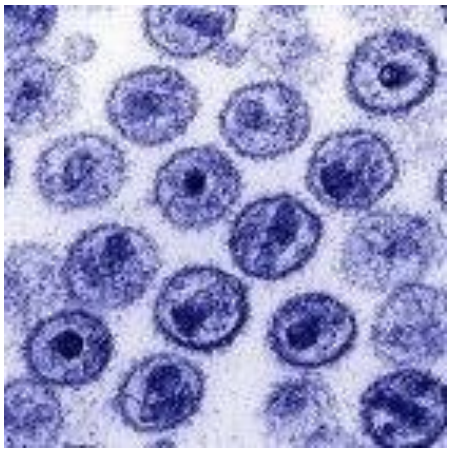
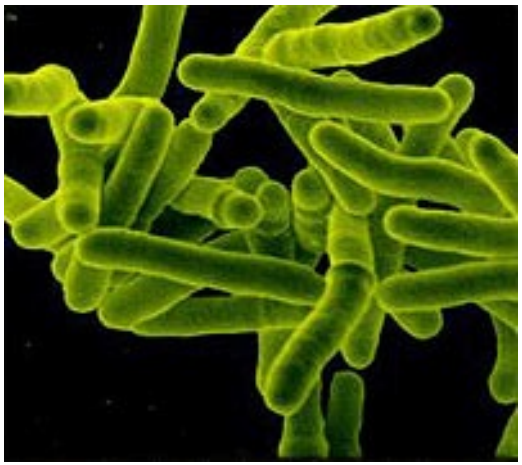
Innate Immunity

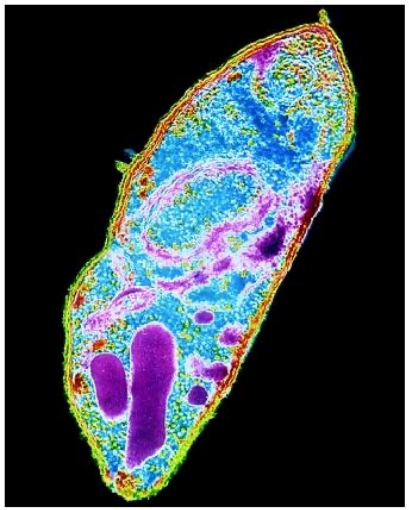
The point of the immune system is to defend against pathogens

Therefore, to understand immunity, you need to appreciate something about the many different pathogens

Pathogens can be classified in many ways

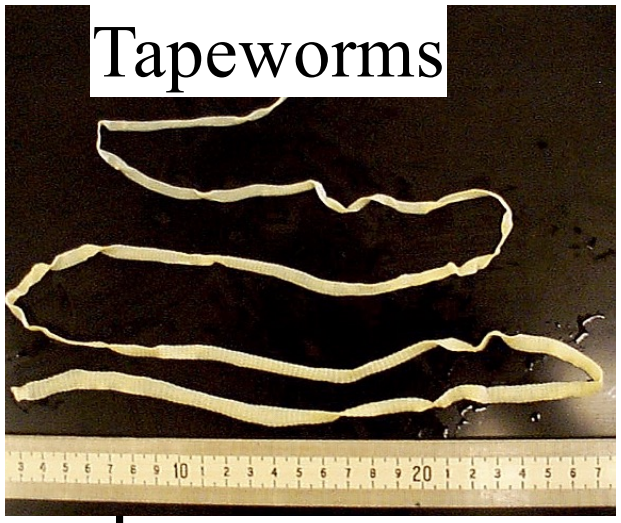


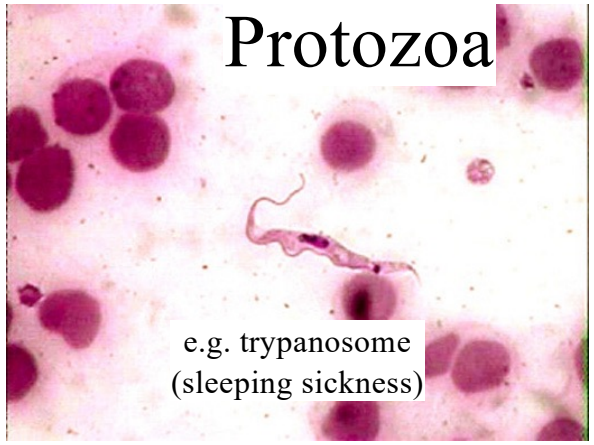


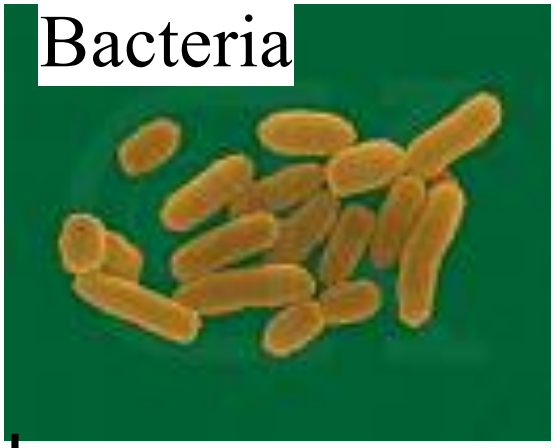


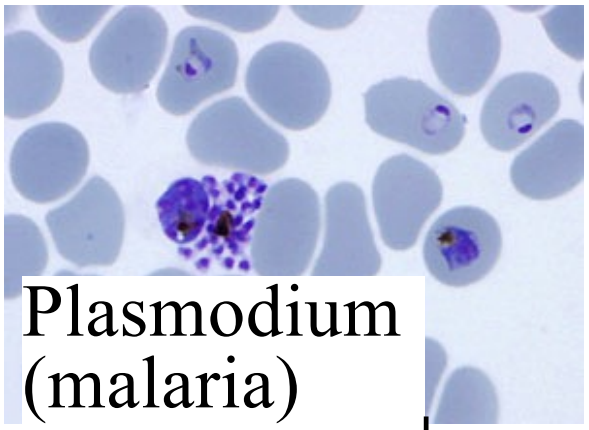
HIV	Tuberculosis	Malaria
Virus	Bacterium	Protozoan
	Prokaryotic	Eukaryotic

Pathogens range in size



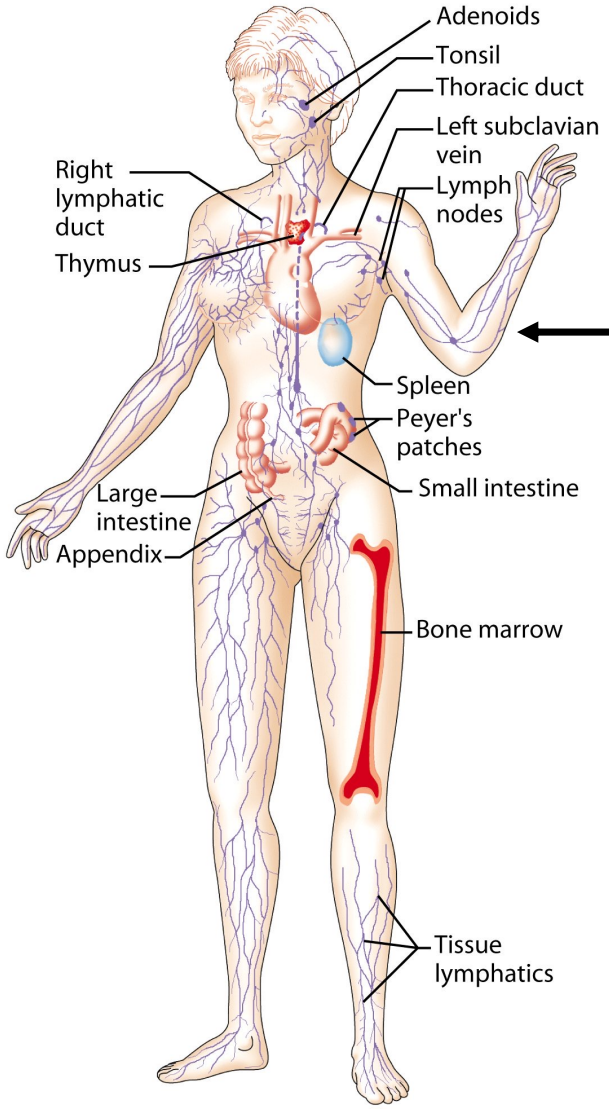






1m 1cm 1mm 0.001mm =1µm 0.01µm

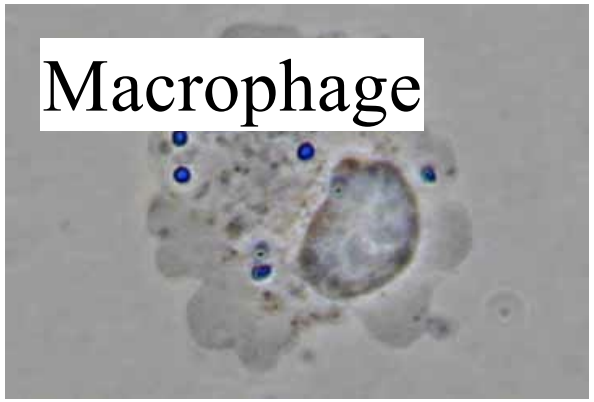
White blood cells circulate through blood vessels and the lymph system

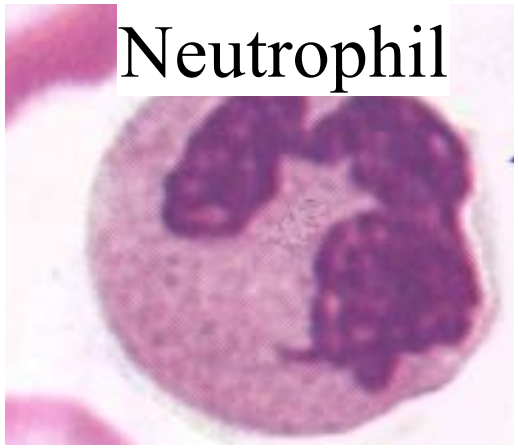


All white blood cells are immune cells, and they provide constant surveillance for signs of infection

The initiation of immune responses often begin in lymph nodes nearest to the site of infection

Innate Immune cells

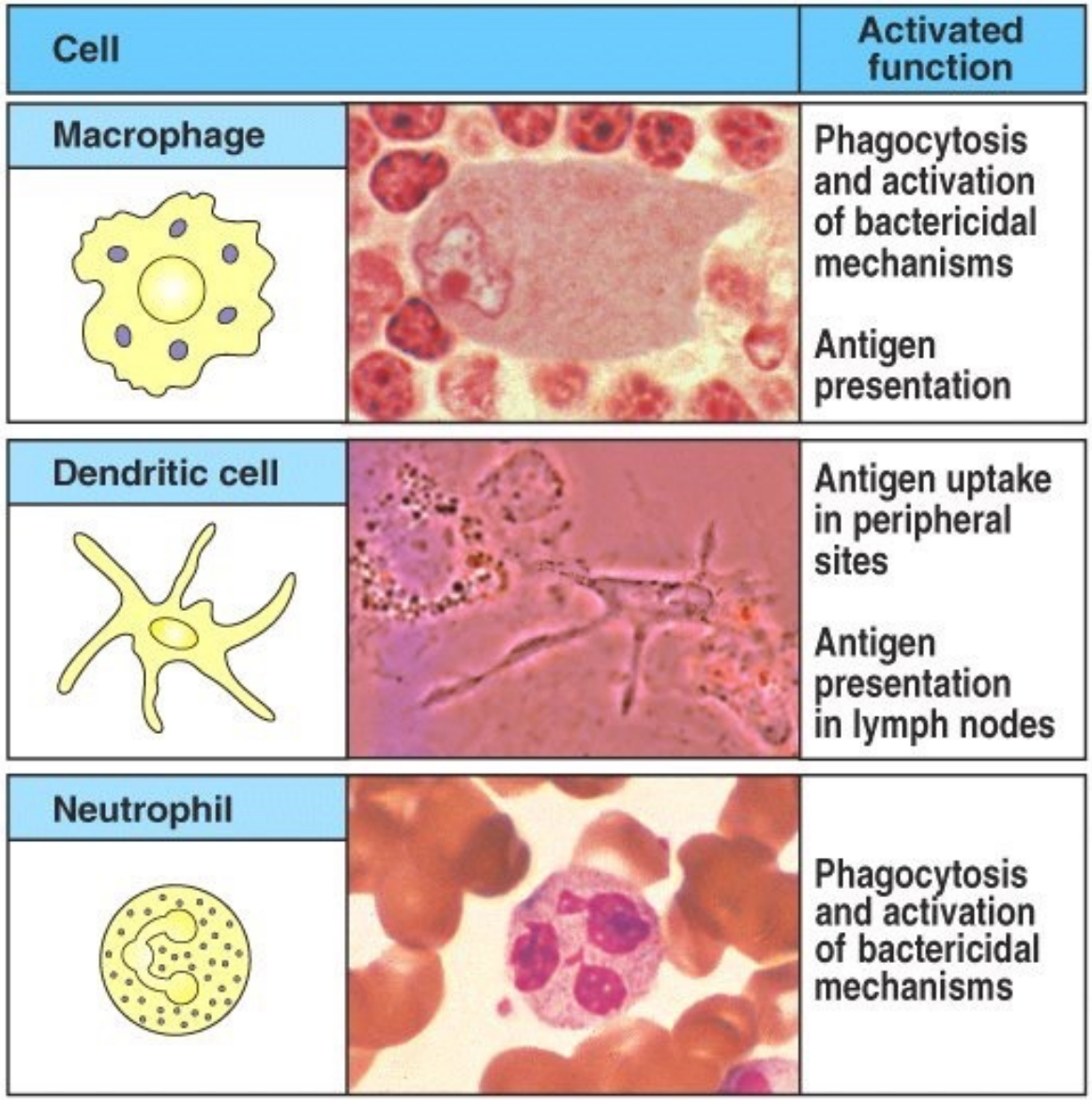




Key aspects of these innate immune cells

1. They are all PHAGOCYTIC and can kill bacteria and virus by engulfing them.
2. Release mediators which directly kill pathogens.
3. They make cytokines that can trigger more inflammation and attract other cells.
4. Macrophages (Macs) /dendritic cells (DCs) play a key role in **activating adaptive immunity**.

Macrophages, Dendritic Cells, and Neutrophils are all Phagocytes (white blood cells that 'eat')

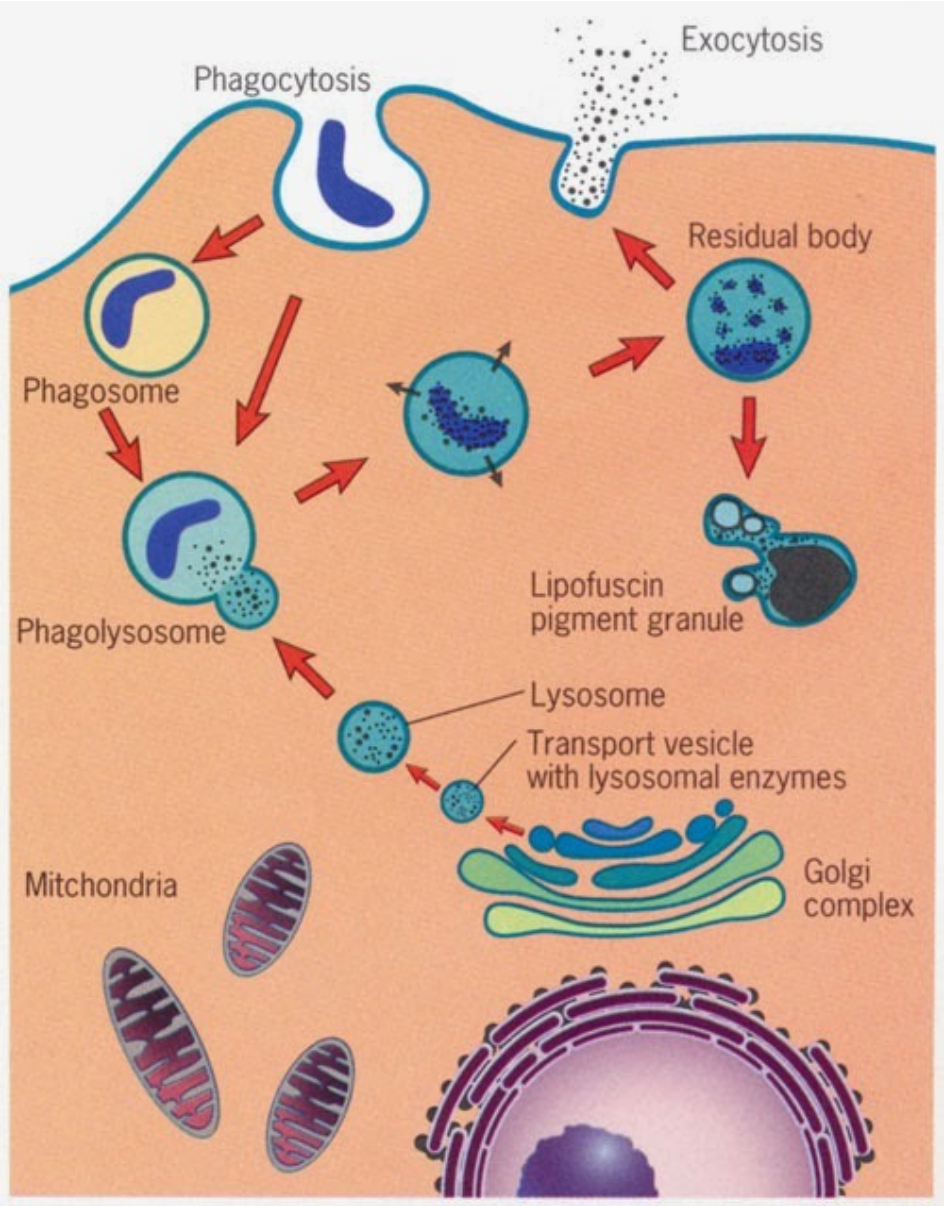


Phagocytosis

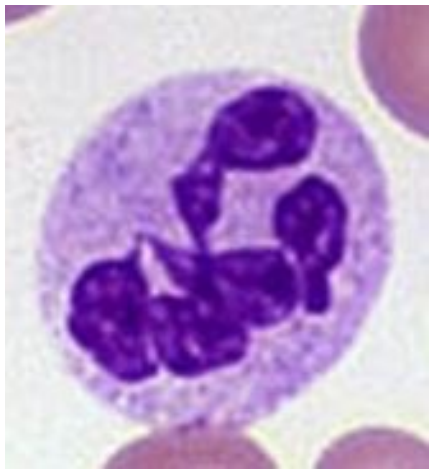
Phagocytosis is the engulfment of particulate material within a membrane-bound intracellular compartment called a phagosome.

The material is degraded by enzymes found in lysosomes.

This mechanism of endocytosis is critical mechanism of innate immunity to ”kill” bacteria and viruses.



Neutrophils are the important cells for killing bacteria



Characteristics of Neutrophils for killing bacteria

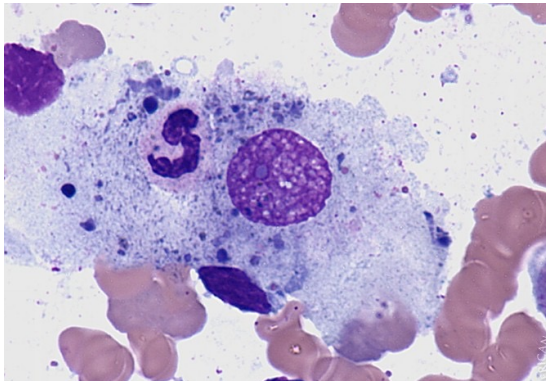
1. Neutrophils are highly phagocytic.
2. Neutrophils are loaded with granules that contain enzymes that kill bacteria
3. Neutrophils are loaded with granules that contain reactive oxygen species that kill bacteria

But they also cause a lot of tissue damage, so they are dangerous cells to unleash

Neutrophils are usually short-lived (1-3 days when activated) but can be replenished quickly from the bone marrow

Note** Neutrophils are also sometimes called Polymorphonuclear cells (PMNs) or Granulocytes

Macrophages and Dendritic Cells (DCs)



- Found in virtually every tissue;
- Like neutrophils, macrophages and DCs can engulf and kill bacteria. But they have additional functions as well, e.g., Phagocytose senescent (old) RBCs and apoptotic (dying) cells, orchestrate wound repair, stimulate adaptive immunity by antigen presentation, etc.
- Secrete dozens of products which orchestrate inflammation including cytokines, proteases, and nucleases.
- A very important function of macrophages and DCs is to detect pathogens. They do this by using special pathogen sensor proteins.

Antimicrobial activities of phagocytes

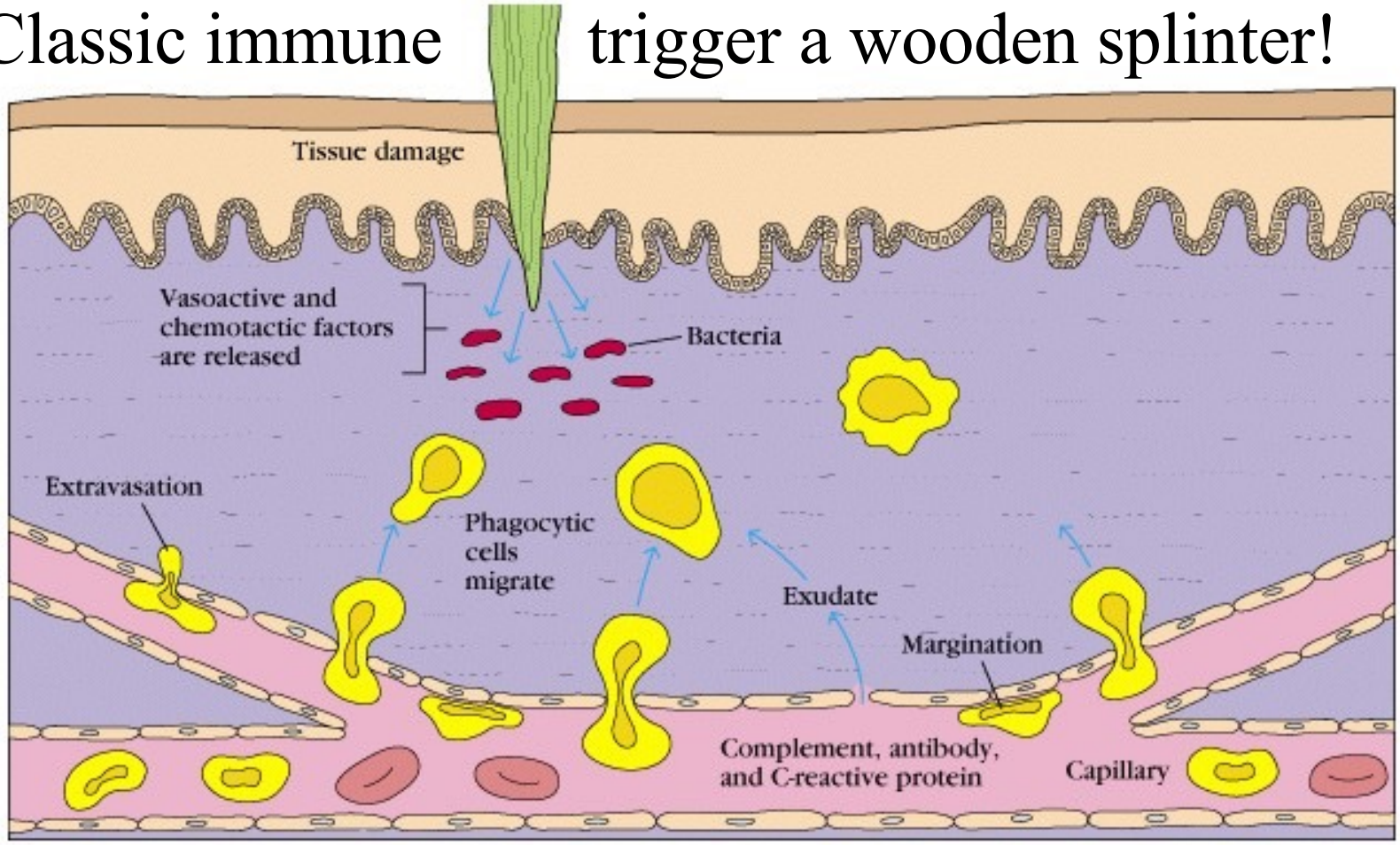
i.e., various ways phagocytes kill bacteria they engulf

Class of mechanism	Specific products
Acidification	pH=~3.5–4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^*$ hydroxyl radical $^*OH$, hypohalite OCl^-
Toxic nitrogen oxides	Nitric oxide NO
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	Lysozyme—dissolves cell walls of some Gram-positive bacteria. Acid hydrolases—further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

Figure 2-9 Immunobiology, 7ed. (© Garland Science 2008)

A primary role of innate immunity is to activate acute inflammation

Classic immune trigger a wooden splinter!



Inflammation is triggered by tissue damage or presence of pathogens.

What are the benefits of acute inflammation?

1. Inflammation brings **innate immune cells** to an infection site to phagocytize (kill) pathogens

2. Inflammation brings **fluid** to "cleanse" site

3. Inflammation brings **immune molecules** (such as antibodies) to the site of infection

4. Inflammation can increase **"signals" to activate adaptive immune system**

Inflammation also causes damage to uninfected cells

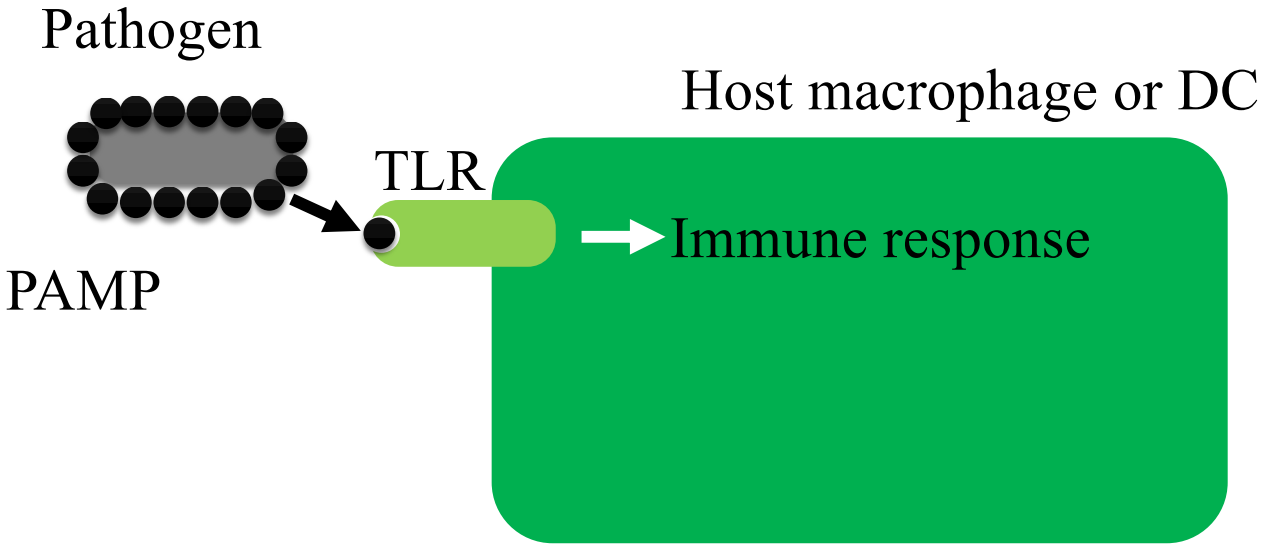
Inflammation is a symptom of damage or infection

Acute inflammation
leads to classic symptoms
Redness Pain
Swelling Heat

The goal of inflammation is to eliminate infection and return tissue to normal. However, excessive acute inflammation can lead to severe disease such as pneumonia resulting from SARS CoV-2 or influenza infection.
(Also, chronic inflammation is part of many diseases including autoimmunity, cancer, heart disease or Alzheimer's. But we will not focus on these diseases.)

How do innate immune cells recognize pathogens?

The cells have Toll-like receptors (TLR) that bind to PAMPs and send signals that start immune responses = inflammation and more



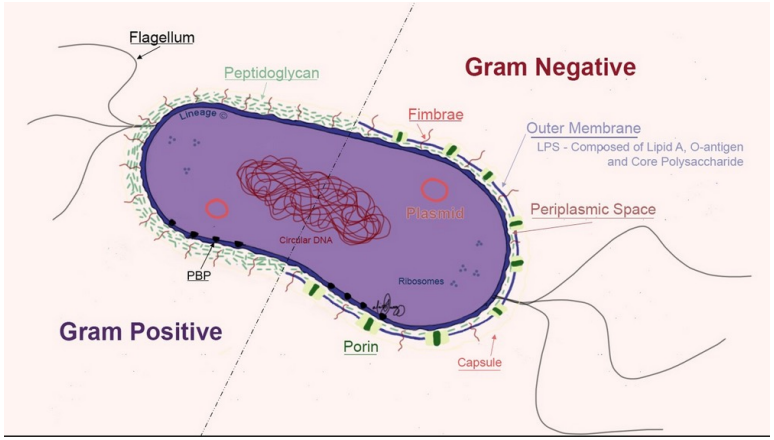
Pathogen-associated molecular patterns (PAMPs)

PAMPs are relatively invariant ("conserved") molecular structures unique to microbes

Examples of PAMPs

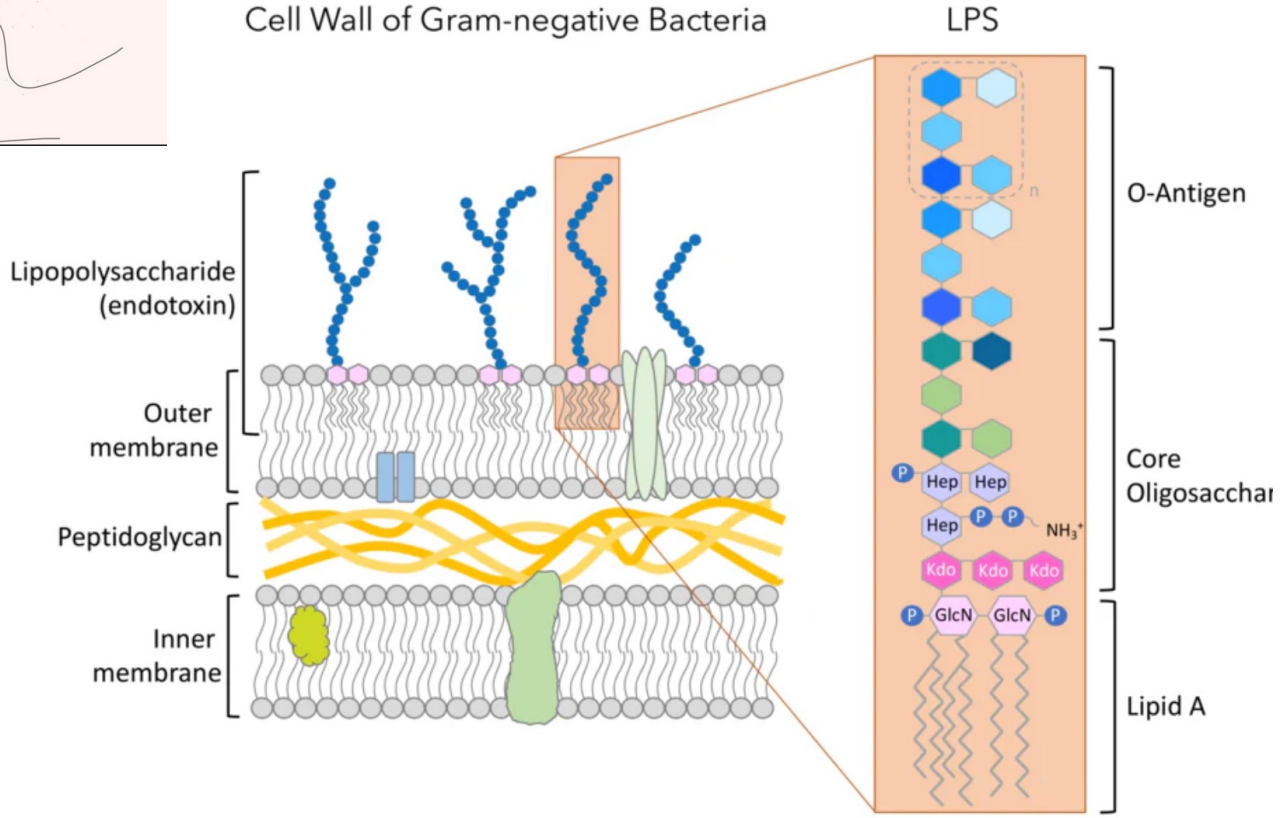
Flagellin, Lipopolysaccharide (LPS) (=part of the outer membrane of gram-negative bacteria), Peptidoglycan (=part of the bacterial cell wall)

Bacterial pathogens have distinct /unique structures



LPS and peptidoglycan are unique and common on bacterial surface.

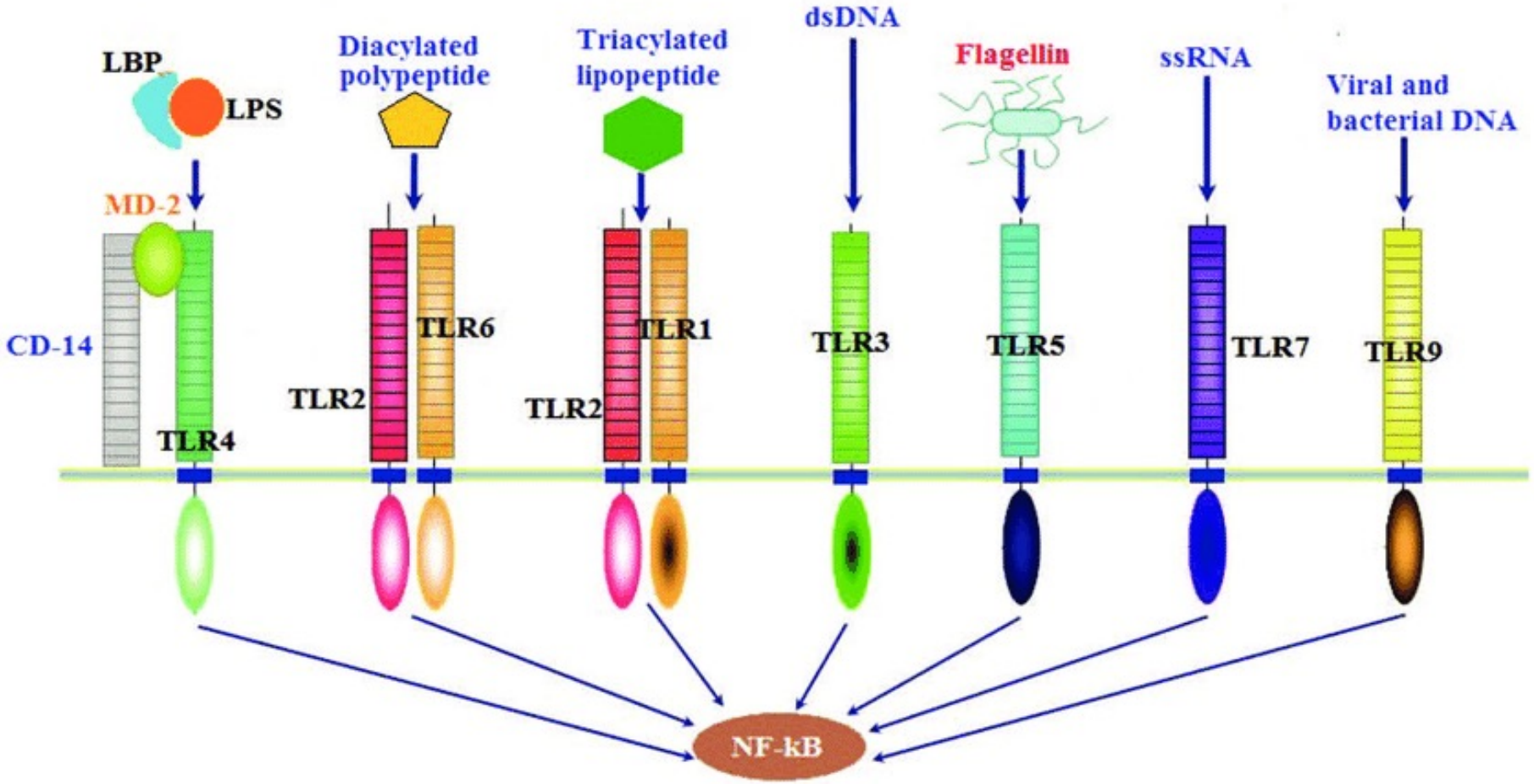
Bacteria (prokaryotes) are structurally distinct from eukaryotes (plants and animals). These distinct surface structures have become PAMPs.



https://abbiosciences.com/blogs/blogs/regarding endotoxin

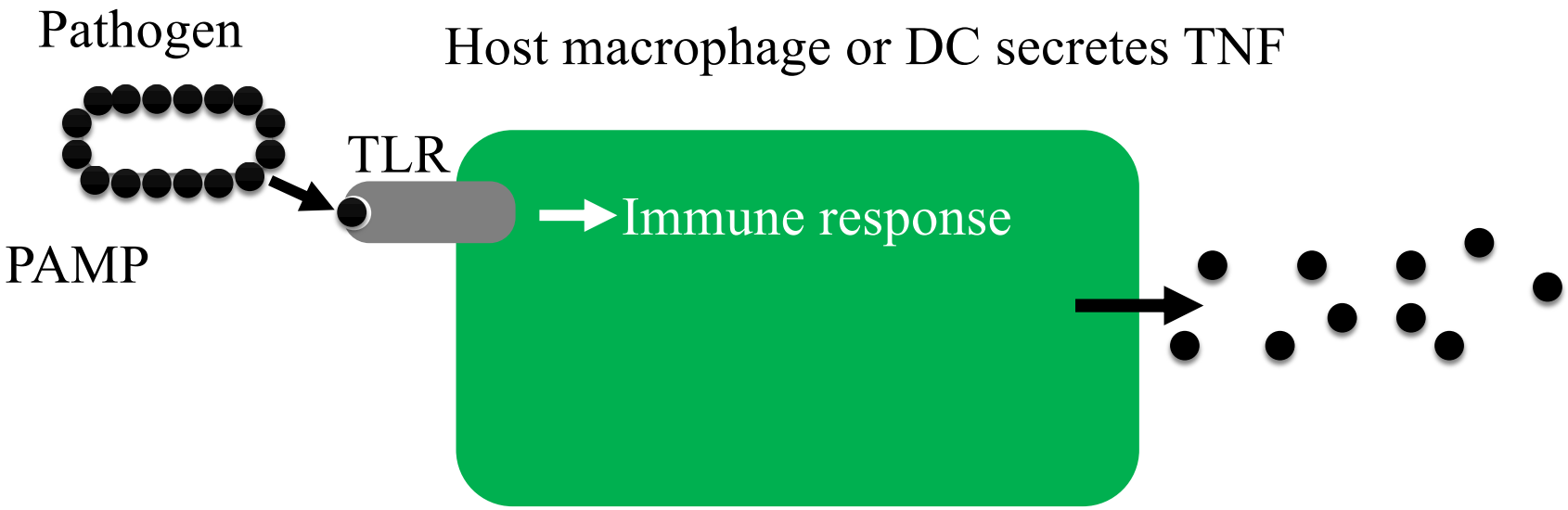
YouTube video on TLRs https://www.youtube.com/watch?app=desktop&v=4aqCKizVBkE

Activation of TLRs by PAMPs on pathogens



Activation of TLRs on macrophages and dendritic cells produces cytokines/chemokines that activate inflammation and act as signals to activate adaptive immunity.

TLR activation will trigger activation of macrophages and DCs to release cytokines



Cytokines are secreted proteins that are considered immune hormones.
TLRs release cytokines that act as 'alert signals' to activate inflammation.

Tumor necrosis factor (TNF) is an example of a cytokine

Cytokines

When cells of the immune system detect a pathogen, they send molecular signals to the rest of the immune system (particularly the adaptive immune system)

These “signals” take the form of secreted proteins called cytokines

These proteins are released at the site of infection and primarily work close by but can travel through the blood Importantly these cytokine bind to receptors on other blood cells and thereby transmit signals that increase both innate and adaptive immune responses

Successful immune responses involve a balanced cytokine response

Too much cytokine

=

Activation of too many immune cells

=

‘shock’ or death

Too little cytokine

=

Activation of too few immune cells

=

failure to contain infection

Viral DNA and RNA can be PAMPs

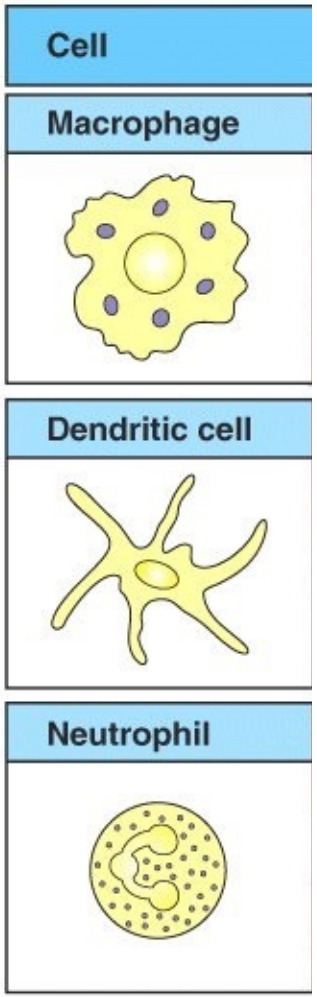
Why don't we recognize our own host cell DNA/RNA?

ANSWER: when DNA or RNA is recognized as a PAMP, it is usually found in a place or form that is distinct from its normal place or form.

EXAMPLES:
1. Viral DNA in the cytosol is a PAMP. Host cell DNA is normally only in the nucleus
2. Double-stranded viral RNA is a PAMP. Host cell self RNA is normally single stranded.

Review of simplified innate immunity

Macrophages and dendritic cells are the key innate immune cells that activate inflammation and adaptive immunity.



Innate immune cells detect pathogens using TLRs that recognize PAMPs.

TLR engagement causes cells to make cytokines that can trigger inflammation and activation of other immune cells.

These cytokines include **TNF** and other cytokines called **interleukins** and **interferons**.