

## THE IMMUNE SYSTEM

Disease-causing microorganisms are called **pathogens**.

They include bacteria, viruses, protozoans and fungi.

**Immunology** is the study of specific defense mechanisms.

Two major kinds of defense have evolved to counter the threat of infection.

1. **Innate immunity**: rapid response to a broad range of microbes.
2. **Acquired immunity**: slower response to specific microbes; it is also called **adaptive immunity**; it includes lymphocytes and antibodies.

There are **specific defense mechanisms** and **nonspecific defense mechanisms** also known as **innate immune response**.

### INNATE IMMUNITY

It provides a wide range of defenses. These defenses are not specific for a type of pathogen.

#### External Defense Mechanisms

These mechanisms are nonspecific and include mechanical and chemical barriers.

- **Mechanical barriers** include skin, hair, mucous.
- **Chemical barriers** include sweat, sebum, tears, and stomach acid; **lysozymes** digest the cell wall of bacteria.

Intact **skin** is barrier that prevents pathogens from penetrating into the body.

**Secretions** from sweat and sebaceous glands give the skin a pH of 3 to 5, which is acidic enough to prevent colonization by many microbes.

Saliva, tears and mucus also kill bacteria.

**Lysozymes** are enzymes found in tears, sebum and tissues that attack the cell wall of bacteria.

Acid secretions and enzymes in the stomach kill most ingested pathogens.

#### Internal Cellular And Chemical Defenses.

Invading organisms are ingested and destroyed through **phagocytosis**.

White blood cells or **leukocytes** are involved in this process.

**1. Phagocytes** destroy bacteria and other cells.

There are four types of white blood cells (leukocytes) that are phagocytes.

- **Neutrophils** are the first phagocytes to arrive usually within an hour of injury.
- Neutrophils make about 60%-70% of all white blood cells.

- Damaged cells secrete chemical signals that attract neutrophils: **chemotaxis**.
- **Monocytes** arrive next and become large **macrophages**.
- Monocytes make about 5% of WBC.
- Macrophages are long-lived cells.
- Ingest the bacterium into a food vacuole that fuses with a lysosome which secretes superoxide ions,  $O_2^-$ , and nitric oxide, NO, both strong antimicrobial substances; hydrolytic enzymes digest the microbial components.
- Macrophages are found in the lungs, liver, lymph nodes, kidney, brain, spleen, and connective tissues.
- Both phagocytize pathogens, their products and dead and injured cells.
- A neutrophil can phagocytize about 20 cells and a macrophage 100 cells before they become inactive and die.
- Pus consists of dead phagocytic cell, fluid and proteins leaked out of capillaries.
- Some bacteria are resistant to macrophage digestion.
- **Eosinophils** make about 1.5% of all leukocytes.
- They attack large parasitic invaders like blood flukes.
- They discharge hydrolytic enzymes on the surface of the parasite.
- They have limited phagocytic activity.

## 2. Antimicrobial proteins

**Complement system** proteins are regulatory proteins secreted by cells of the immune system.

- There are about 30 of these serum proteins.
- Two types of **interferon** provide innate defense against viral infection.
- Some lymphocytes secrete a third type of interferon that activates macrophages.
- They are important signaling cells during immune responses and lead to the lysis of the viruses, yeast and bacteria, and enhance their phagocytosis by macrophages.
- They are inactive until an infection occurs.
- **Defensins** are secreted by activated macrophages.

**Interferons** are proteins produced by virus infected cells. They signal other cells to produce chemicals that inhibit viral replication.

## 3. Inflammation is a protective mechanism.

- Damage to tissue by physical injury or by infection triggers the inflammatory response.
- It is regulated by proteins in the plasma, by cytokines, and by substances called **histamines** released by platelets, by basophils (WBC), and by mast cells.
- Blood flow increases bringing phagocytic cells to the site of infection. This is probably the most important element of inflammation.
- **Histamines** released in response to injury cause vasodilation and make capillaries more permeable allowing antibodies to enter the tissues; postcapillary venules constrict.
- Histamines are released by circulating leukocytes called **basophils** and by **mast cells** found in connective tissue.
- Leukocytes and damaged cells release **prostaglandins** that increase blood flow to the injured area.

- **Chemokines** secreted by blood vessel endothelial cells and monocytes attract phagocytes to the injured area.
- Blood flow to the injured area brings clotting elements to initiate tissue repair, makes the skin feel warm, and may cause redness.
- **Edema** (swelling) occurs.

Injured cells put out chemical signals that cause the release of leukocytes from the bone marrow.

#### 4. Natural Killer Cells

- **Natural killer cells (NK)** are large, granular lymphocytes that originate in the bone marrow.
- Attack cancer cells, infected cells and pathogens including certain fungi.
- Release proteins that destroy target cells by lysing the cells.
- NK cells trigger apoptosis of infected cells.

#### 5. Invertebrate Immune System

Invertebrates depend mostly on innate, non-specific mechanisms of defense.

Invertebrates apparently lack cells equivalent to lymphocytes responsible for specific immune response.

Insects defend themselves by mechanisms similar to those of vertebrates.

**Hemocytes** of insects ingest bacteria and damaged cells.

Invertebrates have a simple defense system. Their system is **nonspecific**.

Invertebrates in general do not have immunological memory.

Earthworms have immunological memory.

Echinoderms have **coelomocytes** that phagocytose foreign cells, and produce interleukins.

Cytokines have been found in some invertebrates.

### ACQUIRED IMMUNITY - LYMPHOCYTES

Pathogens always come in contact with lymphocytes when they invade a vertebrate.

Phagocytes secrete **cytokines** that activate lymphocytes when they phagocytose microbes.

Pathogens have macromolecules on their cell surfaces that the body recognizes as foreign.

These foreign substances stimulate an immune response. They are called **antigens**.

Lymphocytes recognize and bind to a small portion of the antigen called the **epitope**.

An antigen that is a protein has a specific sequence of amino acids that makes up the **epitope** or **antigenic determinant**.

An antibody interacts with a small, accessible portion of the antigen, the epitope.

An epitope interacts with a specific antibody and is capable of inducing the production of the specific antibody.

These antigen determinants vary in number from 5 to more than 200 on a single antigen.

The shape of the epitope can be recognized by the antibody or a T cell receptor.

## **ANTIGEN RECOGNITION BY LYMPHOCYTES**

Cells of the immune system include lymphocytes: **T lymphocytes or T cells, B lymphocytes or B cells, natural killer (NK) cells and phagocytes.**

These cells circulate throughout the body in the blood and lymph, and are concentrated in the spleen, lymph nodes and other lymphatic tissues.

**T lymphocytes and B lymphocytes target specific invaders.**

B cells and T cells recognize antigens by means of antigen-specific receptors embedded in their plasma membranes.

Each of these cells bears about 100,000 of these antigen receptors.

All the receptors on a single cell are identical, that is, they all recognize the same **epitope**.

Each lymphocyte displays specificity of a particular epitope on an antigen and defends against that antigen or a small set of closely related antigens.

### **B Cells Receptors For Antigens**

A typical **B-cell receptor or antibody** is a Y-shaped molecule consisting of **four polypeptide chains**:

- Two **identical heavy chains** and two **identical light chains** joined by **disulfide bridges** to form the **Y-shaped molecule**.
- The transmembrane region of the tail portion anchors the receptor in the plasma membrane and a short portion penetrates into the cytoplasm.
- The tips of the Y are the variable regions, **V regions**, of the heavy and light chains.
- The tail of the Y shaped antibody is made of the constant or C regions of the heavy chains.

The interaction between the antigen-binding site and its corresponding antigen is stabilized by multiple noncovalent bonds between chemical groups on the respective molecules.

The receptor binds to molecules that are on the surface of the infectious agent.

- They recognize **intact antigens**.

Antibodies have two main functions:

1. Combine with antigen and labels it for destruction.
2. Activates processes that destroy the antigen that binds to it.

Antibodies do not destroy the antigen. It labels the antigen for destruction.

Secreted antibodies are serum globular proteins also known as **immunoglobulins**, Ig.

### **T Cell Receptors For Antigens And The Role Of The MHC**

- T cell receptors consist of two polypeptide chains,  $\alpha$  and  $\beta$  chains linked by disulfide bridge.
- They have a straight shape, not a Y shape like the B-cell receptors.
- The transmembrane region anchors the antibody to the plasma membrane.
- The variable V regions at the other end of the antigen form a single antigen-binding site.
- The remainder of the molecule is made up of the constant C region.

The T cell receptors bind with antigens like the B cell receptors.

T cell receptors are capable of recognizing small fragments of the antigen that are bound to normal cell-surface proteins called MHC molecules.

- B cell receptors recognize intact antigens on the surface of the pathogen.
- T cell receptors recognize fragments of antigens presented by the MHC complex.

### **MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)**

The ability to distinguish self from non-self depends largely on a group of cell surface proteins known as **MHC antigens**.

These proteins are synthesized by a group of genes called the **major histocompatibility complex**, MHC.

The principal function of the MHC is to present antigens on the surface of cells recognition by T lymphocytes: cytotoxic T cell (T<sub>c</sub>) and helper T cells (T<sub>H</sub>).

Class I MHC molecules and Class II MHC molecules mark body cells as "self".

It permits recognition of self, a biochemical "fingerprint".

The MHC antigens are a group of membrane **glycoproteins** that act as markers on the surface of the cells of the individual.

- Glycoproteins are proteins with a sugar chain attached to it.

#### **Antigen presentation:**

When a cell is infected or a macrophage engulfs a pathogen, antigen protein fragments are combined with Class I or II MHC proteins and transported to the surface of the cell to be presented to a nearby T cell.

There are two sets of MHC genes that code for proteins.

- **Class I MHC molecules.** Found on all nucleated cells. Distinguish self from non-self. Forms MHC-antigen complex with fragments of proteins made by the infecting microbe, usually a virus, on the surface of the cell surface. These MHC-antigen complexes are recognized by a subgroup of T cells called **cytotoxic T cells**.

<http://www.cryst.bbk.ac.uk/pps97/assignments/projects/coadwell/004.htm>

- **Class II MHC molecules.** Found on specialized antigen-presenting cells including macrophages, B cells, dendritic cells, activated T cells, spleen cells, lymph node cells, and the cells in the interior of the thymus. Class II MHC molecules form complexes with antigens from protein fragments of digested bacteria that have been digested after being taken in by phagocytosis. These complexes stimulate **helper T cells** to form interleukins and activate B cell. These phagocytic cells are called antigen-presenting cells.

The class II MHC antigens regulate the interaction between B cells, T cells and antigen-presenting cells.

<http://www.cryst.bbk.ac.uk/pps97/assignments/projects/coadwell/006.htm>

An engulfed bacterium...

- Macrophage engulfs bacterium.
- Antigen forms complex with the class II MHC protein.
- Macrophage displays MHC-antigen complex on its cell surface.
- **Helper T cells** are activated when their receptors combine with the MHC-antigen complex.

An infected body cell...

- Pathogen invades the body and infects cells.
- Macrophage engulfs pathogen.
- Antigen forms complex with the class I MHC protein.
- Macrophage displays MHC-antigen complex on its cell surface.
- **Helper T cells** recognize the foreign antigen-MHC complex.

Each vertebrate species possesses numerous different alleles for each class I and class II MHC gene.

- A group of closely linked polymorphic genes, e.g. multiple alleles for each locus; sometimes up to 200 alleles for one gene determine these glycoproteins.
- They are located on chromosome 6 in humans.

### **Lymphocyte development.**

- **T lymphocytes** or T cells are responsible for **cellular immunity**.
- Originate in the bone marrow.
- In the **thymus** they become immunocompetent that is capable of immune response.
- In the thymus they divide many times and some develop specific surface proteins with receptor sites. These cells are selected to divide: positive selection.
- The T of T cells comes from “thymus”.
- **B cells** are responsible for **antibody-mediated immunity**.
- Produced in the bone marrow daily by the millions.
- They mature in the **bone marrow**.
- Carry specific glycoprotein receptor to bind to a specific antigen.
- When a B cell comes into contact with an antigen that binds to its receptors, it clones identical cells, and produces **plasma** cells that manufacture antibodies.
- Also produce **memory B cells** that continue to produce small amounts of antibody after an infection.
- The B of B cells comes from “bursa of Fabricius” and organ unique to birds where the cells were first found. You may associate the B with “bone marrow”.

## Lymphocyte diversity by gene rearrangement

The sequence of amino acids at the tip of the variable regions of the receptor determines the specificity of an antigen receptor.

During the early development of the B and T cells, genes are rearranged under the influence of enzymes called **recombinases**.

- Maturing lymphocytes have genes that code for antigen receptor chains, V regions.
- These genes consist of numerous coding gene segments that undergo random, permanent rearrangement, forming functional genes that can be expressed as receptor chains.
- The V coding genes are separated by an intron from an exon that codes for the constant chain C.
- Portions of the DNA between segment genes (V) are deleted and the new segments of DNA rejoined including the exon C.
- The new gene is then transcribed and introns are removed during processing of the pre-mRNA.
- Poly A and cap are added to the mRNA and processing is finished.
- The mRNA is translated into variable and constant regions.

See Fig 43.11, page 906.

The rearrangement of genes occurs at random during maturation, and by chance a chain may end up being able to recognize a particular antigen.

## Immune responses and immunological memory

Antigens cause the lymphocytes to form two clones of cells: **effector cells** and **memory cells**.

1. Antigen molecules bind to the antigen receptors of a B cell.
2. The selected B cell multiplies and gives rise to a clone of identical cells bearing receptors for the selecting antigen.
3. Some proliferating cells develop into short-lived plasma cells that secrete antibody specific for the antigen.
4. Other cells develop into long-lived memory cells that can respond rapidly upon subsequent exposure to the same antigen.

Response caused by the first exposure to an antigen is called **the primary immune response**.

- During the primary immune response, antibody-producing B cells called **plasma cells** and **effector T cells** multiply.

Exposure to the same antigen at a later time causes a more rapid and effective response called secondary immune response.

- Antibodies produced in the secondary immune response are more numerous and have greater affinity for the antigen.
- This is called **immunological memory**.

## CELL-MEDIATED IMMUNITY

Cytotoxic T lymphocytes and macrophages are responsible for cell-mediated immunity.

Cytotoxic T cells destroy infected cells and cells altered in some way like cancer cells.

Cytotoxic T cells recognized antigens only when they are presented forming the MHC-antigen complex.

**Cytokines** are proteins and peptides that stimulate other lymphocytes.

### Helper T Cells

When a helper T cell encounters and recognizes a class II MHC molecule-antigen complex on an antigen presenting cell, the helper T cell proliferates and differentiates into a clone of activated helper T cells and memory helper T cells.

- Pathogen invades the body and infects cells.
- Macrophage engulfs pathogen.
- Antigen forms complex with the **class II MHC protein**.
- Macrophage displays MHC-antigen complex on its cell surface.
- CD4 proteins enhance the recognition of the MHC-antigen complex by **helper T cells**.
- Helper T cells recognize the foreign antigen-MHC complex and secrete the cytokine IL-2.
- Competent T cells are in turn activated, increase in size and divide mitotically.
- Clones of competent T cells are produced.
- Clones differentiate into memory T cells, cytotoxic T cells and other types of cells.
- Cytotoxic T cells leave the lymph nodes and migrate to the area of infection.

### Cytotoxic T cells

Cytotoxic T cells are the effectors of cell-mediated immunity.

They destroy pathogens, cancer and transplanted cells.

At the site of infection,

- All nucleated cells have **class I MHC proteins** on its surface.
- In infected cells, cancer cells and foreign cells, their proteins are broken down and carried by newly made class I MHC proteins to the surface of the cell.
- The infected cell displays class I MHC-antigen complex on its surface.
- Cytotoxic T cells recognize the displayed complex and binds to the infected cell with the help of CD8 proteins.
- Cytotoxic T cells release proteins (lymphotoxins, **perforins**) in the site of infection and destroy pathogens by lysing.
- Macrophages are attracted to the site to ingest pathogens.

MHC proteins have the ability to bind to different antigenic peptides displayed by the macrophage. Short peptides are flexible in solution and can adapt to the binding site of the MHC protein. Also, the MHC binding site is somewhat flexible and can accommodate a variety of peptides with not the exact homology.

### B cells

B cells are responsible for antibody-mediated immunity, also called humoral immunity.

Antibody molecules serve as cell surface receptors that combine with antigens.

Only B cells bearing a matching receptor on its surface can bind a particular antigen.

Antigens that cause helper T cells produce cytokines and stimulate the production of memory cells and plasma cells, are known as **T-dependent antigens**. They can be produced only with help from a helper T cell.

Some polysaccharides and bacterial proteins can cause a B cell to proliferate into antibody-producing plasma cell without the intervention of helper T cells. These antigens are called **T-independent antigens**.

B cell must be activated.

- Macrophage engulfs bacterium.
- Antigen forms complex with the **class II MHC protein**.
- Macrophage displays MHC-antigen complex on its cell surface.
- Helper T cells are activated when their receptors combine with the MHC-antigen complex with the help of a CD4 protein.
- Activated helper T cells secrete cytokines that activate B cells.
- Independently B cells bind with complementary antigen and forms MHC-antigen complex on its own surface.
- MHC-antigen complex stimulate B cells to divide and differentiate.
- Cytokines also stimulate cytotoxic T cells to become active killers.
- Activated B cells form many clones, some of which differentiate into **plasma cells** and some into **memory B cells**.

Plasma cells remain in the lymph nodes and secrete **specific antibodies**.

Antibodies are transported via lymph and blood to the infected region.

Antibodies form complexes with antigens on the surface of the pathogen.

Antibodies combine with antigens to forms specific complexes that stimulate phagocytosis, inactivate the pathogen, or activate the complement system.

Memory cells survive for a long time and continue to produce small amounts of antibody long after the infection has been overcome.

Memory cells when stimulated can produce clones of plasma cells.

### **Antibody classes**

Antibodies are grouped into five classes of immunoglobulins or Ig based on the constant region of the heavy chains.

1. IgG and IgM defend the body against pathogens in the blood and stimulate macrophages and the complement system.
2. IgA is present in the mucus, saliva, tears and milk. It prevents pathogens from attaching to epithelial cells.

3. IgD found on B cells surface helps activate them following antigen binding. They are needed to initiate the differentiation of B cells into plasma and memory B cells.
4. IgE when bound to an antigen releases histamines responsible for many allergic reactions. It also prevents parasitic worms.

Antibodies combine with antigens to form specific complexes that stimulate phagocytosis, inactivate the pathogen, or activate the complement system.

- Antibodies may inactivate a pathogen, e.g. when the antibody attaches to a virus, the virus may lose its ability to attach to a host cell. This is called **neutralization**.
- The antigen-antibody complex may stimulate phagocytic cells to ingest the pathogen. Antibodies enhance macrophage attachment to the microbes for phagocytosis. This is called **opsonization**.
- Clumping of bacteria and viruses neutralizes and opsonizes the microbes for phagocytosis. This is called **agglutination**.
- Antibodies can bind to soluble antigens and form immobile precipitates that can be disposed of by phagocytes. This is called **precipitation**.
- The antigen-antibody complex allows complement system proteins to penetrate the pathogen's membrane and open a pore that causes the lysis of the pathogenic cell. These proteins form a **membrane attack complex (MAC)** that opens the pore. This is called **complement fixation**.
  - The **classical pathway** is triggered by antibodies bound to antigen and is part of the humoral response.
  - The **alternative pathway** is triggered by substances already present in the body and does not involve antibodies; it is part of the nonspecific defense system.

Microbes coated with antibodies and complement proteins tend to adhere to the wall of blood vessels, making them easy preys for phagocytes.

Opsonization, agglutination and precipitation enhance phagocytosis of the antigen-antibody complex.

## **Immunization**

Constant evolution of pathogens causes different antigens that are no longer recognizable by memory cells and thus cause the disease again, e.g. cold, flu.

Types of immunity:

**Active immunity** is developed by exposure to antigens.

- **Naturally induced** by an infection.
- **Artificially induced** through a vaccine.

**Passive immunity** is caused by the injection of antibodies produced by other organisms.

- **Naturally induced** by the mother to the developing baby.
- **Artificially induced** through injection of antibodies (gamma globulin).

Babies who are breastfed continue to receive immunoglobulins (IgA) in the milk.

## **Blood groups and blood transfusion**

The ABO system is based on the antigens found on the surface of the RBC. *See Ch. 14, table 14.2.*

These "antigens" are **polysaccharides** that if placed in the system of another person will cause a devastating reaction; they are NOT antigens to the owner.

Type A has antigen A protein in the RBC plasma membrane; Type B has antigen B; Type AB has both antigens; and Type O has neither of the two antigens on its surface.

- e. g. Type A blood will have antibodies against the B antigen. Type AB does not have antibodies against antigens A or B.

The **Rh factor** is an antigen that can cause problem if the mother is Rh negative and the fetus is Rh positive.

Late in pregnancy or during delivery the Rh-positive factor of the baby can cause the formation of Rh antibodies, anti-Rh-positive IgG, in the mother that will endanger the life of future Rh positive babies by destroying their RBC.

## **Grafts and organ transplants**

Graft rejection is an immune response against transplanted tissue.

T cells are responsible for the destruction of the transplanted organ.

The transplanted tissue has MHC antigens that are different from those of the host that stimulate the immune response.

Certain part of the body accepts any foreign tissue, e.g. cornea.

Because of the difficulty of finding a good match to transplant tissues or organs, biologists are investigating techniques to transplant animal tissues and organs to humans. This procedure is called **xenotransplantation**.

Animals can be genetically engineered so that they do not produce antigens that stimulate the immune system of the host.

## **Abnormal immune functions**

### **Allergic reactions**

**Hypersensitivity** is an exaggerated immunological response to an antigen that is harmless.

Mild antigens called **allergens** cause allergic reactions.

It involves sensitization, activation of mast cells and allergic response.

It involves the production of IgE by plasma cells.

Hayfever reaction:

- Exposure to pollen causes B cell to develop into plasma cells, which make pollen specific IgE antibodies.
- IgE becomes attached to mast cells receptors.
- When more pollen is inhaled, allergen pollen molecules attach to the IgE on the mast cells surface.
- Mast cells then release histamine and serotonin, in a process called **degranulation**.
- These chemicals cause vasodilation, increase permeability and inflammation.

Allergic asthma occurs when the IgE becomes attached to mast cells in the bronchioles of the lungs.

Chemical released by mast cells cause smooth muscles to contract and airways narrow making breathing difficult.

When the allergen reaction takes place in the skin, the person develops hives.

**Systemic anaphylaxis** is hypersensitivity to a drug like penicillin, compounds in food, insect sting or venom.

- The reaction is widespread.
- Massive amounts of histamine are released into the blood.
- Extreme vasodilation and permeability follows causing a rapid drop in blood pressure, shock and death.

Antihistamine drugs (epinephrine) block the effect of histamines released by mast cells.

**Autoimmune disease** is a form of hypersensitivity when the body reacts against its own tissues.

- E.g., Multiple sclerosis, insulin-dependent diabetes mellitus, rheumatoid arthritis, lupus and psoriasis.

During lymphocyte development complex mechanisms are developed so the WBC become self-tolerant and do not attack the tissues of their own body.

It is known that some lymphocytes capable of attacking self. There is a regulatory mechanism that prevents this from happening in healthy individuals. Failure to regulate these lymphocytes results in autoimmune diseases.

**Primary immunodeficiency diseases** result from hereditary or congenital defects that prevent proper functioning of innate, humoral, and/or cell mediated defenses.

An immunodeficiency that develops later in life following exposure to various chemical and biological agents is classified as an acquired or **secondary immunodeficiency**.

Stress can harm the immune system. Hormones secrete by the adrenal glands during stress affect the numbers of white blood cells and may prepress the immune system response.

Neurotransmitters released when the person is relaxed and happy may enhance immunity.

## **AIDS - ACQUIRED IMMUNE DEFICIENCY SYNDROME**

It is cause by the retrovirus **HIV, human immunodeficiency virus**.

**Retroviruses** are RNA viruses that use RNA as a template to make DNA with the help of reverse transcriptase.

The DNA produced by the virus is inserted in the host DNA and exists as a **provirus** for the life of the infected cell. Because of its provirus existence, immune responses fail to eradicate the virus.

Frequent mutations at every viral replication compound the problem of eliminating the HIV.

HIV destroys **helper T cells** and macrophages by attaching to the **CD4 molecules** on the surface of the T lymphocyte.

There are some evidence of destruction of the lymph nodes.

The ability of suppress infection is impaired and the patient falls victim to infectious diseases and cancer.

AZT (acidothymidine) blocks the action of reverse transcriptase.