ADVANCE IMMUNITY :
MSc Microbiology :
Lecture Three

Innate Immunity:

The innate immune system is composed of physical barriers, cells, and circulating factors that are always active and ready to repel microbes

THE BARRIER

Mechanical Barrier, Chemical Barrier& Biological Barrier.

Complement

The complement system consists of approximately 20 proteins that are present in normal human (and other animal) serum. The term *complement* refers to the ability of these proteins to complement (i.e., augment) the effects of other components of the immune system (e.g., antibody). Complement is an important component of our innate host defenses.

There are three main effects of complement:

(1) **lysis** of cells such as bacteria, allografts, and tumor cells;

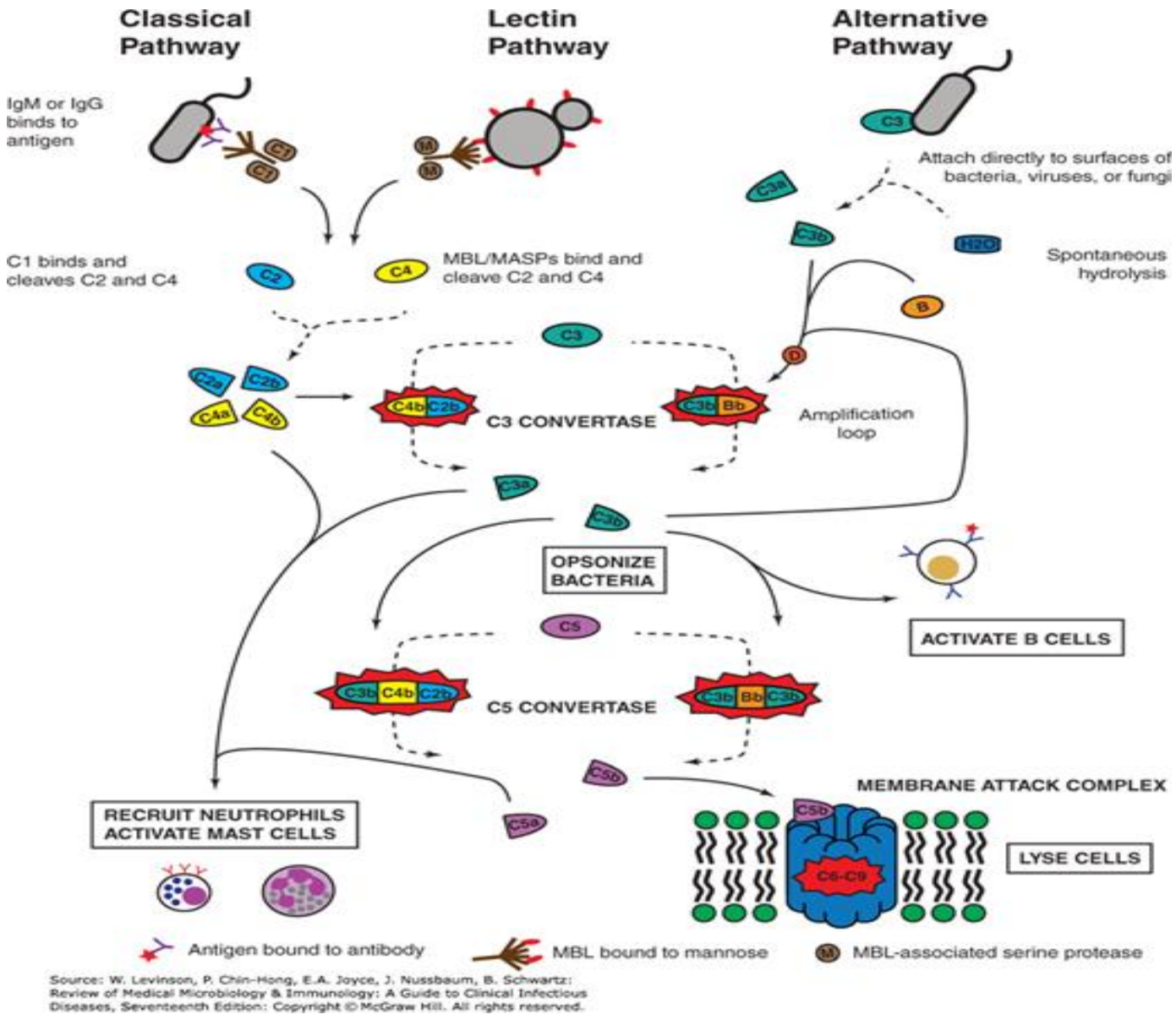
(2) **generation of mediators** that participate in inflammation and attract neutrophils;
(3) **opsonization** (i.e., enhancement of phagocytosis).

Complement proteins are synthesized mainly by the liver.

Several complement components are proenzymes that must be cleaved to form active enzymes. Activation of the complement system can be initiated either by antigen–antibody complexes or by a variety of non-immunologic molecules (e.g., endotoxin).

Sequential activation of complement components (Figure1) occurs via one of three pathways:

The *classical* pathway, the *lectin* pathway, and the *alternative* pathway . Of these pathways, the **lectin and the alternative pathways are more important the first time** , we are infected by a microorganism because the antibody required to trigger the classical pathway is not present.



PHAGOCYTES AND OTHER MYELOID CELLS

Innate immune cells are the second line of defense, and the most important of these cells are phagocytes. The name "phagocyte" derives from Greek, emphasizing these cells' ability to "eat" foreign material and debris. (Innate immune phagocytes also play a role in repairing damage, even in the absence of a foreign infection.)

There are several key phagocytic cells:

tissue macrophages are the first cells to encounter invaders;

neutrophils then migrate into damaged tissue and contribute to inflammation;

and dendritic cells carry away microbial material to the lymph nodes or spleen, where they activate the adaptive immune response.

A fourth cell, called a monocyte, can be recruited into inflamed tissue to take on the role played by macrophages or dendritic cells.

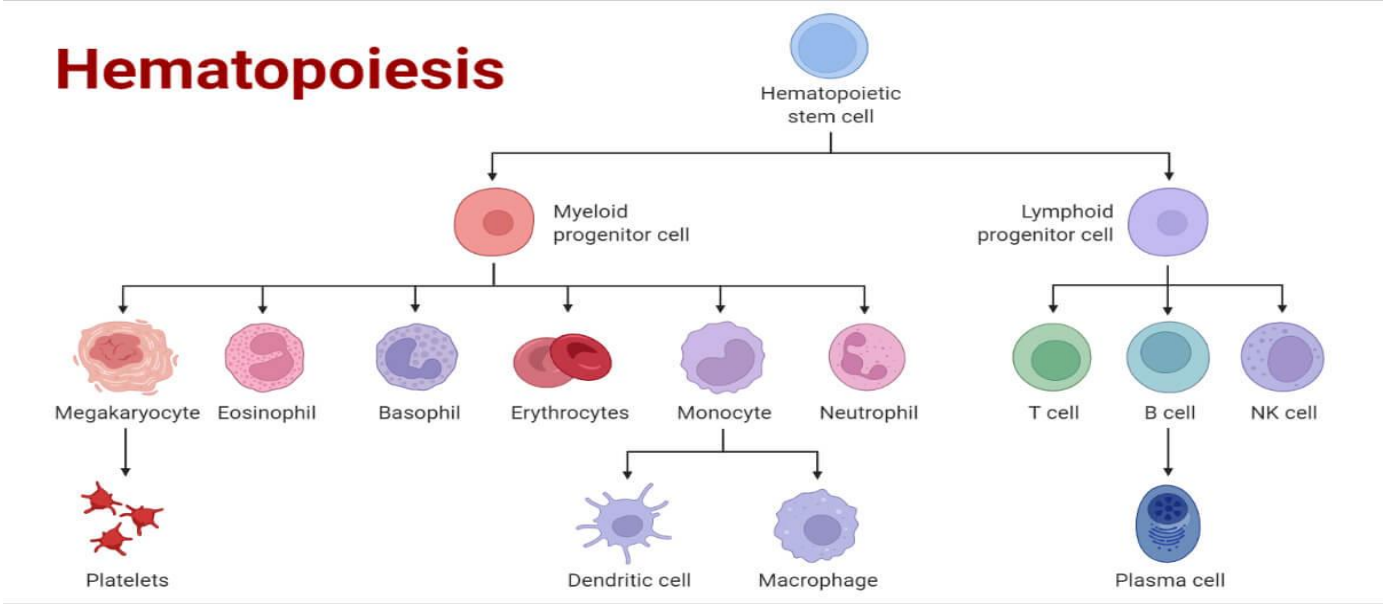
Phagocytes belong to the family of immune cells called myeloid cells because they originate from bone marrow "myeloid" progenitor stem cells origin of hematopoietic cells. Stem cells in the bone marrow (or fetal liver) are the precursors of all blood cells.

Stem cells differentiate into myeloid or lymphoid progenitor cells. The myeloid cells are the source of platelets, erythrocytes, granulocytes, macrophages, and dendritic cells.

Monocytes are a special type of myeloid cell that can differentiate into macrophages or dendritic cells when needed.

The lymphoid cells are the source of T lymphocytes, B lymphocytes, and natural killer (NK) cells.

All blood cells are produced by a mechanism known as hematopoiesis, arising from a single cell type known as a hematopoietic stem cell (HSC). Stem cells in the bone marrow continuously produce daughter cells that give rise to all red and white blood cells.



Immune cells are often called white blood cells, or leukocytes, and include lymphoid cells and myeloid cells. In contrast to T lymphocytes and B lymphocytes, which differentiate from lymphoid stem cells, most cells of the innate immune system arise from myeloid precursors.

PATTERN RECOGNITION RECEPTORS OF INNATE IMMUNE CELLS

The first step of an immune response is that innate immune cells recognize foreign material. To identify what is foreign, innate immune cells have receptors, called pattern recognition receptors (PRRs), that recognize a molecular pattern, called a pathogen associated molecular pattern (PAMP), that is common among many microbes but—very importantly—is not present in human cells and is difficult for those microbes to alter through mutation. Some examples of PAMPs include carbohydrates, lipids, or nucleic acids (e.g.,double stranded RNA). With the ability to recognize PAMPs, innate immune cells do not need a highly specific receptor for each individual microbe strain but can still broadly distinguish what is foreign from what is "self."
Examples of the four major classes of PRRs.

Location	Receptor	Examples	Activating Microbial Ligands
Extracellular	Toll like receptors (TLRs)	TLR2	Peptidoglycan (gram positive bacteria)
		TLR4	Lipopolysaccharide (bacterial endotoxin)
		TLR9	Bacterial DNA
	C type lectin receptors (CLRs)	MBL	Mannose (viral, fungal, and bacterial carbohydrate)
		Dectin1	Glucans (fungal cell wall)
Intracellular	NOD like receptors (NLRs)	NOD2	Peptidoglycan (gram positive bacteria)
		NLRP3	Staphylococcus α toxin
	RIGI Helicase like receptors (RLRs)	RIGI	Double stranded RNA (viral)

MBL = mannan binding lectin; NOD = nucleotide binding oligo merization domain; RIGI= retinoic acid inducible gene I.

There are two classes of PRRs (Toll like receptors [TLRs] and C type lectin receptors

[CLRs]) that recognize microbes that are outside of cells or within the cells' vesicles.
Two other classes of receptors in the cytoplasm of cells (NOD like receptors [NLRS] and RIGI helicase like receptors [RLRs]) recognize microbes that have invaded the cell's cytoplasm. Mutations in the genes encoding these PRRs result in a failure to recognize pathogens and predispose to severe bacterial, viral, and fungal infections.

Toll Like Receptors

TLRs are a family of 10 receptors found on the surface of many cells, including epithelial cells and immune cells.
Each of the ten TLRs recognizes a core microbial building block (e.g., endotoxin or peptidoglycan), and all of them signal through transcription factors to release pro inflammatory cytokines and cell surface molecules that enhance adaptive immune activation.
Endotoxin is a lipopolysaccharide (LPS) found on the surface of most gram negative bacteria (but not on human cells).
When released from the bacterial surface, LPS combines with LPS binding protein, a normal component of plasma, that transfers LPS to a receptor on the surface of macrophages called CD14. LPS then stimulates a PRR called Toll like receptor 4 (TLR4), which transmits a signal to the nucleus of the cell. Note that a different TLR, TLR2, signals the presence of peptidoglycan from gram positive bacteria, which has a different molecular pattern but produces the same innate cell activation.
Excessive macrophage TLR activation may contribute to systemic inflammation and septic shock.

C Type Lectin Receptors

A PRR called mannan binding lectin (MBL) is one of the CLR family and can be found both in the plasma and attached to the surface of dendritic cells and macrophages. Many bacteria and yeasts have mannan (a polymer of the sugar mannose) on their surface that is not present on human cells.MBL binds mannose on the surface of the microbes and then activates complement , resulting in death of the microbe.
MBL also enhances phagocytosis (acts as an opsonin) via receptors to which it binds on the surface of phagocytes, such as macrophages.
MBL is a normal serum protein whose concentration in the plasma is greatly increased during the acute phase response .
A different CLR, called dectin1, recognizes beta glucan in the cell wall of fungi such as Candida albicans.

NOD Like Receptors

NLRs recognize part of the peptidoglycan cell wall of bacteria (NOD stands for nucleotide binding oligo merization domain). These receptors are located within the cytoplasm of

human cells (e.g., macrophages, dendritic cells, and epithelial cells); hence, they are important in the innate response to intracellular bacteria such as Listeria.

RIGI Helicase Like Receptors

RLRs recognize microbial nucleic acids in the cytoplasm of infected cells (RIGI stands for retinoic acid–inducible gene I).For example, certain viruses synthesize double stranded RNA during replication that is recognized by RLRs.

Activation of these RLRs results in the synthesis of alpha and beta interferons that promote antiviral immune responses.

What are Toll-Like Receptors?

Toll-like receptors (**TLRs**) are membrane-bound proteins that play a key role in microbial identification in the innate immune system. They are single-pass membrane-spanning receptors.

Generally, these receptors are expressed by sentinel cells such as macrophages and dendritic cells. When microbes breach physical barriers like the skin or intestinal mucosa, they are recognized by these membrane-bound receptors in order to activate immune responses.

The TLRs members include TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13. Humans do not possess genes for TLR11, TLR12, and TLR13, while mice do not possess a functional gene for TLR10.

Moreover, TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are located on the cell membrane, whereas TLR3, TLR7, TLR8, and TLR9 are located in intracellular vesicles. TLR3, TLR7, TLR8, and TLR9 receptors are sensors of nucleic acids.

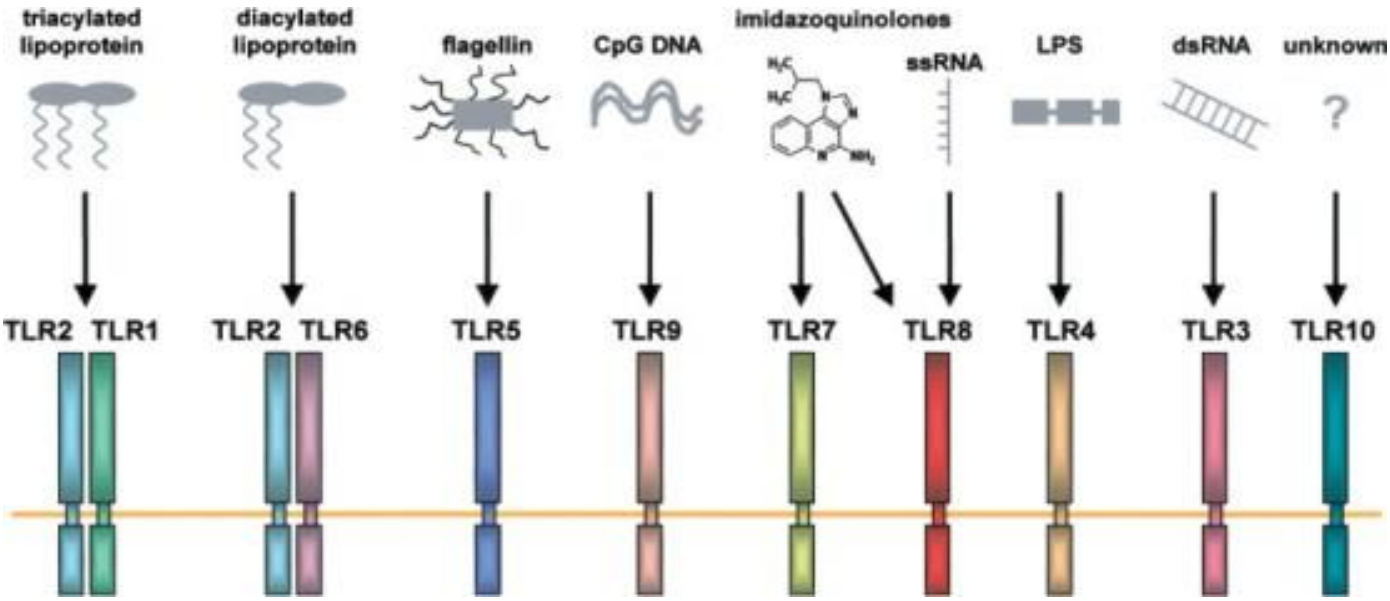


Figure: Toll-Like Receptors

TLRs received their name due to their similarity to the protein encoded by the toll gene.

Upon activation, these receptors ultimately lead to the upregulation or suppression of genes that orchestrate inflammatory responses and other transcriptional events.

Some of these important events lead to cytokine production, proliferation, and survival. On the other hand, other events lead to greater adaptive immunity.

Furthermore, medically certain drugs (imiquimod, resiquimod) called TLR agonists (TLR7 & TLR8) have been explored in cancer immunotherapy. TLR ligands are in clinical development as vaccine adjuvants.

What are Nod-Like Receptors?

Nod-like receptors (NLRs) are proteins present in the cytoplasm and play a key role in microbial identification in the innate immune system.

They are also called nucleotide-binding oligomerization domain-like receptors. They are intracellular sensors.

These receptors identify pathogen-associated molecular patterns (PAMPS) that enter the cell via phagocytosis or pores and damaged associated molecular patterns (DAMPs) that are associated with cell stress.

NLRs are divided into 4 subfamilies based on the type of N terminal domain: NLRA, NLRB, NLRC, and NLRP. There is also an additional subfamily called NLRX, which does not have significant homology to any N terminal domain. Moreover, NLRs can be divided into 3 subfamilies based on their phylogenetic relationships, such as NODs, NLRPs, and IPAF.

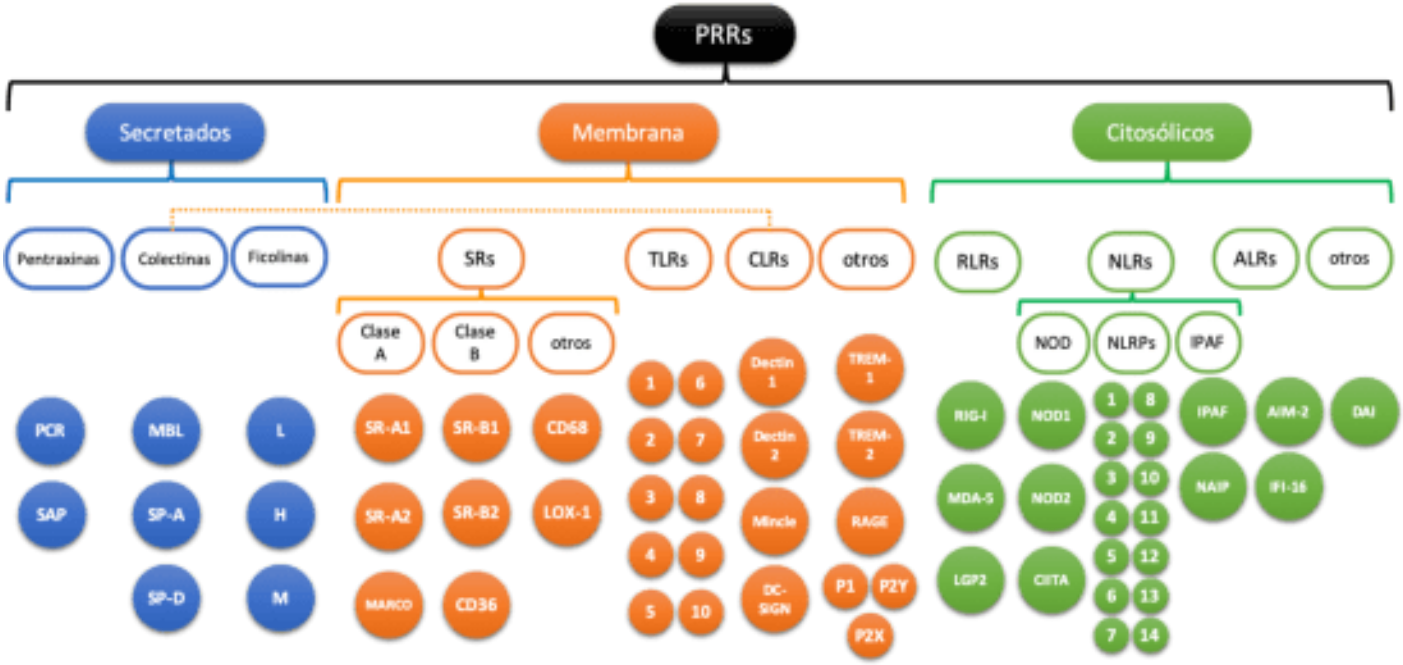


Figure 02: Nod-Like Receptors

NLRs can cooperate with TLRs and regulate inflammatory and apoptotic responses. Furthermore, their homologs have been identified in different animal species (APAF1). These homologs are also discovered in the plant kingdom (disease resistance R protein).

What are the Similarities Between Toll-Like Receptors and Nod-Like Receptors?

- Toll-like receptors and Nod-like receptors are two different types of receptors in the innate immunity system.
- Both receptors are proteins made up of amino acids.
- These receptors can cooperate with each other to regulate inflammatory and apoptotic responses.
- Both receptors are highly conserved through evolution.
- These receptors contain leucine-rich repeats.
- They contribute to the onset of adaptive immunity.

What is the Difference Between Toll-Like Receptors and Nod-Like Receptors?

Toll-like receptors are membrane-bound proteins that play a key role in microbial identification in the innate immune system, while Nod-like receptors are proteins present in the cytoplasm that play a key role in microbial identification in the innate immune system. Thus, this is the key difference between Toll-like receptors and Nod-like receptors. Furthermore, Toll-like receptors are extracellular sensors of pathogen-associated molecular patterns (PAMPs). On the other hand, Nod-like receptors are intracellular sensors of pathogen-associated molecular patterns (PAMPs).

The below infographic presents the differences between Toll-like receptors and Nod-like receptors in tabular form for side by side comparison.

Summary – Toll-Like Receptors vs Nod-Like Receptors

Toll-like receptors and Nod-like receptors are two different types of receptors in the innate immunity system. Both receptors are sensors of pathogen-associated molecular patterns (PAMPs). Toll-like receptors are membrane-bound proteins while Nod-like receptors are proteins present in the cytoplasm. So, this is the key difference between Toll-like receptors and Nod-like receptors.