Immune system = cells, tissues, and molecules that mediate resistance to infections.

Immunity: which refers to all the mechanisms used by the body as protection against infectious disease or environmental agents that are foreign to the body. These agents may be microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair and dander.

The word immunity was derived from the Latin word "immunis" meaning “exempt,” is the source of the English word immunity.

Immunology: - is a branch of science that study the immune system, including its responses to microbial pathogens and damaged tissues, and its role in disease.

Immune responses: - are the cells and molecules responsible for immunity.

Significance of the Immune System

Beneficial:

Protection from Invaders

Elimination of Altered Self

Detrimental (harmful):

Discomfort (inflammation)

Damage to self (autoimmunity)

Immune system

The immune system refers to a collection of cells and proteins that function to protect all the body (skin, respiratory and intestinal tract, and other areas) from foreign antigens, such as microbes (bacteria, fungi, viruses, and parasites).

Two important types of immune responses

I. Innate (natural) or non-specific immunity
II. II. Adaptive (acquired) or specific immunity

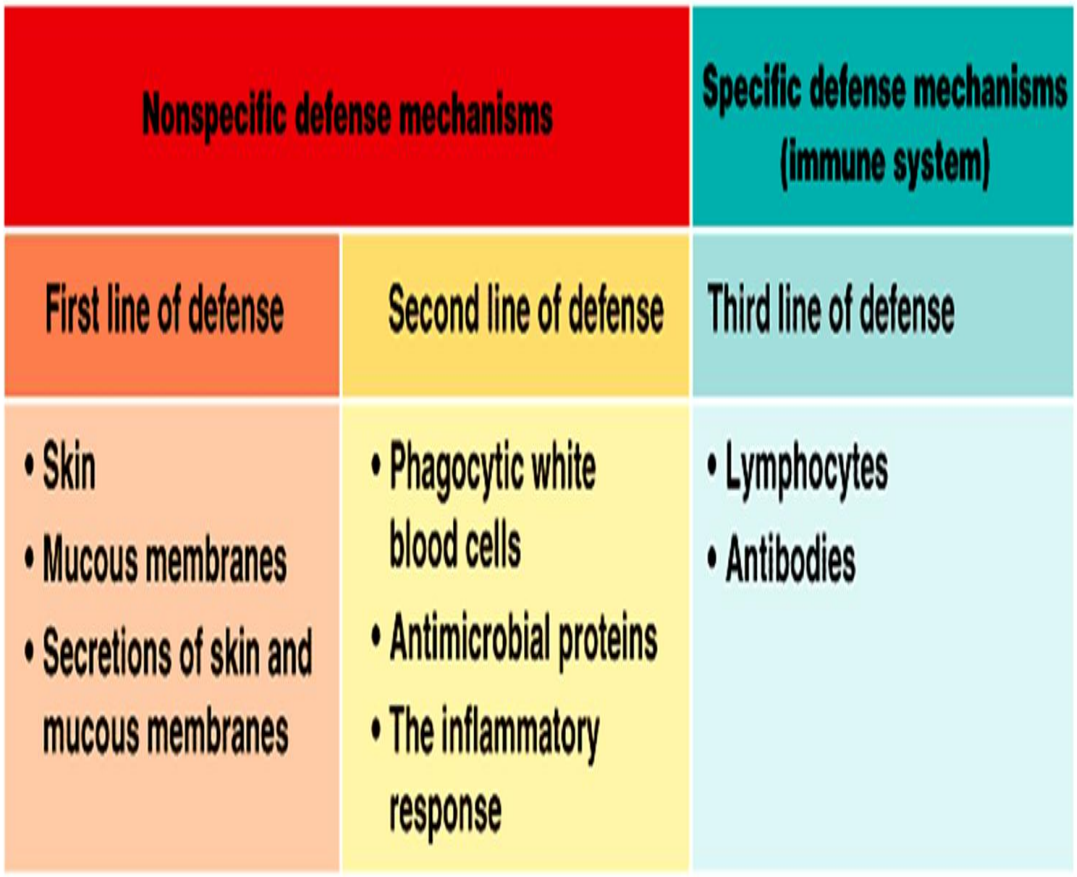
Barriers to Invasion of Pathogens

1. First Line of Defense: Non-specific natural barriers which restrict entry of pathogen. Examples: Skin and mucous membranes.

2. Second Line of Defense: Innate non-specific immune defenses provide rapid local response to pathogen after it has entered host. Examples: Fever, phagocytes (macrophages and neutrophils), inflammation, an interferon.

3. Third line of defense: Antigen-specific immune responses, specifically target and attack invaders that get past first two lines of defense.

Examples: Antibodies and lymphocytes.



Innate immunity

It is first line of defense against invading organisms (bacteria, viruses, parasites and fungus), **characterized by**:

* Most components of innate immunity are present before the onset of infection.

*Not antigen specific.

*Effective immediately after exposure to antigen.

*Has no immunological memory.

Factors affecting Innate Immunity:

1. **Species**: e.g. Human not affected by plants pathogens.

2. **Race**; genetic play role in this factor e.g. all members of particular race are resistance to certain infections like people of African race are resistant to malaria.

3. Individual Factors include:

 Age: increased age causes increase ability to get infections. Also, new born are more susceptible to infections due to immature immune system.

 Hormones: e.g. Stress causes release of steroid hormones causing easy to get infections. Also hyperthyroidism can cause immune-suppression.

 Nutrition: vitamins play role in good immunity.

4. **Geographic location**: this factor effects on normal flora composition and exposure to the epidemic disease.

Mechanisms of non-specific I.R:

A. Anatomical barriers to infections

1. Mechanical factors

- **Intact skin** :- is the first line of defense against infection consisting of the keratinized outer of dead cells and the successive layers of epidermis which prevent invading of microorganisms(m.o).
- **mucus** - which is coat the epithelial cells of the mucosa, preventing contact between many pathogens and area not covered by skin.
- Shedding of cells that carry microbes.

- Saliva, tears, urine and other body fluids to assist in flushing microbes from the body.
- vomiting, diarrhea and other body functions also eliminate pathogenic organisms.

2. Chemical factors

- Fatty acids in sweat inhibit the growth of bacteria.
- Lysozyme and phospholipase found in tears, saliva and nasal secretions can breakdown the cell wall of bacteria and destabilize bacterial membranes.
- The low pH of sweat and gastric secretions prevents growth of bacteria.
- Defensins (low molecular weight proteins) found in the lung and gastrointestinal tract have antimicrobial activity.
- Surfactants in the lung act as opsonins (substances that promote phagocytosis of particles by phagocytic cells).

3. Physical factors

- Body temperature (m.o grows poorly at 37c^{o}).
- tension which is high in the upper lobes of the lungs , favors the growth of obligate aerobes such as tuberculosis organisms.
- hormonal balance. An increase in corticosteroids decreases the inflammatory response and lower the resistance to infection. Thus people receiving corticosteroids to control autoimmune disease or graft rejection have a heightened susceptibility to infectious agent.
- Age: to very young or too very old person susceptible to infection because I.R is sub optimal.

4. Biological (normal flora)

Normal flora is formed when nonpathogenic bacteria colonize epithelial surfaces. Normal flora protects the host by:

- Competing with pathogenic bacteria for nutrients and attachment sites
- Production of antibacterial substances

B. Humoral barriers to infection

The anatomical barriers are very effective in preventing colonization of tissues by microorganisms. However, when there is damage to tissues the anatomical barriers are breached and infection may occur. Once infectious agents have penetrated tissues, another innate defense mechanism comes into play, namely acute inflammation. Humoral factors play an important role in inflammation, which is characterized by edema and the recruitment of phagocytic cells. These humoral factors are found in serum or they are formed at the site of infection.

1- C-reactive protein functions as a soluble protein and can bind to bacteria to promote their removal by phagocytosis. It is a major acute-phase protein, so named as it binds to the C-polysaccharide cell wall component on a variety of bacteria and fungi.

2. **Complement system** – The complement system is the major humoral non-specific defense mechanism.

3. Coagulation system –Some products of the coagulation system can contribute to the non-specific defenses because of their ability to increase vascular permeability and act as chemotactic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly antimicrobial. For example, beta-lysin.

4. Lactoferrin and transferrin – By binding iron, an essential nutrient for bacteria, these proteins limit bacterial growth.

5. Interferon's – interferon's are proteins (cytokine) that can limit virus replication in cells.

6. Lysozyme – Lysozyme breaks down the cell wall of bacteria.

7. Interleukin-1 – IL-1 (Cytokine) induces fever and the production of acute phase proteins, some of which are antimicrobial because they can opsonize bacteria.

C. Cellular barriers to infection

1. **Neutrophils** – Polymorph nuclear cells (PMNs) are recruited to the site of infection where they phagocytose invading organisms and kill them intracellularly. 2. **Macrophages** –macrophages are capable of extracellular killing of infected or altered self-target cells. Furthermore, macrophages contribute to tissue repair and act as antigen presenting cells, which are required for the induction of specific immune responses.

3. **Natural killer (NK) and lymphokine activated killer (LAK) cells** – NK and LAK cells can nonspecifically kill virus infected and tumor cells.

4. **Eosinophil's** – Eosinophil's have proteins in granules that are effective in killing certain parasites.

Acquired Immunity

Acquired or specific immunity is more specialized than innate immunity, it can recognize and selectively elimination specific antigens. Acquired immunity is induced by passive or active immunization, which can be achieved in several ways: 1- Artificial active immunity refers to immunization of an individual by administration of an antigen.

2- **Natural active immunity-** immunization is a natural outcome of infection.

3- **Artificial passive immunity** refers to immunization through the transfer of specific antibody from an immunized individual to a nonimmunized individual.

4-**Natural passive immunity**- Newborns receive antibody from mothers.

5- A**doptive transfer (immunization)** refers to the transfer of immunity by the transfer of immune cells.

Innate immunity	**Adaptive immunity**
•Present from birth	•present after exposure to an antigen (Ag)
• Not antigen-specific	•Pathogen-specific immunity
• Not enhanced by second exposure	• Enhanced by second exposure
• No memory	• Memory
•Uses cellular and humoral components	•Uses cellular and humoral components
•Is poorly effective without adaptive immunity	• Is poorly effective without innate immunity

Antigens and Antibodies

Antigen

Most are proteins or large polysaccharides from a foreign organism.
Microbes: Capsules, cell walls, toxins, viral capsids, flagella, etc.

Non-microbes

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.

- Molecular weight of 10,000 KD or higher.

Immunogens

Are foreign macromolecules that induce an immune response. Molecular size, complexity, and physical form are intrinsic properties of immunogens. Molecular size is an important component of immunogenicity. For example, low molecular-weight compounds called haptens cannot induce an immune response but can bind to antibodies. Because haptens are bound by antibodies, they are antigens even though they are not immunogenic. When foreign immunogens are introduced into a host in an appropriate dose and route, they initiate an immune response.

Hapten

Small foreign molecule that is not antigenic. Must be coupled to a carrier molecule to be antigenic. Once antibodies are formed they will recognize hapten.

Epitope

Small part of an antigen that interacts with an antibody. Any given antigen may have several epitopes. Each epitope is recognized by a different antibody.

Super Ags

In contrast to conventional Ags. Which are processed intra cellularly , super Ags. Simultaneously activate large number of T-cells carrying a particular T-cell receptor variable beta gene , by binding directly to MHC class II molecule at a site distinct from the Ag - binding groove. This cross - linking is a powerful signal of mitosis , causing activation of large number of helper T-cells. These molecule are able to induce the release of large amount of cytokines such as IL-1, IL-2, and TNF from Tcell which in turn contribute to local tissue pathology.

Antibodies

1. Proteins that recognize and bind to a particular antigen with very high specificity.

2. Made in response to exposure to the antigen.

3. One virus or microbe may have several antigenic determinant sites, to which different antibodies may bind.

4. Each antibody has at least two identical sites that bind antigen (Antigen binding sites)

5. Valence of an antibody: Number of antigen binding sites.

6. Belong to a group of serum proteins called immunoglobulins (Igs).

Antibody Structure :-

1. Monomer: A flexible Y-shaped molecule with four protein chains :

- 2 identical light chains
- 2 identical heavy chains

2. Variable Regions: Two sections at the end of Y's arms. Contain the antigen binding sites (Fab). Identical on the same antibody, but vary from one antibody to another.

3. Constant Regions: Stem of monomer and lower parts of Y arms.

4. Fc region: Stem of monomer only. Important because they can bind to complement or cells.

Immunoglobulin Classes

- **IgG**
- Structure: Monomer
- Percentage serum antibodies: 80%
- Location: Blood, lymph, intestine
- Half-life in serum: 23 days
- Complement Fixation: Yes
- Placental Transfer: Yes
- Known Functions: Enhances phagocytosis, neutralizes toxins and viruses, protects fetus and newborn.
- **IgM**
- Structure: Pentamer
- Percentage serum antibodies: 5-10%
- Location: Blood, lymph, B cell surface (monomer)
- Half-life in serum: 5 days
- Complement Fixation: Yes
- Placental Transfer: No
- Known Functions: First antibodies produced during an infection. effective against microbes and agglutinating antigens.
- **IgA**
- Structure: Dimer
- Percentage serum antibodies: 10-15%
- Location: Secretions (tears, saliva, intestine, milk), blood and lymph.
- Half-life in serum: 6 days

- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Localized protection of mucosal surfaces. Provides immunity to infant digestive tract.
- **IgD**
- Structure: Monomer
- Percentage serum antibodies: 0.2%
- Location: B-cell surface, blood, and lymph
- Half-life in serum: 3 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: In serum function is unknown. On B cell surface, initiate immune response.
- **IgE**
- Structure: Monomer
- Percentage serum antibodies: 0.002%
- Location: Bound to mast cells and basophils throughout body. Blood.
- Half-life in serum: 2 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Allergic reactions. Possibly lysis of worms.

How Do B Cells Produce Antibodies?

- B cells develop from stem cells in the bone marrow of adults (liver of fetuses).
- After maturation B cells migrate to lymphoid organs (lymph node or spleen).
- Clonal Selection: When a B cell encounters an antigen it recognizes, it is stimulated and divides into many clones called plasma cells, which actively secrete antibodies.
- Each B cell produces antibodies that will recognize only one antigenic determinant.

Consequences of Antigen-Antibody Binding

Antigen-Antibody Complex: Formed when an antibody binds to an antigen it recognizes.

Affinity: A measure of binding strength.

1. Agglutination: Antibodies cause antigens (microbes) to clump together.
   - IgM (decavalent) is more effective that IgG (bivalent).
   - Hemagglutination: Agglutination of red blood cells. Used to determine ABO blood types and to detect influenza and measles viruses.
2. Opsonization: Antigen (microbe) is covered with antibodies that enhances its ingestion and lysis by phagocytic cells,
3. Neutralization: IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.
4. Antibody-dependent cell-mediated cytotoxicity: Used to destroy large organisms (e.g.: worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific immune cells.
5. Complement Activation: Both IgG and IgM trigger the complement system which results in cell lysis and inflammation.

Lecture 8,9

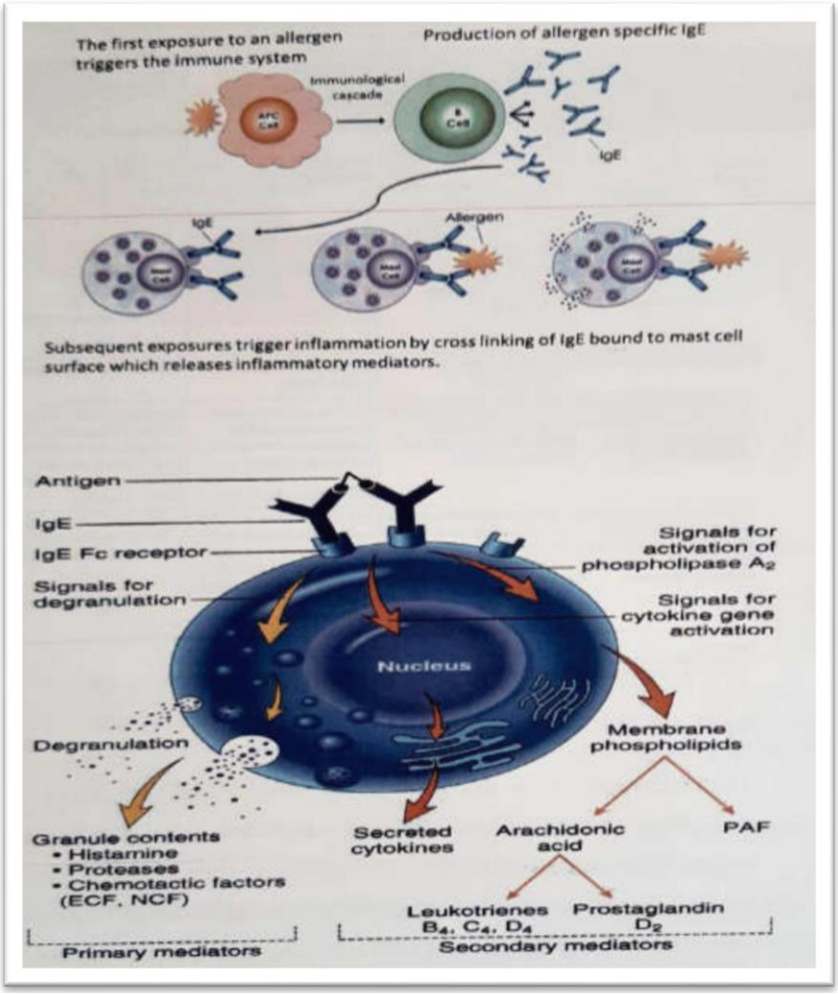
Hypersensitivity

Excessive immune response lead to tissue damage resulting from prolonged or repeated antigen exposure , these reactions caused tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in inflammation. Hypersensitivity reactions commonly are classified on the basis of the principle immunological mechanism that is responsible for tissue injury and disease.

1. Type I: Immediate IgE-mediated
2. Type II: Cytotoxic
3. Type III: Immune complex-mediated
4. Type IV: Delayed cell-mediated

Hypersensitivity-Type I reactions

Type I hypersensitivity is also called immediate hypersensitivity, allergy or atopy. These reactions only occur in some individuals in response to foreign antigens (allergens)for whom the individuals have been already exposed. Immediate hypersensitivity depends on Th2-induced release of IgE by B-cells which, in turn, super-activate mast cells with consequent excessive release of histamine and other vasoactive molecules.



type I hypersensitivity reactions, which encompass the most common allergic reactions, including hay fever, asthma, atopic dermatitis, and food allergies. The incidence of allergy continues to rise in the human population.

Type II hypersensitivity reactions

involve antibody-mediated destruction of cells by immunoglobulinsof heavy chain classes other than IgE. Antibody bound to a cell-surface antigen can induce death of the antibodyboundcell by three distinct mechanisms :

First, certain immunoglobulin subclasses can activate the complement system, creating pores in the membrane of a foreign cell. Secondly,

antibodies can mediate cell destruction by antibody dependent cellmediatedcytotoxicity (ADCC), in which cytotoxic cells bearing Fc receptors bind to the Fe region of antibodies on target cells and promote killing of the cells. Finally, antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic
cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell.

Ex:

1-Transfusion reactions
2- Hemolytic disease of new born
3-Drug induced hemolytic anemia.

Type III Hypersensitivity (Immune Complex Mediated)

The reaction of antibody with antigen generates immune complexes. Generally, these complexes facilitate the clearance of antigen by phagocytic cells and red blood cells. In some cases, however, the presence of large numbers and networks of immune complexes can lead to tissue-damaging type III hypersensitivity reactions.

The reaction depends on :

1- the number and size of immune complexes,
2-their distribution within the body
3- the ability of the phagocyte system to clear the complexes and thus minimize the
tissue damage.

--The deposition of these complexes initiates a reaction that results in the recruitment of complement components and neutrophils to the site, with resultant tissue injury.
--Immune complexes bind to mast cells, neutrophils, and macrophages via Fc receptors, triggering the release ofvasoactive mediators and inflammatory cytokines, which interact with the capillary epithelium and increase the permeability of the blood vessel walls. Immune complexes

then move through the capillary walls and into the tissues where they are deposited and set up a localized inflammatory response. Complement fixation results in the production of the anaphylatoxinchemokines C3a and C5a, which attract more neutrophils and macrophages. These in turn are further activated by immune complexes binding to their Fe receptors to secrete proinflammatorychemokines and cytokines, prostaglandins, andproteases. Proteases digest the basement membrane proteins collagen, elastin, andcartilage. Tissue damage is further mediated by oxygen free radicals released by theactivated neutrophils. In addition, immune complexes interact with platelets and induce the
formation of tiny clots. Complex deposition in the tissues can give rise to symptoms such as fever, urticaria (rashes), joint pain, lymph node enlargement, and protein in the urine. The resulting inflammatory lesion is referred to as vasculitisif it occurs in a blood vessel, glomerulonephritis if it occurs in the kidney, or arthritis if it occurs in the joints.

Examples of diseases resulting from type III hypersensitivity reaction

Autoimmune diseases:

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Multiple sclerosis

Drug reactions : Allergies to penicillin and sulfonamides

Infectious diseases :

- Poststreptococcal glomerulonephritis
- Meningitis
- Hepatitis, Mononucleosis
- Malaria
- Trypanosomiasis

Type IV hypersensitivity

commonly referred to as Delayed-Type H ypersensitivity (DTH), is the only hypersensitivity category that is purely cell mediated rather than antibody mediated. In1890, Robert Koch observed that individuals

infected with Mycobacterium tuberculosis developed a localized inflammatory response when injected intradermally (in the skin) with a fi ltrate derived from a mycobacterial culture. He therefore named this localized skin reaction a tuberculin reaction. Later, as it became apparent that a variety of other antigens could induce this cellular response (Table 15-6), its name was changed to delayed-type, or type IV, hypersensitivity. The hallmarks of a type IV reaction are its initiation by T cells (as distinct from antibodies), the delay required for the reaction to develop, and the recruitment of macrophages (as opposed to neutrophils or eosinophils) as the primary cellular component of the infiltrate that surrounds the site of inflammation. The most common type IV hypersensitivity is the contact dermatitis that occurs after exposure to Toxicodendron species, which include poison ivy, poison oak, and poison sumac. This is a significant public health problem.

Tumor Immunology

In most organs and tissues, a balance is maintained between cell renewal and cell death. The various types of mature cells in the body have a given life span; as these cell die, newcells are generated by the proliferation and differentiation of various types of stem cells.Under normal circumstances, the production of new cells is regulated so that the number of any particular cell remains constant. Cells arise that no longer respond to normal growth
control mechanisms, these cells give rise to clones of cells that can expand to aconsiderable size, producing a tumor, or neoplasm.

Types of tumors

1- Benign tumor: a tumor that is not capable of indefinite growth and does not invade the healthy surrounding tissues.
2- Malignant tumor (cancer): A tumor that are continues to grow and becomes progressively invasive (metastasis), all clusters of cancerous cells dislodge from a tumor invade the blood or lymphatic vessels, and are carried to other tissues, where they continue to proliferate. (In this way a primary tumor at one site can give rise to a secondary tumor at another site.

Transformation

Transformation- alteration of morphology,growth properties caused by:
· Chemical carcinogens
· Irradiation
· Viruses (oncoviruses, retroviruses, dna viruses)

· Properties of transformed cells
· Decreased requirements for growth factors (serum).
· No longer anchorage dependent.
· Loss of contact inhibition.
· Immortal.
· Two phases-- initiation and promotion

Classification of cancers according to embryonic origin:

1- Carcinomas: a tumor that a rise from endodermal or ectodermal tissues such as skin or the epithelial lining of the internal organs and the glands(cancer of
colon, breast, prostate, and lung).

2- Leukemias and lymphomas: are malignant of hematopoietic cells of the bone marrow. Leukemias proliferate as single cells, where as lymphomas tend to growth as tumor masses.

3- Sarcomas: a tumor that a rise from mesodermal connective tissues such as bone, fat, and cartilage.

Cancer causes:

· Mutation of a normal gene = change in DNA sequence
· UV light, X-rays,
· Natural or synthetic chemicals
· Virus (ex. HPV and cervical cancer)
· Genetic factors

Tumor Antigens

Two types of tumor antigens have been identified on tumor cells:

1. Tumor-specific transplantation antigens (TSTAs).
2. Tumor-associated transplantation antigens (TATAs)

Tumor specific transplantation antigens

(TSTAs)-- unique to tumor cells and do not occur on normal cells. Result from mutations in tumor cells that generate altered proteins (present with MHC class).

· Chemical or physical carcinogens and some virally induced tumors.

Tumor associated transplantation antigens

(TATAs)-- proteins that are not unique to tumor cells (may be fetal proteins that are not normally expressed in adults but would not be recognized as foreign).

Oncofetal tumor antigens

Are found not only on cancerous cells but also on normal fetal cells, these antigens appear early in embryonic development, before the immune system acquires immunocompetence.

If these antigens appear later on cancer cells, they are recognized as nonself and induce an immunological response.

1- Carcinoembryonic antigen: circulate at elevated levels in the serum of many patients with carcinoma of colon, pancreas ,breast, liver. It is found in fetal gut, liver, and pancreas, and in very small amount in normal cera.

2- Alpha fetoprotein : is present at elevated levels in the sera of hepatomapatients and is used as a marker for this disease, and it occurs in several other malignant and non-malignant diseases. It is produced by fetal liver and is found in small amounts insome normal sera.

Immune response to tumors

1-Humoral immunity: Antibody production by the host against host tumor cells or their constituents for tumor antigens.

2-Cellular immunity :

- Cytotoxic T lymphocyte cells (CTLs) mediated lysis
- NK cells activity
- Macrophage-mediated tumor destruction
- Destruction mediated by ADCC.

CIL (Cytotoxic T-lymphoctyes)

CTLs are the major immune defense mechanism against tumors ,these cells recognize peptides derived from cytoplasmic proteins that are displayed bound to class I major histocompatibility complex (MHC) molecules. CTLs play a protective role against virus associated neoplasms (e.g., EBV- and HPV induced tumors).

NK cells

are capable of destroying tumor cells without prior sensitization - 1' line defense against tumor cells, after activation with IL-2 and IL-15, NK cells can lyse a wide range of human tumors, recognize stress-induced antigens that are expressed on tumor cells and cells that have incurred DNA damage and are at risk for neoplastic transformation.

Macrophages

Activated macrophages exhibit cytotoxicity against tumor cells in vitro. Activated macrophages may kill tumors by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen metabolites or by secretion of TNF). T cells, NK cells, and macrophages may collaborate in antitumor reactivity. Interferon-y, a cytokine secreted by T cells and NK cells, is a potent activator of macrophages.

Tumor Evation of The Immune System

Tumors use several strategies to evade the immune response:

1. Anti-tumor antibodies can enhance tumor growth Anti-tumor antibody acts as a blocking factor, these antibodies binds to TSTAS and mask the antigens fromCTLs.

2. loss or reduced expression of histocompatibility antigens

•tumor cells may fail to express normal levels of HLA class I molecules, thereby escaping attack by cytotoxic T cells Such cells, however, may trigger NK cells

3. Lack of costimulation

•sensitization of T cells requires two signals, one by a foreign peptide presented by MHC molecules and the other by costimulatory molecules although tumor cells may express peptide antigens with class I molecules, theyoften do not express costimulatory molecules.

4. Immunosuppression

Many oncogenic agents (e.g., chemicals and ionizing radiation) suppress host immune responses.Tumors or tumor products also may be immunosuppressive. For example, TGF-B,secreted in large quantities by many tumors, is a potent immunosuppressant.

5. Antibodies can modulate tumor antigens.

•Certain tumor specific antigens have been observed to disappear from the surfaceof tumor cells in the presence of serum antibody and then to reappear after the antibody is no longer present this phenomena called antigenic modulation.

6. Apoptosis of cytotoxic T cells

•Some melanomas and hepatocellular carcinomas express FasL. It has been postulated that these tumors kill Fas-expressing T lymphocytes that come in contact with them, thus eliminating tumor-specific T cells.

→ Determination of site of origin of metastatic tumors

→ Detection of molecules that have prognostic or therapeutic significance

Immunity to infection

Infectious diseases are the major cause of morbidity and mortality worldwide.

We have 4 kinds of infection these are:

1. Bacterial infection
2. viral infection
3. parasitic infection
4. fungal infection

For most infection there is a balance between the virulence of microorganism and host defense mechanism, if imbalance happened the M.omay become pathogenic and cause disease. On the other hand we have a strong host defense mechanism which give us immune protection.

Factors influencing the extent and severity of an infection

1. Pathogen factors

- Dose (i.e. degree of exposure)
- Virulence of m.o
- Route of entry

2. Host factors

- Integrity of non-specific defenses
- Competence of the immune system
- Genetic capacity to respond effectively to a specific m.o
- Evidence of previous exposure(natural or acquired)
- Existence of co-infection

bacterial infection:

infection caused by bacteria are either:

- **acute infection :**

1. invasive
2. Toxogenic
3. local invasion

- **chronic infection**

I.R to bacterial infection

In acute and toxogenic infection:

1. complement fixing Ab :- like IgG and IgM.
2. opsonic Ab :- like IgG which coat the bacteria and make it susceptible for PNC and other phagocytes.
3. agglutinating Ab :- by IgM which will cause aggregation of bacteria with less nutrition leading to killing of bacteria.
4. Ab. Dependant cell cytotoxicity (ADCC) by IgG and IgM
5. blocking Ab :- which block the adherence of m.o to mucus membrane (vibrio cholera) e.g. IgG and IgM.
6- Neutralizing Ab :- Neutralized the toxin If m.o produced toxin causing destruction of tissues. In chronic infection: - removal of m.o is by CMI e.g. T.B the main characteristic of this bacteria is that once it infect it will enter into the reticuloendothelial system and hidden inside the cell, so it will live inside the cell macrophages) and multiply there. On second exposure of T.B this will activate the sensitized T-cells and then production of lymphokines like macrophage activating factor, macrophage chemotactic factor, and macrophage migrating inhibitory factor which will act on the resting and waiting macrophages and activate them which will produce H2O2 to kill the inside bacteria by (respiratory burst).

Mechanisms of immune evasion by bacteria:

1. Capsular polysaccharide which has anti-phagocytic role

2. Mucoid secretion which decrease alt. pathway of complement activation
3. Antigenic variation
4. Production of protease enzyme causing mucosal IgA ineffective
5. Intracellular living causing hidden from I.R.

Viral infection

IR to viral infection (Humoral& Cellular IR)

Humoral IR

1- Ab.(spe. Sec. IgA): block binding virus to host cells thus preventing infection or re-infection.
2- IgG, IgM, IgA : block fusion of viral envelope with host cell.
3- IgG, IgM : enhance phagocytosis, viral particle (opsonization)
4- IgM : agglutination
5- Complement : Activated by Ab, mediate opsonization by C3b and lyses of envelopedviral particle by MAC.

Cellular IR

1- IFN-gamma: direct antiviral action by Th or Tc.
2- Te : kill the virus infected self-cell.
3- NKC & Macrophages: kill virus infected cell by ADCC.

Escape mechanisms of viruses from I.R

1. Non-expression of viral genome e.g. HSV (latent)
2. Production of antigenic variation e.g. influenza, HIV
3.Inhibition of MHC expression e.g. adenovirus
4. Production of inhibitory cytokines e.g. EBV & IL-10
5. Viral persistence e.g. HCV

Parasitic infection

1- Protozoal infection:- e.g.
- ***Plasmodium (malaria)***
- ***Leishmania (leishmaniasis),***

- ***Trypanosome (trypanosomiasis)***

2- Helminthes (worms):- e.g.
- ***Nematodes (e.g. Ascaris spp.)***
- ***Trematodes (e.g. Schistosoma spp.)***
- ***Cestodes (e.g. Taenia spp.)***

I.R to parasitic infection

Humoral I.R:

1. direct damage or complement mediated lyses e.g. malaria, intestinal worm,
trypanosomes
2. neutralizing Ab. e.g. malaria, T. ceuzi
3. opsonic Ab, e.g. malaria, trypanosomes
4. ADCC e.g. schistosoma

Cellular I.R:

1. Parasite is focused by APCs then presentation to T-cell which secret MAF by T-cell lead to activation of macrophages and kill the parasite by production of H2O2.
2. In helminthes infection T-cells secret eosinophilic stimulating factor which attract andactivate eosinophil cells then exert their function which are:

a) produce substance to suppress mast cell granules like histamine
b) eosinophil with IgE kill the target in a similar manner of ADCC
c) there are lymphokines which stimulate goblet cells to secret more secretion leading to increase perstalsis movement of intestine and expulsion of worm outside the
GIT.

Mode of escape mechanisms of parasites from I.R:

1. location:

a. intracellular habitat e.g. T. cruzi which live inside the macrophages.
b. cyst production e.g. E. histolytica
c. live in gut e.g. intestinal worm

2. avoidance of recognition:

a. antigenic variation, change the coat
b. acquired surface layer from the host

3. suppression of I.R by:

a. some parasite continue to release Ag. Causing fit antigenic receptor of Tcells leading to saturation and tolerance (unresponsive state).
b. some other parasite produce substance causing activation of suppressor cells.

Fungal infection:

Fungi cause many diseases which can be classified into superficial, subcutaneous, or deep mycosis (systemie) Factor contributing fungal infection.

1. Antibiotic abuse
2. Hormonal change
3. Traumatic change
4. Debilitating disease e.g, DM carcinoma etc...
5. Change in PH e.g. Candida.

IR to fungal infection:

Cell mediated immunity play an important effective mechanisms especially in deep mycosis, since disseminated fungal infection is a feature of patient with impaired T-cell or neutrophil although rare in Ab, deficiency.

Complement

•A system of serum and cell surface proteins that interact with one another and with other molecules of the immune system to generate important effectors of innate and adaptive immune response.

There are three pathways of complement activation that differ in how they initiated:

1. Classical pathway activated by antigen antibody complex.

2. Alternative pathway, by microbial surface.

3. Lectin pathway, by plasma lectins that binds to microbes.

Each complement pathway consists of a cascade of protolytic enzymes that generate inflammatory mediators and opsonins that lead to formation of a lytic complex that insert in cell membrane.

The function of complement system include:

1- Triggering and amplification of inflammatory reactions.

2- Attraction of phagocytes by chemotaxis.

3- Clearance of immune complexes and apoptotic cells.

4- Cellular activation for microbial killing.

5- Direct microbial killing.

6- An important role in the efficient development of Ab response.

Stages of Complement Activation

All three pathways involves:

1. Activation of C3 which is the most abundant and most important of complement proteins.

2. Comprise protolytic cascade in which complexes of complement proteins create enzymes that cleave other complement proteins in an order manner to create new enzymes.

3. All activation pathways converge on a common terminal pathway- formation of membrane attack complex (MAC), causing membrane disruption and lytic killing of pathogens.

4. All the three pathways differ from each other in their initiation till formation of C3 convertase. Then, the remaining stages are identical in all the pathways.

Classical Pathway

This pathway involves complement components C1, C2 and C4. The pathway is triggered by antibody-antigen complexes binding to Cl, which itself has three subcomponents Clq, Clr and Cls. The pathway forms a C3 convertase, C4b2a, which splits C3 into two fragments; the large fragment, C3b, can covalently attach to the surface of microbial pathogens and opsonise them; the small fragment, C3a, activates mast cells, causing the release of vasoactive mediators such as histamine.

Alternative Pathway

This pathway involves various factors, B, D, H & I, which interact with each other, and with C3b, to form a C3 convertase, C3bBb, that can activate more C3, hence the pathway is sometimes called 'the amplification loop'. Activation of the loop is promoted in the presence of bacterial and fungal cell walls, but is inhibited by molecules on the surface of normal mammalian cells.

Mannose-binding Lectin Pathway

This pathway is activated by the binding of mannose-binding lectin (MBL) to mannose residues on the pathogen surface. This in turn activates the MBLassociated serine proteases, MASP-1 and MASP-2, which activate C4 and C2, to form the C3 convertase, C4b2a.

Lytic Pathway

This pathway is initiated by the splitting of C5, and attachment of C5b to a target. C6, C7, C8 and C9 unite with C5b, and this membrane-attack complex (MAC), when inserted into the outer membrane of some bacteria, can contribute to their death by lysis. Red cells which have antibody bound to the cell surface can also activate the classical and lytic pathways, and become susceptible to lysis.

Cytokines

1- are small soluble proteins that regulate the immune system, both innate and the adaptive response to infection.

2- These chemical messengers, produced by several different types of cells.

3- They exert activity-modulating effects on cells of hematopoietic and immune system through the activation of cell-bound proteins.

4- Cytokins are induced in response to specific stimuli such as bacterial liposacchrides, flagellin, or other bacterial products through the ligation of celladhesion molecules or through the recognition of forign antigens by host lymphocytes.

The major cytokine families include:

1- Interleukins (IL)

2- Tumor necrosis factors (TNF)

3- Interferons (IFN)

4- Chemokines

5- Transforming growth factors (TGF)

6- Colony stimulating factors (CSF)

Chemokines

Are a family of cytokines that enhance motility and promot migration of many types of white blood cells toword the source of chemokine (chemotaxis). Most of the chemotactic activity of leukocytes is regulated by the activity of chemokines, including the response to infection diseases, autoimmune inflammation, cancer, and the homing of the lymphocytes to all the lymphoid tissues The chemokines are classified into four families based on the position of Nterminal cysteine residues.

1. Alpa, or CXC, chemokines consist a single amino acid between the first and second cysteines.

2. Beta , or CC, chemokines --has adjacent cysteine residues

3. C chemokines- lack one of the cysteines

4. CX3C, has three amino acids between the cysteines

Major Histocompatibility Molecules

The major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) complex, is a segment of chromosome 6 containing several genes that are critical to immune function.Gene map of the Human Leukocyte Antigen These include genes encoding various enzymes and structural molecules needed for the activation and function of B and T cells. The encoded molecules fall into three groups or classes known as MHC (or HLA) class I, II, and III molecules. MHC class III molecules include complement components C4, Bf, and C2.

A. MHC class I molecules

Codominantly expressed 45-kDa MHC class I molecules, in association with B2 microglobulin (B2 m, 12 kDa), are found on the surfaces of all nucleated cells. Three genetic loci, HLA-A, HLA-B, and HLA-C, are highly polymorphic, with many alleles at each locus. Al together, up to six different class I molecules (if heterozygous at all three loci) can be displayed simultaneously on each cell. MHC class I molecules fold to form a cleft between the al, and a2 domains that noncovalently binds an 8-9 amino acid peptide. Because of slight structural variations in the binding cleft (or binding groove) among the different allelic forms, different peptides may preferentially fit into clefts of some MHC class I molecules better than others. Additional ("nonclassical" or class I b) class I molecules (e.g., those encoded by the HLAE, -F, -G, -H loci) show limited variability and tissue distribution and may function to present carbohydrate and peptide fragments.

B. MHC class II molecules

MHC class II molecules are normally only expressed on the surfaces of dendritic, macrophage, and B-cell surfaces; on some activated T cells; and on some specialized epithelial cells in the thymus and intestine. Codominantly expressed as non covalent dimers, a 32- to 38-kDa a β chain and 29- to 32-kDa β chain form a binding groove (al and β 1 domains) that can accommodate peptides of 18- to 20-amino-acid length. Encoded within the HLA-DP, -DO, and -DR regions are both a and ß loci (DP a, DP , DO ,DO β, DR a, DRβ).After synthesis, MHC class II a and

B chains combine only with others encoded within the same region (e.g., DP a associates only with DP B but never with DO B or DR B). However, within each of these regions, a chains can combine either with B chains encoded on the same chromosome (cis) or on the other member of the chromosome pair (trans).Termed cis-trans complementation, this allows individuals that are heterozygous at one or more of the class II loci to produce a greater variety of class II dimers than would be possible if they were homozygous. The range of different MHC class I and II molecules expressed can affect the overall immune capacity of an individual.

MHC Restriction

MHC-restricted antigen recognition, or MHC restriction, refers to the fact that a given T cell can interact with both the self-major histocompatibility complex molecule and the foreign peptide that is bound to it, but will recognize and respond to the antigen, only when it is bound to a particular MHC molecule. MHC class I is recognized by CD8, while MHC class II is recognized by CD4.

Medical importance of HLA typing

1. Paternity testing.
2. Disease association.

- HLA-B27→ Ankylosing spondylitis
- HLA-DR4 RA
- HLA-CW6→ psoriasis

3. HLA typing for determination of HLA compatibility between donor and recipient before transplantation.
4. Anthropology to study races & nations.

HLA Nomenclature

HLA association with autoimmune diseases

The risks for many autoimmune diseases appear to be associated with the presence of particular HLA genes. In some cases (e.g., HLA-B27 and HLADR3), a single HLA gene is associated with increased risk for multiple autoimmune diseases. The molecular mechanisms underlying these statistical associations are still uncertain but presumably involve some influence on processing and presentation of self-

epitopes to self-reactive T cells. Because genetics is only one of several possible factors contributing to the risk of a particular autoimmune disease, some HLA genes display much higher associations. For example, over 90% of individuals with ankylosing spondylitis are HLA-B27+.

HLA Typing

HLA typing is a crucial step in transplantation, as recognition of foreign HLA by recipient T lymphocytes would trigger an immune response. T lymphocyte activation initiates a cascade of mediators that direct the immune system against the allograft. HLA laboratories currently perform serologic as well as molecular typing methods.

A. Serological typing

In this approach, a special tray (Terasaki plate) containing sera with antibodies to a panel of known HLA alleles is used. Recipient lymphocytes are introduced into the tray wells contacting sera, complement and dye. Specific antibodies can bind to the HLA antigens on the surface of lymphocytes, complement is activated. This results in the complement pathways triggered resulting in cell death, ultimately allowing the dye to enter the cell. Tray wells with significant cell death are then identified under phase contrast microscopy.

B. Molecular typing

1. Sequence-specific primer polymerase chain reaction: In this approach extracted DNA from the subject is amplified in several wells. Each well has primers that are complementary to specific HLA alleles. In wells where DNA probes are complementary to the specific sequence of the HLA molecule, an amplification product is formed. This is then instilled into an agarose gel and undergoes electrophoresis where they appear as a band. HLA typing is then allocated by matching the primers of the amplification product to DNA sequences of several candidate alleles.
2. Sequence specific oligonucleotide probes: Amplified DNA is mixed with oligonucleotide probes that are complementary to specific segments of the

DNA of different alleles. Unique HLA alleles are then can be identified using fluorescent tags.

3. Direct DNA sequencing: This method determines the precise order of nucleotides in the gene of interest.

Phagocytosis

- A very important process during non-specific immune response when specialized cells engulf foreign body like bacteria or molecule like toxin or virus.

- The cells that able to do phagocytosis are (monocytes, macrophage, PMNs and Dendric cells).

Types of phagocytic cells

A. neutrophils (polymorph nuclear leukocytes (PMNs)]: are granulocytes that circulate in blood and migrate quickly in response to local invasion of m.o.
B. monocytes: also circulate in blood, but much lower in number than PMNs. They migrate to the tissue where differentiate into macrophages which reside in all body tissues. Ex:
    - connective tissue macrophage_ Histiocytes
    - liver macrophages – Kupffer cells
    - Brain macrophages – Microglial cells
    - Lung macrophages – alveolar macrophages
    - Macrophages in granulomas – epithelioid cells
    - Cluster of epithelioid cells – giant cells

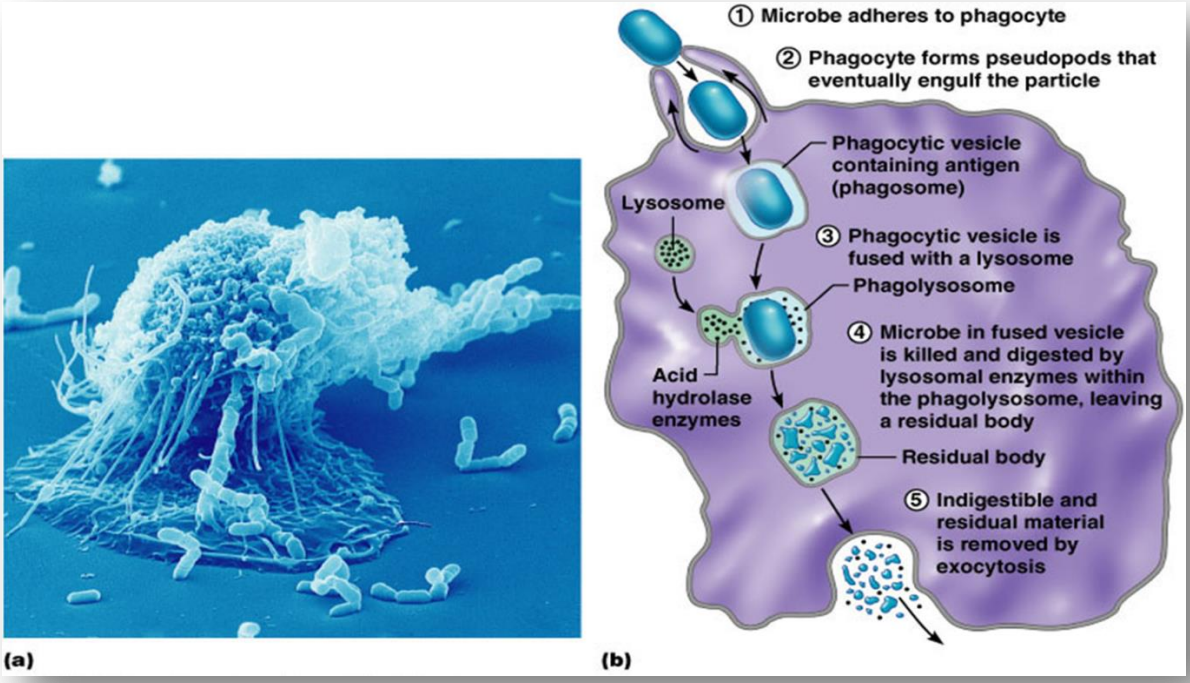
Steps of phagocytosis

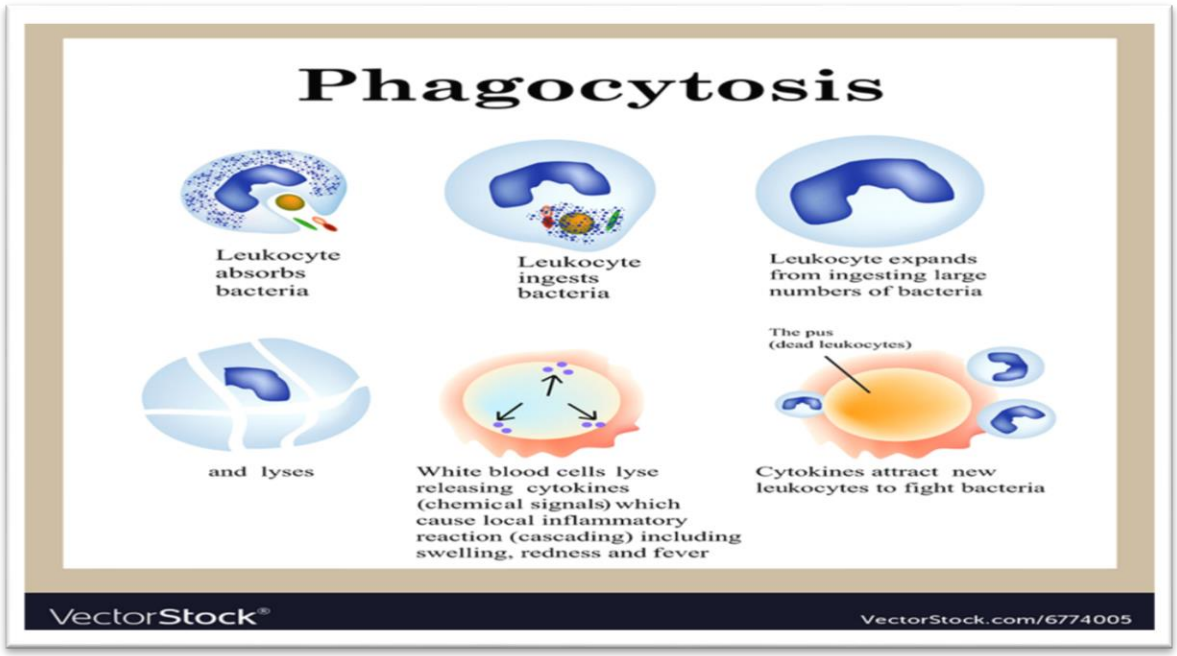
Step 1: Activation of the Phagocyte. ...

Step2: Chemotaxis of Phagocytes (Neutrophils and macrophages are attracted to the site of infection by chemokines, which are small polypeptides produced by cells at the infected site) ...

Step 3: Attachment of the Phagocyte to the Microbe or Cell. ...

Step 4: Ingestion of the Microbe or Cell by the Phagocyte


(a)
(b)
① Microbe adheres to phagocyte
② Phagocyte forms pseudopods that eventually engulf the particle
Phagocytic vesicle containing antigen (phagosome)
Lysosome
③ Phagocytic vesicle is fused with a lysosome
Phagolysosome
④ Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body
Acid hydrolase enzymes
Residual body
⑤ Indigestible and residual material is removed by exocytosis


Phagocytosis
Leukocyte absorbs bacteria
Leukocyte ingests bacteria
Leukocyte expands from ingesting large numbers of bacteria
and lyses
White blood cells lyse releasing cytokines (chemical signals) which cause local inflammatory reaction (cascading) including swelling, redness and fever
The pus (dead leukocytes)
Cytokines attract new leukocytes to fight bacteria
VectorStock®
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The results of phagocytosis are

1. Complete destruction of foreign body and excretion (e.g. PMNs)

2. Complete destruction of foreign body and some parts (polypeptides) of it will be processed and presented on the surface of the phagocytic cells (monocytes, macrophage and dendric cells) then the phagocytic cell will be antigen presenting cell (APC).

Inflammation

Tissue damage caused by a wound or by an invading pathogenic microorganism induces a complex sequence of events collectively known as the inflammatory response.

Major Symptoms of Inflammation

1. Redness 2. Pain

3. Heat 4. Swelling

5. Loss of function (may also observe)

This process consists of four major events:

1. Increased blood supply to the region.

2. Increased capillary permeability in the affected area (vasodilation).

3. Increase the degree of temperature (fever).

4. Migration of W.B.Cs from the blood vessels into the tissues.

Types of inflammations

1. **Acute inflammation**

The most common type of inflammations characterized by swallow, pain, redness and heat at the site of inflammation due to or edema, increase blood supply and toxic effects of inflammatory products on nerves in the site of inflammation the most important sign of acute inflammation is exudate formation.

Exudate defined as the edema inflammatory liquid forms during acute inflammations contain high levels of protein, many inflammatory cells, low glucose, pus and sometimes fibrin clot.

2. Chronic inflammation

Occurs when the pathogenic infection last for long time without treatment or with low immune response or when the pathogen is intracellular parasite lives inside cells and escape immune system defence mechanisms and has no Immunogenic antigens, also when the acute inflammation left without treatment will become chronic inflammation. (e.g., arthritis, inflammatory bowel disease).

Signs of chronic inflammation

1) Long standing inflammation.
2) Low exudate.
3) Histological changes in tissue (most important sign) e.g.: Hyperplasia, hypertrophy.

The Importance of inflammation

- mobilizes defensive cells
- limits spread of pathogens
- kills pathogens
- initiates tissue repair

Lymphoid Tissues & Organs

Leukocytes may be found in the body as single cells or lymphoid accumulations in the tissues circulation, or within lymphoid organs(thymus spleen lymph nodes).Lymphoid organs are classified as Primary or secondary. Lymphocytes develop within primary organs. The secondary lymphoid organs trap immunogens & provide sites where large numbers of circulating immune cells can make contact with each other initiating specific immune reaction.

A-Primary or central lymphoid organs:

1-Thymus: The first lymphoid organ to develop. The thymus is composed of two identical lobes and is located anatomically, in front of the heart and behind the sternum. Histologically, the thymus can be divided into a central medulla and a peripheral cortex which is surrounded by an outer capsule. The thymus provides an environment for maturation of T-lymphocytes from hematopoietic progenitor cells (thymocytes). The thymus is largest and most active during the neonatal and pre-adolescent periods.

2-Bone marrow: Is the flexible tissue found in the interior of bones Bone marrow in large bones produces new blood cells, there are two types of bone marrow (red marrow), whichconsists mainly of hematopoietic tissue, and (yellow marrow), which is mainly made up of fat cells. At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type: only around half of adult bone marrow is red. Red marrow is found mainly in the flat bones, and in the ("spongy") material at the ends of long bones such as the femur and humerus. Yellow marrow is found in the interior of the middle. portion of long bones. The bone marrow contains hematopoietic stem cells, which give rise to the three classes of
blood cells that are found in the circulation: white blood cells (leukocytes), red blood cells (erythrocytes), and platelets (thrombocytes).Both T&B cells are formed in bone marrow. Only Bcells mature in bone marrow then leave it and migrate to peripheral lymphoid tissues, such as a lymph node.

B-Secondary or peripheral lymphoid organs:

Maintain mature naive lymphocytes and initiate an adaptive immune response.. Mature lymphocytes recirculate between the blood and the peripheral lymphoid

organs until theyencounter their specific antigen leading to lymphocyte activation, clonal expansion&differentiation. So lymphoid tissue provides the environment for the foreign or altered molecules (antigens) to interact with the lymphocytes. It is represented by the lymph nodes, spleen and the lymphoid follicles in the mucosa-associated lymphoid tissue(MALT) include tonsil sin the nasopharynx & Peyer's patches in the sub mucosal surfaces of the small intestine.

1-Lymph nodes: Small round or oval shape secondary lymphoid organs. They function as filters to purify lymph and provide site for interaction of lymphocytes, monocytes for initiating immune responses. Anatomically, a lymph node is divided into:

cortex& medulla.

The cortex: The superficial (outer cortex) consists mainly of the B cells (B cell rich area) arranged as follicles, which may develop a germinal center when challenged with an antigen, and the deep (para cortex) mainly consisting of the T cells (T cell rich area). Circulating cells enter the outer cortical area & filter through the deep cortex and into the medulla before leaving the lymph node.

The Medulla: The medulla lymphatic tissue, include plasma cells, macrophages, and B
cells.

2-Spleen:The largest lymphoid organ cleans microbes &blood born Ags. In addition to T&B lymphocytes, the spleen contains large numbers of plasma cells secreting Igs. Histologically it is divided into: Lymphocyte rich white pulp & Erythrocyte rich red pulp.

Cellular bases of immune response

Antigen presenting cells (APC): A cell that displays peptide fragments of protein antigens, in association with major histocompatibility (MHC)molecule on its surface, and activates antigen - specific T cells. In addition to display peptide-

MHC complexes, APC also must express costimulatory molecules to optimally activate T-Lymphocytes.

•Lymphocytes

1-B-lymphocytes: The mature inactive B cells express membrane Abs that recognize Ags but do not secrete Abs, activation of these cells stimulate their differentiation into effector B-cells(plasma cells) secrete the antibodies that neutralize & eliminate the Ag. B-cells make 10-20%of lymphocytes.

2-T-lymphocytes: The mature inactive T-cell express (T-cell antigen receptors TCRs) which are membrane receptors and are not secreted. Subpopulations of T-cells defined according to their function & cell membrane molecules (CD cluster of differentiation) into:

A -T-Helper(CD4+): They recognize protein Ags displayed by Ag presenting cells in association with class II MHC which bind to TCRs causing their activation proliferation clonal expansion and secretion of cytokine(soluble mediators of IR) that provide help for
cellular &humoral IR as follows:

1-T-lymphocytes activate phagocytes to destroy ingested microbes.
2-Activate B-lymphocytes to produce Abs.
3-Activate both cytotoxic &further T-helper cells.
B-Cytotoxic-T cells (CD8+): They recognize protein Ags displayed by Ag presenting cells in association with class I MHC which bind to its TCRs and may require help from CD4+ Tcells to differentiate into effector CTLs that contains two types of cytolytic granules perforin (pore forming protein)&granzmes (serine protease enzymes), thereby killing target cells.

C-Regulatory T cells (formerly known as suppressor T cells) : Play important roles in the regulation of immune responses by blocking the actions of some other types of lymphocytes, to keep the immune system from becoming over-active. They express CD4,CD25,TGFB(the latter differentiate them from CD4+ cells).

Non specific Cellular components

1-Natural killer cells (NK): Small population of lymphocytes circulate in peripheral blood do not express receptors, named for their ability to kill

abnormal(infected or malignant)cells by the release of their cytoplasmic granules that damage the membrane of the cells they attack.(non-specific IR).

2-Granulocytes

1-Neutrophils: They are also called polymorphnuclear cells because of variable number of nuclear segments (2-5), comprising 60% of peripheral blood leukocytes. They are very effective at killing bacteria .An increase in their number is often an indicator of acute infection.

2-Eosinophils: They are bilobed granulocytes with cytoplasmic granules that take eosin dye, comprising (0-5) % of peripheral blood leukocytes. Eosinophils participate in innate &adaptive immune responses to parasitic worm infection.

3-Basophils&Mast cells: Basophils are bilobed granulocytes with acidic cytoplasmic granules stain with base dye, contains histamine &other molecules associated with allergic reactions. They compromise (0-1) %of peripheral blood leukocyte. Mast cells are the tissue resident form of basophils which are also important in allergic reactions.

3-Monocytes-Macrophages:

1-Monocytes: Circulate in blood stream spend 1-2 days then cross the endothelium to enter the tissues where they remain up to several months as macrophages.

2-Macrophages: cells located in body tissues, their main functions are:

- They are phagocytic cells that engulf &digest microorganisms.
- Antigen presentation: Ags are ingested, broken into pieces & presented surface of macrophages to be seen by immune cells.
- Production of several cytokines (proteins that regulate the intensity &duration of immune response) asIL-1that activate T-Helper cells.