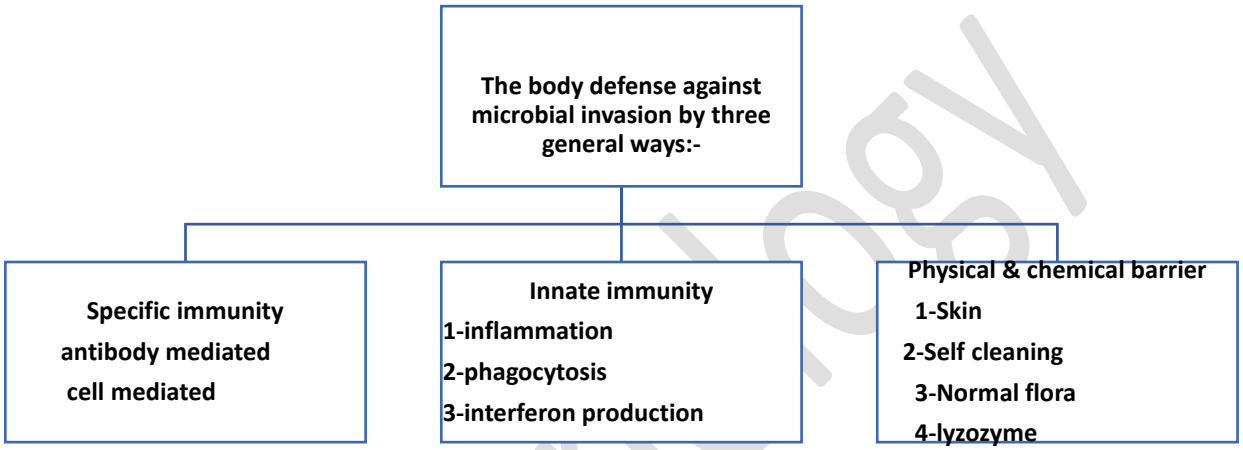
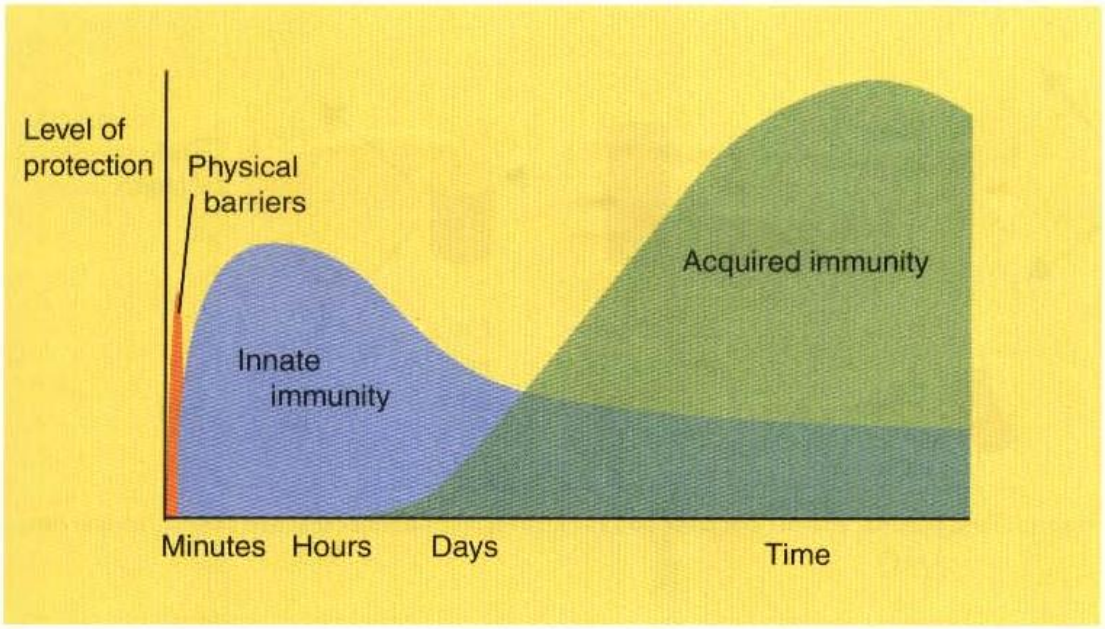
Nonspecific Immune System

the defence of the body that is present at birth, it provides a rapid response against disease, it has no specific response or specific recognition of microbes or memory cells. But it responds rapidly to invaders by detecting them and attempting to eliminate them.



The time course of innate and acquired immunity



Factor their determined the nonspecific immunity:-

1- Genetic influence.
2- Difference due to age.
3- Hormonal effect.
4- Interferon.
5- Normal flora.
6- Other effects as:- a- Physical effect → Skin
→ Self- cleaning

b- chemical effect- enzyme.

c- Cellular effect → Phagocytosis
→ Natural killer cells

Physical effect:

The major physical barrier is:-

1- Skin:- the microbes cannot penetrate the intact skin, and continual shedding of the top layer of the skin helps to remove microbes at the surface, dryness of the skin plays a major role in microbial inhibition.
2- Mucous membrane: - entire gastrointestinal, respiratory, and urogenital tract with Secretions of mucin to form viscous glycoprotein membrane (mucus membrane) helps to inhibit the entrance of many microorganisms
3- Lacrimation: continual washing action from tears helps keep microorganisms from settling on the surface of the eye.
4- Ciliary action:- the removal of dust, pollutants and microorganisms outside of the trachea.

chemical effect:

1- Skin: The sebaceous gland found in the skin produces sebum, which consists of unsaturated fatty acid and prevents the growth of certain pathogenic bacteria and fungi, also lower pH of skin helps to reduce the growth of many microbes.

2- Saliva:- contain lysozymes and have low pH

Normal flora:-

It is not considered part of body defence, but flora helps the body to prevent infection by:-

a- Competing with them for nutrients
b- Changing the condition that affects the survival of the pathogen as pH or oxygen availability (alter of vagina pH by action of *lactobacillus bacteria* to prevent infection by *candida*)
c--Produce substances that are harmful to pathogens. (bacteriocins produced by *E.coli* prevent salmonella infection)

Cellular effect:- It consist of

1- **Natural killer cell**
2- **Phagocytosis**
3- **Inflammation**

Natural killer cells (NK cells):-

It is a part of large granular lymphocytes that are found in normal unsensitized hosts and can recognise and kill a wide variety of infected body cells and tumour cells; NK cells produce proteins which cause cell self-destruction or apoptosis.

Phagocytosis:-

In Greek, it means eating the cells. It is the ability of cells to eating or engulfment and destroy foreign substance particles or microorganisms

Most cells that eat foreign substances and microorganisms are neutrophils, macrophages, and eosinophils these cells are called **phagocytes**

Phagocytosis can be divided into several stages

1- Activation
2- Chemotaxis
3- adherence and opsonization
4- ingestion and digestion.

A- activation:- although neutrophils are always ready to attack and destroy invading organisms, they can under some conditions become activated and degranulated, mount respiratory burst and release elastase and oxidant material these promote adhesiveness and attract more neutrophils.

B- Chemotaxis :- directed migration of neutrophils called chemotaxis. bacteria invasion and the resulting tissue damage generate many different attractants including peptides like C5a generated from complement, and different chemokines, all these attract the phagocytic cells (neutrophils, eosinophils, and monocytes).

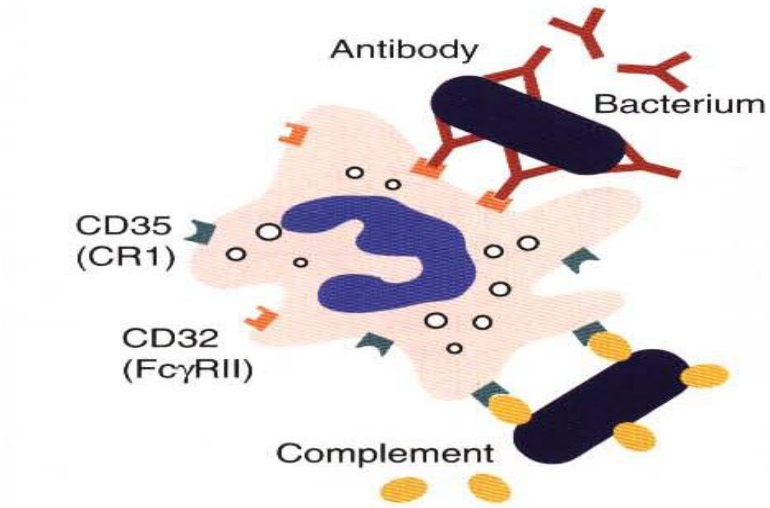
Chemokines:- a family of proinflammatory and chemotactic cytokines. they regulate the emigration of leukocytes from blood into tissue.

Cytokines:- a protein that mediates cellular interaction and regulates cell growth and secretion. So they regulate many aspects of the immune system.

C- Adherence and opsonization:-

Opsonins:- molecules that coat bacteria and promote phagocytosis

The opsonin makes the bacteria tastier for the neutrophil and promotes phagocytosis either by specific in conjunction with complement or by antibodies and this process is called opsonization.



D- Ingestion:- as neutrophils crawl towards a chemotactic source.

1- a pseudopod advances first, the pseudopod flows over and around bacteria.

2-Then binding occurs between opsonin on the organism and receptors on the neutrophil this binding enables cup-like pseudopod to cover the particles and drown them in the cytoplasm

3- the cytoplasm engulfs and becomes enclosed in a vacuole called a phagosome.

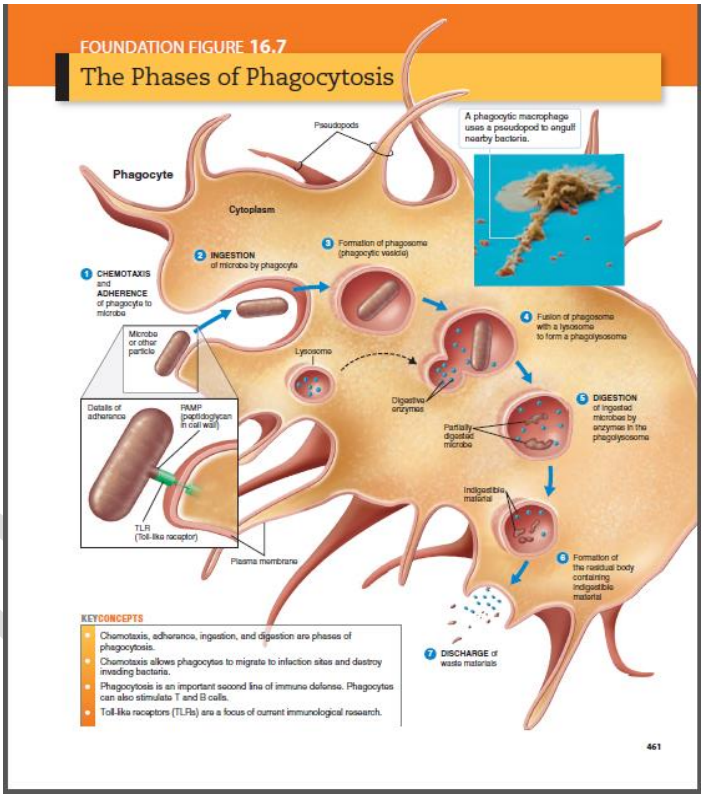
E- Destruction or Digestion:- destruction of the ingested bacterium occurs through two important processes

1- involve the generation of potent oxidants (respiratory burst)

2- release of lytic enzyme and antimicrobial peptide from intracellular granules.

Respiratory Burst (oxidative burst):-

It is an increase in enzymatic activity during digestion in phagocytes involving increased oxygen consumption 100 fold by neutrophils and these lead to the activation of several oxidation/catalyzation processes ending by the production of toxic oxygen products which have antibacterial activity.



Lysozyme:-

It destroys bacterial peptidoglycan in bacterial cell walls, especially in gram-positive bacteria leads to destroying cell walls. It is found in all body fluids except cerebrospinal fluid, sweet and urine and is found in high concentration in saliva, tears, and nasal secretions.

Lectins:-

These are a group of proteins that bind to the carbohydrate of the bacterial cell walls and play a role in the activation of the complement system also promoting phagocytosis of invading microorganism ex:-

a- mannose-binding lectin(MBL):-
b- C- reactive proteins and serum amyloid
c- Iron binding protein

Interferon:-

types of cytokines that can interfere with virus replication and play a role in the regulation of immune response. It is a glycoprotein and has nonspecific broad-spectrum antiviral effects on viruses.

It is secreted from leukocytes then binds to individual cells and inhibits viral replication within them also helps in the activation of natural killer cells and phagocytes.

Inflammation

Inflammation:- is the response of tissues to invading microorganisms or tissue damage and this involves the activation and directed migration of many different cells especially (Neutrophils and Macrophages) from the bloodstream to the site of invasion.

Inflammation is characterized by:- redness, pain, heat, and swelling.

The invading microorganism is recognised by phagocytic cells and attached to it through toll-like receptors found on the surface of the macrophage this will regulate the initiation of inflammatory response.

Toll-like receptor (TLR):-

Receptors are found in the cell surface of macrophages, and mast cells and bind to many Components of microorganisms. this binding induces cell production molecules that trigger innate immunity, especially inflammation.

Pathogen-associated molecular pattern (PAMPS):-

Its Components found in the bacterial act as the binding site for Tolls like receptors in macrophages which include DNA of bacteria, DNA and RNA of virus, flagellin from flagella, lipopolysaccharide …….ect

Stages of inflammation response:-

1- **Vasodilation**:- after the tissue damage, the capillary permeability of the blood vessels in the area increases leading to soluble mediators and fluid reaching to site and causing oedema (swelling), also redness and heat in the area resulting in to increase in blood flow to it. pain associated with inflammation is due to nerve damage and pressure from oedema.

2- Migration of the leukocytes to the site of invasion:- particularly phagocytes (neutrophils and macrophages) these are needed to destroy and remove pathogens and tissue damage within an hour after tissue damage or bacterial infiltration by phagocytosis.

3- Tissue repair: the last stage of inflammation in which dead or damaged tissue cells are replaced, this process begins during the early stages of inflammation but it is lastly ended after all dead tissue is removed. the ability of tissue regeneration is dependent on the amount of damage and tissue type.

The Complement

Complement:- a complex of serum and cell surface proteins that act as a defence mechanism after being activated by both innate and acquired immune mechanisms, It consists of a set of enzymic pathways that produce specific proteins that bind with the surface of invading microbes. It can be active by three different mechanisms these are classical, alternative and lectin pathways. The classical pathway is activated by antibodies bound to antigens and this association with acquired immunity. The others are activated directly by microbial carbohydrates this typical example of the pathogen – associated to of innate immunity.

Complement components:-

There are at least 30 such proteins. some are free in the serum others are cell-bound receptors. The complement protein about is 15 % of the globulin fraction of serum. complement are synthesized at various sites throughout the body .

C_3 , C_6 , C_8 and B made in liver.

C_2 , C_3 , C_4 , C_5 , B , D , P and I made in macrophage.

C_6 , C_7 , large quantities in neutrophils.

The cascade of complement are:-

C_1 , C_4 , C_2 , C_3 , C_5 , C_6 , C_7 , C_8 , C_9 ,

C_1 → C_{19} → C_{1r} → C_{1s}

C_4 → C_{4a} → C_{4b}

C_2 → C_{2a} → C_{2b}

C_3 → C_{3a} → C_{3b}

C_5 → C_{5a} → C_{5b}

B, D , P , I extra.

Function of complement

1- cytolysis (cell membrane lysis)
2- Inflammation
3- Opsonization and immune adherence
4- Chemotaxis

1- Cytolysis:- the most important function of the complement is to destroy foreign cells. this is accomplished by damaging the cell membrane which is involved in the complement component of C_5 and C_9 in a way called membrane attack complex (MAC).

Membrane Attack Complex (MAC):- this is a complex of complement components that consist of C5b6789, which inserts itself in microbial cell membrane formation ring shape structure on the microbial surface which acts as punching holes in the invader and is killed by osmotic lysis.

2- Opsonization and Adherence:- component of C3b coats foreign cells and interacts with special receptors on phagocytes to promote phagocytosis. This is called opsonization, C3b also can coat particulate antigens that can bind with tissue by a process called immune adherence.

3- Inflammation:- components of C3a and C5a cause acute inflammation by their binding to mast cells causing its degranulation, and stimulating blood platelets resulting in the release of histamine and serotonin which increase the permeability of blood vessels and release of lysosomal enzymes from neutrophils and stimulate macrophages.

4- Chemotaxis:- it has chemotactic action after activation in any pathway ex:- C5a attracts neutrophils, eosinophils, basophils and macrophages but C5b67 is chemotactic for neutrophils and eosinophils.

Pathways of complement activation

1- Classical pathway
2- Alternative pathway
3- Lectin pathway

1- Classical pathway:- This depends on the reaction between antigen and antibody, which is a part of acquired immunity and requires antigen-antibody complex that is attached to complement component C1 to start activation.

the stimulation occurs from $C1q$ activating $C1r$, and $C1r$ activate $C1s$ and the other extra as a cascade each enzyme activates the other(C4b2a which acts as C3 convertase to activate C3).

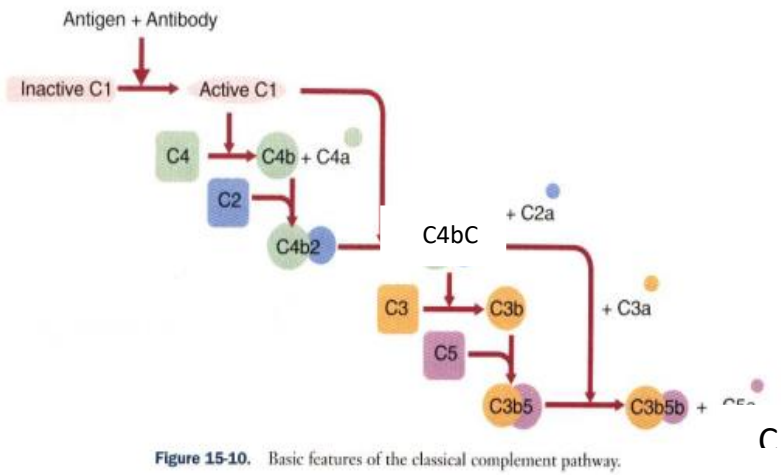


Figure 15-10. Basic features of the classical complement pathway.

2- Alternative pathway:- The alternative pathway of complement activation is triggered by contact between microbial cell walls and complement components, it is activated immediately when an invading

organism comes in to contact with blood and this key component in innate immunity (**alternative pathway does not require the formation of antigen – binding complexes**). This pathway is incited by the C_3 that is synthesized from liver cells and macrophages and present in higher concentrations in serum. This pathway is triggered by various substances including lipopolysaccharide (Endotoxins) of gram-negative bacteria or factors present in cobra venom to form complex C3bBb which act as C5 convertase to activate C5.

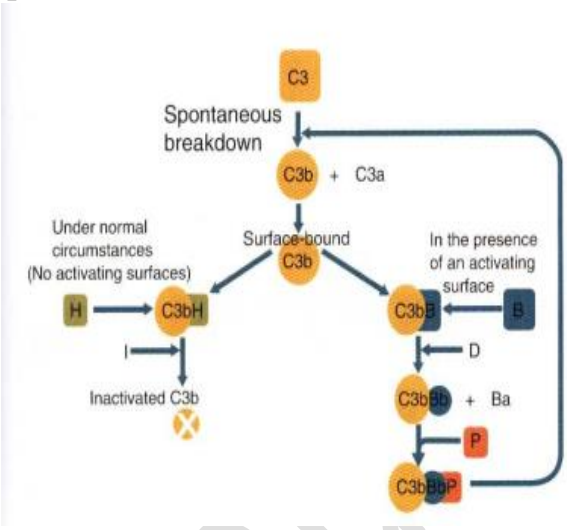


Figure 15-2. The alternative complement pathway. Surface-bound C3b may either be destroyed, as normally happens, or be activated by the presence of an activating surface.

3- Lectin pathway:- This is like an alternative pathway this is an innate defence mechanism activated by bacterial cell wall carbohydrates in the bloodstream. when macrophages ingest bacteria viruses or other foreign matter, they release cytokines that stimulate the liver to produce lectin proteins (MBL, C-reactive protein) that bind to carbohydrates.

serum mannose-binding lectin protein (MBL) can bind with microbial cell walls of bacteria, fungi, parasites, protozoa and viruses, the (MBL) will form complexes with and then activate the serum protease MASP-1, MASP-2 (mannose-associated serine protease) and this process effect on protein C_4. C_4 is cleavage to C4a, C4b. C4b activates C_2 and C_2 cleavage C2a, and C2b and this activates C_3 and cleavage

to C3a and C3b. C3b activate C5 in terminal all these doing for killing the organism by membrane attack complexes (MAC).

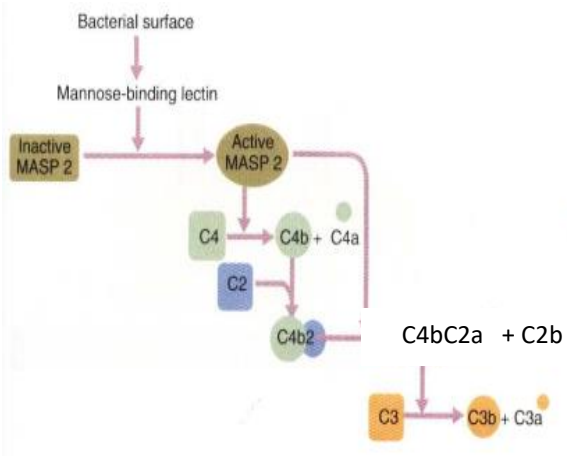
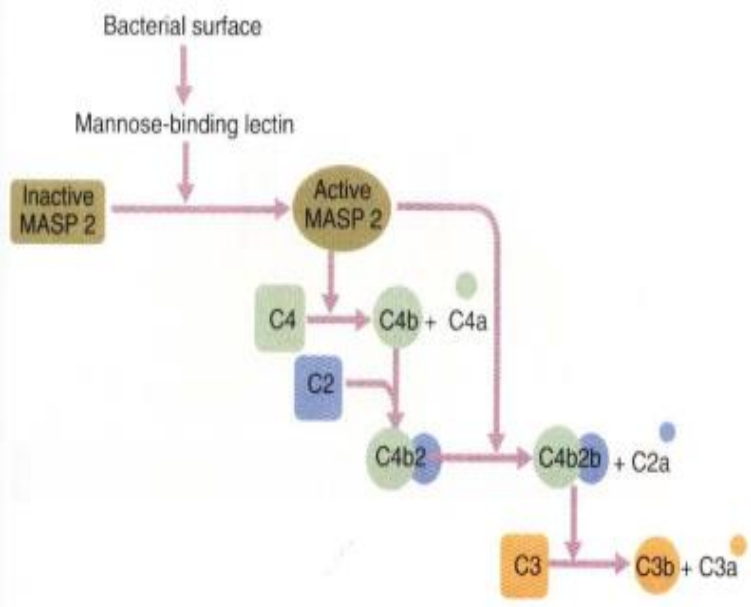


Figure 15-9. Complement activation by the lectin pathway.



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