- Serum tryptase
In vivo Allergy testing

- **Epicutaneous (Scratch – Prick):**
  - **Technique:**
  - **Advantages:**
    1. Rapid.
    2. Relatively safe.
  - **Disadvantages:**
    1. Qualitative measure of allergy only.
    2. False negative.
    3. Grading of skin test is subjective.
Intradermal Tests

- **Technique**
- **Advantages:**
  1. Highly sensitive.
  2. Reproducible in one office visit.
- **Disadvantages:**
  1. Qualitative.
  2. Grading subjective.
  3. No standardization to the amount of test dose.
  4. Variable results between offices.
  5. False positive, due to high sensitivity.
Intradermal Dilution titration

- Three methods
  - 1:10 dilutions Some general allergists
  - 1:5 dilutions ENT allergists
  - 1:3 dilutions for antigen standardization

**Advantages:**
1-Quantitative.
2-Highly producible.
3-Very sensitive.
4-Safe.

**Disadvantages:**
1-Time consuming.
2-False positive.
3-Need more supplies.
Factors Affecting Whealing Response

- **Degree of sensitization of cutaneous mast cells**
  - Recent exposure
  - Prior immunotherapy

- **Area of body tested**
  - upper back > lower back > upper arm > lower arm

- **Age of patient**
  - pediatric, geriatric patients may be less sensitive

- **Local axonal reflexes**
  - Separate tests by 2 cm.
Factors Affecting Whealing Response

- Concomitant foods

- Circadian rhythms
  - Most sensitive 7:00-11:00 PM

- Dermatopathology
  - Eczema

- Medications
Medication Effect on Skin Whealing

- **Supress whealing; within 48-72 hours**
  - Antihistamines
  - Tricyclic antidepressants

- **Do not significantly affect whealing**
  - Oral Corticosteroids
  - Leukotriene modifiers
  - Bronchodilators
  - Decongestants
  - NSAIDS
Skin Test Controls

- **Positive control** (is the skin able to react?)
  - Histamine 0.0004 mg/ml
  - 4 mm wheal should grow to 7 mm or greater

- **Negative control** (reaction to physical trauma?)
  - Diluent
  - 4 mm wheal should grow to 5 mm or less
In vitro Allergy testing

- **Total IgE**
  - Initially used in screening for atopic and Type 1 hypersensitivity reaction.
  - Non-specific because too many symptomatic patients with normal level total IgE.
  - Total IgE together with specific IGE levels were proposed for a more efficient diagnosis.
  - Serial measurement of total IgE is useful in the management of patients with allergic fungal sinusitis.
Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis
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Abstract
Concerning allergic diseases, the incidence of allergic symptoms, as well as their severity, seems to decrease with age. The decline of onset of allergic symptoms observed in ageing might result from a decrease of serum total and specific IgE. Atopic disorders are complex diseases that involve interactions among several physiological systems, e.g. skin, lung, mucosae, and the immune system. It was the aim of this study to compare the effects of age on total and specific IgE in patients with atopic dermatitis (AD), allergic rhinitis or asthma, and insect allergy, respectively.

The study population consisted of 559 individuals (male: 229 and female: 330). Total and allergen specific IgE was measured in every individual. From the whole study population, 113 patients suffered from atopic dermatitis (AD), 132 had allergic rhinitis or asthma, and 314 were tested because of insect allergy. Total and specific serum IgE was significantly decreased as a function of age in patients with allergic rhinitis and asthma and with insect allergy. In contrast, no significant decrease of total and specific serum IgE in old individuals with AD was observed. Additionally, in the group of patients with a total IgE < 300 kU/l a reduction of total serum IgE was significantly correlated with age. In contrast, patients with IgE levels > 300 kU/l showed no correlation with age. Immunosenescence does not affect increased IgE levels in atopic patients with AD and/or high serum IgE levels indicating that in these subgroups of patients the atopic propensity remains into advanced age. One may hypothesize that either onset of allergic sensitization during life or the kind of atopic disease influences the correlation between age and IgE synthesis.

Conclusion
In summary, this study shows that total and allergen specific IgE production is reduced in the elderly with the exception of old patients with either high serum IgE or AD, indicating that atopic mechanisms underlying AD or other atopic diseases with high serum IgE are particularly robust, and the atopic propensity among these patients remains into advanced age. However, further studies are required to clarify the immunological mechanisms which are responsible for IgE synthesis during immunosenescence.
In vitro Allergy testing

- **RAST test**
  - radioallergosorbent test.
  - detect specific IgE antibodies to suspected or known allergens.
**Advantages:**
1. Eliminates variability of the skin test.
2. Eliminate drug effects.
3. Done in one blood test.
5. Quantitative assessment.
6. Safe

**Disadvantages:**
1. More expensive.
2. Less sensitive than skin test.
ELISA

- enzyme-linked immunosorbent assay.

- It measures the blood level of a type of antibody (called immunoglobulin E, or IgE).

- The process involves enzymatic or fluorometric processes rather than a radioactive marker.
## Comparison of In Vitro and Skin Testing Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>In Vivo</th>
<th>In Vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>high</td>
<td>less</td>
</tr>
<tr>
<td>Specificity</td>
<td>less</td>
<td>high</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>high*</td>
<td>high</td>
</tr>
<tr>
<td>Quantitation</td>
<td>high*</td>
<td>high</td>
</tr>
<tr>
<td>Safety</td>
<td>good</td>
<td>excellent</td>
</tr>
<tr>
<td>Cost</td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td>Time for Results</td>
<td>minutes</td>
<td>hours-days</td>
</tr>
<tr>
<td>Staff Time Required</td>
<td>more</td>
<td>less</td>
</tr>
<tr>
<td>Comfort</td>
<td>fair</td>
<td>high</td>
</tr>
<tr>
<td>Convenience</td>
<td>less</td>
<td>very high</td>
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<tr>
<td>Affected by Drugs</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Affected by Skin Condition</td>
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<td>no</td>
</tr>
<tr>
<td>Test Antigens Available</td>
<td>most</td>
<td>most</td>
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<tr>
<td>Technical Complexity</td>
<td>no</td>
<td>yes**</td>
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<td>Quality Control</td>
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<td>required</td>
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<td>Covered by OSHA regulations</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Covered by CLIA regulations</td>
<td>no</td>
<td>yes</td>
</tr>
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</table>

* When SET is used, ** Not complex if automated equipment used.
REFERENCES


• K.J LEE : Essential otolaryngology, Head & Neck Surgery, 9th ed.