Department of Biotechnology

Immunity - (Innate and Acquired)

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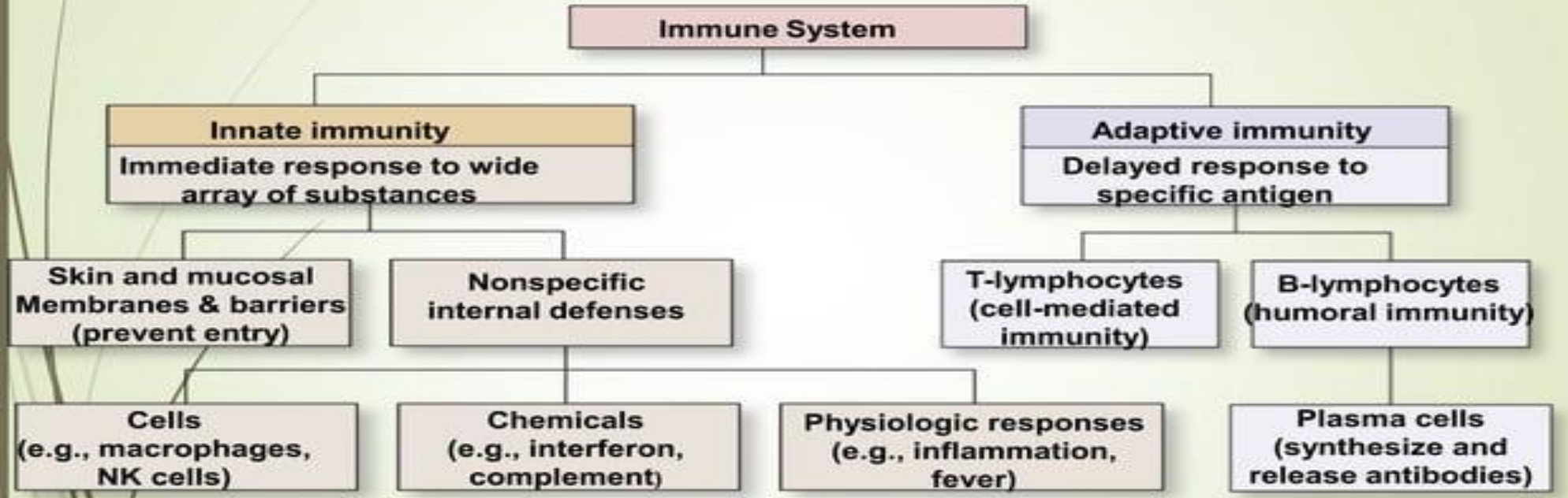
IMMUNITY

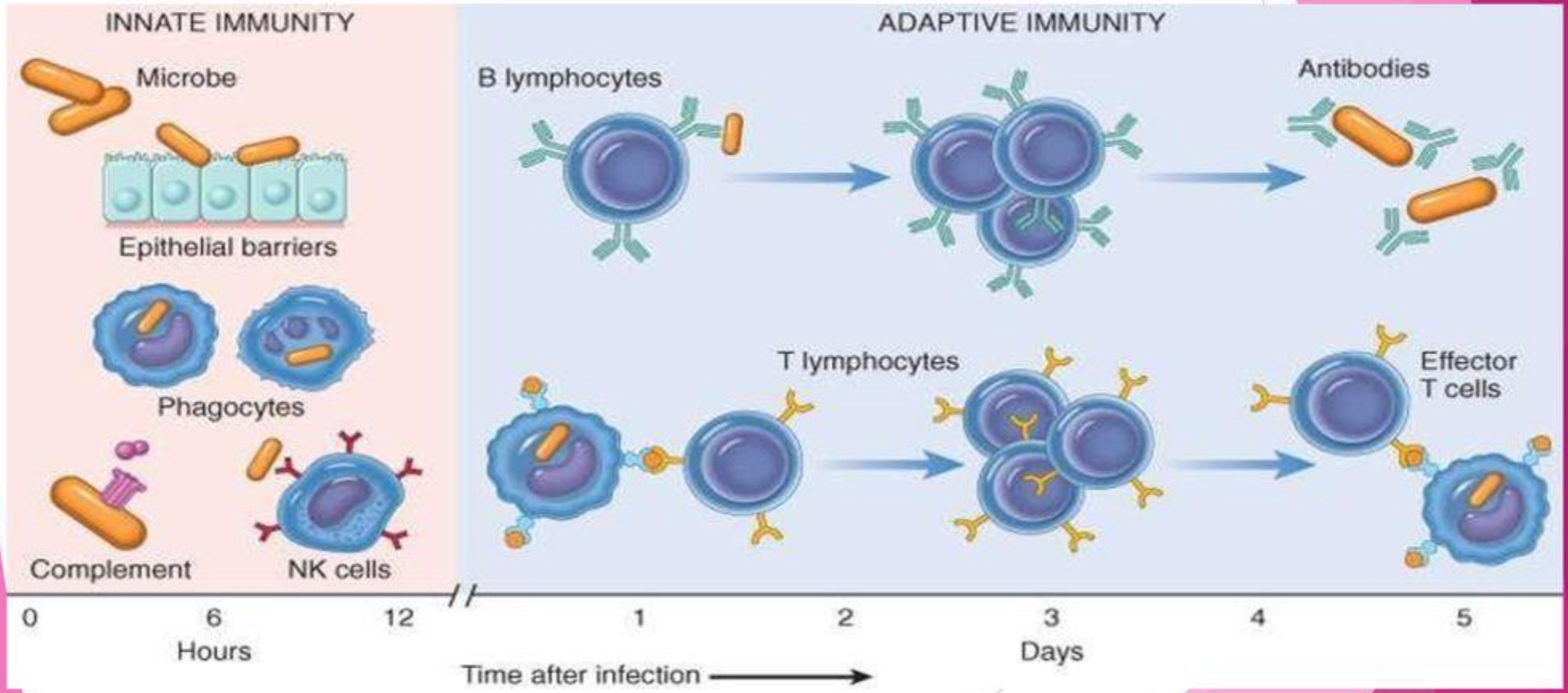
- The term 'immunity' (Latin word '*immunitas*', means freedom from disease) is defined as resistance offered by the host against microorganism(s) or any foreign substance(s).

- Immunity can be broadly classified into two types-
  - Innate immunity- present right from the birth
  - Acquired / Adaptive- acquired during the course of the life

Immune System



Immunity


INNATE IMMUNITY
ADAPTIVE IMMUNITY
Microbe
Epithelial barriers
Phagocytes
Complement
NK cells
B lymphocytes
Antibodies
T lymphocytes
Effector
T cells
0
6
12
1
2
3
4
5
Hours
Days
Time after infection

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Resistance to infection that an individual possesses since birth	Resistance to infection that an individual acquires during his lifetime
Immune response occurs in minutes	Immune response occurs in days
Prior exposure to the antigen is not required	Develops following the antigenic exposure
Diversity is limited, acts through a restricted set of reactions	More varied and specialized responses

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Immunological memory responses are absent	Immunological memory responses are present
Respond to microbial antigens that are not specific to some microbe, rather shared by many microbes (called as microbes-associated molecular patterns)	Respond to specific microbial antigens
Host cell receptors (pattern recognition receptors) are non- specific – e.g. Toll-like receptor	Host cell receptors are specific- e.g. T cell receptors and B cell immunoglobulin receptors

Differences between innate and acquired immunity

Innate immunity	Acquired / Adaptive immunity
Components of innate immunity Anatomical barriers such as skin and mucosa Physiological barriers (e.g. body temperature) Phagocytes (neutrophils, macrophages & monocytes) Natural killer (NK) cells Other Classes of lymphocytes -γδ T cells , NK-T cells, B-1 cells and marginal-zone B cells Mast cells Dendritic cells Complement pathways- alternate & mannose binding pathways Fever and inflammatory responses Normal resident flora Cytokines- TNF-α, certain interleukin (IL-1, IL-6, IL-8, IL-12, IL-16, IL-18), IFN-α, β and TGF- β Acute phase reactant proteins (APRs)	Components of acquired immunity T cell B cell Classical complement pathway Antigen presenting cells Cytokines (IL-2, IL-4, IL-5, IFN-γ)

INNATE IMMUNITY

- Innate immunity is the inborn resistance against infections that an individual possesses right from the birth, due to his genetic or constitutional makeup.

Features of innate immunity:

- Acts in minutes
- Prior microbial exposure is not required
- Diversity is limited
- Non-specific
- No memory

Innate immunity

Type of innate immunity	Explanation	Examples
Species immunity	Innate immunity towards a microbe exhibited by all members of a given species	frogs are resistant to *Bacillus anthracis*; while toads are susceptible.
Racial immunity	innate immunity confined to a particular race; may be absent in other communities	Negroes of America are more susceptible to tuberculosis than the whites.
Individual immunity	Antimicrobial defense mechanisms that are confined to a particular individual; may not be exhibited by others.	One exception is identical twins

Innate - Nonspecific Defenses

- 1st line of defense
  - *Physical barriers:* Skin and mucosal barriers - keep hazardous materials outside the body
- 2nd line of defense
  - *Phagocytes: neutrophils and macrophages:* *engulf pathogens and cell debris*
  - *Immunological Surveillance:* *natural killer cells (NK cells) destroy abnormal cells.*
  - *Interferons:* Chemical messengers that coordinate the defenses against viral infections. Antiviral proteins do not kill viruses but block replication in cell
  - *Complement:* Complement action of antibodies to destroy pathogens
  - *Inflammation:* Triggers a complex inflammatory response limiting the spread of infection
  - *Fever:* A high body temperature which increases body metabolism, and accelerates body defenses

Factors influencing innate immunity

Age

- Very old or very young more susceptible to infectious disease

Hormone

- Endocrine disorders such as **Diabetes Mellitus, hypothyroidism and adrenal dysfunctions** – enhanced susceptibility to infection

Nutrition

- Immune response is reduced in malnutrition patient

Components of innate immunity

1. Anatomical and physiological barriers
2. Antibacterial substance in blood and tissues
3. Complement pathways
4. Inflammatory response
5. Microbial antagonism
6. Cytokines
7. Acute phase reactant proteins (APRs)

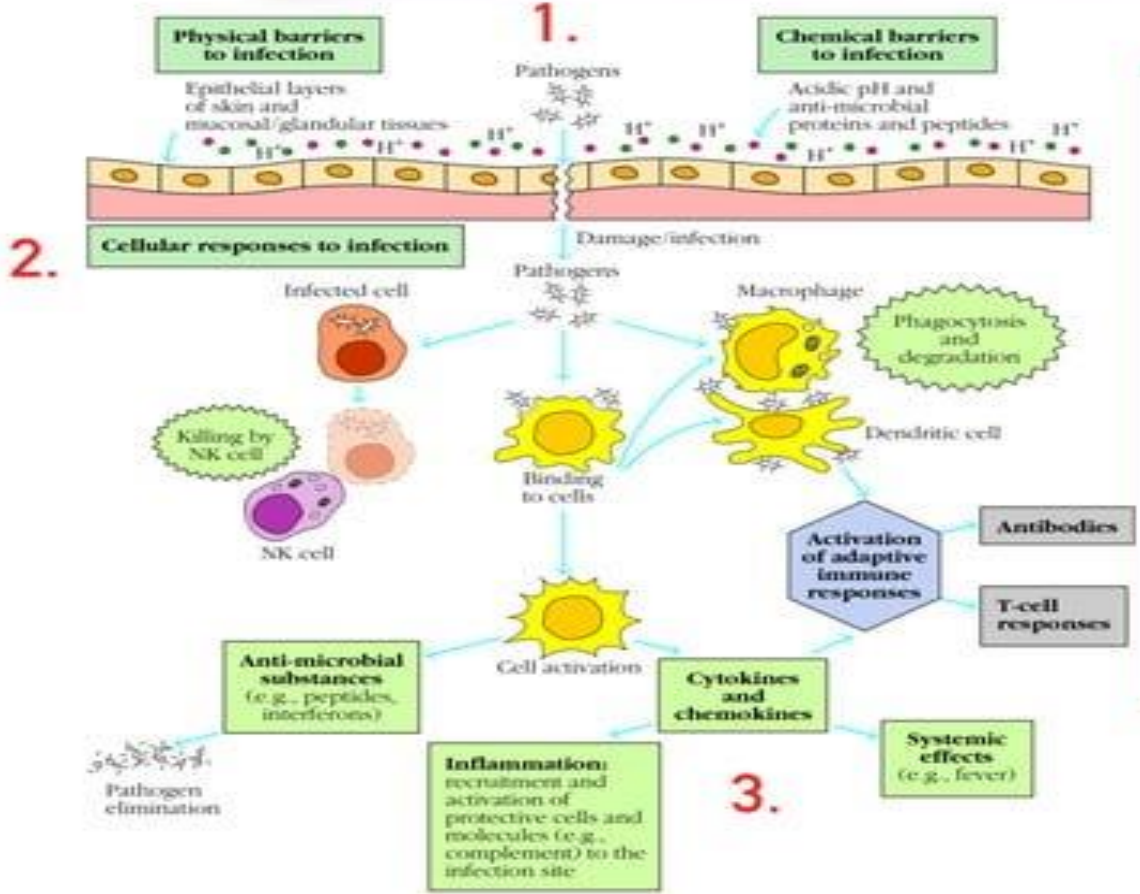
Anatomical and physiological barriers

Anatomical Barrier	Function
Skin Barrier	
	• Mechanically prevents entry of microbes • Produces sebum containing antimicrobial peptides and fatty acids • Killing of microbes by intraepithelial lymphocytes
Mucosal Barrier	
1. Mucous membrane	Prevents entry of microbes mechanically and by producing mucous which entraps microbes
2.Cilia	Cilia present in the lower respiratory tract propel the microbes outside
3.Normal flora	Intestinal & respiratory mucosa are lined by normal flora.

Anatomical and physiological barriers

Physiological Barrier	Function
1. Temperature	Normal body temperature inhibits the growth of some microbes
2. Low pH	Gastric acidity inhibits most of the microbes
3. Secretory products of mucosa	
Saliva	Enzymes in saliva damage the cell wall and cell membrane of bacteria
Tears	Contains lysozyme, that destroys the peptidoglycan layer in bacterial cell wall
Gastric juice	HCl kills microbes by its low pH
Trypsin	Hydrolyse bacterial protein
Bile salts	Interfere with bacterial cell membrane
Fatty acids	Denature the bacterial proteins
Spermine	Present in semen, inhibits growth of Gram positive bacteria
Lactoferrin	Binds to iron, thus interferes with acquisition of iron by bacteria

Component of innate immunity

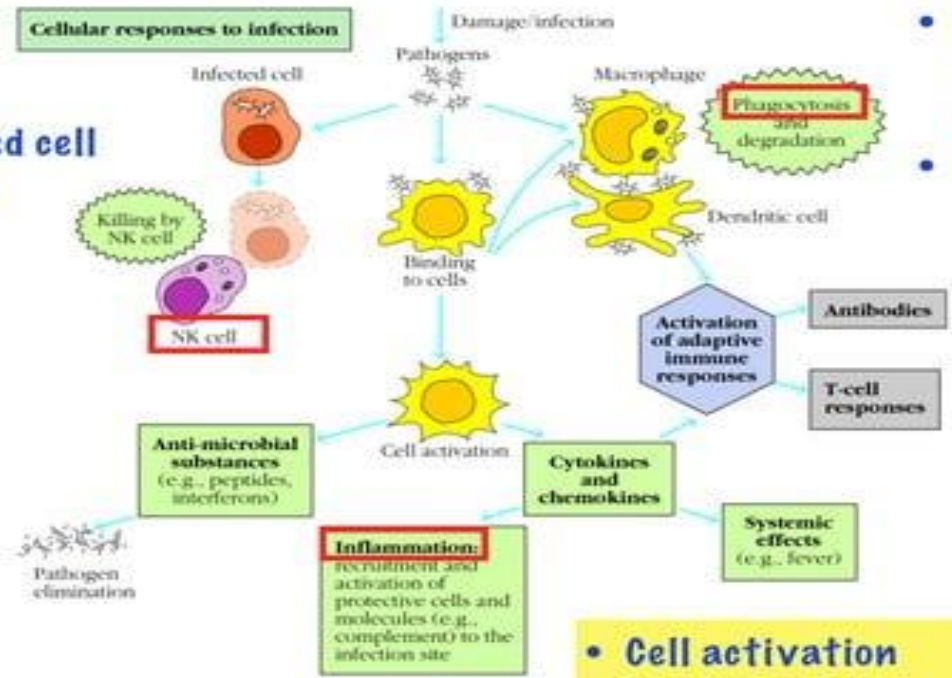


1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines
   - Anti-microbial substances

Kuby Immunology 7th edition.

2.) Cellular Response (Recognized pathogen by receptors : PRRs)
3.) Soluble proteins

- NK cell
  - Viral infected cell
  - Malignancy



- Phagocytic cells
  - -Macrophage, Neutrophil
  - " Phagocytosis "
- Dendritic cell
  - >> Activated adaptive immune response

- Cell activation
  - >> Inflammation
  - >> Antiviral defense

Kuby Immunology 7th edition.

MECHANISMS OF INNATE IMMUNITY

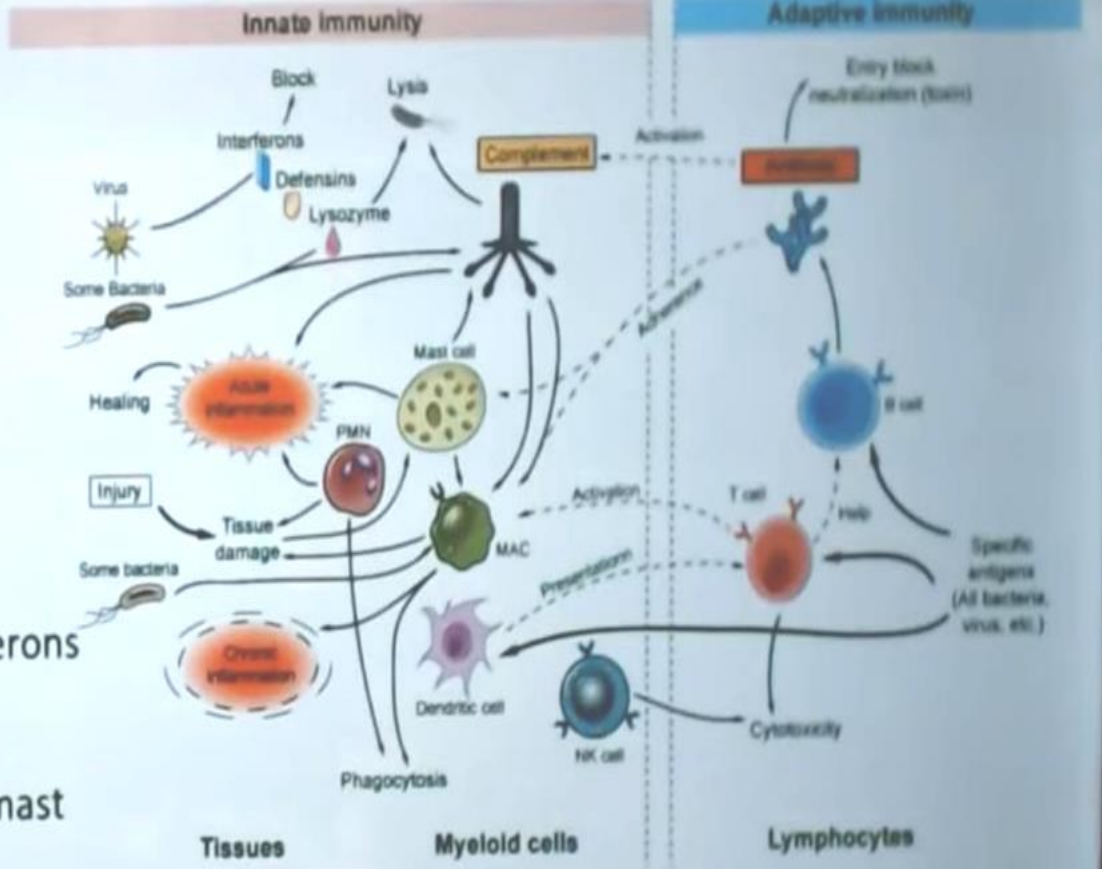
- **Receptor interaction**
  - Following the exposure of microorganisms, several mediators of innate immunity are recruited to the site of infection.
  - The first step that takes place is *attachment*, which involves binding of the surface molecules of microorganisms to the receptors of cells of innate immunity.
- ***Microbial surface molecules***-
  - Repeating patterns of conserved molecules which are common to most microbial surfaces; called as *Microbes-associated molecular patterns (MAMPs).*
  - Examples - peptidoglycan, lipopolysaccharides (LPS), teichoic acid and lipoproteins present on bacterial surface.

MECHANISMS OF INNATE IMMUNITY

- ***Pattern recognition receptors (PRRs)-***
  - Molecules present on the surface of host cells (e.g. phagocytes) that recognize *MAMPs*.
  - Conserved regions, encoded by germ line genes.
  - *Toll like receptors(*TLRs) - classical examples of pattern recognition receptors.
- There are **13 types** of Toll like receptors (TLR 1 to 13). Important ones are-
  - TLR-2 binds to bacterial peptidoglycan
  - TLR-3 binds to dsRNA of viruses
  - TLR-4 binds to LPS of Gram negative bacteria
  - TLR-5 binds to flagella of bacteria
  - TLR-7 & 8 bind to ssRNA of viruses
  - TLR-9 binds to bacterial DNA

Innate immunity mechanism

- Mechanical barriers / surface secretion
  - skin, acidic pH in stomach, cilia
- Humoral mechanisms
  - lysozymes, basic proteins, complement, interferons
- Cellular defence mechanisms
  - natural killer cells neutrophils, macrophages, mast cells, basophils, Eosinophils



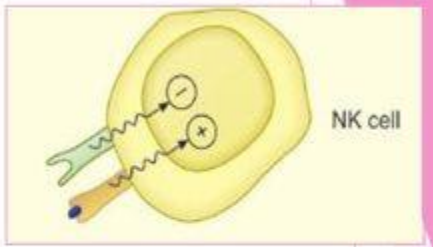
Phagocytosis

- Phagocytes - *neutrophils, macrophages* including *monocytes* are the main component of innate immunity.
- Rapidly recruited to the infection site. Phagocytosis involves three sequential steps:
  - Engulfment of microbes and subsequent hosting in phagosome.
  - Fusion of lysosome with phagosome to form phagolysosome
  - Microbial killing

Cellular components of Innate immunity

NK cells:

Class of lymphocytes that kill virus infected cells and tumor cells.



Mast cells:

Present lining the respiratory and other mucosa.

Activated by microbial products binding to toll like receptors or by IgE antibody dependent mechanism.

They release abundant cytoplasmic granules rich in histamine, prostaglandins & cytokines that initiate inflammation and proteolytic enzymes that can kill bacteria

Dendritic cells:

Respond to microbes by producing numerous cytokines that initiate inflammation.

Serve as vehicle in transporting the antigen(s) from the skin and mucosal site to lymph nodes where they present the antigen(s) to T cells - bridge between innate and acquired immunity.

Complement pathways

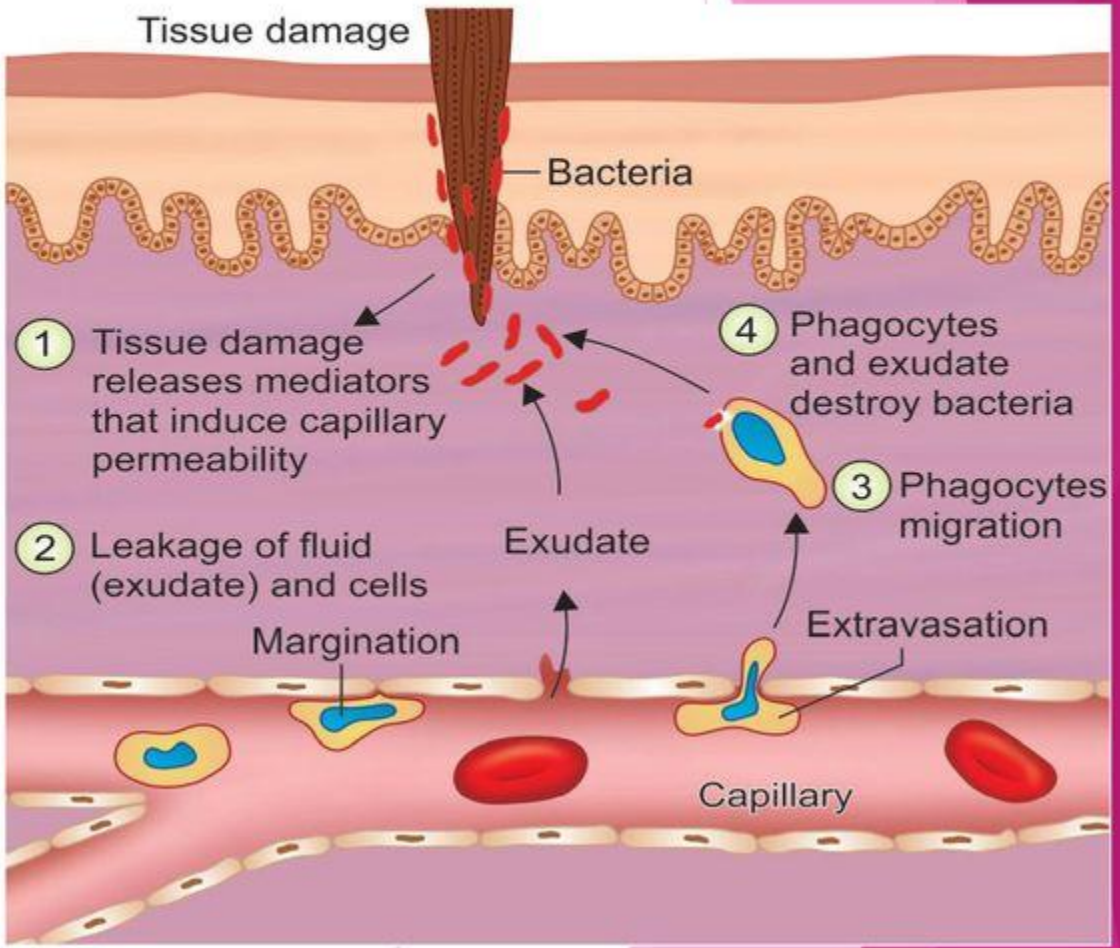
- ***Alternate** complement pathway* is activated in response to bacterial endotoxin.
- ***Mannose binding** pathway* is stimulated by mannose carbohydrate residues on bacterial surface.

Biological function;

- Lysis of the target microbes (by forming pores on the microbial surfaces)
- Stimulate inflammation (by secreting inflammatory mediators)
- Stimulate acquired immunity- Complements are another bridge between innate and acquired immunity.

Inflammatory response

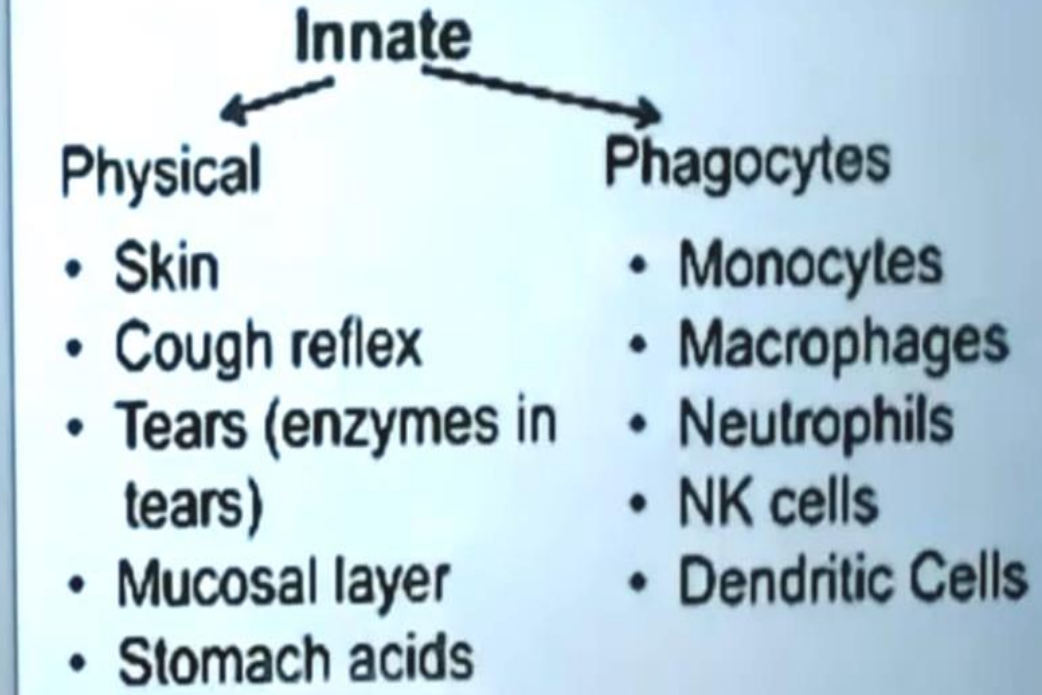
- *Vasodilation*
- *Leakage* of plasma proteins through blood vessels
- Recruitment of phagocytes (e.g. neutrophils) to the site of inflammation
- Engulfment of microbes and dead material by the phagocytes
- Destruction of the microbes



• Natural killer cells	• Kill virus infected cells
• Neutrophils	• Ingest and destroy microbes
• Macrophages and dendritic cells	• Ingest and destroy microbes, and present antigen to helper T-cells
• Interferons	• Inhibit viral replication
• Complement	• C3b is an opsonin, membrane attack complex creates holes in bacterial membranes
• Transferrin and Lactoferrin	• Sequester iron required for bacterial growth
• Fever	• Elevated temperature retards bacterial growth
• Inflammatory response	• Limits spread of microbes

Innate immune Response

- Mediated (initiated) by phagocytes, NK cells and soluble proteins
- **Phagocytes**
  - Cells specialized in the process of phagocytosis
- **Macrophages**
  - Reside in tissues and recruit neutrophils
- **Neutrophils**
  - Enter infected tissues in large numbers
  - Recognize common molecules of bacterial cell surface using a few surface receptors
- **Phagocytosis**
  - Capture, engulfment and breakdown of bacterial pathogen



Cytokines

- In response to the microbial antigens, dendritic cells, macrophages, and other cells secrete several cytokines that mediate many of the cellular reactions of innate immunity such as:
  - Tumor necrosis factor (TNF),
  - Interleukin-1 (IL-1), IL-6, IL-8, IL-10 & IL-16
  - Interferons (IFN-α, ß) and
  - Transforming growth factor (TGF-ß)

Cellular response

- Innate immune system recognizes
  - PAMPs (Pathogen-associated molecular pattern)
    : molecular structures of microbial pathogen that required for survival
  - DAMPs (Damage-associated molecular pattern)
    : result of cell damage by infections

- Cellular receptors : PRRs (Pattern recognition receptors)

Abbas 8th Edition Innate Immunity, 51-86.

Acute phase reactant proteins (APRs)

- Proteins synthesized by liver at steady concentration, but their synthesis either increases or decreases exponentially during acute inflammatory conditions.
- APRs can also be synthesized by various other cells such as endothelial cells, fibroblasts, monocytes and adipocytes.
- APRs have various antimicrobial and anti-inflammatory activities (e.g. complement factors)

C- Reacting protein (CRP)

- CRP belongs to beta globulin family.
- CRP is so named because it precipitates with C- carbohydrate (polysaccharide) antigen of *Pneumococcus*.
- CRP not an antibody against the C- carbohydrate antigen of *Pneumococcus*; it is non-specific, can be raised in any inflammatory conditions.
- Commonest markers of acute inflammation, used in most diagnostic laboratories.

C- Reacting protein (CRP)

- Normal level - <0.2mg/dl.
- Increases by several folds in acute inflammatory conditions:
  - *Insignificant increase* (<1 mg/dl) –heavy exercise, common cold, and pregnancy
  - *Moderate increase* (1-10 mg/dl)- bronchitis, cystitis, malignancies, pancreatitis, myocardial infarction
  - *Marked increase* (>10 mg/dl)- acute bacterial infections, major trauma and systemic vasculitis

Detection of CRP

- Precipitation method using C carbohydrate antigen (obsolete, not in use now)
- Latex (passive) agglutination test using latex particles coated with anti-CRP antibodies -most widely used.
- Detection limit of CRP by latex agglutination test – 0.6mg/dl

Highly sensitive CRP (hs-CRP)test

- Minute quantities of CRP can be detected by various methods (e.g. nephelometry, enzyme immunoassays).
- Useful in assessing the risk to cardiovascular diseases

Innate immunity further classified

- Main Components of Innate and acquired Immunity that contribute to humoral (antibody-mediated) immunity and cell mediated immunity

	Humoral Immunity	Cell mediated Immunity
Innate	Complement Neutrophil	Macrophages Natural killer cells
Acquired	B cells Antibodies	Helper Tcells Cytotoxic T cells


THANK YOU