

## WORKING OF THE IMMUNE SYSTEM-IV

### Structure

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### 12.1 INTRODUCTION

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In this unit, we will study the details of cytokines and complement systems. The cytokines are low-molecular-weight signalling proteins or glycoproteins. They mediate and regulate immunity, inflammation and haematopoiesis. In addition, they act as humoral regulators that modulate individual cells' functions and assist in regulating the development of immune effector cells. In addition, WBCs and various other cells secrete cytokines. Moreover, the recombinant cytokines are pharmaceutical analogues of endogenously produced cytokines to treat multiple infections or immune disorders.

This unit will also study the complement system, which consists of many small proteins found in plasma. It is activated by pathogens directly or indirectly through pathogen-bound antibodies, resulting in a cascade of reactions. There are three pathways to activate a complement: classical, lectin, and alternative and generate active components with various effector functions on the surface of pathogens. For initiation, the classical pathway requires antigen-antibody complexes, whereas the alternative path does not. In addition, when lectin attaches to hexoses containing carbon 3 and 4 - OH groups, such as N-acetyl-d-glucosamine, glucose, fucose, and mannose found on the surfaces of bacteria, yeast, parasites, mycobacteria, and some viruses, the lectin pathway is triggered.

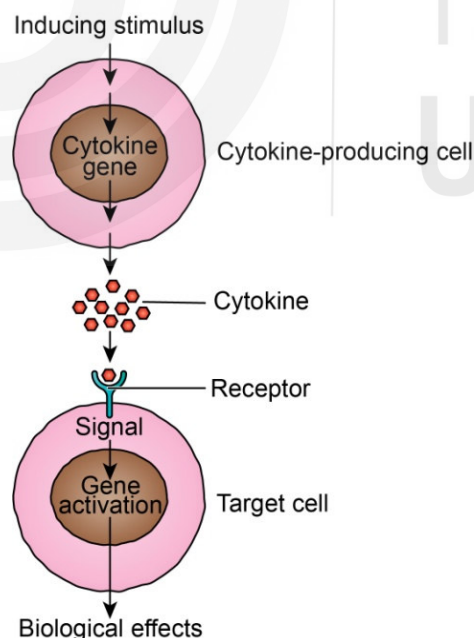
## Objectives

After studying this unit, you should be able to:

- ❖ define cytokines,
- ❖ enlist the actions and properties of cytokines,
- ❖ discuss the function of cytokines,
- ❖ explain how Cytokines differ in innate and adaptive immunity,
- ❖ list of recombinant human cytokines and their uses,
- ❖ define complement system and list out its functions,
- ❖ describe various complement activation pathways,
- ❖ explain how does mannose lead to complement activation,
- ❖ give examples of complements related diseases, and
- ❖ explain the regulation of the complement system.

## 12.2 CYTOKINES AND THEIR ACTION AND FUNDAMENTAL PROPERTIES

Chemokines are a subpopulation of cytokines and represent a class of chemoattractants. Their primary function is to mobilize immune cells from one area to another (Fig.12.1).



**Fig. 12.1: Cytokines as humoral regulators modulate the functions of a target cell.**

### 1. Cytokines and their actions

Cytokines exhibit the following three types of action (Fig.12.2).

- i) **Autocrine action:** Cytokine binds to membrane receptors of the same cell that secreted it.

- ii) **Paracrine action:** A cytokine binds to receptors on a target cell near the producer cell.
- iii) **Endocrine action:** Cytokine travels through circulation and acts on target cells in distant body parts.

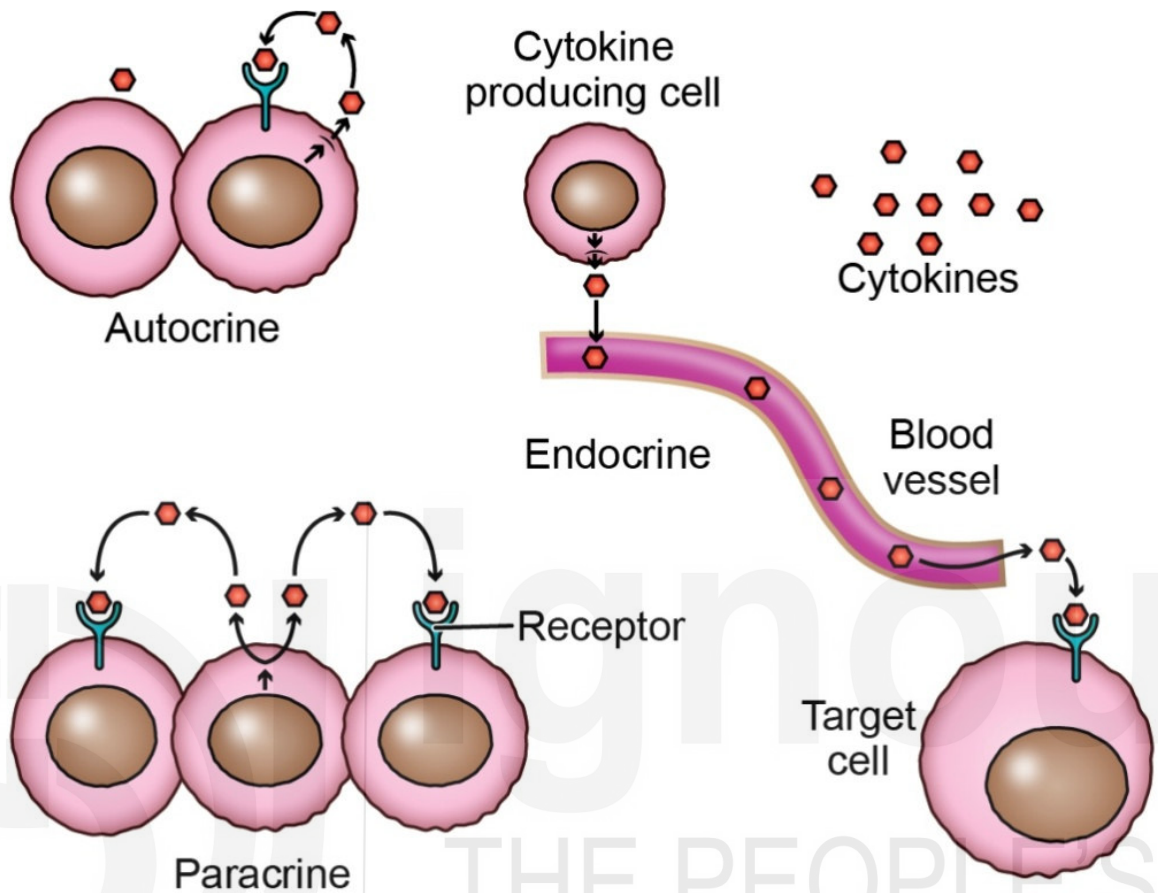
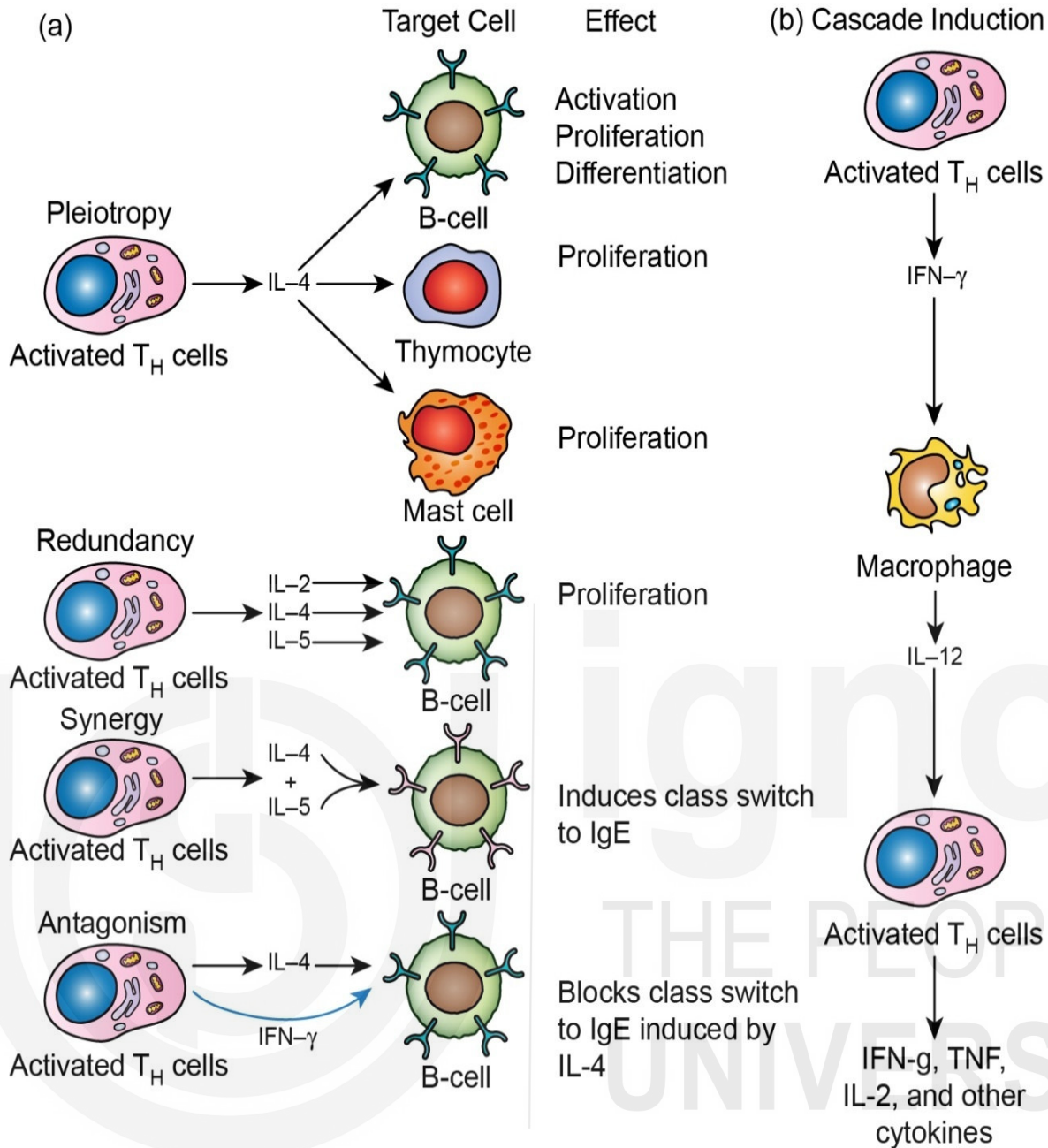


Fig. 12.2: Cytokines exhibiting Autocrine, Paracrine and Endocrine functions.

## 2. Fundamental properties of cytokines

The properties of cytokines include pleiotropy, redundancy, synergy, antagonism and cascade induction (Fig.12.3). Let us discuss these terms in this section.

- i) **Pleiotropism:** it refers to a cytokine's ability to operate on different cell types and cause various biological effects.
- ii) **Redundancy:** It indicates the property where two or more cytokines have the same functional effects.
- iii) **Synergism:** It refers to the combined effect of multiple cytokines. The combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines.
- iv) **Antagonism:** This property is just opposite to the synergism. In this case, one cytokine inhibits the effects of another cytokine.
- v) **Cascade induction:** It is the multiple-step feed-forward mechanism. The cytokine secreted by one cell type activates a second cell type; the second cell type, in turn, secretes a cytokine that acts on another cell type.



**Fig.12.3: Properties of cytokines: Pleiotropy, Redundancy, Synergy, Antagonism and Cascade Induction.**

**SAQ 1**

- a) What are chemokines? How do they help in immune response?
- b) Cytokines exhibit the property of Cascade Induction. Explain.

**12.3 FUNCTIONS OF CYTOKINES**

Based on structural studies cytokines, belong to 6 families. They are the Interleukin family, Hematopoietin family, Interferon family, Tumour necrosis factor family, Chemokines family and Interleukin-17 or Transforming growth factor-beta family. The functions of cytokines belonging to these six groups are described in Table 12.1.

Table 12.1: Functions of Cytokines belonging to six different groups.

S. No.	Cytokines	Functions
1.	<p><b>Interleukin Family:</b> Members of this family include important proinflammatory mediators between leukocytes. These are produced by T-helper cells and are secreted early in an immune response. IL-1 was the first non-interferon cytokine to be identified.</p> <p>Ligands- IL-1<math>\alpha</math>, IL-1<math>\beta</math>, IL-1Ra, IL-18, IL-33.</p>	<p>Depending on the Interleukin and cell type, there are a variety of actions.</p> <p>Proliferation and differentiation of cells. Antibody secretion and chemoattractants.</p>
2.	<p><b>Hematopoietin Family:</b> It is a large family of small cytokine molecules which promote cell proliferation and differentiation. They exhibit functional diversity. As these were structurally characterized first, they are called <b>CLASS I</b>.</p> <p>Ligands- IL-2, IL-3, IL-4, IL-5, IL-6, IL-13, IL-15, IL-21, IL-27.</p>	Promote cell proliferation and differentiation.
3.	<p><b>Interferon (Class II) Family:</b> Interferons are the first cytokines to be discovered. They are essential modulators of immune responses and have roles in antiviral responses. They are of two types:</p> <p>TYPE I- Macrophages, dendritic cells, and virus-infected cells all release interferons.</p> <p>TYPE II- Activated T and Natural Killer (NK) cells generate various interferons.</p> <p>Ligands- IFN- <math>\alpha</math>, IFN- <math>\beta</math>, IFN <math>\gamma</math> -, IL-10, IL-19, IL-20, IL-22, IL-24</p>	Antiviral proteins. Inhibit viral replication and cell proliferation.
4.	<p><b>Tumor Necrosis Factor Family:</b> Members of this family are involved in immune system development, effector functions, and homeostasis. They may be either soluble or membrane-bound. In addition, they are involved in signal development, activation, or death of specific cells.</p> <p>Ligands- TNF- <math>\alpha</math>, TNF- <math>\beta</math>, TNF-<math>\gamma</math>, IL-10, IL-19, IL-20, IL-21, IL-24.</p>	Regulate inflammatory and immune responses like phagocytosis and cytotoxicity.

5.	<p><b>Chemokines Family:</b> All the members of this family serve as chemoattractants. They stimulate the migration and activation of phagocytes.</p> <p>Ligands- IL-8, RANTES, MIP-1, PF4, MCAF, NAP-2, CCL19, CCL-21</p>	Regulate cell migration, adhesion and activation.
6.	<p><b>Interleukin 17 Family or Transforming Growth Factor Beta Family:</b> Members of this family are most recently discovered. They promote neutrophil accumulation, activation and are proinflammatory cytokine clusters.</p> <p>Ligands-IL-17(IL17-A), IL17B,C,D and F</p>	Regulate Immune cells.

Cytokines play an important role in both innate immunity and adaptive immunity. Some of the cytokines of innate immunity are listed in Table 12.2, and cytokines of adaptive immunity are listed in Table 12.3.

**Table 12.2: Cytokines of Innate Immunity.**

S. No.	Cytokines	Principal cell sources	Principal cell targets and biological effects
1.	IL-1(IL-1 $\alpha$ and - $\beta$ )	Endothelial cells, macrophages, and certain epithelial cells	Endothelial cells in the liver: Activation, Inflammation, Coagulation, and Acute-phase Protein Synthesis
2.	IL-10	Macrophages and T cells	Anti-inflammatory macrophages (APCs) suppress IL-12 cytokine production as well as the expression of co-stimulators and class II MHC molecules
3.	IL-12	Macrophages, B cells, and dendritic cells are all types of immune cells	T <sub>C</sub> and NK- Proliferation, IFN- $\gamma$ synthesis, increased cytolytic activity
4.	TNF	Macrophages, T cells	Tumour cells, Neutrophils, Macrophages Cytotoxicity, induction of cytokine secretion, phagocytosis, Many cells -Apoptosis

Table 12.3: Adaptive Immunity Cytokines.

S. No.	Cytokines	Principal cell sources	Principal cell targets and biological effects
1.	IL-2	T <sub>H</sub> 1 cells	T cells and NK cells- Proliferation, activation.  B cells-Proliferation, antibody synthesis
2.	IL-4	T <sub>H</sub> 2 cells, Mast cells, NK cells	T cells, Mast cells - Proliferation.  Macrophages-Inhibition of IFN- $\gamma$ mediated activation.  B cells- Isotype switching to IgE
3.	IL-5	T cells	Eosinophils-Proliferation and differentiation activation.  B cells-Proliferation, IgA production
4.	IFN- $\gamma$	T cells and NK	Activation of Macrophages  Inhibitor of viral replication. Cell proliferation inhibitor. Increased antigen processing and presentation to T cells in various cells due to greater expression of class I and class II MHC molecules.

Recombinant DNA technologies produce several human cytokines. They are being used to treat various infections or immune disorders. Some are listed in Table 12.4.

Table 12.4: List of some Recombinant Human Cytokines and their uses.

S. No.	Recombinant Human Cytokines	Treatment of Disease/Disorder
1.	Recombinant interferon alfa-2a ( <i>Roferon-A</i> )	It's a cytokine that's used to treat Kaposi's sarcoma, chronic myelogenous leukaemia, and hairy cell leukaemia, among other diseases.
2.	Peginterferon alfa-2a ( <i>Pegasys</i> )	It's a drug that's used to treat hepatitis C. (HCV).

3.	Recombinant interferon-alpha 2b ( <i>Intron A</i> )	Hepatitis B, Malignant melanoma, Kaposi's sarcoma, Follicular lymphoma, Hairy cell leukaemia, Warts, and Hepatitis C are all treated with it.
4.	Recombinant interferon-alpha n3 ( <i>Alferon N</i> )	It's used to get rid of warts.
5.	GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor)	It's used to help people with lymphoid malignancies rebuild their hematopoiesis following a bone marrow transplant.

### SAQ 2

Give one example of recombinant human cytokines and their uses.

## 12.4 COMPLEMENT SYSTEM: COMPONENTS

The complement system is made up of more than 20 inert proteins that circulate in the blood and tissue fluids. Complements are proteins that participate in the complement system. Complements were found by Jules Bordet (1895) as heat-labile components in the blood that have non-specific antibacterial activity. Soluble proteins and glycoproteins are these supplements. They're mostly made by liver cells. The complement system works as a biological cascade wherein a series of proteins interact highly, each being the catalyst for the next. Thus, the complement system works in both innate and adaptive immunity.

Complement activation is induced by several innate immune components, as well as by an antibody attached to an antigen. The complement cascade boosts phagocytes' and antibodies' ability to remove germs and injured cells, attack the pathogen's cell membrane, and induce inflammation. Components of the Complement system include serum components, membrane regulatory proteins and membrane receptors. Following are the main components of the complement system:

- There are nine central components in the cascade.
- Complements are typically denoted by the capital letter C followed by a number, such as C1, C2, C3, C4, C5, C6, C7, C8, and C9.
- For example, C1 has three sub-units; C1q, C1r and C1s.
- C2-C5 have two components, a and b; the larger subunits are denoted by b, whereas the smaller ones are indicated by a. However, there is an exception wherein C2a is larger than C2b.
- Some components are designated by alphabet, e.g., B and D.
- Multiple activation products such as C3a and C3b.

- Regulators and inhibitors, e.g., Factor H and C4BP.
- Proteases and newly assembled enzymes, e.g., C4b2a and Factor B.
- Effector molecule receptors such as C3aR and C5aR.

## 12.5 COMPLEMENT SYSTEM: PATHWAYS

The complement system activation occurs via three biochemical pathways (Fig.12.4). They are:

1. Classical pathway: activated by the antigen-antibody reaction.
2. Alternative pathway: activated on microbial cell surfaces.
3. Lectin pathway or Mannose-binding Lectin pathway: activated by plasma lectin binds to mannose residues on microbes.

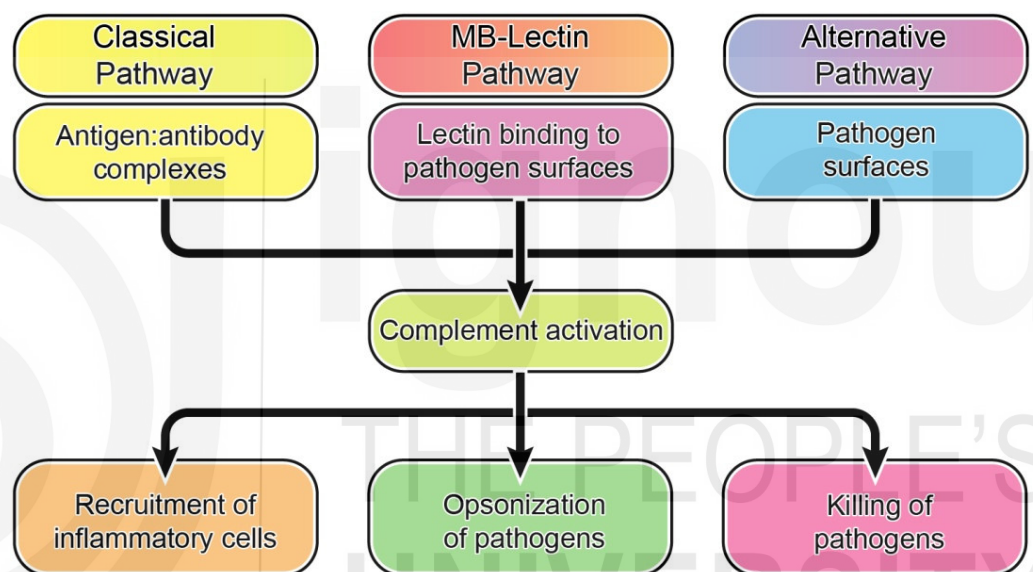


Fig.12.4: Activation of Complement system via three biochemical pathways.

### 12.5.1 Classical Pathway

Antibody-antigen complexes trigger the classical pathway (Fig.12.5). It involves complement components **C1**, **C2** and **C4**. The antibodies IgM and IgG bind to antigens as they enter into the body. It causes conformational changes in the antibody's Fc region, exposing a binding site for component C1. C1 is a large multimeric protein complex that consists of one C1q, two C1r, and two C1s molecule subunits. C1q interacts with the Fc region of the antigen-bound antibody. The C1r and C1s proteases are involved in the cleavage of C4 and C2. C4 is divided into smaller C4a and larger C4b units when the immune complex links to C1. C4a diffuses away, but activated C4b attaches to the target surface at C1q and attracts C2, which is cleaved into two units, C2a and C2b, in a similar manner (Exception as the larger unit is a and smaller unit is b). The bigger unit, C2a, forms the C4bC2a complex with C4b, while the smaller unit, C2b, diffuses away. C3 is engaged when C4bC2a is active. Because it is responsible for turning C3 into an active form by separating smaller unit C3a from larger unit C3b during the conversion process, the C4bC2a complex is also known as a C3 convertase. C4bC2a is

capable of cleaving a high number of C3 molecules with a single molecule. C3b forms a strong bond with C4bC2a. Some of the C3b molecules do not bind with C4bC2a. Instead, they attach to the microbial cell surfaces or coat immune complexes, act as opsonins, and enhance phagocytosis. The smaller unit C3a activates mast cells, causing the release of histamine. When C3b binds to C3 convertase, it becomes C4bC2aC3b, sometimes known as C5 convertase, because it activates C5.

The C5 convertase enzyme breaks down C5 into smaller C5a and larger C5b pieces. As a result, C5a diffuses away, but C5b is preserved by adhering to C6. C5bC6 then forms a link with C7. The C5bC6C7 complex is subsequently injected into the phospholipid bilayer of the cell membrane, where it interacts with C8. C9 is activated by all of them (C5b678), resulting in the formation of a macromolecular structure known as the membrane attack complex (MAC). This causes pores to form in the bacteria, allowing internal components to flow out and chemicals from the environment to enter. As a result, the cell's osmotic stability is compromised, and lysis ensues as a result of an influx of water and electrolyte loss.

This is particularly effective in Gram-negative bacteria since the development of MAC in the outer membrane of these bacteria is quite straightforward. It is difficult in the case of Gram-positive bacteria because of the presence of a rigid thick layer of peptidoglycan. Smaller complement subunits disperse from the location throughout the pathway, where they bind to particular receptors to cause localised inflammatory reactions.

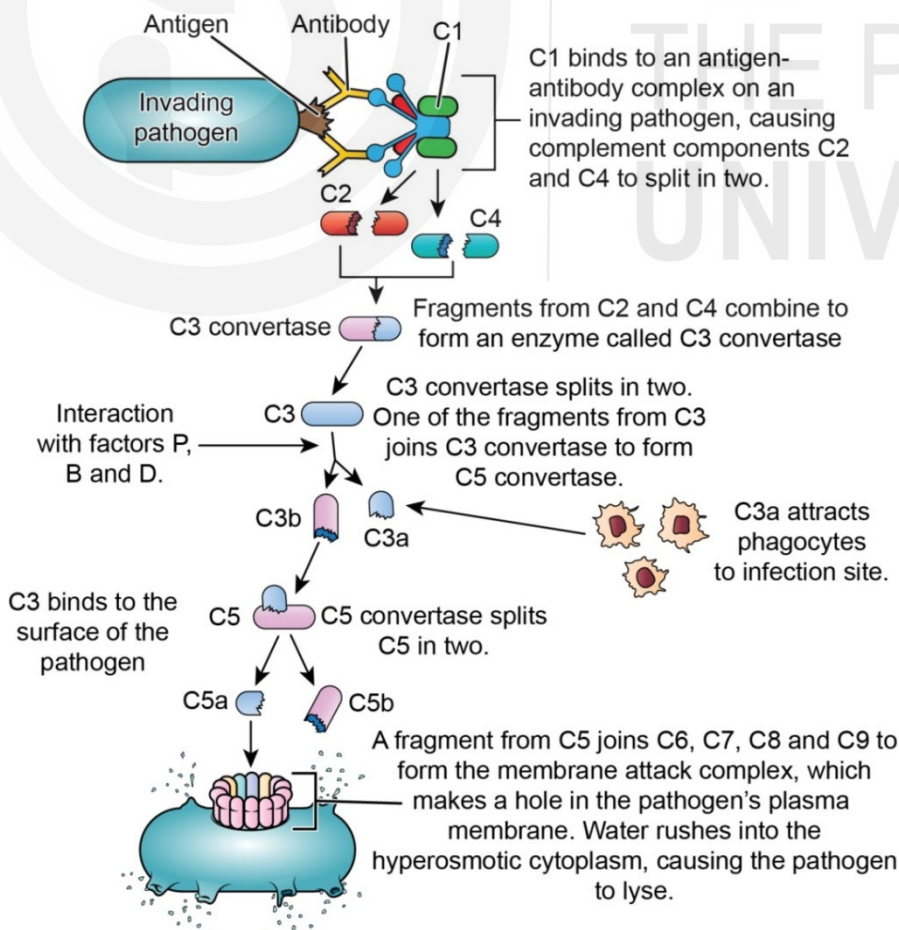
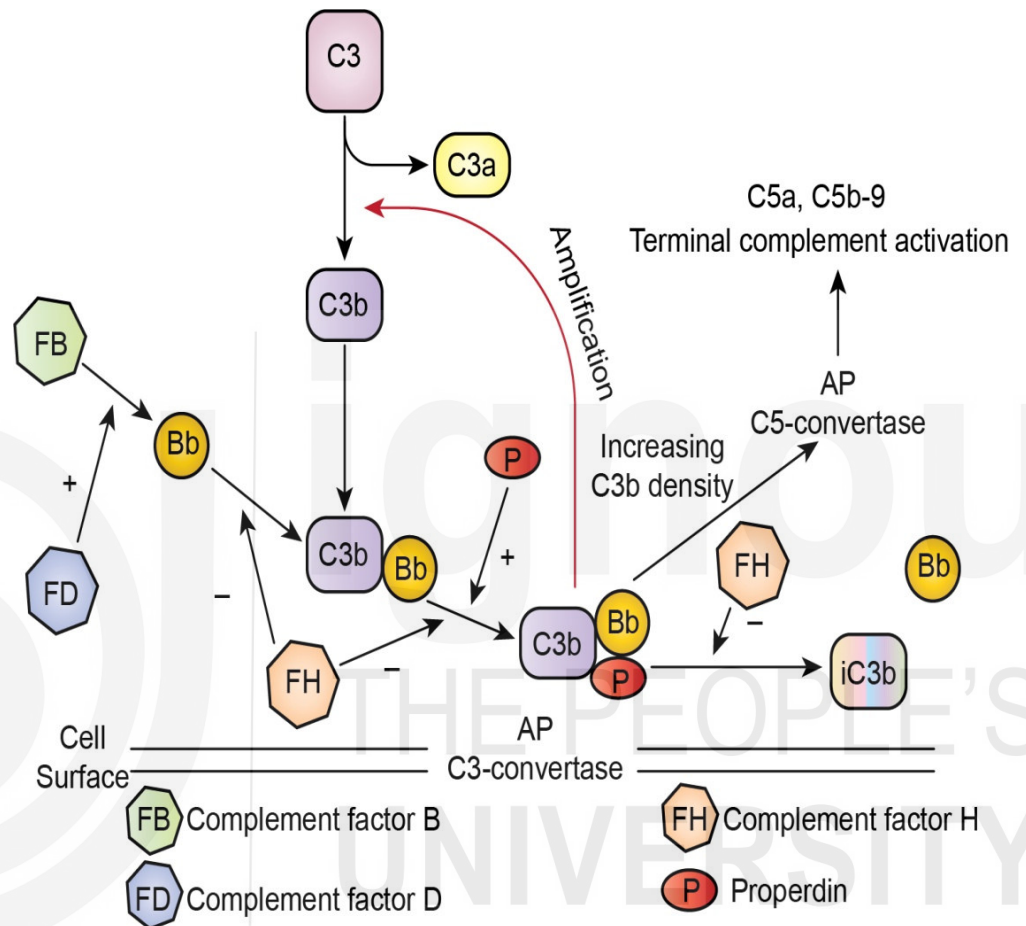


Fig. 12.5: The Classical Pathway.

### 12.5.2 Alternative Pathway

This pathway is activated by cell surface elements foreign to the host, such as lipopolysaccharide (Fig.12.6), which initiate the process. It does not require an antigen-antibody complex for the initiation of the alternative complement pathway. If a bacterium infiltrates the host body as a result of inflammation, complements travel to the site of infection, where C3 molecules immediately contact antigen and activate.



**Fig. 12.6: Activation of the Alternative Complement Pathway.**

In this pathway (Fig.12.7), serum C3 undergoes slow spontaneous hydrolysis to yield C3a and C3b. The B, D, H, and I factor interact with each other and with C3b to produce a C3 convertase in this pathway.

C3b binds to the surface of foreign cells and subsequently binds to another serum protein known as factor B, which is responsible for the binding. Factor B reveals the location on serum protein D that serves as a substrate for the enzymatically active form of the protein. Then factor D breaks down B into Ba and Bb, resulting in the formation of C3 convertase (C3bBb). According to the conventional pathway, C3 convertase creates C5 convertase, which forms a MAC at the end of the process.

C3bBb can activate more C3; consequently, the pathway is frequently called 'the amplification loop'. Activation of the loop is enhanced in the presence of bacterial and fungal cell walls but is inhibited by chemicals on the surface of normal mammalian cells.

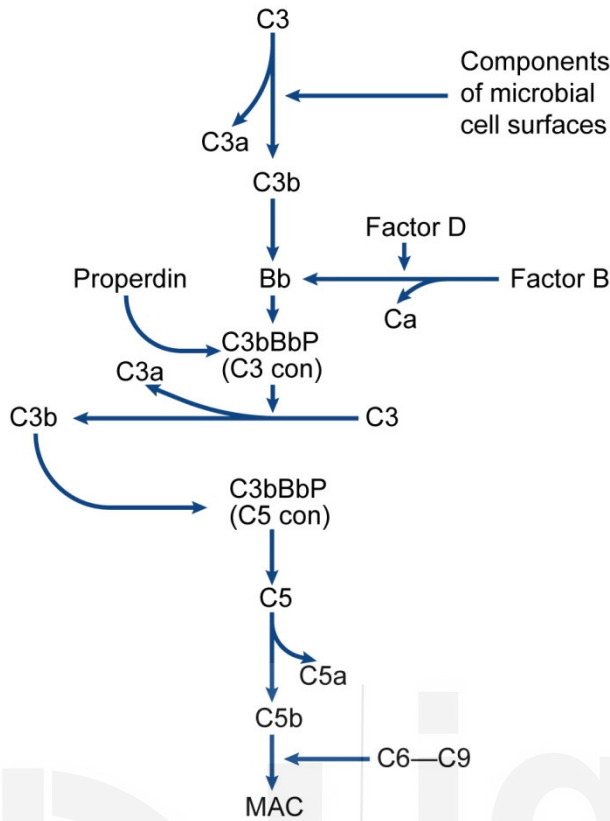


Fig.12.7: The Alternative Pathway.

### 12.5.3 Lectin Pathway or Mannose-binding Lectin Pathway

Some bacteria such as *Salmonella*, *Listeria*, and *Neisseria* can activate the complement system without having antibodies and endotoxin. Some fungi and viruses, notably the HIV-1 virus, have the ability to activate the MBL pathway. Mannose Binding Lectin (MBL) is an acute-phase protein antibody, and its concentration rises dramatically during inflammation, indicating that the body is responding to the stimulus. It is the mannose residues on glycoproteins or carbohydrates that are present on the surface of microorganisms or the target cell that are recognised and bound by the circulating lectin. The complement system is then activated as a result of this (Fig.12.8).

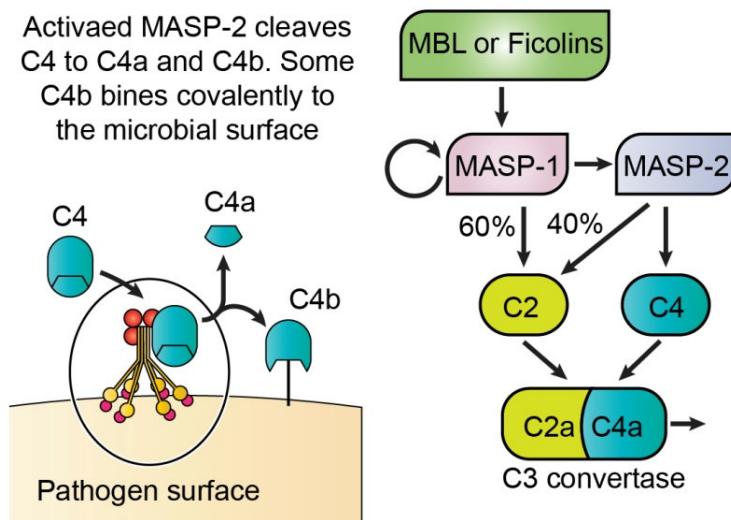


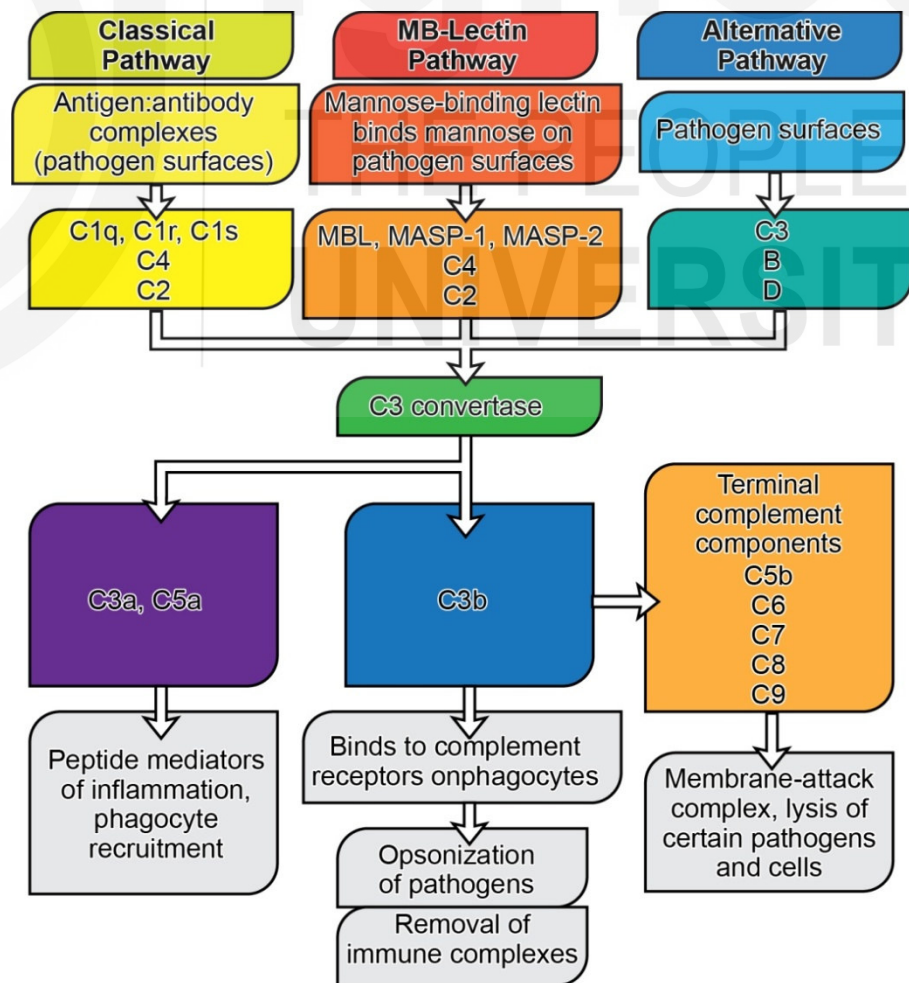
Fig.12.8: Activation of Mannose Binding Lectin Pathway.

MBL pathway resembles the classical pathway of activation of the complement system. Mannose Binding Lectin (MBL) is an acute-phase protein antibody, and its concentration rises dramatically during inflammation, indicating that the body is responding to the stimulus. It is the mannose residues on glycoproteins or carbohydrates that are present on the surface of microorganisms or the target cell that are recognised and bound by the circulating lectin. The complement system is then activated as a result of this (Fig.13.8).

When mannose-binding lectin (MBL) binds to mannose residues on the pathogen surface, the MBL-associated serine proteases MASP-1 and MASP-2 are activated. MASP-1 and MASP-2 cleave C4 and C2 to form C3 convertase C4bC2a, which is analogous to the tetrameric complex formed by C1r and C1s. The procedure now proceeds to make C5 convertase and the MAC, as it did previously.

**i) Lytic Pathway**

Splitting C5 and attaching C5b to a target kickstarts the lytic pathway. The complements C6, C7, C8, and C9 then join C5b to form the membrane attack complex (MAC). Membrane-attack complex can kill bacteria by lysis when inserted into their outer membrane. Furthermore, if antibodies are bound to the surface of red cells, they can activate the classical and lytic pathways, making them vulnerable to lysis (Fig.12.9).



**Fig.12.9: Complement Pathways-Classical Pathway, MBL Pathway and Alternative Pathway.**

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### SAQ 3

Which pathways will be followed in the following cases? Give your answer in the space provided.

- i) This process involves many components, including B, D, H, and I, which interact with one another as well as with C3b to produce a C3 convertase enzyme.
- ii) Immune complexes trigger this pathway.
- iii) Antigen-Antibody complexes are not required for inducing this pathway.

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#### ii) Role of C3 in Complement Pathways

The complement system's first step differs in each of the three paths. All of the routes, however, create enzyme complexes, such as C3 convertase, which cleaves C3 into C3a and C3b.

C3 plays an important role in this process by keeping the complement cascade alert. It acts as a point of convergence of all three pathways. It helps in the amplification of the complement response. It helps in better coordination of various immune responses by exerting direct effector functions. C5 convertase is formed when C3b attaches to C3 convertase, and C5 convertase cleaves C5 into C5a and C5b. The activation of other complement system components by C5 convertase, which is produced through the alternative, classical, or lectin pathways, results in the development of the Membrane Attack Complex (MAC), which kills the pathogen in the long term.

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## 12.6 FUNCTIONS OF COMPLEMENT

The primary functions of complements include chemotaxis, opsonization, cell lysis, activation of mast cells, production of antibodies and immune clearance (Fig.12.10).

We will elaborate these terms as follows:

- a) **Chemotaxis:** It is the movement of a cell in response to a chemical stimulus. Complement fragments recruit neutrophils and macrophages to the antigenic region. Complement fragments recruit neutrophils and macrophages to the antigenic region. Receptors for complements, like C5a and C3a, are present on the cell surface of neutrophils and macrophages. They move towards the site of inflammation.
- b) **Opsonization:** It is an immune process that uses opsonins to tag pathogens for elimination by phagocytes. The complement fragment C3b binds to the immune complex or is coated on the pathogen's surface and enhances phagocytic activity. Complements bind to specific receptors on the surface of phagocytic cells, allowing them to engulf the cell.
- c) **Celllysis:** In the presence of C5b6789 components, a membrane attack complex (MAC) is generated, which induces a rupture of the microbiological cell surface and subsequent cell lysis.

- d) **Activation of mast cells:** The proteolytic complement fragments, C5a, C4a, and C3a, bind to mast cells and neutrophils and induce acute inflammation. Because they induce the mast cell degranulation reactions characteristic of anaphylaxis, these peptides are also known as anaphylatoxins. By connecting to certain complement receptors on immune cells, they also induce specific cell activities, inflammation, and the production of immunoregulatory chemicals.
- e) **Production of antibodies:** B cells have a receptor for C3b. Therefore, B cells secrete more antibodies when C3b binds to them. Thus, C3b is an antibody-producing amplifier that helps to destroy invading microorganisms and make the defence mechanism more effective.
- f) **Immune clearance:** The complement system has an anti-inflammatory role because it removes immune complexes from the circulation and stores them in the spleen and liver, thereby reducing inflammation. Furthermore, complement proteins aid in the solubilization of immune complexes and the subsequent clearance of these complexes by phagocytosis.

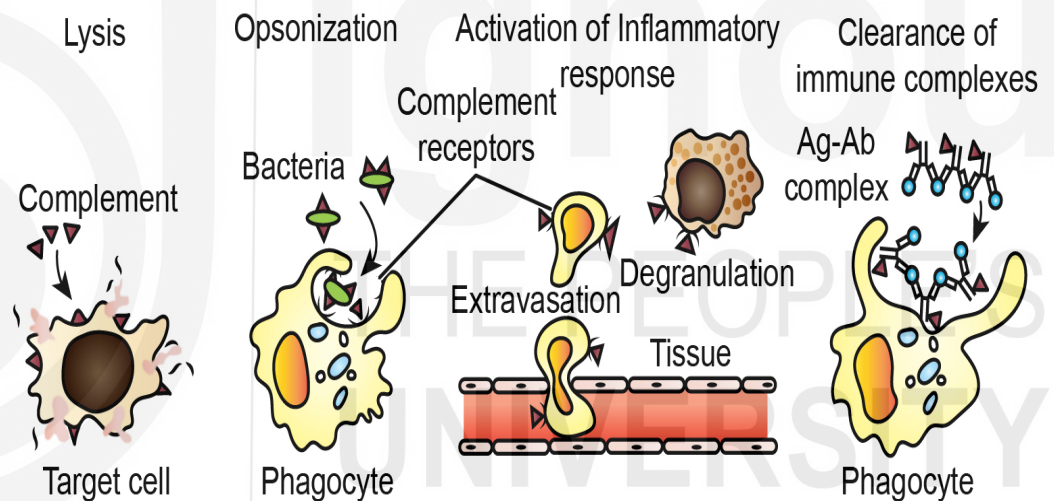


Fig.12.10: Functions of Complements.

## 12.7 DISEASES RELATED TO COMPLEMENT SYSTEM

Complement-related diseases can be caused by defects in any of the complement cascade's protein or regulatory components.

- C2 and C4 deficiency can lead to systemic lupus erythematosus.
- Pyogenic bacterial infection can be caused by a lack of C3 and factor D.
- C5-C9 deficiency (also known as MAC deficiency) can result in Neisseria infections such as gonorrhoea and meningitis.
- Due to a lack of regulatory proteins, complements and sites become too activated, resulting in unwanted inflammation and cell lysis. Such deficiencies result in pyogenic bacterial infection and glomerulonephritis.

- Atypical hemolytic uremic syndrome, age-related macular degeneration, hereditary angioedema, and other diseases can be caused by mutations in the complement regulators factors.
- It is also possible that abnormal stimuli, such as persistent microorganisms, antibodies against self-antigens, or immune complexes accumulated in tissues, will excite the complement system. As a result, even when the system is properly controlled and activated, it has the potential to cause considerable tissue damage.

Let us discuss these terms in this section:

- Systemic Lupus Erythematosus** is a disease in which your immune system attacks your own cells and tissues. It causes inflammation in various parts of the body for some time. It can harm your joints, tendons, kidneys, and skin. It also can affect blood vessels.
- Gonorrhoea and Meningitis:** Gonorrhoea is a sexually transmitted bacterial infection that affects both males and females. The urethra, rectum, and throat are the most common sites of gonorrhoea. Gonorrhoea can also infect the cervix in women, while meningitis is a condition in which the fluid and membranes (meninges) that surround your brain and spinal cord become inflamed. Typical signs and symptoms of meningitis include a headache, fever, and stiff neck. A viral infection most commonly causes meningitis, but it can also be caused by bacterial, parasitic, or fungal infections.
- Glomerulonephritis:** Glomerulonephritis is a condition in which the tiny filters in your kidneys become inflamed (glomeruli). Glomeruli remove extra fluid, electrolytes, and waste from the bloodstream and excrete them in the urine. Glomerulonephritis can strike suddenly (acute) or slowly (chronic).
- Hemolytic uremic syndrome** is a condition in which your kidneys' tiny blood vessels become damaged and inflamed. Clots in the vessels can form as a result of this damage. The clots clog the kidneys' filtering system, resulting in kidney failure, which can be life-threatening.
- Age-related macular degeneration:** it is a progressive eye disease that can lead to blindness. In people over the age of 60, it's the leading cause of severe, permanent vision loss. It occurs when the macula, the small central portion of your retina, wears down.
- Hereditary angioedema:** Hereditary angioedema is characterised by recurrent episodes of fluid accumulation outside of blood vessels, which block the normal flow of blood or lymphatic fluid and cause rapid swelling of tissues in the hand, feet, limb, face, intestinal tract, and airway. It's a rare inherited condition.

## 12.8 REGULATION OF COMPLEMENT SYSTEM

Regulatory mechanisms are required to restrict the complement pathway as it can be highly damaging to host tissues. Complement activation is regulated by

a number of cell membrane and plasma proteins. Different phases in the complement cascade are inhibited by them. The high quantity of sialic acid in the membrane of most mammalian cells causes complement inactivation.

## 12.9 SUMMARY

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Let us summarise what you have learnt in this unit:

- Cytokines are tiny proteins that play critical roles in cell signalling. Cells release them, and they have paracrine, autocrine, and endocrine activities.
- The properties of cytokines include pleiotropy, redundancy, synergy, antagonism, and cascade induction.
- Cytokines are classified into various categories that include chemokines, interferons, and interleukins, lymphokines, tumour necrosis factor, and others.
- A wide spectrum of cells, including immune cells such as macrophages, B lymphocytes, T lymphocytes, and mast cells, release cytokines.
- The complement system comprises more than 20 inactive proteins that circulate in the blood and tissue fluids.
- Complements are proteins that participate in the complement system. The complement system is a biological cascade in which a series of proteins interact in a controlled manner, each acting as a catalyst for the next.
- The complement system activation occurs via three biochemical pathways. They are the classical pathway (triggered by an antigen-antibody interaction), the alternative pathway (triggered on microbial cell surfaces), and the Lectin pathway (also known as the Mannose-binding Lectin pathway in which plasma lectin binds to mannose residues on microbes and activated).
- Regulatory mechanisms are required to restrict the complement pathway as it can be highly damaging to host tissues.
- Complement-related diseases can be caused by any of the complement cascade's protein or regulatory components.

## 12.10 TERMINAL QUESTIONS

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1. What are cytokines?
2. Write your comments on "Cytokines are pleiotropic and redundant".
3. How is the classical complement pathway activated?
4. What triggers alternative complement pathways?
5. Write the salient features of Lectin Pathway.

## 12.11 ANSWERS

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### Self Assessment questions

1.
  - a) Chemokines are a subpopulation of cytokines and represent a class of chemo attractants. Their primary function is to mobilize immune cells from one area to another.
  - a) Cascade Induction is the multiple-step feed-forward mechanism. The cytokine secreted by one cell type activates a second cell type; the second cell type, in turn, secretes a cytokine that acts on another cell type.
2. Hepatitis B, malignant melanoma, Kaposi's sarcoma, follicular lymphoma, hairy cell leukaemia, warts, and Hepatitis C are treated with recombinant interferon-alpha 2b (Intron A).
3.
  - a) Alternative Pathway.
  - b) Classical Pathway.
  - c) MBL Pathway.

### Terminal Questions

1. Cytokines are soluble proteins with a low molecular weight produced in response to an antigen and act as chemical messengers for controlling the innate and adaptive immune systems.
2. Pleiotropic cytokines are those that act on a variety of cell types rather than just one. Because numerous different cytokines can perform the same job, they are referred to as redundant cytokines.
3. The classical pathway is one of the three complement pathways. Antigen-antibody complexes initiate it, or immune complexes bind with IgG and IgM. In addition, the apoptotic cells, necrotic cells, and acute-phase proteins can also activate this pathway.
4. When the C3b protein directly attaches to a bacterium, the alternative pathway is activated. It results in opsonization and killing of pathogens. Foreign materials and damaged tissues can also initiate it.
5. The lectin complement pathway provides an effective defence against invading pathogens and apoptotic cells in an organism. It is also a proteolytic cascade similar to the classical pathway. In addition, this pathway elicits various effector functions including, phagocytosis, cell lysis, inflammation etc.

## SUGGESTED READINGS

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