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Module: Infection & Immunity
Semester: 5
Session: 3
Lecture: 2
Lecture Duration: 1h.

Lecture Title:

Innate Immunity

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This Lecture was loaded in blackboard and you can find the material in: ***Jawetz Melnick & Adelbergs Medical Microbiology, 28e. 2019,***

For more detailed instructions, any question, or you have a case you need help in, please post to the group of session

Learning Outcomes

- **Describe the important barriers to infection (LO 3.7)**

- **Describe the components of the Innate Immune system and their role in preventing infection and in the inflammatory response (LO 3.8)**

Some key definitions (LO 3.7)

- **Immunology** is an emerging branch of medical science that deals with the studies of immune system like the organs, cells, structure, function, response against antigens, and disorders.

- **Immune system** is a collection of cells, organs, and chemicals, processes and mechanisms that contribute to immune defenses against infectious and non-infectious conditions (self vs non-self).

- **Immunity** (Latin immunis refers to the resistance) host defensive mechanism against any foreign body.

- **Infectious disease.**
  - When the pathogen succeeds in evading and/or overwhelming the host's immune defenses

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Role of the immune system

(LO 3.7)

Pathogens

Immune Response

Protection

- **Pathogen recognition** = *Cell surface and soluble receptor*
- **Contain/eliminate the infection** = *killing and clearance mechanism*
- **Regulating itself** = *Minimum damage to the host (resolution)*
- **Remembering Pathogen** = *Preventing the disease from recurring*

Immune Responses(IR) (LO 3.7)

❖Innate immunity

Immediate Protection

- Fast (within seconds)
- Lack of specificity
- No memory
- No change in intensity

❖Acquired immunity

Long Lasting Protection

- Slow (days)
- Specificity
- Immunologic memory
- Change in intensity

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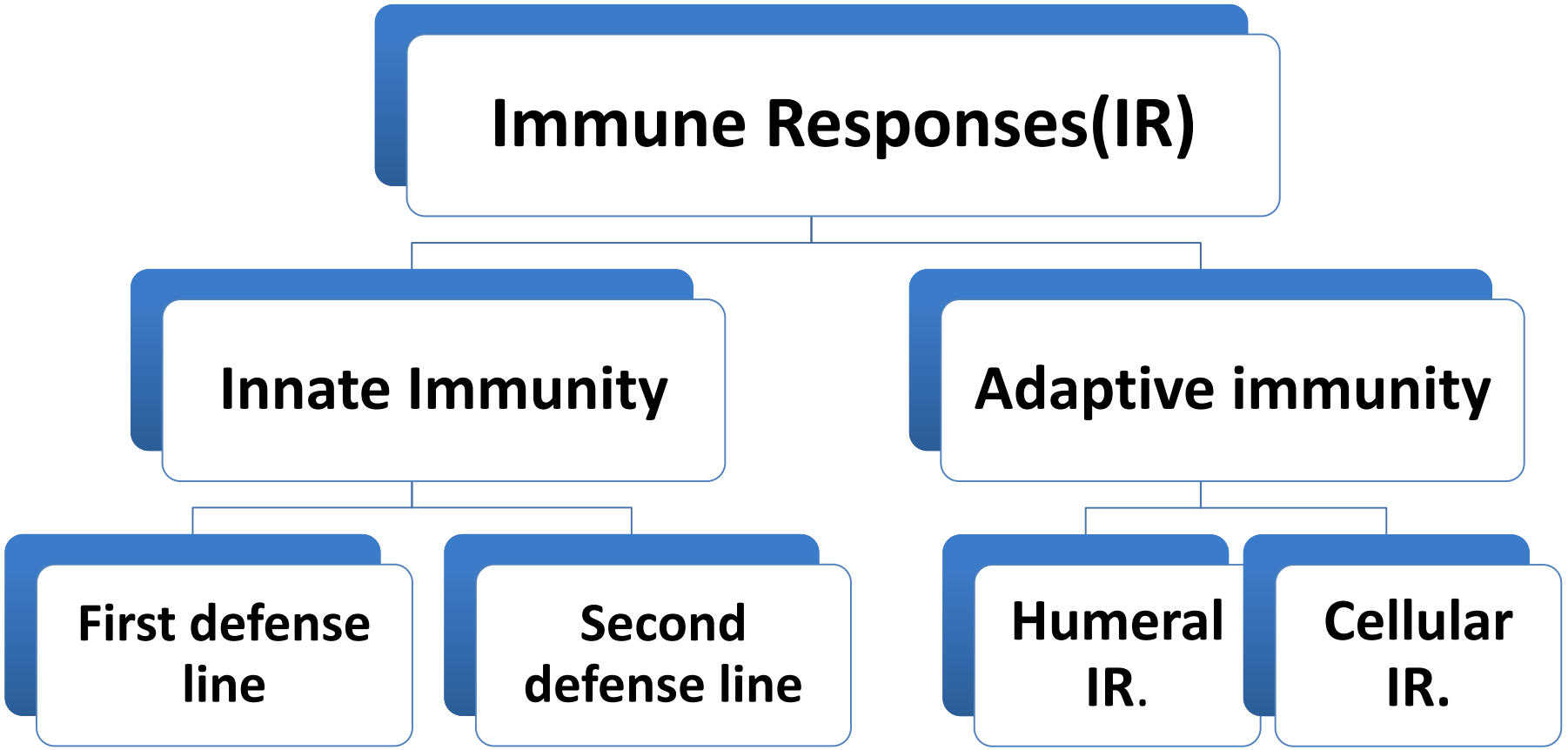
(LO 3.7)


Immune Responses(IR)
Innate Immunity
Adaptive immunity
First defense line
Second defense line
Humeral IR.
Cellular IR.

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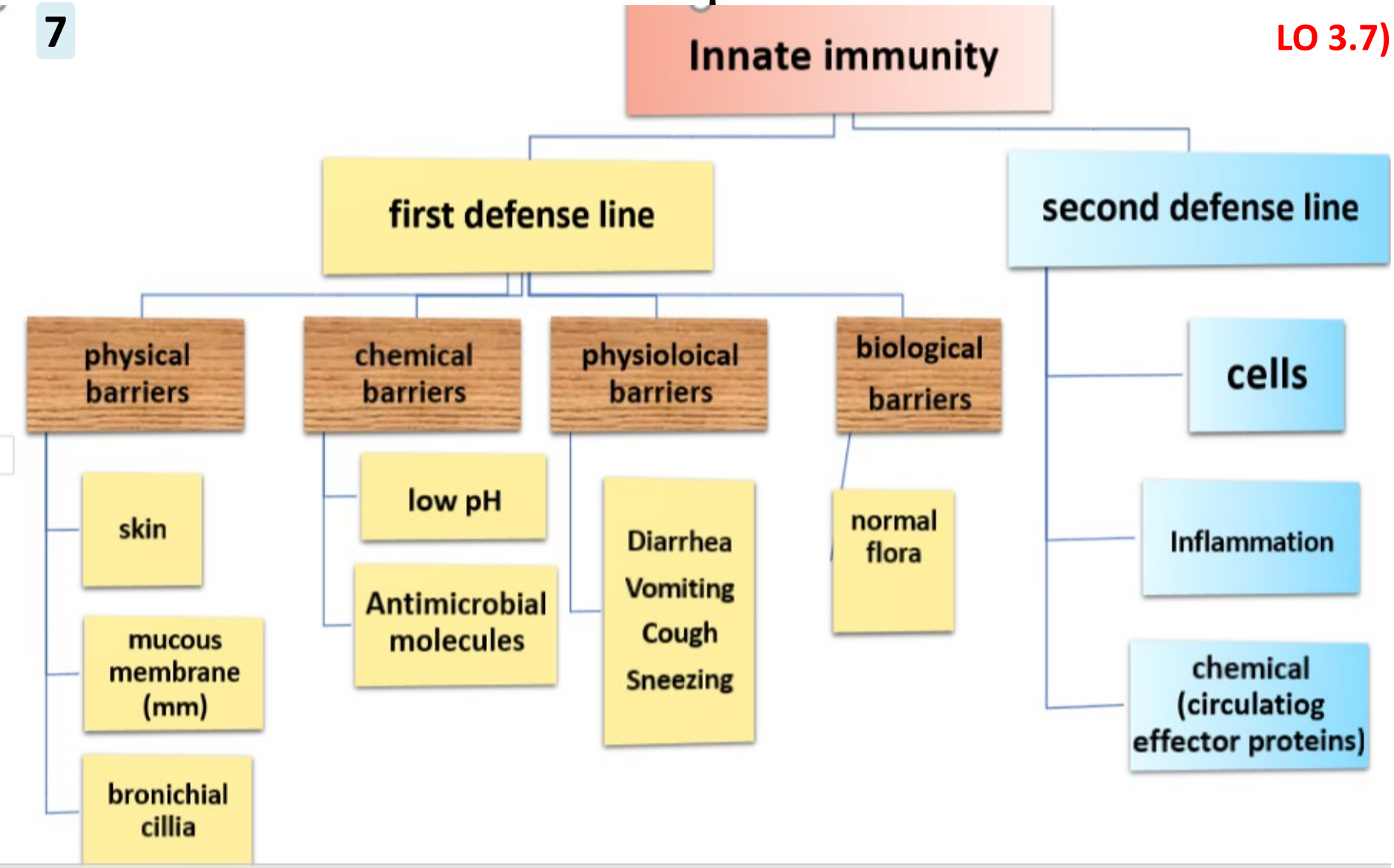
LO 3.7)


Innate immunity
first defense line
second defense line
physical barriers
chemical barriers
physioloical barriers
biological barriers
cells
skin
mucous membrane (mm)
bronichial cillia
low pH
Antimicrobial molecules
Diarrhea
Vomiting
Cough
Sneezing
normal flora
Inflammation
chemical (circulatiog effector proteins)

The immune response

(LO 3.7)

- Pathogens

Innate immunity

Adaptive immunity

Protection

First lines of defense

- Physical barriers
- Physiological barriers
- Chemical barriers

[redacted]

Factors that prevent entry and limit growth of pathogens

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The Innate Barriers

(LO 3.7)

- Pathogens

Innate immunity

Adaptive immunity

Protection

Physical barriers

- Skin (surface area 1-2 m^2)

- Mucous membrane
  - ✓ Mouth
  - ✓ Respiratory tract
  - ✓ GI tract
  - ✓ Urinary tract

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The Innate Barriers

(LO 3.7)

- Pathogens

Innate immunity

Adaptive immunity

Protection

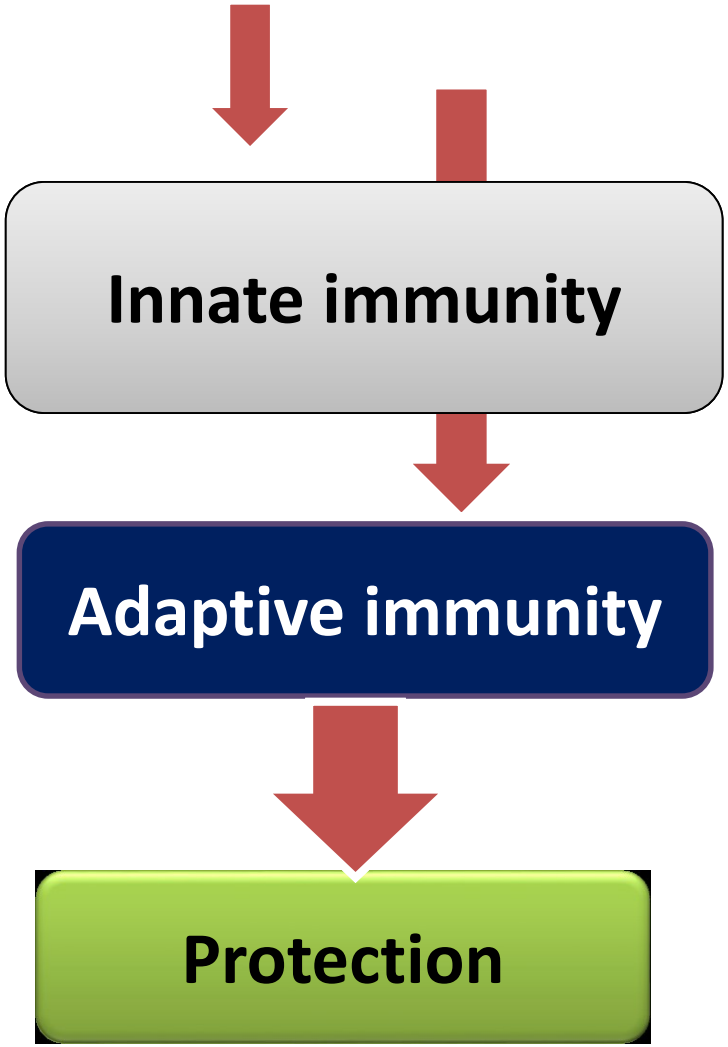
Physiological barriers

- Diarrhea
  - Food poisoning
- Vomiting
  - Food poisoning ،
  - Hepatitis
  - Meningitis
- Cough
  - Pneumonia
- Sneezing
  - Sinusitis

The Innate Barriers

(LO 3.7)

- Pathogens



Chemical barriers

- Low PH
  - Skin 5.5
  - Stomach 1-3
  - Vagina 4.4
- [redacted]
  - IgA* (tear, saliva, mucous membrane)
  - Lysozyme (sebum, perspiration, urine)
  - mucous (mucous membrane)
  - β-defensins (epithelium)
  - Gastric acid + pepsin

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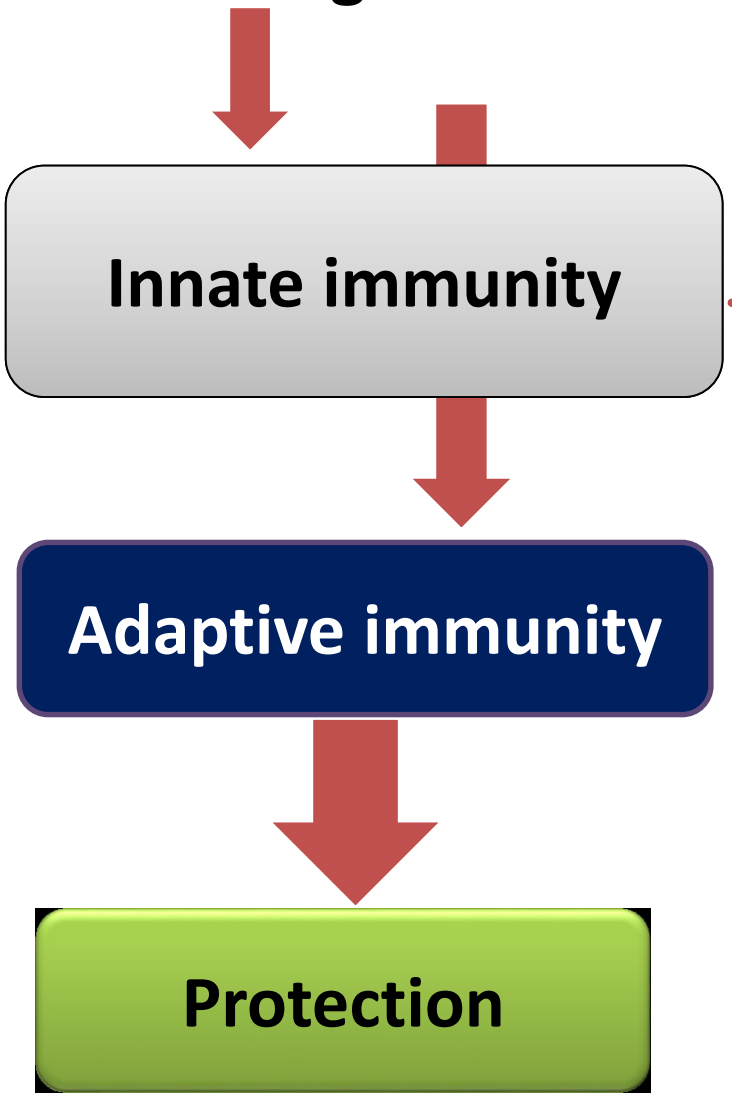
The Innate Barriers

(LO 3.7)

- Pathogens



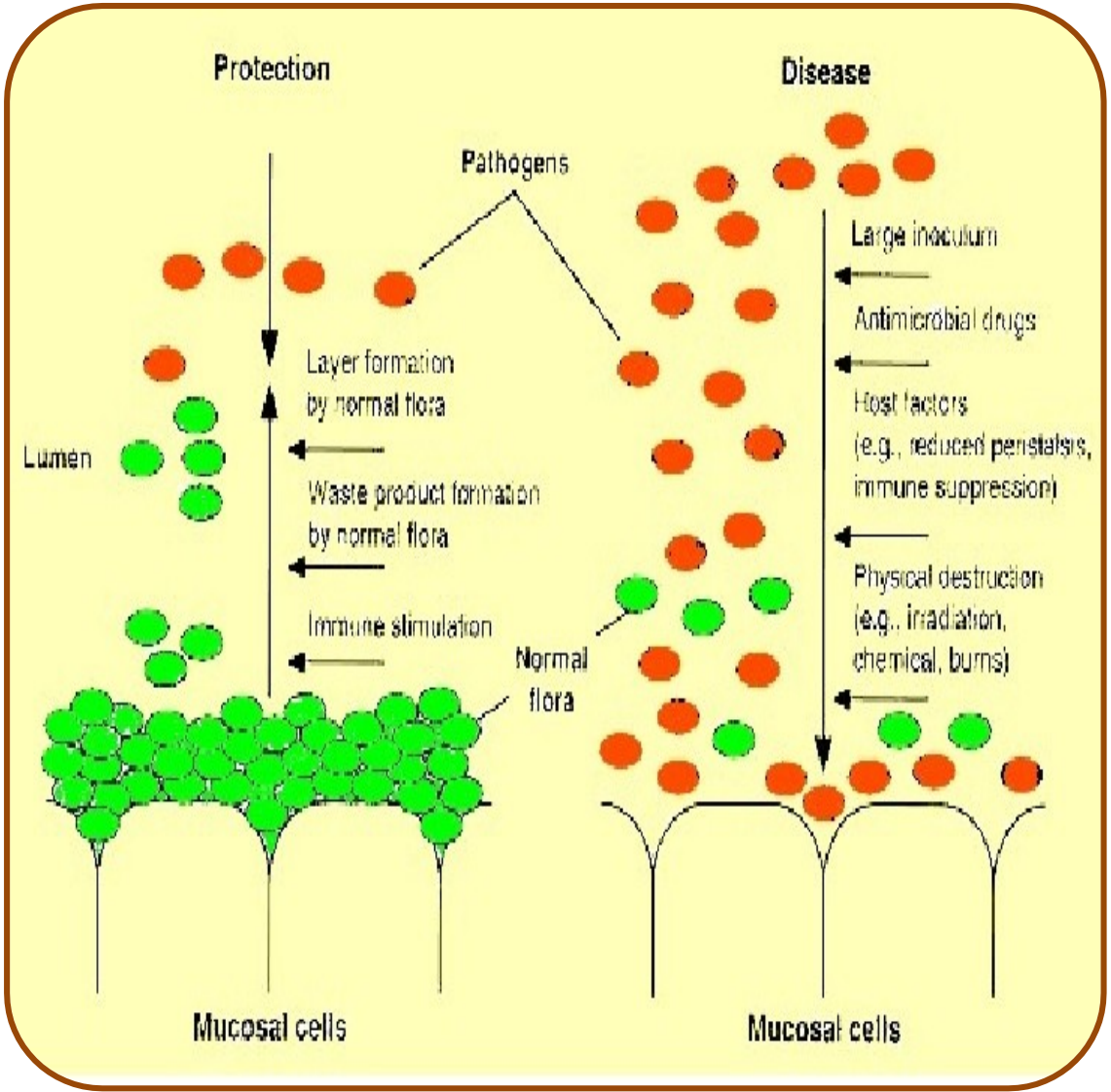
Biological barriers

- Normal flora -NF
  - Non pathogenic molecule
  - Strategic locations
    - Nasopharynx
    - Mouth
    - Throat
    - Skin
    - GI tract
    - Vagina (*lactobacillus* spp)
  - Absent in internal organ/ tissues

Benefits of the normal flora

(LO 3.8)

- Compete with pathogen for attachment site and resources
- Produced antimicrobial chemicals
- Synthesize vitamins (K, B12, other B vitamins)



(LO 3.8)

Examples of normal flora that inhabit…

- **The skin**
  - ***Staphylococcus aureus*** **(week 1, case 1)**
  - ***Staphylococcus epidermidis***
  - ***Streptococcus pyogenes***
  - ***Candida albicans***
  - ***Clostridium perfringens***

- **The nasopharynx**
  - ***Streptococcus pneumoniae*** **(week 3, case 2)**
  - ***Neisseria meningitides*** **(week 3, lecture case)**
  - ***Haemophilus*** **species**

But could become pathogenic !!!!!

Clinical problems start when … (LO 3.8)

1- Normal flora is displaced from the normal location to sterile location

- **Breaching the skin integrity**
  - Skin loss (burn)
  - Surgery
  - Injection drug user
  - IV line

- **Fecal – oral rout**
  - Foodborn infection

- **Fecal-perineal– uretheral rout**
  - Urinary tract infection (women)

Clinical problems start when … (LO 3.8)

2- Normal flora is displaced from its normal location

- **Poor dental hygiene/dental work**

➢ ***Common cause of harmless bacteremia***

- **Dental extraction**
- **Gingivitis**
- **Brushing/Flossing**

wikipedia

=> Serious infections in high-risk patients

- ***Asplenic (and hyposplenic) patients***
- ***Patients with damaged or prosthetic valves***
- ***Patients with previous infective endocarditis***

-> Antibiotic prophylaxis

Clinical problems start when … (LO 3.8)

3- Normal flora overgrows and becomes pathogenic when host becomes immuno-compromised

- Diabetes (session 3, case 2)
- AIDS
- Malignant diseases
- Chemotherapy (neutrophils)

4- When normal flora is depleted by antibiotics

- Intestine : severe colitis (*Clostridium difficile*)
- Vagina : thrush (*Candida albicans*)

First barriers at the portal of entry (LO 3.8)

1- skin

- Epidermis , Sebaceous gland (fatty acids) and sweat gland (lactic acid)

2- conjunctiva:-Blinking reflex and tear (lysozyme)

3- Respiratory system: Hairs in nose, Mucous membrane, mucous, cilia, coughing and sneezing

4- Ear: Wax

5-Digestive System: Saliva, low pH of the stomach, digestive enzymes, normal flora, diarrhea and vomiting.

6- Genitourinary tract: Flushing of urine, normal flora in vagina (lactobacilli)

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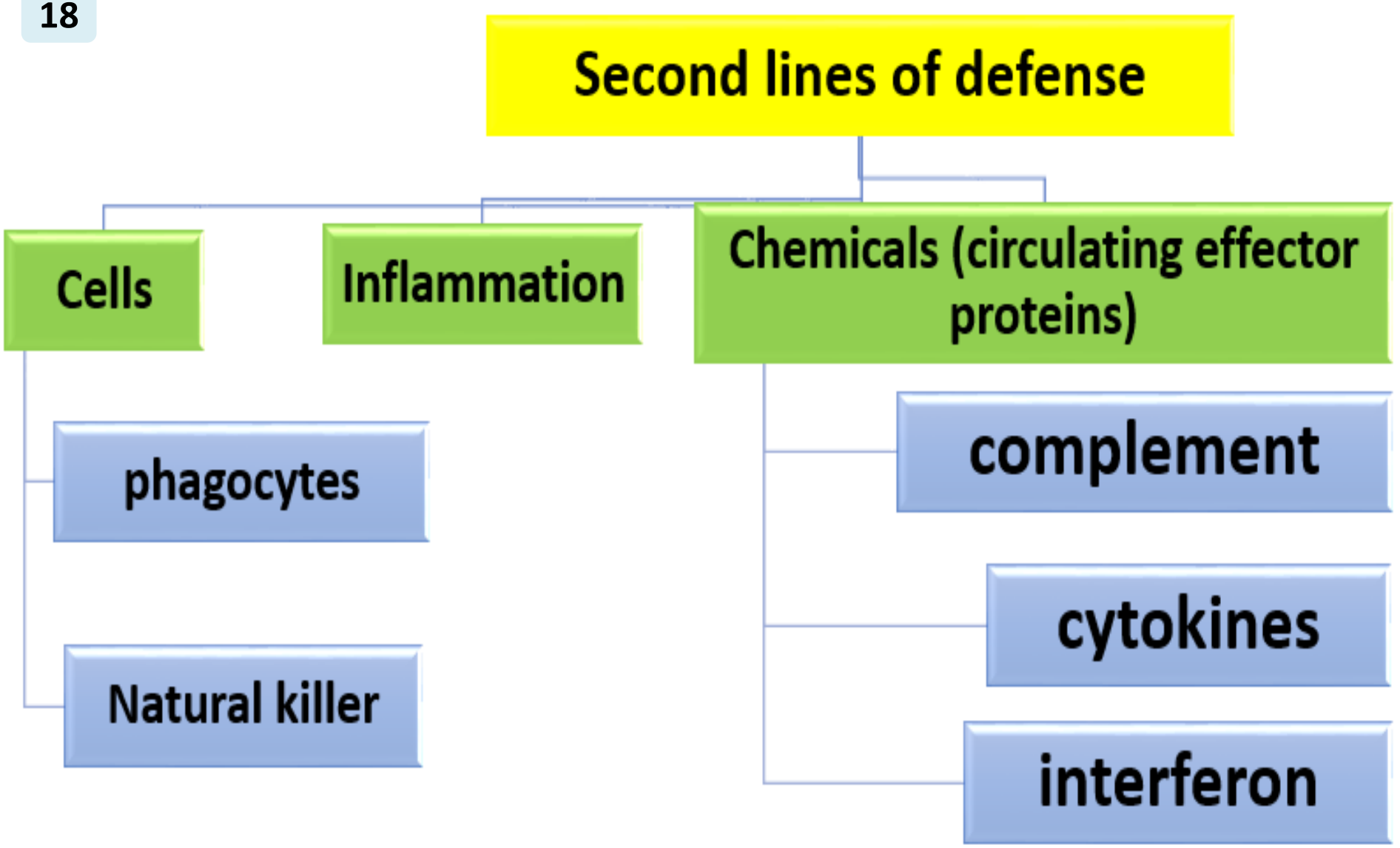
Second lines of defense
Cells
Inflammation
Chemicals (circulating effector proteins)
phagocytes
Natural killer
complement
cytokines
interferon

The Immune Response

(LO 3.8)

- Pathogens

Innate immunity

Adaptive immunity

Protection

Innate barriers

Second lines of defense

- Cells (Phagocytes & NK)
- Chemicals (circulating effector proteins).

[redacted]

Factors that contain and clear the infection

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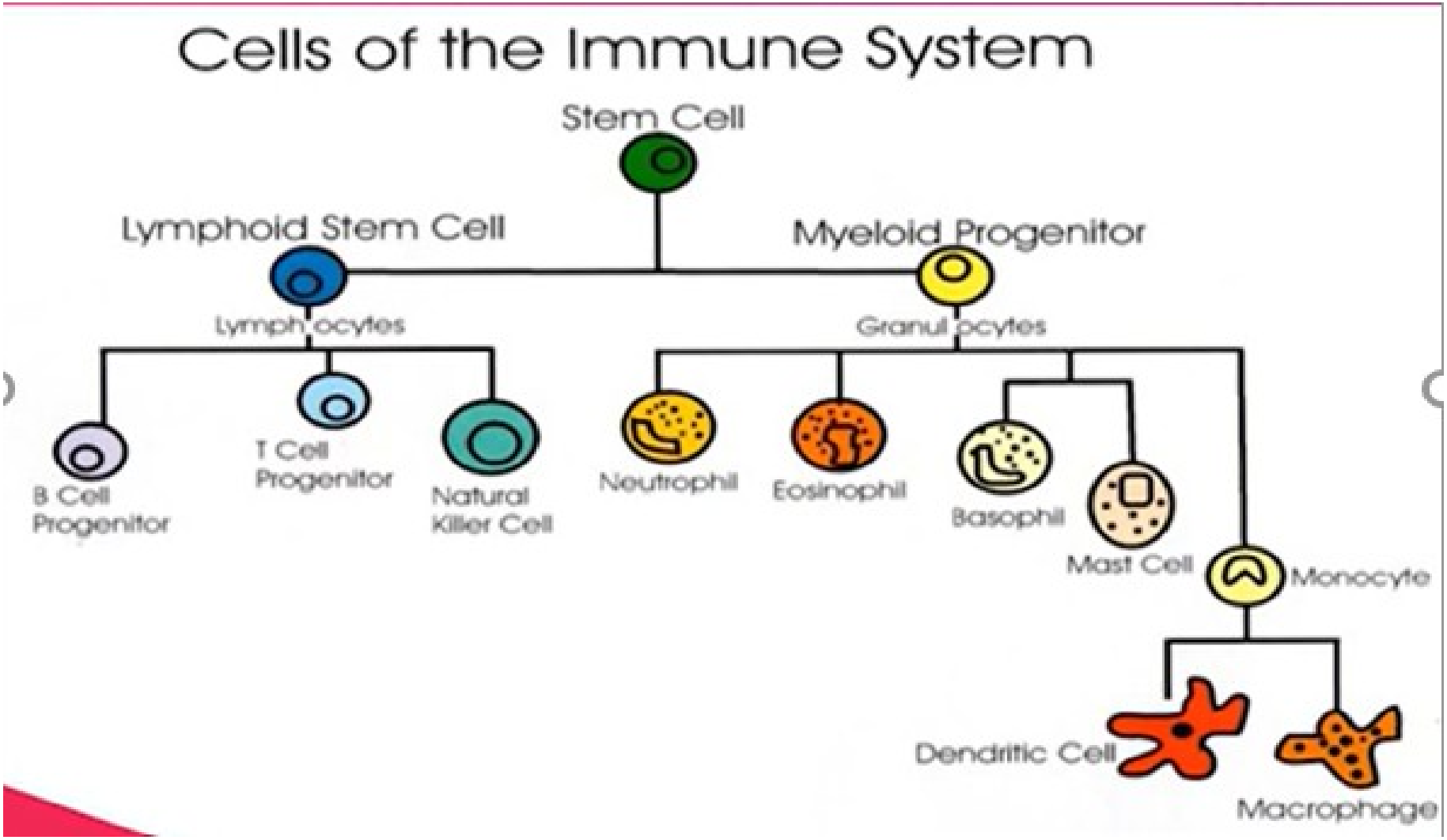
(LO 3.8)

Cells of innate immunity



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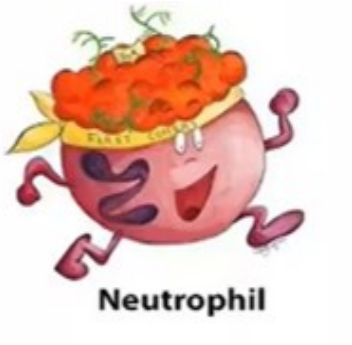
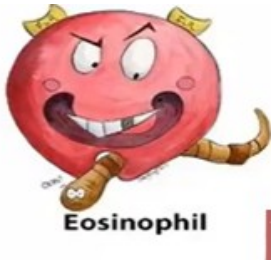
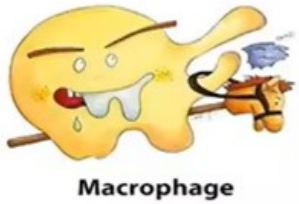
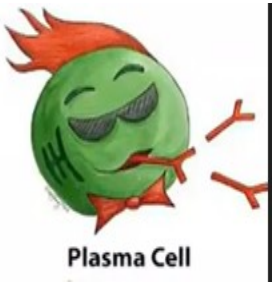
Cells of innate immunity

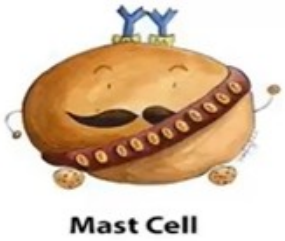
(LO 3.8)

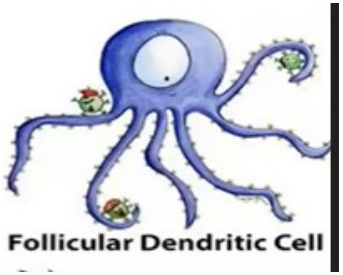






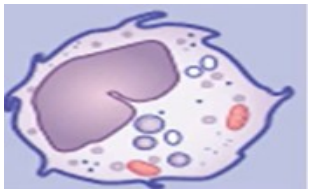
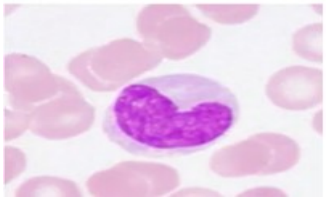
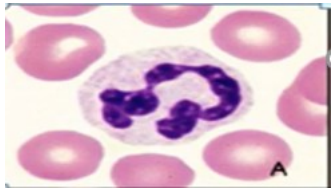






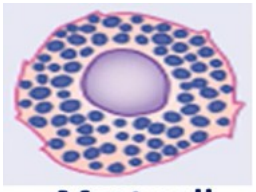
Main phagocytes

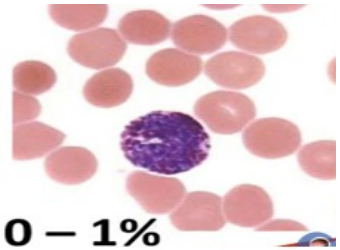
(LO 3.8)

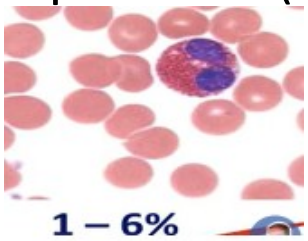
Cell type	location and function
Macrophages 	• Present in all organ • Ingest and destroy microbes (phagocytosis) • Present microbial antigen to T cells (adaptive immunity) • Produce cytokine/ chemokines
Monocytes 	• Present in the blood (5- 7%) • Recruited at infection site and differentiate into macrophages
Neutrophils 	• Present in the blood (60% of blood leukocytes) • Increased during infection • Recruited by chemokine to the site of infection • Ingest and destroy pyogenic bacteria: ***staph. aureus*** and ***Strep. Pyogenes.***

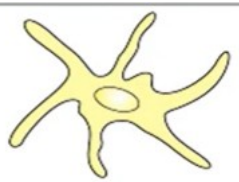
Other key cells of innate immunity (LO 3.8)

Cell type	function
Basophile / mast cells	• Early actors of inflammation (vasomodulation) • Important in allergic responses
Eosinophil cells	• Defense against multicellular parasites (worms)
Dendritic cells	• Present microbial antigens to T cells (APC)(acquired immunity)

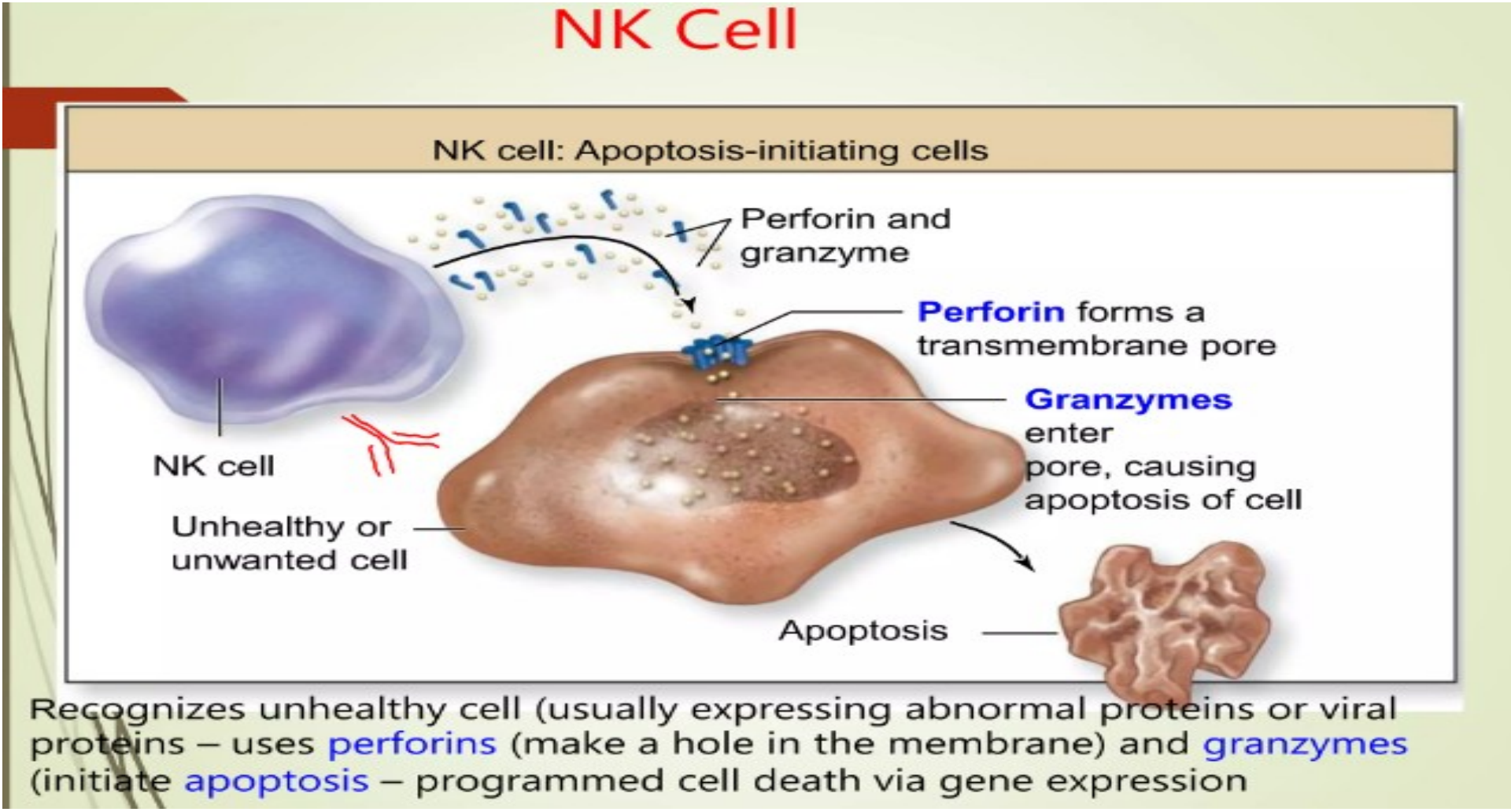

Mast cell







Natural Killer cells: Kill all abnormal host cells (virus infected or malignant)



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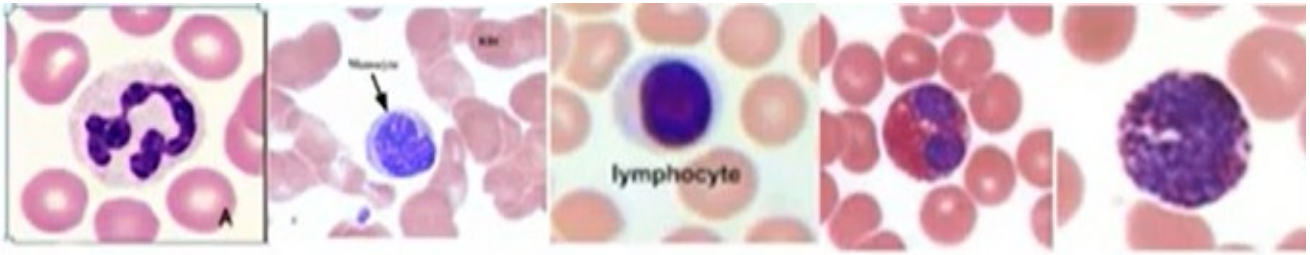
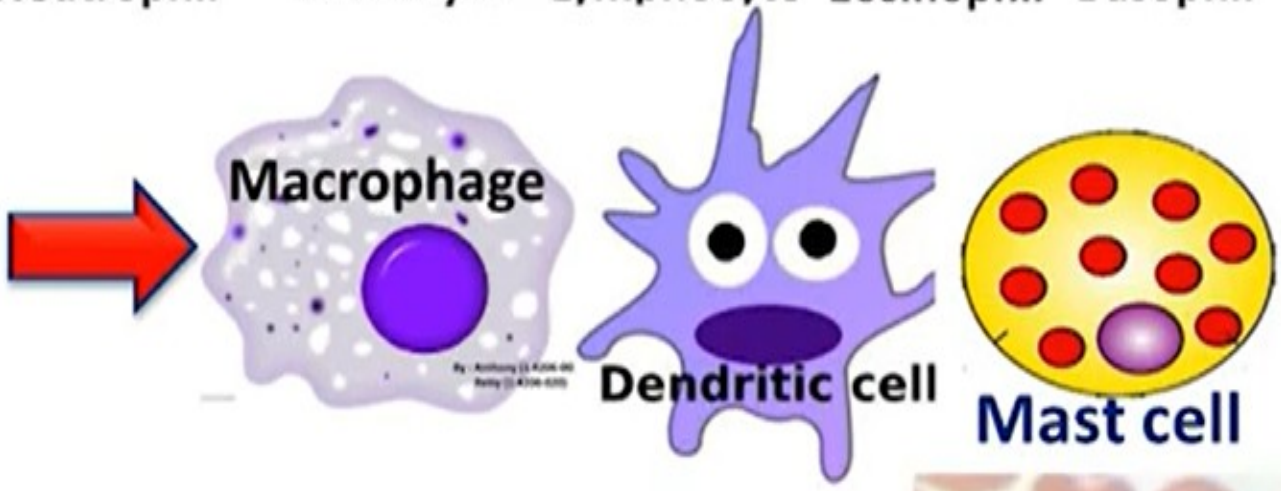
- Circulating in Blood

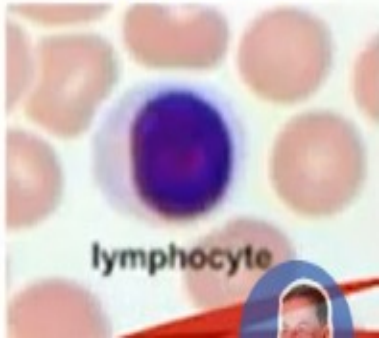


Neutrophil Monocyte Lymphocyte Eosinophil Basophil

- Residing in tissues



- Present in tissues & Blood



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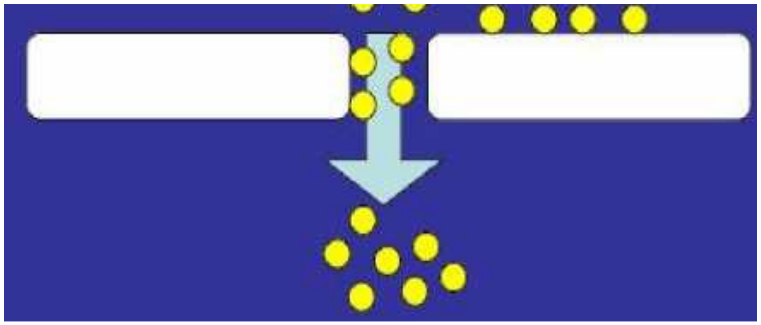
Microbes

Skin

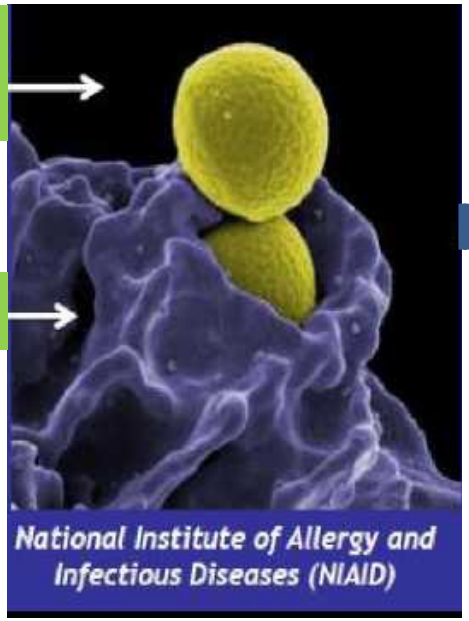


Innate factors

(LO 3.8)

Staphylococcus aureus

Phagocyte

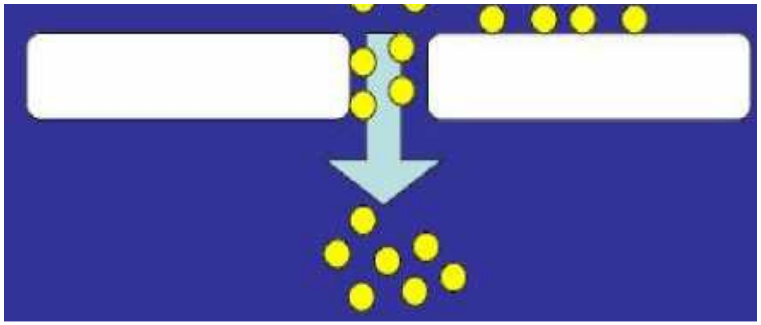


Phagocyte –Microbe interaction

- Recognition process
- Killing process of infectious microbes

Microbes

Skin

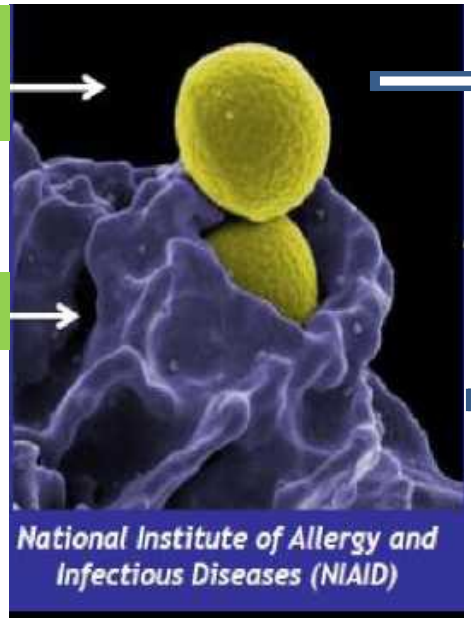


Innate factors

(LO 3.8)

Staphylococcus aureus

Phagocyte



Pathogen recognition

– Microbial structure

- pathogen associated molecular pattern (PAMPs): Carbohydrate, Lipids, Protein, Nucleic acids

- Phagocytes:

- Pathogen recognition receptor (PRRs). Toll like receptors

Examples of microbial PAMPS and PRRs (LO 3.8)

	Cognate PRRs
➢ Gram negative bacteria	
Lipopolysaccharide (LPS)	TLR4
Lipoproteins and lipopeptides	TLR2
Porins	
➢ Gram positive bacteria	
Peptidoglycan	TLR2
Lipoteichoic acids	TLR4
➢ All mycobacteria	
Lipoarabinomannan	TLR2
Mannose-rich glycans	
➢ Bacterial flagella	
Flagellin	TLR5

(LO 3.8)

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Which microbial components are recognized by TLRs ?

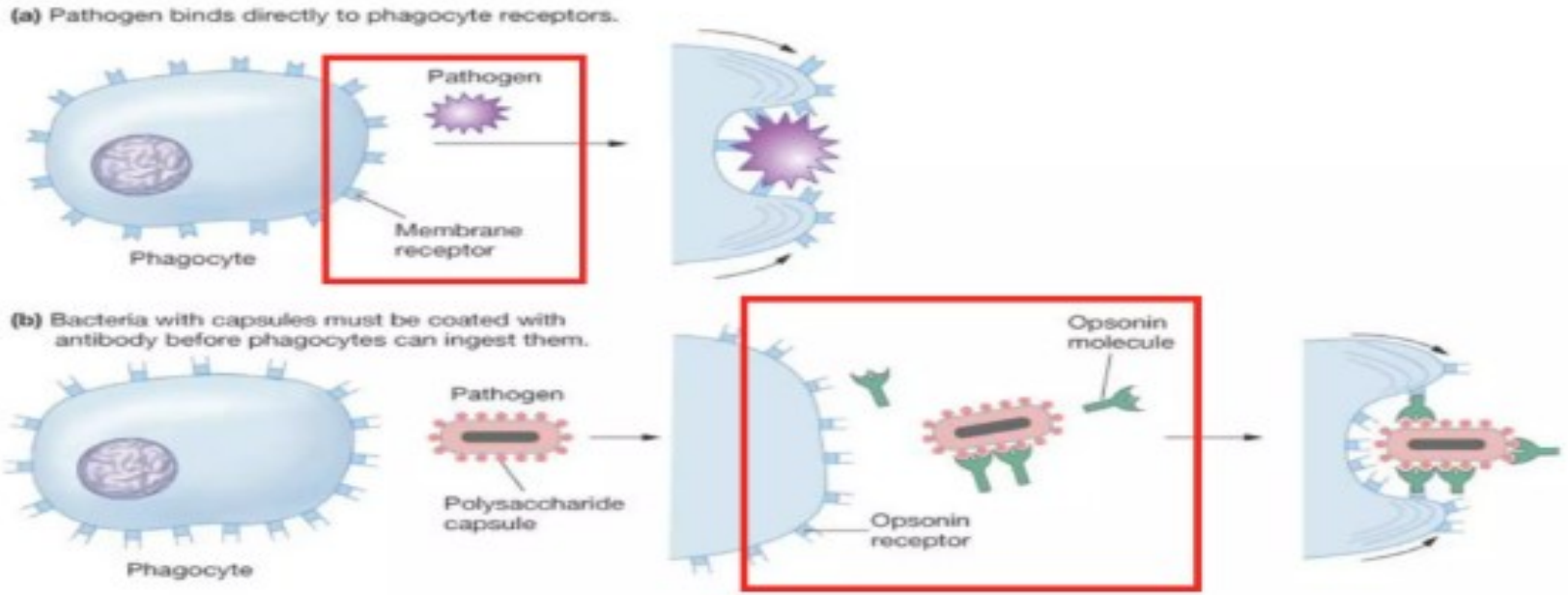
- There are 13 types of TLRs. Important ones are:
- TLR- 2 bind to bacterial peptidoglycan.
- TLR- 3 binds to ds RNA of viruses.
- TLR- 4 binds to LPS of G-ve bacteria.
- TLR- 5 binds to flagella of bacteria
- TLR- 7 & 8 binds to ssRNA of viruses.
- bacterial DNA.
- TLR-2, TLR-3 & TLR- 7 binds to coronavirus

(LO 3.8)

Pathogen recognition

Opsonization of microbes:

- Coating protein called **opsonins** that bind to the microbial surface leading to enhance attachment to the phagocytes and clearance of microbes



Examples of opsonins

(LO 3.8)

Complement proteins

- C3b
- C4b

Antibodies

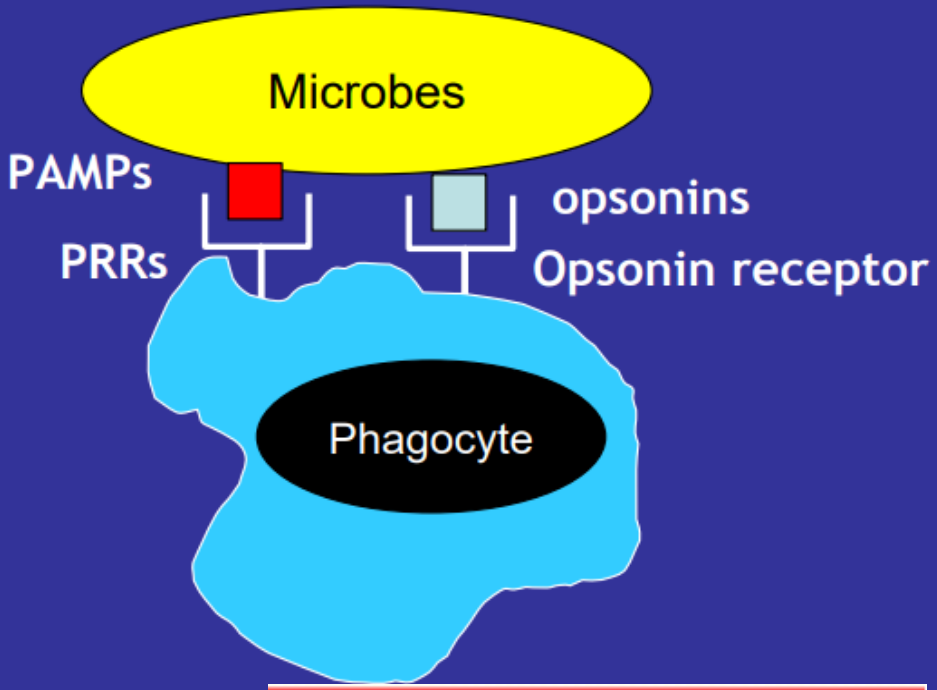
- IgG
- IgM

Acute phase proteins

- C-reactive protein (CRP)
- Mannose-binding lectin (MBL)

→ *Essential in clearing encapsulated bacteria:*

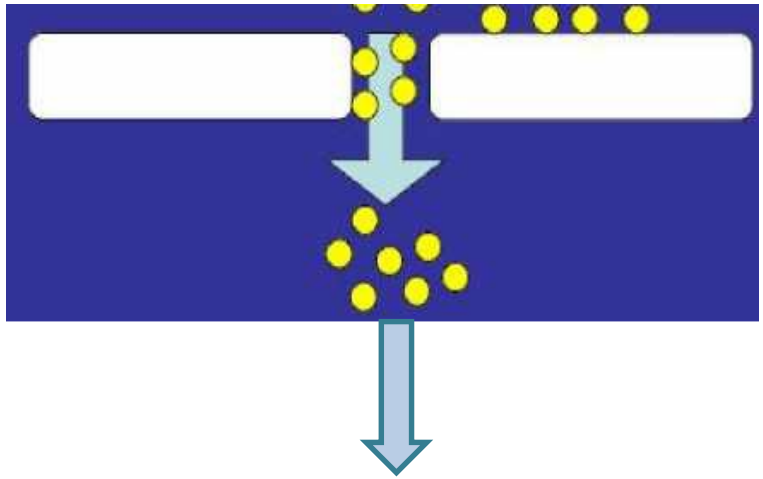
- *Neisseria meningitidis,*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae. b*



Major opsonin 1.) Lectin
2.) C3b
3.) IgG

Microbes

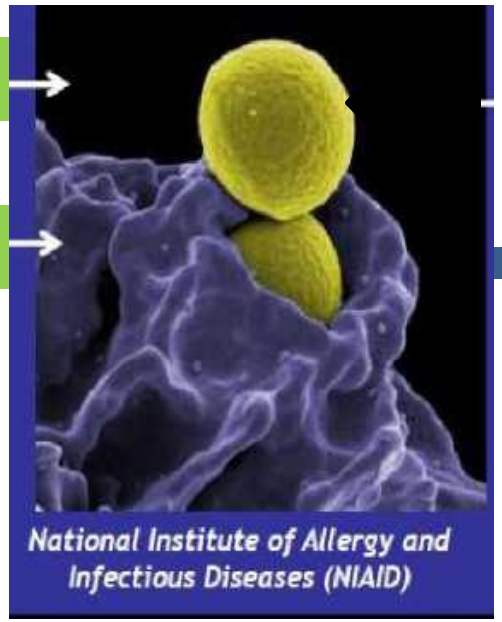
Skin



(LO 3.8)

MRSA

Neutrophil



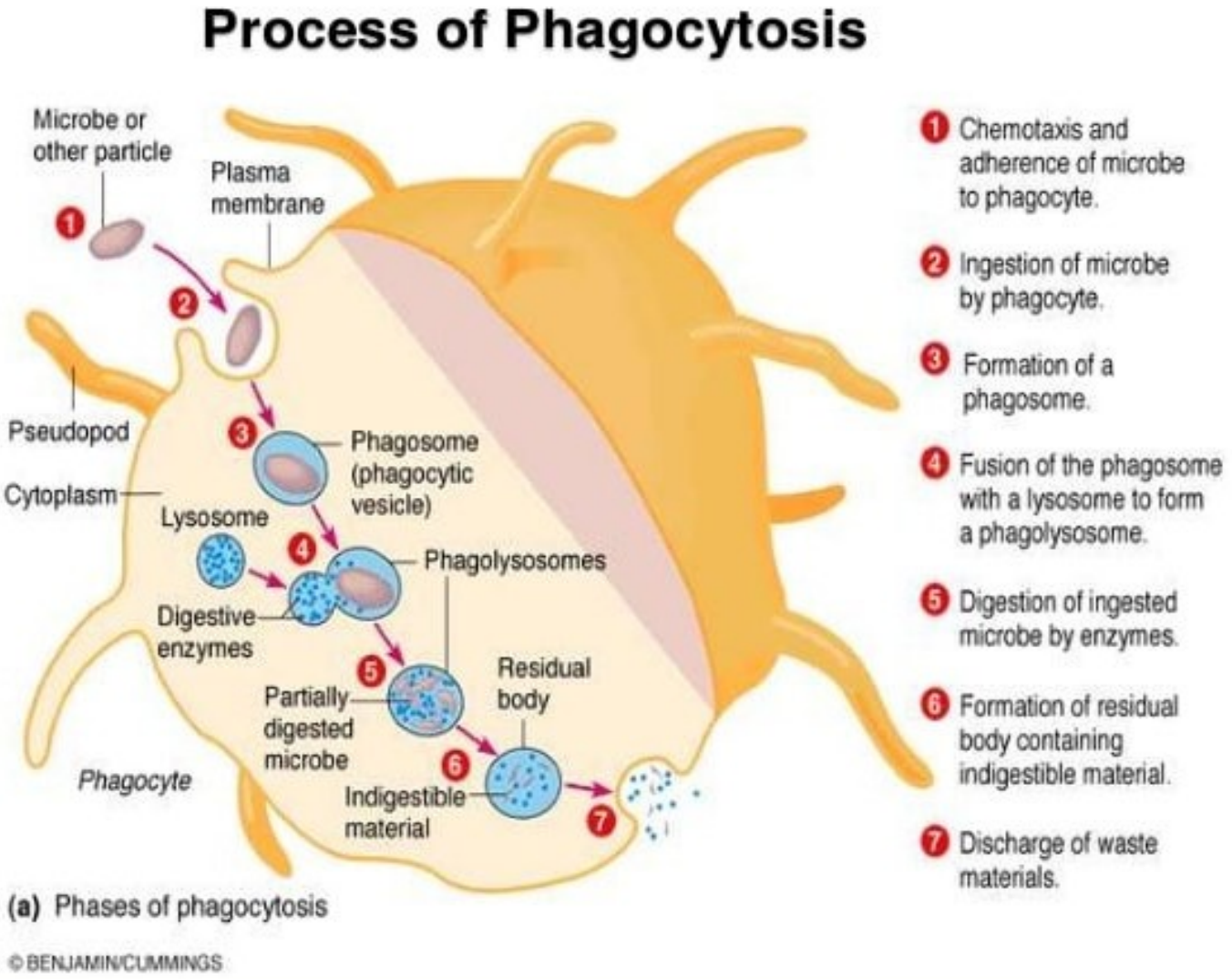
Phagocytes

- Recognition
  - PAMAS
  - Opsonins
- Engulfment
- Degradation of infectious microbes

Phagocytosis: killing of pathogens (LO 3.8)

Stages of phagocytosis

- ✓ Chemotaxis
- ✓ Adherence
- ✓ Phagosome formation
- ✓ Digestion



Phagocyte intracellular killing mechanisms

(LO 3.8)

Oxygen dependent (respiratory burst)

- Hydrogen peroxide
- Hydroxyl radical
- Nitric oxide
- Singlet oxygen
- hypochlorite

Oxygen independent

- Lysozyme
- Acid hydrolases
- Lactoferrin
- Cationic proteins
- Neutral proteases
- Lysosomal contents

The Immune Response

(LO 3.8)

- Pathogens

Innate immunity

Adaptive immunity

Protection

Innate barriers

Second lines of defense

- ✓ Cells (Phagocytes & NK)
- ✓ Chemicals
  - Complement system
  - Cytokine
  - Interferon

[redacted]

Factors that contain and clear the infection

The complement system

(LO 3.8)

Complement pathways

- 20 serum proteins
- Most important C1-C9

❖ 2 activating pathways

- **Alternative pathway**
  Initiated by cell surface microbial constituents (LPS on *E. coli)*
- **MBL (mannose binding lectin) pathway**
  Initiated when MBL binds to mannose containing residues of proteins found on
  Salmonella spp.
  Candida albicans

Antimicrobial actions

C3a and C5a: Recruitment of phagocytes

C3b-C4b: Opsonization of pathogens

C5-C9: Killing of pathogens membrane Attack complex

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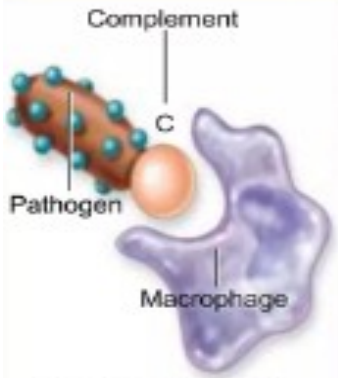
(LO 3.8)

Complement pathways

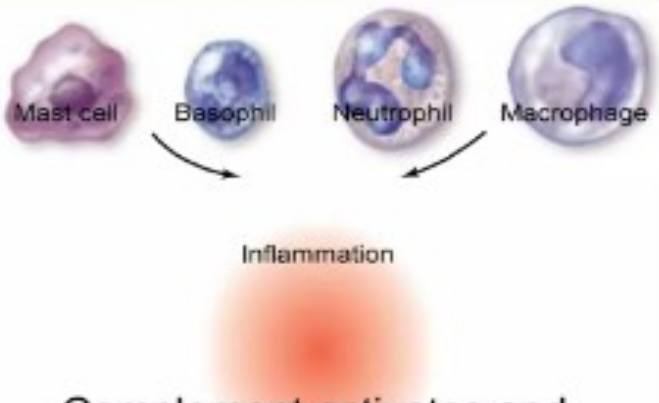
Complement have a number of functions (below) to defend against pathogens

Opsonization



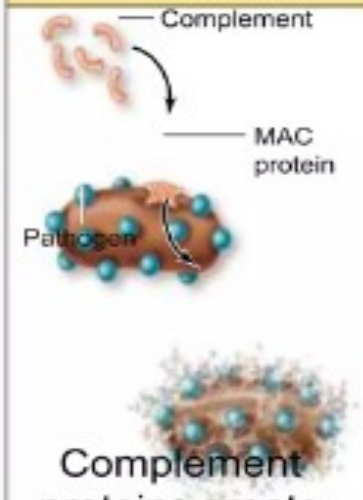
Complement (C) binds to pathogen; acts as opsonin

Inflammation



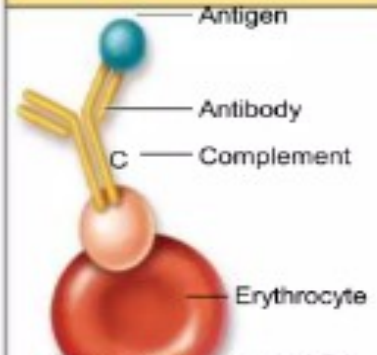
Complement activates and attracts various cells of innate immunity.

Cytolysis



Complement proteins create MAC to lyse cell.

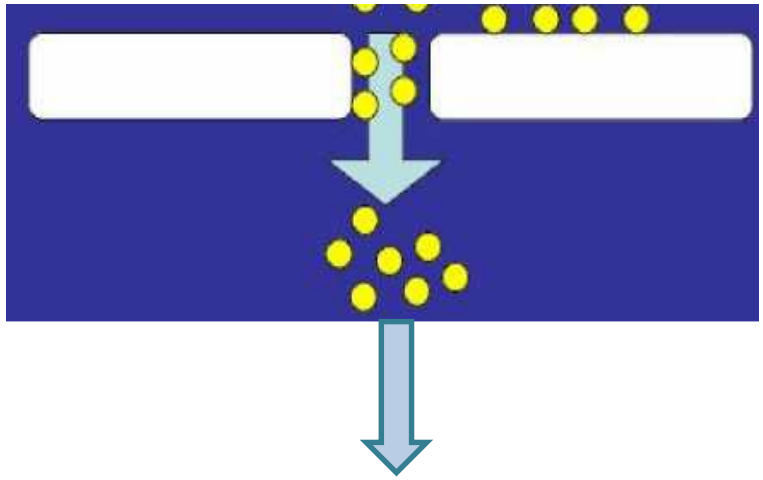
Elimination of immune complexes



Complement (C) cross-links immune (antigen-antibody) complexes to erythrocyte and transports to liver and spleen.

Microbes

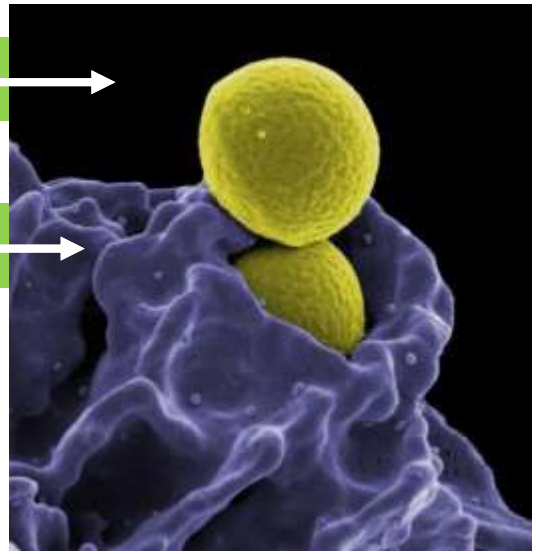
Skin



(LO 3.8)

MRSA

Neutrophil



National Institute of Allergy and Infectious Diseases (NIAID)

Phagocytes

- **Phagocytosis**
- **Cytokines/Chemokines**
  - **Chemoattraction**
  - **Phagocyte activation**
  - **Inflammation**

Acute phase proteins

(LO 3.8)

- C-reactive protein
- Fibrinogen

C-reactive protein (CRP)

↓

Attached to bacteria

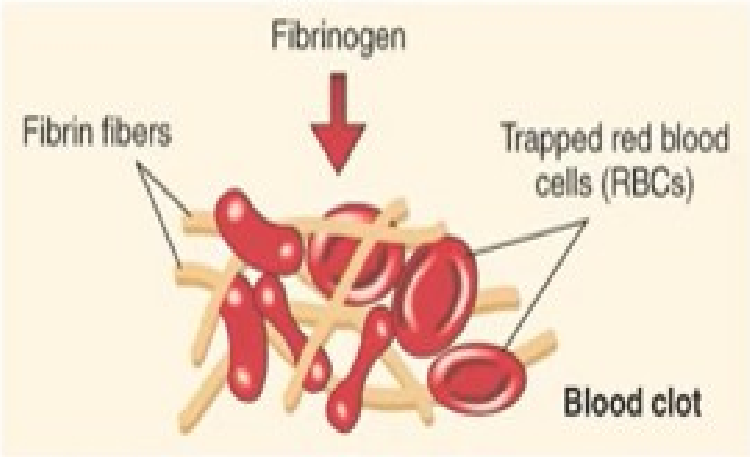
↓

Activation complement → Lysis

(LO 3.8)

❑ Fibrinogen

Prevent spread of infection



Anti-microbial actions of macrophage-derived TNFα/IL-1/IL-6

(LO 3.8)

- Liver (opsonins)
  - CRP
  - MBL (-> complement activation)
- Bone marrow
  - Neutrophil mobilization
- Inflammatory actions
  - Vasodilation
  - Vascular permeability
  - Adhesion molecules -> attraction of neutrophils
- Hypothalamus
  - Increased body temperature

Clinical problems start when…

(LO 3.8)

Infection

↓

Microbial toxins (LPS)

↓

Overreaction of TLR4 receptor
Overreaction of complement

- Neutrophils
- Endothelium
- Monocytes

↓

Excessive systemic inflammatory response

↓

- Cytokine shower
- Coagulopathy
- Vasodilation
- Capillary leak

→ ↓ Tissue/organ perfusion

Sepsis and multi-organ failure

Clinical problems start with reduced phagocytosis…. (LO 3.8)

- Decrease spleen function
  - Asplenic patients
  - Hyposplenic patients
- Decrease neutrophil number (1.8 x10^9/l)
  - Cancer chemotherapy
  - Certain drugs (phenytoin)
  - Leukemia and lymphoma
- Decrease neutrophil function
  - Chronic granulomatous disease (No respiratory burst)
  - Chediak-Higashi syndrome (no phagolysosomes formation)

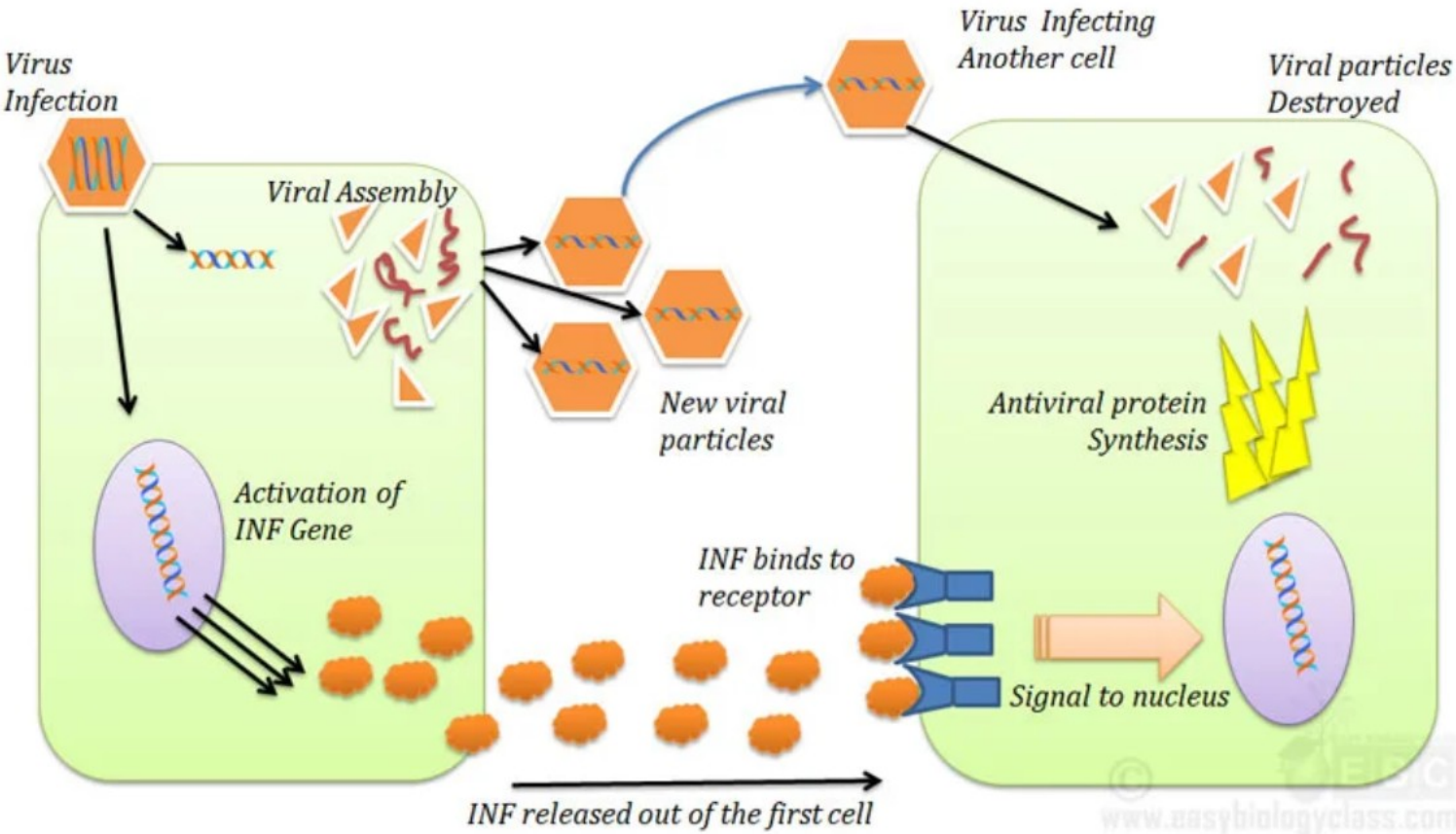
- **Interferons (IFNs)** (LO 3.8)

are a group of signaling proteins made and released by host cells in response to the presence of several viruses.

Types of Interferons

Type	Example	Produced by	Main Action
Type I	IFN-α, IFN-β	Leukocytes, fibroblasts	Antiviral defense NK activation
Type II	IFN-γ	T cells NK cells	Activate macrophages, enhance antigen
Type III	IFN-λ	Epithelial cells	Protect mucosal surfaces

(LO 3.8)


ANTIVIRAL ACTION OF INTERFERON (INF)
Virus Infection
Viral Assembly
Virus Infecting Another cell
Viral particles Destroyed
New viral particles
Antiviral protein Synthesis
Activation of INF Gene
INF binds to receptor
Signal to nucleus
INF released out of the first cell

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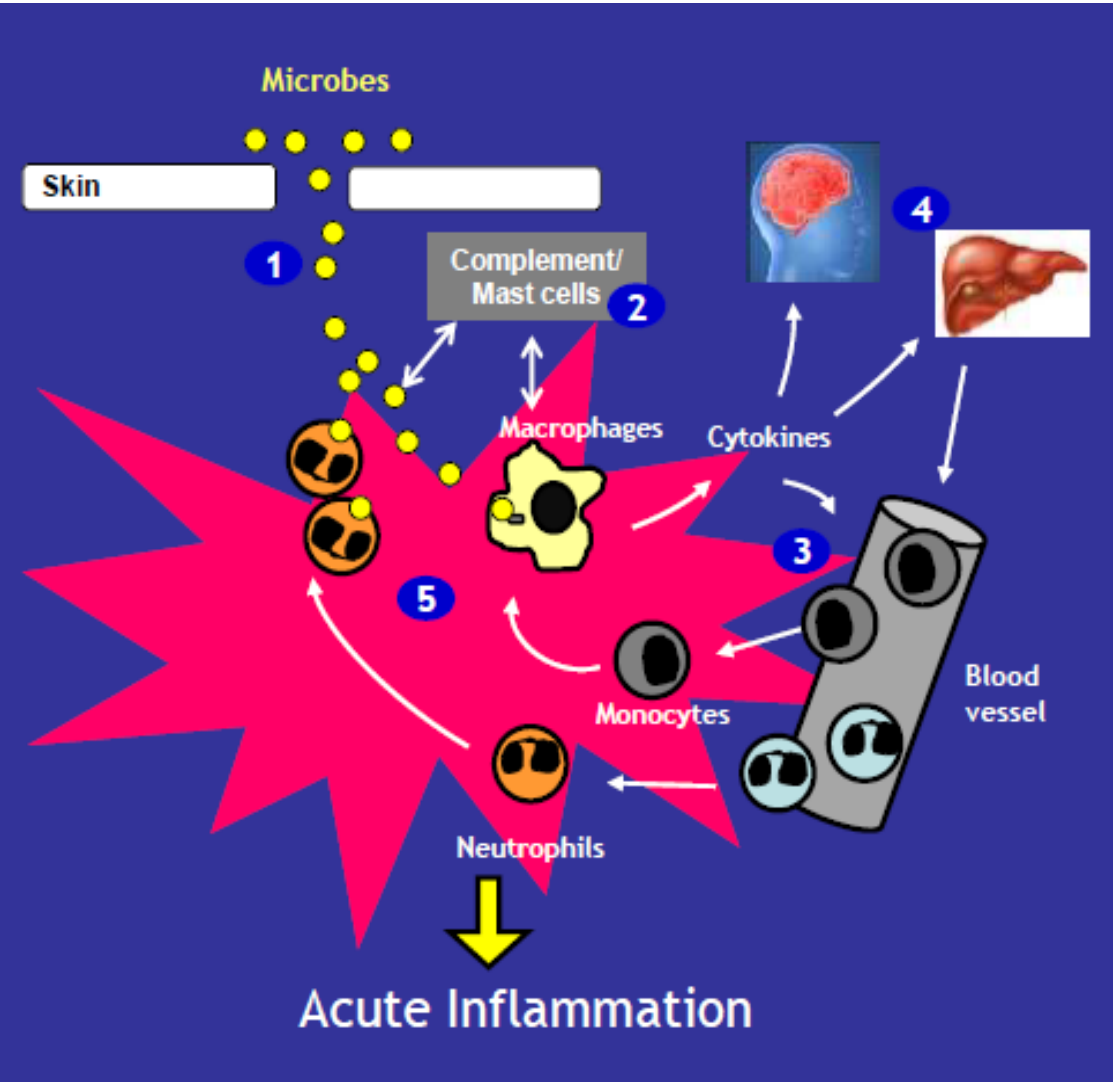
Summary of the innate immunity



1. ***Innate barrier breached***: entrance and colonization of the pathogens.
2. ***Complement, mast cells and macrophages activation (PRR)***
   Phagocytosis (opsonins)
   Cytokine/chemokine production
3. ***Vascular changes***
   Vasodilation/Vascular permeability
   Chemoattraction
   Neutrophils
   Monocytes (TNF, IL-8)
4. ***Hypothalamus***
   Fever
   Liver
   Acute phase response
5. ***Redness, heat, swelling and pain***: local inflammation

The Immune Response

- Pathogens

Innate immunity

Adaptive immunity

First lines of defense

Various barriers

Limit **entry** and **growth** of pathogens at portals of entry

Second lines of defense

Phagocyte/Chemicals

Contain and **eliminate** the infection

“ We always work together as a team ”