Objectives

- Describe the components of the innate and adaptive immune systems
- Describe the main mechanisms in innate immunity
- List the two types of adaptive immunity and briefly compare their features
- List the mechanisms of self tolerance
- Understand the pathogenesis and give examples of the four types of hypersensitivity reactions
- List common features of autoimmune diseases
- List examples of primary and secondary immunodeficiencies

Outline

I. Normal immune response

a. **Inflammatory Cell Types**
b. **Categories of Immune Mechanisms:** *Innate vs Adaptive immunity*
c. **Innate Immunity**
d. **Adaptive Immunity:** *Humoral vs Cell-mediated immunity*
e. **Self-tolerance:** *Central vs Peripheral tolerance*

II. Hypersensitivity reactions

a. **Classification and examples**
b. **Type I Hypersensitivity:** *Local vs Systemic reactions; Pathogenesis*
c. **Type II Hypersensitivity:** *Mechanisms of antibody-mediated injury*
d. **Type III Hypersensitivity:** *Systemic vs Local disease*
e. **Type IV Hypersensitivity:** *CD4+ T cell-mediated inflammation, CD8+ T cell-mediated cytolysis*

III. Autoimmune diseases

a. **Pathogenesis**
b. **General Features**
c. **Example: Systemic Lupus Erythematosus (SLE)**

IV. Immunodeficiency diseases

a. **Primary Immunodeficiency:** *Defects in innate vs Adaptive immunity*
b. **Secondary immunodeficiency:** *Cancers, Malnutrition, Radiation/chemotherapy, Immunosuppressive medications, Splenectomy, HIV infection*

References

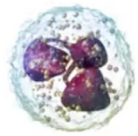
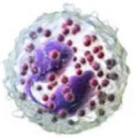
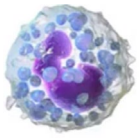
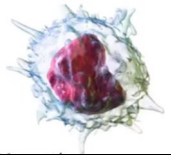
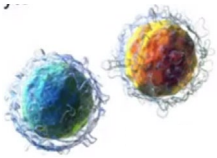
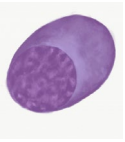
Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

Diseases of the immune system generally result from either too little or too much immunologic reactivity. First, a brief overview of the normal immune system is as below.

I. NORMAL IMMUNE RESPONSE

Inflammatory cell types

					
Neutrophil	**Eosinophil**	**Basophil**	**Monocyte**	**Lymphocytes**	**Plasma cell**
Granulocytes			*Agranulocytes*		
Myeloid lineage				**Lymphoid lineage**	

Picture credits: Medical gallery of Blausen Medical 2014; plasma cell – A/Prof Nga Min En

2 broad categories of immune mechanisms:

Immune mechanism	Features	Components
Innate immunity	First line of defence – intrinsic mechanisms that can react immediately (hours)	- Epithelial barriers that block microbe entry e.g. skin, mucosa - Phagocytic cells e.g. neutrophils, monocytes / macrophages (destroyers) - Dendritic cells (antigen presenting cells) - Innate lymphoid cells e.g. Natural killer (NK) cells (tissue-resident lymphocytes that lack T-cell antigen receptors but are activated by mediators and produce cytokines) - Other cell types e.g. mast cells - Plasma proteins e.g. complement system
Adaptive immunity	Mechanisms that are stimulated by microbes / other foreign substances → slower onset (usually days) but more powerful	- T lymphocytes (cell mediated immunity) - B lymphocytes and their products (antibodies) (humoral immunity)

Innate immunity

Cell components in the innate immune system have pattern recognition receptors (~100); however, these receptors do not have as fine antigen specificity nor memory compared to adaptive immunity

Pattern recognition receptors = cellular receptors that recognize molecules shared among related microbes (pathogen-associated molecular patterns) or released by injured or necrotic cells (damage-associated molecular patterns)

- **Toll-like receptors (TLRs)**: recognizes microbial molecules. Pathway signalling results in activation of NF-KB transcription factor and interferon regulatory factors, to stimulate cytokine production

- **NOD-like receptors (NLRs)**: recognizes damage-associated molecules and some microbial molecules. Pathway signalling via the inflammasome generates activated cytokine interleukin 1 (IL-1)
- **Others** e.g. C-type lectin receptors, RIG-like receptors

Main mechanisms of host defence in innate immunity

1. **Inflammation**: Cytokines, products of complement activation and other mediators are produced by the innate immune system, triggering the vascular and cellular components of inflammation as well as repair of damaged tissues
2. **Antiviral defence**: Type I interferons are produced in response to viruses and activate enzymes that degrade viral nucleic acids and inhibit viral replication. NK cells also recognize and destroy virus-infected cells
3. **Production of signals that stimulate the adaptive immune response**: Antigen presenting cells (APCs) are activated to express costimulators (e.g. B7 proteins) and secrete cytokines that stimulate the proliferation and differentiation of T cells

Adaptive immunity

Two types of adaptive immunity:

1. **Humoral immunity**: Protects against **extracellular** microbes and their toxins. Mediated by **B lymphocytes** and their secreted products (antibodies / immunoglobulins)
2. **Cell-mediated (cellular) immunity**: Defence against **intracellular** microbes and cancers. Mediated by **T lymphocytes**

Lymphocytes have highly diverse antigen receptors even before exposure to any antigen, which is generated by somatic recombination of genes encoding antigen receptors. These are called **naïve lymphocytes**. After exposure to an antigen (antigen recognition), the particular antigen-specific cells are selectively activated (clonal selection) and differentiate into **effector cells** (eliminates microbes) and **memory cells** (to react rapidly and strongly to the same antigen stimulation in future). Once the antigen is eliminated, the adaptive immune response declines and the memory cells remain as long-lived survivors.

T cell antigen receptors (TCR) require peptide antigens to be bound to and presented by major histocompatibility (MHC) molecules on the surface of antigen-presenting cells (APCs) i.e. T cells are MHC restricted. APCs include dendritic cells, macrophages and B cells. **B cell antigen receptors** (BCR) compose of a membrane-bound immunoglobulin and other signalling molecules.

MHC molecules are also known as human leukocyte antigens (HLA) in humans:

- **Class I MHC molecules**: expressed on all nucleated cells and platelets. Display peptides derived from cytoplasmic proteins e.g. normal proteins, virus- and tumour-specific antigens
- **Class II MHC molecules**: mainly expressed on APCs. Display antigens derived from extracellular microbes and proteins following their ingestion into endosomes or lysosomes

Lymphocyte type	Function
B cell T-dependent (requires T cell help for activation) T-independent (does not require T cell help)	- After stimulation, develops into plasma cells and produces antibodies of different classes with distinct functions - Neutralises microbes, opsonizes microbes to target them for phagocytosis, activates the complement system
T helper cell Usually CD4+ >> binds to class II MHC molecules Th1, Th2 and Th17 subtypes	• Activation of macrophages to destroy microbes • Stimulates B cells to make antibodies • Secrete cytokines that activates other T cells, promotes and limits inflammation
Cytotoxic T lymphocyte (CTL) Usually CD8+ >> binds to class I MHC molecules	• Kills infected cells and tumour cells • Also secretes cytokines
Regulatory T cell	• Limits immune responses and prevents reaction against self-antigens

Self-tolerance

- Lack of responsiveness to an individual's own antigens, due to mechanisms that prevent adaptive immune responses to self-antigens
- 2 mechanisms:
    - **Central tolerance (negative selection)**: Immature self-reactive T and B lymphocyte clones that recognise self-antigens during their maturation (in the primary lymphoid organs i.e. thymus or bone marrow, respectively) and bind to self peptide-self MHC with high affinity are either killed by apoptosis or undergo receptor editing (the latter in B cells only) to express new antigen receptors that are not specific for self-antigens
    - **Peripheral tolerance**: Potentially autoreactive mature T or B cells that escape central tolerance into the periphery are silenced via the following mechanisms:
        - **Anergy**: Lymphocytes that recognise self-antigens are rendered functionally unresponsive due to inadequate costimulatory signals (e.g. B7 proteins on APCs) even in the presence of antigen recognition
        - **Suppression by T regulatory cells**: T regulatory cells (classically CD4+ CD25+) secrete inhibitory cytokines (e.g. IL-10, TGF-β) that suppress immune responses
        - **Deletion by apoptosis**: Similar to in central tolerance, T cells that recognise self-antigens receive signals that trigger their apoptosis

II. HYPERSENSITIVITY REACTIONS

Hypersensitivity reaction is a form of immune reaction that causes **tissue injury due to an excessive or harmful response to an antigen**, often associated with the inheritance of particular susceptibility genes. Antigens may be both exogenous (e.g. dust, pollen, food, microbes) or endogenous self antigens (i.e. autoimmune diseases)

Classification of hypersensitivity reactions: based on the underlying immunologic mechanism. Certain diseases may have more than 1 type of hypersensitivity reaction contributing to tissue injury

Type	Immune mechanism	Examples of diseases
Type I (immediate hypersensitivity)	Injury caused by Th2 cells, IgE antibodies, mast cells etc.	Anaphylaxis Allergies
Type II (antibody-mediated)	Injury caused by secreted IgG and IgM antibodies that promote lysis or phagocytosis of cells and induce inflammation Can also cause disease without tissue injury by interfering with cellular function	Autoimmune haemolytic anaemia (AIHA) Goodpasture syndrome Myasthenia gravis
Type III (immune complex-mediated)	Injury caused by antigen-antibody complexes (immune complexes) that form in the circulation and deposit in tissues, inducing inflammation and tissue damage by recruited leukocytes (neutrophils and monocytes)	Systemic lupus erythematosus (SLE)
Type IV (cell-mediated)	Injury caused by T lymphocytes (Th1, Th17 and CTLs)	Contact dermatitis Tuberculosis

Type I hypersensitivity

- Rapid, occurs in a previously sensitized person, triggered by binding of an antigen (allergen) to IgE antibody on the surface of mast cells
- Can be a **local** reaction (e.g. hives, allergic rhinitis) or **systemic** reaction (anaphylaxis – vascular shock, widespread oedema, breathing difficulties). Local reactions usually have **2 distinct phases**:
    - Immediate short-lived reaction (minutes-hours from antigen exposure): vasodilation, vascular leakage, smooth muscle spasms / glandular secretions
    - Second late-phase reaction (2-24hr after initial exposure that lasts several days): tissue infiltration by eosinophils as well as neutrophils, basophils, monocytes and CD4+ T cells that amplify and sustain the inflammatory response without additional exposure to the triggering antigen, and cause tissue injury (usually affecting mucosal epithelium)
- **Pathogenesis**: Sensitization is caused by excessive Th2 responses –
    1. Naïve CD4+ T helper cells are exposed to an allergen and differentiate into Th2 cells
    2. Th2 cells facilitate IgE class switching in B cells (through production of cytokine IL-4), resulting in the formation of IgE-secreting plasma cells and production of IgE. Th2 cells also produce other interleukins e.g. IL-5 (important in activation of eosinophils) and IL-13 (enhances IgE production and acts on epithelial cells to stimulate mucus secretion)
    3. IgE binds to Fc receptors on mast cells
    4. Subsequent exposure to the allergen results in cross-linking of IgE on the mast cells and activates the mast cells to rapidly release mediators (e.g. histamine, proteases, prostaglandins) responsible for the pathologic manifestations of Type 1 hypersensitivity (immediate response). Other cytokines and chemokines are also released that attract more Th2 cells and other leukocytes to the reaction site (late phase reaction)
- **Predisposing factors**: Genetic factors (atopy = propensity to develop immediate hypersensitivity reactions) and environmental factors (exposure to allergens, 'hygiene hypothesis' etc.)

Type II hypersensitivity

- Caused by antibodies reacting with antigens on cell surfaces or in the extracellular matrix, resulting in cell destruction, inflammation or interference with normal functions
- **Mechanisms of antibody-mediated injury**:
    - **Opsonization and phagocytosis**: Cells coated with antibodies (opsonized) are removed through phagocytosis. IgM and IgG antibodies may also activate the complement system by the classical pathway, generating complement products (C3b and C4b) that further deposit on cells and facilitate phagocytosis, as well as form the membrane attack complex on cells.
      Prototypical example: autoimmune haemolytic anaemia
    - **Inflammation**: Antibodies bind to Fc receptors of leukocytes, and also activate complement, resulting in recruitment of leukocytes that cause inflammation and tissue injury through release of enzymes and reactive oxygen intermediates
      Prototypical example: pemphigus vulgaris
    - **Disturbance of functional regulation**: Antibodies such as anti-receptor antibodies can inhibit binding of ligands to receptors or stimulate receptors, without cell injury
      Prototypical examples: myasthenia gravis, Graves disease

Type III hypersensitivity

- Antigen-antibody complexes form in the circulation and deposit in tissues (**systemic** disease e.g. systemic lupus erythematosus), or less frequently, form at sites where the antigen had been previously deposited (in-situ immune complexes – **local** disease e.g. poststreptococcal glomerulonephritis). The immune complexes then elicit inflammation and tissue damage
- **Pathogenesis**: 3 phases for systemic immune complex disease
    1. **Formation of immune complexes**: Protein antigen is introduced and triggers an immune response that results in formation of circulating antibodies (usually 1 week after the antigen is introduced). The antibodies react with the antigen still present in the circulation and forms antigen-antibody complexes
    2. **Deposition of immune complexes**: The antigen-antibody complexes are deposited primarily in blood vessel walls as well as sites where blood is filtered to form other fluids (e.g. glomeruli in kidneys, joints where synovial fluid is produced)
    3. **Inflammation and tissue injury**: The deposited immune complexes initiate acute inflammation through antibody-mediated mechanisms (see "Type II hypersensitivity – Inflammation"). The clinical and pathologic manifestations are thus usually vasculitis (fibrinoid necrosis) and glomerulonephritis

Type IV hypersensitivity

- Caused mainly by inflammation from cytokines produced by CD4+ T cells; may also be due to cytolysis by CD8+ T cells (CTLs)

CD4+ T cell-mediated inflammation

- Classically also known as delayed-type hypersensitivity (as the visible reaction occurs after 24-48 hours rather than immediately)
- **Pathogenesis**:
  1. **Activation of CD4+ T cells**: Naïve CD4+ T cells recognise peptides presented by dendritic cells and secrete IL-2, an autocrine growth factor that stimulates proliferation of the antigen-responsive T cells. Cytokines produced by APCs (IL-12 or IL-1/IL-6/IL-23) then drive the differentiation of the antigen-stimulated T cells to **Th1** or **Th17** subsets, respectively
  2. **Responses of effector T cells**:
     - On repeat antigen exposure, **Th1 cells** secrete cytokines (esp. IFN-γ) responsible for the pathologic manifestations of delayed-type hypersensitivity. IFN-γ activated macrophages ("classically activated") have enhanced phagocytic and antigen-presenting capabilities, secrete TNF, IL-1 and chemokines that promote inflammation, and also produce IL-12 (amplifying the Th1 response). Sustained activation of these macrophages thus result in continued inflammation and tissue injury e.g. with persistent or nondegradable antigens such as foreign bodies, mycobacteria. In such situations, the activated macrophages transform into epithelioid macrophages (with abundant cytoplasm) and form aggregates around the antigens (granulomas)
     - Activated **Th17 cells** secrete IL-17, IL-22, chemokines and other cytokines; these recruit neutrophils and monocytes to the site of inflammation
- **Prototypical examples**: Tuberculin reaction, multiple sclerosis, contact dermatitis

CD8+ T cell-mediated cytolysis

- **Pathogenesis**:
  - CD8+ T cells kill antigen-expressing target cells through release of preformed mediators (perforins and granzymes) that induce apoptosis of the target cells, as well as via expression of Fas ligand that binds and activates Fas receptor on target cells, triggering apoptosis
  - CD8+ T cells can also produce cytokines (such as IFN-γ) and be involved in reactions similar to CD4+ T cell-mediated inflammation
- **Prototypical example**: Type 1 diabetes

III. AUTOIMMUNE DISEASES

Autoimmune disorders result from **failure of the normal immune tolerance to self-antigens, resulting in tissue damage or physiological dysfunction**. As autoantibodies may be found in seemingly normal individuals, autoimmune diseases should fulfil 3 criteria:

1. Presence of an adaptive immune reaction specific for some self antigen/tissue
2. The reaction is of primary pathogenic significance rather than secondary to tissue damage
3. Absence of an alternative cause of the disease

The autoimmune response may be **tissue/organ-specific** (e.g. β cells of the pancreatic islets in Type 1 diabetes), or against widespread antigens, resulting in **systemic** disease (e.g. DNA, platelets etc. in systemic lupus erythematosus)

Pathogenesis of failed immune tolerance: Combination of **inheritance of susceptibility genes** (HLA and non-MHC genes involved in immune regulation / responses to microbes) and **environmental triggers** (e.g. infections, tissue damage) that promote the activation of self-reactive lymphocytes (e.g. by upregulating co-stimulators on APCs or through molecular mimicry / cross-reactivity with self-antigens). This results in the following abnormalities -

- **Defective tolerance or regulation**
- **Abnormal display of self-antigens**: Self-antigens that are normally cleared may persist, have increased expression or have structural changes to form neoantigens (e.g. from cellular stress such as UV radiation, injury or post-translational modifications) that the immune system may not be tolerant to
- **Inflammation / initial innate immune response**: Microbes or cell injury may elicit an innate immune response that serves as a subsequent trigger for autoimmunity by the adaptive immune response

General features of autoimmune diseases

- **Chronic and progressive with relapses and remissions**: Due to intrinsic amplification mechanisms in the immune system, and epitope spreading (immune response against one self antigen causes tissue damage and release of other antigens and the subsequent activation of lymphocytes reactive against these newly released antigens)
- **Nature of the dominant immune response determines the type of tissue injury**: e.g. excessive Th1 and Th17 responses in multiple sclerosis, both antibodies and T-cell mediated inflammation in rheumatoid arthritis

Example: Systemic lupus erythematosus (SLE)

- Autoimmune disease involving multiple organs characterised by multiple autoantibodies, including antinuclear antibodies (ANA) and anti-double-stranded DNA. Injury is caused mainly by deposition of immune complexes (type III hypersensitivity) and antibodies in various cells and tissues
- As with other autoimmune diseases, the pathogenesis of SLE has both genetic and environmental factors contributing to failure of the mechanisms that maintain self-tolerance
- Clinical manifestations are extremely varied, with the most characteristic lesions occurring in the kidneys (glomerulonephritis), blood vessels (vasculitis), skin (butterfly rash), joints (non-erosive synovitis), as well as haematologic and neurologic abnormalities.

IV. IMMUNODEFICIENCY DISEASES

Classified as primary immunodeficiencies (congenital), or secondary immunodeficiencies (acquired). As a result of immunodeficiencies, patients have increased risk of infections (can be reactivation of latent infections, unusually recurrent/ persistent / severe infections, and/or opportunistic infections). Patients may also have increased incidence of certain cancers, particularly viral-associated cancers.

Primary immunodeficiencies: These are inherited (genetically determined) intrinsic defects in the immune system, relatively rare and usually manifests at a young age

- **Defects in innate immunity**:
    - **Affect leukocyte functions** e.g. leukocyte adhesion (leukocyte adhesion deficiency), microbicidal activity (chronic granulomatous disease), phagolysosome function, TLR signalling
    - **Affect the complement system and its regulators** e.g. C3 deficiency, C1 inhibitor deficiency
- **Defects in adaptive immunity:** abnormalities in maturation / activation of B and T cells
    - **Severe combined immunodeficiency (SCID)**: Group of genetically distinct syndromes that have defects in both humoral and cell-mediated immune responses (although most often, the defect is in the T cell component, which then affects humoral immunity). Without haematopoietic stem cell transplantation or enzyme/gene therapy, death usually occurs in the first year of life due to recurrent severe infections by a wide range of pathogens (fungal, viral, bacterial)
    - **X-linked agammaglobulinemia**: Failure of B cell precursors to develop into mature B cells due to mutations in a cytoplasmic tyrosine kinase BTK. T-cell mediated immunity is intact. Recurrent infections thus tend to be bacterial or certain viral infections that are dependent on humoral immunity. Patients can be treated with intravenous immunoglobulins. Patients have increased incidence of autoimmune diseases
    - **Others e.g. common variable immunodeficiency (CVID), X-linked lymphoproliferative disease**
- **As part of inherited systemic disorders** e.g. Wiskott-Aldrich syndrome, ataxia telangiectasia

Secondary immunodeficiencies: More common than primary immunodeficiencies, due to an underlying condition that adversely affects the immune system

- **Involvement of bone marrow by cancers**: reduces site of leukocyte development
- **Protein-calorie malnutrition**: inhibits lymphocyte maturation and function e.g. Ig synthesis
- **Radiation / chemotherapy**: decreases bone marrow leukocyte precursors
- **Immunosuppressive medications**: e.g. to treat autoimmune diseases, prevent transplant graft rejection
- **Splenectomy**: decreases phagocytosis of microbes
- **Human immunodeficiency virus (HIV) infection**: Cause of Acquired Immunodeficiency Syndrome (AIDS). Depletion of CD4+ T helper cells results in a profound immunosuppression (primarily affecting cell-mediated immunity) that leads to opportunistic infections and secondary neoplasms

(often caused by oncogenic DNA viruses that are usually latent infections in healthy people e.g. HHV-8 causing Kaposi sarcoma, or B cell lymphomas). Patients also have CNS abnormalities

- **Transmission**: Sexual contact, parenteral transmission, vertical transmission (mother to infant)
- **Risk factors**: Men who have sex with men, heterosexual transmission with members of other high-risk groups, intravenous drug users, newborns of HIV-positive women, recipients of large amounts or infected blood products
- **Pathogenesis**: HIV infects cells using the CD4 molecule as a receptor and other chemokine receptors as co-receptors i.e. HIV usually infects CD4+ T cells and other monocytes/ macrophages and dendritic cells. The virus undergoes reverse transcription in the cell to form double-stranded complementary DNA (cDNA) that can remain in episomal form or integrates into the host genome
    - Activation of the infected T cells by antigens or cytokines upregulates transcription factors that also activates the expression of HIV genes, resulting in the production of virions and eventual cell lysis. In addition to the direct cytopathic effects of the replicating virus, loss of T cells may result from chronic activation of uninfected cells, pyroptosis, progressive destruction of lymphoid tissues, etc.
    - Infected macrophages are more resistant to cytopathic effects of HIV compared to CD4+ T cells, and thus may be an important site of continued viral replication and persistence even after CD4+ T cells are depleted
- AIDS patients also demonstrate abnormalities of B cell function, which may be due to the lack of T cell help but also possibly due to intrinsic defects in the B cells