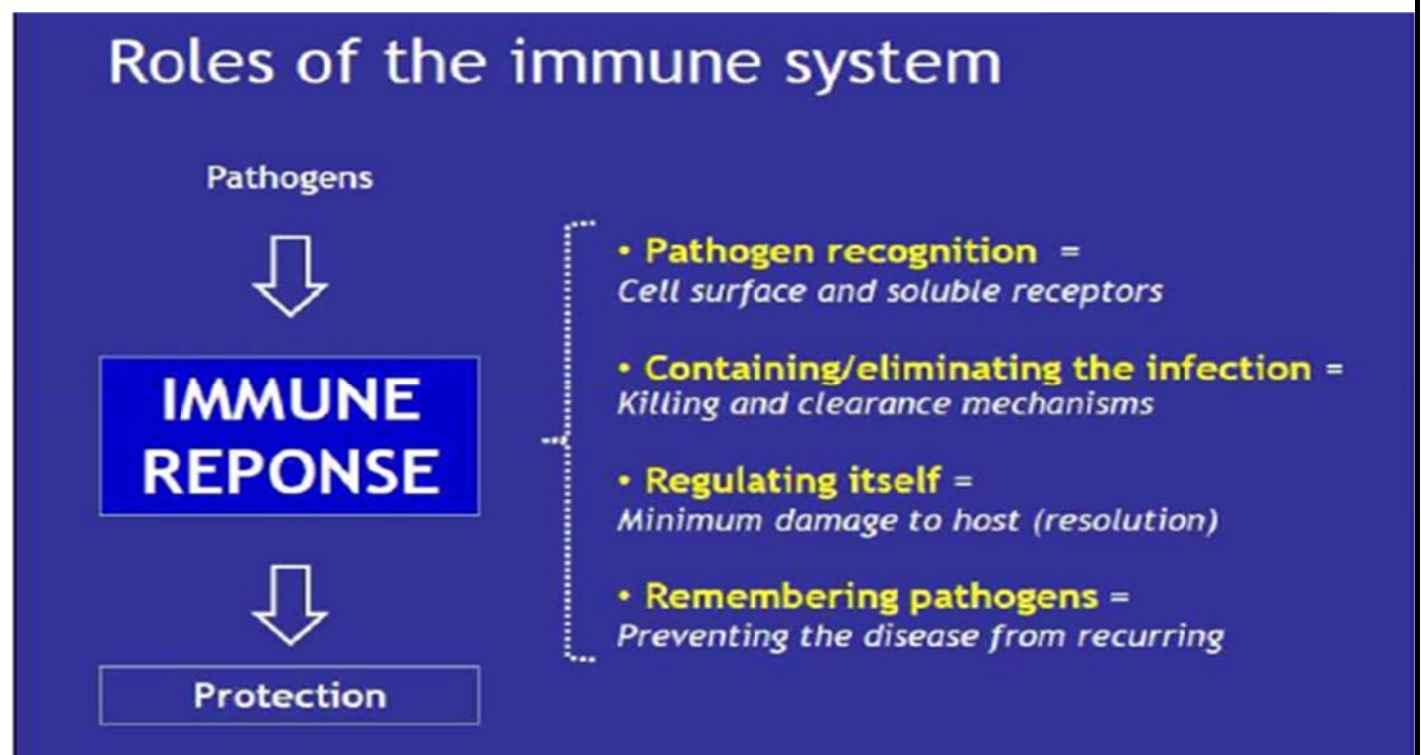


## **Immune system**

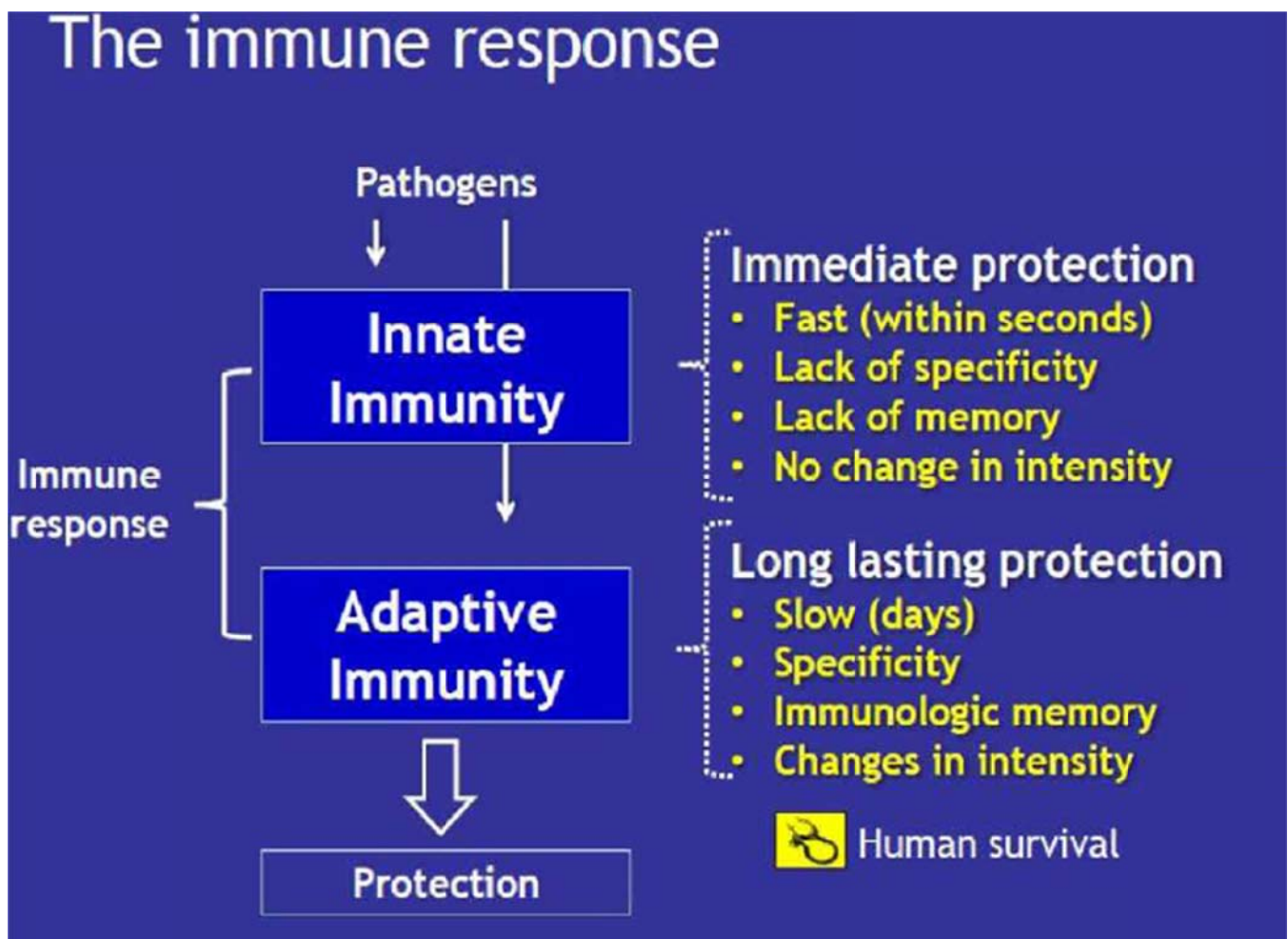
A complex network of interacting cells, cell products, and cell forming tissues or organs that protects the body from pathogens and other foreign substances, destroys infected and malignant cells, and removes cellular debris: the system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines (cytokines). The main function of the immune system is to prevent or limit infections by microorganisms such as bacteria, viruses, fungi, and parasites. The immune system consists of a vast array of components (tissues, cells and soluble factors).

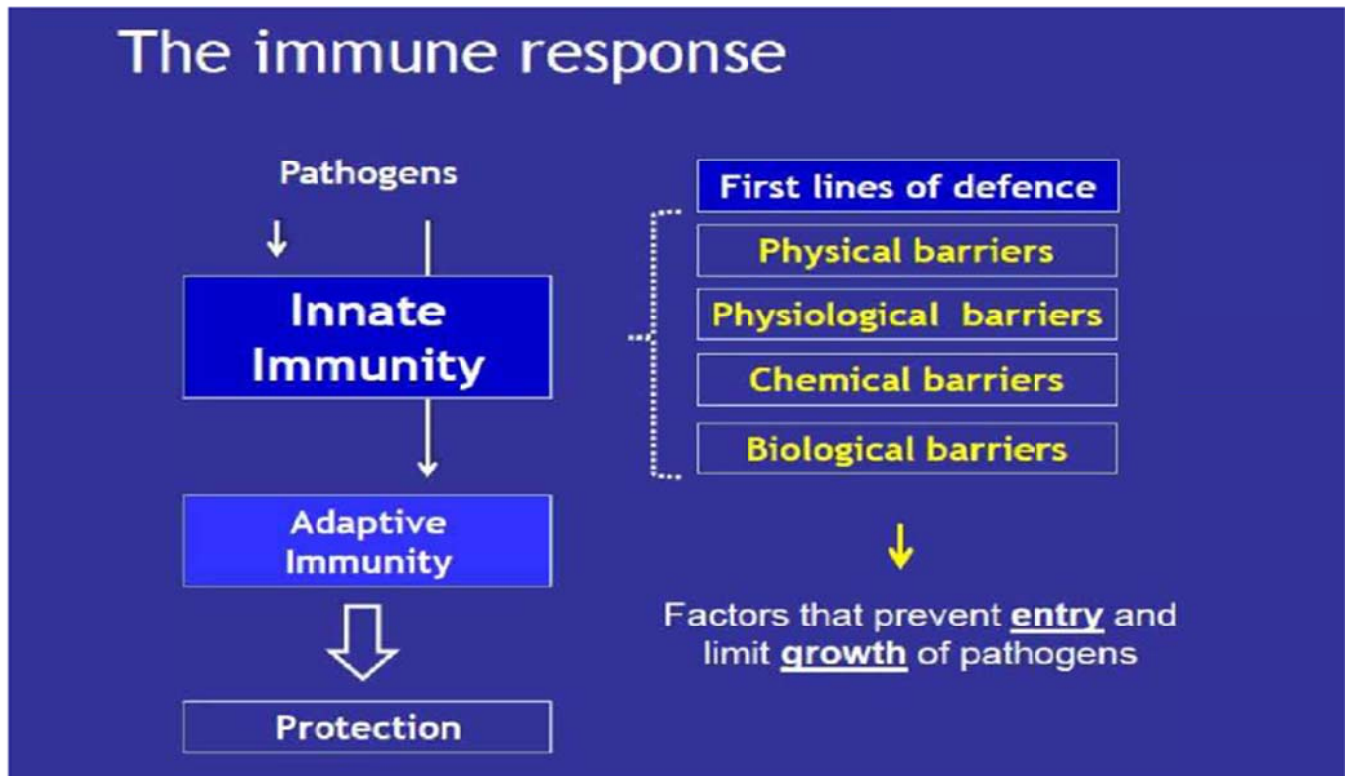
There are two types of immune response: Innate (Natural) & Adaptive (Acquired)



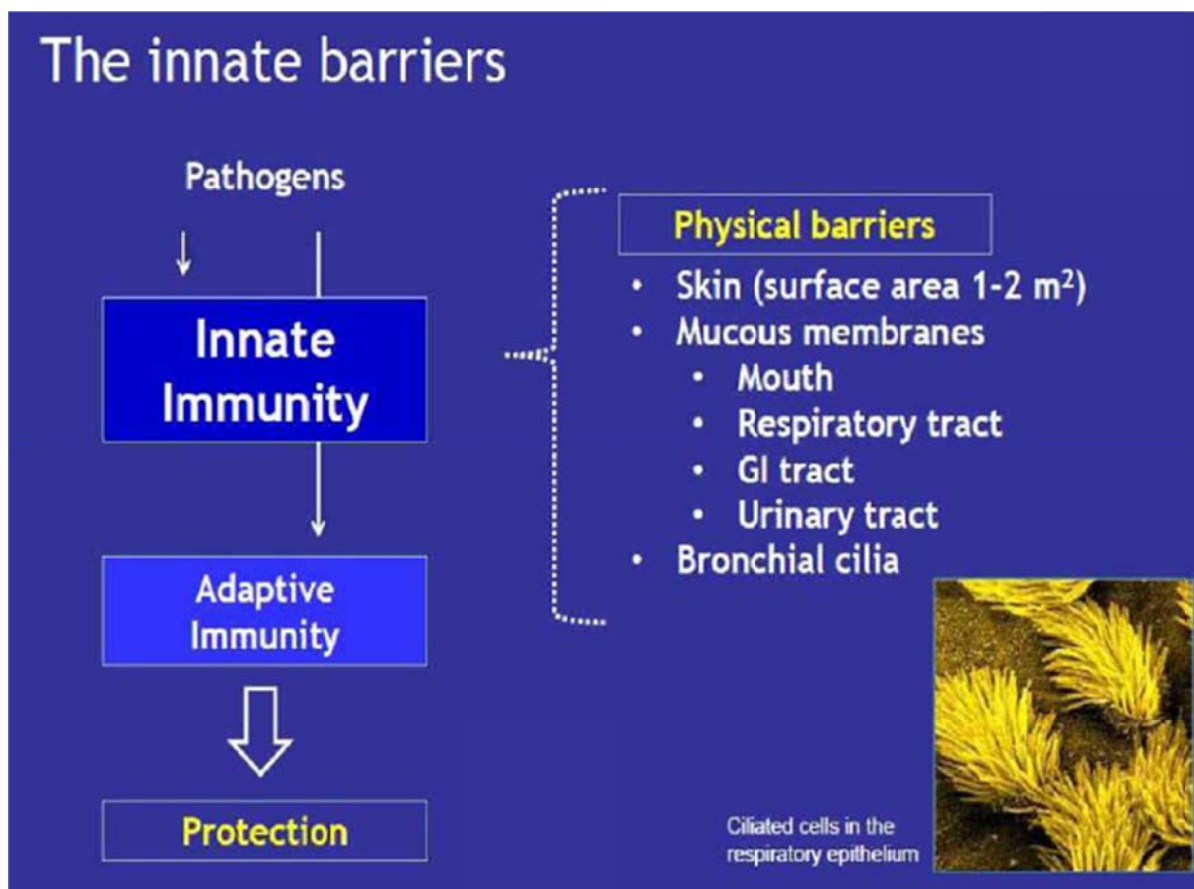
### Innate Immunity:

**Innate** means “inborn”, Innate immunity is resistance that **exists prior to exposure** to the microbe (antigen). **It is nonspecific, Innate immunity does not improve after exposure** to the organism, in contrast to acquired immunity, In addition **innate immune processes have no memory**, whereas acquired immunity is characterized by long-term memory. Innate immunity achieves two major functions: killing invading microbes and activating acquired (adaptive) immune processes.





## The innate barriers:



### **A-The physical barriers**

#### 1-SKIN:

The first line of defense against microorganisms is the **intact skin and mucous membranes**. Skin provides a microbe- inhospitable dry environment Continuous sloughing of superficial epidermal layer which removes attached pathogens.

#### **Mucous membranes:**

#### 2-Mucous membrane

An **intact epithelium** is hard to pass. Mucous can trap pathogens at mucosal surfaces and preventing their attachment and entry.

Mucous traps pathogens ,sloughing of mucous membrane of GIT remove pathogens like in skin. Mucus contains a number of types of anti-microbial compounds, including lysozyme and secretory antibodies (IgA).

If microorganisms breach these lines and enter the body, then the **innate arm** of the immune system (second line of defense) is available to destroy the invaders. Because the components of the innate arm are preformed and fully active, they can function immediately upon entry of the microorganisms. The ability of the innate arm to kill microorganisms is not specific. For example, a neutrophil can ingest and destroy many different kinds of bacteria. Mucus contains a number of types of anti-microbial compounds, including lysozyme and secretory antibodies (IgA).

#### 3-Cilia

The respiratory system is equipped with mechanical hurdles like the **ciliary escalator** that transports airborne particles out of the bronchial tree. Cilia Help by

moving the secretions or mucous containing trapped pathogens outward for expulsion by sneezing or coughing.

### **B-The physiological barriers**

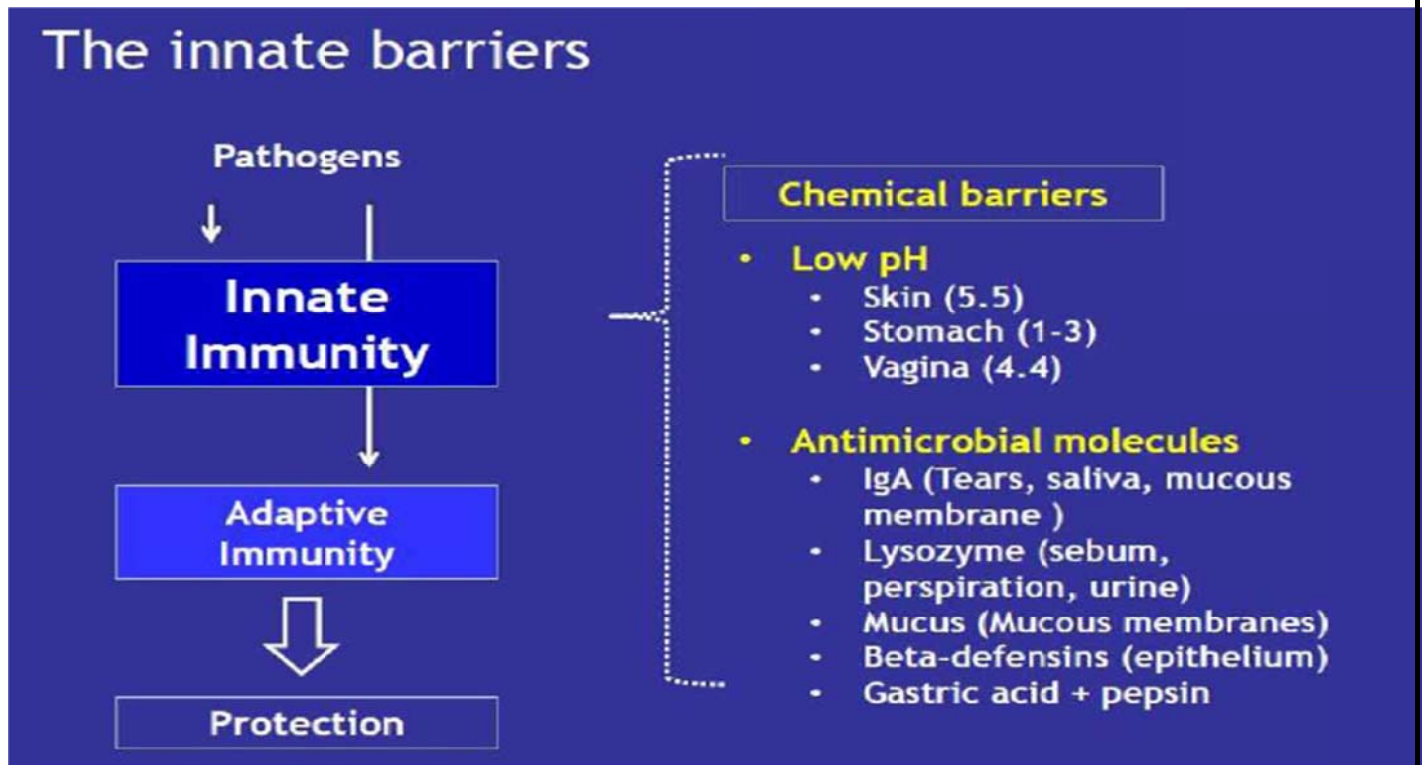
- Diarrhea e.g food poisoning
- Vomiting e.g food poisoning , hepatitis
- Cough e.g pneumonia
  - The peristaltic action of the intestine ultimately flushes out organisms which have not succeeded in colonization.
  - Eyes (Conjunctiva). The conjunctiva of the eye is remarkably free of most microorganisms. Blinking mechanically removes microbes, the lavaging action of tears washes the surface of the eye...
- Some of Physiological barriers offer inhospitable environments to pathogens even they enter the body for example:

1-Body temperature(high or low) can restrict microbial pathogenicity some viral infection restricted in the upper respiratory tract but not in the lower respiratory tract.

2-O<sub>2</sub> tension: Anaerobic organisms e.g. *closteridium perfringens* cannot grow

In the presence of O<sub>2</sub>

## C-Chemicals barriers



1-pH :

In the gastrointestinal tract the **low pH** in stomach is protective against many infectious pathogens. Alkaline pH of the lower intestine can discourage other organisms. The acidity of urine maintain the bladder and most of the urethra free of microorganisms. The vaginal epithelium of the female maintains a high population of Doderlein's bacillus (*Lactobacillus acidophilus*) whose acidic end products of metabolism (lactic acid) prevent colonization by most other types of microorganisms including potentially-pathogenic yeast (*Candida albicans*).

2-Antimicrobial molecules

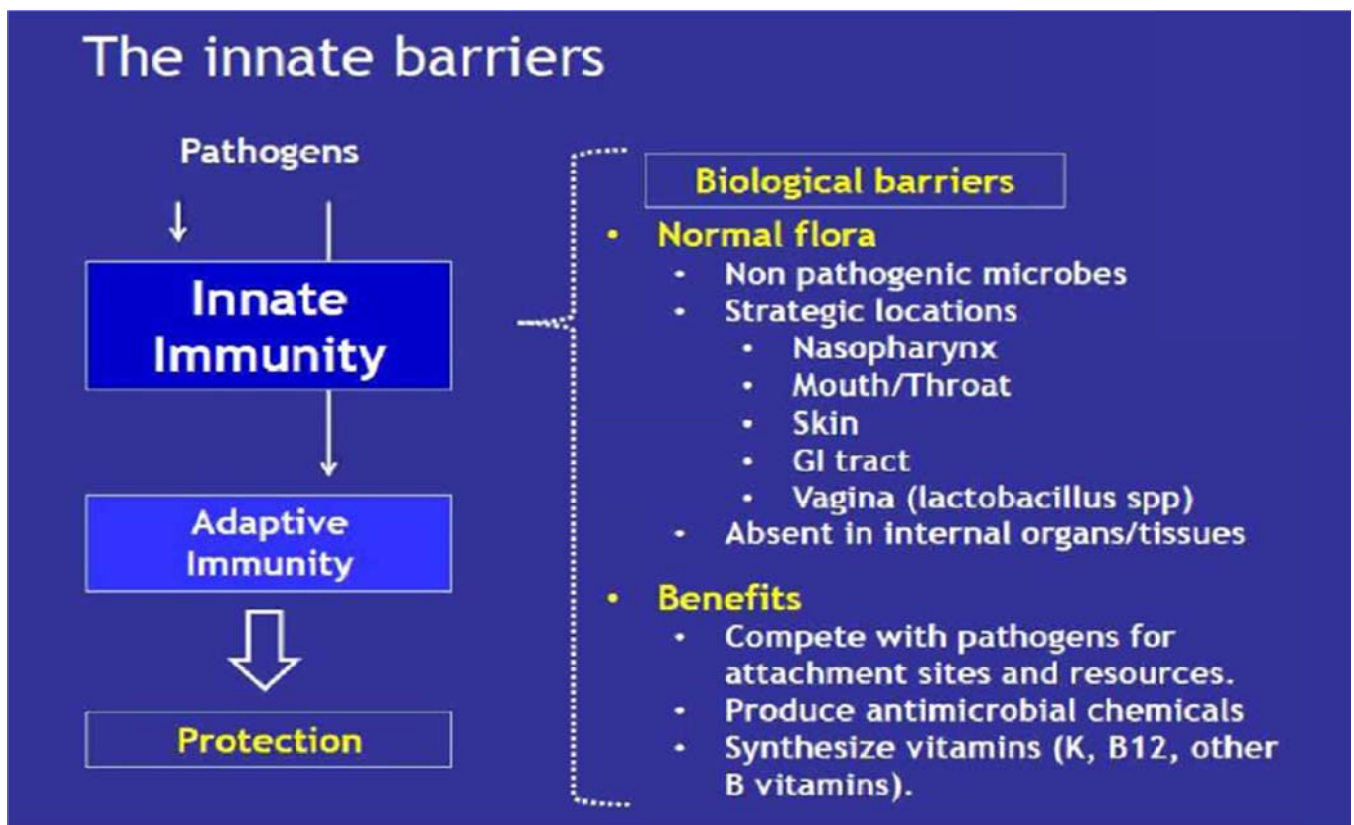
Skin contain many types of microcidal molecules:



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- Alpha – defensins, Beta- defensins, cathelicidin which may damage microbial cell membrane ,Meanwhile ,it serves as chemo attractant for cells of innate immunity
- Lysozyme secretes by sweat gland.
- RNases, DNases ...
- Evaporation of sweat lead to salty environment that inhibit pathogen growth
- Bile salts kill or inhibit many types of bacteria.

### D-Biological barriers



Finally, by living in symbiosis with non-pathogenic organisms, we reduce the potential for infection with pathogenic organisms. For example, the large bowel is extensively colonized by bacteria which exist as **commensals**. By occupying

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the majority of potential binding sites (or portals of entry), they reduce the risk of pathogenic bacteria attaching to the gut and causing disease.

- Examples of normal flora that inhabit...

**1-The skin:** *Staphylococcus aureus*, *Staphylococcus epidermidis*,  
*Streptococcus pyogenes*, *Candida albicans*, *Clostridium perfringens*

**2-The nasopharynx :** *Streptococcus pneumoniae*, *Neisseria meningitides*,  
*Haemophilus species*

**3- The mouth:** **Poor** dental hygiene/dental work infection may start by the normal flora of the mouth like *Streptococcus mutans*

**4-Large intestine :** most common is *Escherichia coli*

### Clinical problems start when...

- Normal flora is displaced from its normal location to sterile location
  - Breaching the skin integrity
    - Skin loss (burns)
    - Surgery
    - Injection drug users
    - IV lines
  - Fecal-oral route
    - Foodborne infection
  - Fecal-perineal-urethral route
    - Urinary tract infection (women)



Wikipedia



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Serious clinical problems start when

1-Normal flora overgrows and becomes pathogenic when host becomes immunocompromised like in Diabetes, AIDS Malignant diseases and Chemotherapy administration

2-When normal flora is depleted by antibiotics as what happened in intestine when the normal flora *Clostridium difficile* is depleted which will lead to severe colitis(pseudomembranous colitis)

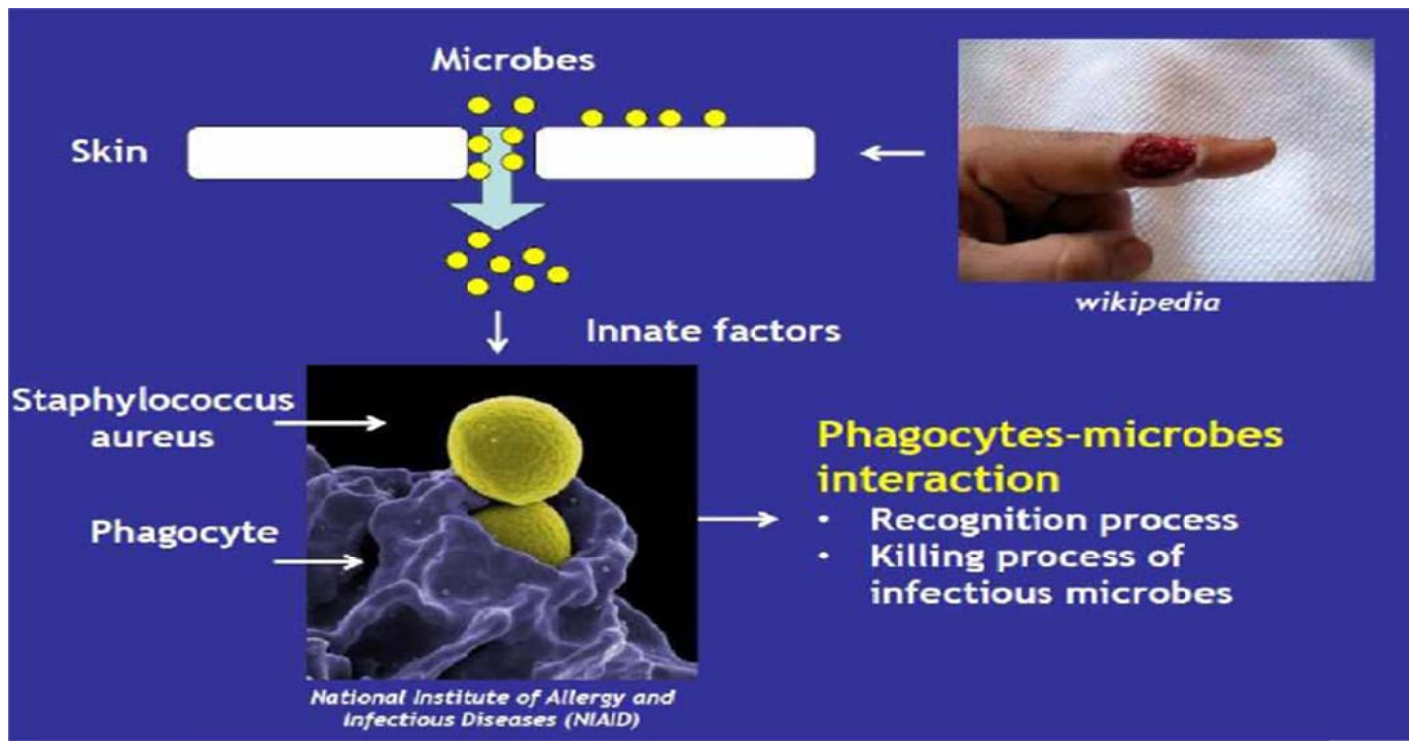
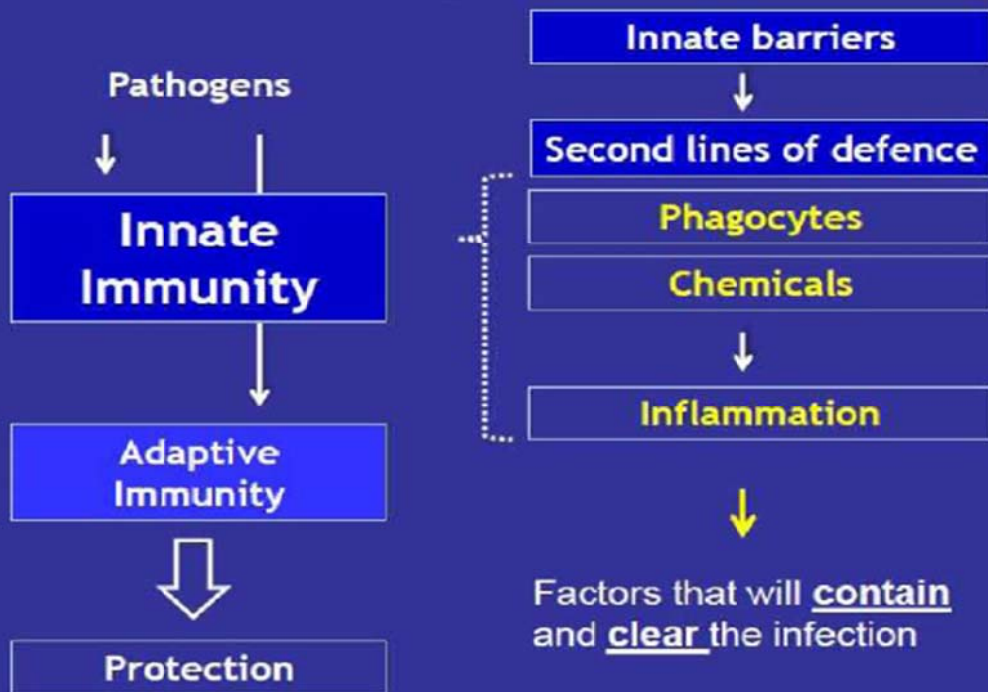
- Vaginal thrush caused by *Candida albicans* is occurring after eradication of

### **The innate immune response**

Innate immunity is the first line of immune response to infection conferred after innate physical barriers such as the skin or mucous membranes have been breached.

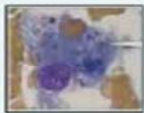


The main cellular effectors of innate immunity include the **neutrophil granulocytes**, also called **neutrophils** or **Polymorphonuclear cells**, and **monocytes** (in blood) or **macrophages** (in tissues). In addition to the cellular components, there is an important soluble component of innate immunity, this is the **complement system**.

## The immune response

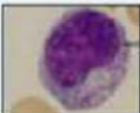



## **The main immune phagocytes:**

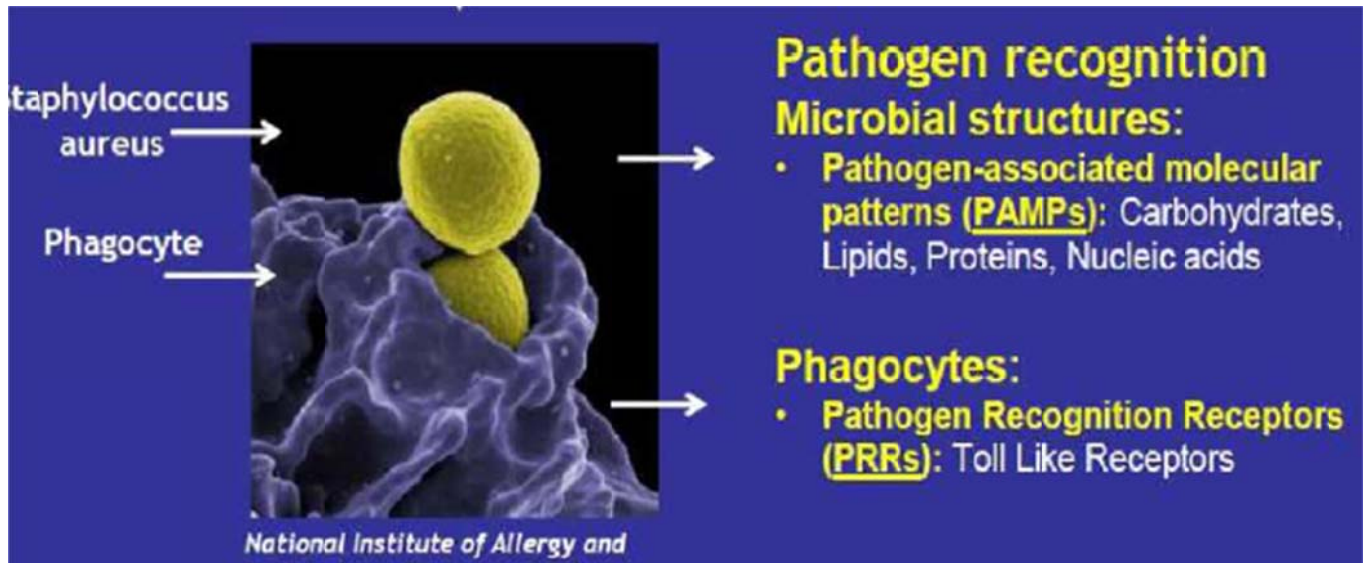
### **Main phagocytes**

Cell type	Function
Macrophages 	<ul style="list-style-type: none"><li>▪ Present in all organs</li><li>▪ Ingest and destroy microbes (<b>Phagocytosis</b>)</li><li>▪ Present microbial antigens to T cells (adaptive immunity)</li><li>▪ Produce <b>cytokines/chemokines</b></li></ul>
Monocytes 	<ul style="list-style-type: none"><li>▪ Present in the blood (5-7%)</li><li>▪ Recruited at infection site and differentiate into macrophages</li></ul>
Neutrophils (pus) 	<ul style="list-style-type: none"><li>▪ Present in the blood (60% of blood leukocytes)</li><li>▪ <b>Increased during infection</b></li><li>▪ Recruited by <i>chemokines</i> to the site of infection</li><li>▪ Ingest and destroy pyogenic bacteria: Staph. aureus and Strep. pyogenes</li></ul>

### **Other key cells of the innate immunity**

Cell type	Function
Basophils/ Mast cells	<ul style="list-style-type: none"><li>▪ Early actors of inflammation (vasomodulation)</li><li>▪ Important in allergic responses</li></ul>
Eosinophils	<ul style="list-style-type: none"><li>▪ Defence against multi-cellular parasites (worms)</li></ul>
Natural Killer cells 	<ul style="list-style-type: none"><li>▪ Kill all abnormal host cells (virus infected or malignant)</li></ul>
Dendritic cells 	<ul style="list-style-type: none"><li>▪ Present microbial antigens to T cells (<b>acquired immunity</b>)</li></ul>





## Examples of microbial PAMPS and PRRs

### Gram negative bacteria

Lipopolysaccharide (LPS)  
Lipoproteins and lipopeptides  
Porins

### Cognate PRRs

TLR4  
TLR2

### Gram positive bacteria

Peptidoglycan  
Lipoteichoic acids

TLR2  
TLR4

### All mycobacteria

Lipoarabinomannan  
Mannose-rich glycans

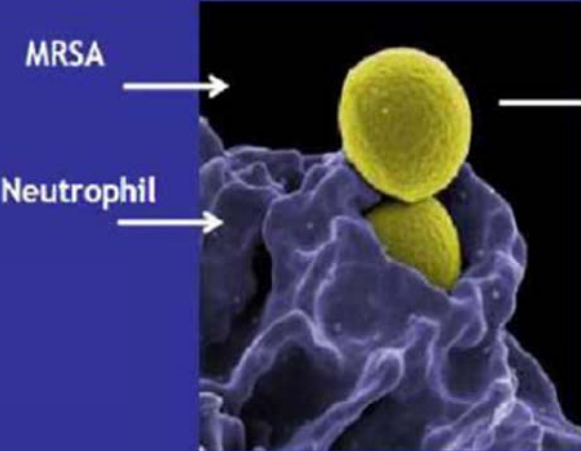
TLR2

### Bacterial flagella

Flagellin

TLR5

## **Opsonization:**



**Pathogen recognition**  
**Opsonisation of microbes:**  
Coating proteins called *opsonins* that bind to the microbial surfaces leading to enhanced attachment of phagocytes and clearance of microbes

*National Institute of Allergy and Infectious Diseases (NIAID)*

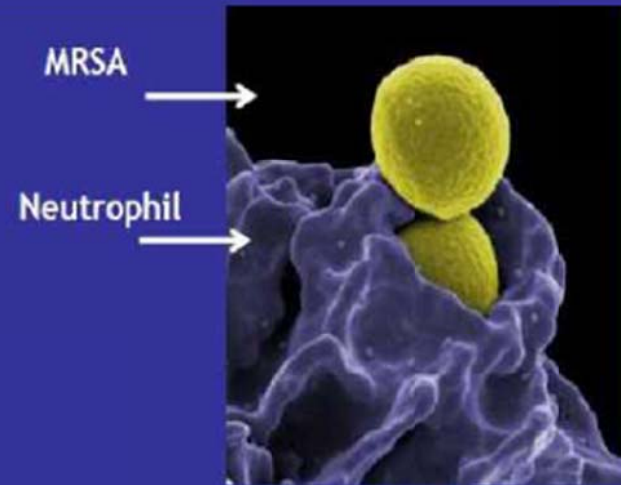
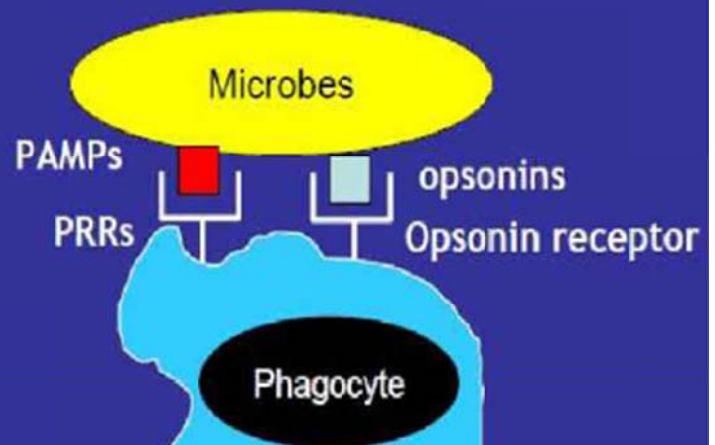
## **Examples of opsonins**

### **Complement proteins**

- **C3b**
- C4b

### **Antibodies**

- **IgG**
- IgM



**Phagocytes**

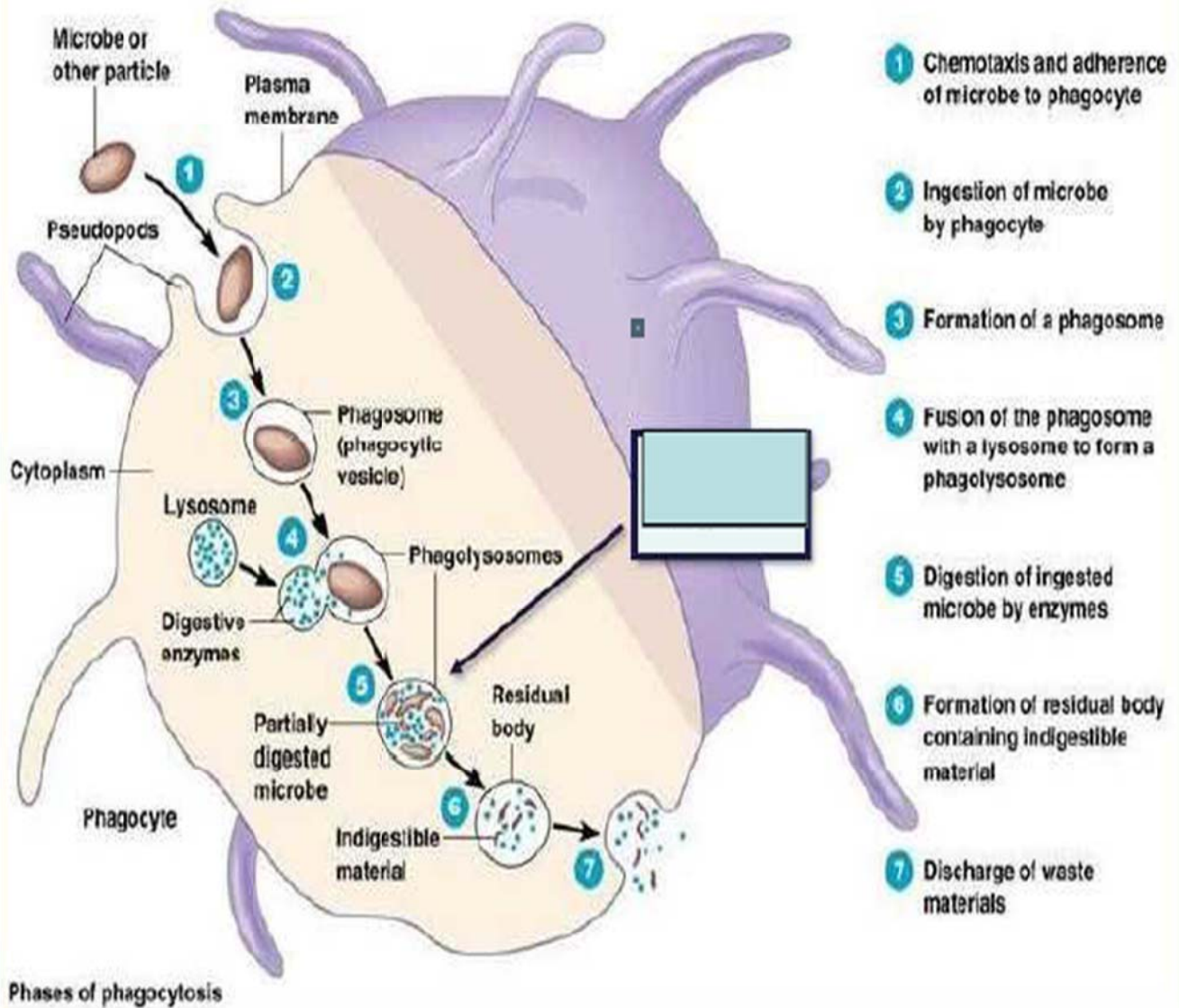
- Recognition
  - PAMPs
  - Opsonins
- **Engulfment**
- **Degradation of infectious microbes**

*National Institute of Allergy and Infectious Diseases (NIAID)*



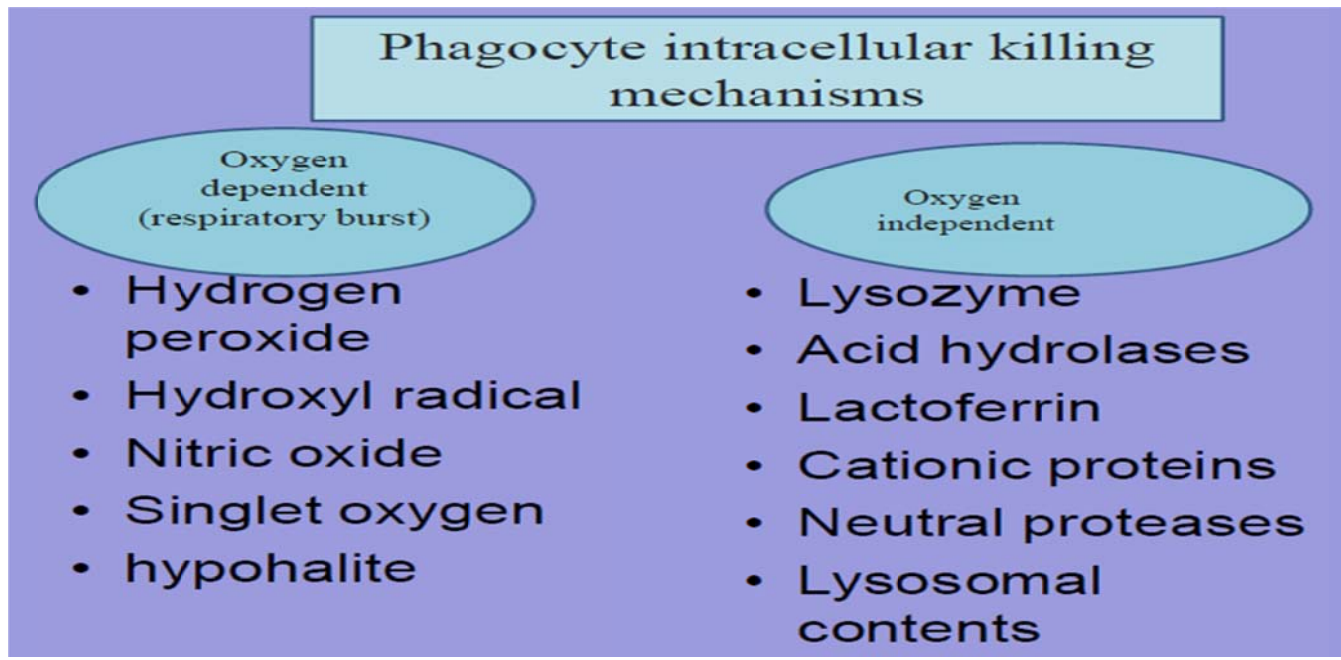
**Phagocytosis and microbes killing**

# Phagocytosis: killing of pathogens

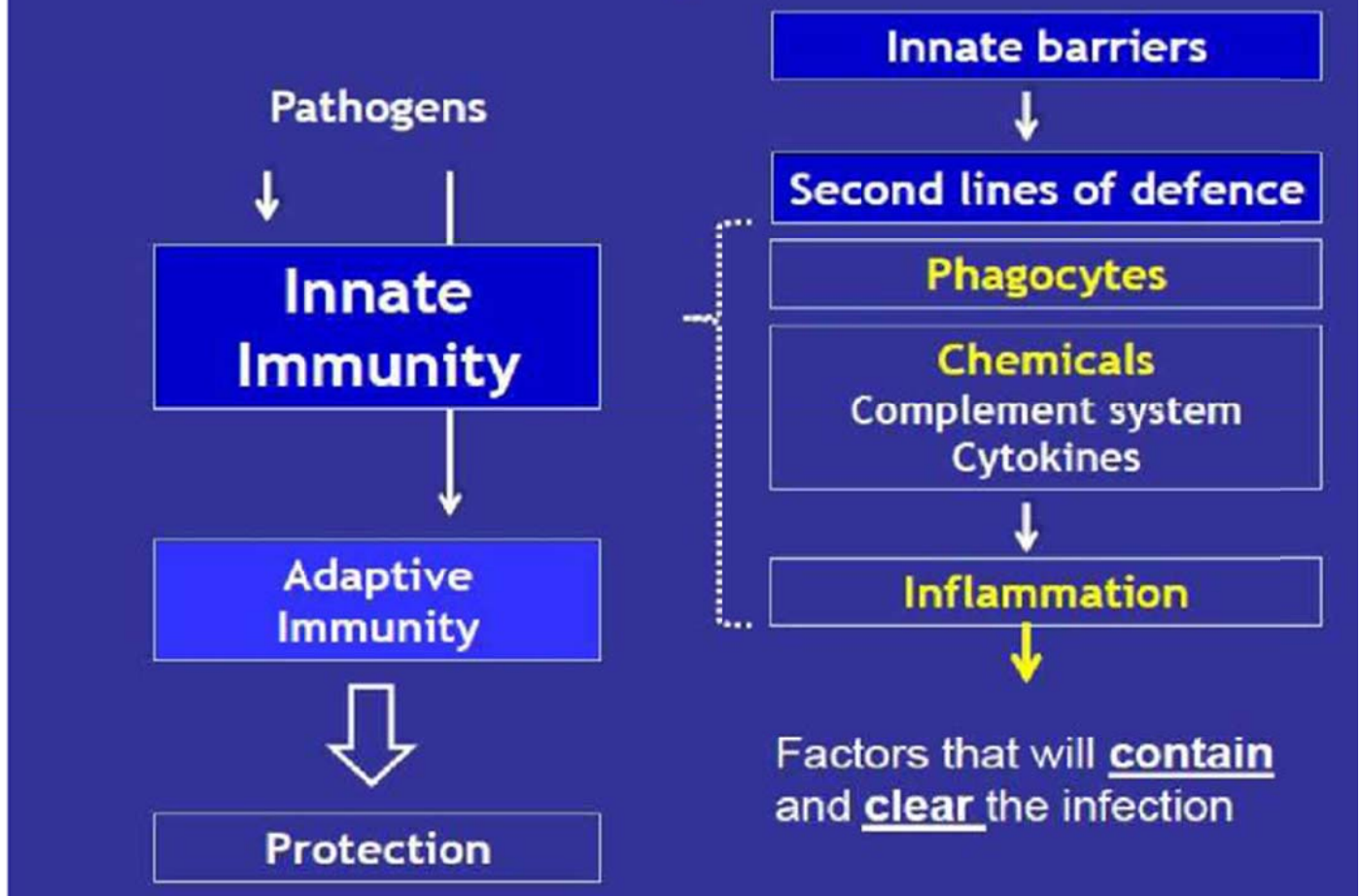


**Neutrophils Macrophages**

**Killing mechanisms inside phagocytes**



**The immune response**



**Complement:** The complement system consists of approximately 20 proteins that synthesized mainly by the liver and present in normal human (and other animals) serum. The term "complement" refers to the ability of these proteins to complement or augment, the effects of other components of the immune system, e.g., antibody. Complement is an important component of our innate host defenses.

There are four main effects of complement: (1) **Lysis** of cells such as bacteria, viruses allografts, and tumor cells; (2) **Generation of mediators** that participate in inflammation e.g., (C5a, C3a) and attract neutrophils (C5a); (3) **Opsonization**, i.e., enhancement of phagocytosis e.g., (C3b).

**4-Removing** of immune-complex from the circulation with the assistance of reticulo-endothelia system.

### **Nomenclature of complement proteins**

- ▣ **Components C1 through C9, B, D, and P are native complement (protein) components.**
- ▣ **Fragments of native complement components are indicated by lowercase letter (e.g., C4a, C5b, Bb).**
- ▣ **Smaller cleavage fragments are assigned the letter "a," and major (larger) fragments are assigned the letter "b."**

### **Activation of Complement:**

Several complement components are proenzymes, which must be cleaved to form active enzymes. Activation of the complement system can be initiated either by antigen–antibody complexes or by a variety of nonimmunologic molecules, e.g., endotoxin.

Sequential activation of complement components occurs via one of three pathways: the classic pathway, the lectin pathway, and the alternative pathway. All three pathways lead to

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the production of **C3b**, the **central molecule** of the complement cascade. The presence of C3b on the surface of a microbe marks it as foreign and targets it for destruction. C3b has two important functions: (1) It combines with other complement components to generate C5 convertase, the enzyme that leads to the production of the Membrane Attack Complex(MAC) and (2) it opsonize (opsonin) bacteria because phagocytes(neutrophils &macrophages) have receptors for C3b on their surface.

### **1-The classical pathway**

Antigen–antibody complexes activate C1 to form a protease, which cleaves C2 and C4 to form C4b2a complex. The latter is C3 convertase, which cleaves C3 molecules into two fragments, C3a and C3b. C3a, an **anaphylatoxin** which increases vascular permeability and causes vasodilation .

C3b forms a complex with C4b2a, producing a new enzyme, C5 convertase (C4b,C2aC3b), which cleaves C5 to form C5a and C5b. C5a is an anaphylatoxin and a chemotactic factor.

C5b binds to C6 and C7 to form a complex that interacts with C8 and C9 to produce the **membrane attack** complex (C5b,6,7,8,9), which causes cytolysis.

Note that the "b" fragment of complement proteins continues in the main pathway, whereas the "a" fragment is split off and has other activities (except in c3 convertase ,c4a keep in the pathway)

Only IgM and IgG fix complement. One molecule of IgM can activate complement; however, activation by IgG requires two cross-linked IgG molecules. C1consist of three proteins: C1qC1r &C1s. C1 is bound to a site located in the Fc region of the heavy chain(C<sub>H</sub>2)of IgG & IgM. Of the IgGs, only IgG1, IgG2, and IgG3 subclasses fix complement; IgG4 does not.

### **2-The lectin pathway**

Mannan-binding lectin (MBL) (also known as mannose-binding protein) binds to the surface of microbes bearing mannan (a polymer of the sugar, mannose). This activates proteases associated with MBL that cleave C2 and C4 components of complement and activate the

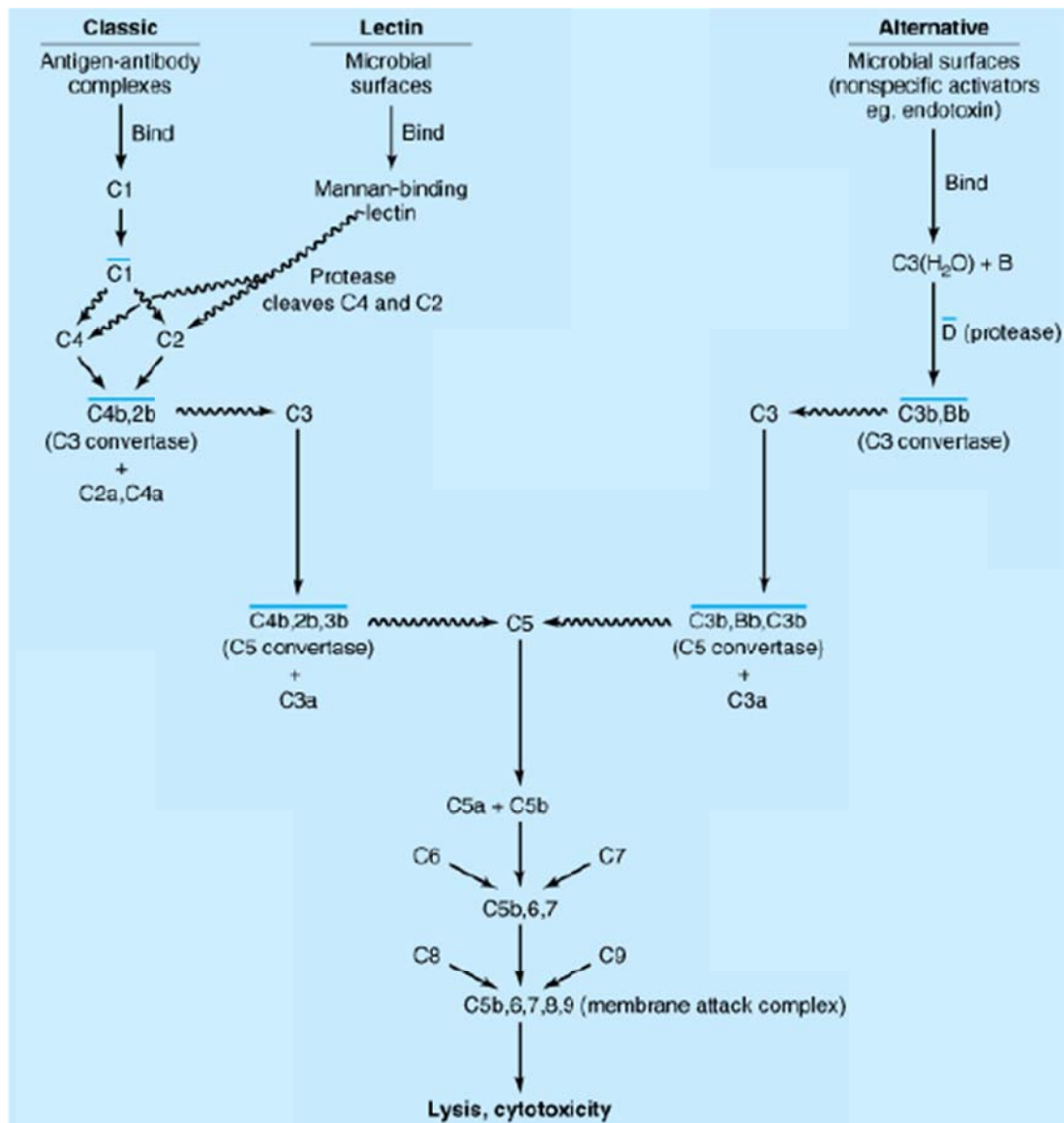


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classic pathway. Note that this process bypasses the antibody-requiring step and so is protective early in infection before antibody is formed.

### **3-The alternative pathway**

Many cell surface substances, e.g., bacterial lipopolysaccharides (endotoxin), fungal cell walls, and viral envelopes, can initiate this pathway by binding to C3(H<sub>2</sub>O) and factor B. This complex is cleaved by a protease, factor D, to produce C3b,Bb. This acts as a C3 convertase to generate more C3b. Then, 2C3b\_Bb forming C5 convertase which split C5 to C5a & C5b and sequentially forming membrane attack complex.





### **Acute-phase response:**

The **acute-phase response**, which consists of an increase in the levels of various plasma proteins, e.g., C-reactive protein and mannose-binding protein, is also part of innate immunity. These proteins are synthesized by the liver and are nonspecific responses to microorganisms and other forms of tissue injury. The liver synthesizes these proteins in response to certain cytokines, namely, IL-1, IL-6, and TNF, produced by the macrophage after exposure to microorganisms. These cytokines, IL-1, IL-6, and TNF, are often called the **proinflammatory cytokines**, meaning that they enhance the inflammatory response.

### **Cytokines/Chemokines**

Cytokines are a large group of secreted proteins which regulate and coordinate many activities of the cells of innate and adaptive immunity. All cells of the immune system secrete at least some. The nomenclature for cytokines is varying, with some named *Interleukin* followed by a number, and others named for a biological activity first attributed to them, such as tumor necrosis factor (TNF) or interferon.

#### **Functions:**

- **Chemo attraction**
- **Phagocyte activation**
- **Inflammation**

Some of innate cytokines(proinflammatory cytokines )

**1-IL-1** is a protein produced mainly by macrophages. It activates a wide variety of target cells, e.g., T and B lymphocytes, neutrophils, and endothelial cells

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plays an important role, along with tumor necrosis factor (TNF), in inducing inflammation. In addition, IL-1 is **endogenous pyrogen**, which acts on the hypothalamus to cause the fever associated with infections and other inflammatory reactions. (Exogenous pyrogen is endotoxin, a lipopolysaccharide found in the cell wall of gram negative bacteria

2- IL-6 is produced by helper T cells and macrophages. It stimulates B cells to differentiate, induces fever by affecting the hypothalamus, and induces the production of acute-phase proteins by the liver. Acute-phase proteins are described in Innate Immunity.

3-TNF- $\alpha$  is Proinflammatory cytokine produced mainly from macrophages . Low concentration: activates neutrophils and increases their adhesion to endothelial cells. High concentration: mediates septic shock, acts as cachectin, causes necrosis of tumors.