University of Basrah
Medical College, Microbiology Dep.

Ministry of Higher Education
& Scientific Researches

Microbiology/ 3rd Year M.B.CH.B. Students
Part V: Basic & Clinical Immunology (17 hours)
Lecture 2
Duration: 1 hour

Immune Responses (Part I)

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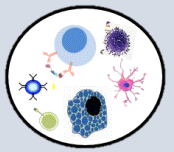
Reference: Roitt's Essential Immunology 13th Edition

For more detailed instruction, any question, cases need help please post to the group of session.



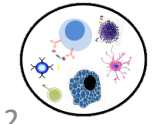
Key definitions

Immune system: cells and molecules that contribute to immune defenses against infectious and non-infectious conditions (self-vs non-self).

Pathogen-associated molecular patterns (PAMPs): particular molecular patterns that are typically associated with infectious agents. PAMPs after being recognized, trigger activation of the innate immune system.

Pattern recognition molecules: present either as cell-associated receptors (PRR) on the surface of the immune cells [Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-1-like receptors (RIRs)] or soluble molecules [complement, mannose binding lectin, C-reactive protein, and lysozyme]. Pattern recognition molecules can recognize the PAMPs.

Complement: comprises approximately 30 circulating and membrane expressed proteins. Play a major role in defense against many infectious organisms as part of both the innate and antibody-mediated adaptive immune responses.



Necrosis: necrosis caused by tissue trauma, burns, certain toxins that lead to rapid swelling and rupture of the plasma membranes of damaged cells.

DAMPs: During the rupture of necrotic cells' plasma membranes, danger-associated molecular patterns (DAMPs) release and activate the immune system.

Apoptotic cells: cells undergo apoptosis (programmed cell death) which display molecules on their plasma membranes that mark these cells for removal through phagocytosis before they can rupture and release their intracellular contents. Apoptotic cells do not activate the immune system in that case.

Infectious disease: when the pathogen succeeds in evading and/or overcome the host's immune defenses, it causes disease.

Antigens (Ag): any foreign structures (proteins, carbohydrates, lipids, nucleic acids, etc.,) recognized by the specific acquired immune response. They possess a three-dimensional shape that is complementary to the antibody (Ab) molecules (the Ag receptor on B-lymphocyte).

Antibody (Ab): is an immunoglobulin (Ig) that reacts specifically with Ag that stimulated its production. Abs are present as receptors for Ag on B-cell, also secreted by specialized B-cell called plasma cell.

Cytokines and Chemokines: proteins involved in signaling and communication between cells of the immune system, serve in chemoattraction, phagocyte activation and in the inflammation.

MHC: major histocompatibility complex that involved in displaying the breakdown products of pathogens (on antigen presenting cell ''APC'') to the cells of adaptive immune system. It also involved in transplantation.

APCs: a group of immune cells that mediate the cellular immune response by processing and presenting Ag (displayed by MHC). Classical APCs (dendritic cells, macrophages, Langerhans cells and B cells).

T-cell: belongs to a group of white blood cells known as lymphocytes that requires maturation in the thymus. It plays a central role in cell-mediated immunity.

B-cell: belongs to a group of white blood cells known as lymphocytes that develops in bone marrow. It plays a central role in humoral immunity in Ab production.

Learning objectives (LOs)

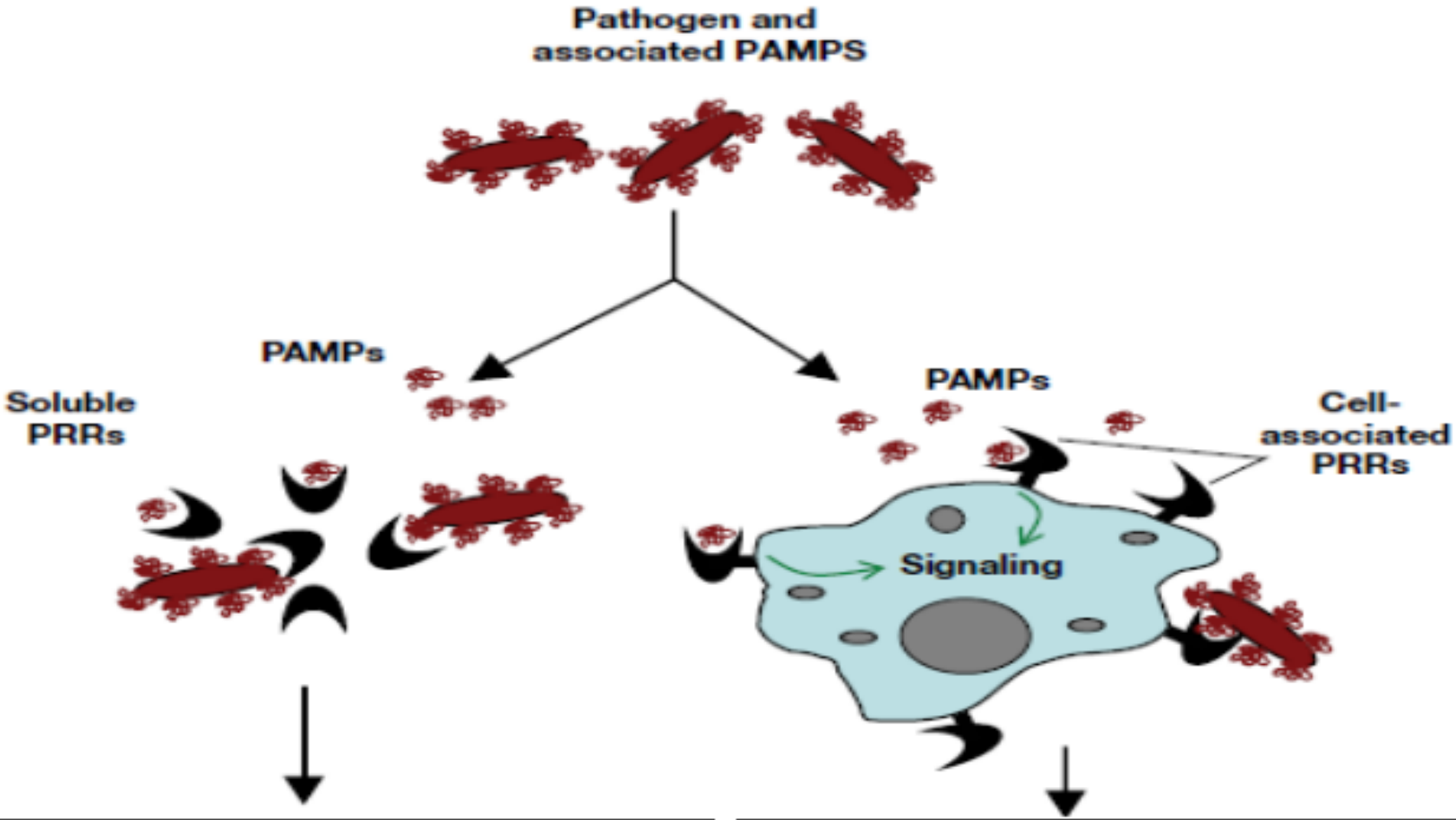
Basic roles of immune system	LO.1
Dealing with bacteria and viruses in the extracellular space	LO.2
Dealing with intracellular pathogens	LO.3
How does the immune system being alert to the presence of infectious agents inside the cells?	LO.4

Basic roles of immune system

LO.1

1. **Recognition** of foreign substances and microorganisms that have overcome the outer defenses (skin epithelium, mucosal surfaces of the gut, respiratory and reproductive tracts). The critical role of the immune system is to determine what is foreign (non-self) and what is normally present in the body (self). Therefore, the cells and molecules that comprise the innate immune system are preoccupied with detecting the presence of PAMPs.

LO.1



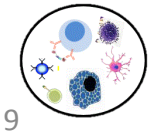
- Binding of microorganism by soluble PRR molecules
- Enhancement of phagocytosis of PRR-bound PAMPs
- Proteolytic cascade resulting in lysis of microorganism

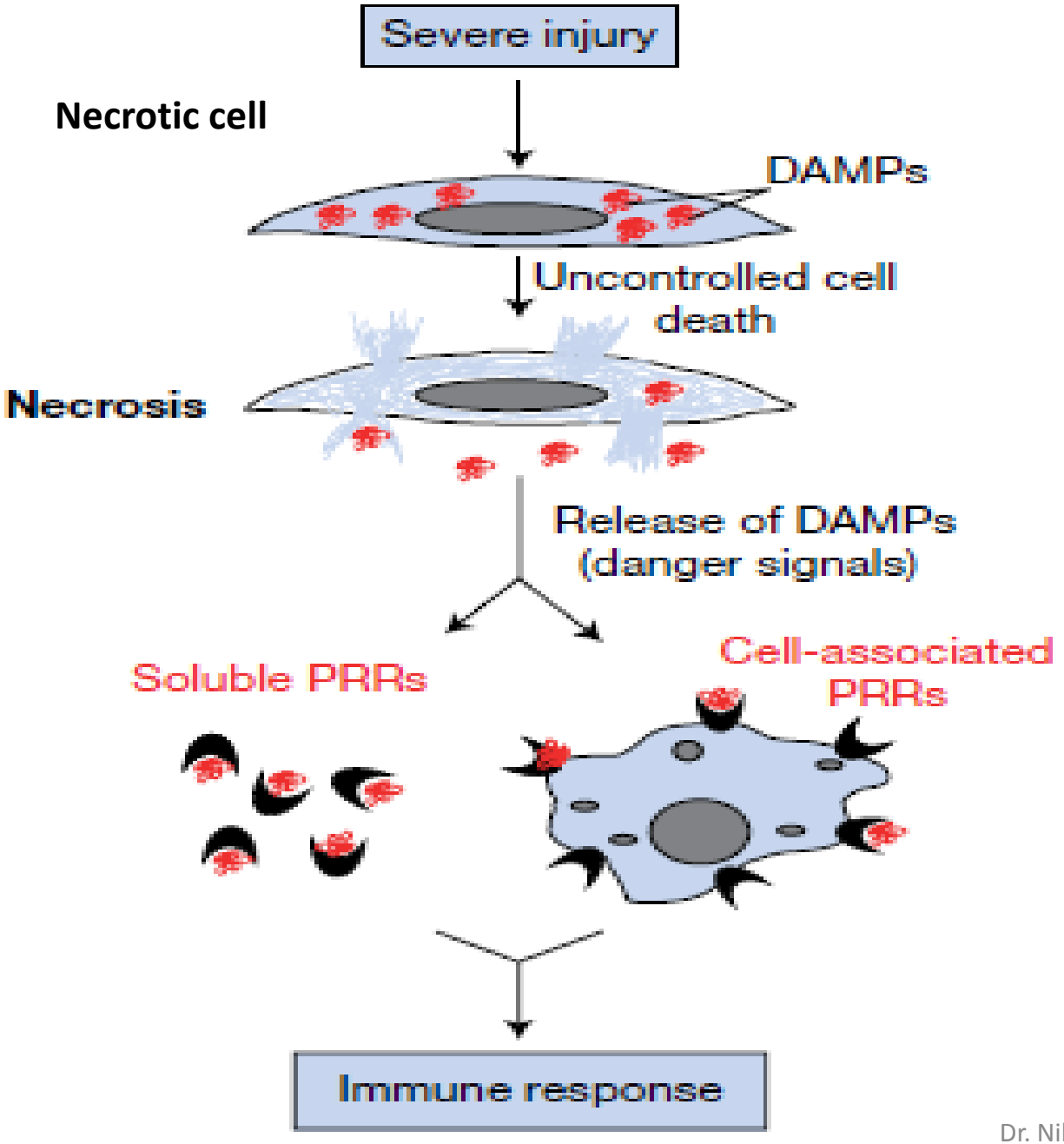
- Phagocytosis of PAMP and associated microorganism
- Activation of immune cell encountering PAMP
- Release of 'cytokines to amplify response

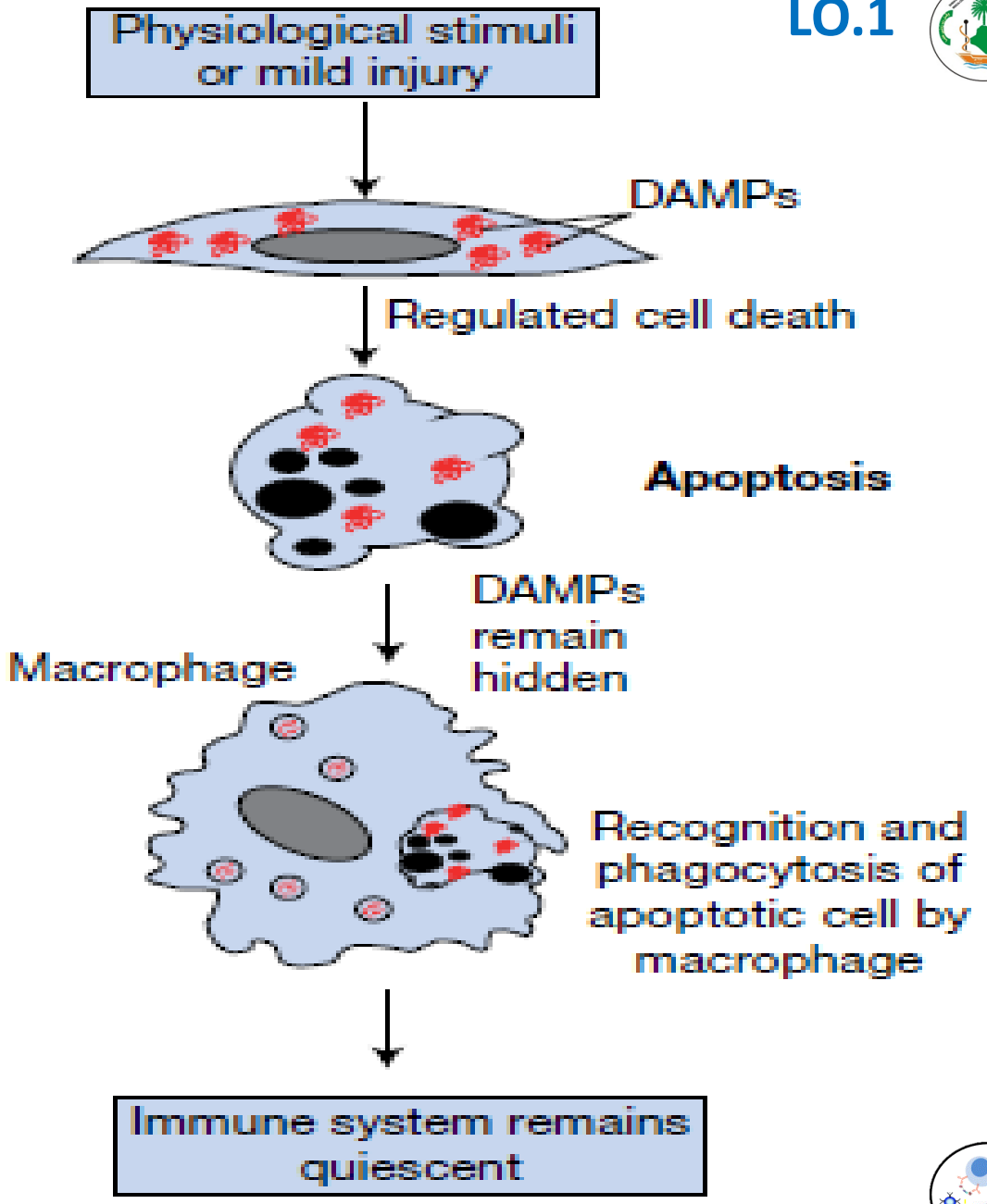
2. Elimination of these agents by a diverse repertoire of cells and molecules that act in concert neutralize the potential threat.

3. Memory: immune system is able to learn from encounters with pathogens and to maintain a reserve of cell that are able to respond swiftly to a new infection with previously encountered microbe. Immune system have acquired (adapted) an ability called (immunological memory).

4. Immune regulation (immune checkpoints): A number of immune regulatory mechanisms exist to ensure that immune responses are proportional to the level of threat that a particular infectious agent poses, as well as to ensure that immune responses are not been directed against self and that responses directed against non-self stop when the infectious agent has been successfully terminated from the body.




Severe injury
Necrotic cell
DAMPs
Uncontrolled cell death
Necrosis
Release of DAMPs (danger signals)
Soluble PRRs
Cell-associated PRRs
Immune response


Physiological stimuli or mild injury
DAMPs
Regulated cell death
Apoptosis
DAMPs remain hidden
Macrophage
Recognition and phagocytosis of apoptotic cell by macrophage
Immune system remains quiescent

Dealing with bacteria and viruses in the extracellular space

LO.2

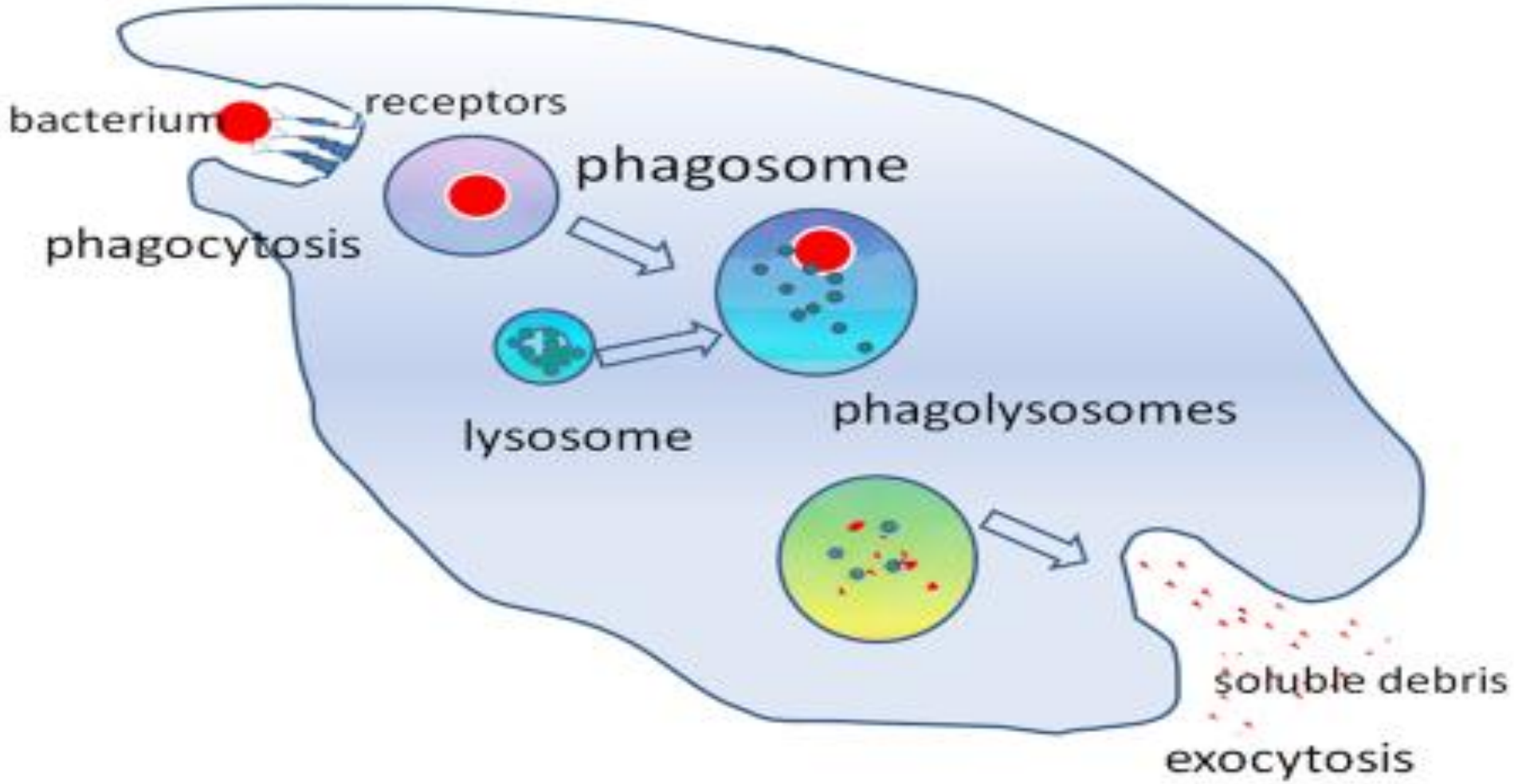
For both pathogen classes, immune system recognize these agents by (complement, acute phase proteins, and antimicrobial peptides) then remove them by destroying them through membrane lysis.

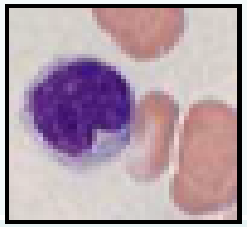
The same classes of protein involved in decorating infectious agents for recognition and phagocytosis by phagocytic cells (e.g., macrophages and neutrophils). Molecules that are involved in the decoration of infectious agents to prepare them for removal called opsonins (prepare for eating).

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

LO.2

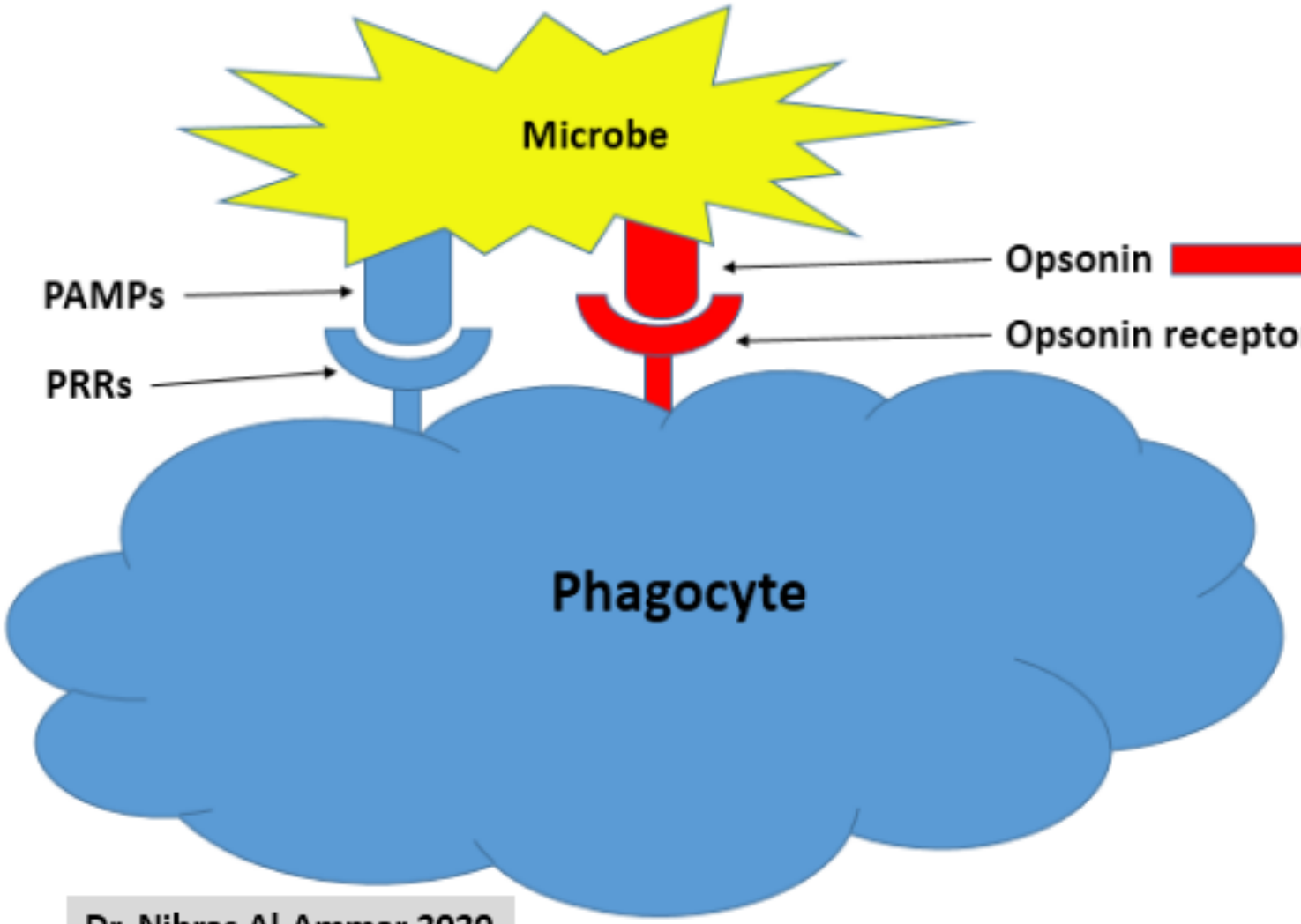
Role of phagocyte in killing extracellular pathogens



Cell type	Function
Macrophages 	▪ Present in all organs ▪ Ingest and destroy microbes (Phagocytosis) ▪ Present microbial antigens to T cells (adaptive immunity) ▪ Produce cytokines/chemokines
Monocytes 	▪ Present in the blood (5-7%) ▪ Recruited at infection site and differentiate into macrophages
Neutrophils (pus) 	▪ Present in the blood (60% of blood leukocytes) ▪ Increased during infection ▪ Recruited by *chemokines* to the site of infection ▪ Ingest and destroy pyogenic bacteria: Staph. aureus and Strep. pyogenes

Examples of opsonins

LO.2



Opsonins include:

Complement proteins
-C3b
-C4b

Antibodies
-IgG
-IgM

Acute phase proteins
-C-reactive protein (CRP)
-Mannose-binding lectin (MBL)

Dealing with intracellular pathogens

LO.3

Once the virus enters a cell, the proteins and phagocytic cell no longer be of any use in dealing with this type of infection because proteins cannot freely diffuse across the plasma membrane of the infected cell to either lyse or tag the infectious agent for phagocytosis. Although some specialized phagocytic cells, (macrophages) can kill intracellular bacteria that have invaded them, most cells cannot do that very effectively.

Role of phagocyte in killing intracellular pathogens

LO.3

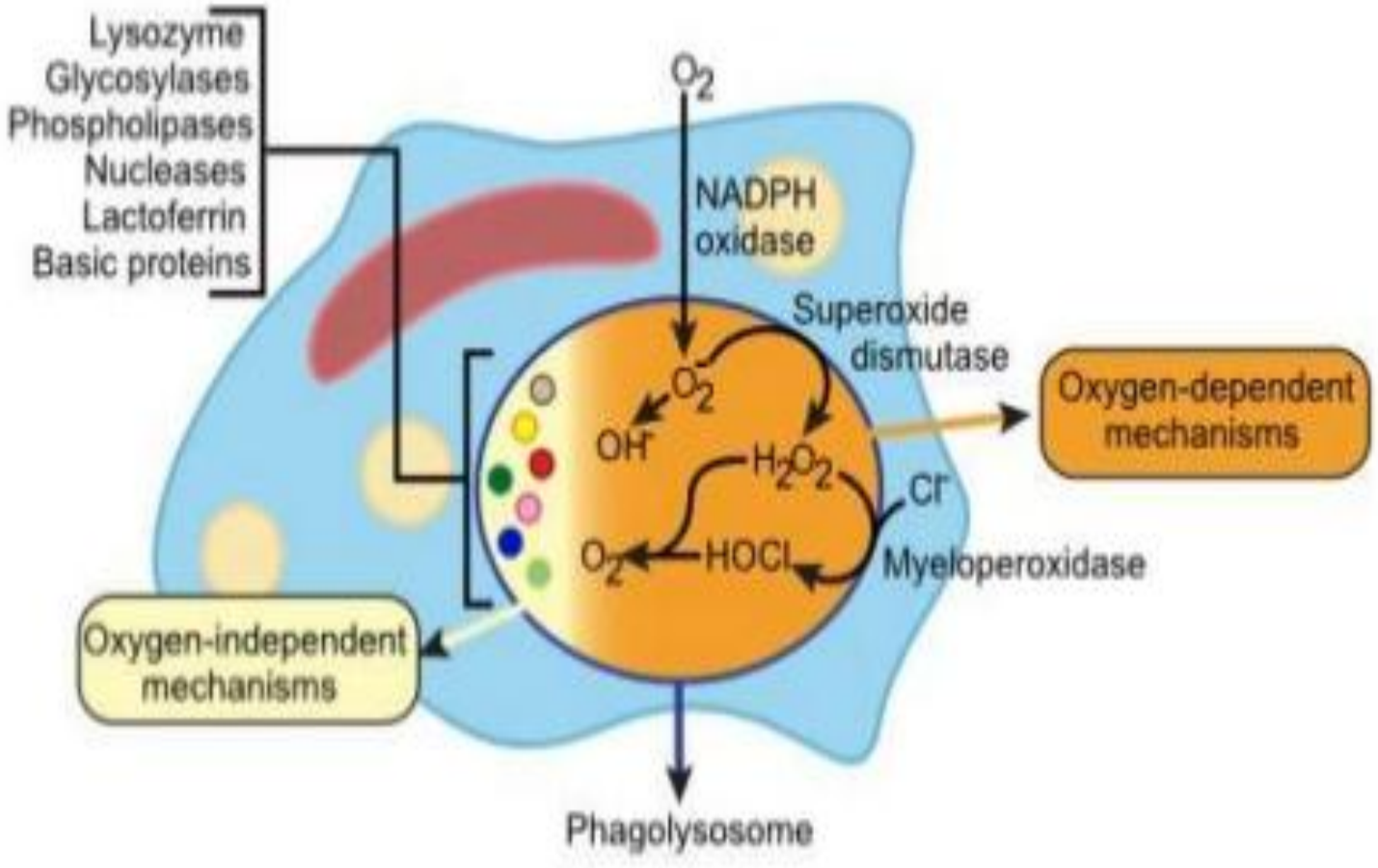
Phagocyte intracellular killing mechanisms

Oxygen-dependent pathway (respiratory burst)

- *Toxic O_2 products for the pathogens:* Hydrogen peroxide, Hydroxyl radical, Nitric oxide, Singlet oxygen, Hypohalite

Oxygen-independent pathways

- Lysozyme
- Lactoferrin or transferrin
- Cationic proteins (cathepsin)
- Proteolytic and hydrolytic enzymes



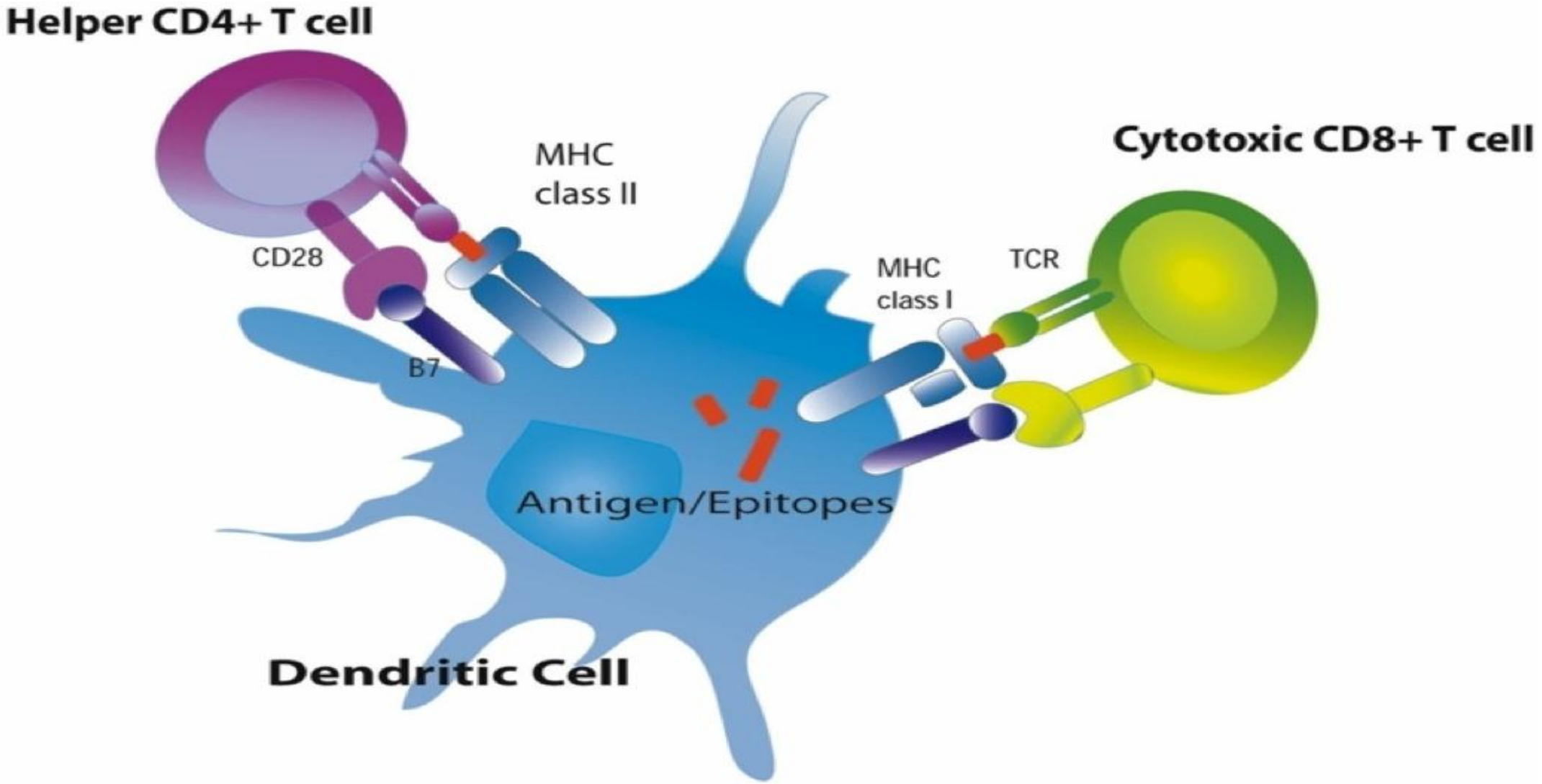
How does the immune system being alert to the presence of infectious agents inside the cells?

LO.4

- There are a number of intracellular PRRs can detect pathogens that have entered cells.
- This results in production of signals (e.g., cytokines and chemokines) that alert immune system to the presence of an infectious agent.
- There is a clever way of displaying the breakdown products of pathogens (after being phagocytosed) to cells of the immune system (MHC molecules involved in this process).

Displaying breakdown products by MHC to cells of immune system

LO.4



Thank You