Inflammation, Fever, Pattern-recognition receptor

Lecture 3

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Inflammation

What is Inflammation?

It is the response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, and is a protective response **to the elimination of pathogens and to aid tissue repair** its involving immune cells, blood vessels, and molecular mediators.

Inflammation

Mediators: are the substances that initiate and regulate inflammatory reactions. These are: cell-derived or plasma protein derived

The released chemical mediators include:

- vasoactive amines, such as histamine
- lipid products prostaglandins
- cytokines
- products of complement activation

The basic stages of inflammation are as follows:

- Vasodilation & increased capillary permeability

(increases blood flow to the area, blood fluid in tissue)

causes swelling of the region (edema), redness (erythema), fever, and pain

- Migration of phagocytes, phagocytosis (phagocytes exit the blood, enter affected tissue via chemotaxis & consume pathogens)

Chemotaxis: movement of the cells in response to a chemical stimulus.

- Tissue repair (removal of dead cells, regeneration of the tissue)

Fever

- Higher body temperature occurs as a result of certain cytokines called pyrogens
- Cytokines carried in the bloodstream to the hypothalamus
- Hypothalamus responds by raising the temperature

Antimicrobial Substances

- ✓ **Sensor Systems used by the Immune System**

These systems are used to detect signs of either tissue damage or microbial invasion

They respond by either directly destroying invading microbe or recruiting other components of the host defenses

The system we are focusing on:

- ✓ **Complement system**

Series of proteins that constantly circulate in blood and fluids that bathe tissues

When they detect the presence of foreign material, a cascade of reactions follows Complement proteins activated

When activated, cooperate with other host defense systems to rapidly get rid of the invader

- ✓ **Acute phase proteins**: C-reactive protein, CRP is secreted by the liver in response to a variety of inflammatory cytokines. Levels of CRP increase very rapidly in response to trauma, inflammation, and infection.
- ✓ Acute phase proteins such as **C-reactive protein (CRP), defencins, mannan-binding lectin, Apolipoprotein B, serum amyloid protein, C9, factor B, and fibrinogen.** All act either to limit the spread of the infectious agents or to stimulate the host response.

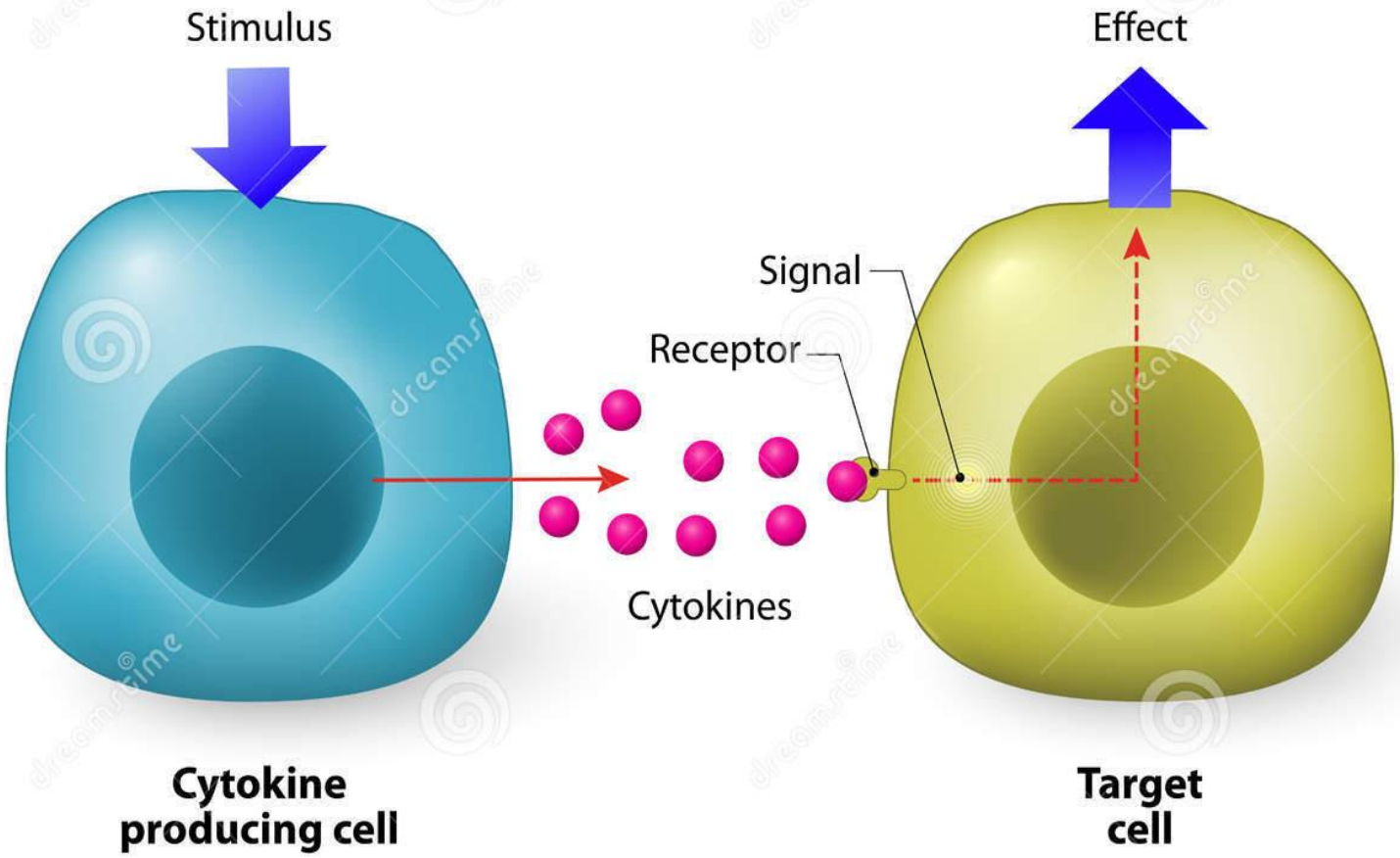
✓ Interferons

Interferon sometimes secreted by virus-infected cells inhibits viral replication.

The interferons (IFN-α, IFN-β & IFN-γ) are a class of cytokines (soluble protein signals) released by virally infected cells and certain white blood cells to stimulate other cells to protect themselves from viral infection.

Cytokines: Small proteins – secreted by cells of the immune system that are used for cell signaling, or cell-to-cell communicate

CYTOKINES



- **Lysozymes:** these are anti-microbial enzymes that hydrolyze bacterial cell wall; they split the peptidoglycan of bacterial cell walls which is the major component of gram-positive bacterial cell wall. Lysozymes are found in tears, nasal secretions, and saliva; it is also present in cytoplasmic granules of the macrophages and the polymorphonuclear neutrophils (PMNs).

- ✓**Defensins**: these are cationic peptides produced by neutrophils, epithelial cells of the kidney, pancreas, and intestine; they have antimicrobial effect by disrupting the cell membrane of microbes and have intracellular effects on microbes by inhibiting the synthesis of DNA, RNA, and proteins.

✓**Lactoperoxidase**:

it is a peroxidase enzyme secreted from mammary, salivary, and other mucosal glands that functions as a natural antibacterial agent. It is present in milk, saliva, and some other body sections. The oxidized products produced through the action of this enzyme have potent bactericidal activities.

- ✓ **gastric acid (HCl)** of the stomach and fatty acids of skin and sweat, both (gastric acid and fatty acid) denature proteins
- ✓ **Lactic acid** in the female genital tract
- ✓ **Transferrins (bind & keep iron away from pathogens)**

(interfere with microbial acquisition of iron)

Molecules: Membrane-associated receptors (membrane-associated molecules)

- **Pattern recognition receptors (PRR):** these are an example of Membrane – associated receptors; these receptors of innate immunity recognize pathogen-associated molecular patterns (PAMPs) which are molecules found in microbes. Toll like receptors (TLRs) are important category of PRRs;

Pattern-recognition receptor (PRR):

- It is a component of the innate arm that recognizes what is foreign by detecting certain carbohydrates or lipids on the surface of microorganisms that are different from those in human cells.

There are two example on PRR

- **1. Toll-like receptor (TLR)**
- Endotoxin (LPS) found on the surface of Gram-negative bacteria responsible for septic shock in hospitalized patients.
- LPS binds with protein present normally in the plasma called LPS-binding protein.
- This binding protein transfer LPS to a receptor on the surface of macrophage called CD14.
- LPS stimulates a pattern recognition receptor called **toll-like receptor 4 (TLR4),** which transmits the signal to the nucleus of the cell as a result cytokines will be produced.
- **TLR2**, signals the presence of Gram-positive bacteria and yeast

Toll like receptors (TLRs)

-Transmembrane proteins that play a key role in the innate immune system and are usually expressed on sentinel cells such as macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes. i.e each TLR detects a distinct subset of pathogens and can detect a wide variety of viruses, bacteria, fungi, and protozoa.

TLRs – What do they do ?

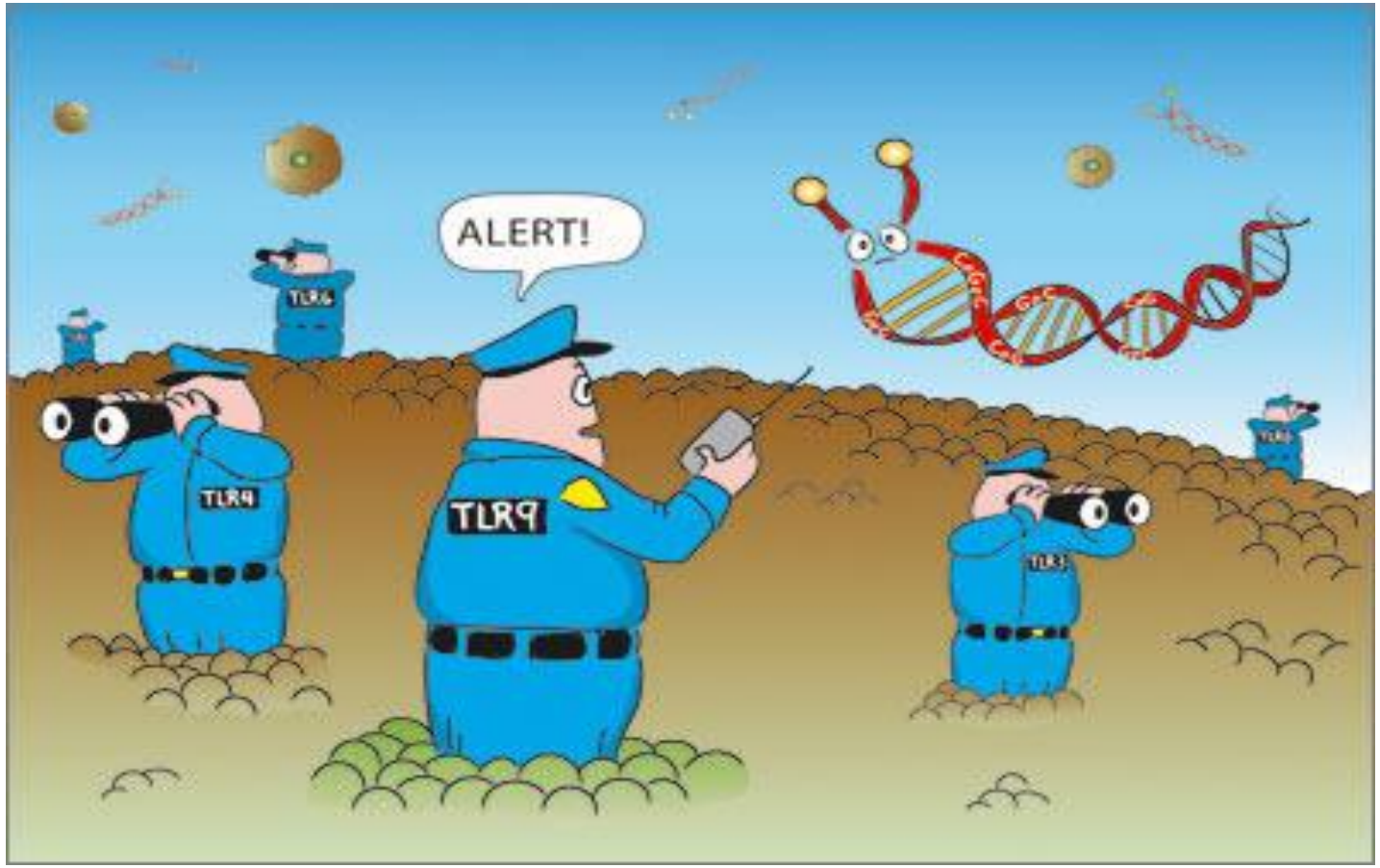
They look out for microbes (or their components)

They bind to the microbes (or their components)

They trigger a cascade of events to kill or protect against pathogens

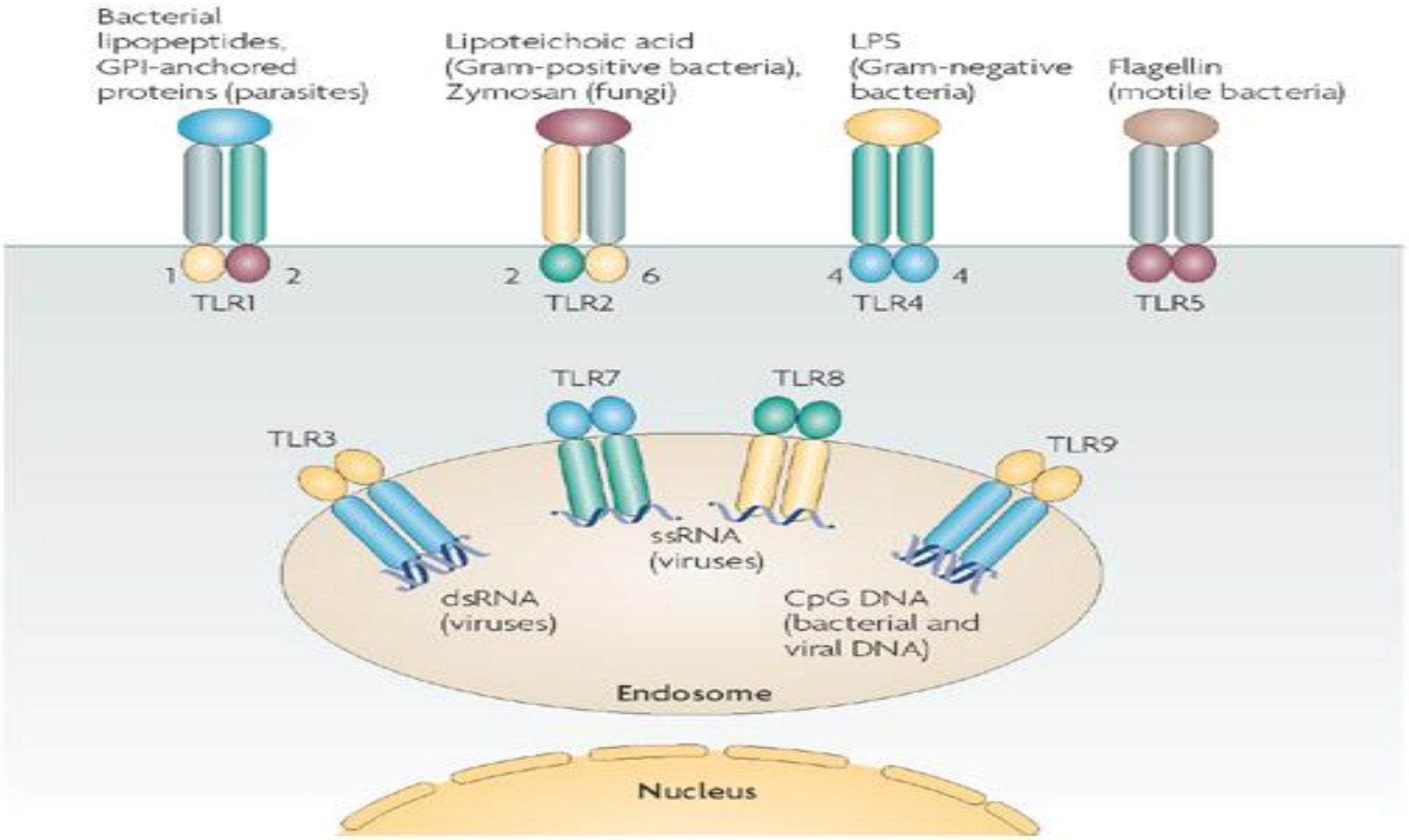
They are Innate Immune Sensors

TLRs – look out for microbes



TLRs – bind to microbes / components of microbes

Which microbial components are recognized by TLRs ?



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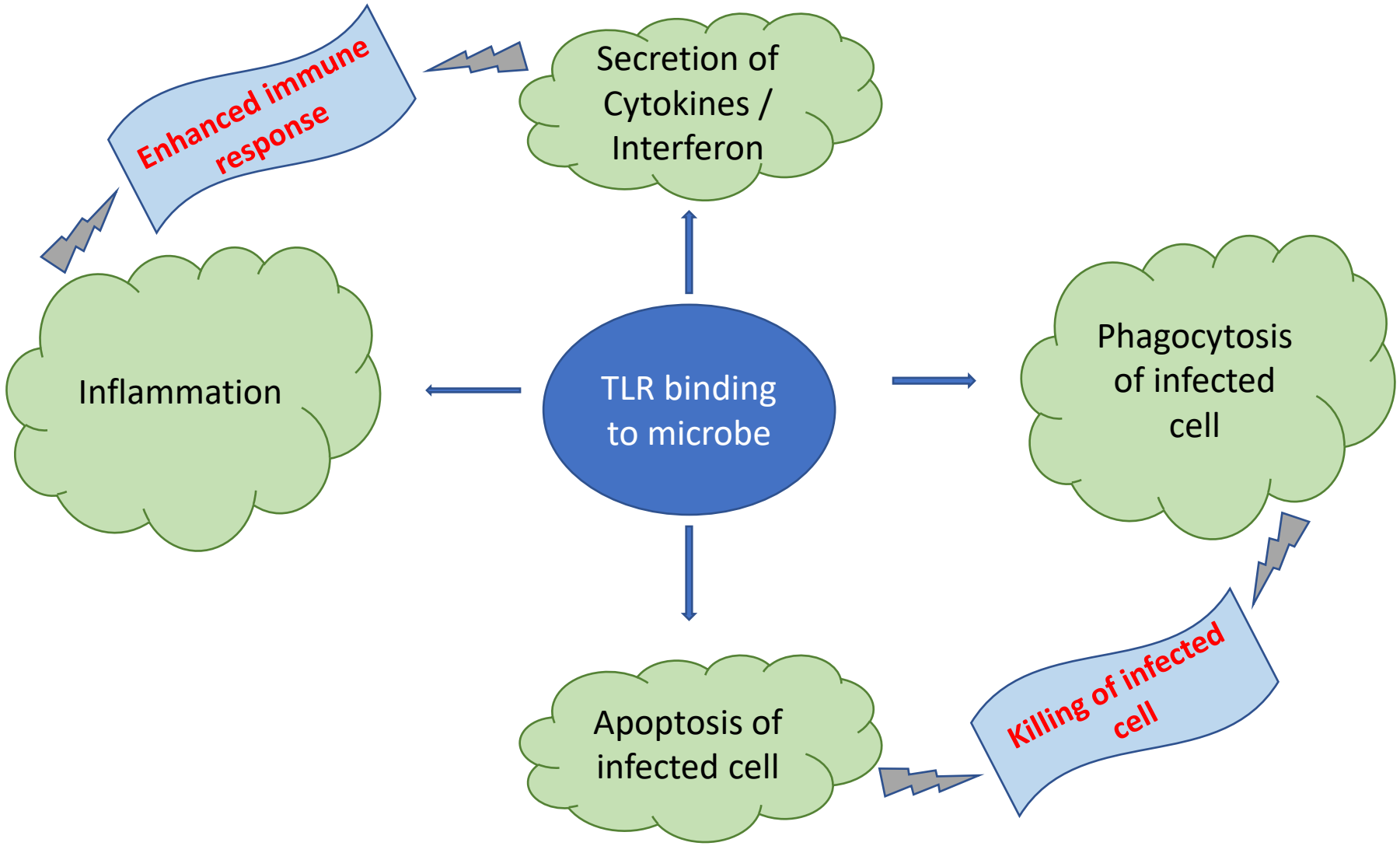
PAMP	PRR of immune cells
Lipopolysaccharides (LPSs)	Toll like receptor 4 (TLR4)
bacterial flagellin	TR5
lipoteichoic acid from gram-positive bacteria, peptidoglycan, double-stranded RNA (dsRNA) of viruses	TR3

What happens when a TLR bind to a microbe ?



PRR……..continue

2-Mannan binding lectin (MBL)or mannose-binding protein:

Many bacteria and yeast have a polysaccharide called mannan on their surface that is not present in human cells

MBL bind to the mannan on the surface of the microbes, which then activates the complement resulting in the death of the microbe.

MBL also enhances phagocytosis(acts as an opsonin) via receptors to which it binds on the surface of the macrophage.

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THANKS
for listening