

COMMUNITY

HOST DEFENSE

Non-Specific Immunity (Innate immunity)

- ❑ First line defense
- ❑ Second line defense

First Line Defense

- Physical barrier on all surfaces of body;
 - Skin
 - Mucous membranes—nasal, respiratory
 - Lining of mouth
 - Lining of gut
 - Lining of vagina/urethra
 - Surface of eye

- Chemical barrier—antibacterial secretions;

Sebum and fatty acids in skin (e.g. unsaturated fatty acids as Olic acid).

Gastric Juice (Low pH stomach).

Lysozyme: degrade the bacterial cell wall

Antimicrobial peptides (β Lysine) with high quantity of Lysine or Arginine. Act by disruption of plasma membrane of microorganisms.

- Resident microbes—have commensal or mutualistic bacteria and fungi that are normally present and out-compete potential pathogens

Skin

- Difficult for a pathogen to penetrate,
 - Sweat creates high salt conditions.
 - Oil layer, fatty acids and acid pH present makes an inhospitable environment for microorganisms.
- Normal flora prevent other microorganisms from establishing an infection – “competitive exclusion”.

Mucus and Cilia

- Mucus contains lysozymes, enzymes that destroy bacterial cell walls.
- The normal flow of mucus washes bacteria and viruses off mucus membranes.
- Cilia in the respiratory tract move mucus out of the lungs to keep bacteria and viruses out.

- Stomach acid (HCl) kills pathogens and sterilizes food.
- Mucus lining of lungs traps pathogens and cilia move particles out to throat and it is swallowed.
- Coughing and sneezing.
- Tears wash away pathogens and have bacteriocidal enzymes.
- Flushing action of urine
- Circulating cells and tissue cells
- Wax in ears
- Normal flora prevents growth of opportunistic pathogens in mouth, large intestine and reproductive system

Second Line Defense

- Phagocytosis
- Inflammation
- Complement
- Fever
- Interferon

1-Phagocytosis

- 1. Initiation** is caused by damage to the tissues, either by trauma or as a result of microbial multiplication.
- 2. Chemotaxis**, attraction of leukocytes or other cells by chemicals.
- 3. Opsonization** - Opsonization coating a pathogen by substances so as to enhance phagocytosis.
- 4. Adherence** - firm contact between phagocyte and microorganism.

5. Engulfment into cytoplasm and enclosed in a vacuole.

6. Digestion enzymatic contents in vacuole destroy the microorganism.

- Number of killing mechanisms operating in the vacuoles of phagocytic cells.
- One of the major mechanisms involves hydrogen peroxide which, acting along with an intracellular enzyme, is rapidly lethal to many bacteria.
- Phagocytes are attracted by an inflammatory response of damaged cells.

- ❑ **Opsonization** - coating microorganisms with plasma proteins – aids phagocytosis.
- ❑ The opsonization; is the phenomenon that opsonins surround phagocytes and prepare phagocytes.
- ❑ **Opsonin** binds to **receptors on phagocyte membrane**.
- ❑ Complement binds to antibody-antigen targets.
- ❑ **Promotes adhesion** between **opsonized cell & macrophages**.

- Phagocytosis continues to be common way to kill pathogenic cells in both specific and non-specific response

10th lecture

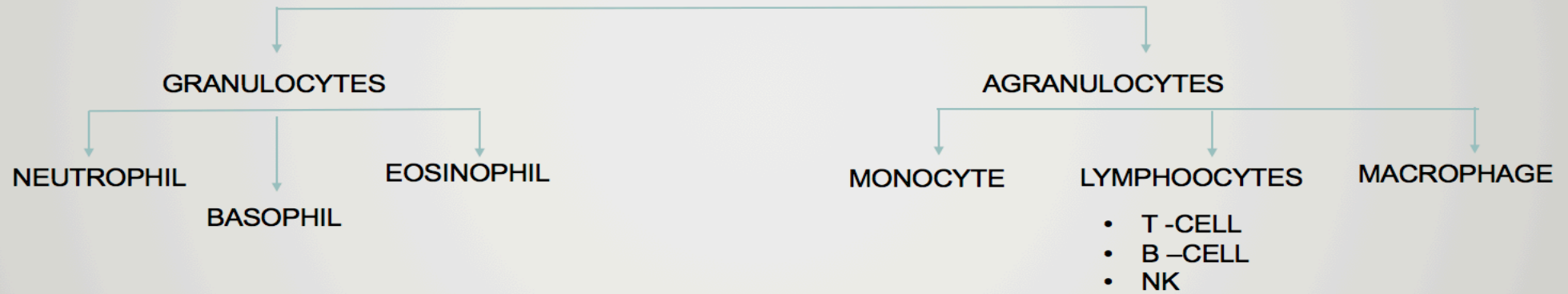
The phagocyte cell in the organism

- **Microphages:** (Leukocytes with particulate nuclei):

These cells are the most prominent phagocytic cell in the blood. Neutrophils are active, eosinophils are less active.

- **Macrophages:** Larger phagocytes. They start phagocytosis later than neutrophils. Two types;
 - 1- Wandering macrophages (mainly monocytes)
 - 2- Settled macrophages.
- System formed by both => Mononuclear Phagocytic System - Reticulo Endothelial System (RES) is called.

LEUKOCYTES



LEUKOCYTES

- Divided into two main categories based on their appearance under the light microscope:
- **Granulocytes** Versus **Agranulocytes**.
- **Granulocytes**: Neutrophils(stain lilac), Basophils (stain blue-purple), and Eosinophils (stain red or orange).

GRANULOCYTES

NEUTROPHILS (60% of WBC)

- Commonly called polymorphonuclear leukocytes (PMNs).
- Highly phagocytic and motile.
- Active in the initial stages of infection.
- Short life span (hours)
- Very important at “clearing” bacterial infections
- Innate Immunity

BASOPHILS (1% of WBC)

- Role is not clear.
- Release substances, such as **histamine**, that are important in **inflammation**.
- Might be “blood Mast cells”
- Important in allergic reactions

EOSINOPHILS (3% of WBC)

- Somewhat phagocytic.
- Have the ability to leave the blood.
- Major function is to produce toxic proteins against certain parasites such as worms.
- Involved in allergic inflammation
- Double Lobed nucleus
- Orange granules contain toxic compounds

AGRANULOCYTES

- Monocytes (5% of all WBC)
- Lymphocytes (30% of all WBC)
- Macrophages

MONOCYTES

- Phagocytosis and killing of microorganisms
 - Activation of T cells and initiation of immune response
- Monocyte is a young macrophage in blood
- There are tissue-specific macrophages
- Antigen Presentation

LYMPHOCYTES

Many types:

- **B-cells** produce antibodies(Humoral immunity)
- **T- cells** (Cellular immunity)
 - Cytotoxic T cells
 - Helper T cells

Memory cells

Plasma Cell (in tissue): Fully differentiated

B cells, secretes Ab

■ Natural Killer cells

- Natural killer (NK) cells are large granular lymphocytes derived from the common lymphoid progenitor cells (lymphoblasts).
- NK cells constitute 5%-10% of lymphocytes in human peripheral blood.
- NK cells are cytotoxic; small granules in their cytoplasm contain proteins such as perforin and proteases known as granzymes, that will trigger either apoptosis or cell lysis in an abnormal cell.
- Defensins, an antimicrobial secreted by NK cells, directly kills bacteria by disrupting their cell walls.
- NK cells differentiate and mature in thymus, spleen, bone marrow, lymph nodes and tonsils.

MACROPHAGES

- Macrophages are born from white blood cells called monocytes, which are produced by stem cells in our bone marrow. Monocytes move through the bloodstream and when they leave the blood, they mature into macrophages. They live for months, patrolling our cells and organs and keeping them clean.

2- Inflammation

(Continue to the second line defense)

- Response to tissue damage from any source (burn, cut etc.)
- Blood vessels dilate allowing for better delivery of nutrients, O₂, antibodies, complement, immune cells
- Phagocytes (monocytes and neutrophils) migrate out of capillaries
- Inflammation works to allow both specific and non-specific immune response to accelerate

- **Inflammatory response** - *four classic signs are redness, swelling, heat and pain.*
 - **Dilation of capillaries** (hyperemia) to increase blood flow to area
 - **Chemotaxis** - chemicals released which cause phagocytic white cells to migrate to the area.
 - **Increased capillary permeability** allowing white cells to go to injured area, a process known as “diapedesis”
 - **Formation of exudate** - same composition as plasma and it contains antibacterial substances, phagocytic cells, and drugs and antibiotics, if present.

- **Kinins**: cause vasodilation and increased permeability of blood vessels.
- **Prostaglandins**: released by damaged cells, and intensifies the effects of histamin and kinins.
- **Leukotrienes**: produced by mast cells and basophils- Cause increased permeability, and attract phagocytes to pathogens.

- Vasodilation and increased permeability of blood vessels also help to deliver clotting elements to injured area.
- Blood clots prevent microbe from spreading, so a localized collection of pus results (abcess).

3-Complement

- Group of free proteins in blood that respond to antigen/antibody complex
- complex of almost 30 proteins (Glycoproteins) present in normal serum) C1, C2, C3etc.
- **Function:** Lysis of microbes, Neutralization of viruses, Enhancement of phagocytosis, Damage of plasma membrane, Recruitment of Phagocytes,
- Cascade of reactions eventually makes MAC's—membrane attack complex—that bores hole in bacterial membrane.

4-Fever

Trigger not completely understood but Muscular contraction and constriction of skin blood vessels cause temperature to rise.

- Inhibit microbial growth
- Enhance immune cell performance
- Speed tissue repair

Cause;

- Malaise
- Body aches
- Chills

Fever also allows for better performance in both specific and non-specific function

5-Interferon

- Family of glycoproteins that block viral replication by rendering host cells
- Interferons play an important role in the first line of defense against viral infections
- Interferons are part of the non-specific immune system
- Interferons are made by cells in response to an appropriate stimulus
- It is not specific to one kind of viruses
- It is only effective in organism that produce in

Types of interferon

- **alpha (leukocyte interferon):** produced by virus infected leukocytes
- **beta (fibroblast interferon):** produced by virus infected fibroblasts or epithelial cells
- **gamma (immune interferon):** produced by certain activated T cells & NK cells

Factors affect defense mechanism

- Age
- Hormones
- Drugs and chemicals
- Malnutrition
- Fatigue and stress
- Genetic determinants

Specific immunity (Adaptive Immunity)

- Third line of defense
- Pathogen specific
- Involves antigens and antibodies
- Two types; Humoral and Cell mediated

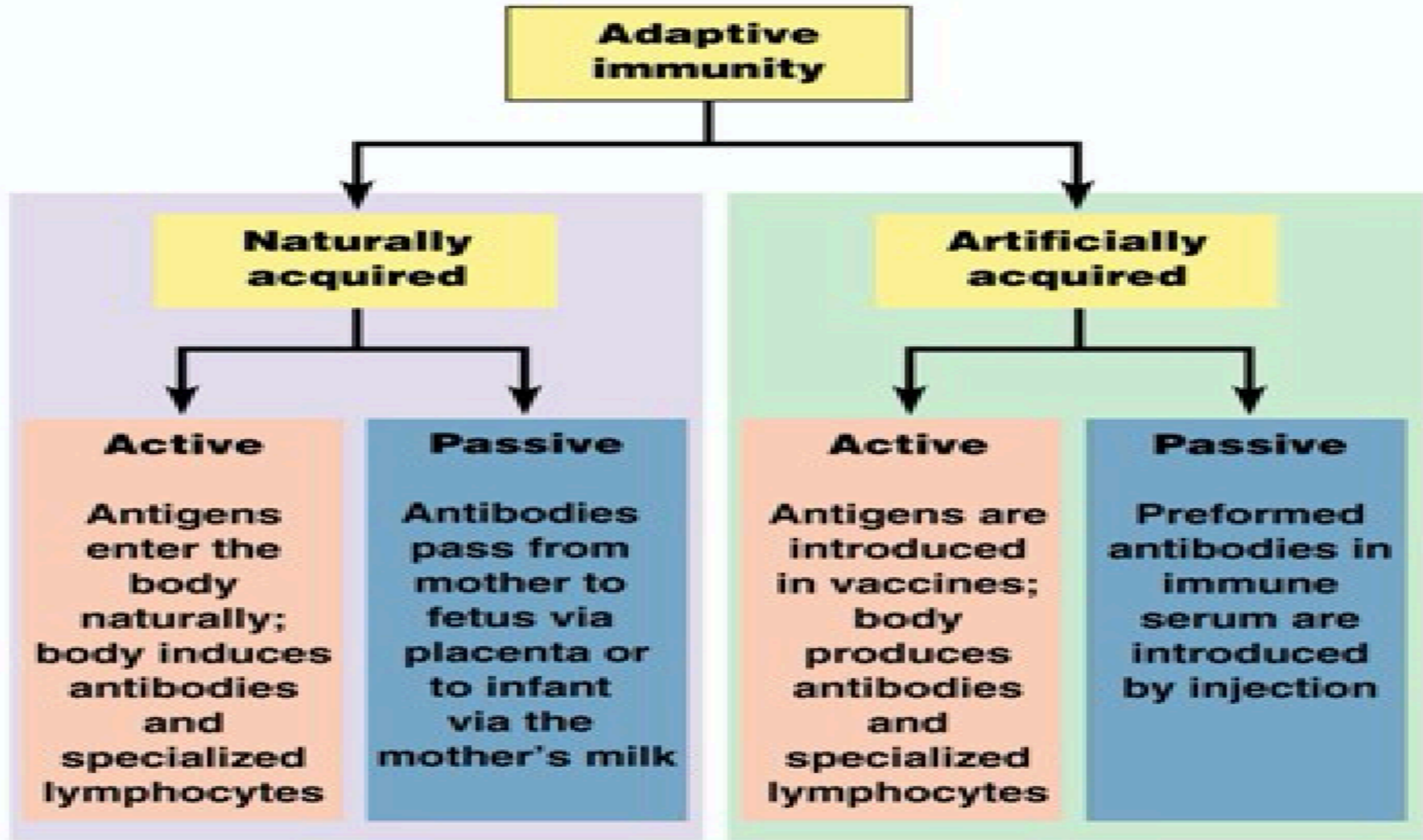
Humoral immunity: Antibody mediated immunity

- Results in production of proteins called “immunoglobulins” or “antibodies”.
- Body exposed to “foreign” material termed “antigen” which may be harmful to body: virus, bacteria, etc.

The humoral response (or antibody-mediated response) involves B cells that recognize antigens or pathogens that are circulating in the lymph or blood (“humor” is a medieval term for body fluid). The response follows this chain of events:

- Antigens bind to B cells.
- Interleukins or helper T cells costimulate B cells. In most cases, both an antigen and a costimulator are required to activate a B cell and initiate B cell proliferation.
- B cells proliferate and produce plasma cells. The plasma cells bear antibodies with the identical antigen specificity as the antigen receptors of the activated B cells. The antibodies are released and circulate through the body, binding to antigens.
- B cells produce memory cells. Memory cells provide future immunity.

- **Cell-mediated immunity** is an immune response that does not involve antibodies or complement but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T- lymphocytes, and the release of various cytokines in response to an antigen.
- The second arm of the immune response is referred to as Cell Mediated Immunity (CMI). As the name implies, the functional "effectors" of this response are various immune cells.
- These functions include:
 - Phagocytosis and killing of intracellular pathogens
 - Direct cell killing by cytotoxic T cells
 - Direct cell killing by NK and K cells



SPECIFIC RESISTANCE (IMMUNITY)

Responds to threats on an individualized basis

ACQUIRED IMMUNITY

Produced by prior exposure or antibody production

INNATE IMMUNITY

Genetically determined—no prior exposure or antibody production involved

ACTIVE IMMUNITY

Produced by antibodies that develop in response to antigens
(Immune response)

Naturally acquired immunity

Develops after exposure to antigens in environment

Induced active immunity

Develops after administration of antigen to prevent disease

PASSIVE IMMUNITY

Produced by transfer of antibodies from another person

Induced passive immunity

Conferred by administration of antibodies to combat infection

Natural passive immunity

Conferred by transfer of maternal antibodies across placenta or in breast milk

Naturally acquired passive immunity

- Maternal passive immunity is a type of naturally acquired passive immunity, and refers to antibody-mediated immunity conveyed to a fetus or infant by its mother. Naturally acquired passive immunity can be provided during pregnancy, and through breastfeeding

Artificially acquired passive immunity

- It is a short-term immunization achieved by the transfer of antibodies, which can be administered in several forms; as human or animal blood plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized donors or from donors recovering from the disease, and as monoclonal antibodies (MAb). Passive transfer is used to prevent disease or used prophylactically in the case of immunodeficiency diseases, such as hypogammaglobulinemia.
- Passive immunity provides immediate protection, but the body does not develop memory, therefore the patient is at risk of being infected by the same pathogen later unless they acquire active immunity or vaccination

- **Active immunity** → **late onset, long term, strong protection**
- **Passive immunity** → **quick onset, short term, poor protection**

ANTIGEN

- Antigens are substances that induce a specific immune response and subsequently react with the products of a specific immune response.
- Literally Anti-gen means any agent which can generate antibody
- Immuno-gen means any agent which generates immune response. (Antibody mediated or Cell mediated)

Immunogen: a stimulus that produces a humoral or cell-mediated immune response

–Humoral immune response – by antibody

–Cell mediated immune response – by T cells

Antigen: any substance that binds specifically to an antibody or a T-cell receptor

By definition all immunogens are antigens but all antigens are not immunogens.

- Tolerogen - An antigen that invokes a specific immune non-responsiveness due to its molecular form. If its molecular form is changed, a tolerogen can become an immunogen.
- Allergen - An allergen is a substance that causes the allergic reaction. The (detrimental) reaction may result after exposure via ingestion, inhalation, injection or contact with skin.



Most of antigens are proteins or large polysaccharides from a foreign organism.

- Microbes: Capsules, cell walls, toxins, viral capsids, flagella, etc.
- Nonmicrobes: Pollen, egg white , red blood cell surface molecules, serum proteins, and surface molecules from transplanted tissue.
- Lipids and nucleic acids are only antigenic when combined with proteins or polysaccharides.

- An antigen is a molecule that stimulates an immune response.
- The word originated from the notion that they can stimulate antibody generation. We now know that the immune system does not only consist of antibodies.
- The modern definition encompasses all substances that can be recognized by the adaptive immune system.

Substances that act as antigens

Infectious materials

- a. microbial structures

(cell walls, capsules, flagella, pili, viral capsids, envelope- associated glycoproteins, etc.

- b. microbial toxins

Noninfectious materials

- a. allergens (dust, pollen, hair, foods, dander, bee venom, drugs, and other agents causing allergic reactions);
- b. foreign tissues and cells (from transplants and transfusions); and
- c. the body's own cells that the body fails to recognize as "normal self" (cancer cells, infected cells, cells involved in autoimmune diseases).

Classification of antigens

According to chemical nature

1. Proteins- virtually all
2. Polysaccharides – potentially but not always
3. Nucleic acids – poor antigens
4. Lipids- may act as haptens

According to mode of action

- Thymus dependent – Protein antigens
- Thymus independent - Polysaccharides

According to epitope

1. Unideterminant univalent
2. Unideterminant multivalent
3. Multideterminant multivalent

According to Source

1. Exogenous
2. Endogenous

- Antigenes can be classified in order of their origins;
- **Exogenous antigens**

Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection.

- **Endogenous antigens**

Endogenous antigens are antigens that have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection.

The characteristics of antigens

1. Immunogenicity

- The capacity to stimulate the production of antibodies or cell-mediated immune responses.

2- Antigenicity: The ability to bind antibody.

- Complete antigen
- Incomplete antigen

- **Complete antigen**: Substances which can induce antibody formation by themselves and can react specifically with these antibodies
- **Incomplete antigen**, also known as **hapten**: substances unable to induce antibody formation on its own but can become immunogenic when covalently linked to proteins, called carrier proteins
- Incomplete antigens have antigenic determinants, but cannot induce immune responses because they lack one or more of the important attributes needed for this function. Haptens are low molecular weight antigens that cannot activate T cell or B cells due to its inability to bind the MHC proteins.

The properties of antigen

- Foreignness
- Molecular size
- The chemical composition of antigen
- The duration of antigen stay in organism
- The dose of antigen
- The entrance path of antigen
- The host immune defense

The properties of antigen

1. **Foreignness:** Antigen must be foreign to immune system, It is essential to immunogenicity because self-responsive cells are eliminated by lymphocyte, leaving only cells that respond to non-self, so-called "foreign" epitopes.
2. **Molecular weight:** Larger molecules are highly antigenic. Lower molecular weight are either non antigenic or weakly antigenic
3. **Chemical Nature:** Most naturally occurring antigens are either proteins or polysaccharides. Lipids and nucleic acids are less antigenic on their own but do so when combined with proteins.

4. **The duration of antigen stay in organism:** Should be slowly absorb and throw
5. **The dose of antigen:** Very few can not stimulate the immune system
6. **The entrance path of antigen:** Injectable administration increases antigenicity
7. **Usage of adjuvant**

Determinant=epitop

- EPITOPE (= “antigenic determinant” = “antigenic specificity”) - The minimum target structure on an antigen which is bound by a particular antibody molecule. A particular antigen molecule may (and generally does) bear many different epitopes or “determinants”, each of which can be a target for antibody binding.

- **Epitope or Antigenic Determinant** - the region of an antigen that binds to a T cell receptor or a B cell receptor (antibody).
- - Since an epitope is the part of the antigen that binds to the B cell or T cell antigen receptor, it is the part that determines the antigenicity of the antigen - thus the term “antigenic determinant”.
- -T and B cells recognize different epitopes on an antigen
- - **Each different protein and glycoprotein of a virus (or bacterium or foreign cell) constitutes a different antigen**
- **Each different antigen contains a number of different epitopes**

Adjuvant

The Latin "adjuvans" means to help, particularly to reach a goal.

Adjuvant: a substance that, when mixed with an antigen and injected with it, serves to enhance the immune response to the antigen.

Possible mechanisms of action of adjuvants:

- Prolong the persistence of the antigen, thus giving the immune system more time to respond
- Increase the "size" of the antigen by causing aggregation,
- Stimulate lymphocyte proliferation and/or activation
- Stimulate a local inflammatory response, thus recruiting cells to the site of the antigen (GRANULOMA)
- Enhance co-stimulatory signals

- **Commonly used adjuvants: Alum** - aluminum potassium sulfate - precipitates the antigen, resulting in increased persistence of the antigen and induces mild granuloma.
- **Incomplete Freund's adjuvant** - mineral oil-based - increases persistence of the antigen, mild granuloma, and induces co- stimulatory signals
- **Complete Freund's Adjuvant** - mineral oil-based adjuvant containing dead bacteria - increases persistence of the antigen, stimulates a chronic inflammatory response (granuloma), and co-stimulatory signals
- **Bacterial Lipopolysaccharides** - stimulate nonspecific lymphocyte activation and proliferation

Other antigens

- **Heterophilic antigen** : A kind of common antigen, existing in human, animals, and microbes.

Fossman antigen.

- **Xenogenic antigen**

This antigen comes from different genus and generic. For example, pathogenic antigen.

- **Allogenic antigen**

The specific antigen exists in different individuals. Blood type antigens

- **Autoantigens**

- An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should under normal conditions not be the target of the immune system, but due to mainly genetic and environmental factors the normal immunological tolerance for such an antigen has been lost in these patients.

- **Superantigens** are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes . Exp;

1. Toxic shock syndrome toxin-1 (TSST-1),

2. Streptococcal pyrogenic exotoxin (Spe),

produced by rare invasive strains and scarlet fever strains of *Streptococcus pyogenes* (group A beta streptococci).

3. Staphylococcal enterotoxins (SE),

4. Superantigens associated with *Streptococcus pyogenes* are also thought to be responsible for psoriasis.

5. Antigens associated with *Mycobacterium tuberculosis*, the rabies virus, and possibly HIV may also function as superantigens

Antigens of microorganisms

- There are multiple antigens in accordance with the chemical structures of the microorganisms and antibodies against them. With the help of these antibodies;
 - ✓ microorganisms are recognized and typed
 - ✓ diagnosis of some diseases.

REFERENCES

- Hugo and Russell's Pharmaceutical Microbiology. S. Denyer, N.A. Hodges, S.P. Gormen. Seventh Edition, Blackwell Science, 2007
- Pharmaceutical Microbiology. S.S. Purohit, A. K. Saluja, H.N. Kakrani. First Edition Agrobios, 2004
- Medical Microbiology. A guide to microbial infections: Pathogenesis, Immunity, Laboratory Diagnosis and Control. Edt. David Greenwood, Richard Slack, John Peutherer, Mike Barer. 17.th edition, 2007
- Tıbbi Mikrobiyoloji (Medical Microbiology).Çeviri Editörleri. Dürdal Us, Ahmet Başustaoğlu. 7. Baskı 2017.
- Farmasötik Mikrobiyoloji, Edt: Ufuk Abbasoğlu, Adile Çevikbaş. Efil Yayınevi. 1. Baskı 2011.
- Us, Dürdal. Temel İmmünoloji ve Seroloji. Hipokrat Kitabevi.2016