INNATE IMMUNITY

Dr. Rabab Afifi
Lecturer of clinical and chemical pathology
Beni- Suef University

- Susceptibility: Lack of resistance to a disease.
- Immunity: Ability to ward off disease.
- Innate immunity: Defenses against any pathogen

Innate (Nonspecific) Immunity		Adaptive (Acquired) Immunity (Chapter 17)
First line of defense	**Second line of defense**	**Third line of defense**
• Intact skin • Mucous membranes and their secretions • Normal microbiota	• Natural killer cells and phagocytic white blood cells • Inflammation • Fever • Antimicrobial substances	• Specialized lymphocytes: T cells and B cells • Antibodies

Fig 16.1

Innate Immunity

Defensive mechanisms include :

1) Innate immunity (Natural or Non specific)

2) Acquired immunity (Adaptive or Specific)

Cell-mediated immunity Humoral immunity

What is the Innate Immune System?

- includes physical, chemical, and cellular barriers
- **physical** barriers include skin and mucus membranes
- **chemical** barriers include stomach acidity, secreted anti-microbial peptides
- **cellular** barriers include macrophages, neutrophils
- innate immune response activation occurs within minutes of pathogen recognition

Component of Innate Immunity

Innate Immune system

First line

1) Mechanical barriers
2) Chemical & biochemical inhibitors
3) Normal flora

Second line

A- cells
1- Natural killer
2- Phagocytes

B- humeral mediators

C- Inflammatory barriers

First line

I-Epethelial Barriers: Common portal of antigen to the body is through the skin , RT, GIT.

1) Mechanical barriers

- Intact skin
- Mucous coat
- Mucous secretion
- Blinking reflex and tears
- The hair at the nares
- Coughing and sneezing reflex

First line

2) Chemical & biochemical inhibitors

- Sweet and sebaceous secretion
- Hydrolytic enzymes in saliva
- HCl of the stomach
- Proteolytic enzyme in small intestine
- Lysozyme in tears
- Acidic pH in the adult vagina

First line

II-Normal bacterial flora

- Competition for essential nutrients

- Production of inhibitory substances

SECOND LINE

I-HUMERAL MEDIATORS:

- Innate resistance to many pathogens is provided by enzymes and proteins in the blood and tissue fluids.
- These proteins are the effectors of humeral innate immunity.
- They have features in common with each other that are also characteristic with the innate immune system as a whole.

- These proteins are continually expressed through out life whether or not their protective

effects are needed at a given moment or not.

- Although many of these proteins can be produced in higher quantities in time of need, their intrinsic properties (eg, substrate specificity and binding affinity) never change.

- They generally recognize targets or substrates that are found on a wide range of microorganisms that are not normally present in the human body (pathogen specific molecular patterns).

- Innate immune system has evolved mechanisms capable of recognizing these repeating patterns termed **Pattern Recognition Receptors (PRRs)**

- Examples of Pattern Recognition Receptors:
  - Mannose-Binding Lectin (MBL)
  - Macrophage Mannose Receptor
  - Scavenger Receptors
  - Toll-like Receptors (TLRs)
  - Nod-like Receptors (NLRs)
  - RNA helicases (RIG-I, MDA-5)

Innate Immunity Pattern Recognition

Molecular Pattern of Microbe	Source	Pattern Recognition Receptor	Principle Innate Immune Response
dsRNA	Replicating viruses	ds-RNA activated kinase & TLR3	IFNa,b
LPS	Gram-negative bacteria	LBP/CD14/TLR4	Macrophage activation
N-formylmethionyl peptides	Bacterial proteins	NFM receptors	Neutrophil and macrophage act.
Mannose-rich glycans	Microbial glycoproteins	MΦ mannose recptr Plasma mannose lectin	Phagocytosis Opsonization, C' activation
Phosphorylcholine and related	Microbial membranes	Plasma c-reactive protein	Opsonization, C' activation
CpG (PuPuCpGPyPy)	Bacteria	? TLR9/DNAPK	Macrophage activation

Other: teichoic acid,

1-C-reactive protein :

- It is a plasma protein which was identified and named because of its ability to bind to the capsules of pneumococcal bacteria.
- It belongs to the pentraxin family of plasma proteins.
- C-reactive protein binds to bacterial phospholipid phosphorylcholine and coats bacteria for phagocytosis by M Q that express receptors for CRP.

- It functions as an opsonin by binding to C1q receptors and interacting with phagocyte C1q receptors.
- It may also contribute to complement activation through its attachment to C1q and activation of the classical pathway.
- Its an acute phase reactant as its level increases during infection.

2-Cytokines :

- The cytokines of the innate immunity recruit and activate leucocytes .
- In innate immunity the principle source of cytokines are macrophages , neutrophils and NK cells
- Produce systemic alterations ,including increase in the synthesis of effecter cells and proteins that potentiate antimicrobial response.
- .

- Cytokines serve to communicate information among inflammatory cells and between inflammatory cells and responsive tissue cells such as vascular endothelial cells.

- The cytokines of innate immunity include:

  1-Cytokines that control viral infections(IFNα an.d INF β).

  2- cytokines that mediate inflammatiom(TNF and IL-1). And others.

3- The complement:

I. Complement System: Collection of circulating serum proteins and membrane associated protins that participate in the lysis of foreign cells, inflammation, and phagocytosis.

Three mechanisms of complement activation:

1. Classical Pathway: Initiated by an immune reaction of antibodies. Component of adaptive IR.

2. Alternative Pathway: Initiated by direct interaction of complement proteins with microbial polysaccharides.Component of innate immunity

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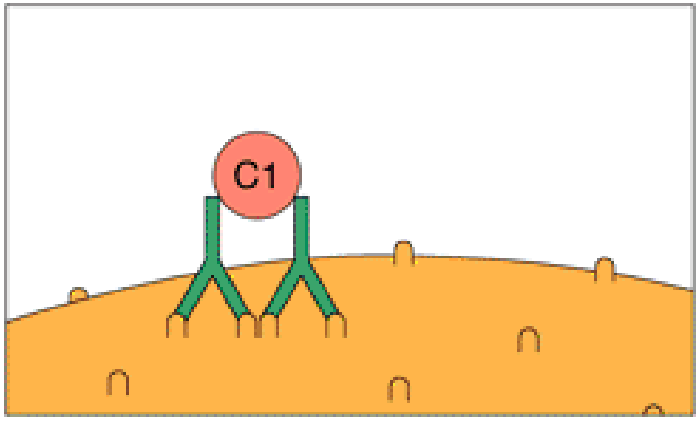
- 3- Lectin pathway: Activated when a plasma protein mannose –binding lectin, binds to terminal mannose residues on the on the surface glycoprotein of bacteria. This lectin activates proteins of the classical pathway but because it is initiated by abacterial product in absence of Ab it is a component of innate immunity.

- Activated complement components function as proteolytic enzymes to cleave other complement proteins, in an enzymatic cascade.

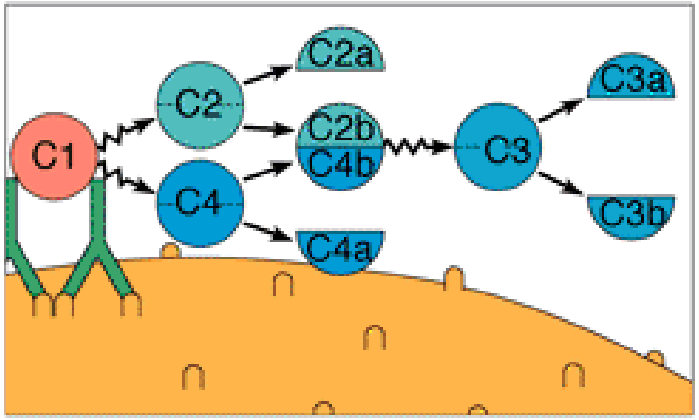
- The central component of complement is a plasma protein is a plasma protein called C3 which is which is cleaved by enzymes generated in the early of the cascade.

- The major proteolytic fragment of C3 bind to microbes and activate down stream components.

Classical Complement Pathway is Triggered by Antibodies Binding to Foreign Cells



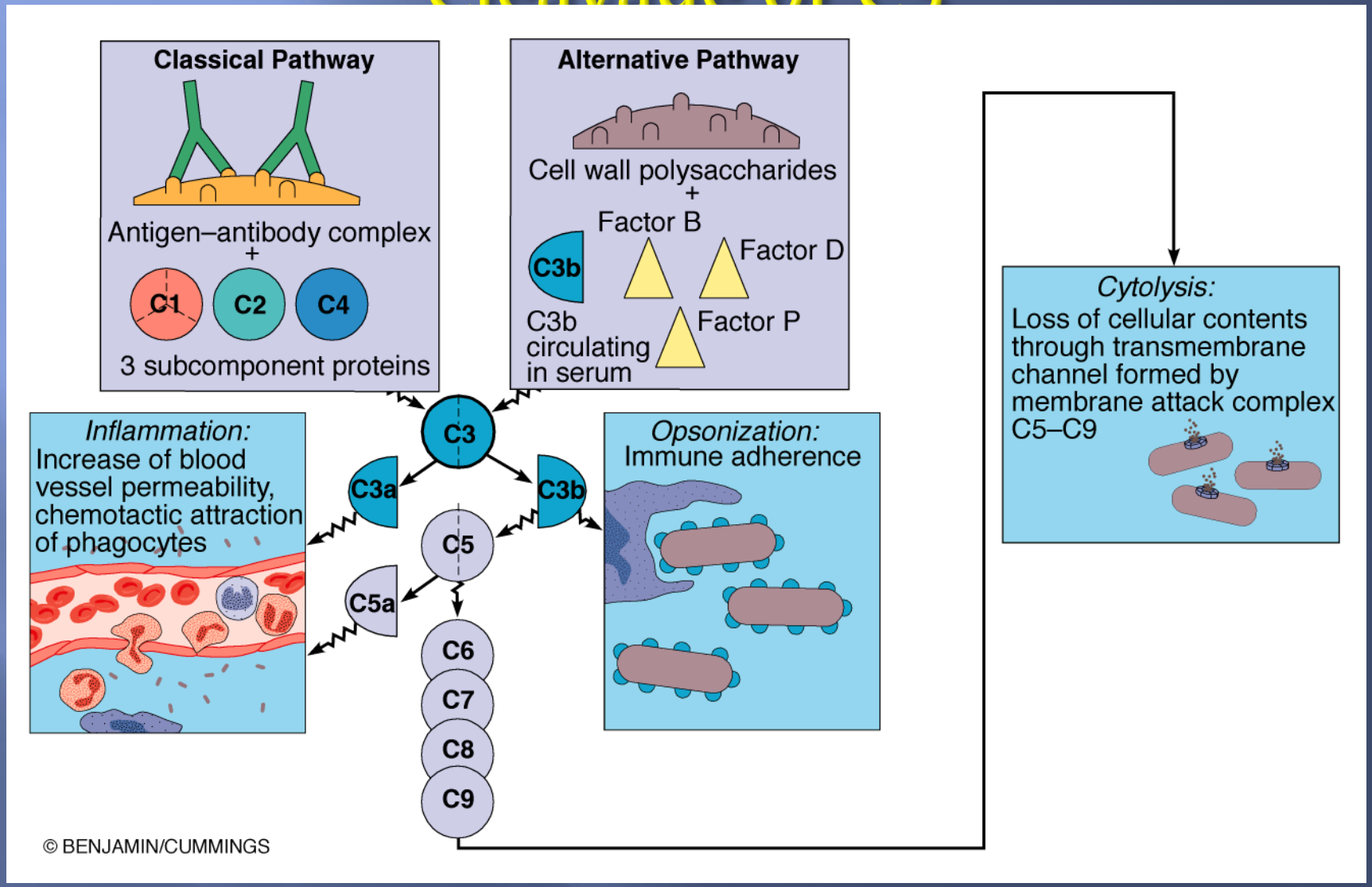
❶ Once antibodies recognize and attach to the antigen, complement protein C1 binds to two adjacent antibodies.



(a)

❷ C1 acts as an enzyme that splits the C2 and C4 proteins into fragments. Fragments C2b and C4b combine to form another enzyme, which splits C3 into two fragments. The active fragment is called C3b.

Both Classical and Alternative Complement Pathways Trigger the Cleavage of C3



Consequences of Complement Activation:

1. Cytolysis: Due to the formation of a membrane attack complex (MAC) which produces lesions in microbial membranes.
2. Inflammation: Complement components (C3a) trigger the release of histamine, which increases vascular permeability.
3. Opsonization: Complement components (C3b) bind to microbial surface and promote phagocytosis.
4. Inactivation of Complement: Regulatory proteins limit damage to host cells that may be caused by complement.

The acute phase proteins

- Apart from C3 , most soluble mediators of innate immunity are found in relatively small quantities in in the serum under normal conditions.

- The concentration of these proteins can increase 1000 folds during serious infections or other crisis as a part of a coordinated reaction called ***acute phase response*** .

The acute phase response

- The acute phase response occurs when the hepatocytes are exposed to particular cytokines (IL-6, TNF) released locally into the blood stream by other host cells.

In this response the liver temporarily increases synthesis of thirty different proteins.

The acute phase response can be viewed as a primitive non specific reaction, mediated by the liver that intensifies some aspects of innate immunity and other protective functions in times of need.

Inflammation

Triggered by tissue damage due to infection, heat, wound, etc.

Four Major Symptoms of Inflammation:

1. Redness
2. Pain
3. Heat
4. Swelling

May also observe:

5. Loss of function

Functions of Inflammation

1. Destroy and remove pathogens

2. If destruction is not possible, to limit effects by confining the pathogen and its products.

3. Repair and replace tissue damaged by pathogen and its products.

Stages of Inflammation

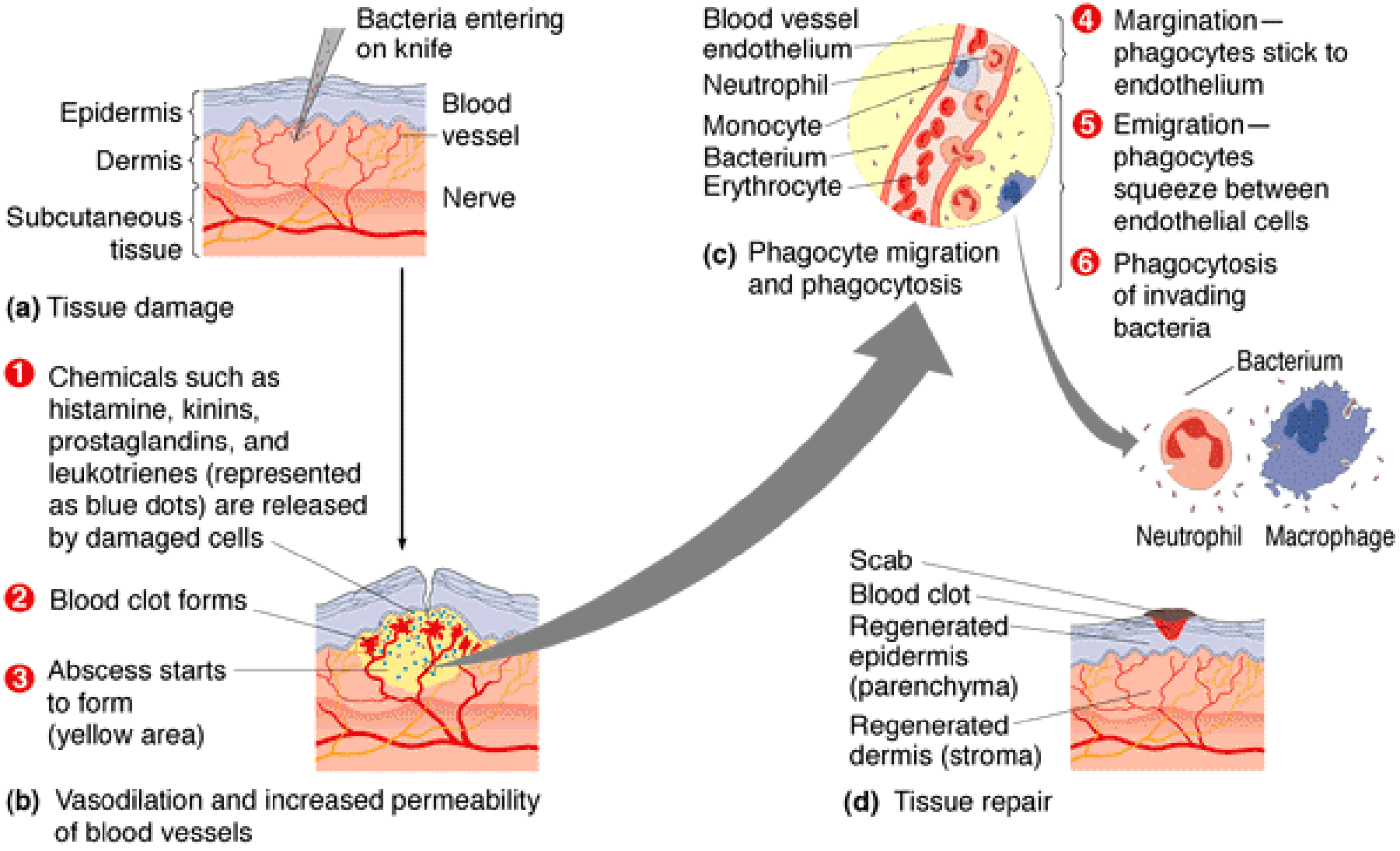
1. **Vasodilation**: Increase in diameter of blood vessels.

   Triggered by chemicals released by damaged cells: histamine, kinins, prostaglandins, and leukotrienes.

2. **Phagocyte Migration and Margination**:
   Margination is the process in which phagocytes stick to lining of blood vessels.

   Diapedesis (Emigration): Phagocytes squeeze between endothelial cells of blood vessels and enter surrounding tissue.

Process of Inflammation



Stages of Inflammation (Continued)

Phagocytes are attracted to site of infection through chemotaxis.

Phagocytes destroy microbes, as well as dead and damaged host cells.

3. **Tissue Repair**: Dead and damaged cells are replaced.

THANK YOU

Second line

A) cells

1- Natural killer (NK)

Definition: Large granular lymphocytes
Innate cytotoxic lymphocytes

Source : Bon marrow precursors

Location : 10% or 15% of lymphocytes in peripheral blood
1% or 2% of lymphocytes in spleen

Function : Cytotoxic for Tumor cells
Viral infected cells
Bacterial, fungal, parasitic infection

Responsible for antibody-dependent cell mediated cytotoxicity (ADCC)

Mechanism of action: activation triggers release of proteins contained in the natural killer granules towards the infected cells . The net result is that NK cells kill infected or stressed host cells.

Activation : determined by a balance between engagement of activating and inhibitory receptors.

Activating receptors: recognize cell surface molecules commonly expressed on stressed cells(tumor cells , viral or bacterial infected cells).

Activating receptors: include NKG2D recognizes a molecule that resembles MHC I expressed on many cells in response to cellular stress.

another recactivating receptor is for IgG (recognizes cells coated with IgG ------- ADDC)

Inhibitory receptors: specific for class I MHC molecules expressed on the surface of healthy nucleated cells and function to block signaling by activating receptors.

Killer cell immunoglobulin inhibitory receptors(KIR)

NKG2 receptors(consisiting of a protein called CD94 and a lectin) subunit

Two major families of inhibitory receptors

How do activating and inhibitory receptors function?

Immunreceptor tyrisine-based activation motive(ITAMS)

- Become phosphorylated on tyrosine residues when receptors bind their ligands
- Activate different downstream signal transduction pathways

Immune receptor tyrosine-based inhibitory

- Bind class I MHC molecules and become phosphorylated on tyrosine residues.
- Bind and promote activation of cytoplasmic phoshatases which dephosphorylate various signaling molecules and hence blocking activation of activating receptors.

Cytokines: secreted proteins that function as mediators of inflammation and immune reactions. In innate immune response they are produced by MQ and NK cells and in adaptive immune responses mainly by lymphocytes.

NK activating cytokines: IL-15, type 1 IFN and IL12.

- IL -15 : secreted by MQ and is important for development and maturation of NK cells.
- Type I INF: secretes by dendritic cell MQ and fibroblasts. Activation and enhancement of the killing action of NK cells.
- IL-12: secreted by MQ and enhance the killing action of NK cells

Second line
2-Dendritic cells

Dendritic cells: the bridge between adaptive and innate immune responses. Respond to microbes by prouducing cytokines that recruit leucocytes and initiate adaptive immune responses.

Second line

3- Phagocytes

Specialized cells for capture, Ingestion and destruction of invading microorganisms

* Polymorphoniclear leucocytes, mainly neutrophils:
granulocytes circulate in blood

* Mononuclear cells (macrophages)

- Monocytes in blood

- Histocytes in connective tissues

- Fixed reticuloendothelial cells in liver spleen, lymph nods, bone marrow

Neutrophils

- An army of more or less identical circulating phagocytes that respond quickly and in vast numbers whenever tissue injury occurs.

- The mature cells known as segments or PMNLs are identified by their characteristic multilobed nucleus and by the abundant storage granules in their cytoplasm.

Chemotaxis and tissue invasion

- At the site of injury or infection, the cells will rapidly adhere to the endothelial lining of local blood vessels.
- This response is directed by neutrophil chemotactic factors.
- The neutrophils respond by rapidly associating with the inner vessel wall in a phenomena known as margination.

A- Margination : 3 phases

- Leucocytes adhesion to the vessel wall occur in three overlapping phases, each is mediated by a particular class of molecules.
- 1- selectin mediated phase:
- First phase of margination .
- Relatively weak.
- Allow neutrophil to roll against vessels wall under force of flowing blood.

Intigrin mediated :

- Second phase .
- Tight:

Neutrophils bind to cell protein, no further movement ---------- flattened against the surface

Components	Principle Functions
Barriers	
Epithelial layers	Prevent entry
Defensins and Cryptidins	Microbial killing
Circulating and Tissue Effector Cells	
Neutrophils	Early phagocytosis and killing of microbes
Mast Cells	Release of inflammatory granules
Macrophages	Efficient phagocytosis and killing of microbes: cytokines
Eosinophils	Nasty toxic cells designed to kill helminths (worms)
NK cells	Lysis of infected cells, activation of macrophages
Circulating Proteins	
Complement (C')	Killing of microbes, opsonization of microbes, actvn leukocytes
Mannose-binding protein	Opsonization of microbes and activation of C'
C-reactive protein	Opsonization of microbes and activation of C'
Lysozyme	Bacterial cell wall lysis
Cytokines	
TNF, IL-1, 6, 18	Inflammation
IFN α, β	Resistence to viral infection
IFN γ	Macrophage activation
IL-12	IFNγ production by NK cells
IL-15	Proliferation of NK cells, memory T cells
IL-10, TGF β	Control of Inflammation

Components of Innate Immunity

Adapted from: Abbas (Saunders)

Second line

B- Soluble factors

1- Acute phase protein (Plasma protein, CRP=C reactive protein, Fibrin.)

2- Complement (proteins in serum, body fluids)

2- Interferons (Proteins against viral infections)

3- Properdin (Complement activation)

4- Beta lysine (Antibacterial protein from Platelets)

5- Lactoferrrin,Transferrin (Iron binding protein)

6- Lactoperoxidase (Saliva & Milk)

7- Lysozyme (Hydrolyze cell wall)