

INNATE IMMUNE RESPONSE

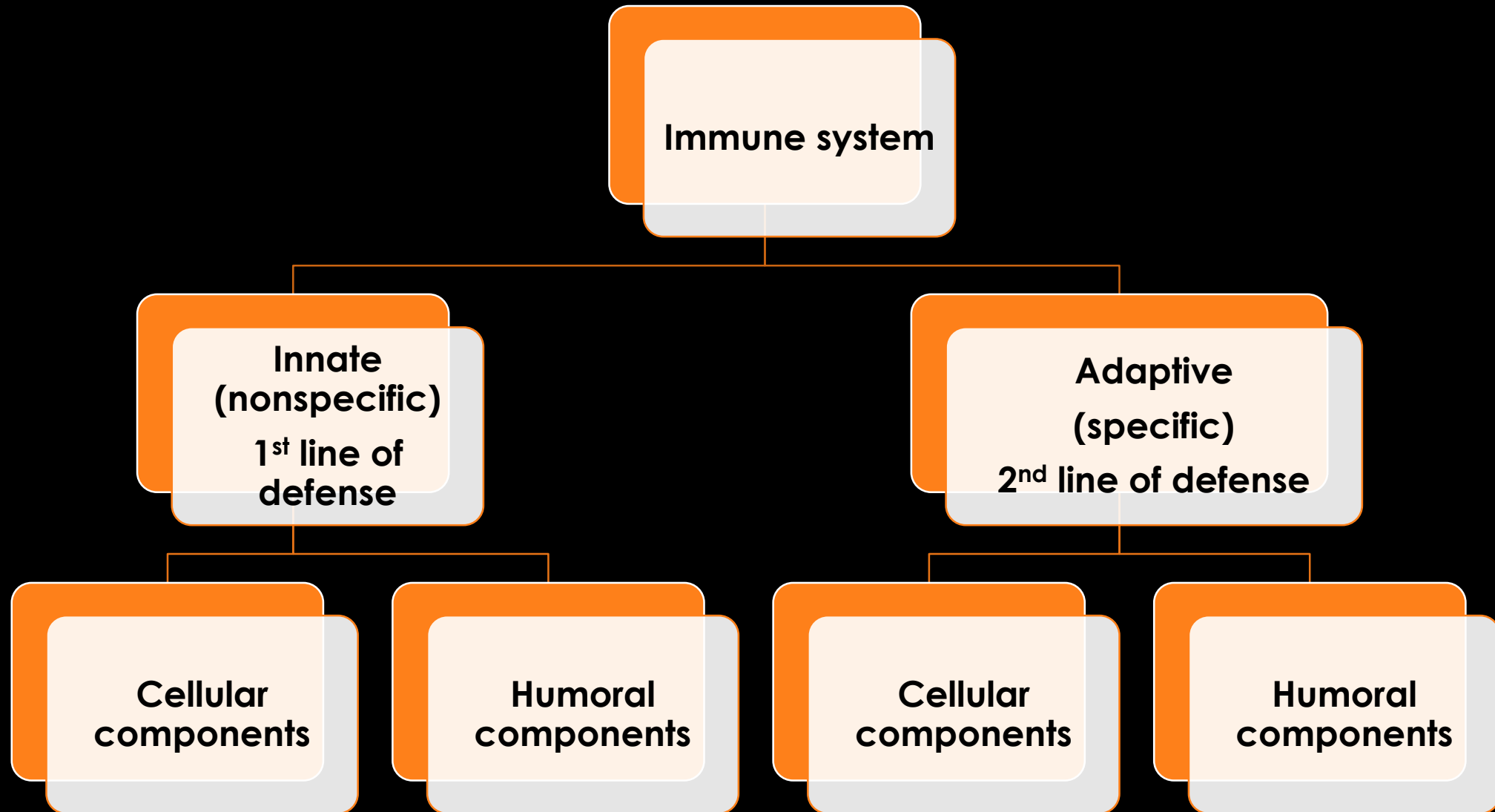
Micro 451

Presented By Dr. Nagwa Aref

TEACHING OBJECTIVES

- Understand the mechanisms of combating infection/disease
 - How does the body kill pathogens?
- To know the humoral and cellular components of the innate immune response
 - What are the key features and timing?
 - What is the mechanism of action of the components of the innate immune response?

OVERVIEW OF THE IMMUNE SYSTEM



INNATE HOST DEFENSES AGAINST INFECTION

- **Anatomical barriers**
 - Mechanical, chemical, biological
- **Humoral components**
 - Complement ,coagulation system, cytokines
 - Cellular components
 - Neutrophils, monocytes & macrophages, NK cells, eosinophils

ANATOMICAL BARRIERS- MECHANICAL

| System/Organ | Cell type | Mechanism |
|------------------|---|---|
| Skin | Squamous epithelium | Physical barrier Desquamation |
| Mucous membranes | Non-ciliated epithelium (e.g. GI tract) | Peristalsis |
| | Ciliated epithelium (e.g. respiratory tract) | Mucociliary elevator |
| | Epithelium (e.g. nasopharynx) | Flushing action of tears, saliva, mucus, urine |

ANATOMICAL BARRIERS- CHEMICAL

| System/Organ | Component | Mechanism |
|------------------|--|--|
| Skin | Sweat | Antimicrobial fatty acids |
| Mucous membranes | HCl (parietal cells), tears & saliva Defensins (respiratory & GI tract) Surfactants (lung) | Low pH Lysozyme & phospholipase A Antimicrobial Opsonin |

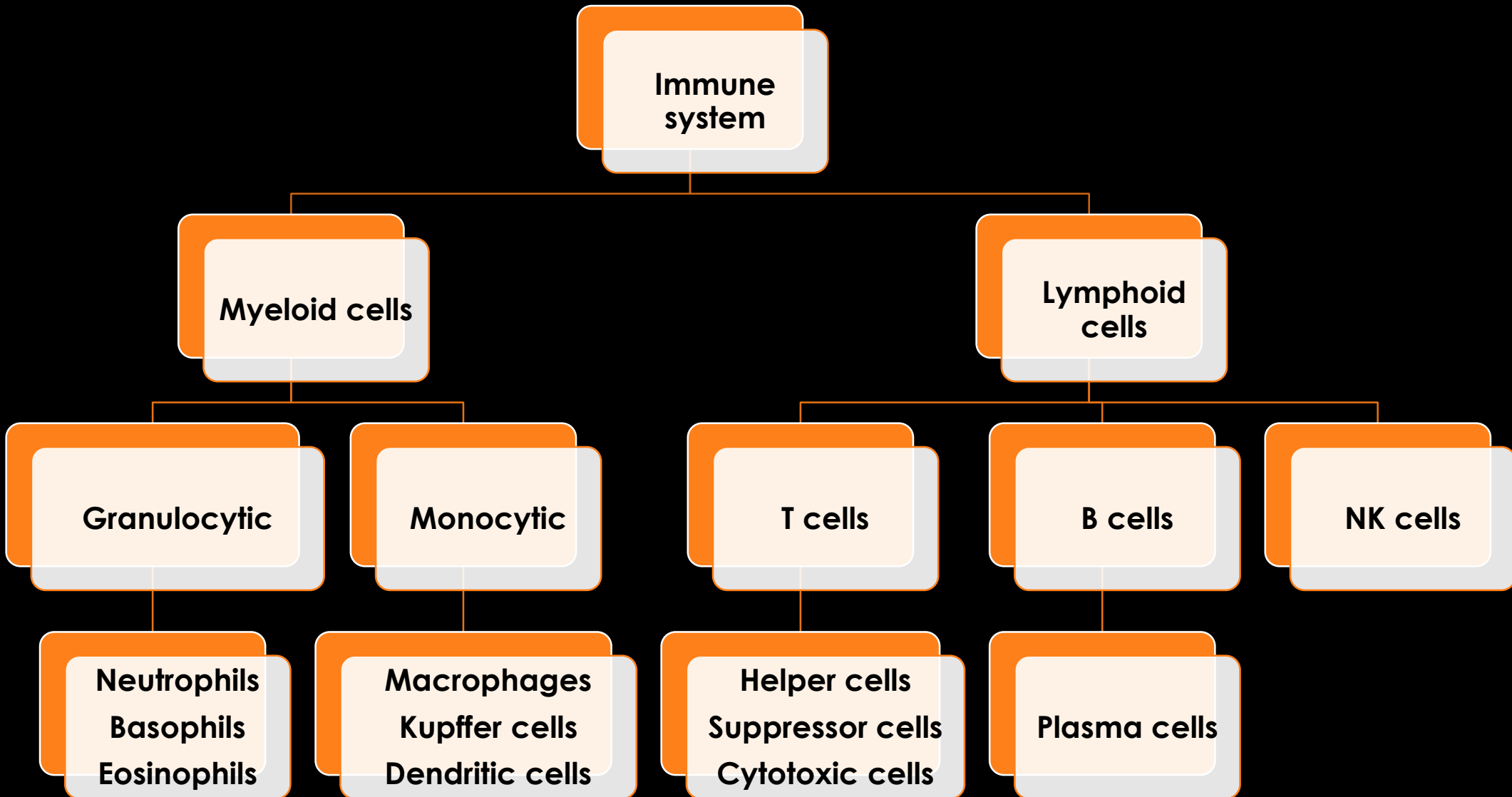
ANATOMICAL BARRIERS- BIOLOGICAL

| System/Organ | Component | Mechanism |
|---------------------------|--------------|--|
| Skin and mucous membranes | Normal flora | Antimicrobial substances Competition for nutrients and colonization |

HUMORAL COMPONENTS

| Component | Mechanism |
|-----------------------------|--|
| Complement | Lysis of bacteria and some viruses Opsonin Increase in vascular permeability Recruitment and activation of phagocytic cells |
| Coagulation system | Increase vascular permeability Recruitment of phagocytic cells B-lysin from platelets – a cationic detergent |
| Lactoferrin and transferrin | Compete with bacteria for iron |
| Lysozyme | Breaks down bacterial cell walls |
| Cytokines | Various effects |

CELLS OF THE IMMUNE SYSTEM



CELLULAR COMPONENTS

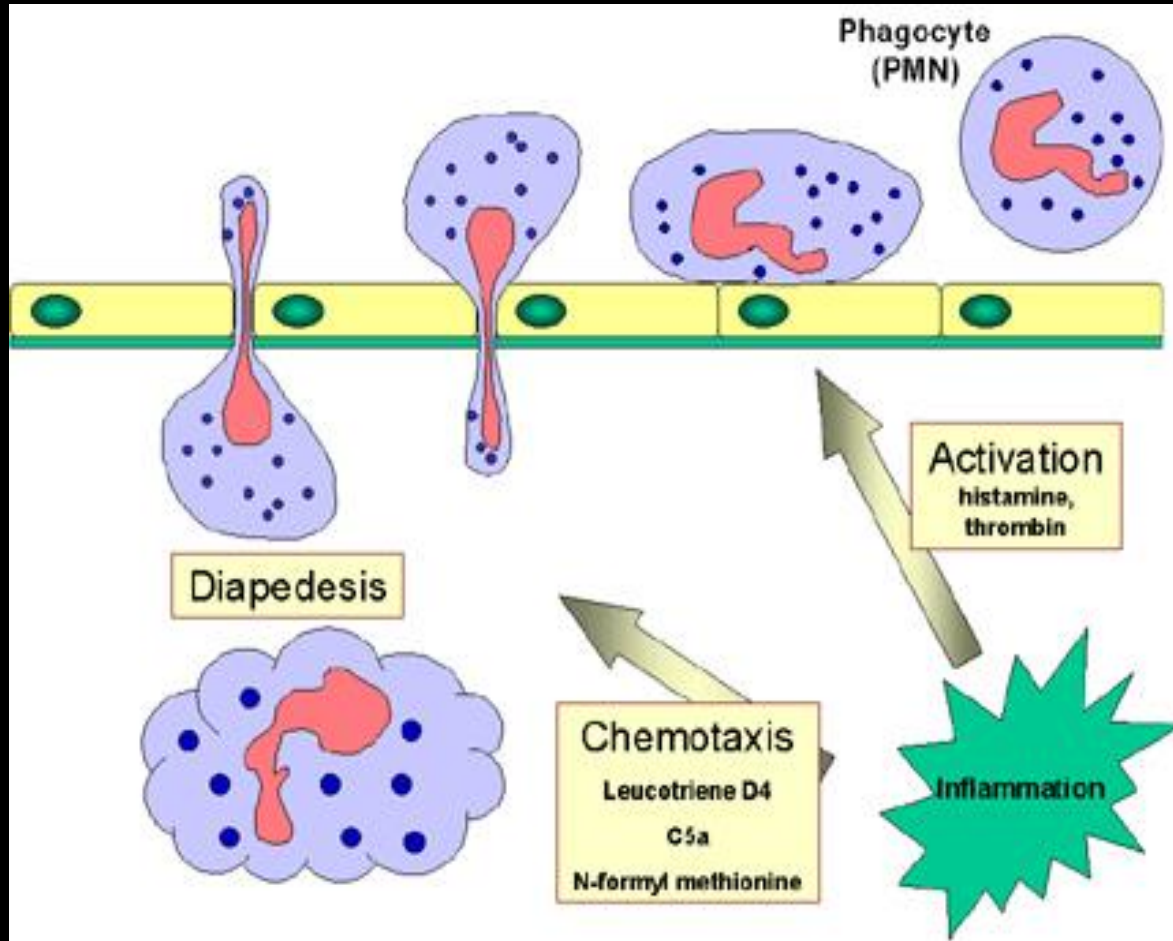
| Cell | Mechanism |
|------------------|---|
| Neutrophils | Phagocytosis and intracellular killing Inflammation and tissue damage |
| Macrophages | Phagocytosis and intracellular killing Extracellular killing of infected or altered self targets Tissue repair Antigen presentation for specific immune response |
| NK and LAK cells | Killing of virus-infected and altered self targets |
| Eosinophils | Killing of certain parasites |



PHAGOCYTOSIS AND INTRACELLULAR KILLING

Neutrophils and Macrophages

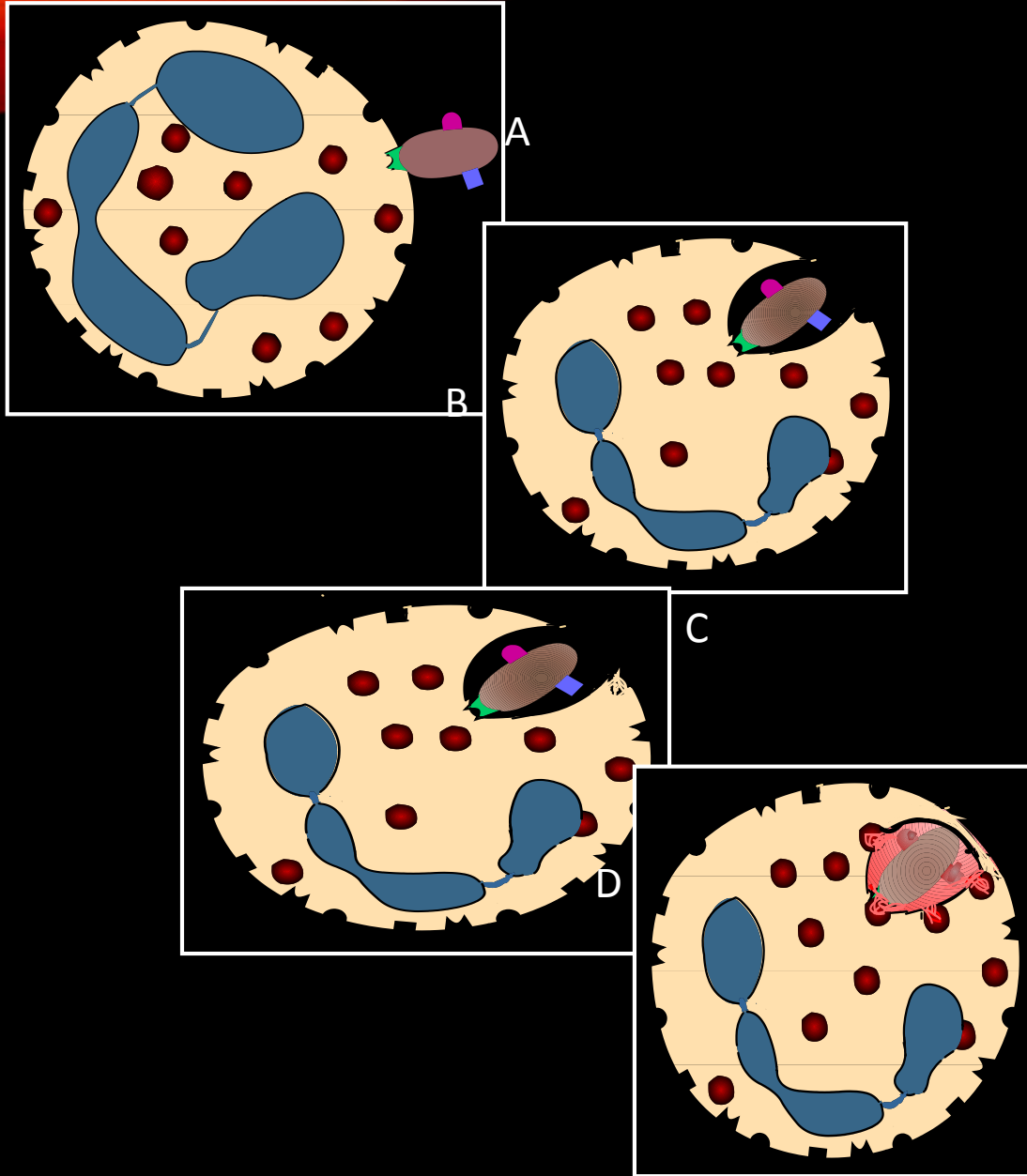
PHAGOCYTE RESPONSE TO INFECTION



Source: SOM PathMicro online textbook

- **The SOS signals**
 - N-formyl methionine-containing peptides
 - Clotting system peptides
 - Complement products
 - Cytokines released by tissue macrophages
- **Phagocyte response**
 - Vascular adherence
 - Diapedesis
 - Chemotaxis
 - Activation
 - Phagocytosis and killing

PHAGOCYTOSIS



A. Attachment via receptors

- FcR, complement R, scavenger R, Toll-like R

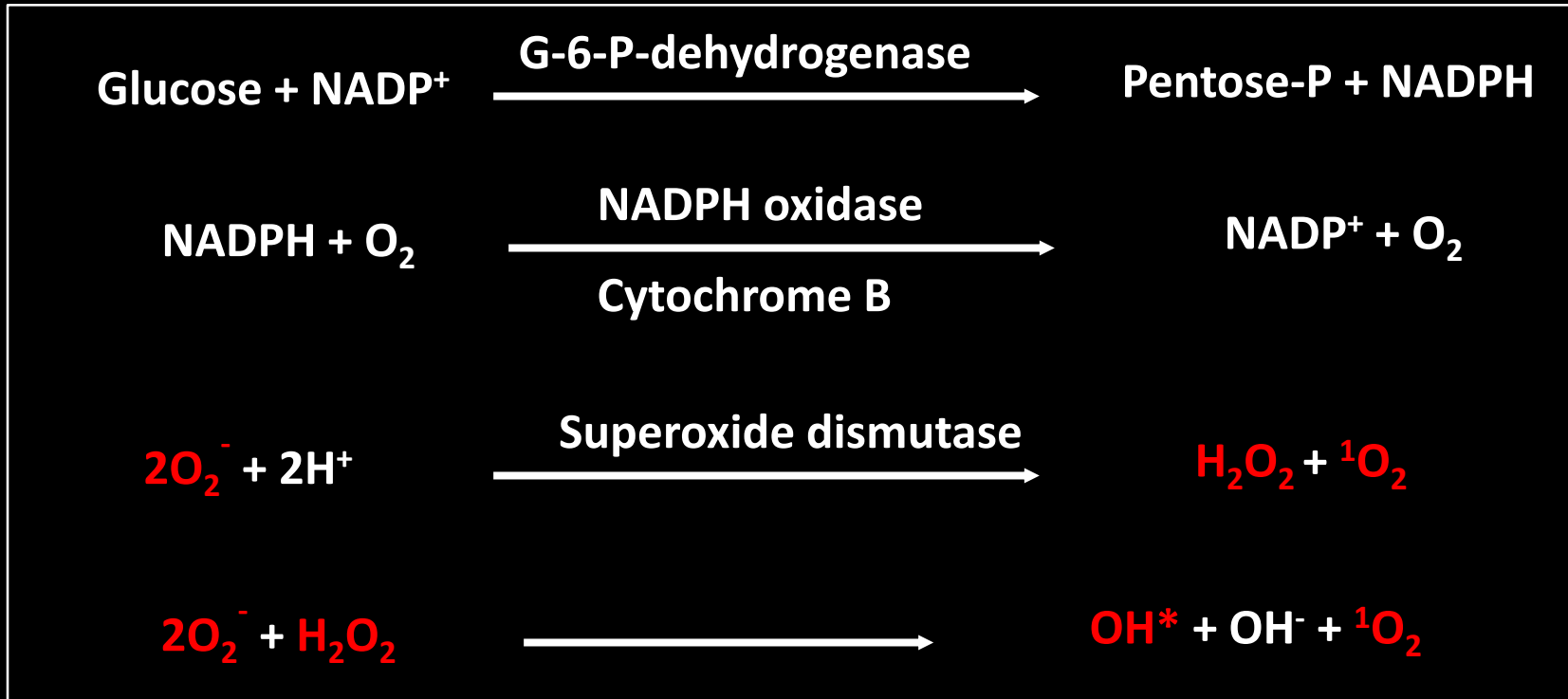
B. Pseudopod extension

C. Phagosome formation

D. Granule fusion and Phagolysosome formation

RESPIRATORY BURST

O₂-dependent MPO-independent reactions



Toxic compounds: superoxide anion O₂⁻, hydrogen peroxide H₂O₂, singlet oxygen ¹O₂, hydroxyl radical OH*

RESPIRATORY BURST

O₂-dependent MPO-dependent reactions



Toxic compounds: hypochlorous acid OCl^- , singlet oxygen ${}^1\text{O}_2$

RESPIRATORY BURST

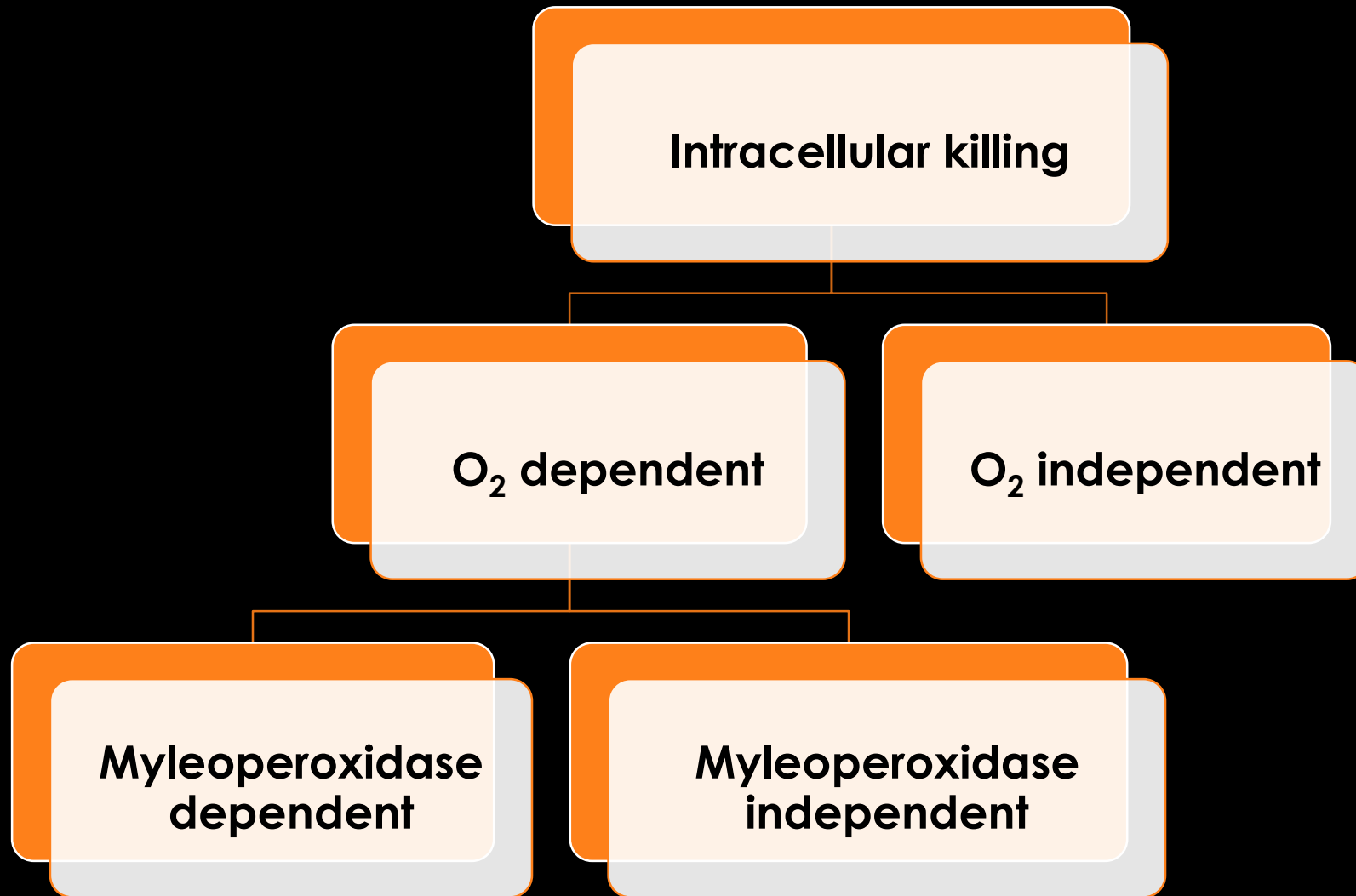
Detoxification reactions



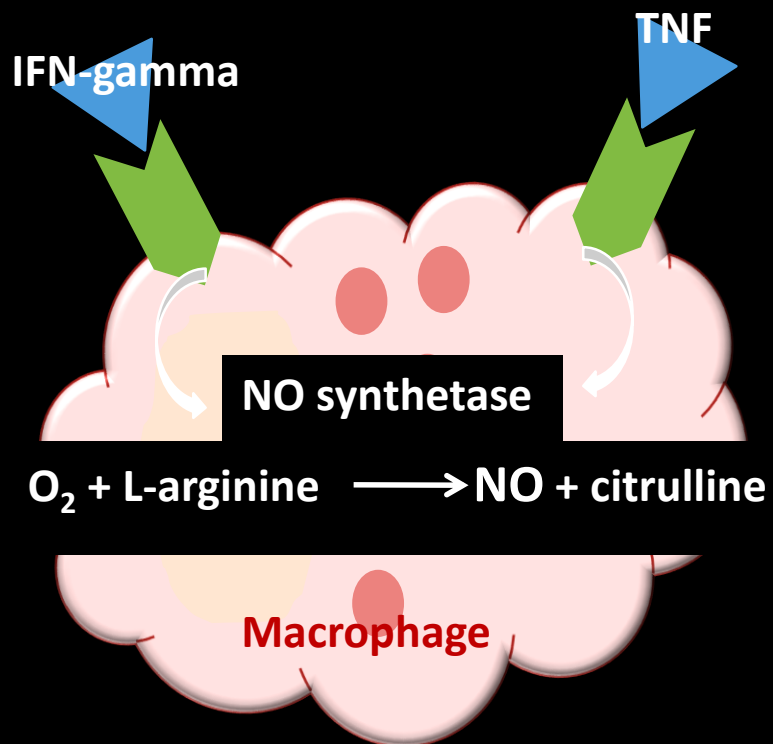
O₂-INDEPENDENT KILLING

| Effector molecule | Function |
|--------------------------------|--|
| Cationic proteins (cathepsin) | Damage to microbial membranes |
| Lysozyme | Hydrolyses mucopeptides in the cell wall |
| lactoferrin | Deprives pathogens of iron |
| Hydrolytic enzymes (proteases) | Digests killed organisms |

SUMMARY OF INTRACELLULAR KILLING PATHWAYS



NITRIC OXIDE-DEPENDENT KILLING



- Bacteria binds to macrophage
- Production of TNF-alpha
- Upregulates iNOS
- Release of NO
- NO is toxic to infected cells in vicinity of macrophage

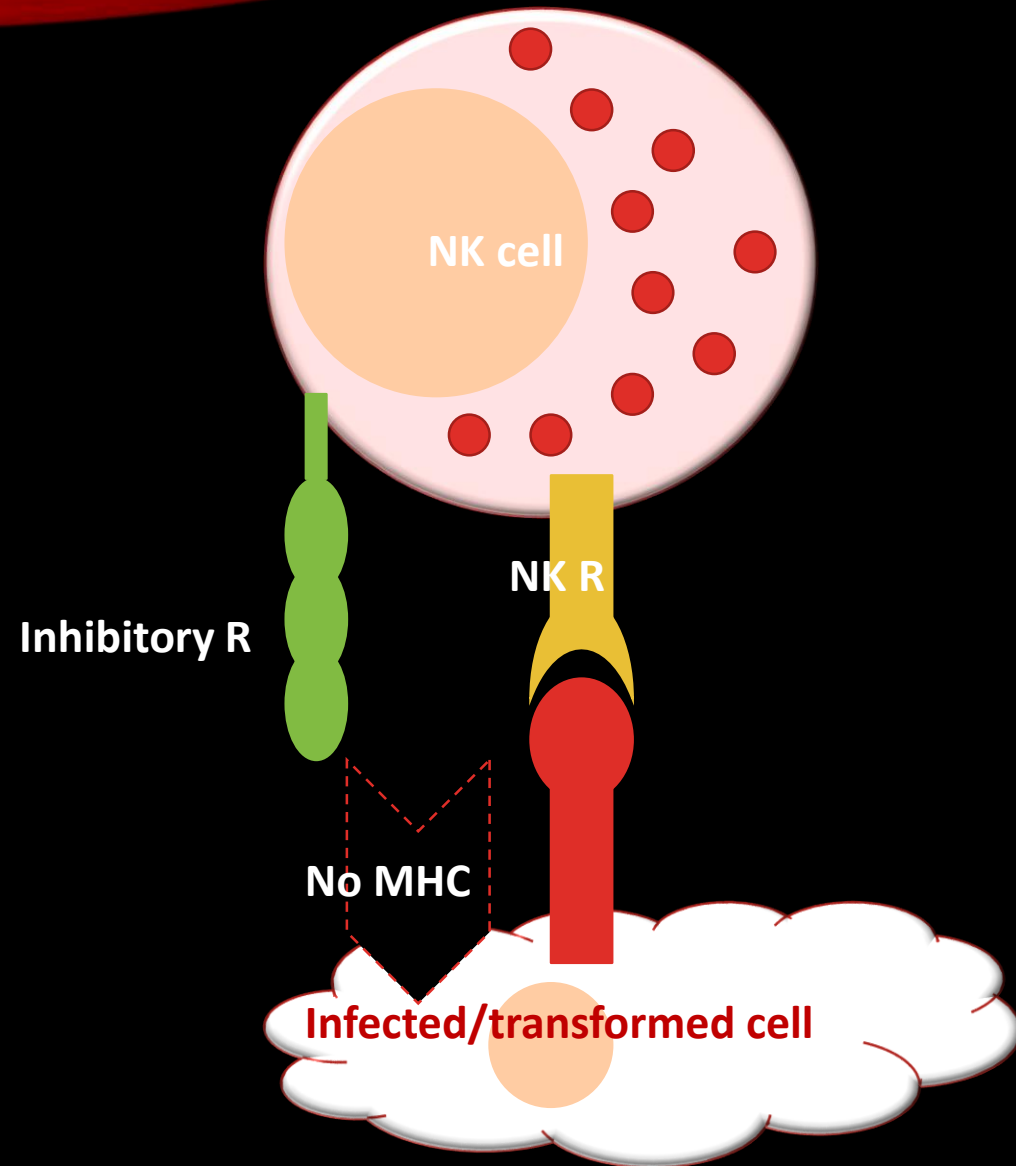
NON-SPECIFIC KILLER CELLS

NK cells

Eosinophils

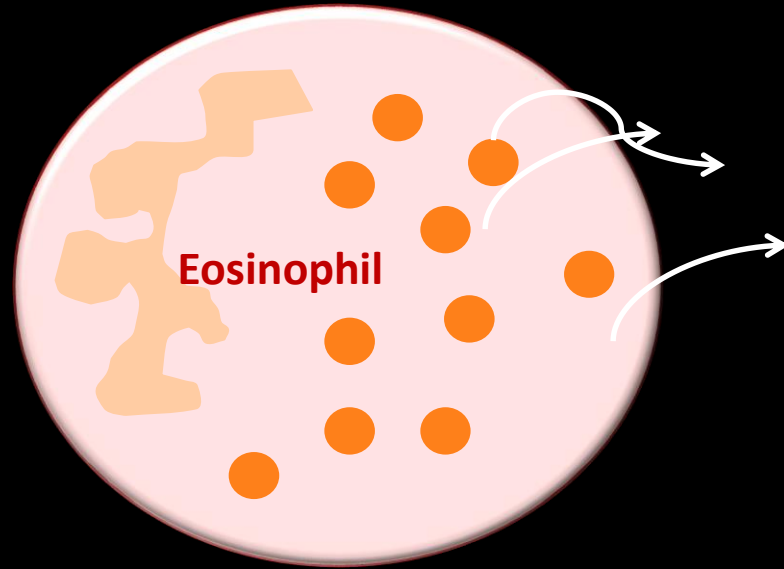
Mast cells

INNATE RESPONSE TO VIRUS INFECTION AND ALTERED SELF



- Infected or altered self (transformed) cell down regulated MHC
- NK does not receive inhibitory signal
- Signals kill infected cell

INNATE RESPONSE TO EXTRACELLULAR MICROORGANISMS (PARASITES)



- Activated eosinophils release granule components
 - Major basic protein
 - Major component of granules
 - Eosinophil peroxidase
 - Cationic hemoprotein
 - Eosinophil cationic protein
 - ribonuclease

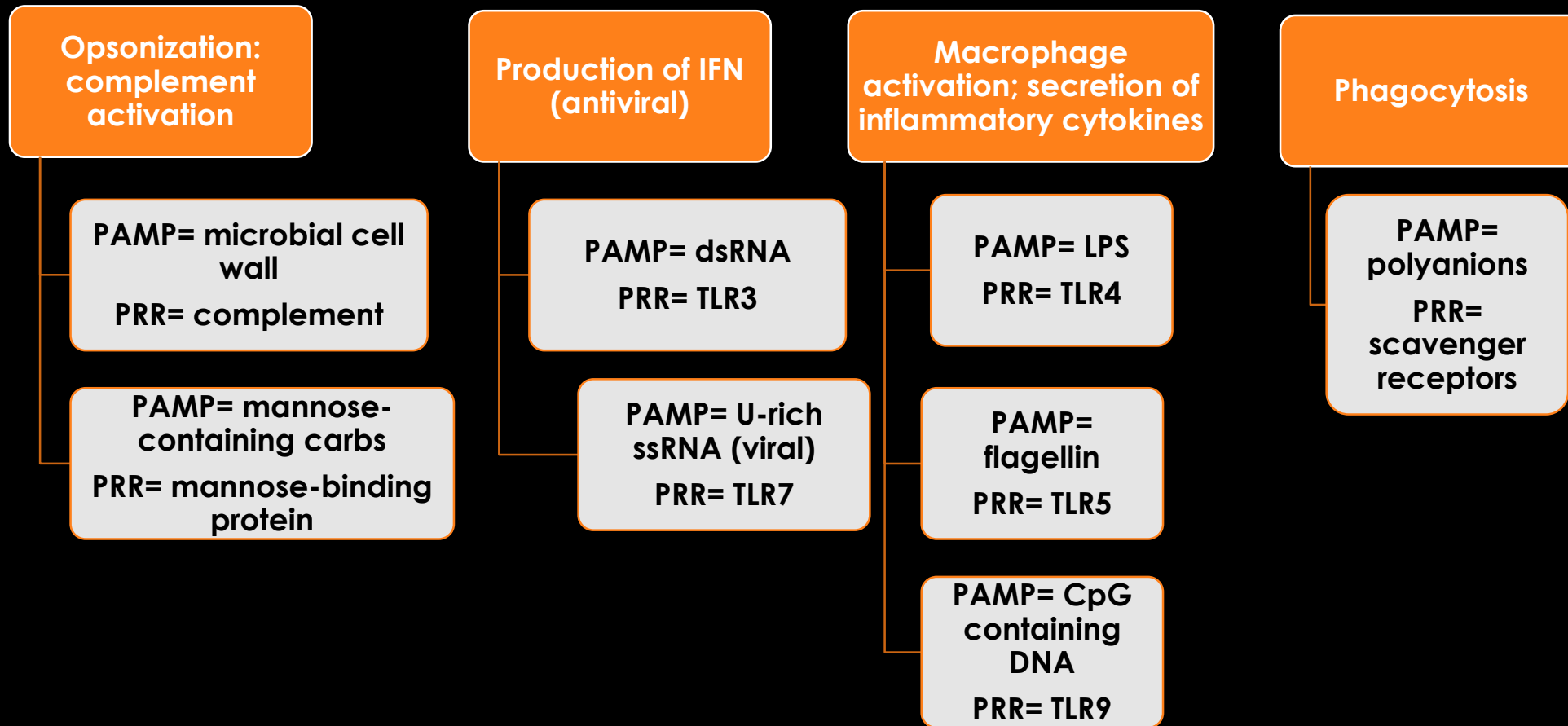
DETERMINANTS RECOGNIZED BY THE INNATE IMMUNE RESPONSE

- **PAMPs- pathogen associated molecular patterns**
- **PRRs- pattern recognition receptors**

PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPS)

- **Non-specific (not antigen specific) receptor recognition**
- **Part of innate antimicrobial defense**
- **Toll-like receptors on macrophages bind pathogen and cause activation**

DETERMINANTS RECOGNIZED BY THE INNATE IMMUNE SYSTEM



IMMUNE RESPONSE TO DAMAGE

- Dependent on what, where and how bad
- Phased response with critical timing
 - Requires chemokine signaling, receptor binding, etc

