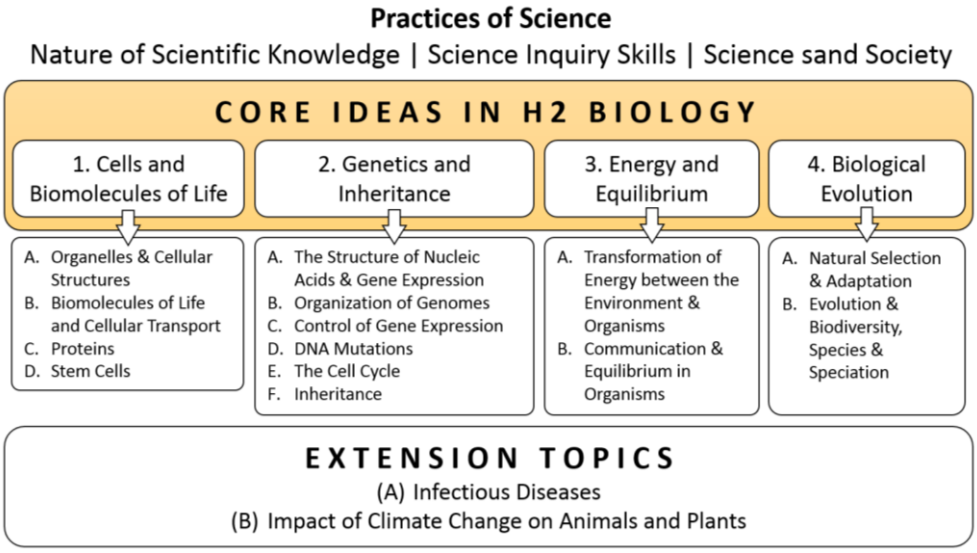
Extension Topic A
14. Immunity and Infectious Diseases



SYLLABUS OVERVIEW		
No.	**Overarching Idea**	**Topics**
1	**Core Idea 1** The Cell and Biomolecules of Life	Cell – The Basic Unit of Life
2		Biomolecules of Life and Cellular Transport
3	**Core Idea 3** Energy and Equilibrium	Transformation of Energy – Photosynthesis and Cellular Respiration
4	**Core Idea 2** Genetics and Inheritance	Genetics and Inheritance (I) – The Cell Cycle
5		Genetics and Inheritance (II) – DNA Replication and Gene Expression
6		Genetics and Inheritance (III) – DNA Mutations and their Consequences
7		Genetics and Inheritance (IV) – Molecular Techniques in DNA Analysis
8		Genetics and Inheritance (V) – Organization of Genome & Control of Gene Expression in Eukaryotes *[Includes Core Idea 1D: Stem Cells]*
9		Genetics and Inheritance (VI) – Organization and Inheritance of Viral Genomes
10		Genetics and Inheritance (VII) – Organization of Genome & Control of Gene Expression in Prokaryotes
11		Genetics and Inheritance (VIII) - Inheritance
12	**Core Idea 3** Energy and Equilibrium	Communication and Equilibrium in Multicellular Organisms
13	**Core Idea 4** Biological Evolution	Biological Evolution
14	**Extension Topic A** Infectious Diseases	Immunity and Infectious Diseases
15	**Extension Topic B** Impact of Climate Change on Animals & Plants	Climate Change – Causes and Impacts on Animals and Plants

TOPIC SYNOPSIS

Micro-organisms, e.g. viruses and bacteria, cause diseases which disrupt the equilibrium of physiological systems in humans. This extension topic explores how some infectious diseases are diagnosed and treated.

The following question should help you frame your learning:

- What cause infectious diseases?
- How does the body respond during an infection?
- How can infectious diseases be prevented or diagnosed and treated?

With an understanding of how the human immune system functions, this concept explores the development of vaccines and vaccines are used to eradicate infectious diseases like smallpox. Yet, not all viruses can be eliminated by vaccines. The influenza virus and HIV infects humans. While treatment is available through vaccines and anti-viral drugs, they are still present in the population due to their high mutation rate. Besides viral infections, diseases can also be caused by bacterial infections. Tuberculosis is caused by the bacteria *Mycobacterium tuberculosis*. Although successful vaccination programs in Singapore have kept the infection under control, there have been new cases appearing in the population and it remains a fatal disease in developing countries.

LEARNING OUTCOMES

Extension Topic A: Infectious Diseases

Candidates should be able to:

a) Describe the specific (adaptive) immune system, including active, passive, natural-acquired and artificially-acquired immunity, and the non-specific (innate) immune system.

b) Outline the roles of B lymphocytes, T lymphocytes, antigen-presenting cells and memory cells in specific primary and secondary immune responses.

c) Explain the relationship of the molecular structure of antibodies to their functions, using immunoglobulin G, IgG, as an example.

d) Explain how somatic recombination, hyper-mutation and class switching result in millions of different antibody molecules.

e) Discuss how vaccination can control disease (e.g. in the eradication of smallpox), limited to vaccination stimulates immunity without causing the disease and vaccination of a high enough proportion of the population can break the disease transmission cycle.

f) Discuss the benefits and risks of vaccination.

g) Explain how viruses, including influenza virus and HIV, cause diseases in humans through the disruption of host tissue and function (e.g. HIV and helper T cells, influenza virus and epithelial cells of the respiratory tract)

h) Explain the mode of transmission and infection of bacterial pathogens, using *Mycobacterium tuberculosis* as an example.

i) Describe the modes of action of antibiotics, including penicillin, on bacteria.

LECTURE OUTLINE

1. Overview of the immune system

2. Innate immunity (non-specific)
- 2.1 Barrier/physical defense
- 2.2 Cellular innate defense
- 2.3 Antimicrobial proteins
- 2.4 Inflammatory response

3. Adaptive immunity (specific)
- 3.1 Antigen recognition by B cells and antibodies
  - 3.1.1 Structure of B cell antigen receptor
  - 3.1.2 Structure of antibody e.g. IgG
- 3.2 Antigen recognition by T cells
- 3.3 Development of B and T cells
  - 3.3.1 Generation of B cell and T cell diversity
  - 3.3.2 Proliferation of B cells and T cells
  - 3.3.3 Immunological memory
- 3.4 Role of T cells, B cells, antigen-presenting cells and memory cells in adaptive immunity
  - 3.4.1 Helper T cell activates B cells and cytotoxic T cells
  - 3.4.2 Cytotoxic T cell kills infected cells
  - 3.4.3 B cell secretes antibodies that bind to and mark pathogens for destruction
  - 3.4.4 Summary of the humoral and cell-mediated immune responses

4. Comparison between innate and adaptive immunity

5. Vaccination and disease control
- 5.1 Types of immunity
- 5.2 Vaccination and the eradication of smallpox virus
- 5.3 Benefits and risks of vaccination

6. Infectious diseases caused by viruses
- 6.1 HIV weakens the immune system by destroying helper T cells
- 6.2 Influenza virus damages respiratory epithelial cells

7. Infectious diseases caused by bacteria
- 7.1 Mycobacterium tuberculosis infects the lung and causes tuberculosis
- 7.2 How antibiotics kill bacteria
- 7.3 How bacteria gain resistance to antibiotics

1. Overview of the immune system

- **Pathogens** e.g. **virus**, **bacterium**, **fungus** are agents that cause diseases and infect a wide range of animals.

- Dedicated **immune cells**, derived from the hematopoietic stem cells in the bone marrow (Fig. 1.1), are found in the body fluids and tissues of most animals. These immune cells specifically interact with and destroy pathogens. Additional responses to infection can take many forms, including proteins that create holes in bacterial membranes or block viruses from entering body cells.

- These and other defenses make up the **immune system,** which enables an animal to avoid or limit many infections.

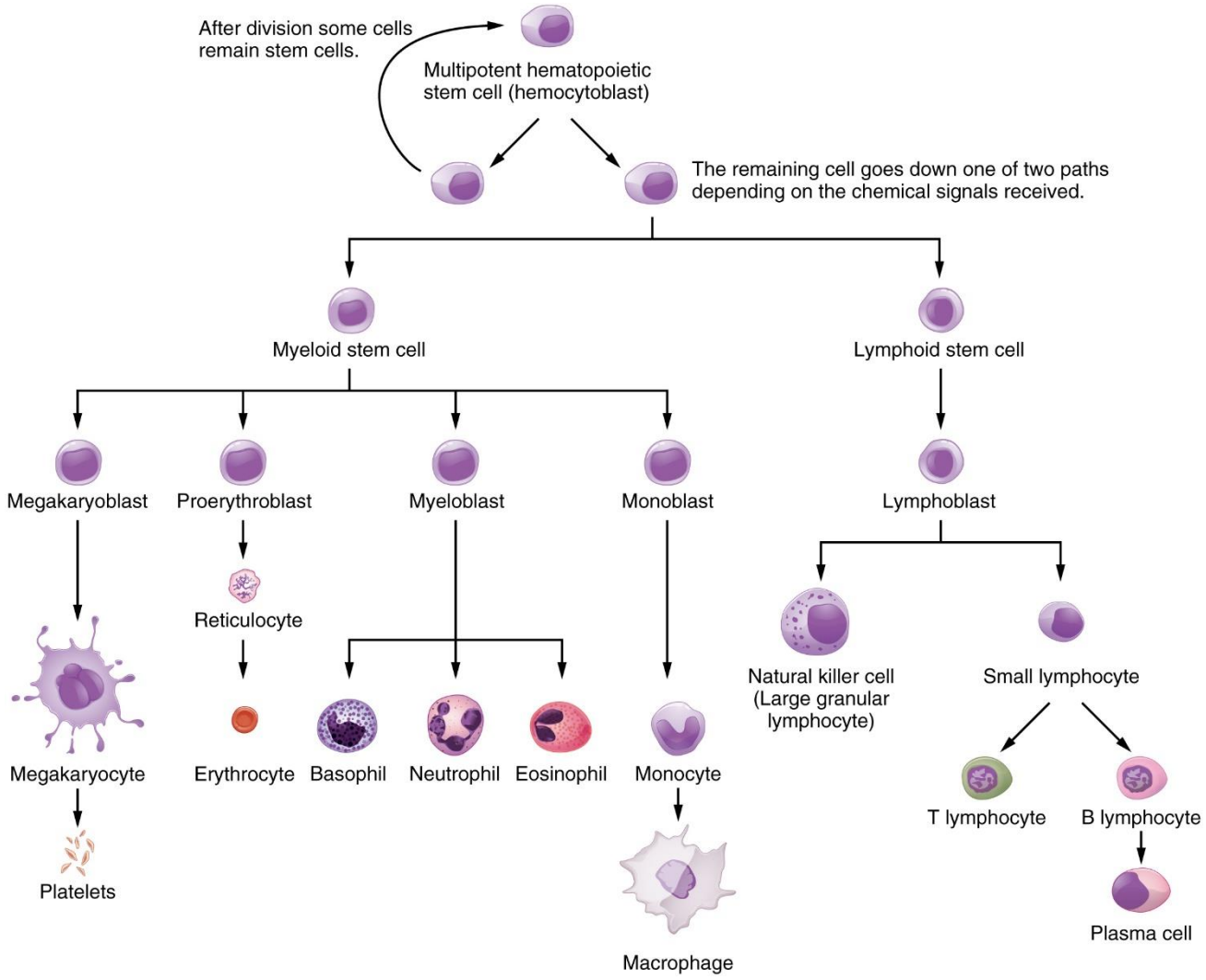


Fig. 1.1: All cellular components in the blood, including the immune cells, arise from multipotent hematopoietic stem cells in the bone marrow.

- All animals have **innate immunity** *(details in Section 2)*, a defense that is **activated immediately upon infection** and is the same whether or not the pathogen has been encountered previously. It provides the **first line of defense** against pathogens (Fig. 1.2a/b).

- **Adaptive immunity** (*details in Section 3*) is activated after the innate immune system activation and **develops more slowly**. This **immune response is enhanced by previous exposure to the infecting pathogen**. It creates an army of **immune cells** specifically designed to attack a **specific pathogen**, conferring **lifelong protective immunity** to reinfection with the **same pathogen** (Fig. 1.2a and 1.2b).

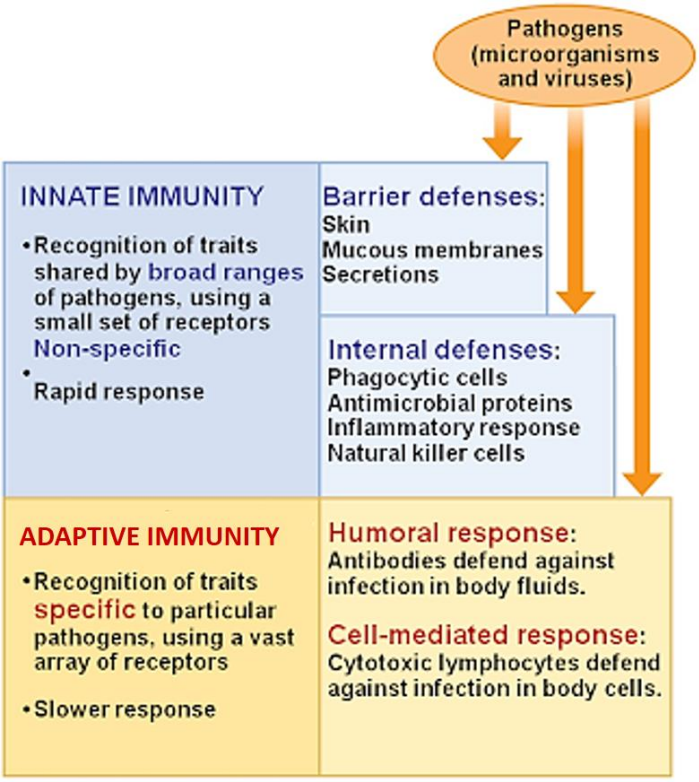


Fig. 1.2a: Overview of animal immunity. Immune responses in animals can be divided into innate and adaptive immunity. Some components of innate immunity contribute to activation of adaptive immune defenses.

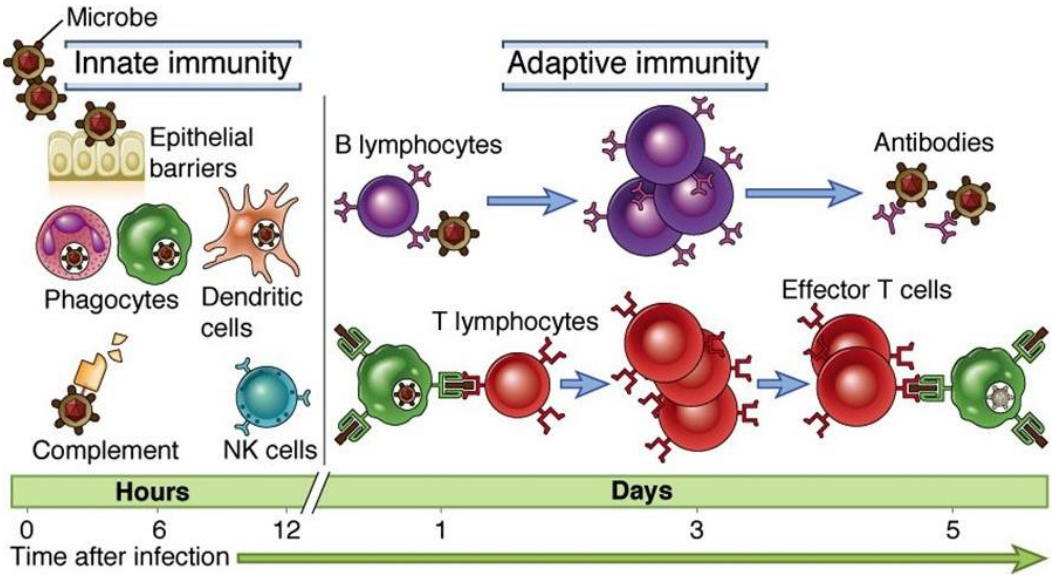


Fig. 1.2b: Immediate and delayed response by the innate and adaptive immunity, respectively.

2. Innate immunity (nonspecific)

Learning outcome:
Describe the specific (adaptive) immune system, including active, passive, natural-acquired and artificially-acquired immunity, and the non-specific (innate) immune system.

- Innate immunity refers to **non-specific** defence mechanisms that is activated immediately or within hours of a pathogen's appearance in the body. These mechanisms include **physical barriers** such as skin, antimicrobial **chemicals/proteins** in the blood, and **immune cells** that attack foreign cells in the body.

2.1 Barrier / physical defense

- In mammals, epithelial tissues block the entry of many pathogens. These **barrier defenses** include the **skin** and also the **mucous membranes** (Fig. 2.1) lining the digestive, respiratory, urinary, and reproductive tracts.

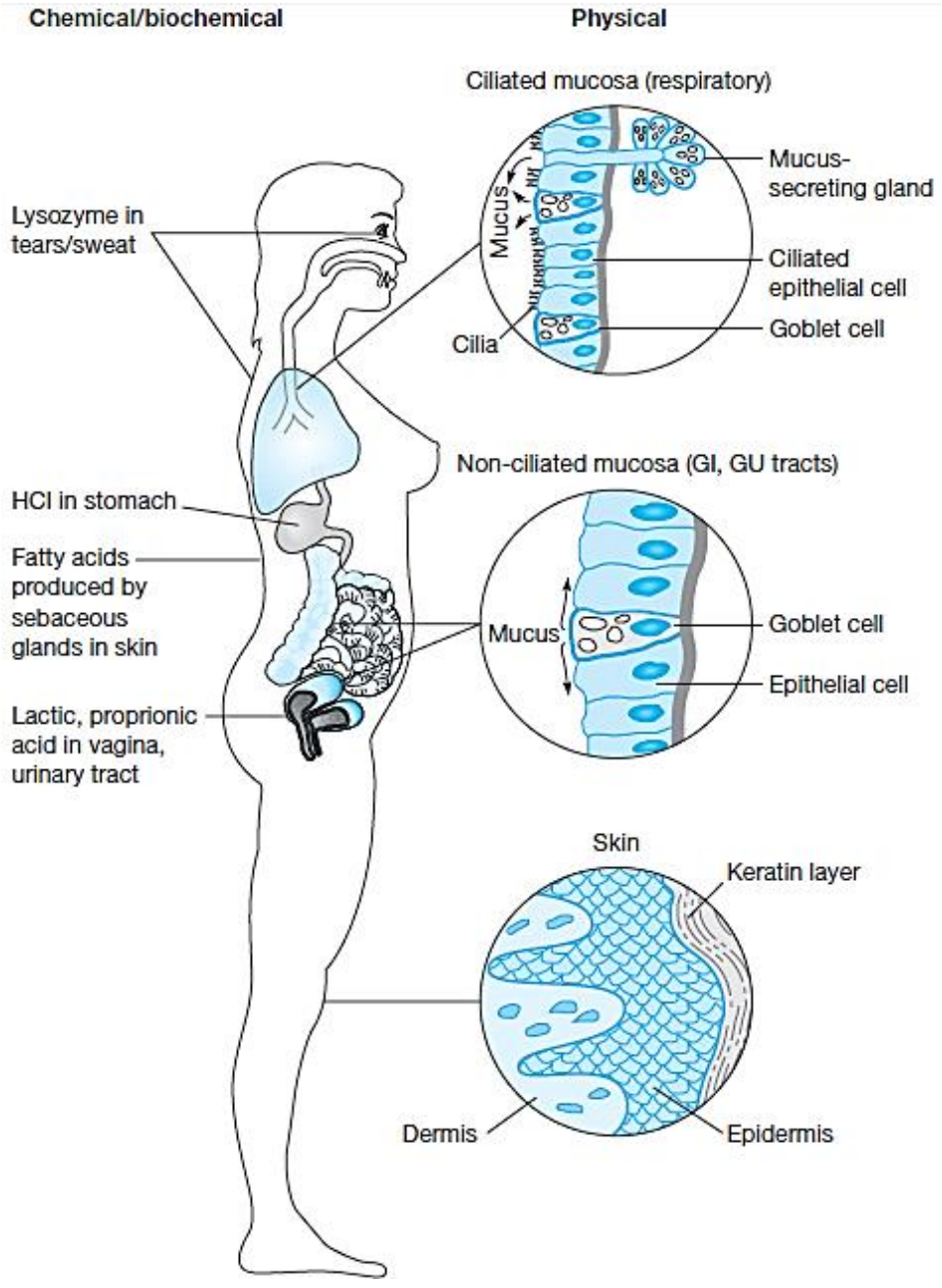


Fig. 2.1: Barrier defense in innate immunity.

- Certain cells of the mucous membranes produce **mucus**, a viscous fluid that **traps pathogens** and other particles.

- In the trachea, **ciliated epithelial cells** sweep mucus and any entrapped microbes upward. This helps to prevent infection of the lungs.

- Saliva, tears, and mucous secretions that bathe various exposed epithelia provide a washing action that also inhibits colonization by fungi and bacteria.

- Beyond their physical role in inhibiting microbial entry, body secretions create an environment that is hostile to many microbes. **Lysozyme** in tears, saliva, and mucous secretions **destroys cell walls** of susceptible bacteria as they enter the openings around the eyes or the upper respiratory tract.

- The **acidic environment** of the stomach also kills most of the microorganisms before these microorganisms can enter the intestines. Similarly, secretions from oil and sweat glands give human skin a pH ranging from 3 to 5, acidic enough to prevent the growth of many bacteria.

2.2 Cellular innate defense

- Pathogens entering the mammalian body are subjected to **phagocytosis** by various types of phagocytic cells (Table 1).

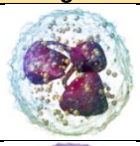
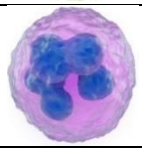
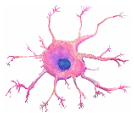
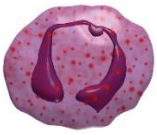
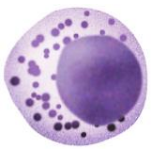
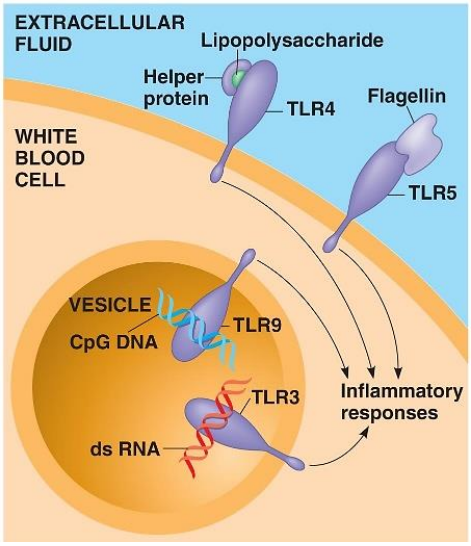
Cell type		Diagram	Description
Phagocyte	Neutrophils		• Circulate in the blood • Attracted by signals from infected tissues and then engulf and destroy the infecting pathogens.
	Macrophages ('big-eaters')		• Large phagocytic cells • Some migrate throughout the body, whereas others reside permanently in organs and tissues where they are likely to encounter pathogens.
	Dendritic cells		• Mainly populate tissues, such as skin, that contact the environment. • Stimulate adaptive immunity against pathogens they encounter and engulf (*Section 3*).
	Eosinophils		• Often found beneath mucosal surfaces • Have low phagocytic activity but are important in defending against multicellular invaders, such as parasitic worms, by discharging destructive enzymes.
Non-phagocyte	Natural killer (NK) cells		• Circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells. • Do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.
	Mast cells (a.k.a. basophils)		• Found in connective tissues • Release histamine (inflammatory molecule) to cause dilation of capillaries

Table 1: Phagocytes and non-phagocytes of the innate immunity

- Phagocytic cells detect fungal or bacterial components using several types of receptors, known as **Toll-like receptors** (TLR). These receptors recognize and bind to a variety of microbial products (Fig. 2.2).



Toll-like receptor	*Ligands*
TLR1	Bacterial lipopeptide
TLR2	Peptidoglycans, lipopeptides, zymosan (from yeast)
TLR3	Double-stranded RNA (viral)
TLR4	LPS (Gram-negative bacterial cell wall)
TLR5	Flagellin
TLR6	Lipopeptide, zymosan
TLR7	Single-stranded RNA
TLR8	Single-stranded RNA
TLR9	Unmethylated DNA (bacterial)
TLR10	? Unidentified molecules on some bacteria

Fig. 2.2: Each mammalian Toll-like receptor (TLR) recognizes a molecular pattern characteristic of a group of pathogens.

- After detecting invading pathogens, a phagocytic cell engulfs them, trapping them in a phagocytic vesicle. The vesicle then fuses with a **lysosome** (Fig. 2.3) and **hydrolytic enzymes** in the lysosome degrade the components of the pathogens.

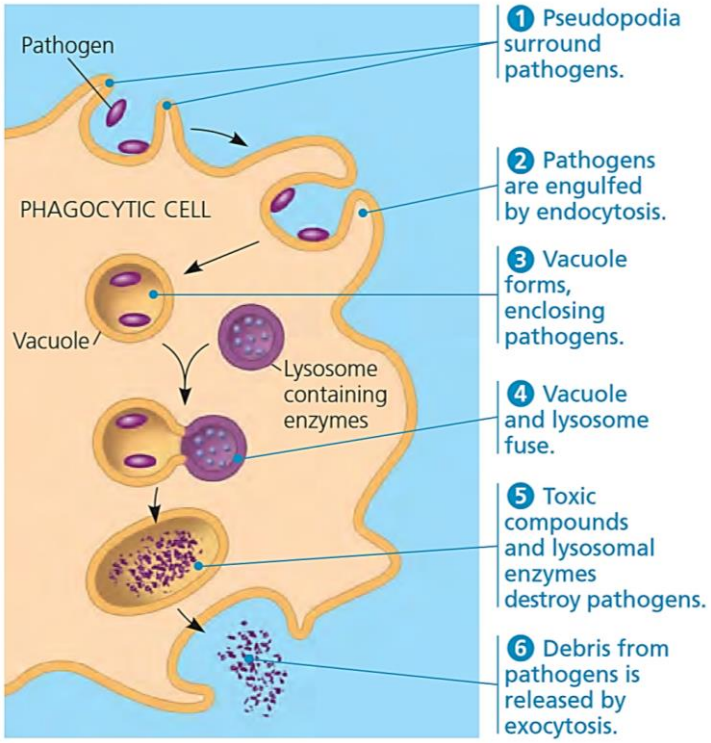


Fig. 2.3: Phagocytosis. This diagram shows the events in the ingestion and destruction of a microbe by a typical phagocytic cell.

2.3 Antimicrobial proteins

- In mammals, pathogen recognition triggers the production and release of a variety of antimicrobial proteins that attack pathogens or impede their reproduction. Two examples of such proteins include **interferons** and **complement proteins**.

(A) Interferons

- **Cytokines** are **small proteins** that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation and infection.

- **Interferons** are a **subset of cytokines** that provide innate defense by **interfering with viral infections** (Fig. 2.4).

- Virus-infected body cells secrete interferons, which induce nearby uninfected cells to **express antiviral genes** that code for antiviral proteins. These antiviral proteins inhibit viral reproduction which limits the cell-to-cell spread of viruses in the body, helping to control viral infections such as influenza infection.

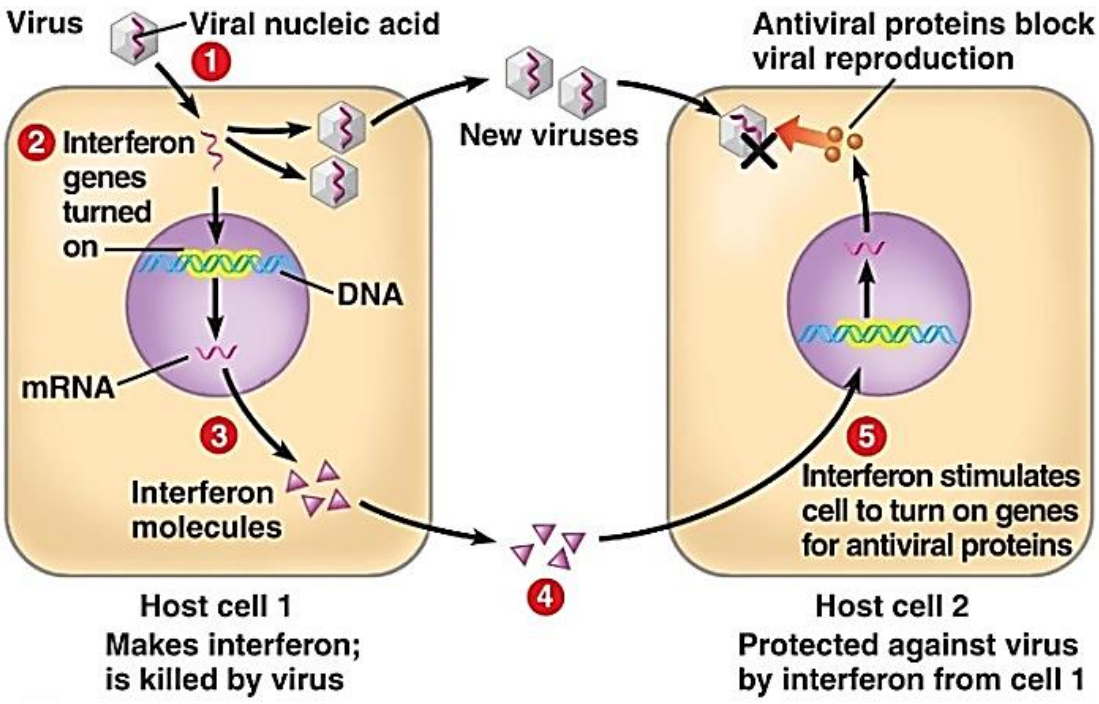


Fig. 2.4: How interferons limit the spread of viruses within the body

(B) Complement system

- The infection-fighting complement system consists of 30 complement proteins in blood plasma. These proteins are made continuously in the liver and are circulated in an inactive state. These inactive complement proteins can be activated by substances on the surface of microbes.

- Once activated, **various different complement proteins assemble into the bacterial membrane** to form the **membrane attack complex (MAC),** which creates a pore on bacterial membrane. Water and salts diffuse into the bacteria via the membrane attack complex, leading to their **lysis** (Fig. 2.5, left).

- In addition, complement proteins attached to bacteria also promote the recognition of bacteria by phagocytes, hence **facilitates phagocytosis** of the bacteria (Fig. 2.5, right).

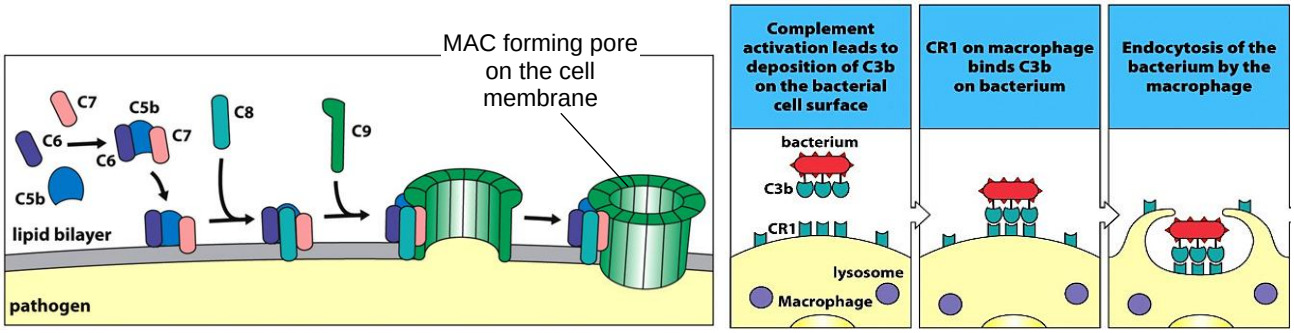


Fig. 2.5: (Left) The assembly of various complement proteins forms the membrane attack complex, which creates a pore on bacterial membrane. **(Right)** Complement-facilitated phagocytosis

2.4 Inflammatory response

- The redness, pain and swelling that alert you to a splinter under your skin are the result of a local inflammatory response, the changes brought about by signaling molecules released upon injury or infection.

- **Histamine**, produced by **mast cells**, is a signaling molecule that triggers the **dilation of blood vessels** and **increase its permeability** to **antimicrobial proteins** (e.g. complement proteins) and **phagocytes** near the site of injury.

- At the same time, **macrophages** at the site of injury **secrete cytokines** which also **dilate blood vessels** and increase blood flow to the site.

- These signals **attract neutrophils** which engulf and digest pathogens and cell debris at the site. (Fig. 2.6)

- The inflammatory response is enhanced by the **activated complement proteins**. These complement proteins stimulate further release of histamine that promotes more phagocytes to enter the site and increases the rate of phagocytosis of the pathogens.

- The outcome is the accumulation of pus – fluid filled with white blood cells, dead pathogens and cell debris.

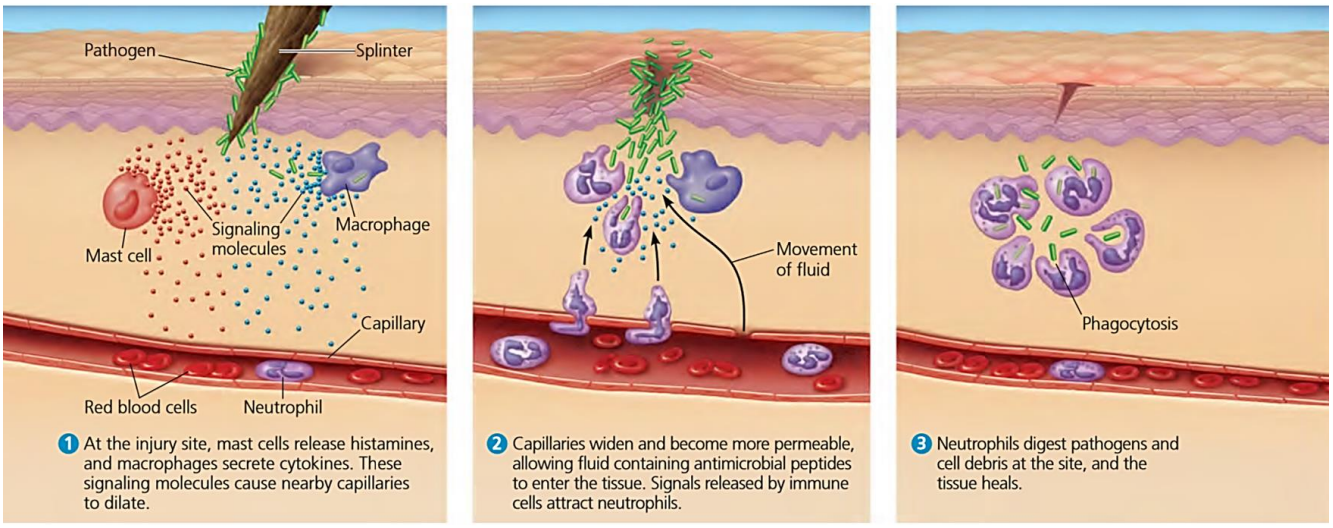


Fig. 2.6: Major events in a local inflammatory response

3. Acquired / adaptive immunity (specific)

Learning outcome:
Describe the specific (adaptive) immune system, including active, passive, natural-acquired and artificially-acquired immunity, and the non-specific (innate) immune system.

- Although the innate immune system provides a first line of defence against many common microbes, they cannot always eliminate infectious organisms, and there are some pathogens that they cannot recognize.

- The **adaptive immune system** has evolved to provide a more versatile means of defence which, in addition, provides increased protection against subsequent reinfection with the same pathogen.

- The adaptive immunity relies on **T cells** and **B cells**, which are types of white blood cells called **lymphocytes**.

- Any substance that elicits a response from a B cell or T cell is called an **antigen**.

- Antigens are usually foreign and are typically **large** molecules, either **proteins** or **polysaccharides**. Many antigens protrude from the surface of foreign cells or viruses. Other antigens, such as toxins secreted by bacteria, are released into the extracellular fluid.

- B cell or T cell has specific lymphocyte cell surface protein called **antigen receptor** (Fig. 3.1). **Specific** antigen receptor (on B cell or T cell) is **complementary in shape** and hence binds to **specific** antigen (e.g. on the surface of pathogen).

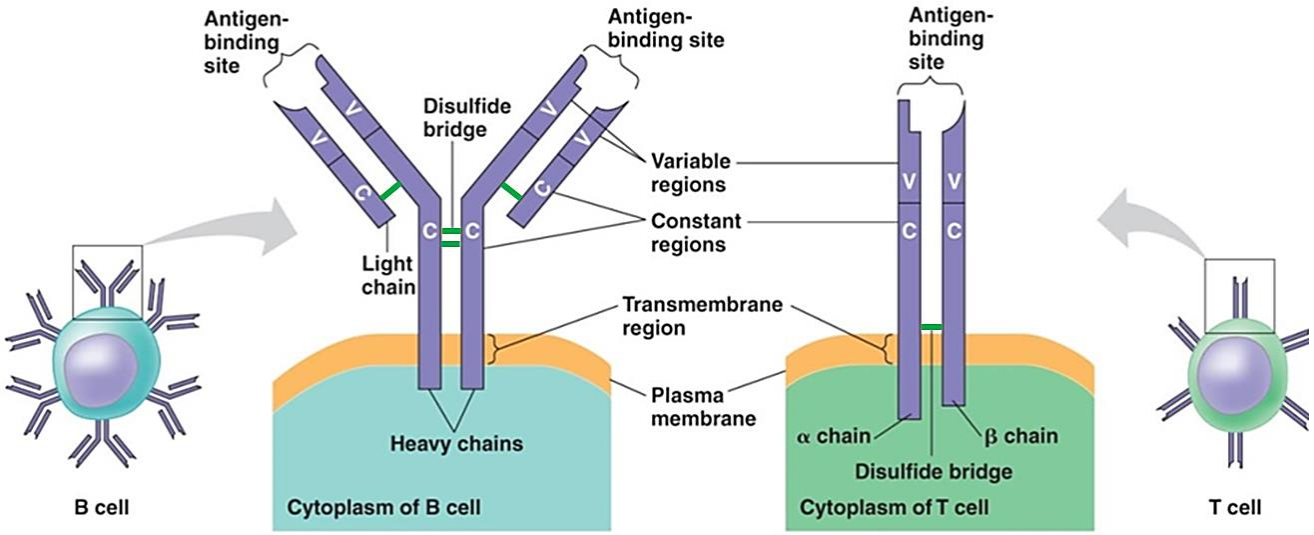


Fig. 3.1: Structure of a (a) B cell antigen receptor and (b) T cell antigen receptor.

- An antigen receptor is also **specific** enough to bind to just **one part** of a molecule from a particular pathogen e.g. bacteria or virus.

- The small, **accessible portion** of an antigen that **binds to an antigen receptor** is called an **epitope**, or *antigenic determinant* (Fig. 3.2a). An example is a group of amino acids in a particular protein.

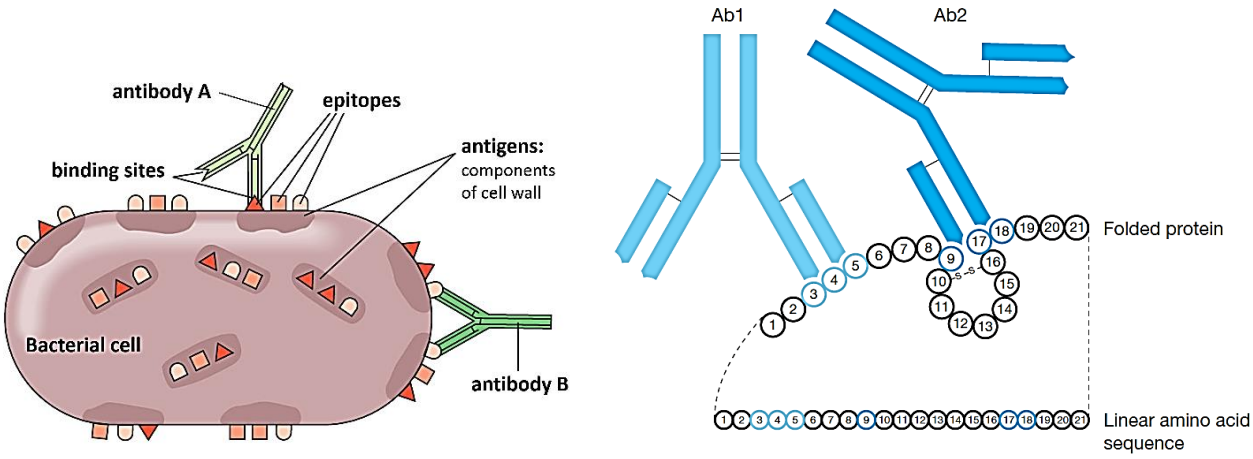


Fig. 3.2: An antigen usually contains more than one epitopes.

- A **single antigen** usually has **several different epitopes**, **each** binding to a **specific antigen receptor via complementary shape** (Fig. 3.2).

- All antigen receptors produced by a **single** B cell or T cell are **identical**, hence, these antigen receptors will bind to the **same epitope**.

- Each B cell or T cell thus **displays specificity for a particular epitope**, enabling it to respond to any pathogen that produces molecules containing that same epitope.

Exercise 1: Complete the table.

Structure	Type of biological molecule	Where is it found?
Antigen receptor		
Antigen		
Epitopes		

3.1 Antigen recognition by B cells and antibodies

3.1.1 Structure of B cell antigen receptor

- Each B cell antigen receptor is a Y-shaped molecule with four polypeptide chains: 2 identical **heavy chains** and 2 identical **light chains**. **Disulfide bridges** link the chains together (Fig. 3.3).

- A **transmembrane region** near one end of each heavy chain anchors the receptor in the cell's plasma membrane. A short tail region at the end of the heavy chain extends into the cytoplasm.

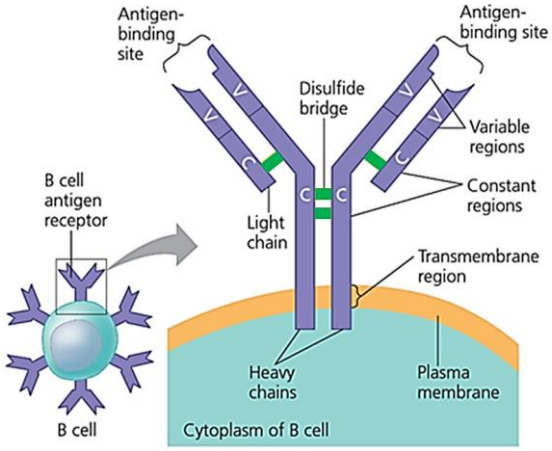
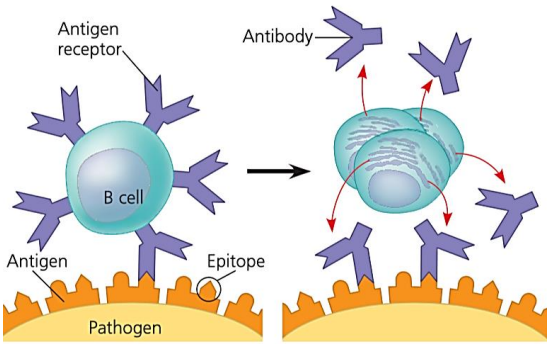


Fig. 3.3: B cell antigen receptor comprises two identical heavy chains and two identical light chains.

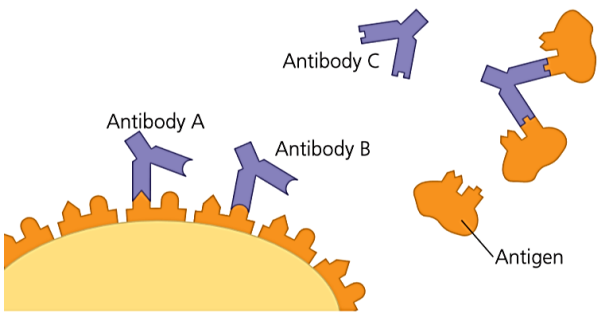
- The light and heavy chains each have a **constant (C) region**, where **amino acid sequences vary little among the receptors on different B cells**. The C region includes the cytoplasmic tail and transmembrane region of the heavy chain and all of the disulfide bridges.

- Within the two tips of the Y shape, the light and heavy chains each has a **variable (V) region**, where **amino acid sequence varies extensively from one B cell to another**. Parts of a heavy-chain V region and a light-chain V region form the binding site for an antigen.

- Each B cell antigen receptor has **two identical antigen-binding sites** (Fig. 3.3), complementary in shape to specific epitope.
    - The binding of a B cell antigen receptor to an antigen is an early step in B cell activation, leading eventually to the formation of plasma cells that secrete a soluble form of the receptor known as **antibody**, or **immunoglobulin** (Ig) (Fig. 3.4).



(a) B cell antigen receptors and antibodies. An antigen receptor of a B cell binds to an epitope, a particular part of an antigen. Following binding, the B cell gives rise to cells that secrete a soluble form of the antigen receptor. This soluble receptor, called an antibody, is specific for the same epitope as the original B cell.



(b) Antigen receptor specificity. Different antibodies can recognize distinct epitopes on the same antigen. Furthermore, antibodies can recognize free antigens as well as antigens on a pathogen's surface.

Fig. 3.4: B cells, upon activation, give rise to plasma cells which secrete soluble form of the antigen receptor called antibodies or immunoglobulins.

3.1.2 Structure of Antibody (e.g. Immunoglobulin G, IgG)

- **Antibodies** have the same Y-shaped organization as B cell antigen receptors, except that antibodies are in a **soluble** and **secreted** form rather than membrane bound.

- The secreted antibody has a **hydrophilic C-terminus** at the heavy chains whereas the membrane-bound B cell antigen receptor has a **transmembrane hydrophobic C-terminus at the heavy chains**. (Fig.3.5)

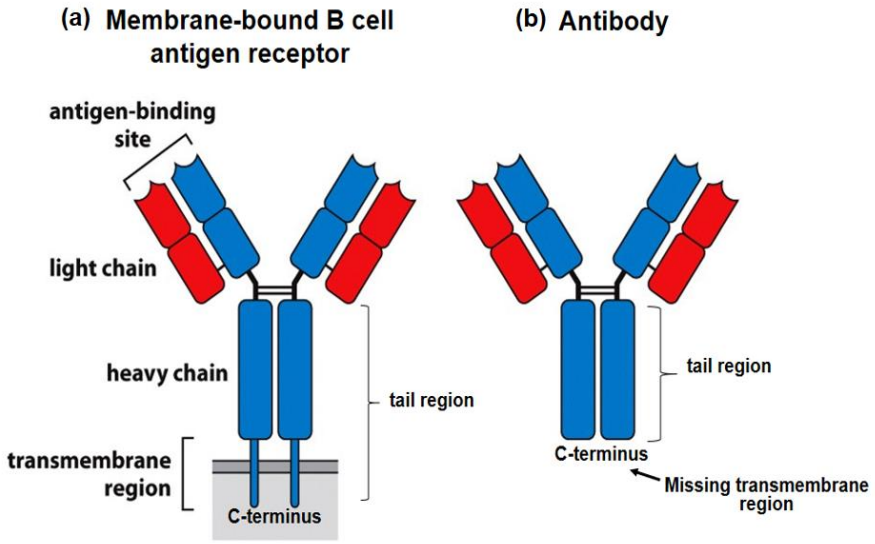


Fig. 3.5: (a) The membrane-bound B cell antigen receptor has a transmembrane hydrophobic C-terminus at the heavy chains where (b) antibody has a hydrophilic C-terminus at the heavy chains (no transmembrane region)

- IgG is the major antibody class in the blood.

- Each IgG is made up of four polypeptide chain: **two heavy chains** and **two light chains** linked via **disulfide bonds**.

- Each heavy chain and light chain comprise a **variable (V) region**. The V regions make up the **antigen-binding site**.

- Similar to the B cell antigen receptor, antibody has **two identical antigen-binding sites** (Fig. 3.6), each has a **complementary shape** that binds to a **specific epitope**.

- The V region of different antibodies has **different amino acid sequences** that lead to **different tertiary structure**. This gives rise to the **diversity of antigen binding sites** where each binds specifically to a different epitope of an antigen. *Differences in the amino acid sequences of variable regions is a result of somatic recombination and somatic hyper-mutation that occur during B cell development (details in Section 3.3)*

- The light and heavy chains each has a **constant (C) region**, where **amino acid sequences vary little among the receptors on different B cells**.

- The constant region at the C-terminus tail region (also known as **Fc region**) of some subclasses of IgG can bind to specific receptors (**Fc receptors**) on macrophages and neutrophils to facilitate phagocytosis (Fig.3.7). This process is known as opsonisation. (*details in Section 3.4.3)*

- The two heavy chains each has a **hinge region** which gives **flexibility** to the structure. This improves the efficiency in which the antibody can bind with antigens. (Fig. 3.6)

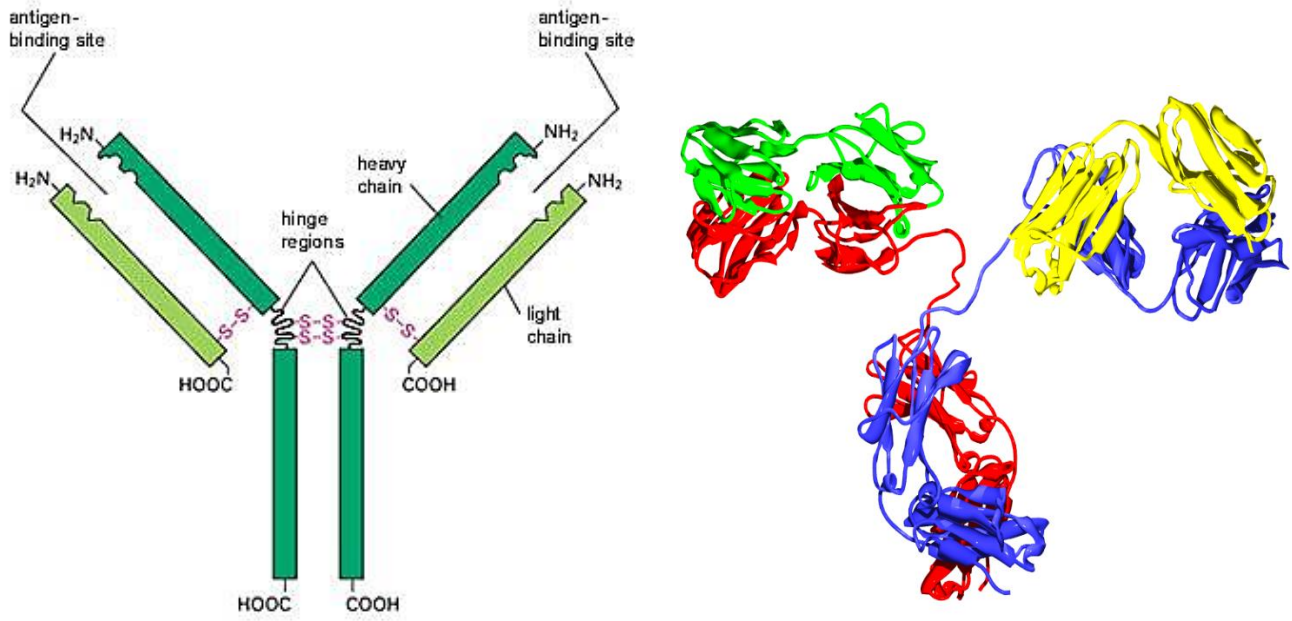


Fig. 3.6: Structure of IgG presented in simplified (left) and ribbon (right) forms.

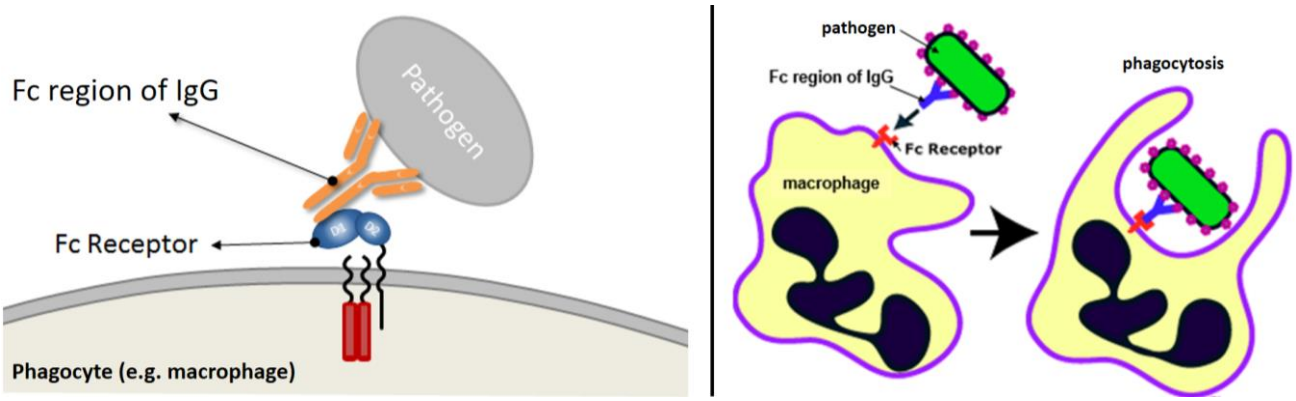


Fig. 3.7: The antigen-binding site of IgG binds to the specific antigen on a microbe. The Fc region of the IgG binds to the Fc receptor on a phagocyte (e.g. macrophage) to facilitate phagocytosis.

Structure of IgG related to its functions

Structure	Structure in relation to function
• **Variable region** of light and heavy chains forms the antigen-binding sites	• The antigen-binding site has a **complementary shape** that binds to a **specific epitope**
• The **two heavy chains** and **two light chains are** linked via **disulfide bonds**	• Holds the heavy and light chains together and maintains **quaternary/3D conformation of IgG**
• Two heavy chains each have a **hinge region**	• The hinge region gives the **flexibility** for the antibody molecule to bind around the antigen
• The constant region at the C-terminus tail region (**Fc region**) has complementary shape with the **Fc receptors** on phagocytes	• Fc region of IgG can bind to specific **Fc receptors** on phagocyte to **facilitate phagocytosis** of the microorganisms.

- There are 5 different classes of antibodies: IgA, IgG, IgM, IgD and IgE (Table 2), each with its own class of heavy chain – α, β, ε, γ and μ respectively. The **constant region of the heavy chain determines the class produced**.

- B cells secrete IgM at first exposure of the antigen (primary response). In subsequent exposures to the same antigen (secondary response), other classes of Ig are produced via **class switching** (*details in Section 3.3*).

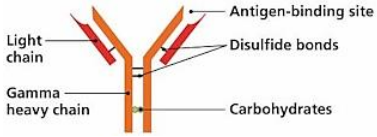
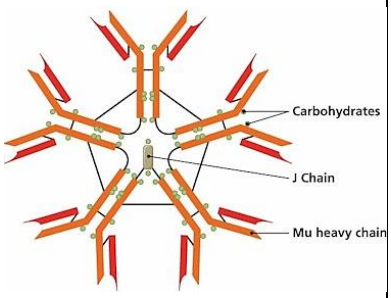
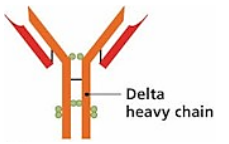
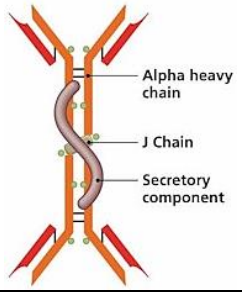
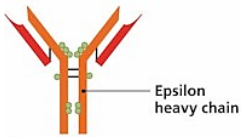
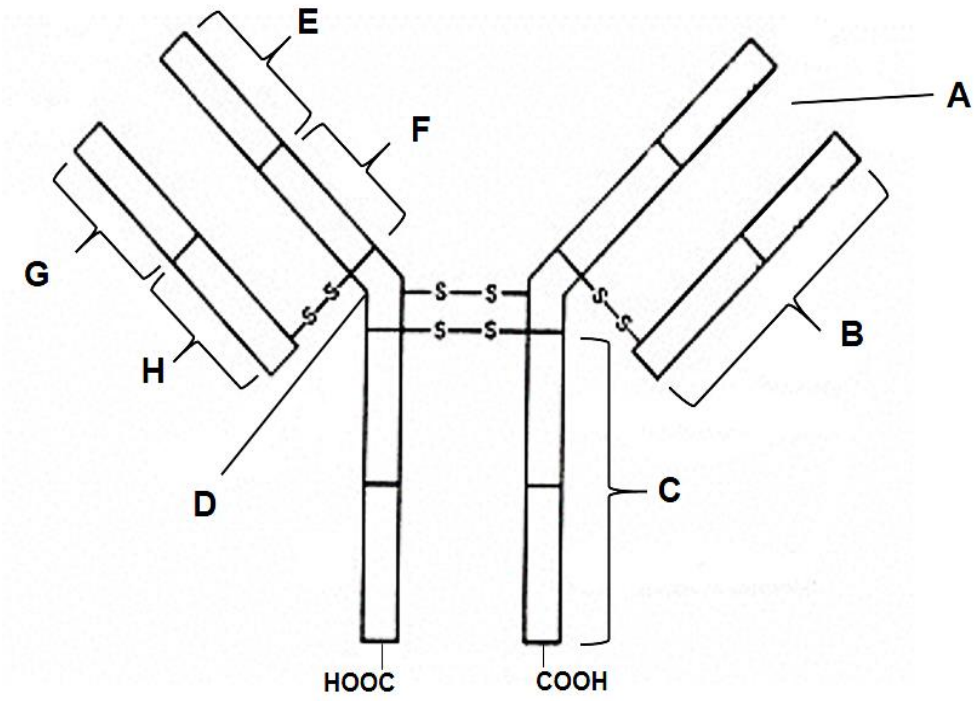
Class	– mer	Structure	Location	Function
IgG	Monomer		• Free in blood plasma • ~80% of circulating antibodies	• Most abundant antibody in primary and secondary immune responses • Neutralize toxins • Crosses placenta and provides passive immunity to fetus
IgM	Pentamer		• Surface of B cells • Free in blood plasma	• Antigen receptor on B cell membrane • First class of antibodies released by B cells during primary response
IgD	Monomer		• Surface of B cells	• Function not understood
IgA	Dimer		• Saliva • Tears • Milk • Other body secretions	• Protects mucosal surfaces • Attack pathogens before they gain access to internal tissues • Secreted into breast milk and provides passive immunity to feeding baby
IgE	Monomer		• Secreted by plasma cells in skin and tissues lining gastrointestinal and respiratory tracts	• When bound to antigens, it binds to mast cells and basophils to trigger release of histamine that contribute to inflammation

Table 2: Structure, location and function of the five classes of immunoglobulins.

An analogy of the different classes of antibodies…
- The police is trying to nail down a drug trafficking syndicate
- There is a tip-off on the venue/time of a drug dealing
- Venue: Taiwan night market
- At different parts of the venue, policemen disguised as Lovers, Stall holders, Patrons, Performers and Beggars
- The syndicate = the foreign Ag
- Policemen = the specific Ab designed to bind to the specific foreign Ag
- The disguise = the different classes of antibodies, each with their specific role/location, but all have one goal: to bind to the foreign Ag

Exercise 2: Label the structure of IgG.



A ……

B ……

C ……

D ……

E ……

F ……

G ……

H ……

3.2 Antigen recognition by T cells

- For a T cell, the antigen receptor consists of **two different polypeptide chains**, an **α-chain** and a **β chain**, linked by a **disulfide bridge** (Fig. 3.8).

- Near the base of the T cell receptor is a **transmembrane region** that anchors the molecule in the cell's plasma membrane.

- At the outer tip of the molecule, the **variable (V)** regions of α and β chains together form a single **antigen-binding site**. The remainder of the molecule is made up of the **constant (C)** regions.

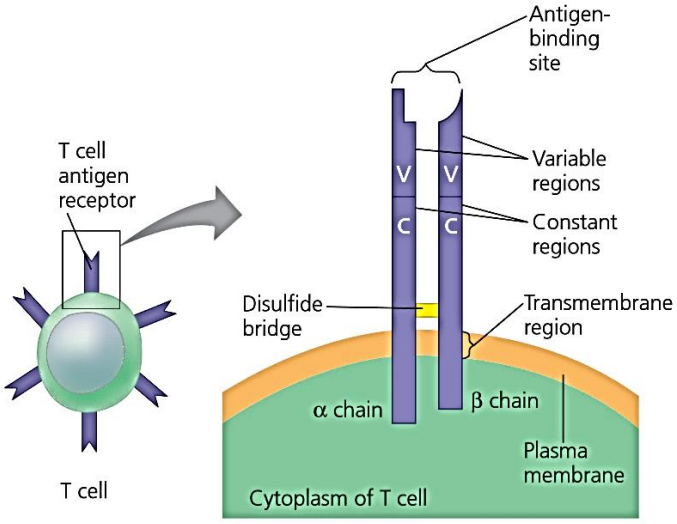


Fig. 3.8: T cell antigen receptor comprises two different polypeptides – α-chain and β-chain

- While the B cell receptors bind to epitopes of **intact antigens** circulating in body fluids, T cell receptors bind only to **fragments of antigens** that are **displayed**, or **presented**, on the surface of host cells.

- The host protein that displays the antigen fragment on the cell surface is called the **major histocompatibility complex (MHC)** molecule (*Sections 3.4.1 and 3.4.2*).

- 2 main classes of MHC proteins (Fig. 3.9)
    - **Class I MHC** protein presents foreign peptides to **cytotoxic T cells** (a.k.a. $CD8^+$ T cells)
    - **Class II MHC** protein presents foreign peptides to **helper T cells** (a.k.a. $CD4^+$ T cells)

- Recognition of protein antigens by T cells begins when a pathogen or part of a pathogen either infects (Fig. 3.9a) or is phagocytosed (Fig. 3.9b) by a host cell.

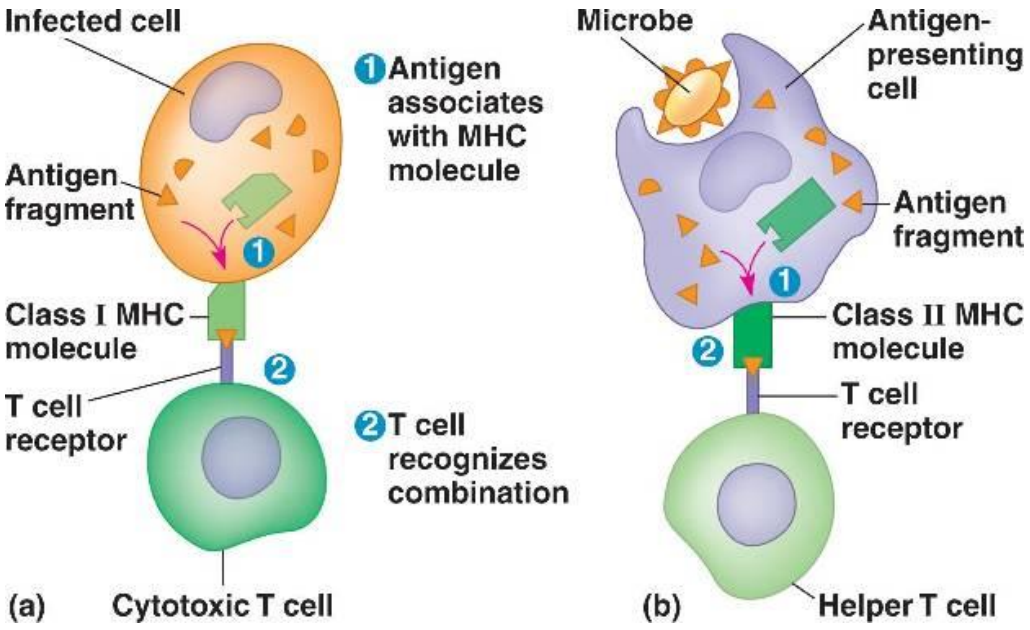


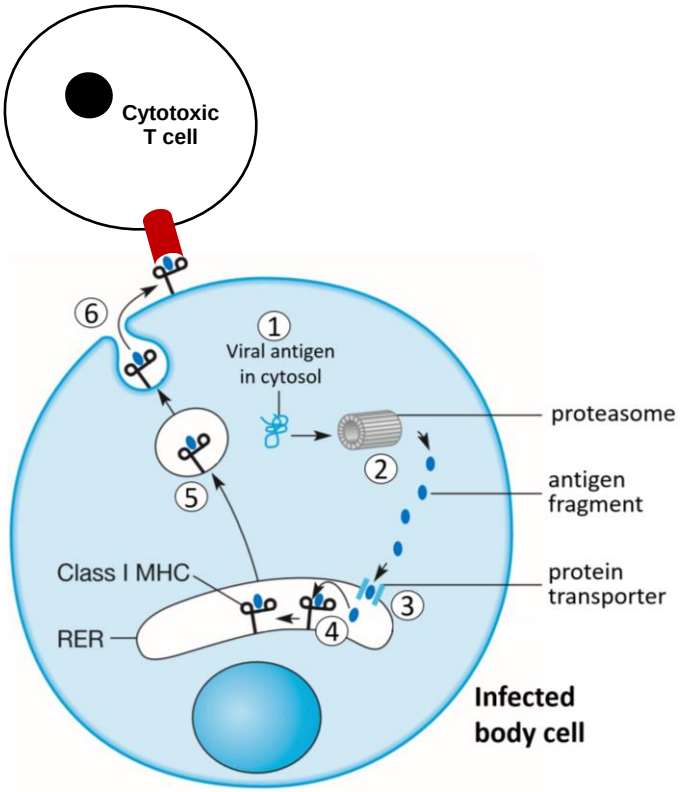
Fig. 3.9: Antigen recognition by a T cell. Inside the host cell, an antigen fragment from a pathogen binds to an MHC molecule and is brought up to the cell surface, where it is displayed. The combination of MHC molecule and antigen fragment is recognized by a T cell.

- Inside the host cell, enzymes in the cell cleave the antigen into smaller peptides. Each peptide, called an **antigen fragment**, then binds to an MHC molecule inside the cell.

- Movement of the MHC molecule and bound antigen fragment to the cell surface results in **antigen presentation**, the display of the antigen fragment in an exposed peptide-binding site of the MHC protein.

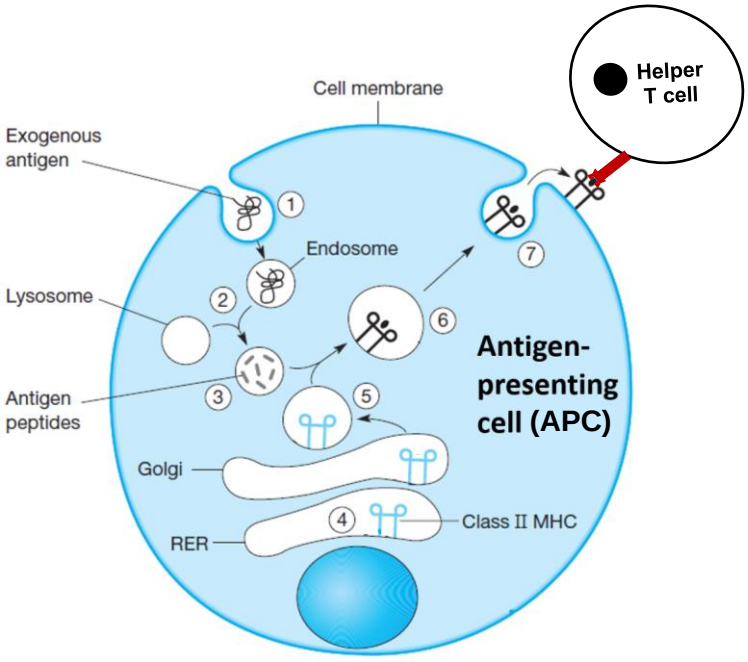
- Fig. 3.10 (a) and (b) show the process of antigen presentation, which signals that a host cell contains a foreign substance.

- If the cell displaying an antigen fragment encounters a T cell with the right specificity, the antigen receptor on the T cell will bind to both the antigen fragment and the MHC molecule. This interaction of an MHC molecule, an antigen fragment, and an antigen receptor is necessary for a T cell to participate in an adaptive immune response (*Section 3.4*).



1. Viral-infected cells contain viral proteins in the cytosol.
2. Viral protein is degraded in the proteasome into small antigenic fragments.
3. The antigenic fragments are transported into the lumen RER via a protein transporter.
4. Loading of antigenic fragment onto class I MHC.
5. Vesicle that contains the antigen-loaded class I MHC buds off from the RER to the Golgi apparatus.
6. The class I MHC is then transported to the cell surface where it presents the viral antigen to cytotoxic T cells.

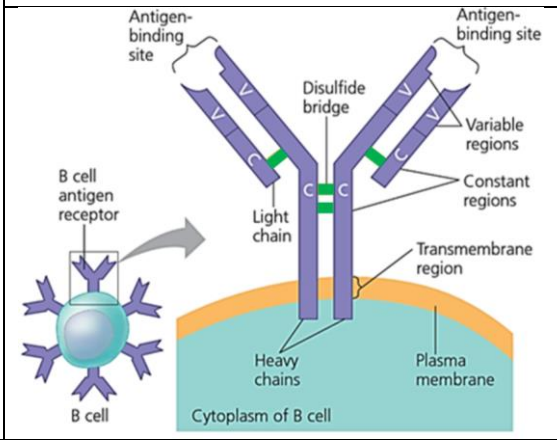
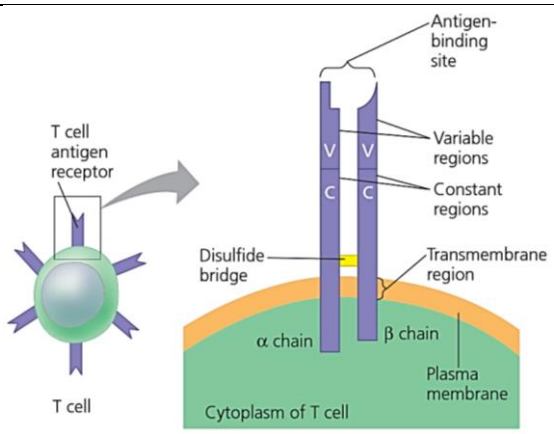
Fig. 3.10a: Antigen presentation by infected body cells via class I MHC.



1. Antigen taken in by the APC (e.g. macrophages) via endocytosis.
2. Fusion of endosome with primary lysosome.
3. Hydrolytic enzymes in the lysosome degrades antigen into smaller peptides.
4. Class II MHC synthesized in the RER and modified in the Golgi apparatus.
5. Class II MHC packaged into Golgi vesicle.
6. Fusion of endosome and Golgi vesicle allows loading of antigenic peptide onto class II MHC.
7. Class II MHC is then transported to the cell surface where it presents the antigenic peptide to helper T cells.

Fig. 3.10b: Antigen presentation by antigen-presenting cells via class II MHC.

Comparison between B cell receptor and T cell receptor

	B cell receptor	T cell receptor
		
Found on….?		
Type of antigen that it recognizes		
No. of polypeptide chains		
No. of disulfide bridges between chains		
No. of antigen-binding sites		

3.3 Development of B and T cells

Learning outcome:
Explain how genetic recombination during development results in millions of different antibody molecules (including somatic recombination, hyper-mutation and class switching).

- Both **T and B cells originate from the bone marrow**, but **immature T cells** migrate to the **thymus** (an organ behind the sternum and between the lungs where T cells undergo maturation) to **complete their development**, while **B cells** continue to **mature in the bone marrow**.

3.3.1 Generation of B and T cell diversity

- Each person makes more than 3 million different B cell antigen receptors and 10 million different T cell antigen receptors. Yet there are only about 20,000 protein-coding genes in the human genome. How, then, do we generate such remarkable diversity in antigen receptors?

(A) Somatic recombination in B cells

- The capacity to generate diversity is built into the structure of Ig genes (Fig. 3.11). *Ig genes in B cell is used here as an illustration. T cell antigen receptor genes undergo very similar transformations*.
  (Note: T cell receptor diversification does not involve somatic hyper-mutation)

- Somatic recombination occurs during the development of a B cell in the bone marrow **before antigenic stimulation**.

- The **heavy chain gene** is made up of 4 segments: a **variable** (V) segment, a **diversity** (D) segment, a **joining** (J) segment, and a **constant** (C) segment.

- The **light chain gene** is made up of 3 segments: a **variable** (V) segment, a **joining** (J) segment, and a **constant** (C) segment.

- The **VDJ segments of H chain gene** and **VJ segment of L chain gene** together encode the **variable region** of the Ig protein, while the **C segment of H chain gene** and **L chain gene** encodes the **constant region** of the Ig protein.

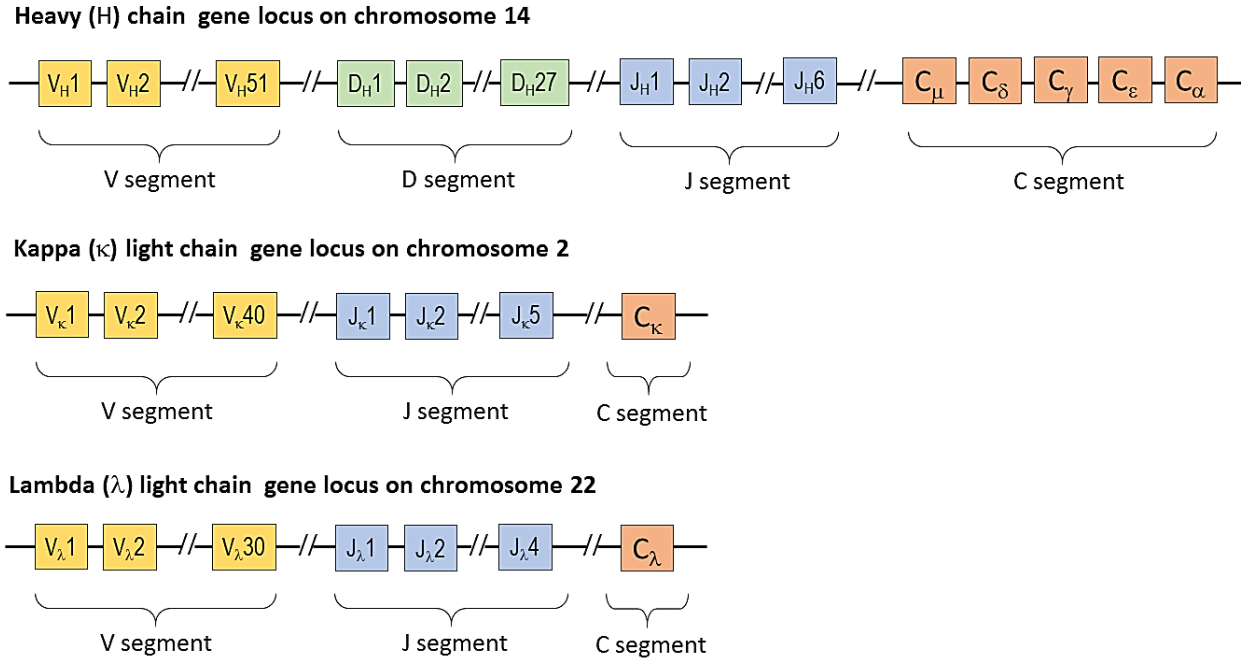


Fig. 3.11: The gene loci of heavy chain, kappa light chain and lambda light chain of B cell.

- Fig. 3.12 shows the number of VJ segments and number of VDJ segments that the light and heavy chain loci contain, respectively.

No. of functional gene segments in human immunoglobulin loci			
Segment	Light chain		Heavy chain
	kappa (κ)	lambda (λ)	H
Variable (V)	40	30	51
Diversity (D)	0	0	27
Joining (J)	5	4	6

Fig. 3.12: Number of V(D)J segments in gene locus.

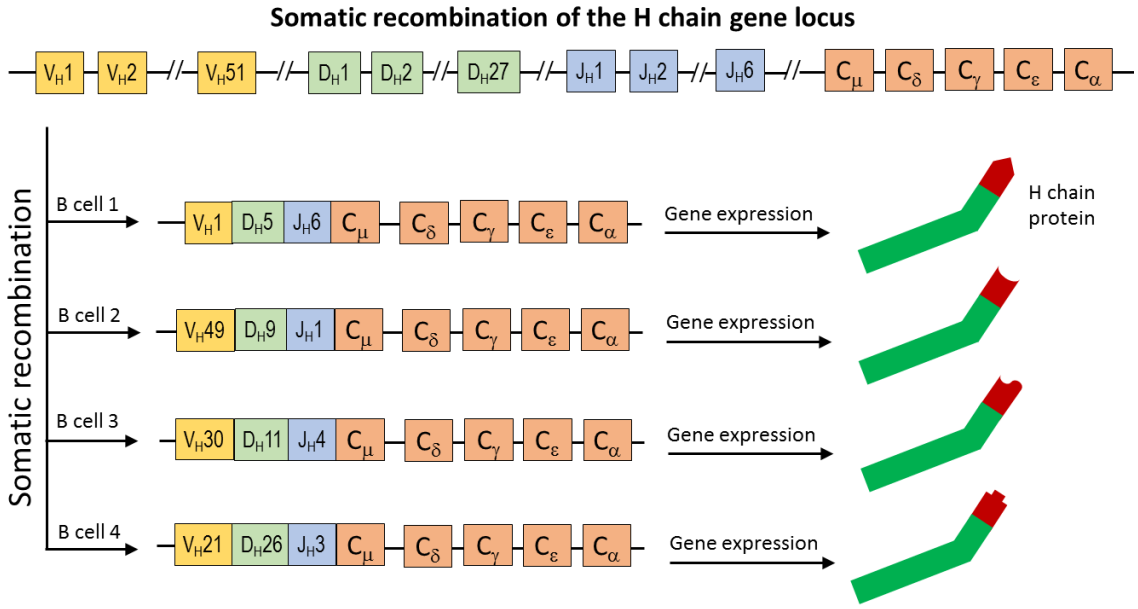


Fig. 3.13a: VDJ recombination at the heavy chain gene locus.

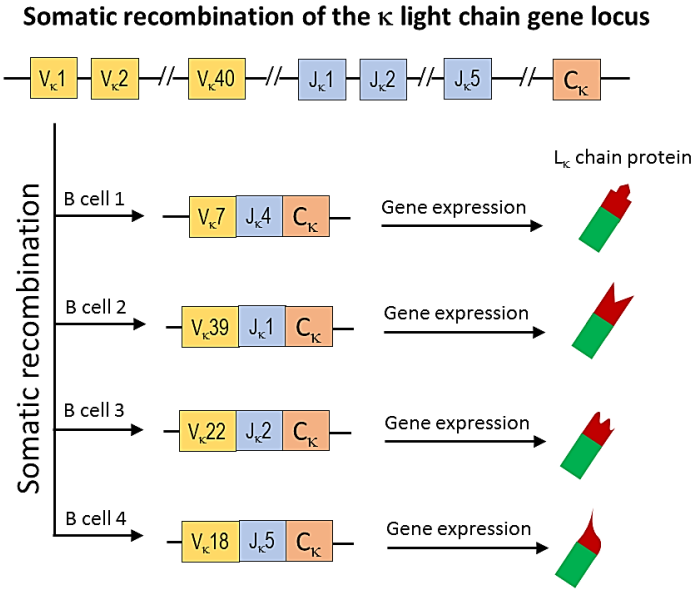


Fig. 3.13b: VJ recombination at the kappa light chain gene locus.

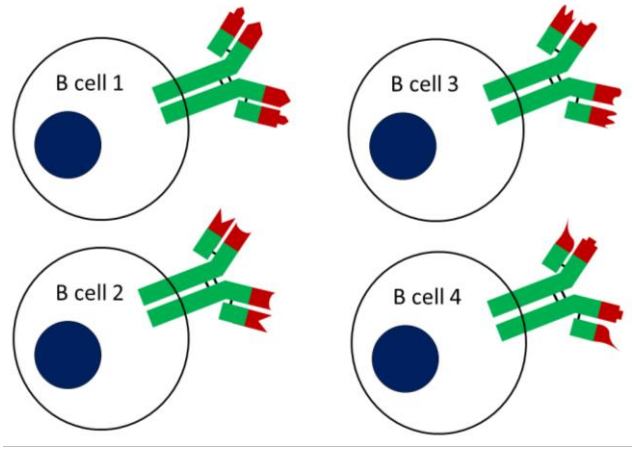


Fig. 3.13c: Assembly of H and L chains forms the B cell receptor, with each B cell having different specificity.

- Somatic recombination requires the enzyme **recombinase** to select and recombine the gene segments coding for the variable region on the Ig (Fig. 3.13a and 3.13b). This gives rise to a great diversity (~2.6 X 10^6) of different Ig, each specific for a particular antigen.

- The **kappa light chain gene locus** for example, contains a **single C segment**, **40 different V segments**, and **5 different J segments**. These alternative copies of the V and J segments are arranged within the gene in a series (Fig. 3.13b). A functional gene is built from one copy of each type of segment, thus, the pieces can be combined in 200 different ways (40V x 5J x 1C).

- Recombinase acts randomly, linking any one of the 40 V gene segments to any one of the 5 J gene segments (heavy chain genes undergo a similar recombination).

- In any given cell, however, **only one allele of a light-chain gene** (either κ or λ) **and one allele of a heavy-chain gene undergo recombination**.

- The **recombination is permanent** and is passed on to the daughter cells when the lymphocyte divides.

- Since the gene segments are **randomly selected and recombined**, some B cells produce receptors specific for epitopes on the organism's own self antigen. If these self-reactive B cells were not eliminated or inactivated, the immune system could not distinguish self from non-self antigen and would attack body proteins, cells, and tissues. These **self-reactive B cells** with receptors specific for the body's own molecules are **destroyed by apoptosis**.

Think about it…
Somatic recombination generates diverse gene products from one gene. For example, the H chain gene can generate many different H chain proteins, each with a specific shape at the variable region.
How is this process different from alternative splicing?

(B) Somatic hyper-mutation in B cells

- When a B cell recognizes an antigen, it is stimulated to divide (proliferate).
- During proliferation, the B cell receptor gene locus undergoes an **extremely high rate of somatic mutation** that is at least 10^5-10^6 fold greater than the normal rate of mutation across the genome.
- Such mutations occur in the **rearranged V(D)J segments** of the light and heavy chain locus, generating B cell receptor of **varying affinity** to that specific antigen (Fig. 3.13).
- Variation is mainly generated via **single base substitutions**.
- B cells with **deleterious (lethal) mutation** undergo **apoptosis**.
- B cells with **increased affinity** for that specific antigen undergo **proliferation** and **class switching**. Each class-specific B cell then **differentiates** into **memory B cells** and **plasma cells** (secrete antibodies). (Fig. 3.14)
- This somatic hyper-mutation allows for the selection of B cells that express immunoglobulin receptors that possess an **enhanced affinity to bind to a specific foreign antigen**.

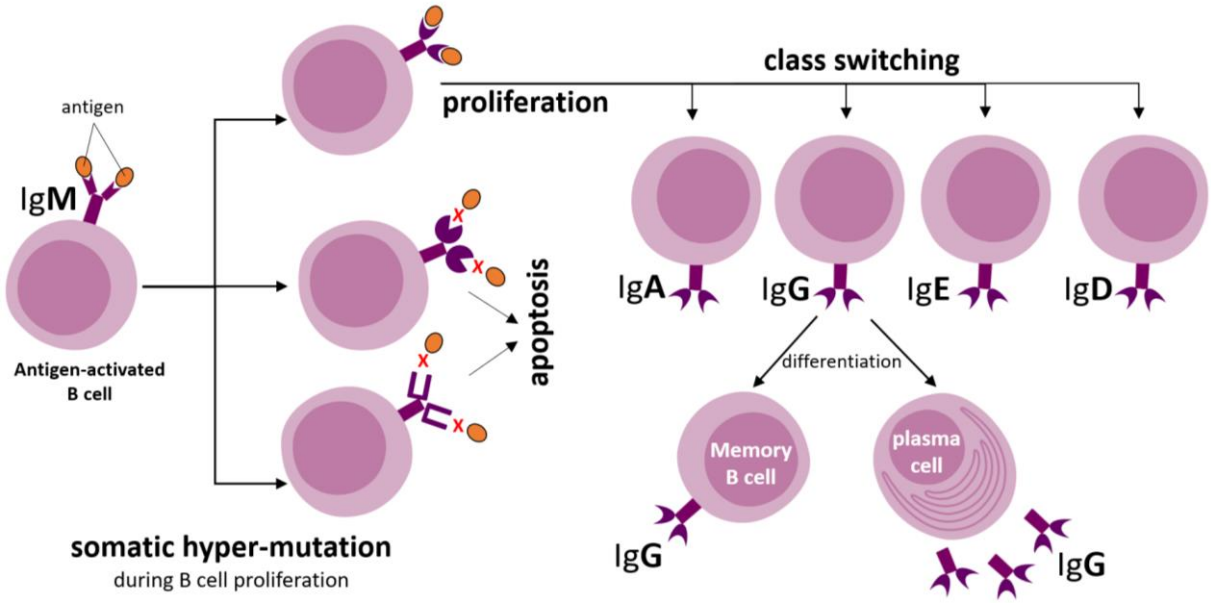


Fig. 3.14: Somatic hyper-mutation results in B cells with increased affinity for that antigen from which a B cell was first activated. Class switching then occurs to produce different classes of Ig. Differentiation then produces memory B cells and plasma cells.

(C) Class switching

- IgM is the first class of antibody produced upon exposure to an antigen, followed by IgG, during a primary immune response (Fig. 3.15a).
- **Class switching** (Fig. 3.15b) is a mechanism to produce the rest of the classes of antibodies after IgM (i.e. IgG, IgA, IgD and IgE), each specific for its biological function (Table 2 on page 16)).
- The biological function of these 5 different classes is determined by the Fc portion of the antibody.
- Like somatic recombination, class switching is **irreversible** as it involves the **removal of DNA of the heavy chain constant region**.
- Since VDJ recombination has already taken place, no further VDJ recombination occurs. Hence, **class switching changes the heavy chain constant region but retains its specificity for the antigen**.
- Note that each plasma cell will secrete only one class of antibody.

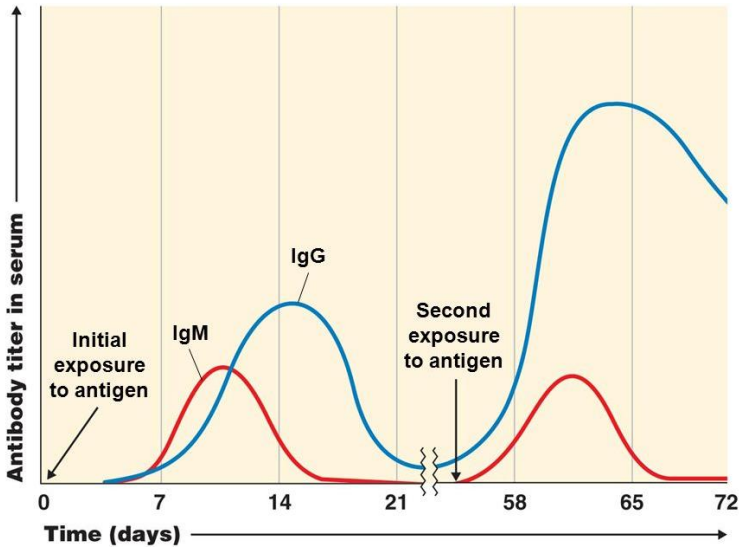


Fig. 3.15a: IgM is the first class of antibody produced during antigen exposure, followed by IgG, during primary immune response.

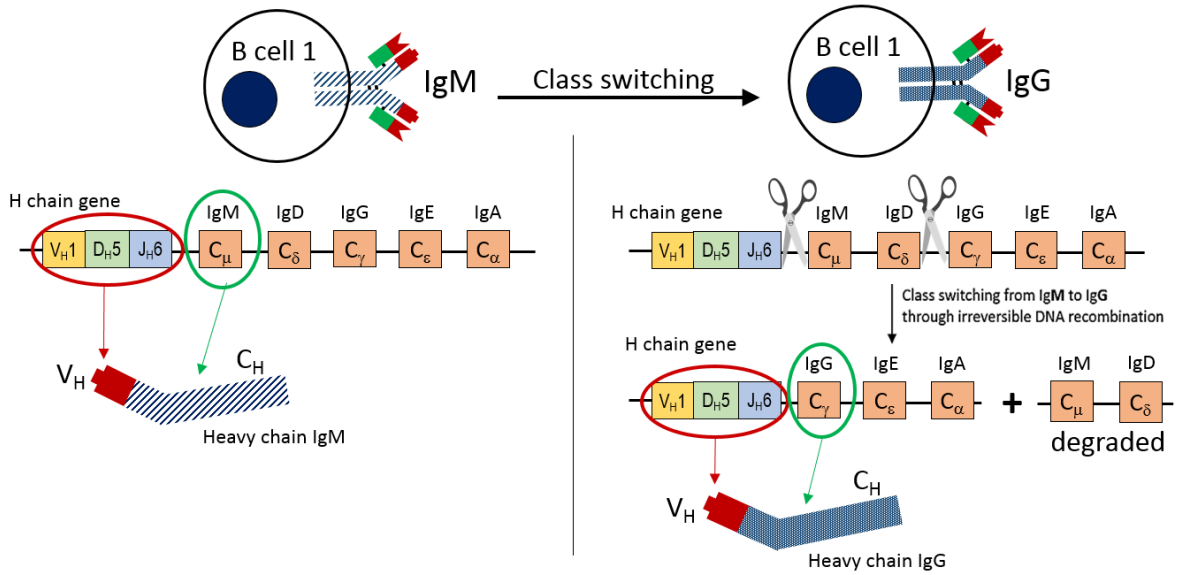


Fig. 3.15b: Class switching from IgM to IgG is illustrated here.

3.3.2 Proliferation of B cell and T cells

- Once a B cell or T cell is activated by an antigen in the lymphoid organ (e.g. lymph node), they are stimulated to divide (proliferate).

- For B cells, somatic hyper-mutation and class switching take place during proliferation.

- After somatic hyper-mutation, the **cell with highest affinity to the antigen** are selected to undergo clonal expansion, while the rest undergo apoptosis. The outcome is a population of cells that are **identical to each other and highly specific to that antigen**. The process is known as **clonal selection and expansion** (Fig. 3.16).

- Some cells from this clone become **effector cells**, short-lived cells that take effect immediately against the antigen and any pathogens producing that antigen.

    - The effector forms of B cells are **plasma cells**, which secrete antibodies.
    - The effector forms of T cells are **helper T cells** and **cytotoxic T cells** (*Section 3.4*).

- The remaining cells in the clone become **memory cells**, **long-lived cells** that can give rise to effector cells **immediately** if the same antigen is encountered later in the animal's life. (Fig. 3.16). These memory B cells have already undergone **affinity maturation** and **class switching,** so are able to develop into **antibodies-secreting plasma cells very rapidly** when they encounter a foreign antigen.

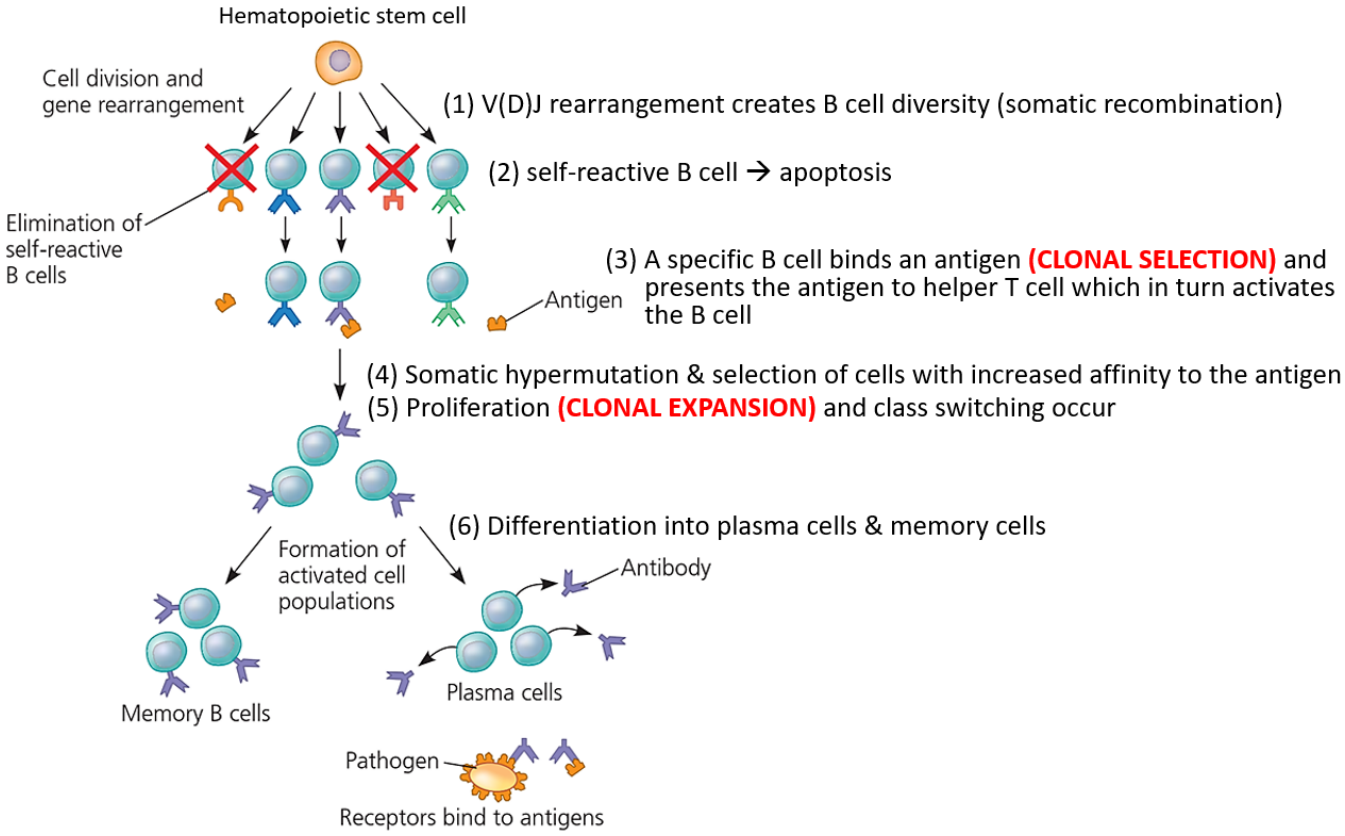


Fig. 3.16: Clonal selection and expansion, using B cells as an example.
In response to a specific antigen and to immune cell signals (not shown), one selected B cell divides and forms a clone of cells. The clone of cells formed by the selected B cell gives rise to memory B cells and antibody-secreting plasma cells.

3.3.3 Immunological memory

- Immunological memory refers to the ability of the immune system to respond more rapidly and effectively to a pathogen that has been **encountered previously**.

- Immunological memory is responsible for the **long-term protection** that a prior infection or vaccination provides against many diseases, such as chickenpox.

- When a B cell or T cell is **first exposed to an antigen**, a **primary immune response** is triggered which peaks at about 10–17 days after the initial exposure. The binding of the antigen to the antigen receptor activates the B cell or T cell to divide and to produce many more cells with the same receptors. Some of these selected B cells differentiate into memory B cells or plasma cells (effector cells) while selected T cells differentiate into memory T cells or helper and cytotoxic T cells (effector cells).

- If an individual is **exposed again to the same antigen**, the immune response is **faster**, of **greater magnitude**, and **more prolonged**. This is because the pre-existing memory B cells and T cells generated during the primary immune response can now respond more readily and rapidly. Such response is known as the **secondary immune response**.

- During the primary immune response, selected B cells give rise to antibody-secreting plasma cells specific to the antigen. If the same antigen is encountered again, these pre-existing memory B cell specific for that antigen enable the rapid formation of clones of thousands of plasma cells to secrete more antibodies. Hence, measuring the concentrations of specific antibodies in blood over time distinguishes the primary and secondary immune responses. (Fig. 3.17)

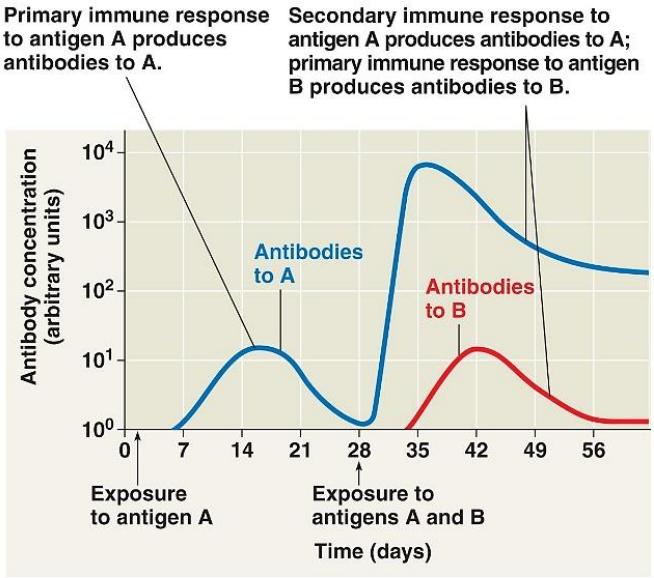


Fig. 3.17: The specificity of immunological memory. Long-lived memory cells generated in the primary response to antigen A give rise to a heightened secondary response to the same antigen, but do not affect the primary response to a different antigen (B).

- The secondary immune response relies on the **pre-existing T and B memory cells** generated following initial exposure to an antigen. These cells are **long-lived**, hence, they provide the basis for immunological memory, which can span many decades.

- Effector cells have much **shorter life spans**, which is why the immune response diminishes after an infection is overcome.

- Although the processes for antigen recognition, clonal selection, and immunological memory are similar for B cells and T cells, these two classes of lymphocytes fight infection in different ways and in different settings (*Section 3.4)*.

In summary, there are five major characteristics of adaptive immunity:

1) Acquired immunity exhibits **high specificity** as each antigen receptor (T-cell receptor and antibody) binds to a specific antigen (epitope) on a pathogen.

2) There is an **immense diversity of lymphocytes and receptors**, enabling the immune system to detect pathogens never before encountered.

3) Adaptive immunity normally has **self-tolerance**, the lack of reactivity against an animal's own molecules and cells.

4) **Cell proliferation** triggered by activation greatly increases the number of B and T cells specific for an antigen.

5) There is a stronger and more rapid response to an antigen encountered previously, due to a feature known as **immunological memory**.

3.4 Role of B cells, T cells, antigen-presenting cells and memory cells in adaptive immunity

Learning outcome:
Outline the roles of B lymphocytes, T lymphocytes, antigen-presenting cells and memory cells in specific primary and secondary immune responses.

- The activities of B and T lymphocytes produce a humoral immune response and a cell-mediated immune response respectively.

- In the **humoral immune response**, which occurs in the blood, **antibodies** help **eliminate toxins and pathogens** in the blood and lymph.

- In the **cell-mediated immune response**, specialized **T cells destroy infected host cells**.

3.4.1 Helper T cell activates B cells and cytotoxic T cells

- 2 main classes of T cells:
  - Helper T cell which helps stimulate the responses of other immune cells e.g. B cells, cytotoxic T cells, macrophages, dendritic cells.
  - Cytotoxic T cell which directly kills cells that are infected with a virus or intracellular pathogen.

- The **helper T cell** triggers both the humoral and cell-mediated immune responses.

- Helper T cells themselves do not carry out those responses. Instead, **signals** from helper T cells initiate production of antibodies from plasma cell. The antibodies neutralize pathogens and activate cytotoxic T cells that kill infected cells (Fig. 3.18).

- Two requirements must be met for a helper T cell to activate adaptive immune responses:

  1. **Presence of a foreign antigen** that can bind specifically to the antigen receptor of the T cell.
  2. This antigen must be **displayed with major histocompatibility complex (MHC)** on the **surface of an antigen-presenting cell**. The antigen-presenting cell can be a dendritic cell, macrophage, or B cell.

- The antigen is presented in complex with **class II MHC**. Class II MHC molecules are present only in **antigen-presenting cells**.

- When the antigen receptor on a helper T cell binds to the class II MHC-antigen complex on the antigen-presenting cell, the antigen-presenting cell produces **cytokines**. The cytokines then stimulate the helper T cell to produce its own set of cytokines.

- Cytokines produced from antigen-presenting cell and helper T cell stimulate the helper T cell to proliferate.

- Following its proliferation, the helper T cells produce other cytokines to

  1. **activate cytotoxic T cells** to **kill infected cells** (*Section 3.4.2*).
  2. **stimulate antigen-activated B cell** to proliferate and **differentiate** into **memory B cells** and **plasma cells** (*Section 3.4.3*)

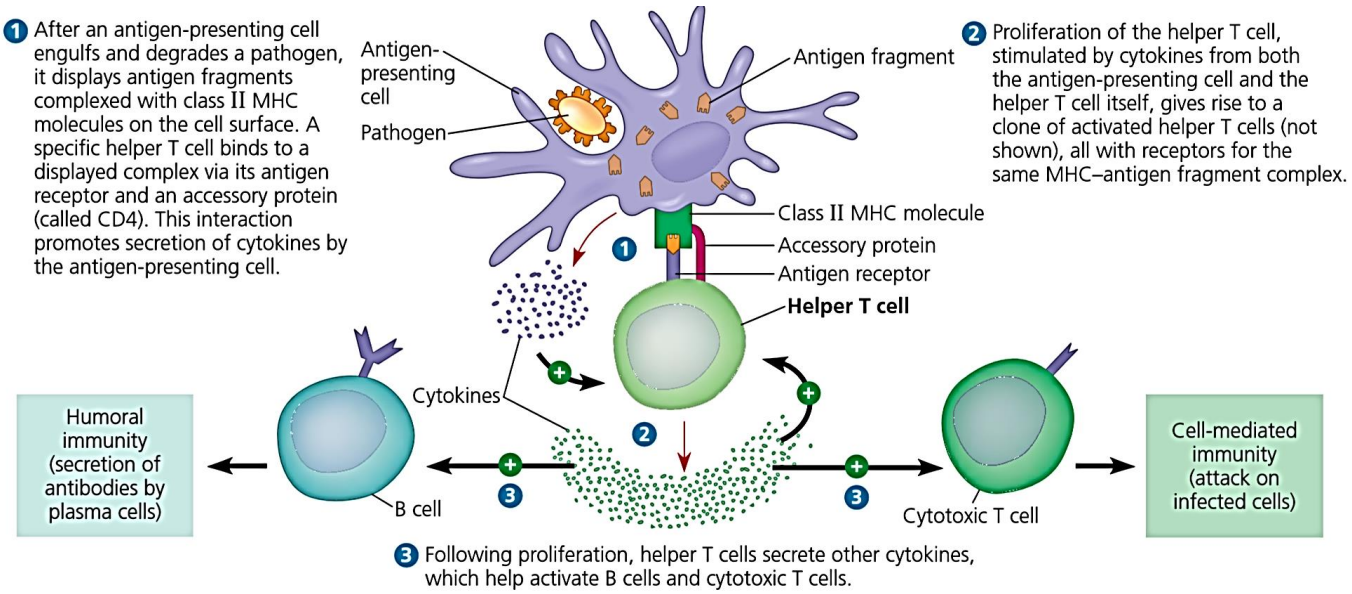


Fig. 3.18: The central role of helper T cells in humoral and cell-mediated immune responses. In this example, a helper T cell responds to a dendritic cell displaying a microbial antigen.

3.4.2 Cytotoxic T cells kills infected cells

- In the cell-mediated immune response, once the **cytotoxic T cells** are **activated by helper T cell**, they can eliminate cells that are infected by viruses or other intracellular pathogens.
- **Infected host cells** present fragments of the foreign protein in complex with **class I MHC molecules** and are displayed on the cell surface. These fragments of foreign protein can be recognized by cytotoxic T cells.
- The killing of an infected host cell by a cytotoxic T cell involves the secretion of proteins that **disrupt membrane integrity** and **trigger apoptosis**. (Fig. 3.19)
- The death of the infected cell not only deprives the pathogen of a place to reproduce, but also exposes cell contents to circulating antibodies. After destroying an infected cell, the cytotoxic T cell can move on and kill other cells infected with the same pathogen.

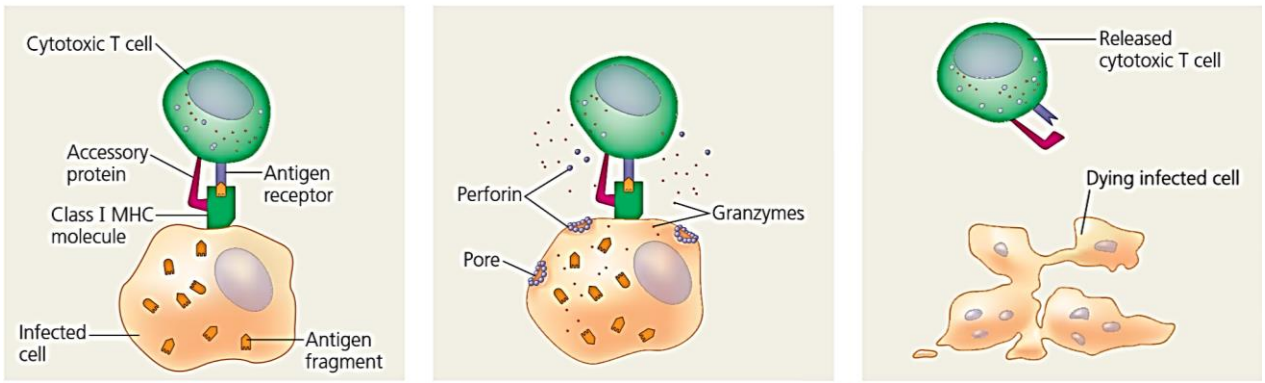


Fig. 3.19: The killing action of cytotoxic T cells on an infected host cell. An activated cytotoxic T cell releases molecules that make pores in an infected cell's membrane and enzymes that break down proteins, promoting the cell's death.

3.4.3 B cell secretes antibodies that bind to and mark pathogens for destruction

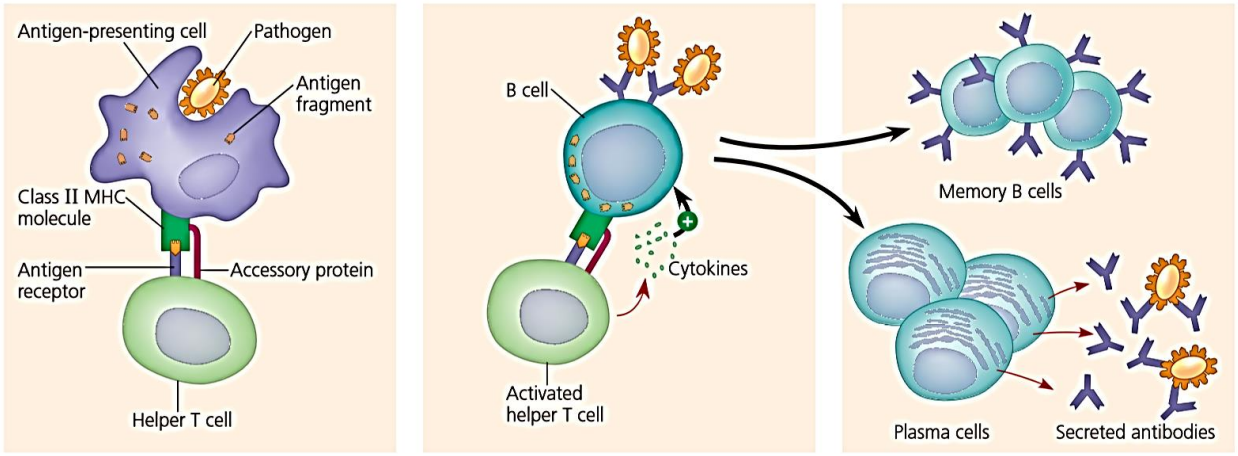
- The humoral immune response involves the secretion of antibodies by clonal-selected B cells.

(A) Activation of B cells

- When a B cell (also an antigen-presenting cell) internalizes the foreign antigen, it displays an antigen fragment in complex with **class II MHC molecule** on its cell surface.

- Antigen receptor on activated helper T cell binds with the class II MHC-antigen complex on the B cell. This leads to the release of cytokines from T cell. (Fig. 3.20)

- These cytokines stimulate the B cell to proliferate and differentiate into memory B cells and plasma cells.



1 After an antigen-presenting cell engulfs and degrades a pathogen, it displays an antigen fragment complexed with a class II MHC molecule. A helper T cell that recognizes the complex is activated with the aid of cytokines secreted from the antigen-presenting cell.

2 When a B cell with receptors for the same epitope internalizes the antigen, it displays an antigen fragment on the cell surface in a complex with a class II MHC molecule. An activated helper T cell bearing receptors specific for the displayed fragment binds to the B cell. This interaction, with the aid of cytokines from the T cell, activates the B cell.

3 The activated B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells. The secreted antibodies are specific for the same antigen that initiated the response.

Fig. 3.20: Activation of a B cell in the humoral immune response. Most protein antigens require activated helper T cells to trigger a humoral response. A macrophage (shown here) or a dendritic cell can activate a helper T cell, which in turn can activate a B cell to give rise to antibody-secreting plasma cells.

- An activated B cell gives rise to thousands of **identical antibodies-secreting plasma cells**.

- Each plasma cell secretes approximately 2,000 antibodies every second of the cell's 4- to 5-day life span.

(B) Antibody function

- Antibodies do not kill pathogens, but by binding to antigens, they mark pathogens in various ways for inactivation or destruction (Fig. 3.21).

1) **Neutralization**
   - The binding of antibodies to **viral surface proteins** prevent infection of a host cell, thus neutralizing the virus.
   - Similarly, antibodies sometimes bind to **toxins** released in body fluids, preventing the toxins from entering body cells

2) **Opsonization**
   - In opsonization, antibodies bound to antigens on bacteria (called opsonized bacteria) present a readily recognized structure for macrophages or neutrophils and therefore **increase phagocytosis**.
   - Antibodies also facilitate phagocytosis by linking bacterial cells, virus particles, or other foreign substances into aggregates.

3) **Facilitate the activation of complement proteins**
   - Binding of antibodies to antigens on the surface of a foreign cell activates the complement system.

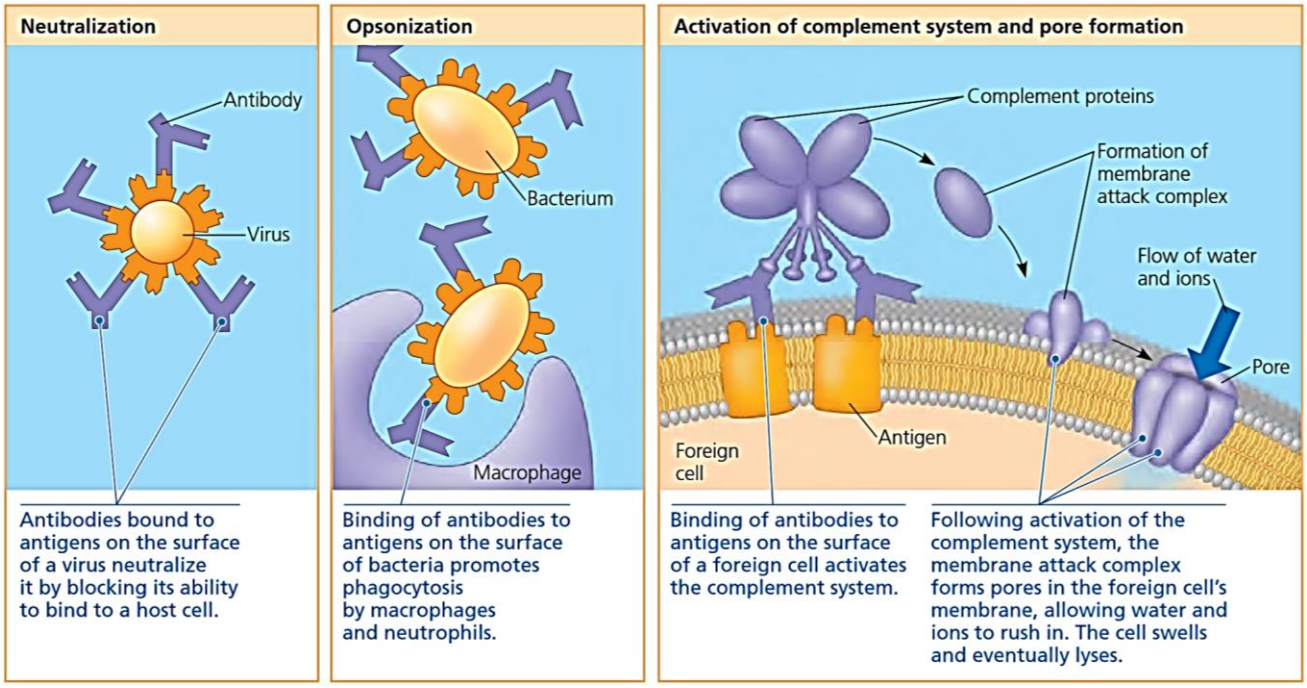


Fig. 3.21: Antibody-mediated mechanism of antigen disposal

4) **Facilitate the destruction of viral-infected cells**
   - When a virus uses a cell's biosynthetic machinery to produce viral proteins, these viral products can appear on the cell surface.
   - Antibodies specific for epitopes on these viral proteins bind to the exposed proteins. The presence of bound antibody at the cell surface can recruit a natural killer cell.
   - The natural killer cell then releases proteins that cause the infected cell to undergo apoptosis.

3.4.4 Summary of the humoral and cell-mediated immune responses

- Both the humoral and cell-mediated responses can include primary and secondary immune responses.
- **Memory cells** of each type – helper T cell, B cell, and cytotoxic T cell – **enable the secondary response**.
- For example, when body fluids are re-infected by a pathogen encountered previously, memory B cells and memory helper T cells initiate a secondary humoral response.
- Fig. 3.22 reviews the events that initiate humoral and cell-mediated immune responses, highlights the central role of the helper T cell, and serves as a helpful summary of adaptive immunity.

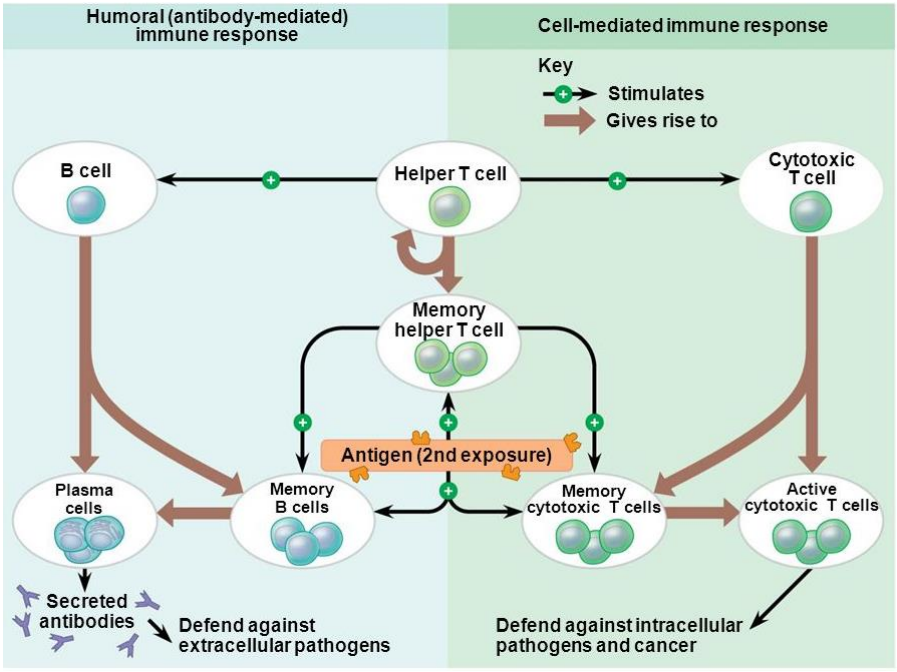
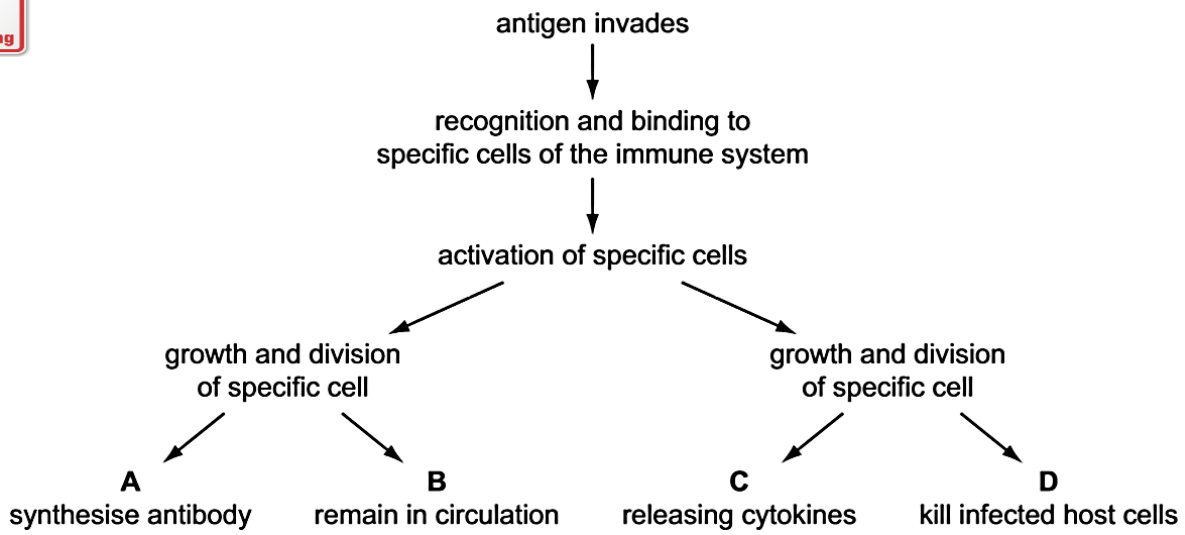


Fig. 3.22: An overview of the humoral and cell-mediated immune responses.

STOP Check With Guard Before Proceeding

Exercise 3: Label A – D



4. Comparison between innate and adaptive immunity

	Innate	Adaptive
Cells involved	Phagocytes, NK cells	B cells, T cells
Proteins involved	Complement proteins, interferons	Antibodies, cytokines
Receptors involved	Toll-like receptor on phagocytes	Antigen receptors on T cells and B cells
Activation through…?	Active even without exposure to antigen	Activated upon exposure to antigen
Antigen specificity	Not antigen specific, i.e. target all pathogens	Highly specific for a particular antigen, i.e. targets specific pathogen
Time lag between exposure to response	Immediate maximal response	Lag time between exposure and maximal response
Does proliferation of cells occur? If so, what kind of cells?	Exposure to antigen does not lead to proliferation of cell involved	Exposure to antigen leads to proliferation of T cells and B cells
Immunological memory?	Response does not alter on repeated exposure (no memory)	Response improves with each successive exposure (memory)
Recognition diversity	Recognizes limited diversity of pathogens	Recognizes large diversity of pathogens

5. Vaccination and disease control

Learning outcome:
Describe the specific (adaptive) and non-specific (innate) immune systems including active and passive, natural and acquired immunity.

5.1 Types of immunity

- Immunity is the ability of an organism to resist infection. This immunity may be naturally acquired or artificially induced.

- **Types of immunity**

    - **Natural immunity** is the immunity which is either inherited, or acquired as part of normal life processes, e.g. as a result of having had a disease.

    - **Artificial immunity** is immunity acquired as a result of the deliberate exposure of the body to **antibodies** or **antigens** in non-natural circumstances, e.g. vaccination.

- Both natural and artificial immunity may be passively or actively acquired.

- **Passive immunity** is immunity acquired from the introduction of antibodies from another individual, rather than one's own immune system. It is generally short-lived.

    - **Natural** passive immunity occurs when an individual receives antibodies from their mother via:
        - the placenta as a foetus
        - the mother's milk during suckling

    - **Artificial** passive immunity occurs when antibodies from another individual are injected. This takes place in the treatment of disease such as tetanus and diphtheria.

- **Active immunity** is immunity resulting from the activities of an individual's own immune system, rather than an outside source. It is generally long lasting.

    - **Natural** active immunity occurs where antibodies acquired as a result of a previous infection producing B lymphocyte memory cells which are reactivated on the second infection.

    - **Artificial** active immunity occurs when antigens are injected or given by mouth as vaccine. The process is known as vaccination. They induce the body to produce its own antibodies.

- Table 3 provides examples of naturally-acquired and artificially-acquired passive and active immunity.

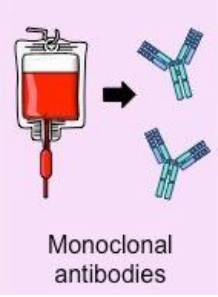
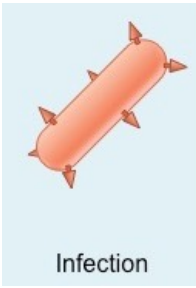
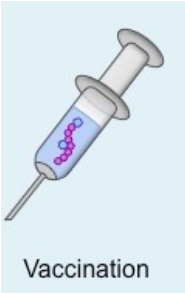
	Naturally-acquired	**Artificially-acquired**
Passive immunity	 Maternal antibodies When the antibodies in the blood of a pregnant female cross the placenta to her foetus.	 Monoclonal antibodies When antibodies extracted from an immune person is injected into a non-immune person.
Active immunity	 Infection When a person is infected with a pathogen. Induces an adaptive immune response.	 Vaccination When a person is vaccinated with attenuated form of a pathogen Induces an adaptive immune response.

Table 3: naturally-acquired and artificially-acquired passive and active immunity

5.2 Vaccination and the eradication of smallpox virus

Learning outcome:
Discuss how vaccination can control disease (e.g. in the eradication of smallpox), limited to vaccination stimulates immunity without causing the disease and vaccination of a high enough proportion of the population can break the disease transmission cycle.

- **Vaccination** is the administration (injection / inhalation / ingestion) of **antigenic material** (**vaccine**) to stimulate an individual's immune system to develop **adaptive immunity** to a pathogen. It is also known as **active immunization**.

- The objective is to provide the individual with long lasting immunologic protection against exposure to infectious pathogens by first eliciting primary immune responses to the antigens on the pathogen. Note that **vaccination does not cause diseases**.

- After an individual is immunized, **exposure to the actual pathogen triggers a secondary response**, which is faster and stronger and hence protecting the individual from the disease.

- There are different forms of vaccine:

    - **Living attenuated microorganisms** are living but weakened microorganisms which do not cause symptoms. They can stimulate the body's immune system. Measles and tuberculosis (TB) can be vaccinated against this way.

    - **Dead microorganisms** that can induce immune response. Typhoid and cholera can be controlled by this means.

    - **Genetically engineered microorganisms** can be produced in which the genes for antigen production are transferred from a harmful microorganism to a harmless one. These are then grown in fermenters and the extracted antigen is separated and purified before injection. e.g. Hepatitis B vaccine.

    - **mRNA** that codes for a surface protein of the pathogen (e.g. covid-19 mRNA vaccine).

    Note: Vaccination can only be used to control diseases caused by pathogen. It is not effective against genetic diseases such as sickle cell anaemia.

- The programme of vaccination against various diseases varies in its success. Features of a successful vaccination programme include:

    - **Few**, if any, **side effects** from vaccination. Unpleasant side effects may discourage individuals in the population from being vaccinated.

    - The ability to **vaccinate the vast majority of the vulnerable population at one time**. This **interrupts the transmission of the pathogen** because for a certain period there are no individuals in the population with the disease. This is known as **herd immunity**.

    - Proper mechanism to produce, store and transport the vaccine.

    - The means of administering the vaccine properly at the appropriate time by trained staff with appropriate skills at different centres throughout the population.

- Eradicating a disease can be unsuccessful even though the criteria for successful vaccination are met. The reasons for this include:
    - Vaccination fails to induce immunity in certain individuals, e.g. ones with defective immune systems that do not produce the necessary clones of B and T lymphocytes.
    - The disease-causing pathogen may mutate frequently so that its antigens change. This means that vaccines suddenly become ineffective as the antibodies produced no longer recognize the new antigens on the pathogen.
    - Some pathogens suppress the body's immune system, so stimulating body immune response against such pathogens through vaccination is ineffective e.g. HIV

Case Study: Successful Eradication Of Smallpox Virus Through Vaccination

- Smallpox is a deadly disease caused by the variola virus that emerged in human populations thousands of years ago. Its symptoms include high fever, fatigue, headache, backache, and a rash characterized by raised red bumps on the skin.
- In 1796, Edward Jenner, an English physician, noted that milkmaids who had cowpox, a mild disease usually seen only in cows, did not contract smallpox, a far more dangerous disease.
- He developed a procedure where he infected a person with cowpox virus and caused the person to develop immunity to smallpox. He called it vaccination.
- In 1979, the World Health Organization (WHO) launch a worldwide project to eradicate smallpox by vaccinating populations in endemic countries, using **live vaccinia virus** that is **closely-related to smallpox virus**, but **does not cause disease**.
- Vaccinia virus has the **same antigen as smallpox virus**. Thus, vaccinating an individual with vaccinia virus allows the **production of B cells and T cells with antigen receptors complementary to the antigen on smallpox virus**.
- Vaccinia virus is **genetically stable** which does not undergo frequent mutation on the gene coding for surface antigen, hence, making the vaccine more effective.
- The effect of the vaccine is **long lasting**. Only one dose of vaccination is enough.
- By **vaccinating a high enough proportion of the population at the same time**, the **disease transmission cycle can be terminated**. This is **herd immunity**. Indeed, in 1980, the World Health Assembly announced that the world was free of smallpox.

5.3 Benefits and risks of vaccination

Learning outcome:
Discuss the benefits and risks of vaccination.

Benefits

1. **Confers immunity** to an individual even if he is previously not exposed to a certain pathogen.

2. Confers long-term / **life-long immunity** to individual due to production of memory B and T cells.

3. **Reduces the spread** of infectious diseases within human population. It is estimated that vaccines annually prevent almost 6 million deaths worldwide.

4. **Herd immunity**: When a critical portion of a community is immunized against a contagious disease at the same time, most members of the community are protected against that disease because there is little opportunity for an outbreak.

5. Vaccines are **cost-effective**: It is always cheaper to prevent a disease than to treat it.

6. **Cancer prevention**: Infective agents cause several cancers. For example, chronic hepatitis B infection leads to liver cancer. Vaccination against such pathogens helps to prevent the associated cancer.

7. **Protection against related diseases**: Vaccines will also protect against diseases related to the targeted disease (e.g. measles vaccination protects against multiple complications such as dysentery, bacterial pneumonia and malnutrition).
8. **Preventing development of antibiotic-resistant bacteria**: by reducing the need for antibiotics, vaccines may reduce the prevalence and hinder the development of resistant bacterial strains.

9. **Safe travel and mobility**: with global air travel rising, there is an increased risk of exposure to infectious diseases abroad, as travelers are capable of transmitting and disseminating diseases

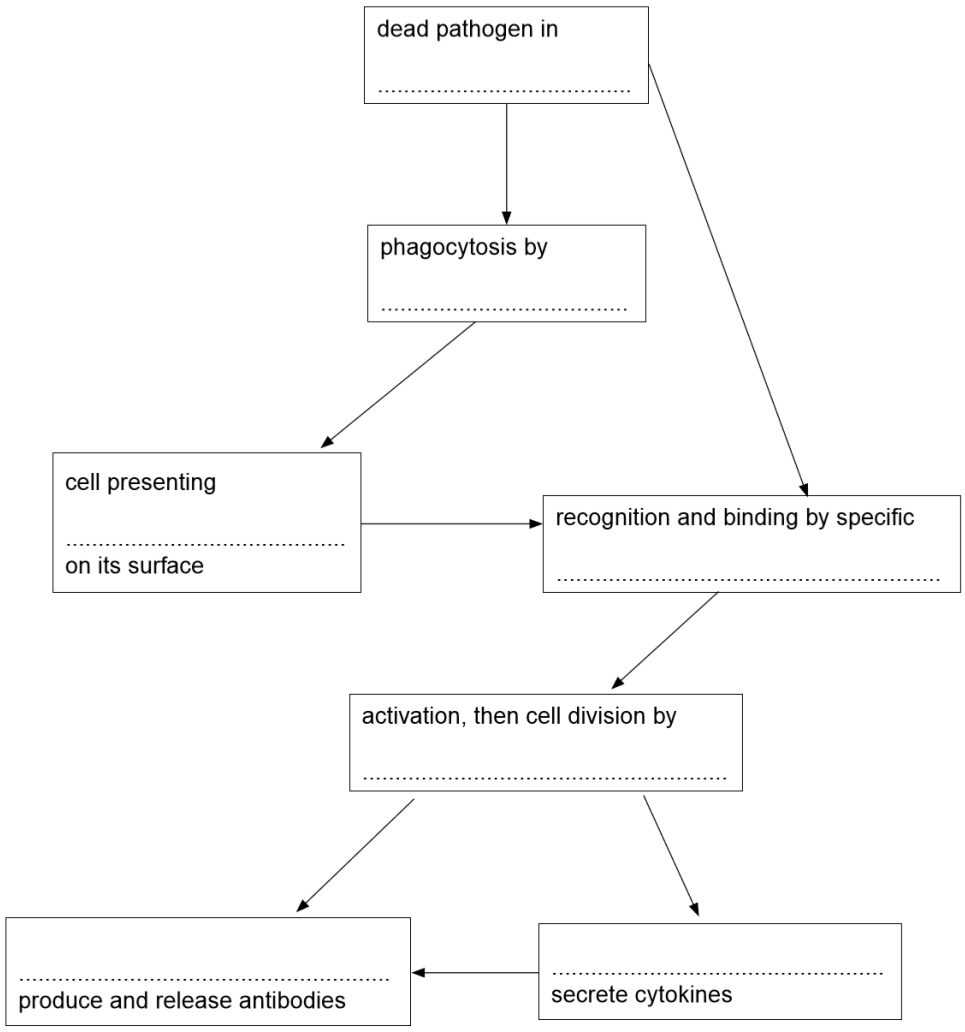
Risks

1. On very rare occasions (1 in a million), a **severe allergic reaction** may happen within a few minutes of the vaccination. This is called an anaphylactic reaction. It can lead to breathing difficulties and, in some cases, collapse.

2. Live attenuated viruses used in vaccine may have a possibility of **regaining virulence** and cause disease.

Exercise 4: The flow chart below shows some of the events of the primary immune response that occur after a person has been given a vaccine. Choose the correct term from the list below to complete the flow chart.

lymphocytes	***antigens***	***mitosis***	***vaccine***
plasma cells	***macrophages***	***helper T lymphocytes***	



6. Infectious diseases caused by viruses

Learning outcome:
Explain how viruses, including influenza and HIV, cause diseases in humans through the disruption of host tissue and function (e.g. HIV and T helper cells, influenza and epithelial cells of the respiratory tract)

6.1 HIV weakens the immune system by destroying helper T cells

- HIV infects helper T cells as the viral glycoprotein gp120 on HIV is complementary in shape to the CD4 receptor present on helper T cells.
- Replication of HIV in helper T cells eventually kills the helper T cells.
- As more HIV are released into the blood and more helper T cells are infected, helper T cells decrease in number.
- Without helper T cells, the **immune system is compromised** because
    1. antigen-activated B cells are unable to differentiate into antibody-secreting plasma cells, resulting in a lack of soluble antibodies to facilitate the removal of pathogen (*Section 3.4.3*).
    2. cytotoxic T cells are unable to kill viral-infected cells (*Section 3.4.2*), allowing the virus to complete its reproduction cycle.
- A person with compromised immune system is **susceptible to opportunistic bacterial / viral infections** and **cancer**. When this happens, the person develops **acquired immunodeficiency syndrome (AIDS)**.
- As **HIV reverse transcriptase is error-prone** and **lacks proofreading activity**, HIV genome is prone to mutation during its reproductive cycle. As a result, antibodies raised against the structures (e.g. gp120) of the initial HIV strain become ineffective against the new mutated strains. This is why it is difficult to produce an effective vaccine against HIV.

6.2 Influenza virus damages respiratory epithelial cells

- The main targets of the influenza virus are the **epithelial cells** of the **respiratory tract**.
- How influenza virus damage epithelial cells leading to **inflammation**:
    - **Interferes with metabolic processes** (e.g. gene expression) leading to epithelial cells undergoing **apoptosis**
    - Viral release via **budding** leads to the partial **loss of the cell surface membrane**
    - Viral-infected epithelial cells **present viral peptide on MHC class I** to **cytotoxic T cells**, which **kills the infected epithelial cell**
    - The cytotoxic T cell / NK cells also secrete cytokines that can **damage nearby healthy epithelial cells**
- In severe cases, the lung inflammation may develop into **pneumonia** as the airways are blocked by fluid and there is reduced clearance of infectious agents. This can result in death.
- Influenza can lead to a **pandemic** (i.e. global outbreak) as its structure does not remain the same over time as a result of antigenic shift and antigenic drift.
- Some subtypes can cause tissue damage, e.g. H5N1 influenza does not only infect the lung epithelial cells, but other tissues in the body such as the gut. Hence it is a more lethal strain.

7. Infectious diseases caused by bacteria

Learning outcome:
Explain the mode of transmission and infection of bacterial pathogens, using *Mycobacterium tuberculosis* as an example.

7.1 *Mycobacterium tuberculosis* infects the lung and causes tuberculosis

- The cell wall structure of *M. tuberculosis* is unique among prokaryotes – apart from peptidoglycan, about 50% of its cell wall is made of **mycolic acids**.

Mode of transmission

- Tuberculosis is an **air-borne disease** that is spread from **person to person**. When people with tuberculosis cough, sneeze or spit, they propel the *M. tuberculosis* into the air in **microscopic droplets**. A person needs to inhale only a few of *M. tuberculosis* to become infected.

Infection and symptoms

- *M. tuberculosis* most commonly infects the **lungs**.
- Once inside the lungs, macrophages will tend to remove the bacteria via phagocytosis. However, the bacteria can **escape the phagosome** to continue to divide by binary fission in the cytosol (Fig. 7.1a). From the lung, they can **move through the blood to other parts of the body**, such as the kidney, spine, and brain.
- Infected macrophages in the lung release chemical to attract many other white blood cells to the site of infection, resulting in **lesions** called **tubercles** (Fig. 7.1b, 7.1c).
- Eventually, the **tubercle ruptures**, allowing *M. tuberculosis* to spill into a bronchiole and **spread throughout the lungs**. This results in development of a **productive cough** that facilitates **aerosol spread** of the infectious bacteria (Fig. 7.1b).
- Symptoms of tuberculosis disease includes fever, persistent cough with sputum (may cough up blood), pain in the chest, fatigue, chills and weight loss.
- Death is often a result of **respiratory failure** (pulmonary tuberculosis) due to damaged alveoli which **compromise gaseous exchange**.
- Due to a compromised immune system, HIV-positive individuals have a higher chance of developing tuberculosis disease upon infection by *M. tuberculosis* as compared to a healthy individual.

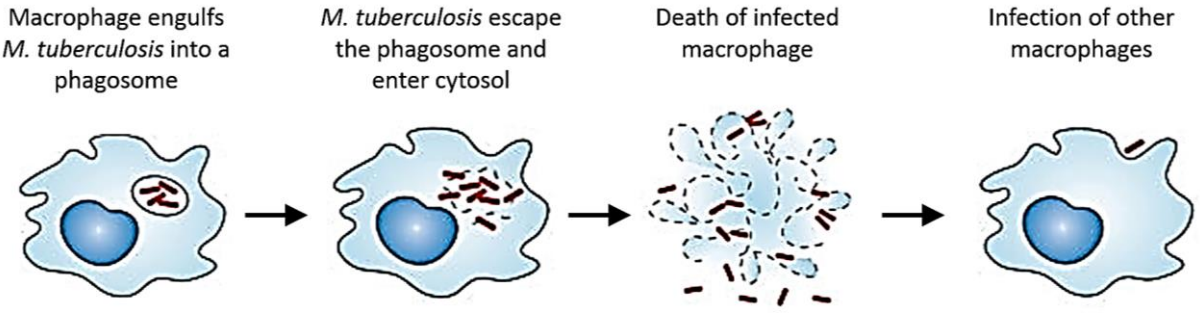


Fig. 7.1a: Multiplication of *M. tuberculosis* within a macrophage in the alveoli.

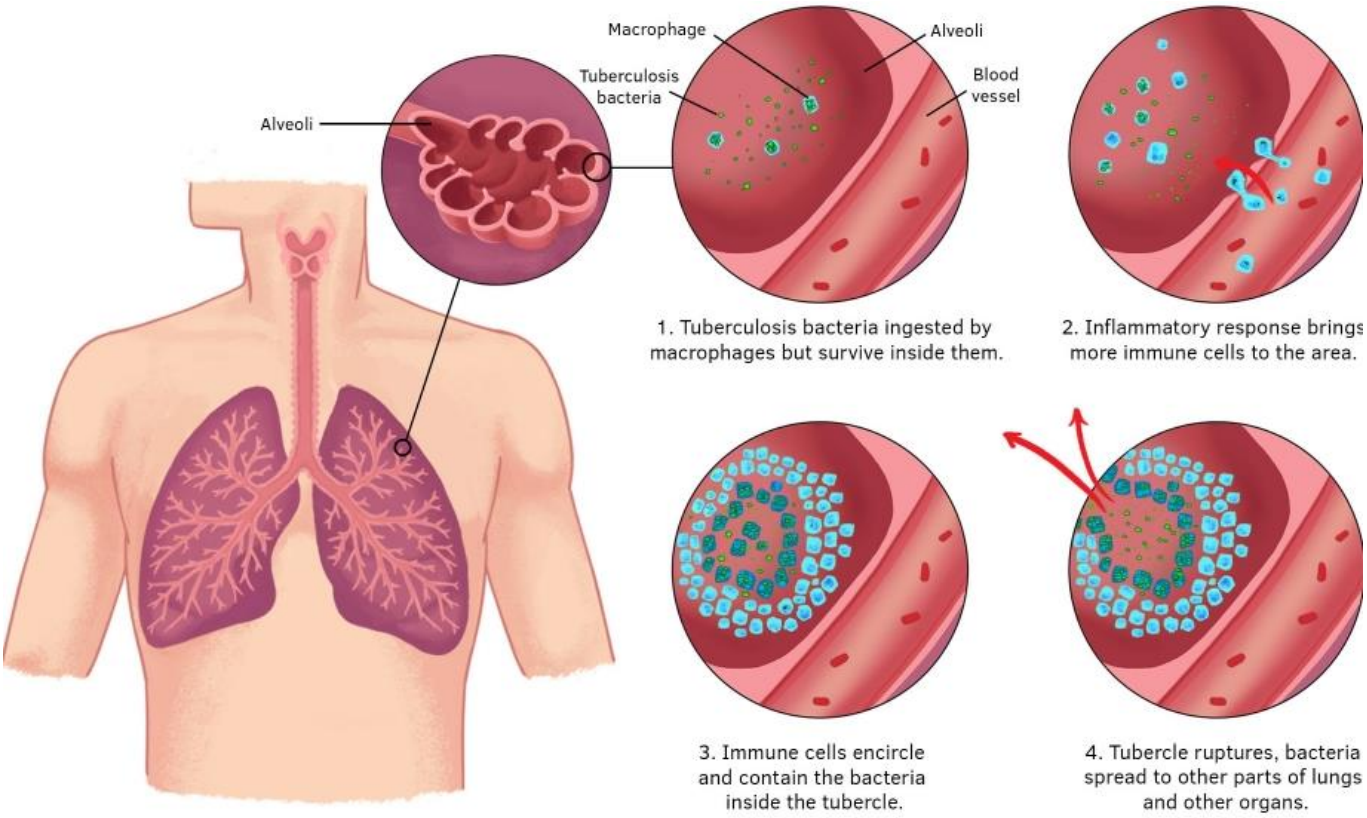


Fig. 7.1b: Formation of lesions (tubercles).

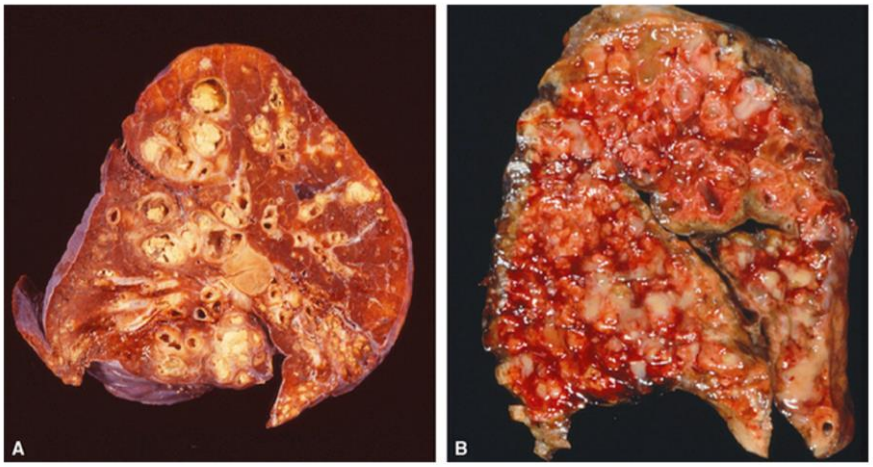


Fig. 7.1c: Healthy lungs VS Lungs with lesions as a result of tuberculosis.

7.2 How antibiotics kill bacteria

Learning outcome:
Describe the modes of action of antibiotics, including penicillin, on bacteria.

- Antibiotics are chemicals produced **naturally by certain bacteria and fungi** to protect them against other species of bacteria.

- Ever since penicillin, the first true antibiotic, was discovered in 1928 by Alexander Fleming, it has been used extensively to fight bacterial infections. Subsequently, many other antibiotics were discovered.

- Antibiotics kill bacteria through one or more of the following ways:

    1. **Interferes with peptidoglycan cell wall formation**: The cell walls of bacteria are essential to prevent the cells from bursting when water enters by osmosis. Antibiotics inhibit the synthesis and assembly of bacterial peptidoglycan cell wall, weakening the cells and causing them to burst, thereby killing the bacteria.

    2. **Disrupts cell membrane**: A disruption or damage of the lipid bilayer could allow the cell contents to escape, thereby killing the cell.

    3. **Interferes with translation** by binding to **large (50S) subunit** or **small (30S) subunit of the 70S ribosomes in bacteria**.

    4. **Interferes with nucleic acid synthesis**
        - DNA replication: by binding to and inhibiting bacterial DNA polymerases
        - Transcription: by binding to and inhibiting bacterial RNA polymerases

    5. **Inhibits the synthesis and use of essential metabolites**, thus interfering with metabolic activities

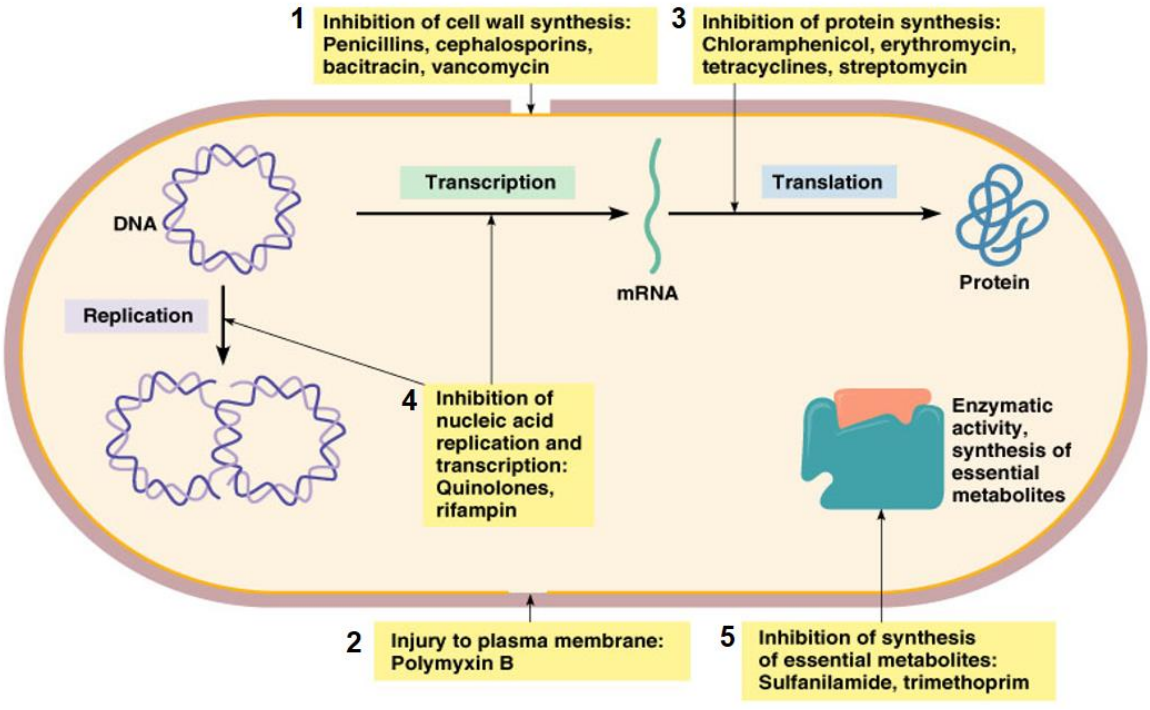


Fig. 7.2: Five mechanism of action of antibiotics.

Mechanism of action of penicillin

- Peptidoglycan cell wall is made up of chains of modified sugars cross-linked by short polypeptides. This cross-link is catalysed by **transpeptidase**.
- Bacteria **constantly remodel their peptidoglycan cell walls**, simultaneously building and breaking down portions of the cell wall as they grow and divide.
- Penicillin inhibits the formation of peptidoglycan cross-links in the bacterial cell wall by binding the **penicillin β-lactam ring to the transpeptidase**.
- The enzymes that hydrolyse the peptidoglycan cross-links continue to function, while transpeptidase that form the cross-links do not, leading to an imbalance between cell wall production and degradation.
- This weakens the cell wall of the bacterium, and **osmotic pressure** becomes increasingly uncompensated, eventually causing cell death. (Fig. 7.3)

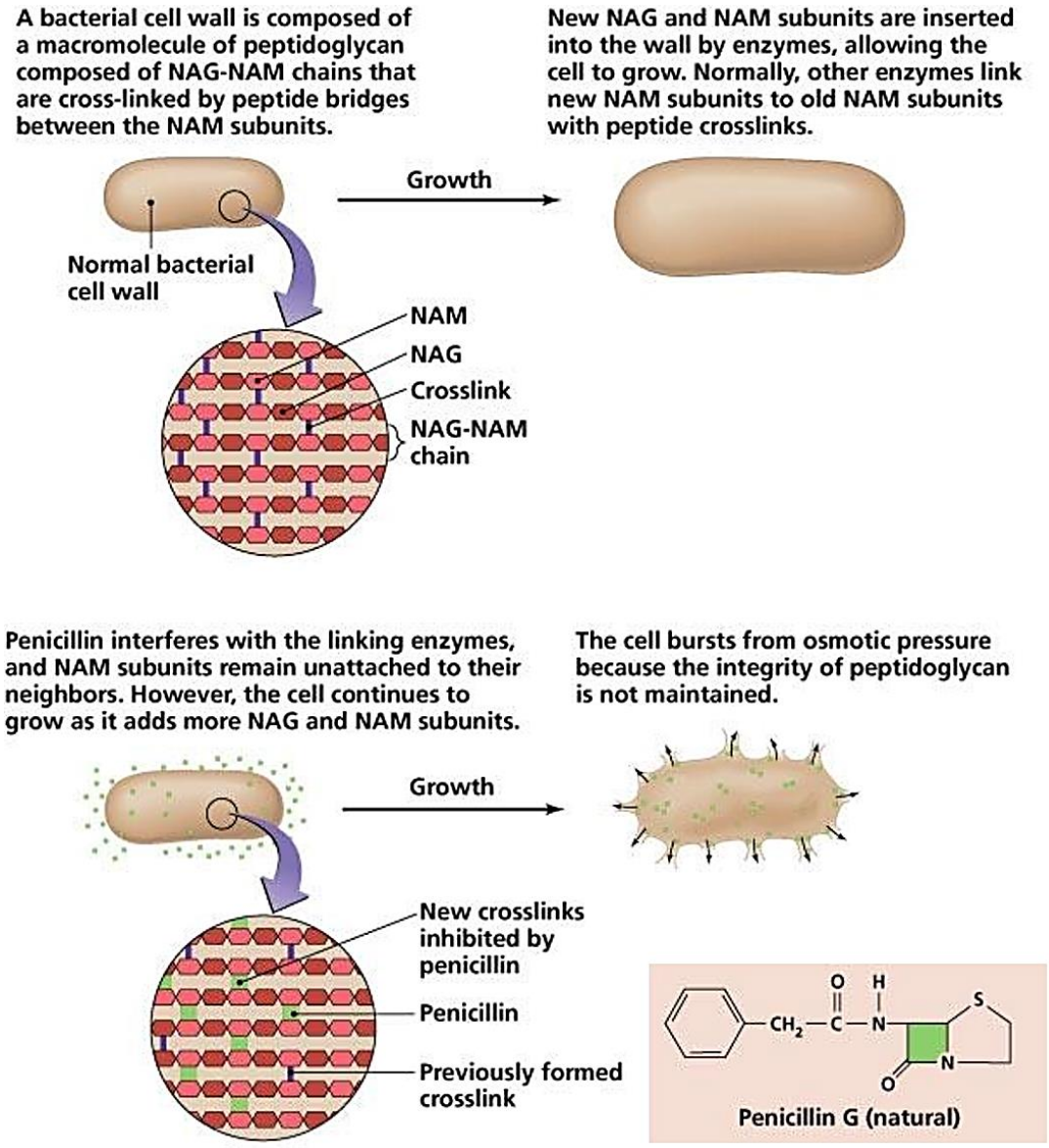


Fig. 7.3: Mechanism of action of penicillin. The linking enzyme is transpeptidase.

7.3 How bacteria gain resistance to antibiotics

- A bacterial population develop resistance to antibiotics due to the initial existence of a very small number of bacteria that already contain the antibiotic-resistant gene as a result of mutation. (*Topic on Biological Evolution*)

- Due to the misuse of antibiotics, bacteria population of many species have evolved to become resistant to even the most powerful antibiotics.

- The antibiotic-resistant genes confer resistance to the bacteria by coding for

  1. protein pump that transports antibiotics out of the bacterial cell before they can exert effect.

  2. enzyme that degrades the antibiotics.

  3. enzyme that alters the antibiotics into a harmless product.

  4. enzyme that alters that cell wall to prevent entry of the antibiotics.

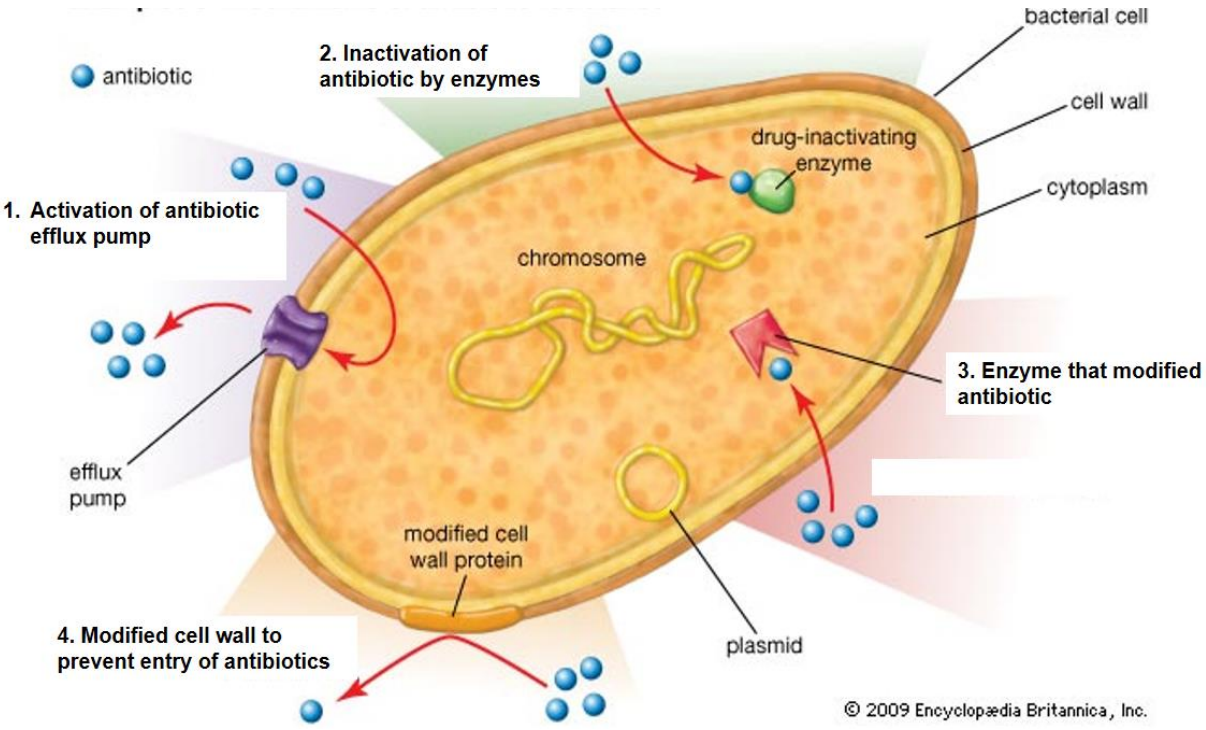


Fig. 7.4: Protein products that antibiotic-resistant genes code for.

Glossary of Terms

Acquired immune response: Immunity mediated by lymphocytes and characterized by antigen-specificity and memory.

Antigen: Any molecule capable of being recognized by an antibody or T-cell receptor.

Antigen-presenting cell (APC): A term most commonly used when referring to cells that present processed antigenic peptide and MHC class II molecules to the T-cell receptor on CD4 + T-cells, e.g. dendritic cells, macrophages, B-cells. Note, however, that most types of cell are able to present antigenic peptides with MHC class I to CD8 + T-cells, e.g. as occurs with virally infected cells.

Antigenic determinant: A cluster of epitopes (see epitope)

B lymphocyte: a type of lymphocyte that originates in the bone marrow and produces antibodies. A precursor of the plasma cell, it is one of the two lymphocytes that play a major role in the body's immune response.

CD4: Cell surface glycoprotein, usually on helper T cells, that recognizes MHC class II molecules on antigen-presenting cells.

CD8: Cell surface glycoprotein, usually on cytotoxic T cells, that recognizes MHC class I molecules on target cells.

Cell-mediated immunity (CMI): Refers to T-cell mediated immune responses.

Class switching: The process by which a B-cell changes the class but not specificity of a given antibody it produces, e.g. switching from an IgM to an IgG antibody.

Clonal selection: The selection and activation by antigen of a lymphocyte bearing a complementary receptor, which then proliferates to form an expanded clone.

Complement: A group of serum proteins, some of which act in an enzymatic cascade, producing effector molecules involved in inflammation (C3a, C5a), phagocytosis (C3b), and cell lysis (C5b–9).

Cytokines: Small proteins that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma.

Cytotoxic: Kills cells.

Cytotoxic T lymphocyte (CTL, Tc): T-cells (usually $CD8^+$) which kill target cells following recognition of foreign peptide–MHC molecules on the target cell membrane.

Dendritic cell: MHC class II-positive phagocyte that presents processed antigens to T-cells.

Diversity (D) gene segments: Found in the immunoglobulin heavy chain gene and T-cell receptor β and δ gene loci between the V and J gene segments.

Effector cells: Cells which carry out an immune function, e.g. cytokine release, cytotoxicity.

Endocytosis: Cellular ingestion of macromolecules by invagination of plasma membrane to produce an intracellular vesicle which encloses the ingested material.

Epitope: That part of an antigen recognized by an antigen receptor (*see antigenic determinant*).

Helper T lymphocyte (T_H): A subclass of T-cells which provide help (in the form of cytokines and/or cognate interactions) necessary for the expression of effector function by other cells in the immune system.

Hematopoiesis: The production of erythrocytes, leukocytes and platelets.

Humoral: Pertaining to extracellular fluid such as plasma and lymph. The term humoral immunity is used to denote antibody-mediated immune responses.

Innate immunity: Immunity which is not intrinsically affected by prior contact with antigen, i.e. all aspects of immunity not directly mediated by lymphocytes.

Interferons (IFN): Proteins produced by virally-infected cells and T lymphocytes that induce an anti-viral state in uninfected cells.

Joining (J) gene segments: Found in the immunoglobulin and T-cell receptor gene loci and, upon gene rearrangement, encode part of the variable region of the antigen receptors.

Leukocyte: White blood cells, which include neutrophils, basophils, eosinophils, lymphocytes and monocytes.

Lipopolysaccharide (LPS): Endotoxin derived from Gram-negative bacterial cell walls which has inflammatory and mitogenic actions.

Lymph: The tissue fluid which drains into and through the lymphatic system.

Lysosomes: Cytoplasmic granules containing hydrolytic enzymes involved in the digestion of phagocytosed material.

Lysozyme: Anti-bacterial enzyme present in phagocytic cell granules, tears and saliva, which digests peptidoglycans in bacterial cell walls.

Macrophage: Large phagocytic cell, derived from the blood monocyte, which also functions as an antigen-presenting cell and can mediate ADCC.

Mast cell: A tissue cell with abundant granules which resembles the blood basophil. Both these cell types bear high affinity Fc receptors for IgE, which when crosslinked by IgE and antigen cause degranulation and the release of a number of mediators including histamine and leukotrienes.

Megakaryocyte: A bone marrow precursor of platelets.

Membrane attack complex (MAC): Complex of complement components C5b –C9 which inserts as a pore into the membrane of target cells leading to cell lysis or apoptosis.

Memory (immunological): A characteristic of the acquired immune response of lymphocytes whereby a second encounter with a given antigen produces a secondary immune response; faster, greater and longer lasting than the primary immune response.

Memory cells: Clonally expanded T- and B-cells produced during a primary immune response and which are 'primed' to mediate a secondary immune response to the original antigen.

MHC (major histocompatibility complex): A genetic region encoding molecules involved in antigen presentation to T-cells. Class I MHC molecules are present on virtually all nucleated cells, whilst class II MHC molecules are expressed on antigen-presenting cells (primarily dendritic cells, macrophages and B-cells). Allelic differences are associated with the most intense graft rejection within a species.

Monoclonal antibody: Homogeneous antibody derived from a single B-cell clone and therefore all bearing identical antigen-binding sites and isotype.

Monocyte: Mononuclear phagocyte found in blood and which is the precursor of the tissue macrophage.

Naive lymphocyte: A mature T- or B-cell which has not yet been activated by encounter with antigen.

Neutrophil: The major circulating phagocytic polymorphonuclear granulocyte. Enters tissues early in an inflammatory response and is also able to mediate antibody-dependent cellular cytotoxicity (ADCC).

NK (natural killer) cell: Large granular lymphocyte which does not rearrange nor express either immunoglobulin or T-cell receptor genes but is able to recognize and destroy certain tumor and virally infected cells in an MHC and antibody-independent manner.

Opsonin: Substance, e.g. antibody or C3b, which enhances phagocytosis by promoting adhesion of the antigen to the phagocyte.

Opsonization: Coating of antigen with opsonin to enhance phagocytosis.

Phagocyte: Cells, including monocytes/macrophages and neutrophils, which are specialized for the engulfment of cellular and particulate matter.

Phagolysosome: Intracellular vacuole where killing and digestion of phagocytosed material occurs following the fusion of a phagosome with a lysosome.

Phagosome: Intracellular vacuole produced following invagination of the cell membrane around phagocytosed material.

Plasma cell: Terminally differentiated B lymphocyte which actively secretes large amounts of antibody.

Pluripotent stem cell: A cell which has the potential to differentiate into many different cell types.

Polymorphic: Highly variable in structure or sequence.

Primary immune response: The relatively weak immune response which occurs upon the first encounter of naive lymphocytes with a given antigen.

Secondary immune response: The qualitatively and quantitatively improved immune response which occurs upon the second encounter of primed lymphocytes with a given antigen.

Somatic hypermutation: The enhanced occurrence of point mutations in the recombined immunoglobulin variable region V[D]J genes which occurs following antigenic stimulation and acts as a mechanism for increasing antibody diversity and affinity.

Stem cell: Multi-potential cell from which differentiated cells derive.

T-cell receptor (TCR): The heterodimeric antigen receptor of the T lymphocyte exists in two alternative forms, consisting of α and β chains, or γ and δ chains. The αβ TCR recognizes peptide fragments of protein antigens presented by MHC molecules on cell surfaces.

Toll-like receptors (TLRs): A family of pattern recognition receptors involved in the detection of structures associated with pathogens or damaged host tissues.

Thymus: An organ behind the sternum and between your lungs where T cells undergo maturation.

Tubercle: a small nodular lesion in the lungs or other tissues, characteristic of tuberculosis.

Variable (V) gene segments: Genes that rearrange together with D (diversity) and J (joining) gene segments in order to encode the variable region amino acid sequences of immunoglobulins and T-cell receptors.