The Immune System

The human immune system is composed of immune organs, immune cells and effecter immune molecules; that work together in a complementary way to protect against infection. The immune system is spread throughout the body, and functions to defend against invading pathogens including viruses, bacteria, parasites and fungi. Moreover, the immune system can also detect and eliminate necrotic, apoptotic and transformed cells such as tumour cells caused by gene mutagenesis .

What is infection?

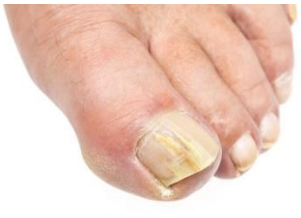
An infection is the invasion of an organism's body tissues by disease-causing agents, and the reaction of host tissues to the infectious agents; and the toxins they produce. Infectious disease, also known as **transmissible disease** or **communicable disease**, is illness resulting from an infection.

An infection happens when a foreign organism enters a person's body and causes harm.

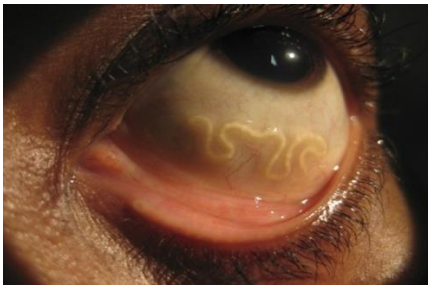
The organism uses that person's body to sustain, reproduce, and colonize. These infectious organisms are known as pathogens. Examples of pathogens include **bacteria, viruses, fungi, and prions**. Pathogens can multiply and adapt quickly.

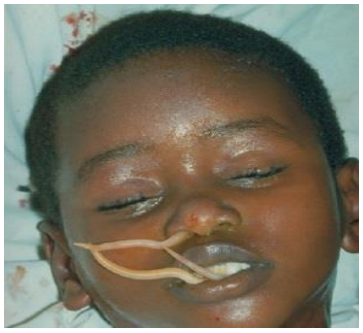
1- **Bacteria:** These one-cell organisms are responsible for illnesses such as strep throat, urinary tract infections and tuberculosis.

2- **Viruses:** Even smaller than bacteria, viruses cause a multitude of diseases ranging from the common cold to **AIDS** (acquired immune deficiency syndromes). A virus is a small infectious agent that replicates only inside the living cells of an organism. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria.

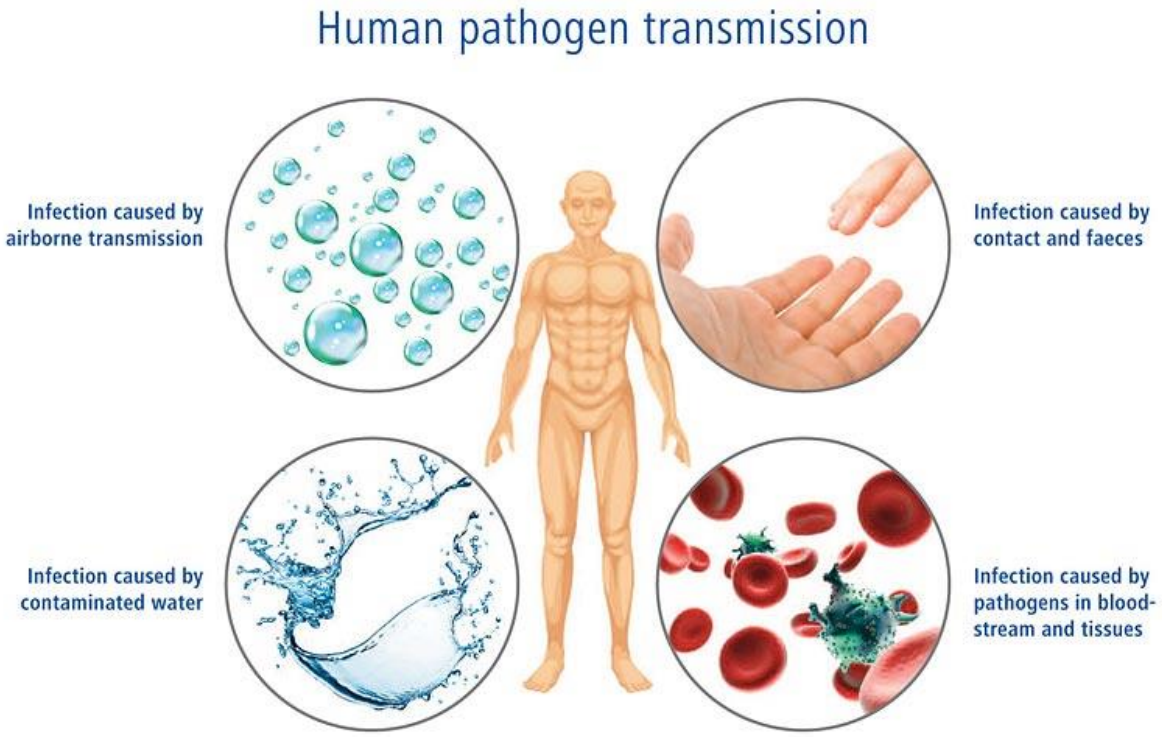


3- **Fungi**

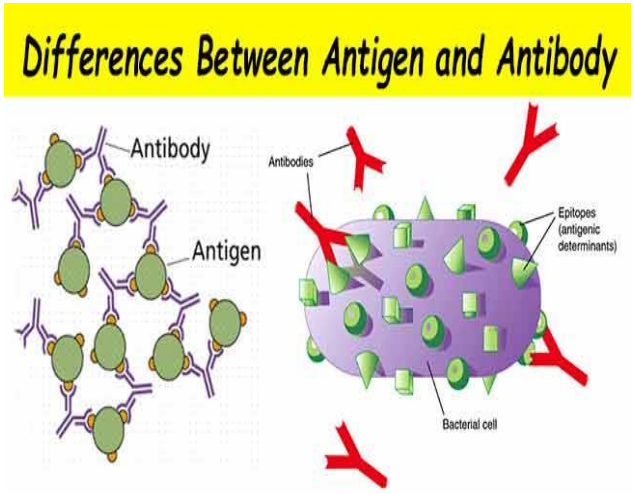


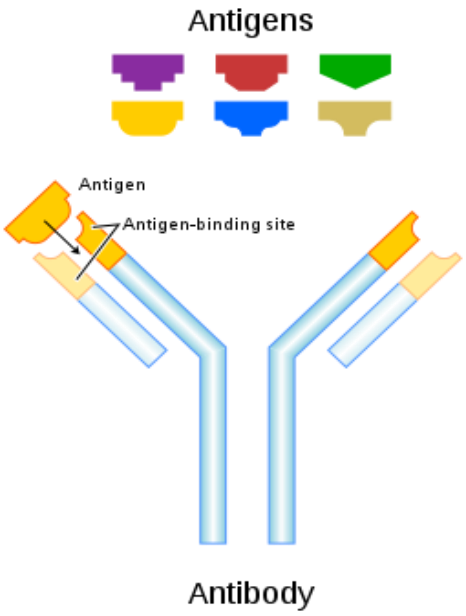


4- **Parasites** like .

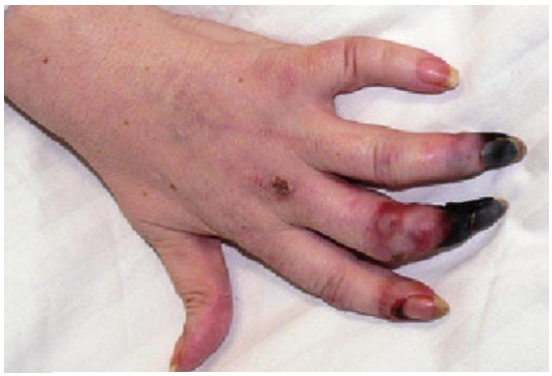


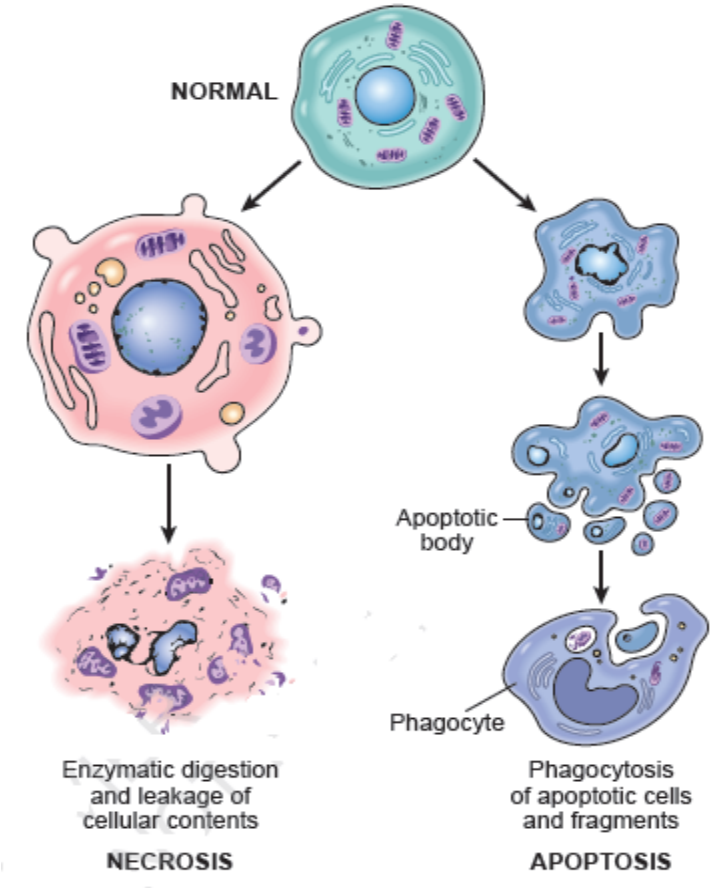
Antigens : The antigen may originate from the body ("self-antigen") or from the external environment ("non-self"). The immune system is supposed to identify and attack "non-self" invaders from the outside world or modified/harmful substances present in the body . Antigens are "targeted" by antibodies





Necrosis is a form of cell injury which results in the premature death of cells in living tissue by autolysis. Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma which result in the unregulated digestion of cell components. In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death. While apoptosis often provides beneficial effects to the organism, necrosis is almost always detrimental and can be fatal. Cellular death due to necrosis does not follow the apoptotic signal transduction pathway, but rather various receptors are activated, and result in the loss of cell membrane integrity and an uncontrolled release of products of cell death into the extracellular space.





Our immune system is essential for our survival. Without an immune system, our bodies would be open to attack from bacteria, viruses, parasites, and more. It is our immune system that keeps us healthy. Crucially, it can distinguish our tissue from foreign tissue or self from non-

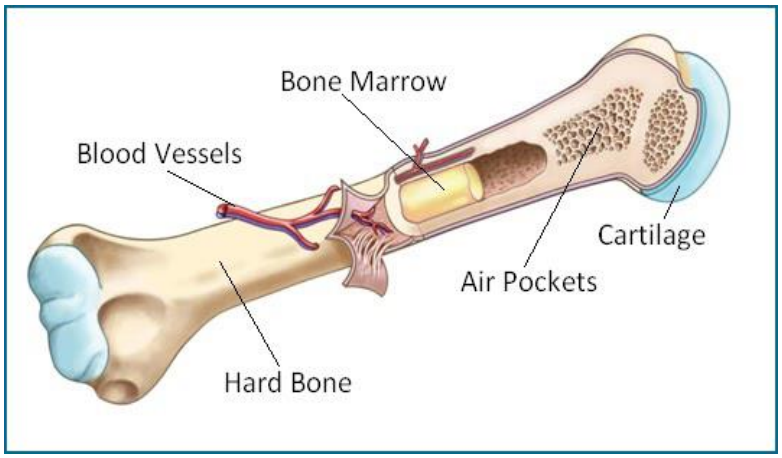
self. Dead and faulty cells are also recognized and cleared away by the immune system. When the immune system encounters a pathogen, for instance, a bacterium, virus, or parasite, then the process called (immune response).

Immune system components:

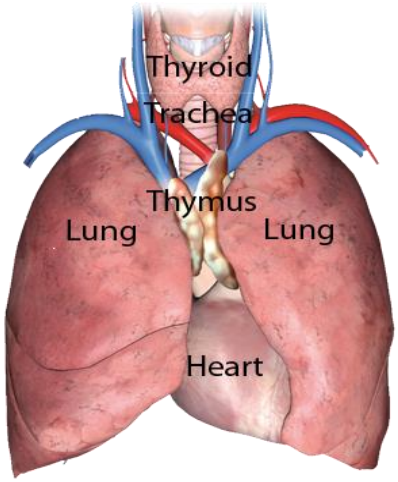
1- Immune organs

a) primary Immune Organs: are those organs where the immune cells are made. These organs include:

- Bone Marrow: a soft tissue inside the bones, and is the birth place of all blood cells, including white blood cells, or lymphocytes, which are the main fighters in the immune system.



2 - Thymus: it is an immune organ responsible for cultivating T-cells, which find both pathogens and infected host cells to destroy them. In children, the T-cells circulate into the thymus, and in the thymus, T-cells mature to recognize what types of cells are self, and what cells are invaders. If the T-cells don't mature properly, a person can develop autoimmune diseases where the T-cells attack the body instead of pathogens.



b) Secondary Immune Organs: are those organs where the lymphocytes fight off invaders. These include:

- Skin and Mucus Membranes: the skin and mucus membranes, like nasal passage, are the first barrier of defence in the immune system.
- Lymph Nodes: Throughout the day, fluid accumulates in the body tissues from the blood vessels. The lymphatic system is a collection of tubes that bring that fluid back to the heart. The lymph fluid also flows through a series of checkpoints called lymph nodes. These are like filtering stations for the blood born pathogens.

- Spleen: The spleen sits in the upper left of the abdomen. spleen's job is to release lymphocytes during an infection and clear out old red blood cells and platelets

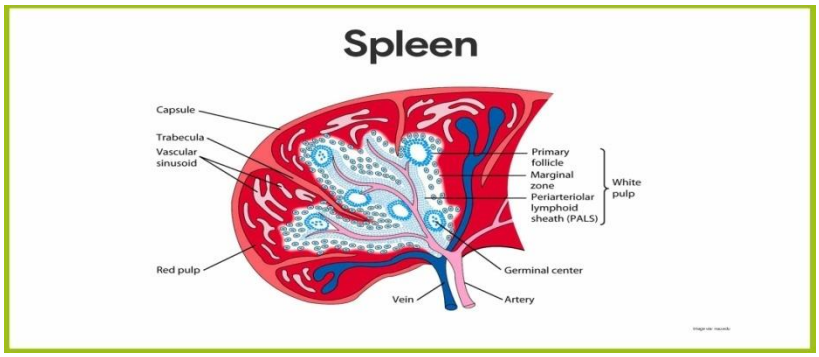


Fig. 3 . the human spleen.

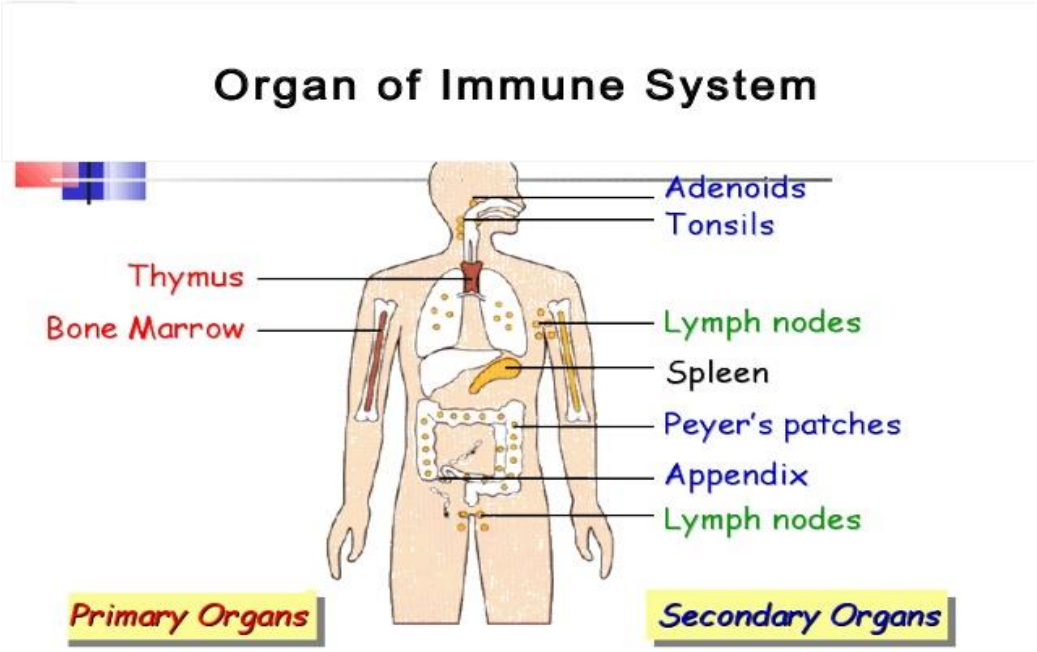


Fig.4 . illustrates primary and secondary immune organs.

- **Immune cells or white blood cells (WBC)**

also called **leukocytes**, they circulate in the body, in blood vessels and the lymphatic vessels , are divided into two types according to immune system:

1- WBCs belong to **innate immunity**

2- WBCs belong to **adaptive immunity**

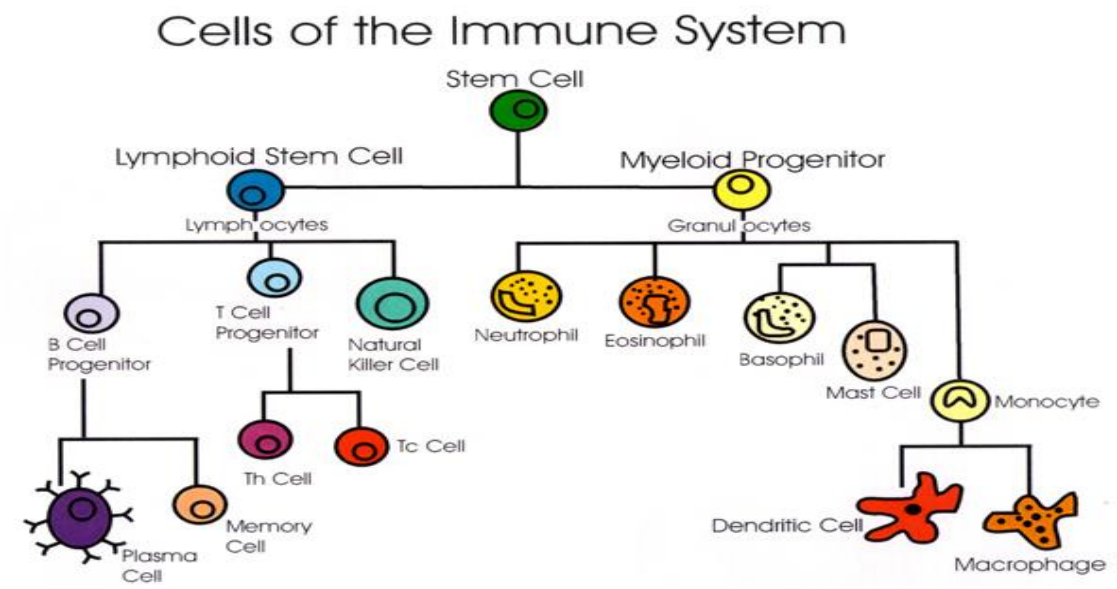


Fig.5. immune cells development

- **Immune molecules**

Cytokines: small proteins or peptides that the cell use to communicate with each other.

Complements: small proteins belong to innate immune system, that eliminate pathogens during innate humeral immune response .

Antibodies: small proteins protects against pathogens, belong to adaptive immunity

Overview of the Immune System

Innate immunity vs Adaptive Immunity

Innate Immunity (first line of defense)	Adaptive Immunity (second line of defense)
No time lag	A lag period
Not antigen specific	Antigen specific
No memory	Development of memory

What is the Innate immune system?

The innate immunity is the first line of defense against pathogens via tissue barrier and innate immune cells and molecules.

It is unspecific, rapid, without immunological memory and controls the infection quickly within the first few days using several strategies

1- Innate immune system function

- Limits infection before adaptive response
- Usually involve nonlymphoid cells(no T and B cells)
- Cells are macrophages and neutrophils.
- Also involves complement and acute phase proteins
- If innate immunity cures infection-no adaptive immunity develops.

2- Innate immune cells

Innate immune cells are developed from myeloid progenitors in the bone marrow, the key innate immune cells including :

1. Neutrophils cells:

- Contain multilobed nucleus
- Neutrophilic granules
- Major cell of acute inflammation
- Their function is to phagocyte cells.

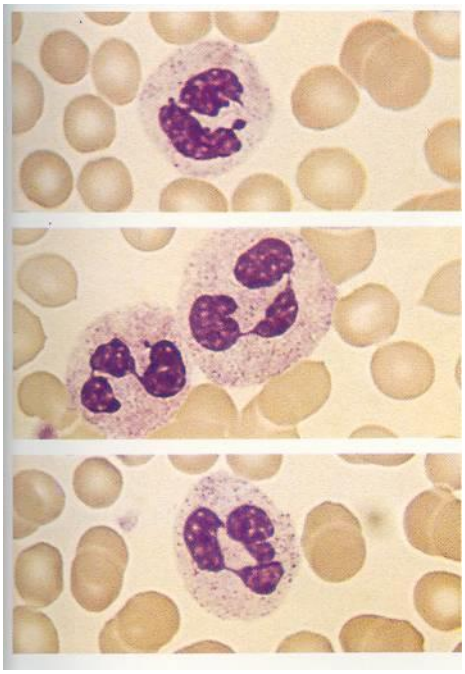


Fig. 6. Neutrophil structure under electronic microscope.

Neutrophils function:

- Bind and phagocytose opsonised antigens
- Regulates activation and recruitment of macrophages by cytokines
- What is Opsonization??: it is an antigen covered by antibodies to make them ready for eating by phagocytic cells).

What is Phagocytosis?

- It is a principal mechanism of pathogens elimination by phagocytic cells
- Taken into vacuole
- Killing by aerobic or anaerobic mechanisms
- Cytokine induction
- Phagocytosis (Phago = to eat .. Cyte = cell)

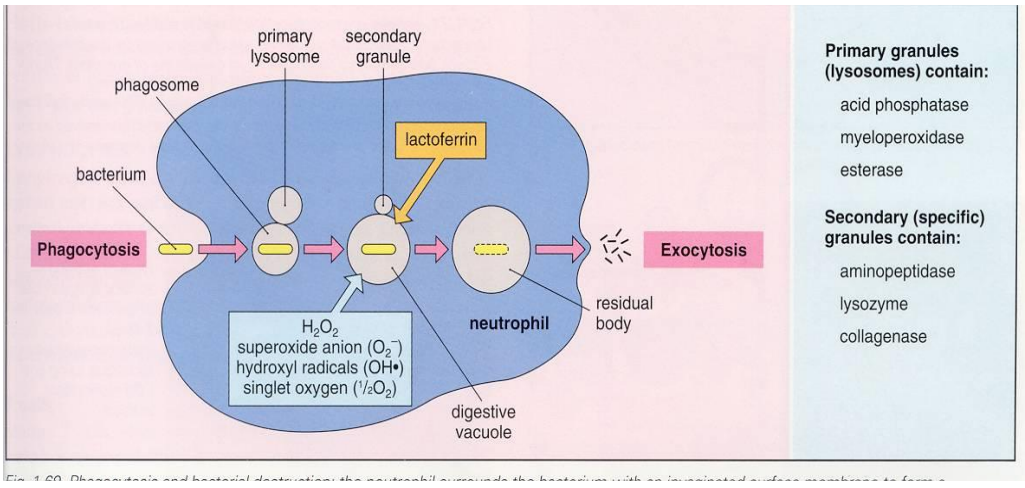


Fig 7. Phagocytosis mechanism

Killing mechanism of phagocytes

1. **Oxygen-dependent intracellular phagocytosis**

- When a phagocyte ingests bacteria, oxygen consumption increase, and the increase in oxygen consumption, called a respiratory burst which produces reactive oxygen species molecules (ROS).
- ROS are anti-microbial are toxic to both the invader and the cell itself, so they are kept in compartments inside the cell.

Oxygen dependent killing mechanism - ROS production (MPO independent)

1) Reaction for super oxide formation

$$NADPH + 2O_2 \xrightarrow{\text{NADPH oxidase}} 2O_2^{-}. + H^+ + NADP^+$$

2) Reaction for hydrogen peroxide formation

$$2O_2^{-}. + 2H^+ \xrightarrow[\text{superoxide dismutase}]{} H_2O_2 + O_2$$

3) Reaction for hydroxyl radical formation

$$O_2^{-}. + H_2O_2 \longrightarrow OH. + OH^- + O_2$$

2. **Oxygen-independent intracellular**

Phagocytes can also kill microbes by oxygen-independent methods, but these are not as effective as the oxygen-dependent ones. There are four main types:

1- The first uses electrically charged proteins that damage the bacterium's membrane

2- The second type uses lysozymes; these enzymes break down the bacterial cell wall .

3. The third type uses lactoferrines, which are present in neutrophil granules and remove essential iron from bacteria. The fourth type uses proteases and hydrolytic enzymes; these enzymes are used to digest the proteins of destroyed bacteria

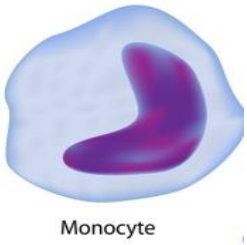
Effector Molecule	Function
Cationic proteins (cathepsin)	Damage to microbial membranes
Lysozyme	Hydrolyses mucopeptides in the cell wall
Lactoferrin	Deprives pathogens of iron
Hydrolytic enzymes (proteases)	Digests killed organisms

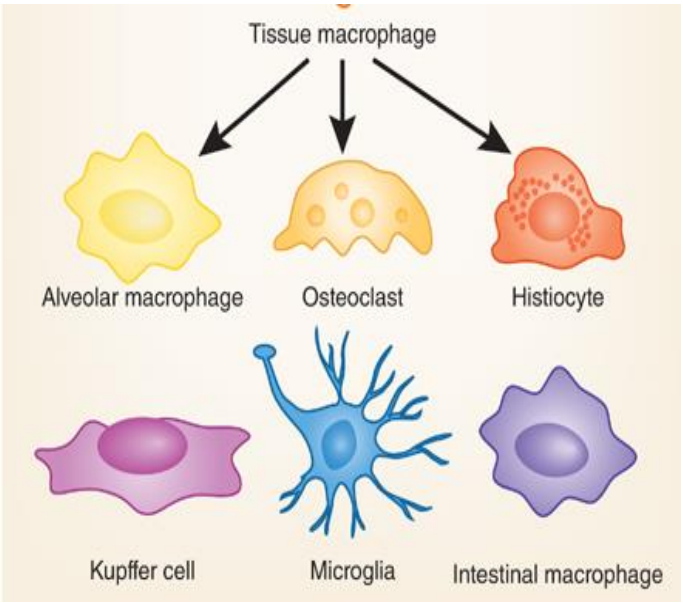
2. **Macrophages** : are generated from monocytes and can differentiate into tissue specific macrophages. The main function of macrophages is their critical role as phagocytic immune cells in the host defence against infectious antigens, cleaning the cell debris and apoptotic cells.

Macrophages function:

- they are Big eaters
- Release inflammatory cytokines
- Act as Antigen Presentation Cell (APC) to T cell.
- Link between innate immunity and acquired humoral and cellular immunity.

3. **Monocytes: m**onocytes (~5% of WBCs), migrate into the tissues and become Macrophages.





4- **Eosinophils:**

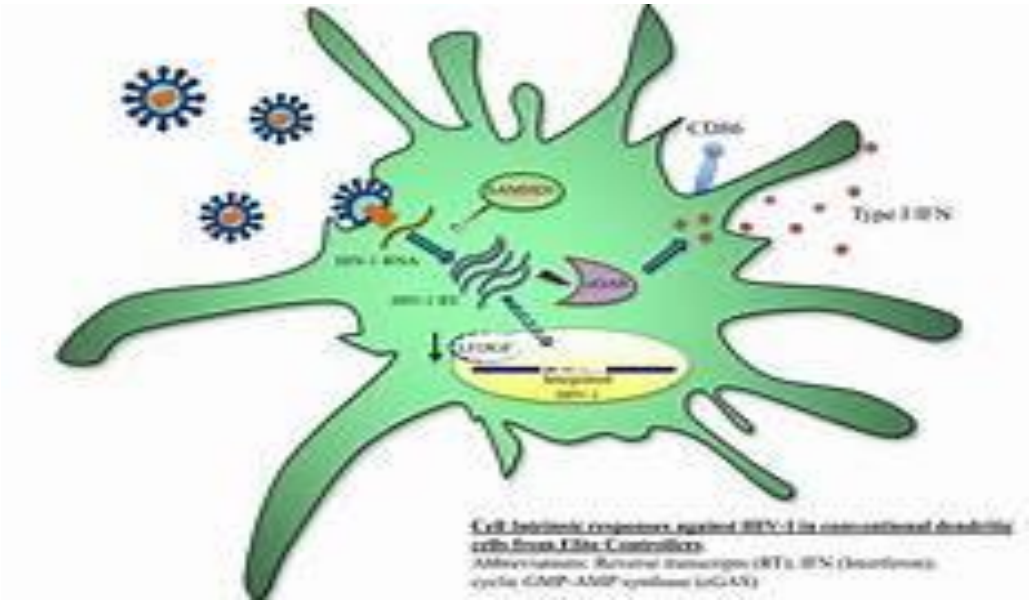
- Contain eosinophilic granules
- Role in immediate hypersensitivity to allergens
- Cause tissue injury and inflammation.

5- Basophils:

- In circulation –basophiles
- In tissue- Mast cells
- Release chemical mediators of immediate hypersensitivity.

6- **Dendritic cells (DCs):**

- Dendritic cells (DCs) are also generated from monocytes. DCs localise in the tissues, their distinct morphology enables them to move to lymph organs all over the body. The main function of DC is to act as professional antigen presenting cell (APC).
- DCs can process antigen, upload it onto their surface major histocompatibility complex (MHC-I) and (MHC-II) molecules and present the peptide antigen to T cells. Thus, DCs are considered to be the key bridging cells between innate and adaptive immunity, in addition, they also generate reactive oxygen species (ROS), NO, and anti-microbial proteins that kill intracellular pathogens.



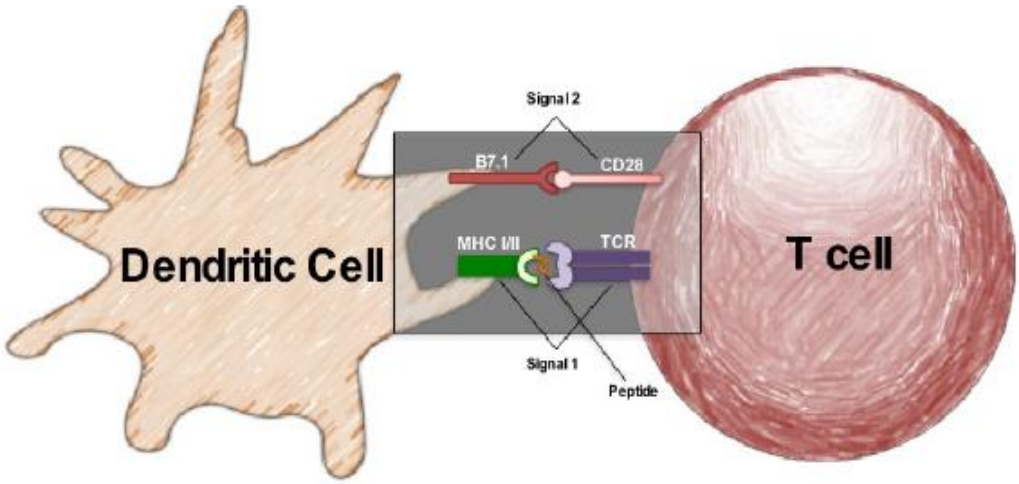
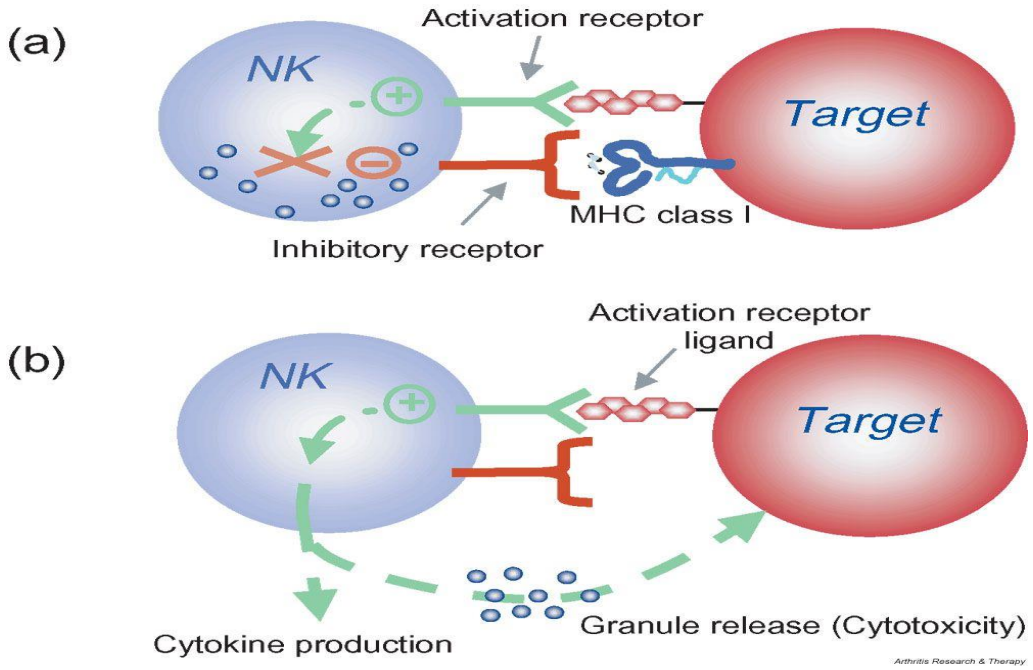


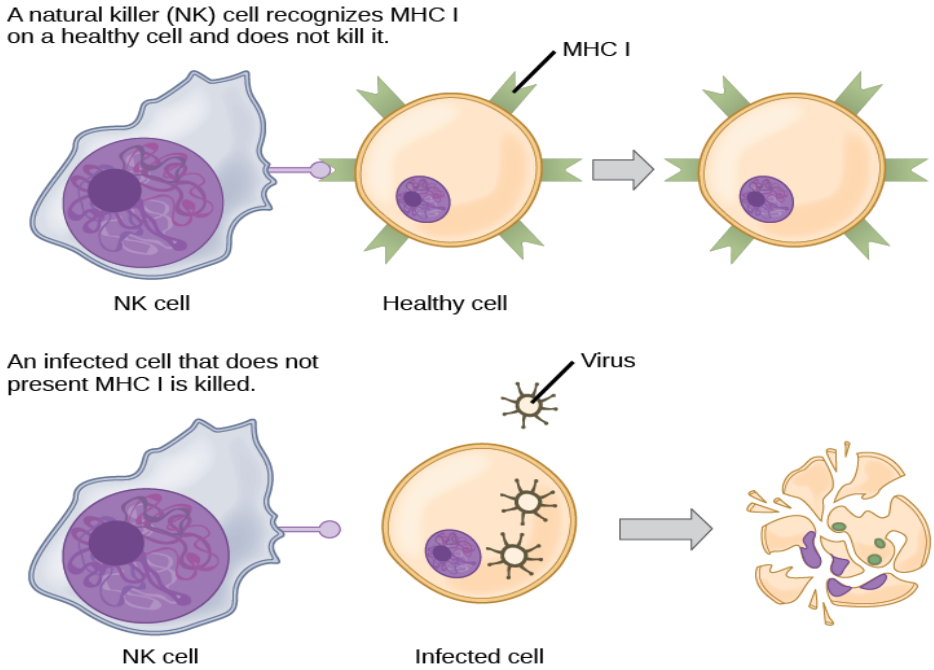
Figure 3. The basics of how a mature dendritic cell activates a T cell via signal 1 and signal 2. Dendritic cells effectively deliver signal 1 by presenting peptide via the MHC to activate the T cell receptor. Signal 2 is critical for complete T cell activation and is done so through ligands specific for the target T cell.

DC presents the antigen to T-cell

7- **Natural killer (NK):** cells NK cells are lymphocytes derived from common lymphoid progenitor, the same as B cells and T cells are derived. However, NKs do not express antigen-binding receptors as B and T cell. They are cytotoxic cells and kill tumour and virus- infected cells..



How does the killer kill ?



The innate immune system has humeral part, which is the complement system that participate in immune response:

The complement system

Complement is a set of plasma proteins that act in a cascade to attack and kill extra cellular pathogen. these small proteins are synthesized by the liver, and circulate in the blood as inactive precursors. Over 30 proteins and protein fragments make up the complement system

Three biochemical pathways activate the complement system:

1- Classical complement pathway

2- Alternative complement pathway

3-lectin pathway Complement

The three terminal effectors pathways of complement work in concert to protect the host from common pathogenic invasions, deficiency in these pathways leads to an impaired host immune response to common pathogens.

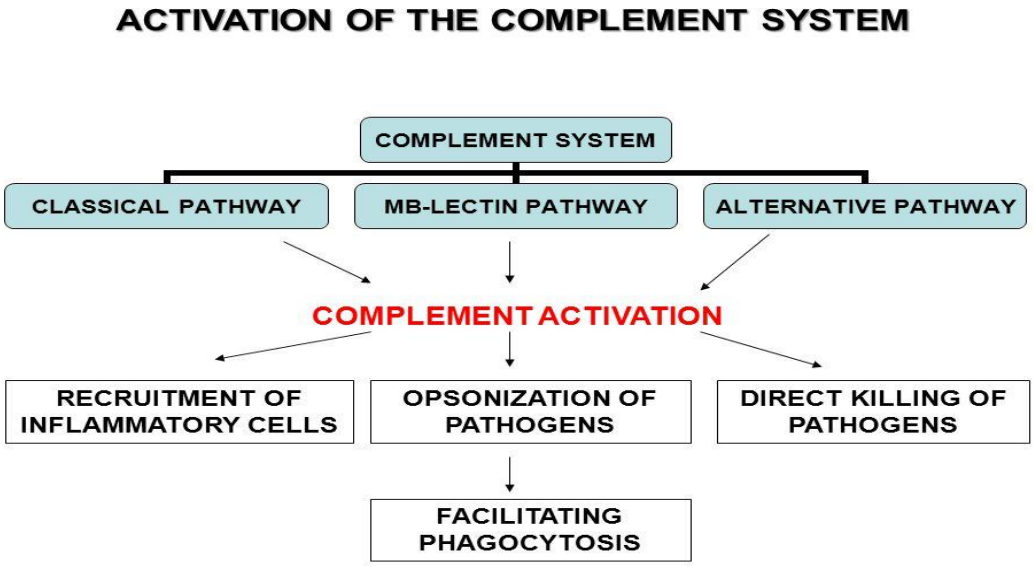
The end result of this complement activation cascade is stimulation of:

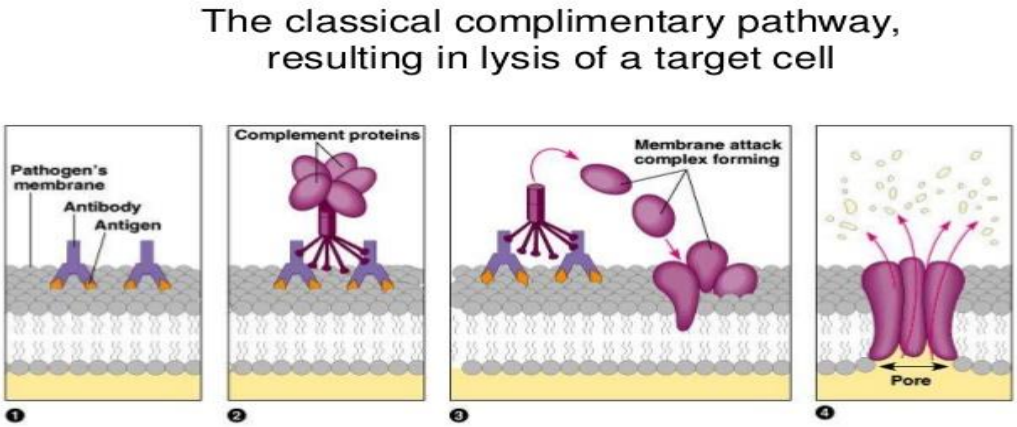
phagocytes to clear foreign and damaged material

inflammation to attract additional phagocytes,

activation of the cell-killing (membrane attack complex).

- The aforementioned functions, oposonization, lysis, and generation of the inflammatory response are component of an innate host defense.





Membrane attack

- Complement **augments the opsonization** of bacteria by antibodies and allows antibodies to kill some bacteria
- Although first discovered as an effector arm of the antibody response, complement can also **be activated early in infection in the absence of antibodies**
- The digestive enzyme pepsin, for example, is stored inside cells and secreted as an inactive precursor enzyme, pepsinogen, which is only cleaved to pepsin in the acid environment of the stomach. The advantage to the host of not being autodigested is obvious.
- In the case of the complement system, the precursor zymogens are widely distributed throughout body fluids and tissues without adverse effect. At sites of infection, however, they are activated locally and trigger a series of potent inflammatory events.
- First, it generates large numbers of activated complement proteins that bind covalently to pathogens, opsonizing them for engulfment by phagocytes bearing receptors for complement.
- Second, the small fragments of some complement proteins act as chemoattractants to recruit more phagocytes to the site of complement activation, and also to activate these phagocytes.
- Third, the terminal complement components damage certain bacteria by creating pores in the bacterial membrane
- the MB-lectin pathway, which is triggered by mannan-binding lectin, a normal serum constituent that binds some encapsulated bacteria; and the alternative pathway, which is triggered directly on pathogen surfaces.

Adaptive immune system

1- T cells

T cells are synthesized in bonmarrow, but develop in the thymus gland. There are two main types of T cells:

1- CD8 T cells (cytotoxic T cells)– Migrate to the site of infection. Kill cells infected with viruses or other intracellular pathogens.

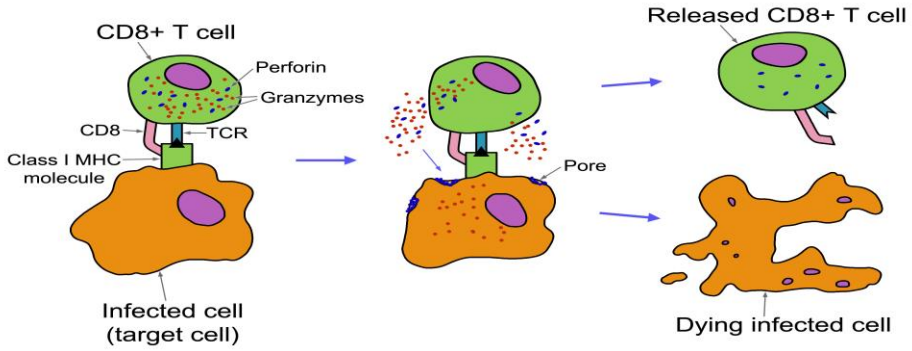
2- CD4 T cells (helper T cells) of two types–express CD4 on their surface:

- **T_H1 cells**– Migrate to the site of infection. Secrete cytokines at site of infection that activate macrophages

T_H2 cells– Stay in secondary lymphoid organs. Secrete cytokines in secondary lymphoid organs that primarily help B cells make Igs

CD8 killing mechanism

Cytotoxic **CD8** T cells carry out their **killing** function by releasing two types of cytotoxic protein: the granzymes, which seem able to induce apoptosis in any type of target cell, and the pore-forming protein perforin, which punches holes in the target-cell membrane through which the granzymes can enter



<u>TH1 and TH2 cells</u>

Most immune responses involve contributions from both T_H1 and T_H2 cells.

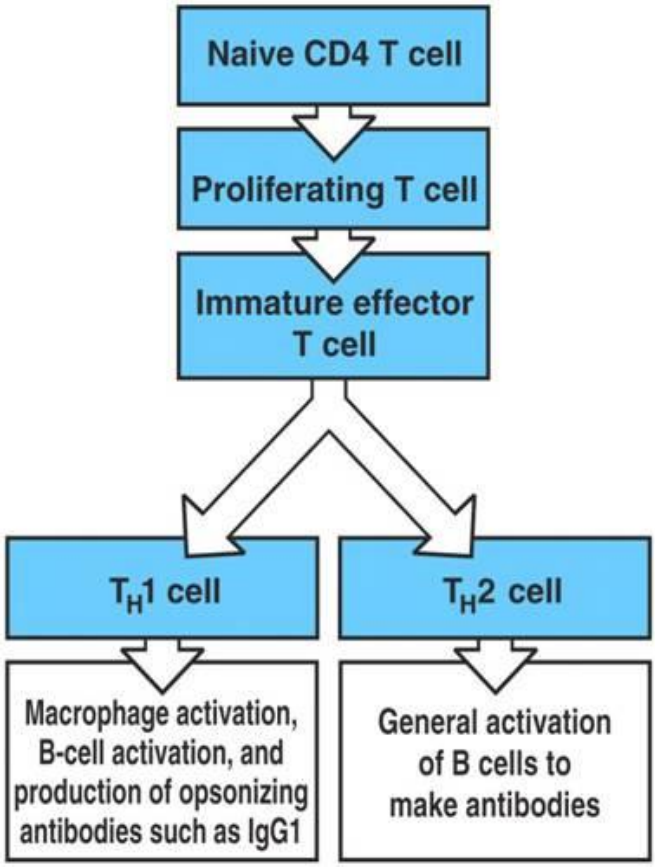
Cytokines secreted by TH1 cells are biased toward a cell mediated immune response dominated by macrophages.

T_H1 cells secretes IFN-g cytokine which activate macrophage respiratory burst

CD8 killing activity: TH1 secrete IL-2 cytokine which is necessary for CD8 driving in to effector CD8 T cell formation and also programs robust memory recall

e **Th1 cells** tend to generate responses against intracellular parasites such as bacteria and viruses,

Th2 cells produce immune responses against helminths and other extracellular parasite

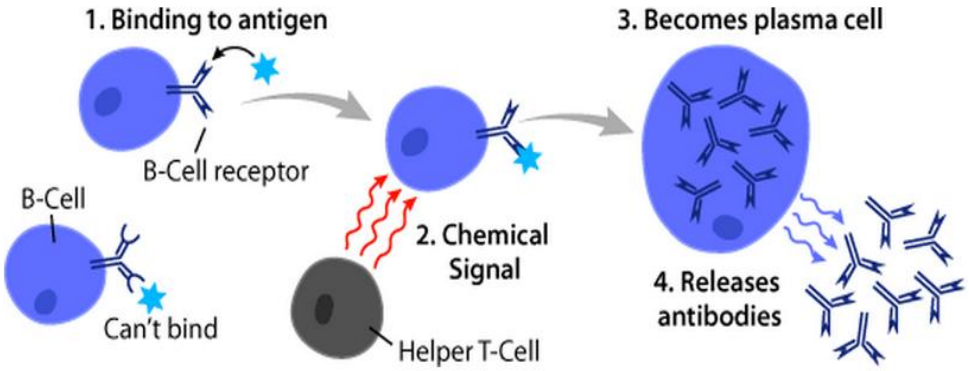


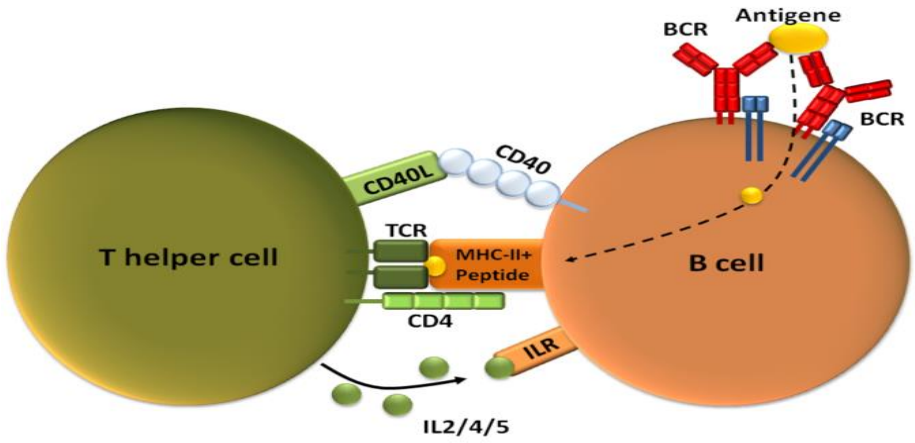
2- B cells

- B cells are produced in the bone marrow and develop their to immature B cells
- When they enter blood and encounter an antigen, they become mature B cells

The human **placenta** manufactures antibodies that may shield the fetus from immune damage, according to new findings. These **placental IgG** antibodies bind to other antibodies and immune cells.
Maternal **IgG** antibodies are known to **cross the placenta** to fortify the immune system of the fetus. maternal **IgG antibodies** may **cross** from mother to fetus by pinocytosis to provide passive immunity in the first few months of life. IgA and IgM **are** excluded from **crossing** the **placenta**. Thus

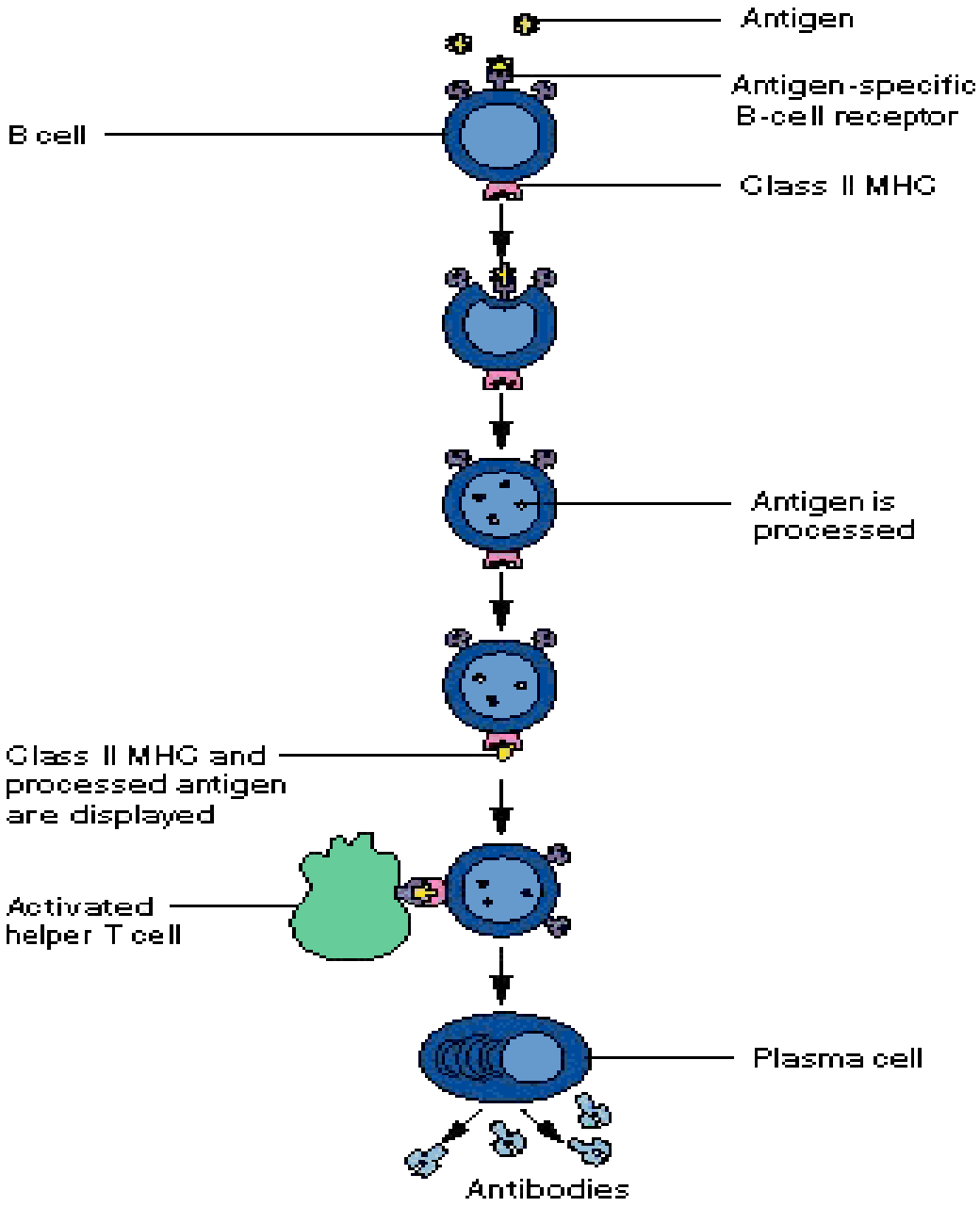
IgM **antibodies** in the newborn indicate a response to intrauterine infection.





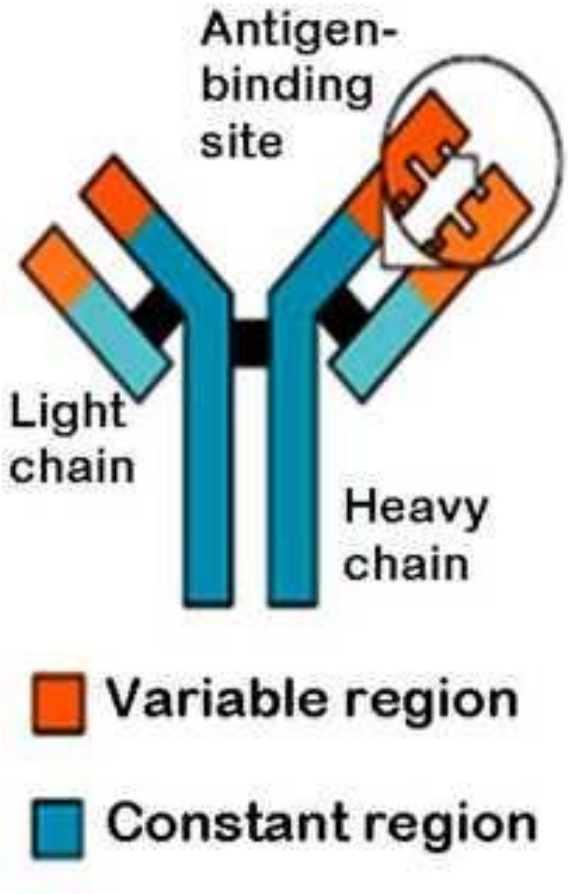
Humeral immune response

1. B lymphocytes recognize specific antigens
   - proliferate and differentiate into antibody-secreting plasma cells
2. Antibodies bind to specific antigens on microbes; destroy microbes via specific mechanisms
3. Some B lymphocytes evolve into the resting state - memory cells.



Antibodies (immunoglobulins)

- Belong to the gamma-globulin fraction of serum proteins
- Y-shaped or T-shaped polypeptides
  - 2 identical heavy chains
  - 2 identical light chains
- All immunoglobulins are not antibodies
- Five kinds of antibodies
  - IgG, IgM, IgA, IgD, IgE .



IgG:

- 70-75% of total immuniglobulin
- Secreted in high quantities in secondary exposures
- Cross the placenta
- Major functions / applications
  - neutralize microbes and toxins
  - opsonize antigens for phagocytosis
  - activate the complement
  - protect the newborn

IgM:

- Secreted initially during primary infection

Cannot cross the placenta

- **Major functions / applications**
  - secreted first during primary exposure
  - activates the complement
  - used as a marker of recent infection.

IgA:

- Monomeric in serum
- Dimeric with secretory component in the lumen of the gastro-intestinal tract and in the respiratory tract.

- **Major function / application**
  - neutralizes microbes and toxins

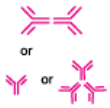
IgD:

- Monomeric
- **Major functions / applications**
  - present on the surface of B lymphocytes
  - functions as membrane receptor
  - role *unclear*
  - *has a role in antigen stimulated lymphocyte differentiation*

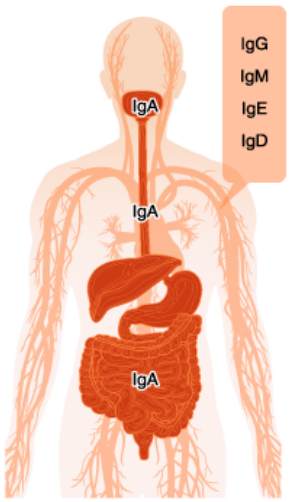
IgE:

- Mediates type I hypersensitivity
- Monomeric
- **Major functions / applications**
  - associated with anaphylaxis
  - plays a role in immunity to helminthic parasites

Types and characteristics of antibodies

IgG		• Highest opsonization and neutralization activities. • Classified into four subclasses (IgG1, IgG2, IgG3, and IgG4).
IgM		• Produced first upon antigen invasion. Increases transiently.
IgA		• Expressed in mucosal tissues. Forms dimers after secretion.
IgD		• Unknown function.
IgE		• Involved in allergy.

Distribution in the body



Innate Immune Response

The innate immune response: innate immune response begins with

1- Physical and Chemical Barriers

Before any immune factors are triggered, the skin functions as a continuous, impassable barrier to potentially infectious pathogens.

- Pathogens are killed or inactivated on **the skin** by desiccation (drying out) and by the skin's acidity. In addition, beneficial microorganisms that coexist on the skin compete with invading pathogens, preventing infection.

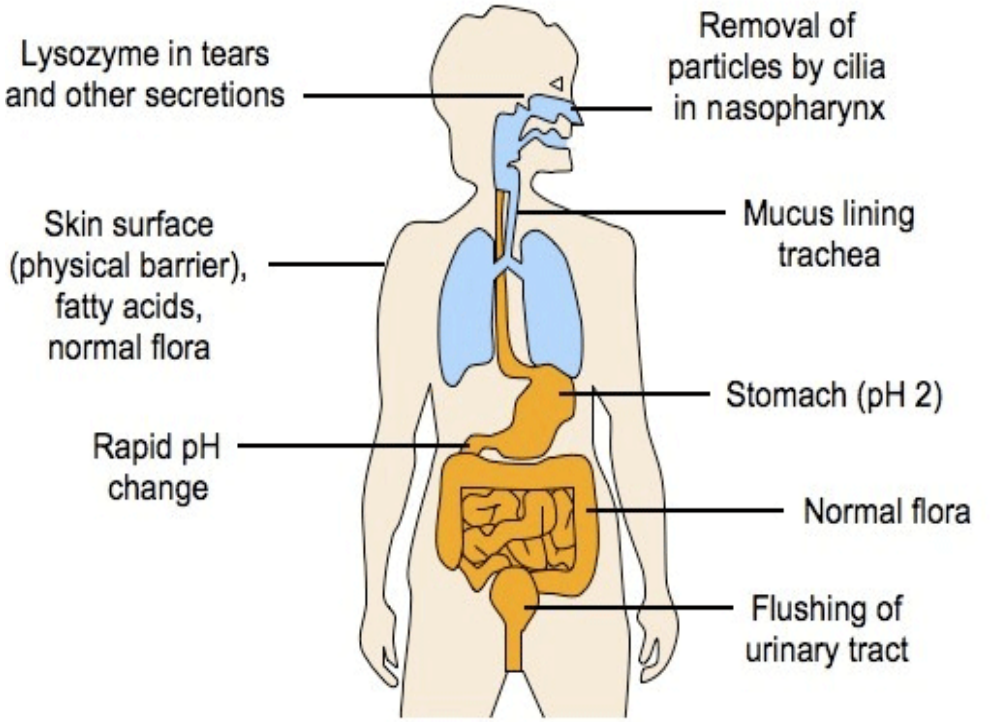
- Regions of the body that are not protected by skin (such as **the eyes and mucus** membranes) have alternative methods of defense, such as tears and mucus secretions that trap and rinse away pathogens, and cilia in the nasal passages and respiratory tract that push the mucus with the pathogens out of the body.

- Throughout the body are other defences, such as the low pH of **the stomach** (which inhibits the growth of pathogens and is fatal to many pathogens, is also a barrier.

- Another barrier is the **saliva in the mouth**, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls.

- Additionally, the mucus layer of the **gastrointestinal tract, respiratory tract**, **eyes, ears, and nose** traps both microbes and debris, and facilitates their removal.

  In the case of the upper **respiratory tract**, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.



Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues

. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

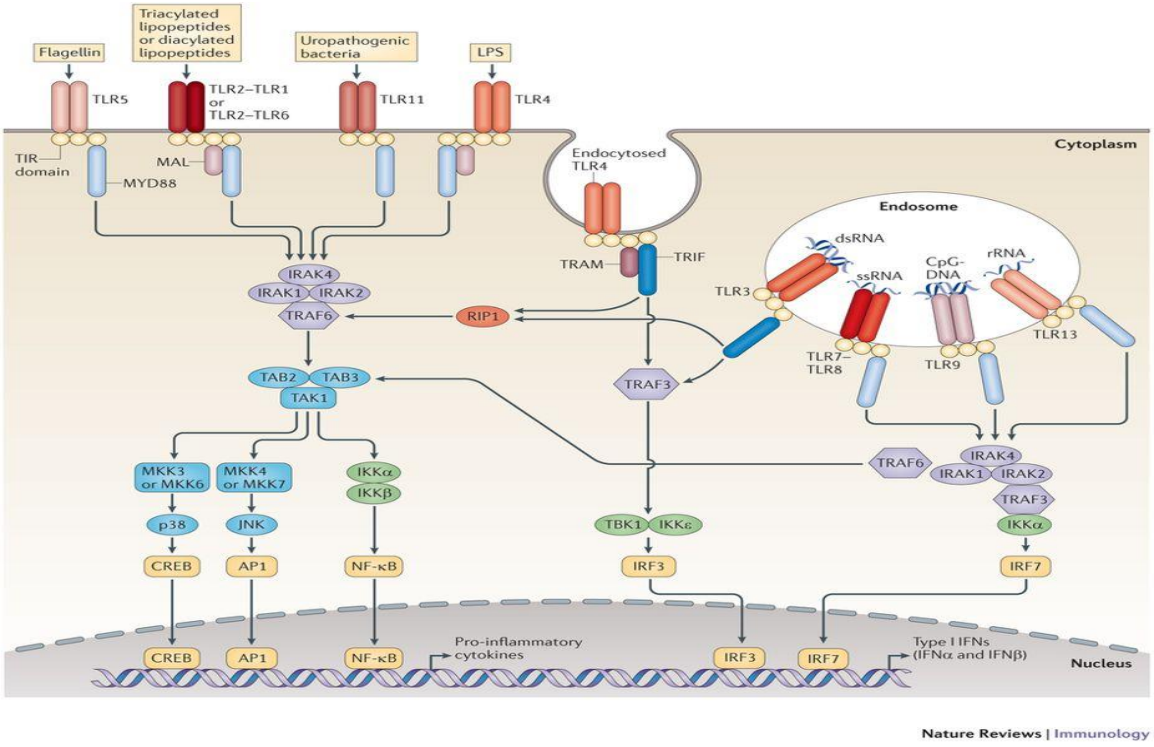
Site	Specific defence	Protective aspect
Skin	Epidermal surface	Keratinized cells of surface,
Skin (sweat/secretions)	Sweat glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH
Mucosal surfaces	Mucosal epithelium	Non-keratinized epithelial cells
Normal flora (non-pathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

Despite these barriers, pathogens may enter the body through skin abrasions or punctures, or by collecting on mucosal surfaces in large numbers that overcome the mucus or cilia. When pathogens do enter the body, the innate immune system responds with inflammation, pathogen engulfment, and secretion of immune factors and proteins.

1- Pathogen Recognition

An infection may be intracellular or extracellular, depending on the pathogen. All viruses infect cells and replicate within those cells (intracellularly), whereas bacteria and other parasites may replicate intracellularly or extracellularly. The innate immune system must respond accordingly: by identifying the extracellular pathogen and/or by identifying host cells that have already been infected.

When a pathogen enters the body, cells in the blood and lymph detect the specific **pathogen-associated molecular patterns (PAMPs)** on the pathogen's surface. PAMPs are carbohydrate, polypeptide, and nucleic acid that are expressed by viruses, bacteria, and parasites, but which differ from molecules on host cells. The immune system cells have receptors that recognize these PAMPs. A **macrophage** is a large phagocytic cell that engulfs foreign particles and pathogens. Macrophages recognize PAMPs via complementary **pattern recognition receptors (PRRs)**. PRRs are molecules on macrophages and dendritic cells which are in contact with the external environment. Toll-like receptors (TLRs) are a type of PRR that recognizes molecules that are shared by pathogens but distinguishable from host molecules). TLRs are present in invertebrates as well as vertebrates, and appear to be one of the most ancient components of the immune system. TLRs have also been identified in the mammalian nervous system.

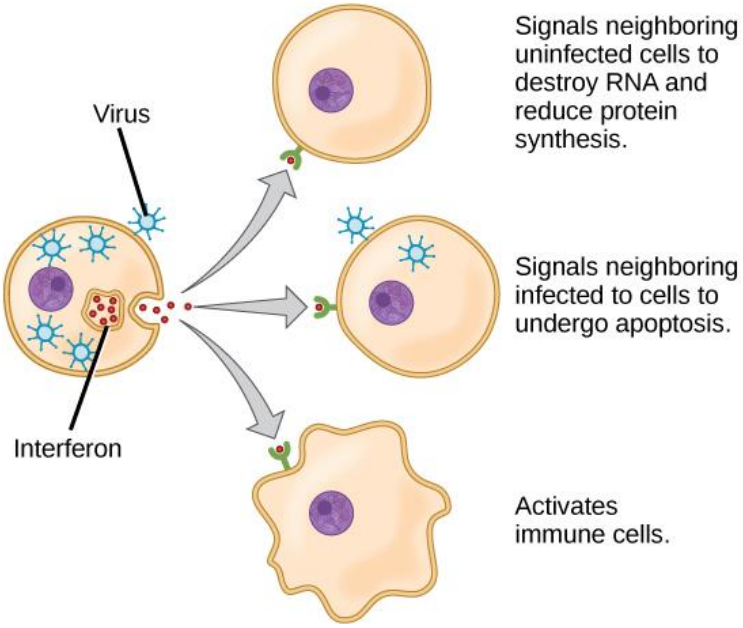


4- Cytokine Release effect

The binding of PRRs with PAMPs triggers the release of cytokines, which signal that a pathogen is present and needs to be destroyed along with any infected cells. A **cytokine** is a chemical messenger that regulates cell differentiation (form and function), proliferation (production), and gene expression to affect immune responses. At least 40 types of cytokines exist in humans that differ in terms of the cell type that produces them, the cell type that responds to them, and the changes they produce.

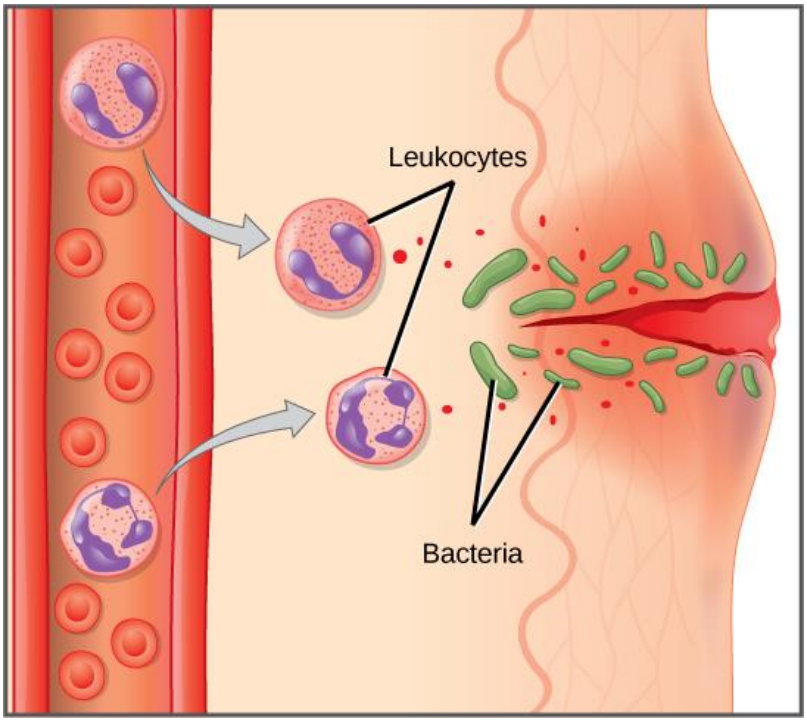
One subclass of cytokines is the interleukin (IL), so named because they mediate interactions between leukocytes (white blood cells). Interleukins are involved in bridging the innate and adaptive immune responses. In addition to being released from cells after PAMP recognition, cytokines are released by the infected cells which bind to nearby uninfected cells and induce those cells to release cytokines, which results in a cytokine burst.

A second class of early-acting cytokines is interferons, which are released by infected cells as a warning to nearby uninfected cells. One of the functions of an **interferon** is to inhibit viral replication. They also have other important functions, such as tumor surveillance. Interferons work by signaling neighboring uninfected cells to destroy RNA and reduce protein synthesis, signaling neighboring infected cells to undergo apoptosis (programmed cell death), and activating immune cells. In response to interferons, uninfected cells alter their gene expression, which increases the cells' resistance to infection. One effect of interferon-induced gene expression is a sharply reduced cellular protein synthesis. Virally infected cells produce more viruses by synthesizing large quantities of viral proteins. Thus, by reducing protein synthesis, a cell becomes resistant to viral infection.



5 - Phagocytosis and Inflammation

The cytokines to be produced are pro-inflammatory; which they encourage **inflammation**, localized redness, swelling, heat, and pain that result from the movement of leukocytes and fluid through increasingly permeable capillaries to a site of infection. Both macrophages and dendritic cells engulf pathogens and cellular debris through phagocytosis. A **neutrophil** is also a phagocytic leukocyte that engulfs and digests.



In response to a cut, mast cells secrete histamines that cause nearby capillaries to dilate.

6- Natural Killer Cells

NK cells identify intracellular infections, especially from viruses, by the altered expression of **major histocompatibility class (MHC) I molecules** on the surface of infected cells. MHC I molecules are proteins on the surfaces of all nucleated cells, thus they are not found on red blood cells and platelets which are non-nucleated. An infected cell (or a tumor cell) is usually incapable of synthesizing and displaying MHC I molecules appropriately. Thus NK cells detect these cells as "unhealthy" or "abnormal" while searching for cellular MHC I molecules. Similarly, the dramatically altered gene expression of tumor cells leads to expression of extremely deformed or absent MHC I molecules that also signal "unhealthy" or "abnormal." NK cells are always active; an interaction with normal, intact MHC I molecules on a healthy cell disables the killing sequence, and the NK cell moves on. After the NK cell detects an infected or tumor cell, its cytoplasm secretes granules comprised of **perforin**, a destructive protein that creates a pore in the target cell. Granzymes are released along with the perforin. A **granzyme** is a protease that digests cellular proteins and induces the target cell to undergo programmed cell death, or apoptosis. Phagocytic cells then digest the cell debris left behind. NK cells are constantly patrolling the body and are an effective mechanism for controlling potential infections and preventing cancer progression.

7- **Complement**

An array of approximately 20 types of soluble proteins, called a **complement system**, functions to destroy extracellular pathogens. Cells of the liver and macrophages synthesize complement proteins continuously; these proteins are abundant in the blood serum and are capable of responding immediately to infecting microorganisms. Complement proteins bind to the surfaces of microorganisms and are particularly attracted to pathogens that are already bound by antibodies.

After the first few complement proteins bind, a cascade of sequential binding events follows in which the pathogen rapidly becomes coated in complement proteins. Complement proteins perform several functions. The proteins serve as a marker to indicate the presence of a pathogen to phagocytic cells, such as macrophages and B cells, and enhance engulfment; this process is called **opsonization**. Certain complement proteins can combine to form attack complexes that open pores in microbial cell membranes. These structures destroy pathogens by causing their content to leak

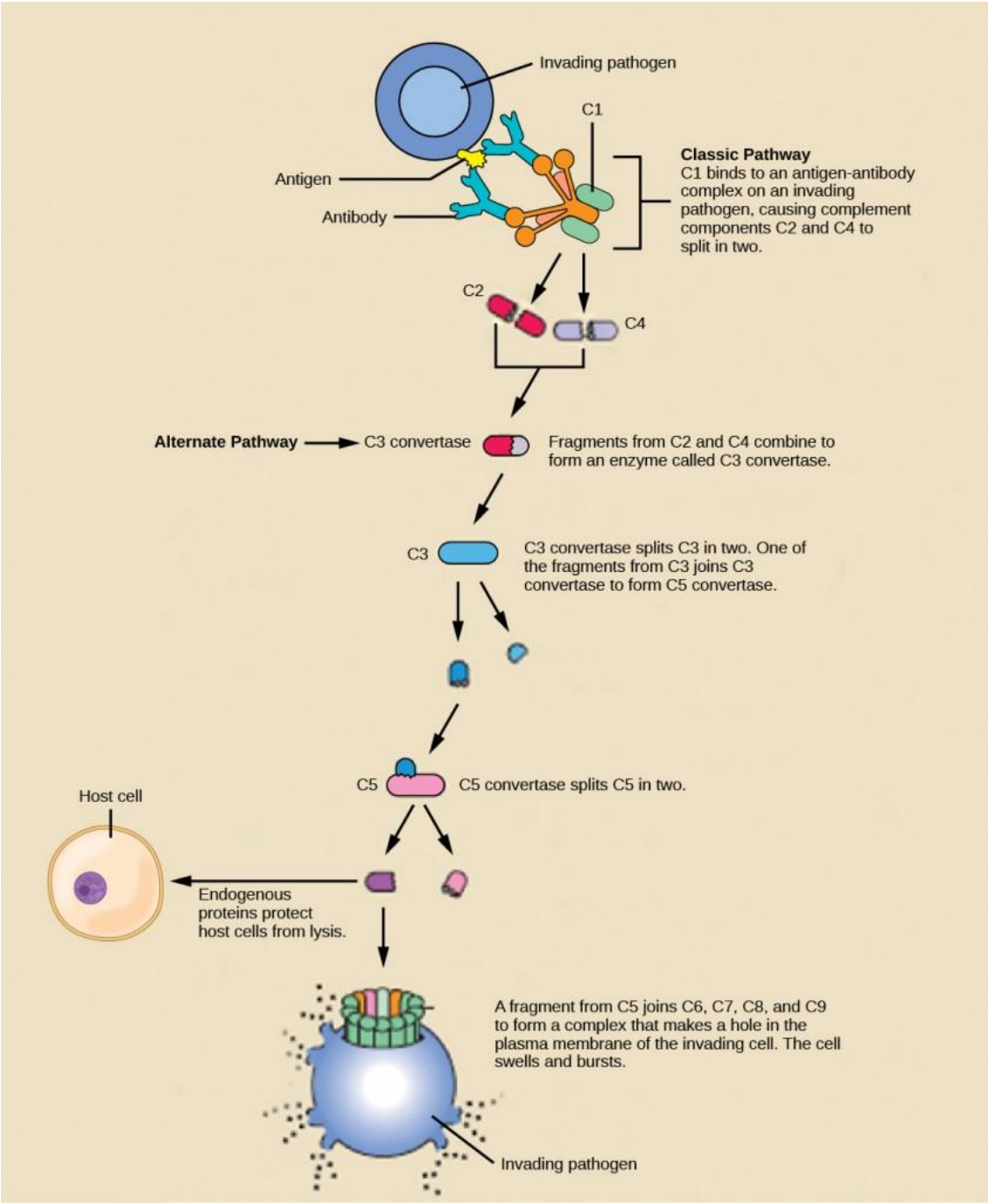


Figure 23.7. The classic pathway for the complement cascade involves the attachment of (للاطلاع) several initial complement proteins to an antibody-bound pathogen followed by rapid activation and binding of many more complement proteins and the creation of destructive pores in the microbial cell envelope and cell wall. The alternate pathway does not involve antibody activation. Rather, C3 convertase spontaneously breaks down C3. Endogenous regulatory proteins prevent the complement complex from binding to host cells. Pathogens lacking these regulatory proteins are lysed. (credit: modification of work by NIH).

Adaptive immunity

The adaptive, or acquired, immune response takes days or even weeks to become established—much longer than the innate response; however, adaptive immunity is more specific to pathogens and has memory. This part of the immune system is activated when the innate immune response is insufficient to control an infection.

There are two types of adaptive responses:

1- The **cell-mediated immune response**, which is carried out by T cells
2- The **humoral immune response**, which is controlled by activated B cells and antibodies.

Activated T cells and B cells that are specific to molecular structures on the pathogen proliferate and attack the invading pathogen. Their attack can kill pathogens directly or secrete antibodies that enhance the phagocytosis of pathogens and disrupt the infection. Adaptive immunity also involves a memory .....why memory???

Answer.....to provide the host with long-term protection from reinfection with the same type of pathogen.

How adaptive immune response happens?

1- Antigen-presenting by Denderitic cells DCs

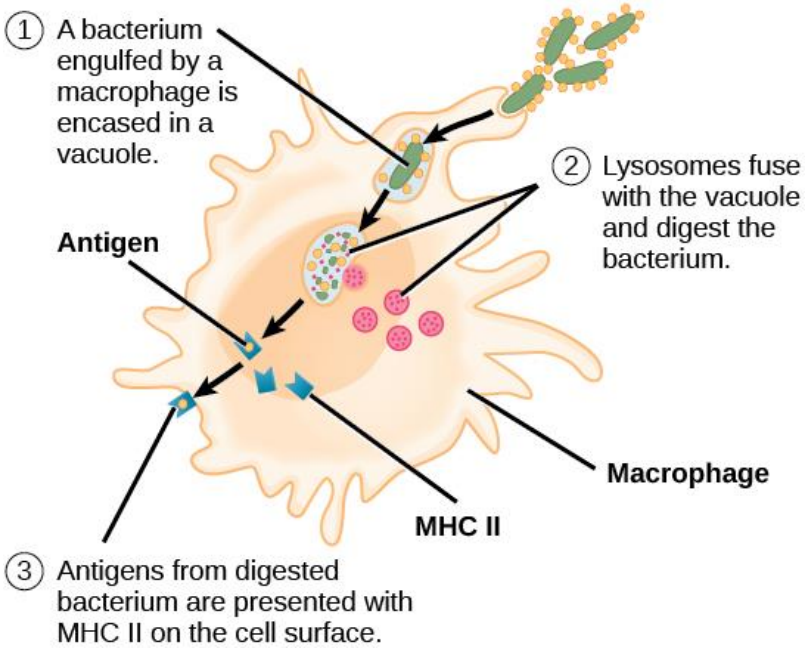
An **antigen-presenting cell (APC)** is an immune cell that detects, engulfs, and informs the adaptive immune response about an infection. When a pathogen is detected, these APCs will phagocytose the pathogen and digest it to form many different fragments of the antigen. Antigen fragments will then be transported to the surface of the APC, uploaded on MHC-ll, where they will serve as an indicator to other immune cells.

Who do Antigen presenting??

Answer : **Dendritic cells** are immune cells that process antigen material; they are present in the skin, and the lining of the nose, lungs, stomach, and intestines. Macrophages also function as APCs.

After phagocytosis by APCs, the phagocytic vesicle fuses with an intracellular lysosome forming phagolysosome. Within the phagolysosome, the components are broken down into fragments; the fragments are then loaded onto MHC class I or MHC class II molecules and are transported to the cell surface for antigen presentation, as illustrated in the figure below,

T lymphocytes cannot properly respond to the antigen unless it is processed and embedded in an MHC II molecule. APCs express MHC on their surfaces, and when combined with a foreign antigen, these complexes signal a “non-self” invader. Once the fragment of antigen is embedded in the MHC II molecule, the immune cell can respond. Helper T- cells are one of the main lymphocytes that respond to antigen-presenting cells.



An APC, such as a macrophage or DCs, engulfs and digests a foreign bacterium. An antigen from the bacterium is presented on the cell surface in conjunction with an MHC II molecule Lymphocytes of the adaptive immune response interact with antigen-embedded MHC II molecules to mature into functional immune cells.

T cells respond to APCs of the innate immune system, and indirectly induce immune responses by releasing cytokines. Other T cells stimulate B cells to prepare their own response.

Naïve T cells can express one of two different molecules, CD4 or CD8, on their surface, and are accordingly classified as $CD4^+$ or $CD8^+$ cells. Naïve $CD4^+$ cells bind APCs via MHC II molecules and are stimulated to become **helper T (T_H) lymphocytes**, cells that go on to stimulate B cells (or cytotoxic T cells) directly or secrete cytokines to inform more and various target cells about the pathogenic threat.

In contrast, $CD8^+$ cells engage antigen-embedded MHC I molecules on APCs and are stimulated to become **cytotoxic T lymphocytes (CTLs)**, which directly kill infected cells by apoptosis and emit cytokines to amplify the immune response.

The two populations of T cells have different mechanisms of immune protection, but both bind MHC molecules via their antigen receptors called T cell receptors (TCRs

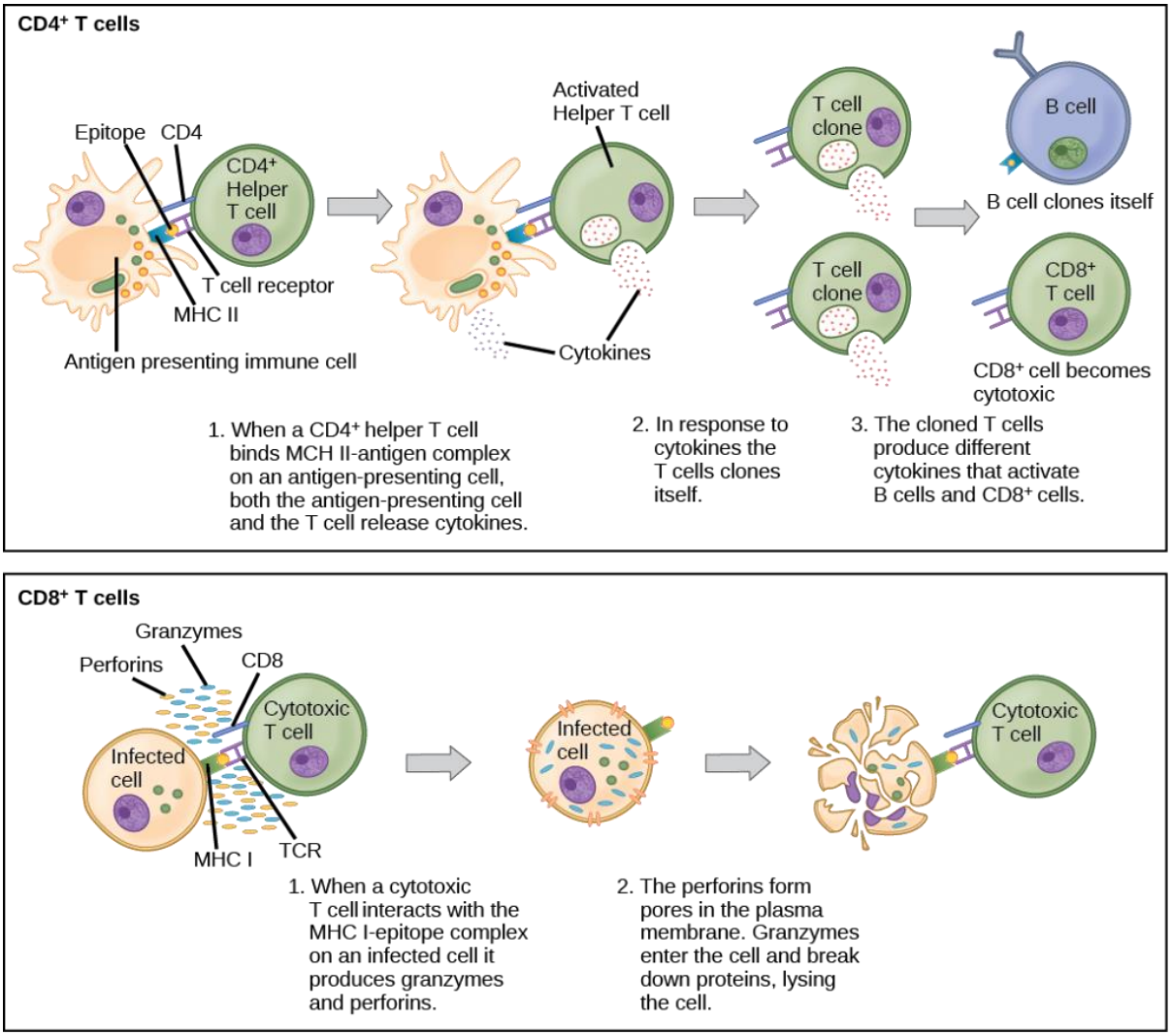


Figure . Naïve CD4+ T cells engage MHC II molecules on antigen-presenting cells (APCs) and become activated. Clones of the activated helper T cell, in turn, activate B cells and CD8+ T cells, which become cytotoxic T cells. Cytotoxic T cells kill infected cells.

B Lymphocytes

When stimulated by the T_H2 pathway, naïve B cells differentiate into antibody-secreting plasma cells. A **plasma cell** is an immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens. B cells bind to antigens by B cell receptors BCR, engulf and present the antigen on their suface bounded to MHC-ll, when T_H2 cell detects that a B cell is bound to a relevant antigen, it secretes specific cytokines that induce the B cell to proliferate rapidly, and then it synthesizes and secretes antibodies with the same antigen recognition pattern as the BCRs

Glossary

B cell

lymphocyte that matures in the bone marrow and differentiates into antibody-secreting plasma cells

basophil

leukocyte that releases chemicals usually involved in the inflammatory response

complement system

array of approximately 20 soluble proteins of the innate immune system that enhance phagocytosis, bore holes in pathogens, and recruit lymphocytes; enhances the adaptive response when antibodies are produced

cytokine

chemical messenger that regulates cell differentiation, proliferation, gene expression, and cell trafficking to effect immune responses

eosinophil

leukocyte that responds to parasites and is involved in the allergic response

granzyme

protease that enters target cells through perforin and induces apoptosis in the target cells; used by NK cells and killer T cells

inflammation

localized redness, swelling, heat, and pain that results from the movement of leukocytes and fluid through opened capillaries to a site of infection

innate immunity

immunity that occurs naturally because of genetic factors or physiology, and is not induced by infection or vaccination

interferon

cytokine that inhibits viral replication and modulates the immune response

lymphocyte

leukocyte that is histologically identifiable by its large nuclei; it is a small cell with very little cytoplasm

macrophage

large phagocytic cell that engulfs foreign particles and pathogens

major histocompatibility class (MHC) I/II molecule

protein found on the surface of all nucleated cells (I) or specifically on antigen-presenting cells (II) that signals to immune cells whether the cell is healthy/normal or is infected/cancerous; it provides the appropriate template into which antigens can be loaded for recognition by lymphocytes

mast cell

leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens and allergens

monocyte

type of white blood cell that circulates in the blood and lymph and differentiates into macrophages after it moves into infected tissue

natural killer (NK) cell

lymphocyte that can kill cells infected with viruses or tumor cells

neutrophil

phagocytic leukocyte that engulfs and digests pathogens

opsonization

process that enhances phagocytosis using proteins to indicate the presence of a pathogen to phagocytic cells

pathogen-associated molecular pattern (PAMP)

carbohydrate, polypeptide, and nucleic acid "signature" that is expressed by viruses, bacteria, and parasites but differs from molecules on host cells

pattern recognition receptor (PRR)

molecule on macrophages and dendritic cells that binds molecular signatures of pathogens and promotes pathogen engulfment and destruction

perforin

destructive protein that creates a pore in the target cell; used by NK cells and killer T cells

T cell

lymphocyte that matures in the thymus gland; one of the main cells involved in the adaptive immune system

MHC II molecules: major histo-compatibility cells type 2