Immunopathology

SCPA202 Basic Pathology

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Objectives

• Understand the **etiology** of immunological disorder
• Understand the **mechanism of hypersensitivity reaction**
• Understand the **pathogenesis and pathology** of common immunological disorder
Normal immune response
Immunopathology is a branch of medicine that deals with immune responses associated with disease:

1. Hypersensitivity reactions (e.g. allergy)
2. Autoimmunity (immune responses to self)
3. Deficiency state (congenital or acquired)
4. Amyloidosis (extracellular protein accumulation)
Hypersensitivity

- **Hypersensitivity** is a set of undesirable reactions produced by the normal immune system, including **allergies** and **autoimmunity**
- An **over-reaction** of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal
- An imbalance between the effector mechanisms of immune responses and the control mechanisms that serve to normally limit such responses
- Require a **pre-sensitized** state of the host
- 4 groups
**Type I: Immediate Hypersensitivity**

- **Rapid** immunologic reaction

- The combination of an antigen with antibody bound to mast cells in individuals *previously sensitized* to antigen

- These reactions are often called *allergy*
Type I: Immediate Hypersensitivity

- **Exposure to allergen**
- **Activation of T\(_{H2}\) cells and IgE class switching in B cells**
- **Production of IgE**
- **Binding of IgE to Fc\(_e\)RI on mast cells**
- **Repeat exposure to allergen**
- **Activation of mast cell; release of mediators**
- **Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)**

**Immediate reaction**
- Vasodilation
- Vascular leakage
- Smooth muscle spasm

**Late phase reaction** (2–24 hours after repeat exposure to allergen)

**Membrane phospholipids**
- Arachidonic acid
- Prostaglandin D\(_2\)
- Leukotrienes B\(_4\), C\(_4\), D\(_4\)

**Granule contents**
- Histamine
- Proteases
- Chemotactic factors (ECF, NCF)

**Secreted cytokines**
- Signals for cytokine gene activation
- Signals for activation of phospholipase A\(_2\)

**Antigen**
- IgE
- IgE Fc receptor

**Signals for degranulation**

**Degranulation**

**Signals for activation of phospholipase A\(_2\)**

**Nucleus**
Type I: Immediate Hypersensitivity

• Prototypic Disorder

1. Systemic reaction
   ▪ The systemic reaction usually follows injection of an antigen into a sensitized individual
   ▪ Sometimes, within minutes the patient goes into a state of shock

2. Local reaction
   ▪ Local reactions are diverse and vary depending on the portal of entry of the allergen

• Pathologic lesions
  • Vascular dilation
  • Edema
  • Smooth muscle contraction
  • Mucus production
  • Tissue injury
  • Inflammation

http://hubpages.com/health/Anaphylaxis-symptoms
Systemic Anaphylaxis

- Characterized by vascular shock, widespread edema, and difficulty in breathing
  - Foreign proteins
  - Food allergens
  - Insect toxins
- Within minutes after exposure, itching, hives, and skin erythema appear, followed by a striking contraction of respiratory bronchioles and respiratory distress
About 10% to 20% of the population suffers from allergies involving localized reactions to common environmental allergens.

- Pollen, animal dander, house dust, foods
- Specific diseases include urticaria, angioedema, allergic rhinitis (hay fever), and bronchial asthma
Type II : Antibody-Mediated Hypersensitivity

- Caused by antibodies that react with antigens present on cell surfaces or in the extracellular matrix
- Inflammation (when antibodies deposit)
- Cellular dysfunction (e.g. myasthenia gravis)

Clinically, antibody-mediated cell destruction occur as following:
- Transfusion reaction
- Hemolytic disease of newborn (erythroblastosis fetalis)
- Autoimmune hemolytic anemia
- Drug reactions
Type II: Antibody-Mediated Hypersensitivity

Mechanisms of antibody-mediated injury

- Acetylcholine (ACh)
- Neuron ending
- Antibody to ACh receptor
- ACh receptor
- Muscle
- Thyroid epithelial cell
- Thyroid hormones
- Antibody against TSH receptor
- Antibody stimulates receptor without hormone
- Neutrophil enzymes, reactive oxygen intermediates
- Complement by-products (C5a, C3a)
- Complement activation
- Myasthenia gravis
- Graves disease (hyperthyroidism symptoms)
Erythroblastosis fetalis

- Erythroblastosis fetalis is hemolytic anemia in the fetus caused by transplacental transmission of maternal antibodies to fetal RBC
# Type II: Antibody-Mediated Hypersensitivity

**TABLE 6-4  Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target Antigen</th>
<th>Mechanisms of Disease</th>
<th>Clinicopathologic Manifestations</th>
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<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Red cell membrane proteins (Rh blood group antigens, I antigen)</td>
<td>Opsonization and phagocytosis of red cells</td>
<td>Hemolysis, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet membrane proteins (GpIib:IIIa integrin)</td>
<td>Opsonization and phagocytosis of platelets</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Proteins in intercellular junctions of epidermal cells (epidermal cadherin)</td>
<td>Antibody-mediated activation of proteases, disruption of intercellular adhesions</td>
<td>Skin vesicles (bullae)</td>
</tr>
<tr>
<td>Vasculitis caused by ANCA</td>
<td>Neutrophil granule proteins, presumably released from activated neutrophils</td>
<td>Neutrophil degranulation and inflammation</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli</td>
<td>Complement- and Fc receptor-mediated inflammation</td>
<td>Nephritis, lung hemorrhage</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen</td>
<td>Inflammation, macrophage activation</td>
<td>Myocarditis, arthritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Antibody inhibits acetylcholine binding, down-modulates receptors</td>
<td>Muscle weakness, paralysis</td>
</tr>
<tr>
<td>Graves disease (hyperthyroidism)</td>
<td>TSH receptor</td>
<td>Antibody-mediated stimulation of TSH receptors</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
<td>Antibody inhibits binding of insulin</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor of gastric parietal cells</td>
<td>Neutralization of intrinsic factor, decreased absorption of vitamin B₁₂</td>
<td>Abnormal erythropoiesis, anemia</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.
Type III: Immune complex-mediated hypersensitivity

• Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition

• Immune complex–mediated diseases can be *systemic*, if immune complexes are formed in the circulation and are deposited in many organs

• *localized* to particular organs, such as the
  • kidney (glomerulonephritis)
  • joints (arthritis)
Pathogenesis of systemic immune complex–mediated disease (type III hypersensitivity). The three sequential phases in the development of immune complex diseases are shown.
Type III: Immune complex-mediated hypersensitivity

- Pathology of immune complex-mediated hypersensitivity
  - Immune complex vasculitis
  - The necrotic vessel wall is replaced by smudgy, pink “fibrinoid” material
  - Fibrinoid necrosis

Immune complex vasculitis. The necrotic vessel wall is replaced by smudgy, pink “fibrinoid” material.
Rheumatoid arthritis

- Rheumatoid arthritis is a chronic systemic inflammatory disorder that may affect many tissues and organs—skin, blood vessels, heart, lungs, and muscles—but principally attacks the joints
- Producing a nonsuppurative proliferative and inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints

- Genetic predisposition, environment, and autoimmunity have pivotal roles in the development, progression, and chronicity of the disease
Cross Section through the Metacarpophalangeal and Proximal Phalanx of the Index Finger

Healthy Synovial Joint

Joint with Bony Ankylosis through Rheumatoid Arthritis

Cross section through middle phalanx

Interosseus muscle

Synovial membrane

Thickened synovial membrane

Articular cartilage

Reduced synovial fluid

Cross section through distal phalanx

Tendon

Joint capsule

Missing articular cartilage

Synovial fluid

Collapsed Eroded bone

The results of rheumatoid arthritis leave the joint so badly eroded through the formation of pannus, that the eroded bone collapses in on itself called bony ankylosis
Type IV: T cell-mediated hypersensitivity

• The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T lymphocytes, including CD4$^+$ and CD8$^+$ T cells

  • **Reactions of CD4$^+$ T Cells**: Delayed-Type Hypersensitivity (DTH) and Immune Inflammation

  • **Reactions of CD8$^+$ T Cells**: Cell-Mediated Cytotoxicity
Type IV: T cell-mediated hypersensitivity

Mechanisms of T cell-mediated (type IV) hypersensitivity reactions
Type IV: T cell-mediated hypersensitivity

Reactions of CD4⁺ T Cells: Delayed-Type Hypersensitivity (DTH) and Immune Inflammation

• **Tuberculin reaction** → inject tuberculin → the accumulation of CD4⁺ T cells and macrophage
Type IV : T cell-mediated hypersensitivity

Reactions of CD8⁺ T Cells: Cell-Mediated Cytotoxicity

- CD8⁺ CTLs kill antigen-bearing target cells
- CTLs directed against cell surface histocompatibility antigens play an important role in graft rejection
- Reactions against viruses infected cells, cancer cells
- The killing of infected cells leads to the elimination of the infection, and is responsible for cell damage that accompanies the infection (e.g., in viral hepatitis)
**Type IV: T cell-mediated hypersensitivity**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Specificity of Pathogenic T Cells</th>
<th>Clinicopathologic Manifestations</th>
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<tbody>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)</td>
<td>Insulitis (chronic inflammation in islets), destruction of β cells; diabetes</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Protein antigens in CNS myelin (myelin basic protein, proteolipid protein)</td>
<td>Demyelination in CNS with perivascular inflammation; paralysis, ocular lesions</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown antigen in joint synovium (type II collagen?); role of antibodies?</td>
<td>Chronic arthritis with inflammation, destruction of articular cartilage and bone</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Unknown antigen; role for commensal bacteria</td>
<td>Chronic intestinal inflammation, obstruction</td>
</tr>
<tr>
<td>Peripheral neuropathy; Guillain-Barré syndrome?</td>
<td>Protein antigens of peripheral nerve myelin</td>
<td>Neuritis, paralysis</td>
</tr>
<tr>
<td>Contact sensitivity (dermatitis)</td>
<td>Various environmental antigens (e.g., poison ivy)</td>
<td>Skin inflammation with blisters</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
Autoimmune diseases

Immune reactions against self-antigens

Autoimmunity results from the loss of self-tolerance

How this happens?

Should be understand the mechanism of immunological tolerance to self-antigen
The phenomenon of unresponsiveness to an antigen

**Self-tolerance** = lack of responsiveness to an individual’s own antigens, the mechanisms of self-tolerance can be broadly classified into two groups

- **Central Tolerance** → negative selection = eliminate self-reactive T cells
  → receptor editing = eliminate self-reactive B cells

- **Peripheral Tolerance**
  - **Anergy** → irreversible functional inactivation of lymphocyte by costimulatory signals
  - **Suppression by regulatory T cells** → IL-10, TGF-β
  - **Deletion by activation-induced cell death** → if T cells recognize self-antigens, they may express a pro-apoptotic member of the Bcl family, called Bim
Mechanism of immunological tolerance

Self-reactive T cells

Self-reactive B cells

Death or inactivation

http://www.daisychung.com/#!immunology-cartoon-project/-c14po
Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes.
Autoimmunity: Mechanisms

Pathogenesis of autoimmunity
Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (tissue injury, inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage.
Autoimmune disease

• Systemic Lupus Erythematosus (SLE)
• Sjögren syndrome
• Systemic sclerosis
Systemic Lupus Erythematosus (SLE)

• Multisystem disease of autoimmune origin, characterized by a vast array of autoantibodies, particularly antinuclear antibodies (ANAs)
• The cause of SLE remains unknown
• Both genetic and environmental factors play a role in the pathogenesis of SLE.
SLE: Possible pathogenesis

Model for the pathogenesis of systemic lupus erythematosus. In this hypothetical model, susceptibility genes interfere with the maintenance of self-tolerance and external triggers lead to persistence of nuclear antigens. The result is an antibody response against self–nuclear antigens, which is amplified by the action of nucleic acids on dendritic cells (DCs) and B cells, and the production of type 1 interferons. TLRs, Toll-like receptors.
• Most of the visceral lesions are caused by immune complexes (type III hypersensitivity)
• DNA–anti-DNA complexes can be detected in the glomeruli and small blood vessels
• Autoantibodies specific for red cells, white cells, and platelets opsonize these cells and promote their phagocytosis and lysis.

Lupus nephritis, focal proliferative type. There are two focal necrotizing lesions in the glomerulus (arrows).

Immune complex deposition in SLE
Sjögren syndrome

- **Sjögren syndrome** is a chronic disease characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) resulting from immunologically mediated destruction of the lacrimal and salivary glands.

- The characteristic decrease in tears and saliva (sicca syndrome) is the result of lymphocytic infiltration and fibrosis of the lacrimal and salivary glands.

**Systemic sclerosis** is a chronic disease characterized by:

1. chronic inflammation thought to be the result of autoimmunity
2. widespread damage to small blood vessels
3. progressive interstitial and perivascular **fibrosis** in the skin and multiple organs

Possible mechanisms leading to systemic sclerosis
Immunodeficiency syndromes

- **Primary immunodeficiencies**
  - X-Linked Agammaglobulinemia (Bruton’s Agammaglobulinemia)
  - DiGeorge Syndrome (Thymic Hypoplasia)
  - Severe Combined Immunodeficiency (SCID)
  - Wiskott-Aldrich Syndrome

- **Secondary immunodeficiencies**
  - Acquired immunodeficiency syndrome (AIDS)
X-Linked Agammaglobulinemia

- One of the more common forms of primary immunodeficiency
- Characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells
- Caused by mutations in the X chromosome at Xq21.22
- In most cases, recurrent bacterial infections of the respiratory tract (These organisms are normally opsonized by antibodies and cleared by phagocytosis)

DiGeorge Syndrome

• Is a **T-cell deficiency** that results from hypoplasia or lack of the thymus
• Deletion of a gene that maps to chromosome 22q11
• Poor defense against certain fungal and viral infections

DiGeorge symptoms can be remembered as CATCH-22:

- Cardiac Abnormality (especially tetralogy of Fallot)
- Abnormal face
- Thymic aplasia
- Cleft palate

Severe Combined Immunodeficiency (SCID)

- Defects in both humoral and cell-mediated immune responses
- Susceptible to recurrent, severe infections by a wide range of pathogens
- Without bone marrow transplantation, death occurs within the first year of life
- The genetic defect in the X-linked form is a mutation in the common γ-chain (γc) subunit of cytokine receptors

“Bubble boy” David Vetter, who lived in the sterile environment of a plastic bubble until he died in 1984 at age 12.

Wiskott-Aldrich Syndrome

• Characterized by thrombocytopenia, eczema, and a marked vulnerability to recurrent infection, ending in early death
• The thymus is morphologically normal, but there is progressive secondary depletion of T lymphocytes in the peripheral blood and in lymph nodes
• Caused by mutations in the gene encoding Wiskott-Aldrich syndrome protein (WASP), which is located at Xp11.23
• The only treatment is bone marrow transplantation

Acquired immunodeficiency syndrome (AIDS)

- Caused by the retrovirus human immunodeficiency virus (HIV)
- Characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations
- While HIV can infect many tissues, there are two major targets of HIV infection
  - **Immune system** → severe loss of CD4\(^+\) T cells and impair function of helper T cells
  - **Central nervous system** → Microglia (macrophage lineage) and macrophage in CNS are infected with HIV, neurologic deficit is probably caused indirectly by viral products and by soluble factors produced by infected microglia.
Pathogenesis of HIV infection

The life cycle of HIV, showing the steps from viral entry to production of infectious virions.
Mechanisms of CD4+ T-cell loss in HIV infection, showing some of the known and postulated mechanisms of T-cell depletion after HIV infection. APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte.
Clinical features of AIDS

- The typical adult patient with AIDS presents with fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disease, and, in many cases, secondary neoplasms.

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<th>TABLE 6-14</th>
<th>AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with HIV Infection</th>
</tr>
</thead>
</table>
| PROTOZOAL AND HELMINTHIC INFECTIONS | Cryptosporidiosis or isosporidiosis (enteritis)  
Toxoplasmosis (pneumonia or CNS infection) |
| FUNGAL INFECTIONS | Pneumocystosis (pneumonia or disseminated infection)  
Candidiasis (esophageal, tracheal, or pulmonary)  
Cryptococcosis (CNS infection)  
Coccidioidomycosis (disseminated)  
Histoplasmosis (disseminated) |
| BACTERIAL INFECTIONS | Mycobacterioses ("atypical," e.g., *Mycobacterium avium-intracellulare*, disseminated or extrapulmonary; *M. tuberculosis*, pulmonary or extrapulmonary)  
Nocardiosis (pneumonia, meningitis, disseminated)  
*Salmonella* infections, disseminated |
| VIRAL INFECTIONS | Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)  
Herpes simplex virus (localized or disseminated)  
Varicella-zoster virus (localized or disseminated)  
Progressive multifocal leukoencephalopathy |

CNS, central nervous system.
Secondary neoplasms in AIDS

• Patients with AIDS have a high incidence of certain tumors
• A common feature of these tumors is that they are all believed to be caused by **oncogenic DNA viruses**
  • Kaposi sarcoma herpesvirus (Kaposi sarcoma)
  • Epstein-Barr virus (B-cell lymphoma)
  • Human papillomavirus (cervical and anal carcinoma)
• The increased risk of malignancy in AIDS patients exists mainly because of failure to contain the infections and reactivation of the viruses, as well as decreased immunity against the tumors.

Kaposi sarcoma

https://healthpolis.wordpress.com
Conclusion

• Immune system is similar to the proverbial double-edged sword
  • Defends us against infections
  • Absent or inadequate (Immunodeficiency), hyperactive (Hypersensitivity) and mistake (Autoimmunity) immune system may cause diseases that can sometimes be fatal
Reference