

Indira Gandhi
National Open University
School of Sciences

Block

4

IMMUNE SYSTEM IN HEALTH AND DISEASES

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Course Design Committee

Prof. M.S. Nathawat
Former Director
School of Sciences, IGNOU
Maidan Garhi, New Delhi-110068

Prof. Pratima Ray
Department of Biotechnology
Jamia Hamdard University, Delhi-110062

Prof. Sarita Sachdeva
Department of Biotechnology
Manav Rachna International Institute of Research and
Studies, Faridabad
Haryana-121004

Dr. Indrakant K. Singh
Molecular Biology Research Laboratory Department of
Zoology, Deshbandhu College University of Delhi,
Delhi-110019

Dr. Moses Rinchui N.
Department of Zoology, Deshbandhu College
University of Delhi, Kalkaji, New Delhi-110019

Prof. Neera Kapoor
School of Sciences, IGNOU
Maidan Garhi, New Delhi-110068

Dr. Bano Saidullah (Retd.)
School of Sciences, IGNOU
Maidan Garhi, New Delhi-110068

Dr. Abdul Kareem
School of Sciences, IGNOU, Maidan Garhi
New Delhi-110068

Dr. Arvind Kr. Shakya
School of Sciences, IGNOU, Maidan Garhi
New Delhi-110068

Dr. Swati Omanwar
Former, Consultant, School of Sciences, IGNOU
Maidan Garhi, New Delhi-110068

Block Preparation Team

Dr. Indrakant K. Singh and Dr. Moses Rinchui N.
Department of Zoology, Deshbandhu College University
of Delhi, Delhi-110019 (Unit 13)

Dr. N. Vijay Kumar
Department of Microbiology
Bhaskaracharya College of Applied Sciences
University of Delhi, Phase 1, Sector 2, Dwarka
New Delhi-110075 (Unit 14)

Prof. Pratima Ray
Department of Biotechnology
Jamia Hamdard University, Delhi-110062 (Unit 15)

School of Sciences, IGNOU

Prof. Neera Kapoor
School of Sciences, IGNOU, Maidan Garhi
New Delhi-110068 (Unit 13)

Dr. Ravi Rajwanshi
School of Sciences, IGNOU, Maidan Garhi
New Delhi-110068 (Units 14, 15)

Course Coordinator	:	Prof. Neera Kapoor
---------------------------	---	---------------------------

Course Editor	:	Dr. Poonam Sharma Department of Zoology Gargi College, University of Delhi New Delhi-1100049
----------------------	---	---

Production

Mr. Hemant Kumar, SO (P), MPDD, IGNOU

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BLOCK 4: IMMUNE SYSTEM IN HEALTH AND DISEASES

The emergence of the study of immunology and the discovery of vaccines are tightly linked. The development of effective vaccines for some pathogens is still a major challenge. However, despite many biological and social hurdles, vaccination has yielded some of the most profound success stories in terms of improving mortality rates worldwide.

However immunology is about more than just vaccines and infectious diseases. Immunity involves both humoral and cellular components. The immune response i.e. innate immunity and adaptive immunity quickly become tailored to suit the assault. Cancer presents a unique challenge to the immune response.

Block 4 consists of three units.

Unit 13 “Immune System in Health and Diseases-I” speaks about hypersensitivity and its classification. Differences between allergy and hypersensitivity, which are otherwise used interchangeably are highlighted. Mechanism of autoimmunity and various autoimmune disorders in vogue are explained in detail.

Unit 14 “Immune System in Health and Diseases-II” explains about cancer cells that divide continually. The role of oncogenesis in causing cancer is discussed. Different immunological approaches for cancer treatment are described in the Unit. Role of nutrients, prebiotics and gut associated lymphoid tissue in immunity are explained in the Unit. Pre and post transplant immunosuppressive treatment modalities and immunological tolerance are discussed at length.

Unit 15 “Vaccines” explains as to how the immune system works for the protection of our body. The unit speaks about types of vaccines and further describes the formulation, function and advantages/disadvantages of each type of vaccine. Different vaccination programmes started by the Govt. of India are also discussed in the Unit.

Objectives

After studying this block you will be able to:

- differentiate between allergy and hypersensitivity,
- discuss different types of hypersensitivity,
- explain various immunological disorders,
- explain the fundamentals of tumor immunology, the origin, different stages and types of cancer,
- explain the role of oncogenes in causing cancer and antigens present on cancer cells,
- discuss the response of the immune system to cancer and how tumor cells escape the immune recognition,
- describe the different immunological approaches for cancer treatment,
- explain the role of nutrients, prebiotics, probiotics and gut-associated lymphoid tissue in immunity,
- describe vaccination and explain the mechanism of vaccines,
- list the types of vaccines and describe the formulation, function and advantages/disadvantages of each type of vaccine, and
- enumerate the different vaccination programmes started by the government for the proper administration of the vaccine in India.

UNIT 13

IMMUNE SYSTEM IN HEALTH AND DISEASES-I

Structure

13.1 Introduction	13.4 Summary
Objectives	13.5 Terminal questions
13.2 Hypersensitivity	13.6 Answers
Classification of Hypersensitivity	
13.3 Immunological Disorders	
Autoimmunity	
Immune Deficiency	

13.1 INTRODUCTION

You know by now after studying the earlier Units that antibodies react with antigens which is known as immune response. Such interactions of antibodies with antigens sometimes produce undesirable symptoms in the body. We call such conditions “allergy” or in immunological term as ‘hypersensitivity’. The term allergy and hypersensitivity are sometimes used interchangeably, however we shall learn in detail that they are not quite so. In this Unit, we shall learn various types of hypersensitivity and immunological disorders prevalent in human beings. Often, our immune system starts to attack its own cells, tissues and other constituents which lead to many diseases. Such diseases are known as autoimmune diseases and the phenomenon is referred to as autoimmunity. On the other hand, one’s immune system can be compromised and an individual can be susceptible to any one or all the diseases. Such condition is known as immune deficiency. We shall learn about them in detail in this Unit.

Objectives

After studying this unit you should be able to:

- ❖ differentiate between allergy and hypersensitivity,
- ❖ discuss different types of hypersensitivity,

- ❖ explain various immunological disorders,
- ❖ describe the mechanism of autoimmunity, and
- ❖ explain various diseases arising from autoimmunity.

13.2 HYPERSENSITIVITY

In general, immune system generates inflammatory response to antigens. Sometimes even under normal condition, our immune system elicits inappropriate reactions in response to antigens. Antigens that are responsible for such inappropriate response are known as allergens. Such reactions are also known as allergy. **Hypersensitivity is a term used to denote excessive immune response to foreign or self antigens.** The term allergy was coined by Clemens von Pirquet and often it is used synonymously with hypersensitivity. **Clemens defined allergy as an altered state of body immune response to foreign substances.** This definition however was applicable for all immunological reactions. But now allergy is known to be a type/class of hypersensitivity. Nonetheless, these immune responses are harmful and cause serious injuries to tissues leading to disease.

13.2.1 Classification of Hypersensitivity

Eukotrienes are a family of inflammatory mediators produced in leucocytes.

Hypersensitivity is composed of two components. It starts with the initial exposure to allergens which is termed as initial dose. Following exposure to the allergens, immune system response may occur within few minutes to days. The second component of hypersensitivity consists of reactions that result in damaging effects. This component is known as *shocking dose*. Based on the nature of reactions and mediator molecules involved Gell and Coombs (1963) classified hypersensitivity into four types as discussed here.

Type-I Hypersensitivity

Allergy comes under type-I hypersensitivity. This type of hypersensitivity is mediated by antibody of certain class, specifically IgE when they react with allergens (antigens) and activate mast cells and basophils. These cells release vasoactive substances such as histamines, leukotrienes and prostaglandins (Fig.1). Type-I hypersensitivity is accompanied by clinical symptoms like: anaphylaxis, angioedema, bronchospasm, hypotension etc. Type-I hypersensitivity is further classified into two subtypes depending on the response time:

- i) **Immediate reaction type:** Immune reaction occurs within few minutes to the exposure of allergens. It includes release of vasoactive substances.
- ii) **Late phase reaction type:** Immune reaction occurs after 2-4 hours to the exposure of allergens. It includes the release of cytokines.

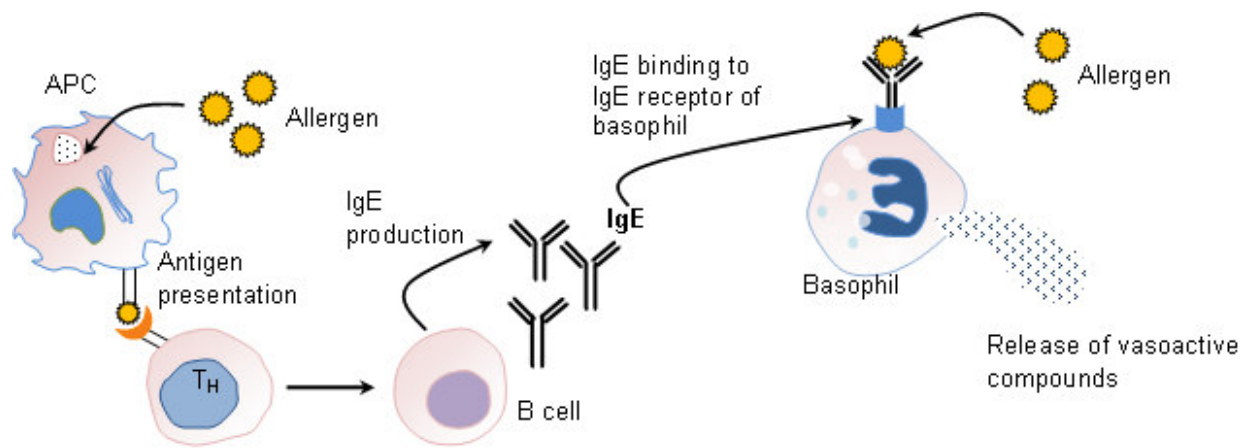


Fig. 13.1: Schematic representation of Type-I hypersensitive reaction through IgE.

Type-II Hypersensitivity

Type-II hypersensitivity is also known as antibody mediated hypersensitive reaction where IgG and IgM are directed against cells with the allergens or extracellular matrix. This type of hypersensitivity is clinically associated with hemolytic anemia, thrombocytopenia, neutropenia. An allergen that is associated with cells are quickly bound with antibodies IgG or IgM causing cell lysis or tissue damage through one of the following ways:

- Activation of classical complement pathway** that involves marking of the pathogens and final destruction of infected cells through phagocytosis.
- Antibody dependent cell mediated cytotoxic pathway** that involves the binding of antigen coated infected cells through Fc receptors and killing of the target cells by NK cells.
- Anti-receptor activity of the antibody** binding on the cell surface receptor starts to act as opsonin and enhances the phagocytotic activity.

Prostaglandins are a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness. They control blood flow, inflammation and the formation of blood clots.

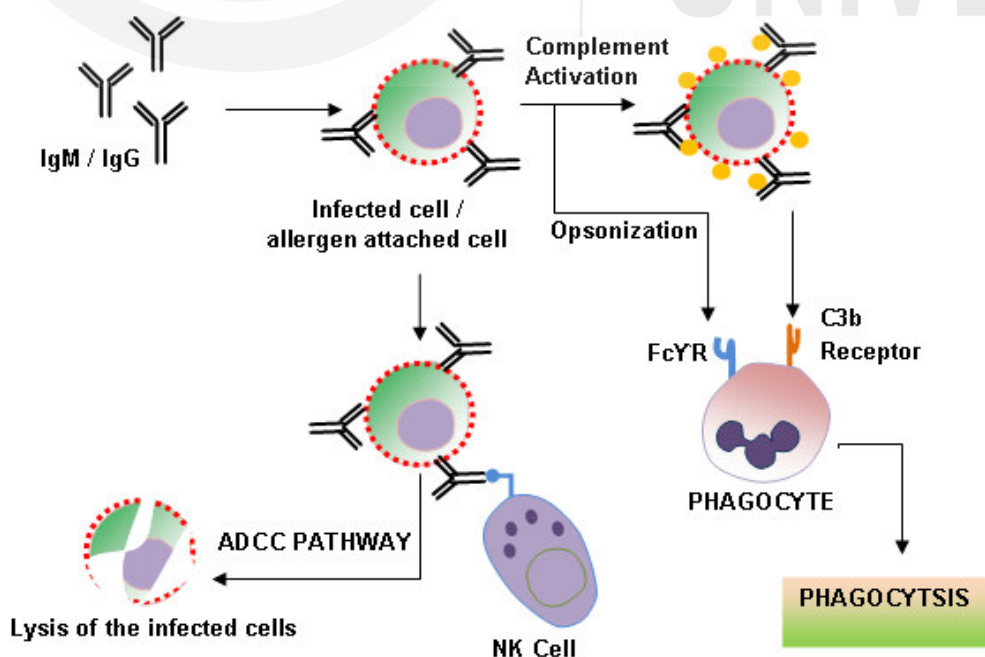


Fig. 13.2: Schematic representation of reaction in Type-II Hypersensitivity through IgM/IgG.

Type-III Hypersensitivity

Serum sickness is a reaction that is similar to an allergy. The immune system can react to antiserum that liquid part of blood that contains antibodies given to person to help protect them against germs.

Type-III hypersensitivity is a condition of immune reactions that arises due to **delayed clearance of antigen-antibody complexes** by the innate immune cells resulting in accumulation of the complex in tissues and blood vessels. This type of hypersensitivity is also known as **immune complex disease**. The deposition of antigen-antibody complexes in tissues or blood vessels causes the activation of complement system along with recruitment of neutrophils to the complex through the Fc region of IgG receptors. Type-III hypersensitivity reactions are clinically associated with serum sickness and Arthus reaction.

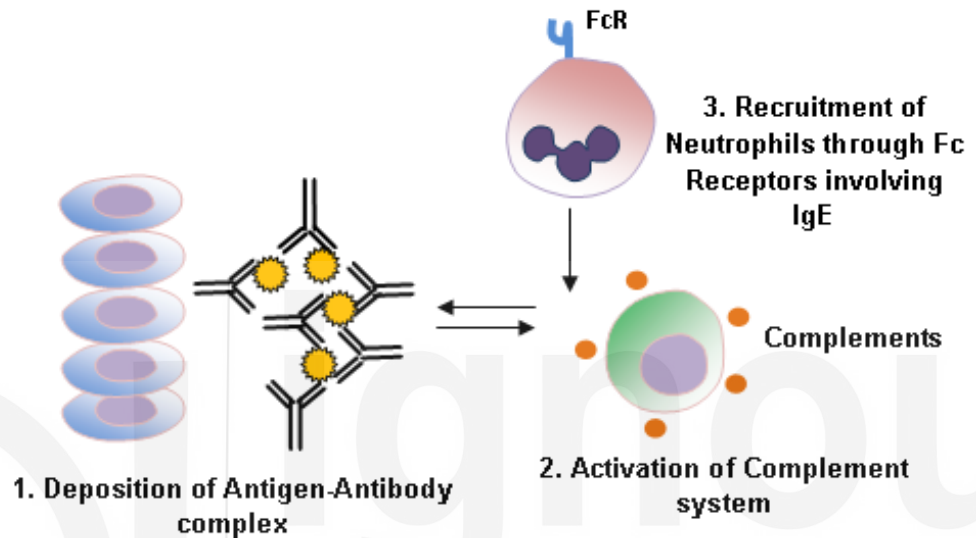


Fig. 13.3: Schematic representation of type-III hyperactivity reaction.

Arthus Reaction is a type of local type III hypersensitivity reaction. This is immune-complex mediated and involves the deposition of antigen/antibody complexes mainly in vascular walls and glomerulus.

Type-IV Hypersensitivity

Type-IV hypersensitivity is also known as delayed hypersensitivity or cell-mediated hypersensitivity. In this type, the immune reaction takes several days to develop and the reaction is mediated by lymphocytes which in other types are mediated by antibody. The exposure of allergens activates T cells which mediates tissue injury through monocytes and macrophages. Type-IV hypersensitivity is clinically associated with **Grave's disease** (You will study it in detail in next section), **contact dermatitis** (redness or inflammation of the skin), **some morbilliform reactions** (generally rash caused by drugs) and **severe exfoliative dermatoses** (extreme shedding of the top layers of the skin). Depending on the type of T cell activated and the type of effector cells recruited, type-IV hypersensitivity can further be divided into four subtypes:

Type IVa: T_H1 and monocytes are activated. Cytokines involved include IL-1, IL-2 and IFN γ .

Type IVb: T_H2 and eosinophils are activated. Cytokines involved include IL-3, IL-4 and IL-5.

Type IVc: CD8 $^+$ T cells are activated. Cytokines like granzyme B, perforin, Fas Ligands are involved.

Type IVd: Cells activated include CD4 $^+$, CD8 $^+$ T cells and neutrophils. Cytokine IL-8 and GM-CSF (Granulocyte macrophage-colony stimulating factor) are involved.

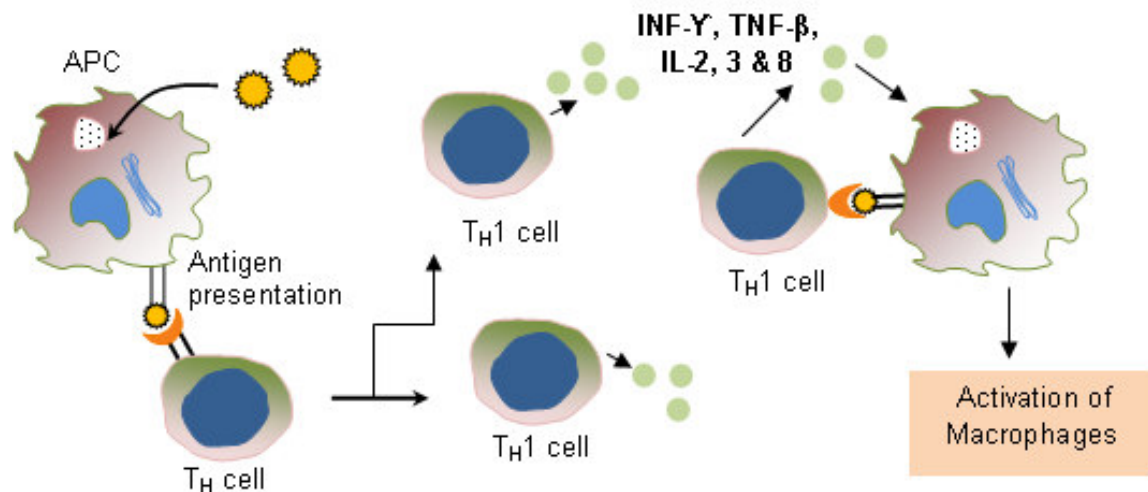


Fig. 13.4: Schematic representation of Type-IV hypersensitivity reaction.

13.3 IMMUNOLOGICAL DISORDERS

13.3.1 Autoimmunity

One of the most important features of our immune system is the ability to differentiate self from foreign entity. The components that are central in differentiating the foreign substances are the antibodies and T cells. When these components fail to recognize self they generate antibodies and T cells in response against itself. Those T cells that are generated against own cells are known as **self-reactive T cells** and the antibodies are **called auto-antibodies**. There are mechanisms within our body to check and ensure the removal of such self-reactive cells. These mechanisms are known as **Tolerance**. During maturation of B cells and T cells in the bone marrow and thymus respectively, the cells carrying self-reactive receptors or antibodies are eliminated. This process of removal is called **Central Tolerance**. However, this elimination is not absolute and some self-reactive cells escape into circulation. These cells are trapped and eliminated in the lymph organs that are located peripherally through a process known as **Peripheral Tolerance**. In addition, the activated lymphocytes have a short life span and they ultimately die by apoptosis or programmed cell death. These mechanisms safeguard the body from self-reactive cells under normal physiological condition. When all the tolerance mechanism breaks down and fails to protect the host from its own immune system, it leads to severe and fatal organ damage. Such condition is known as **Autoimmunity**. The development of autoimmunity in an individual can be caused by several factors like hormones, viruses, genetics, environment and neuro-immunological reasons.

The term autoimmunity was first used by Paul Ehrlich to describe self-toxicity. There are many types of autoimmune disorders related to different tissues like muscle, bone, skin, lungs, nervous system, thyroid, intestinal tract and blood related. Autoimmunity disorder can be specific to an organ or it may affect multiple organs. Accordingly, autoimmunity is classified into two types:

- I. Organ Specific Autoimmunity
- II. Systemic Autoimmunity

SAQ 1

Match the following with the correct option of Column I with Column II.

Column I		Column II	
a)	Allergy	i	Paul Ehrlich
b)	Autoimmunity	ii	Type-IV hypersensitivity
c)	Cell-mediated hypersensitivity	iii	Type-II hypersensitivity
d)	Antibody-mediated hypersensitivity	iv	Type-III hypersensitivity
e)	Arthus reaction	v	Clemens von Pirquet

I. Organ Specific Autoimmunity

Organ specific autoimmunity is a condition where humoral or cell mediated immune system targets only a particular antigen of a single organ. This phenomenon not only affects the normal functioning of the organ but also causes physical damage. In most cases the damaged tissues of the organs from self-reactive components are replaced by connective tissues leading to fibrosis. Sometimes antibodies could also induce overstimulation or antagonize the normal function of a particular organ. Some important organ specific autoimmunity diseases are discussed below:

- **Grave's Disease**

Grave's disease is a condition of over production of thyroid hormone due to generation of auto-antibodies that bind to the receptors of Thyroid stimulating hormone (TSH) on the thyroid cells. Under normal conditions, TSH binds to the TSH receptor to produce adenyl cyclase that signals the secretion of thyroid hormones (T_3 & T_4). Auto-antibodies known as Long-Acting Thyroid stimulating (LATS) antibodies bind with TSH receptors that lead to unregulated stimulation of thyroid cells to produce uncontrolled secretion of thyroid hormones.

- **Hashimoto's Thyroiditis**

Hashimoto's thyroiditis is a condition of inadequate production of thyroid hormone. This condition arises when auto-antibodies and sensitized T_H1 cells start to target thyroglobulin and thyroid peroxidase which are thyroid gland proteins. These two proteins are responsible for the uptake of iodine in the thyroid gland for the synthesis of thyroid hormone. The presence of auto-antibodies and T_H1 lymphocytes in the gland leads to type-IV hypersensitivity recruiting plasma cells and macrophages. This causes the destruction of thyroid cells from the germinal center and lymphatic follicles resulting in hypothyroidism.

- **Goodpasture's Syndrome**

Goodpasture's syndrome is a condition that arises when auto-antibodies are formed against the basement membrane of kidneys or lungs. The auto-antibodies target the basement membrane of glomeruli and alveoli causing damages to the tissue. The condition is further aggravated due to activation of complement system that elicits inflammation response. Such reaction may cause pulmonary hemorrhage and kidney dysfunction, sometimes death within months after its onset.

- **Myasthenia Gravis**

Myasthenia Gravis is a condition of muscular dysfunction arising from the binding of auto-antibodies to the acetylcholine receptor of muscle motor end plate. The binding of these antibodies not only blocks the acetylcholine binding which is necessary for stimulation of muscle but also induces activation of complement system. The activation of complement system further deteriorates the skeletal muscle from lysis of the membrane and receptors of the cells.

- **Autoimmune Anemia**

When auto-antibodies are generated against RBCs, agglutination of auto-antibodies and RBC occurs. This agglutination results in antibody mediated phagocytosis of RBC or complement mediated lysis of RBC. Such anemia resulting from autoimmunity is known as **autoimmune hemolytic anemia**. Another form of anemia known as **pernicious anemia** which occurs from deficiency of vitamin B12 can be caused due to autoimmunity. Vitamin B12 which is essential for hematopoiesis is absorbed by proteins called intrinsic factor. The generation of auto-antibodies against the intrinsic factor prevents the absorption of vitamin B12 from the intestine leading to anemia.

SAQ 2

State whether the following statement are 'True' or 'False':

- i) The removal of self-reactive cells within our body immune system is Tolerance.
- ii) The deposition of antigen-antibody complexes in tissues or blood vessels causes the activation of complement system along with recruitment of neutrophils.
- iii) Type-I hypersensitivity is accompanied by clinical symptoms like: anaphylaxis, angioedema, bronchospasm, hypotension etc.
- iv) Myasthenia Gravis is a condition of muscular dysfunction arising from acetylcholine inadequacy not auto-immunity.
- v) Type-IV hypersensitivity is clinically associated with hemolytic anemia, thrombocytopenia, neutropenia.

II. Systemic Autoimmunity

Systemic autoimmunity is a state of autoimmunity where immune response targets vast range of tissues and organs. It not only targets

single antigen but multiple antigens present across many organs. Hence widespread damage across multiple tissues or organs occurs from auto-antibodies and cell mediated immune response. In systemic autoimmunity, there is dysregulation of immune system and inappropriate inflammatory responses. Some systemic autoimmune diseases are discussed below:

Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus is a condition that causes inflammation of connective tissues that provides flexibility and strength to the body like cartilage, blood vessels, etc. Individuals with SLE show symptoms of arthritis, pleuritis, skin rashes, kidney dysfunction, fever and weakness. For unknown reasons SLE is more prevalent among women of Hispanic origin and American African who are in the age group of 20 to 40 years than Caucasians. In SLE, auto-antibodies target a wide range of tissues including RBCs, platelets, clotting factor, leucocytes, histone and DNA causing multiple pathological conditions.

The self-reactive antibodies attack the wall of blood vessels to form antigen-antibody complex that accumulates in the tissues. The delayed clearance of the complex induces type-III hypersensitivity reaction to activate complement system. This results in inflammation of the wall of blood vessel. Elevated activity of complement system can induce aggregation of neutrophils through CR3 complement receptors on the neutrophils. The inflammatory damage on the wall of blood vessel and accumulation of neutrophils can cause neutropenia (decreased number of neutrophils in circulation) and blockade of blood vessels (vasculitis). The auto-antibodies targeting RBCs and platelets can also lead to formation of immune complexes that activate complement system. Eventually complement mediated lysis of RBCs and platelets leads to hemolytic anemia and thrombosis respectively.

Multiple Sclerosis (MS)

Multiple sclerosis is an inflammatory disease that exclusively affects white matter of the central nervous system. In MS, auto reactive T-cell mediated attacks the myelin sheath of nerves and cause inflammatory reaction leading to demyelination and neurological disorders. Activated auto reactive T-cells from the blood circulation can also enter the brain and cause lesion. MS is one major neurological disorder especially in the western countries prevalent in men and women from 20-40 years.

Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory disease affecting mainly the joints including hands and feet. It is a condition in which auto-antibodies are generated against antibody IgG in the Fc region. The auto-antibodies are IgM immunoglobulins and they are referred to as rheumatoid factors. The auto-antibody IgM molecules form complex with IgG and accumulate in the joints. The delayed clearance of the IgM-IgG complexes ensue type-III hypersensitivity reaction, and, activate complement system that leads to chronic inflammation of joints, cardiovascular, respiratory and hematological system.

SAQ 3

Fill in the blanks:

- a) Hypersensitivity is composed of two components and dose.
- b) Autoimmunity is under the regulatory mechanism of and tolerance.
- c) In systemic autoimmunity there is of immune system and inappropriate responses.
- d) Goodpasture's syndrome is a condition where auto-antibodies are formed against the basement membrane of or
- e) is a disease condition that causes inflammation of connective tissues that provides flexibility and strength to the body.

13.3.2 Immune Deficiency

Immune deficiency is a state where the ability of immune system to fight against infection is compromised partially or totally. It is also known as immune-compromisation. In such conditions, an individual becomes more vulnerable to opportunistic infections than others. Such an individual is said to be immune-compromised. Immune deficiency can be of two types:

Primary Immunodeficiency

Primary immunodeficiency (PID) is also known as congenital immunodeficiency where the immune system of an individual is weak or does not function normally from birth. Most PIDs are diagnosed in children under the age of one. Those suffering from PID show persistent infections, auto-inflammatory disorders, disorders of various organs and tumors. PID disorders are genetic in nature. PID disorders are classified into following types:

- i) **B Lymphocytes deficiency:** Primary immunodeficiency disorders caused from B cell deficiency include X-linked Agammaglobulinemia also known as Bruton disease and Selective Immunoglobulin IgA deficiencies (For details see Table 13.1).
- ii) **T Lymphocytes deficiency:** PID disorders caused from T lymphocyte deficiency include congenital thymic aplasia also known as DiGeorge syndrome, Chronic Mucocutaneous candidiasis and Hyper-IgM syndrome (Table 13.1).
- iii) **B and T cell deficiency:** Primary immunodeficiency due to combined B and T-cell deficiency includes Severe combined immunodeficiency disease (SCID), Wiskott-Aldrich Syndrome and MHC deficiency or Bare leukocyte syndrome (Table 13.1).
- iv) **Phagocyte deficiency:** PID disorders caused by deficiency of phagocytes include chronic granulomatous disease and Leukocyte adhesion deficiency syndrome (Table 13.1).

- v) **Complement deficiency:** Primary immunodeficiency disorder caused from complement deficiency includes hereditary angioedema, recurrent infections and autoimmune diseases (Table 13.1).

Table 13.1: Characteristics of primary immunodeficiency disorders.

Type of Primary Immunodeficiency disorders		Characteristics
B Lymphocytes deficiency:	X-linked Agammaglobulinemia or Bruton disease	• X-chromosome linked disorder • Pre-B cells do not differentiate into mature B cells • Mutation in tyrosine kinase encoding gene • All the Igs present in low level
	Selective Immunoglobulin IgA deficiencies	• Deficiency in IgA • Malfunction in heavy chain switching • Prone to lung infection and recurrent sinus
T Lymphocytes deficiency:	Congenital Thymic Aplasia or DiGeorge syndrome,	• Tetanic seizure prominent • Prone to viral and fungal infection • Treatment through fetal thymus transplantation
	Chronic Mucocutaneous candidiasis	• Selective T-cell function defect • T-cell response to other microbes normal not candida • B cell response normal • Suffers parathyroid deficiency
	Hyper-IgM syndrome	• Very high level of IgM • Normal Lymphocytes count • IgA, IgG, IgE, IgD defective • Compromised B-cell and T-cell immune-cooperation • Failure to interact with CD40
B and T cell	Severe combined immunodeficiency	• Early stem cell fails to differentiate into B and T-cells

deficiency	disease (SCID),	• Prevalent deficiency of IL-2 receptors • Defective Janus Kinase 3, ZAP-70 genes • Defective immune cell receptors RAG1 and RAG2 • Characterized by variety of infections
	Wiskott-Aldrich Syndrome	• Reduced IgM concentration • Elevated IgA and IgE level • Normal T-cell population but reduced function • Reduced F-actin polymerization
	MHC deficiency or Bare leukocyte syndrome	• Lower CD4+ count than normal • Low CD8+ T lymphocytes • Impaired antibody production • Susceptible to bacteremia (bacteria in blood)
Phagocyte deficiency	Chronic Granulomatous Disease	• X-linked disorder • Defective NADPH • Formation of granuloma • Blockade of oesophagus, stomach or bladder due to granuloma
	Leukocyte adhesion deficiency syndrome	• Autosomal recessive disease • Defective phagocytosis of bacteria • Impaired cell adhesion • Pyogenic infection like otitis and pneumonia
Complement deficiency	Hereditary Angioedema	• Autosomal dominant disorder • Causative factor due to deficiency in Complement protein C1 • Formation of edema

	Recurrent infections	• Deficiency in Complement protein C3 • Deficiency in complement protein C5 • Susceptible to bacteremia
	Autoimmune diseases	• Deficiency of complement protein C2 • Deficiency of complement protein C4 • Similar to systemic lupus erymatous

Secondary Immunodeficiency

Secondary immunodeficiency (SID) is also known as acquired immunodeficiency. Secondary immunodeficiency disorders are more common than PID disorders. SID disorder is an impairment of immune system resulting from infectious agents, malnutrition, metabolic disorders, medications or environmental factors. The impaired immune system can be reversed if the underlying illness and the causing agent is taken care of. Based on the causative agent or factor SID can be categorized as:

i) Malnutrition related SID

Malnutrition is considered as the most common cause of SID especially in the developing countries. Malnutrition in early age causes kwashiorkor and marasmus which are protein energy (calorie) malnutrition disease. Such individuals are underlined by underweight and muscle wasting. The thymus glands where maturation of T cells occurs are often atrophic in severe malnutrition case with reduced production of thymic hormones. Consequently, CD4⁺ differentiation of T-cells, lymphocyte proliferation and T-cell mediated hypersensitivity reactions are significantly reduced. Though, production of antibodies is not affected but the ability of the B-cells in antigen processing is compromised. Their neutrophils, polymorph nuclear leucocytes and natural killer cells do not function normally.

ii) Infection related SID

Certain infections from microbes like bacteria, fungi and virus cause impairment of the immune system. Bacterium *Mycobacterium leprae* that causes leprosy, is observed to be closely associated with abnormal T-cell immune response. Impairment in delayed-type hypersensitivity reaction to fungi infection (histoplasmosis and candidiasis) coupled with inability to process antigens.

SID disorders are closely associated with viral infections. Viruses like measles virus cause impairment of functions of B-cells, T-cells and natural killer cells. Cytomegalo virus attacks macrophages rendering inability to process and present antigens. Infection from Epstein-Barr virus causes immune-suppression. Severe infection leads to mononucleosis and reduced natural killer function.

Classical example of SID from infection is Auto-immune Deficiency Syndrome (AIDS). Infection from Human Immunodeficiency Virus (HIV) is marked by progressive reduction in T-cells and B-cells types. Acute depletion in CD4+ T-cell count with low CD4+/CD8+ ratio is observed. In addition, HIV causes impaired natural killer and antibody specific response along with loss of antigen presentation ability of macrophages.

iii) Drug related SID

Use of drugs to improve or cure any immune response related disease is a conventional clinical practice. Most of the drugs with immune-suppression property can be categorized into, corticosteroids, calcineurin inhibitors and cytotoxic drugs. The side effect of all these drugs amount to weakening of immune response. Corticosteroids which include glucocorticoids and mineralocorticoids are good anti-inflammatory drugs for reducing tissue damage against infection. The use of this steroid beyond the saturation of receptor level, results in reduced production of cytokines (TNF- α , IL-1, IL-6), impaired chemotaxis, cell adhesion and phagocytic property of leukocytes. At high dose, impairment of delayed-hypersensitivity response and antibody response can render susceptibility to viral, bacterial and fungal infection.

Calcineurin inhibitor drugs are mostly used for preventing organ graft rejection. They inhibit activation of IL-2 transcription, T-cell response and rapamycin protein which is important for cell activation and proliferation. Cytotoxic drugs are also used in anti-graft rejection medication to control cell growth and removal of bone marrow for transplantation. Cytotoxic drugs prevent DNA synthesis in the S-phase of cell cycle and induce apoptosis. They induce immunodeficiency by inhibiting B-cell and T-cell proliferation, T-cell response activity and macrophage functions.

iv) Aging related SID

Immunity of an individual is affected by aging. This is from the fact that size of thymus glands decreases annually by 3% after reaching puberty till middle age. After which, the size of the gland reduces by 1% annually. Therefore in adult life thymus produces fewer T cells. The T-cell pool is maintained by peripheral proliferation of cell. In addition, impaired neutrophils, macrophages and NK-cell activity leading to immune deficiency has been observed in old age individuals.

v) Environmental factors related SID

Environmental factors that can cause SID disorder include exposure to ionizing radiations, heavy metals and pesticides. Continuous exposure to ionizing radiation weakens immune system as it depletes bone marrow and affects all blood cell lineages. However, immune responses such as phagocytosis and humoral response are observed to be resistant to radiation. Exposure to heavy metals such as lead, cadmium and mercury, through food and water, over a period of time shows decreased polymorphonuclear phagocytic activity, reduced immunoglobulin and complement responses. Immune disorders such as rheumatoid arthritis and systemic lupus erythematosus have been strongly linked with pesticides. But the evidence of immune-suppression is still scarce.

13.4 SUMMARY

Let us summarise whatever you have learnt so far:

- Immune system generates inflammatory response against antigens. Sometimes our immune system elicits inappropriate reactions also in response to antigens.
- Antigens that are responsible for such inappropriate response are known as allergens and the reactions are known as allergy.
- Hypersensitivity starts with initial exposure to allergens which is termed as initial dose. After the exposure to allergens, immune system response results in damaging effects. This component is known as shocking dose.
- Gell and Coombs (1963) classified hypersensitivity into four types i.e. Type I, II, III and IV.
- Type I hypersensitivity is mediated by antibody of certain class, specifically IgE, when they react with allergens (antigens) and activate mast cells and basophils. Allergy comes under type-I hypersensitivity.
- Type-II hypersensitivity reaction involves IgG and IgM and are directed against cells with the allergens or extracellular matrix. They are also known as antibody mediated hypersensitivity.
- Type-III hypersensitivity is a condition that arises due to delayed clearance of antigen-antibody complexes that result in accumulation of the complex in tissues and blood vessels. This type of hypersensitivity is also known as immune complex disease.
- Type-IV hypersensitivity is also known as delayed hypersensitivity or cell-mediated hypersensitivity where the immune reaction takes several days to develop and they are mediated by lymphocytes.
- When all the tolerance mechanism breaks down and fails to protect the host from its own immune system, it leads to severe and fatal organ damage. Such condition is known as autoimmunity.
- Autoimmunity disorder can be specific to an organ or it may affect multiple organs.
- Organ specific autoimmunity is humoral or cell mediated and targets only a particular organ. This phenomenon not only affects the normal functioning of the organ but also causes physical damage.
- Systemic autoimmunity is a type of immune response that targets vast range of tissues and organs. Hence widespread damage across multiple tissues or organs occurs from auto-antibodies and cell mediated immune response.
- Immune deficiency is a state of condition where the ability of immune system to fight infection is compromised partially or totally. It is also known as immunocompromisation. Immune deficiency is of two types- primary and secondary immune deficiency.

- Primary immune deficiency is also known as congenital where the individual has inherent weak immune system.
- Secondary immune deficiency is also known as acquired immune deficiency as an individual may acquire it from environmental factors like infection or chemotherapy or malnutrition.

13.5 TERMINAL QUESTIONS

1. Define allergy.
2. What are the different types of hypersensitivity according to Gell and Coombs?
3. Explain how our immune system prevents autoimmunity?
4. What is immune deficiency?

13.6 ANSWERS

Self Assessments Questions

1. a) v, ii) i, c) ii, d) iii, e) iv.
2. i) T, ii) T, iii) T, iv) F, v) F.
3. i) Initial dose, Shocking
ii) Central, Peripheral
iii) Disregulation, Inflammatory
iv) Kidney, Lungs
v) Systemic Lupus Erythematosus

Terminal Questions

1. Allergy can be defined as inappropriate reactions of immune system in response to antigens.
2. Gell and Coombs (1963) classified hypersensitivity into four types:
 - i) **Type I hypersensitivity:** It is mediated by antibody of certain class, specifically IgE. They react with allergens (antigens) and activate mast cells and basophils. Allergy comes under type-I hypersensitivity.
 - ii) **Type-II hypersensitivity:** It is also known as antibody mediated hypersensitivity. Since it involves IgG and IgM that are directed against cells with the allergens or extracellular matrix.
 - iii) **Type-III hypersensitivity:** It is a condition that arises due to delayed clearance of antigen-antibody complexes that result in accumulation of the complex in tissues and blood vessels. This type of hypersensitivity is also known as immune complex disease.

- iv) **Type-IV hypersensitivity:** It is also known as delayed hypersensitivity or cell-mediated hypersensitivity where the immune reaction takes several days to develop and they are mediated by lymphocytes which in other types are mediated by antibodies.
3. There are mechanisms within our body immune system to check and ensure the removal of self-reactive cells. These mechanisms are known as Tolerance. During maturation of B cells and T cells in the bone marrow and thymus respectively, those cells carrying self-reactive receptors or antibodies are eliminated. This process of removal is called Central Tolerance. Those self-reactive cells that escaped into circulation are trapped and eliminated in the lymph organs that are located peripherally through a process known as Peripheral Tolerance. Also the activated lymphocytes have a short life span and they ultimately die by apoptosis or programmed cell death. These mechanisms safeguard the body from self-reactive cells under normal physiological condition.
 4. Immune deficiency is a state of condition where the ability of immune system to fight against infection is compromised partially or totally. An individual can have inherent weak immune system i.e, since birth or an individual may acquire it from environmental factors like infection or chemotherapy or malnutrition.

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UNIT 14

IMMUNE SYSTEM IN HEALTH AND DISEASES-II

Structure

- | | |
|------------------------------|-------------------------------|
| 14.1. Introduction | 14.4. Transplantation |
| Objectives | Immunology |
| 14.2. Introduction to Tumor | Donor Recipient |
| Immunology | Histocompatibility |
| Types of Tumor | Histocompatibility Antigens |
| Origin and Stages of Cancer | Graft Rejection Mechanism |
| Oncogenes | Immunosuppressive therapy |
| Tumor Antigens | 14.5. Immunological tolerance |
| Immune Response to Cancer | Central Tolerance |
| Immunological Escape | Peripheral Tolerance |
| Immunotherapy | 14.6. Summary |
| 14.3. Nutrition and Immunity | 14.7. Terminal Questions |
| Role of Nutrition in Immune | 14.8. Answers |
| Function | |
| Role of Gut-Associated | |
| Lymphoid Tissue (GALT) | |
| Probiotics, Prebiotics & | |
| Immunity | |

14.1 INTRODUCTION

The present unit explains about the cancer cells that divide continually, forming solid tumors or flooding the blood with abnormal cells and displaying cell surface-specific phenotypes due to various factors such as mutations, exposure to certain chemicals or viral infections. These factors may alter molecular processes that regulate the cell division resulting in the uncontrolled cell growth. These cells display cell surface-specific phenotypes which are different from the parent cells. Such unregulated proliferation of an abnormal cell creates a clone of cells called a tumor. Tumor antigen is an antigenic

substance produced in tumor cells that triggers an immune response in the host. These antigens are the derivatives of cytosolic proteins that are the peptides of cytosolic proteins tumor-specific transplantation antigens. In organ transplantation, the adaptive immunity is considered the main response exerted to the transplanted tissue, since the principal target of the immune response is the major histocompatibility complex (MHC) molecules expressed on the surface of donor cells. MHC is usually identified as human leukocyte antigens (HLA). Coded by the MHC genes, the human HLAs play a major role in differentiating self and non self. The differences between the blood group and HLA antigens are the basis of graft rejection. Various Pre and Post-transplant Immunosuppressive treatment helps in the survival of allogeneic transplant. Various immunotherapy methods are also available to treat cancer viz. administration of monoclonal antibodies, injecting the antigenic peptides as therapeutic vaccine and manipulation of immune activation point. Additionally, the balanced nutrition and gut microbiome such as pro-biotic and pre-biotic influence certain immunological functions and exert a significant impact on the immune competence.

Objectives

After studying this unit, you should be able to:

- ❖ explain the fundamentals of tumor immunology, the origin, different stages and types of cancer,
- ❖ explain the role of oncogenes in causing cancer and antigens present on cancer cells,
- ❖ discuss the response of the immune system to cancer and how tumor cells escape the immune recognition,
- ❖ describe the different immunological approaches for cancer treatment.
- ❖ explain the role of nutrients, probiotics, prebiotics and gut-associated lymphoid tissue in immunity,
- ❖ explain the 'Transplantation Immunology', donor-recipient histocompatibility, HLA & MHC molecules,
- ❖ explain the antigen presentation and processing, graft rejection mechanism- sensitization and effector phase, and
- ❖ discuss the Pre and Post-transplant Immunosuppressive treatment modalities and immunological tolerance.

14.2 INTRODUCTION TO TUMOR IMMUNOLOGY

During the normal growth process, cells divide and acquire the phenotypes of mother cell in a regulated manner. The generation of new cells in a tissue is well regulated so that the cell number remains fairly constant. Occasionally, a cell may become abnormal and divides uncontrollably due to various factors such as exposure to certain chemicals, viral infections, or mutations. These

factors may alter molecular processes that regulate the cell division and hence the cell grows uncontrollably and displays cell surface-specific phenotypes which are different from the parent cells. Such unregulated proliferation of an abnormal cell creates a clone of cells called a **tumor** or **neoplasm**. It may be simplified as new cells are formed when our body does not need them as well as old cells do not die when they should. Often, these tumor cells are recognised differently by the immune system as they may display abnormal cell surface antigens that can elicit an immune response. Thus, the immune system may destroy these tumor cells through immunological attacks by immune cells such as natural killer cells. However, sometimes these immune response mechanisms may be evaded by the tumor cells and become a life-threatening condition called cancer.

14.2.1 Types of Tumors

Tumors are of two types based on the growth stage and the activity.

- i) Benign tumor
- ii) Malignant tumor

In a benign tumor, which is the primary type of tumor, the abnormal clone of cells may remain as clustered and limited to a single site, mostly to the site of the tissue where they originated. These benign tumors grow larger, but do not spread to other tissues of the body. Hence, benign tumors may be defined as a non-malignant or non-cancerous form of a neoplasm. It is often a mild form of the disease. Although the tumor at this stage is not life-threatening but if it grows larger and causes pressure on adjacent tissues involving blood vessels or nerves, then it can lead to serious damages. There are many different types of benign tumors based on the tissue type from which they originate. Some important types are listed in Table 14.1. Tumors in the benign stage can be removed surgically.

Table 14.1: Types of tumors.

Name of the Benign tumor	Affected tissue or organ
Adenoma	Epithelial tissue of gland or gland-like structure. Ex: liver adenoma, colon adenoma, pituitary, thyroid adenoma
Fibroma (Fibroids)	Fibrous or Connective tissue of various organs Ex: Uterine fibroids
Hemangiomas	Abnormal growth of the blood vessels (benign vascular tumor) of the skin or internal organs. Most commonly appears on the chest, scalp, face or back apart from other body parts.
Lipoma	Tumor made up of fat tissues. Often found in the neck, shoulders, back or arms.

Meningioma	Membrane surrounding brain or spinal cord
Myoma	Muscle tumor. Affects the cervix, the lower part of the uterus.
Leiomyoma	Tumor of smooth muscle found in organs such as stomach and uterus.
Neuroma	Tumor of nerves present anywhere in the body
Lymphoma	Lymph node tumor
Osteoma	Tumor of bone

The secondary stage of neoplasm is a malignant stage, in which tumor cells break off from the main tumor mass and may be spread out to any other near or distant parts of the body by the blood or lymph, where they lodge and continue to grow. These malignant tumors growing in distant sites are called **metastases** and the process of dislodging from their site of origin and moving to other sites of the body is called **metastasis**.

14.2.2 Origin and Stages of Cancer

There are several reasons for the origin of cancers. The majority of cancers are due to mutation of specific genes involved in cell division control. Certain genes are involved in controlling the cell division, when undergoing mutation, they no longer function normally and that leads to the proliferation of abnormal cells. This uncontrolled proliferation may be followed by secondary mutations or a primary onset of cancerous cell mass. Successive rounds of mutations and failure of cell division checkpoints together aggravate the condition and result in a tumor mass. This stage of tumor is often referred to as benign tumor and when detected, may be surgically removed. The selective expansion and growth of tumor mass eventually leads to breakage of the basal membrane barrier surrounding tissues and spread to other parts of the body through blood or body fluids. This stage of tumor is called malignant tumor or metastatic tumor and is almost lethal depending on the location of the body part where the broken-off cancerous cells reach (Fig. 14.1). Mortality due to cancer happens as these cells outnumber the normal tissue cells where they are present and interfere in the normal functioning and maintenance of the body parts at the site of their proliferation. In one way they are auto-predatory which results in organ failure and ultimately leads to death.

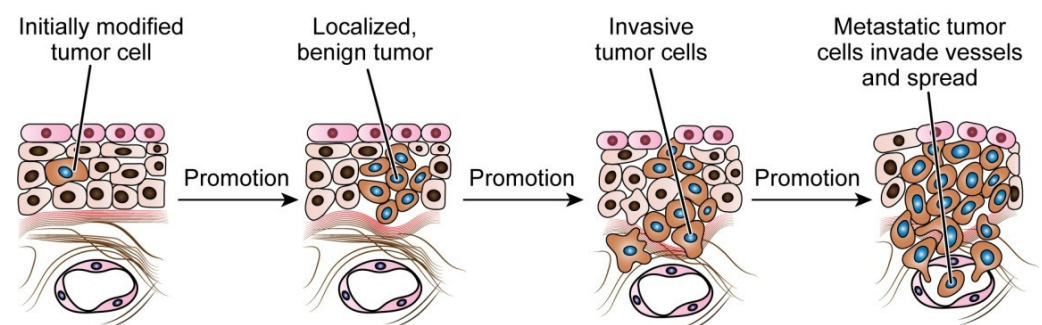


Fig 14.1: Origin and progress of tumor formation.

Initiation and progression of cancer depend on both internal factors such as abnormalities in natural metabolism, inherited mutations, hormones, immune factors, and external factors such as environmental toxins, infectious agents, chemicals, radiation etc. These factors either may act in combinations or isolation would result in damage to the genome and leads to abnormal cell behaviour. Recent research identifies that environmental factors may have a higher impact in causing cancer. However, it may take several years for these genetic mutations to transform a normal cell to a tumor cell and then to a detectable cancerous cell mass.

SAQ 1

- i) The primary stage of tumor is also known as
- ii) The process by which tumor spreads from one part to other tissues of the body is called
- iii) a) Metaphase b) Anaphase c) Metastasis d) Mitosis
- iv) Cancer of lipid tissue is known as
- v) a) Myeloma b) Lymphoma c) Leptoma d) Lipoma
- vi) Unregulated proliferation of an abnormal cell creates a clone of cells called a tumor or
- vii) a) Neoplasm b) Nanoplasm c) Myoplasm d) Myeloma
- viii) In which stage of cancer, tumor cells spread from one place to other part of body?

14.2.3 Oncogenes

Based on types of involvement in cell division functions, various genes associated with cancer may be classified into three major categories:

- i) **Oncogenes:** Genes are involved in growth and proliferation of cancerous cells.
- ii) **Tumor-Suppressor genes:** Genes that limit or inhibit cell growth and proliferation, i.e. they work opposite to oncogenes.
- iii) **Apoptosis genes:** Genes that control programmed death of the cells.

In this section the focus is given on oncogenes:

Normal cellular genes which are involved in various aspects of cell division and proliferation are referred to as “proto-oncogenes”. These proto-oncogenes when undergoing mutation either due to intrinsic or extrinsic factors, their normal functioning is disrupted and the cell growth is unregulated. Thus, the mutant form of proto-oncogenes is referred to as oncogenes (derived from Greek word, onkos, meaning “mass” or “tumor”). Oncogene proteins such as growth factors (eg. Epidermal Growth Factor) and growth factor receptors (eg. ErbB) have a role to play in the signaling pathway that regulates cell

proliferation and survival in response to growth factor stimulation. Any alteration in the expression of these proteins would lead to uncontrolled cell proliferation. These alterations mostly happen due to the action of DNA interacting chemicals, which are also known as chemical carcinogens or certain types of radiation. These DNA damaging agents when interact with proto-oncogenes are converted into cancer-inducing oncogenes. For example, point mutations in *c-ras* gene, which encodes a GTPase, have been observed in cancers of the bladder, colon, and lung. Similarly, overexpression of *ras* oncogene which is part of the Epidermal Growth Factor (EGF) receptor signalling pathway has been noticed in 30% of all human cancers and nearly 90% of all pancreatic cancers. Translocation of chromosomal fragments also results in activation of oncogenes which is observed in a variety of cancers. The first characterized example of oncogene activation by this process is human Burkitt's lymphomas and mouse plasmacytomas which are the cancers of antibody-producing B-lymphocytes. In both of these malignancies, the gene that encodes immunoglobulins undergoes translocation. This is evidenced by the observation that immunoglobulin genes are actively expressed in these tumors. Detailed analysis indicated that a proto-oncogene, *c-myc* from chromosome 8 is translocated into immunoglobulin loci, where it expresses in an uncontrolled manner. The *c-myc* gene which normally encodes a transcription factor in response to growth factor stimulation is capable of driving cell proliferation and contributes to tumor development. Similar, translocation is also observed in myeloid leukemia, where the swapping of DNA between chromosome 9 and chromosome 22 makes chromosome 22 shorter which is called as Philadelphia chromosome. This translocation leads to the formation of a new gene called *BCR-ABL*.

The BCR-ABL fusion protein is capable of transforming cells into malignant types. Another mechanism of oncogene activation in human tumors is gene amplification to the extent of 1000 times than of normal cells, which would result in overexpression of genes such as *c-myc* and two other *myc* family of genes namely N-*myc* and L-*myc*. The amplification of these genes is often observed in a variety of cancers including breast and lung carcinomas. Another example is *erbB-2* gene, amplification of which is often observed in breast and ovarian carcinomas. Many oncogenes express growth factors and growth factor receptors. These growth factors are overexpressed as a result, cells producing these growth factors are also auto stimulated which is known as autocrine stimulation. This drives abnormal cell proliferation and contributes to the development of different human cancers. Although many oncogenes stimulate cell proliferation, certain oncogenic activities of few transcription factors occur due to inhibition of cell differentiation. For example: thyroid hormone and retinoic acid are important in cell differentiation of several cell types. These hormones have intracellular receptors. Mutated forms of receptors ErbA of thyroid hormone and PML/RAR α of retinoic acid block normal cell differentiation signals and cause chicken erythroleukemia and human acute promyelocytic leukaemia, respectively. Cancer may also result from mutation or abnormal function of the genes which suppress the formation of tumors, known as Tumor suppressor genes also known as anti-oncogenes. In contrast to oncogenes, which often are involved in cell proliferation these anti-oncogenes suppress cell proliferation, normally by stopping mutated cells from progressing through the cell cycle. When tumor suppressor genes are

mutated, they cannot do this function: thus allowing abnormal cells to progress through the cell cycle and result in the formation of tumors. However, unlike oncogenes which may result in cancer even when one of the two alleles undergo mutation, tumor suppressor genes need both the alleles to become non-functional, indicating that even one allele is sufficient to suppress the origin and progression of cancer. One of the important tumor suppressor genes is p53, the mutation of which is found in nearly 60% of all cancers including 90% of small cell lung cancers and over 50% of breast and colon cancers. p53 tumor suppressor gene encodes a phosphoprotein that has multifarious roles in growth arrest, DNA repair, and apoptosis. Another important mechanism by which tumors originate is the failure of tumor cells to undergo apoptosis (or programmed cell death). For example, the translocation of an apoptotic protein-encoding gene *bcl-2* results in elevated levels of its protein, which blocks the apoptosis and maintains cell survival whereas similar conditions normally trigger cell death. Thus, the *bcl-2* abnormal expression is observed in human lymphomas. Few proto-oncogenes are listed in Table 14.2 that induce cellular proliferation.

Table 14.2: Functional classification of cancer-associated genes

PROTO-ONCOGENES THAT INDUCE CELLULAR PROLIFERATION

Type/name	Nature of gene product
Growth factors	
<i>Sis</i>	A form of platelet-derived growth factor (PDGF)
Growth factor receptors	
<i>fms</i>	Receptor for colony-stimulating factor 1 (CSF-1)
<i>erbB</i>	Receptor for epidermal growth factor (EGF)
<i>neu</i>	Protein (HER2) related to EGF receptor
<i>erbA</i>	Receptor for thyroid hormone
Signal transducers	
<i>Src</i>	Protein-Tyrosine Kinase
<i>Abl</i>	Tyrosine-protein Kinase
<i>Ha-ras</i>	GTP-binding protein with GTPase activity
<i>N-ras</i>	GTP-binding protein with GTPase activity
<i>K-ras</i>	GTP-binding protein with GTPase activity
Transcription factors	
<i>jun</i>	Component of transcription factor AP1
<i>fos</i>	Component of transcription factor AP1
<i>myc</i>	DNA-binding protein

SAQ 2

- i) Expand the term: EGF & PDGF:
- ii) c-myc is a gene.
- iii) Genes which work opposite in nature to oncogenes are called
- iv) oncogene has role in wide variety of cancers.
- v) Proto-oncogenes convert to oncogenes through events.
- vi) Mutated form of thyroid hormone receptor ErbA causes
- vii) The significant tumor suppressor gene that encodes a phosphoprotein and has a multifarious roles in the growth arrest, DNA repair and apoptosis is named as
- viii) The elevated levels of apoptotic protein is found in human lymphomas.

14.2.4 Tumor Antigens

Most often tumor cells display such immunological tolerance as normal cells and inhibit the development of autoimmune response. However, tumor cells may produce unique or inappropriately expressed proteins, which may be recognized by the immune system. Such proteins of tumor cells that trigger immune responses are called tumor antigens. Tumor antigens may be broadly classified into four different types, based on the type of expression or genes which encode these antigens.

1. Those expressed from normal genes of tumor cells
2. Those expressed from variant or mutant forms of genes of tumor cells
3. Antigens expressed at a specific stage of tumor development
4. Antigens overexpressed in a particular type of tumor

These four types of antigens can be further classified into two categories:

- a. Tumor Specific Antigens (TSAs)
- b. Tumor-Associated Antigens (TAAs)

Type 1 & 2 belong to Category “a” and types 3 & 4 belong to Category “b”. Many therapeutic and clinical diagnostic procedures use these antigens either for tumor detection or treatment.

Tumor Specific Antigens (TSAs)

TSAs are direct targets as they contain unique sequences and help to treat tumors in a specific manner with little damage to surrounding tissue. These antigenic proteins result from DNA mutations which help the immune system

to distinguish self from non-self. TSAs are processed in the cytosol and presented as novel peptides that are expressed with MHC class I molecules on the tumor cell surface (Fig. 14.2). These TSAs induce cell-mediated immune response by tumor-specific CD8⁺ T cells. These CD8⁺ T cells are a critical subpopulation of MHC-I restricted T cells and are the mediators of adaptive immunity. These include cytotoxic T cells, which are important for killing cancerous and viral infected cells. Thus, TSAs represent themselves as a foreign or new peptides and become natural targets for immune recognition.

Tumor-Associated Antigens (TAAs)

Unlike TSAs, these TAAs are not characteristic proteins of neoplastic cells. Most of these TAAs are normal cellular proteins so they tolerate autoimmune reactions. Types 3 & 4 belong to this category and are expressed only during specific developmental stages such as embryonic stage, puberty etc. Their expression levels although at extremely low level at an embryonic stage when they are induced in the neoplastic cells. Proteins produced from genes of the embryonic stage which are reactivated in tumor cells are called **oncofetal tumor** antigens. When normal cells transform into neoplastic cells, these genes are expressed to produce antigens on the surface of tumor cells, which are recognized as aberrant and induce an immunological response (Fig. 14.2).

Two important oncofoetal antigens are **α -fetoprotein (AFP)** and **carcinoembryonic antigen (CEA)**. Although AFP is abundant in fetus to a tune of 100 μ g/ml, but decreases with age whereas an average adult has 6 μ g/ml. Overexpression of this protein can, although be found in pregnant women, high levels of this protein in non-pregnant adults are observed in certain types of cancers like liver, ovarian and testicular cancers where serum level reach above 500 μ g/ml. Monitoring of AFP level can help clinicians to improve their treatment modalities, especially in liver cancer.

CEA is another oncofetal membrane glycoprotein found on gastrointestinal and liver cells of 2-to 6-month-old fetuses. Nearly 90% of patients with advanced colorectal cancer and about 50% of patients with colorectal cancer at its early stages have increased levels of CEA in their serum; however, just presence of AFP and CEA oncofetal antigens is not necessarily a diagnostic method for tumor detection but can still be used to monitor tumor growth. If, for example, a patient who had surgery for removal of colorectal carcinoma, monitoring CEA levels after surgery, helps to show possible regrowth of tumor.

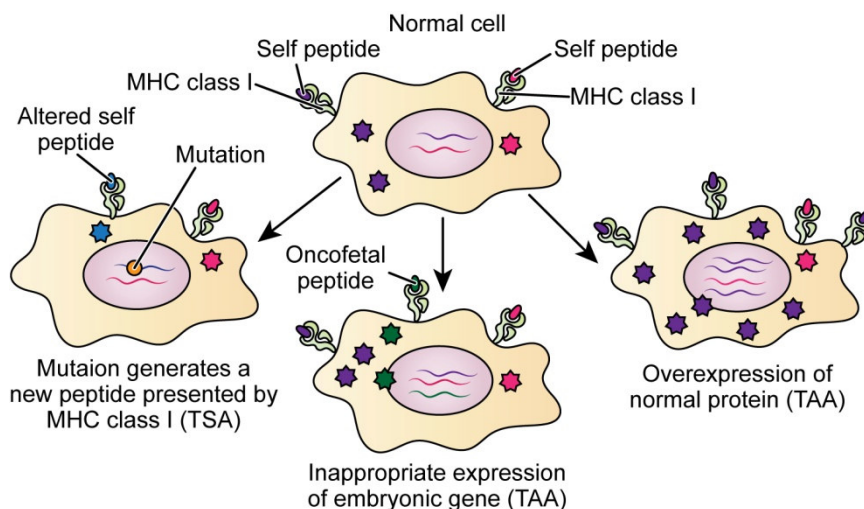


Fig. 14.2: Different tumor antigens.

SAQ 3

- i) Which oncoprotein is abundant in the fetus?
 - ii) Two important oncofoetal antigens are &
 - iii) Which of the following tumor antigens are characteristic of tumor cells?
 - a) TSAs b) TAAs c) Tas d) TBAs
 - iv) Proteins produced from genes of embryonic stage which are reactivated in tumor cells are called
 - v) TSAs stands for
-

14.2.5 Immune Response to Cancer

For a long, it has been argued that the immune system either has no role in cancer or it does not control the growth as often cancer cells originate from normal cell transformation. Although the process is poorly understood, very few mechanisms are proposed. One of the mechanisms by which the immune system is thought to control tumor growth is: by actively recognizing and removing newly transformed cells is referred to as **immunosurveillance**. One of the major challenges involves the non-harming of the self-cells. Several observations suggest that strong immunity has a protective role in giving immunity from cancer cells. For instance, patients on immunosuppressive therapy such as HIV patients or transplant recipients have a higher probability of cancer occurrence than those with strong immunity. These observations suggest that the immune system has a strong role in keeping tumors in control during healthy growth.

Recent data also point towards the potential protumor influence of the immune response during cancer. For instance, chronic inflammation and immune-mediated selection for malignant cells may significantly contribute to cancer cell spreading and survival. In the mid-1990s, research using animal models of cancer suggested that natural immunity could eliminate tumors. This understanding encouraged researchers to identify some of the key cell types and effector molecules involved in cancer. Experimental studies show that mice lacking intact T-cell compartments or Interferon-gamma (IFN- γ) signaling pathways were more susceptible to chemically induced or transplanted tumors, respectively. Likewise, Recombination Activating 2 (RAG2) knockout mice, which lack the enzyme necessarily required for somatic recombination and hence fail to generate T, B, or NKT cells that are more likely to develop cancer naturally as they are more susceptible to chemical carcinogens. Now, it is known that **immunoediting**, through which the immune system engages in both positive (pro-tumor) and negative (anti-tumor) actions that helps to make the foundations of the tumor, by determining the cells fate in order to be eliminated or not. Cancer immunoediting can be studied at three sequential stages: elimination, equilibrium, and escape.

SAQ 4

- i) Define immunosurveillance.
- ii) What is immunoediting?
- iii) The knockout of _____ gene in mice is required for preventing the age related cancers.
- iv) One of the major challenges for immune system is not to harm _____.
- v) Lack of _____ signalling pathway in mice may cause tumors in transplantations.

14.2.6 Immunological Escape

In the first step of immunoediting, the elimination takes place through which newly formed cancer cells are identified and destroyed. Whereas equilibrium is maintained to balance the destruction of cancer cells and leaving small number of cells unharmed and this can be assigned as an important and common reason for the onset of cancer. Whereas, during immune escape which is the final phase of immunoediting, the most aggressive and least immunogenic of the residual tumor cells begin to thrive and spread. Most basic research studies have focused on the role of the immune system in the elimination phase, where both innate and adaptive processes identify and target transformed cells for destruction. In brief, immune escape stage fosters the selection and survival of the cells that develop immunoevasive mutations and develop into fully grown tumor.

14.2.7 Immunotherapy

Anticancer immunotherapy is an approach used in treating cancers that induce or enhance specific antitumor immune responses of the immune system. These treatments are designed to specifically revive, initiate or supplement the *in vivo* antitumor immune responses, by creating signals or cells that will help the immune system to follow the right direction and fight against cancer. These methods involve use of the humanized monoclonal antibodies which will target cancer cells in a specific manner. Similarly, peptides from tumor antigens are administered in a way to induce Cytotoxic T Lymphocyte (CTL) activity. The limitation of this approach is that no single type of immunotherapy be effective for all types of cancers. Some immunotherapies can be applied to cancers which share similarities in their antigens produced.

There are at least three types of immunotherapies that are available where each one is based on a different element of the immune response.

- i) Administration of Monoclonal antibodies to direct the immune response against the cancer cells.
- ii) Injecting with antigenic peptides as therapeutic vaccines: induces tumor specific T-cell responses.

- iii) Manipulation of modulatory signals responsible for stimulation or inhibition of T-cell activation, known as immune activation checkpoint.

In the first approach, monoclonal antibodies (mAbs) recognize the tumor-specific cell surface markers and mark tumor cells for destruction by leukocytes. For example, Trastuzumab is a mAb, that targets HER2 protein in breast cancer cells. It is available commercially under the trade name Herceptin. Similarly, different cancers have therapeutic mAbs.

In the second approach, several tumors have been shown to induce CTLs that recognize the tumor antigens presented by MHC class I on these neoplastic cells. Strong antitumor CTL activity correlates significantly with tumor remission and is primarily credited with maintaining the equilibrium phase of cancer immunoediting, where neoplastic cell survival and death are fairly balanced. This observation has led to the development of some cancer vaccines aimed at inducing strong antitumor CTL responses against tumor antigens: a form of **immunotherapy**. Here, the vaccine is being used to generate an immune response that is therapeutic rather than prophylactic.

SAQ 5

- i) is the final phase of immunoediting.
- ii) Peptides from tumor antigens are administered to induce activity as a form of immunotherapy.
- iii) Trastuzumab is a mAb, that targets protein in breast cancer cells.
- iv) Immunotherapy can be done using monoclonal antibodies.
- v) CTLs are
-

14.3 NUTRITION AND IMMUNITY

It has been a well-known observation that balanced nutrition improves general disease resistance of an individual; hence, nutrition plays a vital role in ensuring a healthy life. In the absence of proper nutrition, a condition known as malnutrition occurs which is an important cause of immunodeficiency that is directly or indirectly linked to mortality among children and poor people worldwide. Weak immunity and malnourished children are more prone to communicable diseases that may further lead to death in most of the developing nations. Deficiency of essential amino acids and balanced nutrition could result in compromised immunity. Lifestyle diseases such as obesity, diabetes are viewed as a problem of poor nutritional management. Balanced nutrition is a diet that includes both micronutrients, macronutrients as well as the gut microbiome. Combating pathogens as well as other immunological responses need deployment of agents of the immune system and swift resolution of immune response is necessary for mitigating the pathogen

growth and invading the tissues. This swift response needs readily available energy and required molecular armour that is synthesised from nutrients to combat pathogens and to stop disease progression.

14.3.2 Role of Nutrition in Immune Function

Adequate and well-balanced nutrition is required for all cells of our body to perform various activities optimally which includes the cells of the immune system. An “activated” immune system further increases the demand for energy during periods of infection, with greater basal energy expenditure during fever and other immunological responses. Thus, balanced nutrition for the best immunological outcomes is mandatory, which supports the functions of immune cells allowing them to initiate effective responses against pathogens. This also helps the body to resolve the response rapidly when necessary and avoids any underlying chronic inflammation. The immune system’s demands for energy and nutrients can be met from exogenous sources i.e., the diet, or if dietary sources are inadequate, from endogenous sources such as body stores. Some micronutrients and dietary components have very specific roles in the development and maintenance of an effective immune system throughout the life course or in reducing chronic inflammation. For example, the amino acid arginine is mandatory for the generation of nitric oxide by cells of the immune system such as macrophages, and the micronutrients as well as vitamin A and zinc regulate cell division and so are essential for an active response of the immune system. A single nutrient can also exhibit several multi facet immunological effects. For example, vitamin E has multiple roles like antioxidant, an inhibitor of protein kinase C activity, potentially interacting with enzymes and transport proteins.

14.3.3 Role of Gut-Associated Lymphoid Tissue (GALT)

The majority of immune cells within the human body are found within the gut-associated lymphoid tissue (GALT), suggesting the importance of GALT tissue in the general health status of the human body. While ingesting food, we subject ourselves to near-constant and aggressive antigenic stimulation, and our immune system must be able to provide a robust and effective immunity against invading pathogens while protecting the nutrient values of food and useful commensal bacteria. To achieve this, the GALT contains a variety of sensing and effector immune functions. Dendritic cells and M cells test the components of the human gut, while plasma B cells within the lamina propria generate Immunoglobulin A (IgA), protecting against pathogens. Specialised immune regions known as Peyer’s patches, rich in immune cells, allow for communication between immune cells residing within the GALT and recruit more cells of immunity.

The microbiome of the human gut will provide antigens and signals with the potential to interact with native and systemic immune cells. The overall composition of the gut microbiome fluctuates over time which is influenced by dietary components as well as environmental factors such as antibiotics and other therapeutic drugs.

14.3.4 Probiotics, Prebiotics & Immunity

Dietary interventions which are used to correct the gut microbiome include probiotics and prebiotics. Probiotics are defined as “live microorganisms, which, when consumed in adequate amounts, confer a health benefit to the host while prebiotics, are the substrates that are selectively utilized by host microorganisms conferring a health benefit”, tend to be non-digestible oligosaccharides such as fructo-oligosaccharides and galacto-oligosaccharides. The inclusion of plant-based diets may enhance the diversity of nutrients that help to grow the gut microbiome, with the indigestibility of plant cell walls enabling peptides and lipids, which may otherwise have been absorbed in the upper digestive tract to reach the microbiome. There may be circumstances in which immune cells of the GALT come into direct contact with nutrients or gut microbiota, such as in the case of reduced epithelial integrity or ‘leaky gut’ observed in both acute and chronic gut inflammation. Such changes in gut permeability may be influenced by micronutrient vitamin D status.

Probiotic foods contain live helpful bacteria, and prebiotic foods contain fiber and oligosaccharides that feed and maintain healthy colonies of those bacteria.

- **Probiotic foods** include kefir, yogurt with live active cultures, fermented vegetables, sauerkraut, tempeh, kombucha tea, kimchi, and miso.
- **Prebiotic foods** include garlic, onions, leeks, asparagus, Jerusalem artichokes, dandelion greens, bananas, and seaweed. However, a more general rule is to eat a variety of fruits, vegetables, beans, and whole grains for dietary prebiotics.

A systematic analysis by utilizing molecular genetic tools verifying the effects of foods on genomes as well as metabolism reveals how nutrients may influence certain immunological functions. Innate immunity and nutrient metabolism are part of complex biological systems that should work hand in hand to sustain and preserve life. Effector cells of the innate immune system rely on essential nutrients to generate energy, produce metabolic precursors for biosynthesis of macromolecules and tune their responses to infectious agents. Thus, any interruptions to normal nutrient uptake may exert a substantial impact on immune competence and can result in increased susceptibility to infection during nutrient deficiency, or chronic inflammation associated with over-nutrition.

SAQ 6

- Balanced nutrition is a diet that includes and as well as the gut microbiome.
 - Specialised immune regions known as are rich in immune cells.
 - Gut permeability may be influenced by micronutrient status.
-

14.4 TRANSPLANTATION IMMUNOLOGY

'Transplantation' the term in Immunology refers to the act of transferring cells, tissues, or organs from one site to another.

Alexis Carrel in 1908 reported the first systemic transplantation where he interchanged kidneys in 9 cats. Some of these maintained kidney function for up to 25 days. Eventually, all died, but this established that organ transplant recipients can carry out its normal function.

First human kidney transplant attempted in 1935 by a Russian Surgeon remained unsuccessful due to a mismatch in blood types between donor and recipient. The first successful human kidney transplant between identical twins was achieved in 1954 in Boston.

Currently the kidney, lungs, heart, pancreas, liver, bone marrow and cornea transplantations are performed among non-identical individuals with increasing frequency and greater success.

Types of graft transplants: Depending upon the degree of immune response there are four types of grafts.

1. **Autograft or Autogenic Graft:** Transfer of self-tissue from one body site to another within the same individual. For example, the grafts performed on patients with burns, where healthy skin is transferred to the burn site and the use of healthy blood vessels to replace the blocked coronary arteries.
2. **Syngraft or Isograft or isogenic graft:** Tissue transferred between genetically identical individuals. It is done between syngeneic mice and humans that are genetically identical (monozygotic twins).
3. **Allograft or Allogenic Graft:** Tissue transferred between genetically different members of the same species. In case of mice, it is done between two inbred strains of mice. In humans unless it is between identical twins, the grafting between two individuals is Allograft.
4. **Xenograft or Xenogenic Graft:** Grafting between two different species. Like graft of a baboon heart to a human. Due to the greatest genetic disparity, this leads to a more severe graft rejection.

Graft versus Host reaction (GVH): Graft tissue elicits an immune reaction against the host antigens that brings about damage to the host and host cells.

14.4.1 Donor Recipient Histocompatibility

Differences in blood group and histocompatibility antigens lead to most intense graft rejection. Therefore, potential donor and recipient cells are screened to assess the likelihood of tissue compatibility. Various procedures have been developed for tissue typing.

ABO blood group typing: At first the ABO blood group is screened for donor and recipient compatibility by typing their RBC antigens. The antigens of A, B,

Auto and isografts are generally acceptable due to genetic identity between graft and host. Allograft is genetically identified as foreign by the immune system and is rejected in allograft reactions.

O are on RBCs, epithelial and endothelial cells of donor and recipient. If in recipients the antibodies are produced against any of these antigens present on transplanted tissues, the antibody plus 108 complement systems get induced and lyse the incompatible cells.

HLA Typing

The HLA typing for the donor and recipient is done by microcytotoxicity assay. In this test, the antibody-mediated microcytotoxicity indicates the presence or absence of various MHC alleles. The white blood cells from potential donors and recipients are added to separate wells of the microtitre plate and then monoclonal antibodies specific for class I and II MHC molecules are added to these wells. After incubation the complement is added to the wells and cytotoxicity is assessed by uptake or exclusion of various dyes (like Trypan blue or eosin Y) by the cells. The added monoclonal antibodies and complement will lyse the cells which express the corresponding specific MHC allele and the dead cells will uptake the dye trypan blue (Fig. 14.3 a, b). More than 60 % tissue match is recommended for transplantation and is achievable with immunosuppressive therapy.

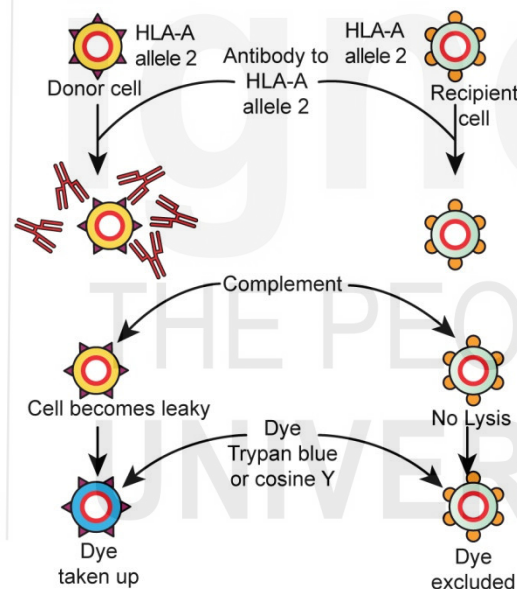


Fig. 14.3 (a): Microcytotoxicity HLA Typing: WBCs from donor and recipient are added to separate wells of the microtiter plate. The experiment depicts only one HLA antigen on donor and recipient and the reaction sequence upon addition of antibody. The numerous antigens expressed on cells are tested with a battery of Mabs (Mono Clonal Antibodies).

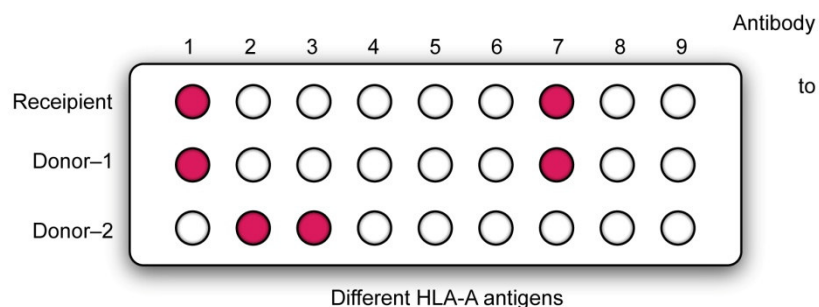


Fig. 14.3 (b): Microcytotoxicity HLA Typing to test the battery of antibodies specific for different HLA-A antigens. : Donor-1 shares HLA-A antigens recognized by antisera in 1 and 7. Donor-2 has no antigens in common with the recipient.

Further, the one-way Mixed Lymphocyte Reaction (MLR) is used to quantitate the degree of class II MHC match between donor and recipient. Lymphocytes from a potential donor X-irradiated or mitomycin-C treated serve as stimulator cells, and recipient lymphocytes do serve as responder cells. The proliferation of responder lymphocytes is indicated by uptake of [^3H] thymidine. The greater is MHC class II tissue mismatch between donor and recipient, the more will be the uptake of [^3H] thymidine as the responder recipient lymphocytes will have intense proliferation and it is considered as a poor prognosis for graft survival. MLR assay is advantageous over microcytotoxicity test as it depicts the degree of tissue mismatch and the extent of T_H cells activation and immune response against the MHC antigens of potential graft. It takes six days to run MLR. Thus in case cadaver being a potential donor, wait for six days is not possible and microcytotoxicity assay remains a remedy to be relied upon (Fig 14.4).

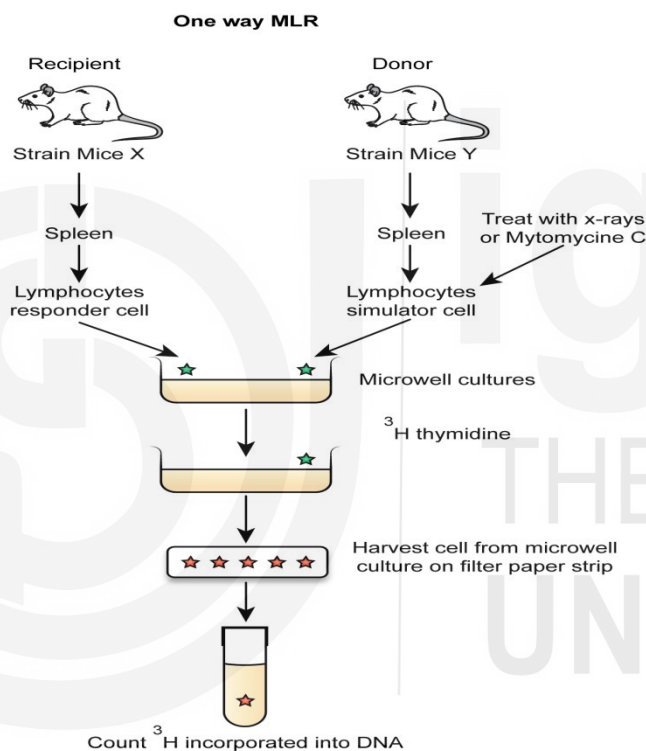


Fig. 14.4: One Way Mixed MLR Reaction: It measures Lymphocyte proliferation from responder strain in response to allogeneic cells of stimulator strain (treated with Mitomycin C). The amount of ^3H thymidine uptake is directly proportional to extent of responder cell proliferation. Higher is the uptake, greater is the difference in MHC II molecules between donor and recipient.

14.4.2 Histocompatibility antigens

Histocompatibility antigens are cell surface glycoproteins called HLA (Human Leukocyte antigens) in humans. These play critical roles in interaction among immune system cells for differentiating self from non-self tissue. These were discovered by the work of R. A. Gorer and G.D. Snell in the 1930s. Human HLAs are controlled and produced by a group of MHC (Major Histocompatibility complex) genes arrayed on chromosome no. 6. These are three classes of molecules (Table 14.3).

Table 14.3: The classification of HLA.

Complex	HLA							
MHC Class	II			III			I	
Region	DP	DQ	DR	C4,	C2,	BF	B A	C
Gene products	DP $\alpha\beta$	DQ $\alpha\beta$	DR $\alpha\beta$	C'	proteins	TNF α TNF β	HLA-B HLA-C	HLA-A

Class I MHC molecules

These are transmembrane glycoproteins, expressed on the surface of almost all nucleated cells. Their intact structure includes a α -heavy chain bound to β -microglobulin molecules. The heavy chain consists of 2 peptide-binding domains, an immunoglobulin (Ig)-like domain, and a transmembrane region with a cytoplasmic tail, and is encoded by A, B, C loci of MHC regions (Fig. 14.5). Class I MHC molecules present the peptide antigens of altered self cells or infected cells acting as APCs (Antigen Presenting Cells) to Tc cells which express CD8 molecules. These Tc cells can recognize such APCs and act as cytotoxic cells. The CD8 molecules on such Tc cells recognise the non-polymorphic part of the heavy chain of class I molecules which are expressed on all nucleated cells (infected ones). These CD8 lymphocytes often have a cytotoxic function with the capability of recognising the infected cells. There are non-classical MHC Class I molecules like HLA-G (protecting the fetus from the maternal immune response) and HLA-E (present peptides to receptors of NK cells).

Class II MHC molecules

These are also glycoproteins encoded by HLA-DP, DQ, DR MHC-regions. They are present primarily on professional APCs (B cells, macrophages, dendritic cells, Langerhans cells), thymic epithelium, and activated (but not resting ones) T cells. Most of nucleated cells can be induced for MHC class II molecules expression by interferon (IFN- γ). Structurally these consist of 2 polypeptides α and β chains consisting of a peptide-binding domain, an Ig-like domain, and a transmembrane domain extending into a cytoplasmic tail. The class II MHC molecules interact with T_H lymphocytes having CD4 receptors (Fig. 14.5).

Class III MHC molecules

These are secreted proteins important in immune processes and include soluble serum proteins, complement system proteins and TNFs. These are encoded by C4, C2, and BF MHC regions.

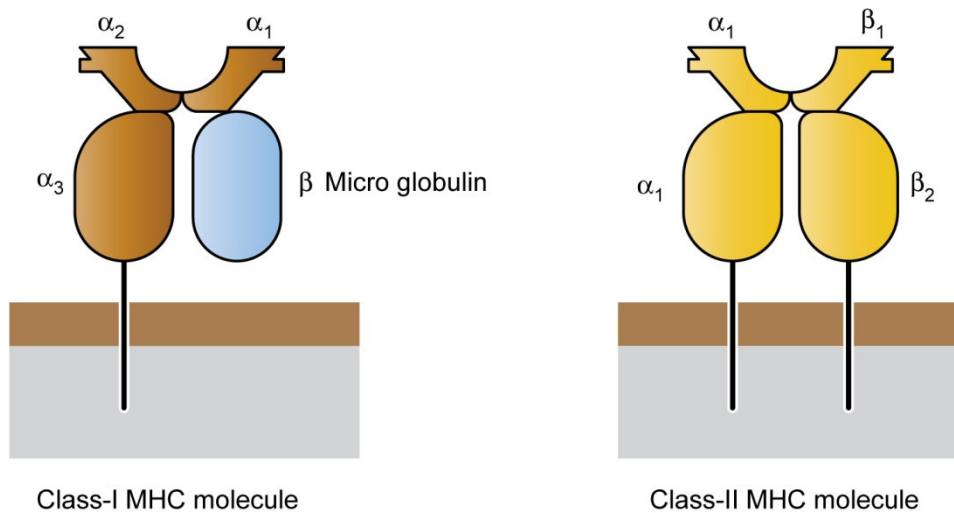


Fig. 14.5: Schematic diagrams of class I and class II MHC molecules showing the external domains, transmembrane segments, and cytoplasmic tails.

Nomenclature of HLA antigens

Serotyped class I and II HLA antigens are designated for instance as HLA-A1, -B5, -C1, -DR1. Alleles defined by gene sequencing are named in the following manner:

The gene name, an asterisk, numbers representing the allele group (corresponding to the serologic antigen encoded by that allele), a colon, and numbers representing the specific allele.

Example: A*02:01, DRB1*01:03, DQA1*01:02

Sometimes, if allelic variants are there then additional numbers are added after a colon to identify allelic variants that encode identical proteins, and after another colon, other numbers are added to denote polymorphisms in introns or 5' or 3' untranslated regions.

Example: A*02:101:01:02, DRB1*03:01:01:02.

The MHC class I and II antigen molecules are the most immunogenic and having been recognised to play an indispensable role during allogenic transplant rejection. The HLA-DR is the strongest determinant, followed by HLA-B and -A. All these three loci play the most important role in donor-recipient match.

Some autoimmune disorders are linked to specific HLA alleles—for example,

Psoriasis to HLA-C*06:02

Ankylosing spondylitis and reactive arthritis to HLA-B27

Narcolepsy to HLA-DR2 and HLA-DQB1*06:02

Type 1 diabetes mellitus to HLA-DQ2 and HLA-DQ8

Multiple sclerosis to HLA-DR2

Rheumatoid arthritis to HLA-DR4

Antigen presentation and processing

The foreign antigen gets recognised by different T Lymphocytes when it is by several steps degraded, processed, and presented attached to MHC molecules as MHC peptide complex. The processing of foreign peptide antigen takes place inside the cell and it is attached to MHC molecules and transported to the cell membrane for presenting to T cells.

Class I MHC molecules- Antigen Presentation Pathway (Cytosolic Pathway)

The class I MHC molecules process and present the intracellular or endogenous pathogens/ antigens which live or are from within the host cell. For example, virus particles. In normal condition MHC class I molecules form complex with self-peptides or self-antigens. Upon viral infection, the peptide derived from viral integration into the host genome is processed and attached to MHC Class I molecules. Such viral peptides are synthesised in host cytosol. The host cytosol proteasome degrades the foreign, unwanted, or damaged proteins such as viral-derived peptides may be degraded into smaller fragments of 8-15 amino acids long. These fragments are transported into the endoplasmic reticulum by a peptide delivery system called the transporter associated with antigen processing (TAP). TAP is made up of two domains or subunits called TAP 1 and TAP 2. Inside ER the α and β chains of MHC class I molecules are synthesised and with the help of chaperons attach to viral peptides at the peptide binding site and forms the MHC class I-peptide complex. Subsequently, this complex through golgi complex and secretory vesicle moves to plasma membrane, presented to and recognised by T cell receptors. The CD8 molecules in Tc cells bind to $\alpha 3$ domain of the MHC class I molecule.

Class II MHC molecules - Antigen Presentation Pathway (Endocytic Pathway)

The class II MHC molecules process and present the antigenic peptides from extracellular or exogenous pathogens, which grow and reproduce outside of the host cell. The example includes Bacteria, exotoxins, parasites. These are engulfed by professional antigen presenting cells (APCs) like B cells, macrophages, and dendritic cells by endocytosis or phagocytosis.

Inside the cell, the engulfed antigenic peptide covered by the endosome gets fused by cytosolic lysosome and forms endolysosomes, where the foreign peptides are degraded by proteolytic enzymes and small antigenic fragments are formed.

The Class II MHC molecules synthesised in ER have α and β chain of the molecule associated with the invariant chain which restricts the binding of self-antigen with the class II MHC molecule. This invariant chain- MHC complex is then transported from the ER to the Golgi apparatus and then to another vesicle. Here, the invariant chain is digested and only a small fragment (Class II-associated invariant chain polypeptide: CLIP) remains attached to the molecule. Subsequently, this vesicle containing the MHC class II molecule is then fused with the vesicle containing fragmented peptides. The fragmented

peptide is then bound with the MHC class II molecule by displacing the CLIP. This newly formed MHC class II-peptide complex is then transported to the surface of the cell and presented to T cells bearing CD4 co-receptor. CD4 recognises the $\beta 2$ domain of the class II MHC molecule.

SAQ 7

- i) The process of replacement of diseased/damaged tissue or organs with healthy ones from a donor is known as _____.
- ii) Grafting between two different species is called _____.
- iii) The presence or absence of various MHC alleles is tested in the antibody-mediated _____ test.
- iv) The one-way _____ is used to quantitate the degree of class II MHC between donor and recipient.
- v) _____ are the transmembrane glycoproteins expressed on the surface of almost all nucleated cells.
- vi) B cells, macrophages, dendritic cells are the examples of the _____ that engulf bacteria, exotoxins and parasites.

14.4.3 Graft Rejection Mechanism

The graft rejection mechanism principally involves the cell-mediated immune response to graft cells alloantigens (mainly MHC molecules). This can imply delayed-type hypersensitive and cell-mediated both types of reactions.

This comprises two phases:

1. A sensitisation phase: Proliferation of recipients antigen reactive lymphocytes to the graft's alloantigens.
2. An effector stage: Immune destruction of graft.

Sensitisation Phase

The recipient's CD4⁺ and CD8⁺ T lymphocytes recognise foreign graft alloantigens (both Major and Minor Histocompatibility molecules) and proliferate. The response to minor HA is generally weak but a combined response to several minor differences could be a vigorous one. The response to major HA involves recognition of both class I and II MHC molecules and an associated peptide ligand in its cleft. In the case of MHC class I molecules such peptides are derived from within the allogenic cell, whereas peptides present in the groove of MHC-II molecules are generally proteins taken up and processed through the endocytic pathway of allogeneic APCs. Sometimes the peptide fragments of allogeneic class- I MHC molecules can be presented within the groove of MHC class- II molecules.

Host T_H cells interact with APCs expressing an appropriate antigenic MHC molecules complex for providing a co-stimulatory signal. Depending upon

graft tissue specificity different cell types can function as APCs. The dendritic cells are major APCs as these express high levels of MHC class-II molecules and are found in most tissues. Host APCs also can migrate into a graft, endocytose the foreign alloantigens (major and minor both types), and can present them as processed peptides with self MHC molecules. In the case of graft of kidney, thymus, and pancreatic islets passenger leukocytes (generally dendritic cells) acting as APCs migrate from graft to regional lymph nodes. These express high class-II MHC molecules along with normal levels of MHC-I. Except brain, such cells are abundant in mammalian tissues. These passenger leukocytes expressing allogeneic MHC antigens of donor graft are recognised as foreign and stimulate T cell activation in lymph nodes. In skin and other grafts instead, passenger leukocytes, lengthens cells and endothelial cells lining blood vessels play a role as APCs. These express MHC-I and II antigens.

The immunologic response varies with types of transplants. In the case of skin grafts having no functional blood vessels, the host lymphocytes encountering the graft cells alloantigens are carried to regional lymph nodes. This generates effector lymphocytes in lymph nodes which are carried by lymphatics back to graft to mount an immunologic attack.

The dendritic cells and vascular endothelial cells from allogeneic graft induces vigorous T cell activation (majorly $CD4^+$ T cells). These can recognise class-II alloantigens directly or alloantigen peptides presented by host APCs. These amplified and activated T_H cells play a central role in inducing various effector mechanisms of allograft rejection.

Effector Stage

Among various effector mechanisms involved in allograft rejection, the most common comprise cell-mediated reactions including DTH and CTL-mediated cytotoxicity. The other less common mechanisms involve antibody - plus-complement lysis and destruction by antibody-dependent cell-mediated cytotoxicity (ADCC). The cell-mediated reactions remain the hallmark of graft rejection. These involve an influx of T cells and macrophages into the graft. Such infiltration histologically resembles a DTH immune response in which cytokines produced by T-DTH cells promote macrophage infiltration. The CTL-mediated killing involves recognition of foreign class-I alloantigens on graft by host $CD8^+$ cells. The $CD4^+$ cytotoxic T cells mediated graft rejection remains class-II MHC restricted. Any of these effector mechanisms involved in graft rejection employ T_H cells secreted cytokines playing a central role like IL-2, IFN- γ , TNF- β . IL-2 promotes T cell proliferation and is generally necessary for the generation of effector CTLs. IFN- γ plays central role during the development of DTH response by promoting the influx of macrophages into the graft and their subsequent activation into more destructive cells. TNF- β causes direct cytotoxic activity on graft cells. Several cytokines promote graft rejection by inducing the expression of class I and II MHC molecules on graft cells. The interferons (α , β , γ), TNF- α and TNF- β all increase class-I MHC expression and IFN- γ increase class-II MHC expression. During graft rejection episodes, the levels of these cytokines increase and induce a variety of cell types within graft to express class I and II MHC molecules. In rat

cardiac allograft rejection, initially, only dendritic cells express class-II MHC molecules but later localised IFN- γ production in graft tissue induces vascular endothelial cells, and myocytes also begin to express these molecules (Fig. 14.6).

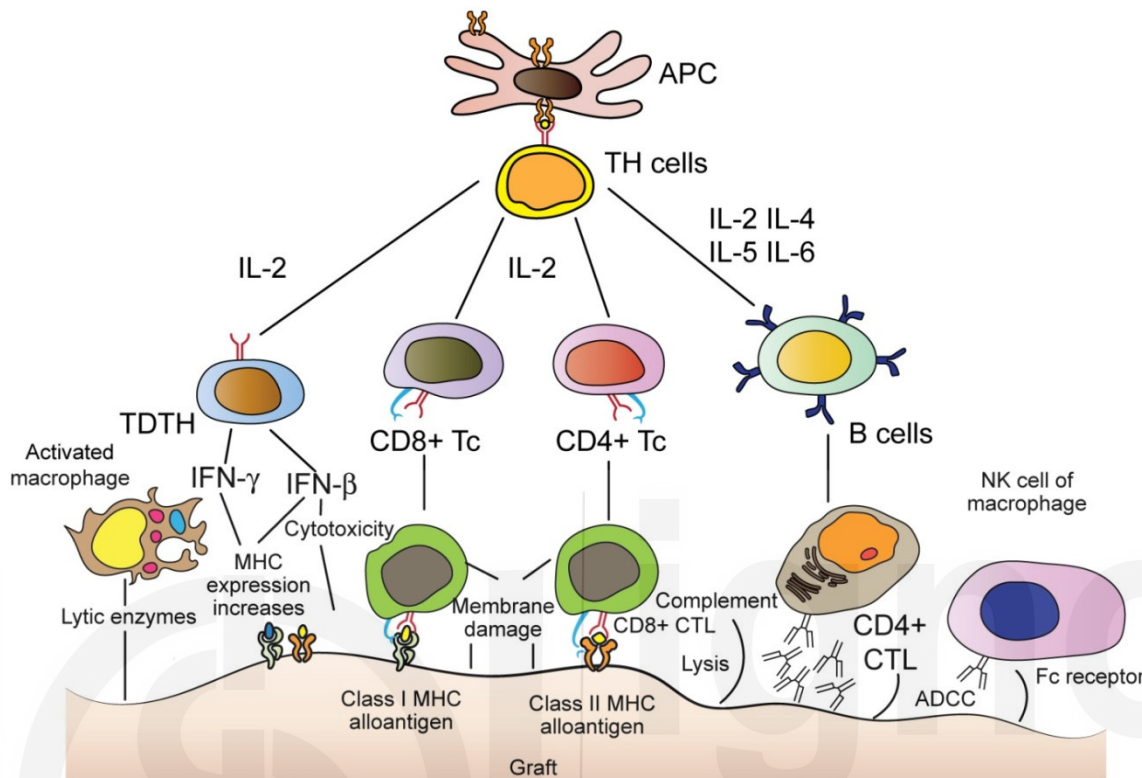


Fig 14.6: Effector mechanisms involved in allograft rejection: The generation or activity of various effector cells depends directly or indirectly on cytokines (blue) secreted by activated T_H cells. ADCC □ antibody dependent cell-mediated cytotoxicity.

14.4.4 Immunosuppressive therapy

Immunosuppressive therapy aids the allogeneic organ transplant to survive. This lowers the recipient's immune response against the foreign graft's alloantigens and prevents its rejection. It plays a vital role in transplantation, hypersensitivity reactions, autoimmune diseases, and inflammatory reactions. Due to immunosuppressive therapy, the fungal infections and cancers may arise secondarily.

Immunosuppressive therapy might be classified into two major categories.

1. Generalised or Non specific
 2. Specific
1. **Generalised or Nonspecific:** Most of the immunosuppressive drugs act in a generalised and non specific way causing the risk for increased infection. Moreover, the immunosuppressive measures which slow down the proliferation of activated lymphocytes affect the non-immune rapidly dividing cells like epithelial cells of gut or bone marrow hematopoietic stem cells pose serious complications. It involves following drug agents.

- i) **Mitotic inhibitors viz. Azathioprine (Imuran):** A potent mitotic inhibitor, given just before and after transplant. It acts in the S phase of mitotically dividing cells and blocks ionising acid synthesis (a precursor of purines adenylic and guanylic acid). Azathioprine can diminish both B and T cells proliferation. The functional immune assays like MLR, CML, and skin tests can depict the same decline. Other mitotic inhibitors which are used in conjugation are cyclophosphamide and Methotrexate. Cycloheximide, an alkylating agent gets inserted into the DNA helix, cross-linked and disrupts the DNA chain. It is specifically active against rapidly dividing cells and is given at the time of grafting. Methotrexate, a folic acid antagonist blocks the purine synthesis.
- ii) **Corticosteroids:** These are potent anti-inflammatory agents given in conjunction with mitotic inhibitors like Azathioprine to transplant recipients for treating acute graft rejections.
- iii) **Cyclosporin A (CsA), FK 506, and Rapamycin:** These are fungal metabolites with immunosuppressive potential. CsA and FK506 both inhibit the IL-2 and IL-2R gene expression, essential for activation of resting T cells. CsA and FK506 both bind to cytoplasmic proteins immunophilins which block the phosphatase activity of calcineurin. This prevents the formation and translocation of cytoplasmic subunit NF-ATc and its assembly into NF-AT (a DNA binding protein important for IL-2 and IL-2R gene expression). Rapamycin structurally similar to CsA and FK506 also binds to immunophilin but doesn't inhibit calcineurin activity instead blocks proliferation and activation of activated T_H cells in the G₁ phase. All these drugs inhibit T_H cells proliferation and their cytokines expression, thereby reduce subsequent effector cells and mechanisms like TD, TH, TC cells, NK cells, macrophages, and B cells involved in graft rejection. Having great value as immunosuppressives these drugs are the mainstay in heart, kidney, liver, bone marrow transplant and have shown long graft survival.
- iv) **Total lymphoid irradiation:** Being lymphocytes extremely sensitive to X-irradiation The recipient's thymus, spleen, lymph nodes receive the irradiation and then get a transplant. A dose of 200 rads per day to a total of 3400 rads is given. Bone marrow being not X-ray irradiated keeps developing the new lymphocytes comparatively more tolerant to graft.

2. Specific Immunosuppressive therapy: In specific immunotherapy antigen-specific immunosuppressant reduces the immune response to the alloantigens of the graft while preserving the response to unrelated antigens. It includes the following strategies.

- i) **Monoclonal antibodies to T- cell components or cytokines:** Anti CD3 of TCR complex monoclonal antibodies have been used

to block T-cell activation and some cases in humans could reverse the acute rejection. Monoclonal antibodies specific for high-affinity IL-2R (anti-TAC) also are used for increasing graft survival. Since IL-2 R are expressed on activated T-Lymphocytes, thus are given post graft. Anti CD4 treated recipients also show increased graft survival. Anti adhesion ICAM-1 and LFA-1 given in pair together results in immunosuppression. Monoclonal antibodies against TNF- α , IFN- γ , and IL-2 also prolonged transplants in mice, still to be tried in humans.

- ii) **Agents that block the co-stimulatory signal:** T-cells activation require a co-stimulatory signal from APCs. One such signal is the interaction between B7 molecules on APCs and CD28 or CTLA4 molecules on T cells. In absence of such a signal T-cells become anergic. The soluble CTLA-4Ig binds to B7 on APCs and blocks the co-stimulatory signal and prevents graft rejection.
- iii) **Donor-cell microchimerism:** It depends upon host tolerance to allogeneic cells. If the donor leukocytes migrate from the graft and survive in the recipient creates a long-term microchimerism in the recipient. Graft acceptance depends upon microchimerism also. The success of the establishment of such microchimerism depends upon the exchange of leukocytes between host and graft cells, the net effect of two-directional immune reactions leads to the immunological tolerance to alloantigens of the graft. Dendritic cells remain the major cell type in chimeras and thus may function as major APCs inducing a state of tolerance to alloantigens.

Anergic is the condition in which the body fails to react to an antigen. Microchimerism is defined as the presence of low concentrations of two genetically different cell populations in the an individual. The possible causes include the bidirectional transfer of cells between mother and fetus during pregnancy, twin-to-twin transfer in utero, from organ transplantation, and blood transfusion.

14.5 IMMUNOLOGICAL TOLERANCE

The immune system, upon encountering an antigen either can develop an immune response or enter a state of unresponsiveness called tolerance. Both require specific recognition of antigen by reactive B or T cells. This is stringently regulated as an inappropriate immunity to self-antigens or tolerance to a potential pathogen can have life-threatening consequences. Tolerance prevents the immune response to a particular antigen. Generally, immune system is tolerant of self-antigens and does not attack the own cells, tissues, and organs. Loss of tolerance causes autoimmune disorders or allergies. Therefore, the ability to distinguish self from non-self is very much integrated with the appropriateness of the immune response. Tolerance to self is maintained by central and peripheral mechanisms. Their failure leads to autoimmune diseases.

14.5.1 Central Tolerance

The adaptive immune B and T lymphocytes when develop and mature, get screened by several checkpoints in the bone marrow or thymus, respectively. If such B cells produce antibodies that recognise host cells or T cells that strongly recognise self-antigens are deleted through apoptosis (a process of cell death).

14.5.2 Peripheral Tolerance

The self-reactive cells which escape the central tolerance are taken care of by other safety measures under peripheral tolerance. This includes:

- a) The self-reactive immune cells which escape central tolerance remain present in healthy individuals are kept in a non-reactive or a state of anergy (antigen encounter leading to a state of no co-stimulatory signals). These self-reactive cells recognise the body's own cells but lack the ability to react and cause damage to the host. The dendritic cells play a major role in inducing anergy through the lack of costimulation of T cells.
- b) There are circulating Tregs (regulatory immune cells) which silence the self-reactive T lymphocytes. Besides limiting the auto-reactive cells, Tregs turn the immune response off after the problem is resolved. Tregs act as drains, these deplete the areas of essential nutrients around the immune cells, required for activation or survival.
- c) There are immunologically privileged sites such as the eye or brain having physical barriers like blood-brain barriers that restrict the entry of immune cells. These areas do not typically elicit a strong immune response. Also, these areas express higher levels of suppressive cytokines preventing robust immune response.
- d) Fetomaternal tolerance prevents the maternal immune actions against the fetus. The fetus bears the paternal MHC or HLA proteins and antigens. Being foreign, a fetus can potentially trigger the mother's immune system but the placenta acts as a barrier. It reduces the exposure of fetus to maternal immune cells. The proteins expressed on the outer layer of the placenta restrict immune recognition. The regulatory cells and immune-suppressive signals also play an important role.

SAQ 8

- i) therapy lowers the recipient's immune response against graft's alloantigens and prevents its rejection.
 - ii) Failure of tolerance to self leads to diseases.
 - iii) acts as a barrier reduces the exposure of fetus to maternal immune cells.
-

14.6 SUMMARY

So far, you have learned that:

- The cells may become cancerous when they become abnormal and divide uncontrollably. The unregulated proliferation of an abnormal cell creates a clone of cells called a tumor or neoplasm.

- Tumors are uncontrolled growth of cells that originate from normal cells. Tumor progresses through two stages that is, benign and malignant. Benign tumor is a non-cancerous form of a neoplasm. During the benign stage, tumors limit themselves to the tissue or body part where they originate. In the malignant stage, tumor spreads to other parts of the body through blood vessels. This process of tumor spreading is the stage of cancer which is called metastasis. In this stage, tumors are difficult to treat as their destination tissue is random.
- The majority of cancers are due to mutation of specific genes involved in cell division control. Mortality due to cancer happens as these cells outnumber the normal tissue cells where they are present and interfere in the normal functioning and maintenance of body parts at the site of their proliferation.
- Oncogenes are those which are responsible for the origin and growth of the tumor. They originate from proto-oncogenes. When these proto-oncogenes undergo mutations they convert to oncogenes, whose expression triggers excessive growth of cells leading to tumor. Several types of oncogenes are known and an important one among them is p53. The mutation of p53 has been identified in several types of cancers. Genes that limit or inhibit cell growth and proliferation are called Tumor-Suppressor genes. Genes that control programmed death of the cells are called Apoptosis genes.
- Tumor cells often display either specific or nonspecific surface antigens such as Tumor-Specific Antigens (TSAs) or Tumor-Associated Antigens (TAAs), respectively. These TSAs or TAAs are of great help in early diagnosis of cancer and planning the treatment. Immune system identifies and attempts to remove tumor cells through immunosurveillance. However, immune system may engage in either positive or negative roles with respect to tumor formation, which is called immunoediting, which determines the occurrence of cancer. By recognizing various factors of the immune system, immunotherapy can be used through the use of mAbs or molecules that limit the growth of cancer. Such molecules are being developed as vaccines which are primarily therapeutic than prophylactic.
- The blood group and HLA antigens differences are the basis of graft rejection. The donor and recipients are screened for such differences to prevent graft rejection. The microcytotoxicity assay is used if a quick check is required in case if its transplant is received from a cadaver. Or else MLR reaction can give fair idea about compatibility.
- The Human HLAs play a major role in differentiating self and non self, and are produced by MHC genes. These are of Class I, II, and III types. Class I are transmembrane glycoproteins, present almost on nucleated cells, include an α -heavy chain bound to β -micro globulin molecule. These present the antigen by the cytosolic process. Class II molecules are glycoproteins and primarily on APCs and most of the nucleated cells can express them and present antigen by endocytic pathway. Class III involves complement system, serum soluble proteins and TNFs.

- Graft rejection is facilitated by cell-mediated immune response to alloantigens. It includes a sensitisation phase where the alloantigens reactive lymphocytes proliferate and an effector phase in which graft is immunologically destroyed. Both the phases involve antigen presenting cells (APCs), MHC molecules and a number of cytokines that mediate as Delayed type and cell mediated immune response.
- Pre and Post transplant Immunosuppressive treatment is important for the survival of allogeneic transplant. It includes mitotic inhibitors, corticosteroids, cyclosporin-A, and irradiation as generalised therapy and monoclonal antibodies, anergic T cells etc. as specialised therapy.

14.7 TERMINAL QUESTIONS

1. Write about the origin and stages of cancer.
2. Define oncogenes.
3. Differentiate between Tumor specific antigens (TSAs) and Tumor-associated antigens (TAAs).
4. Define the terms immunosurveillance and immunoediting.
5. What are the different immunotherapy methods available to treat cancer?
6. Explain the role of nutrition in immune function. How Probiotic and Prebiotic contribute to the immunity?
7. Explain the different types of graft transplants.
8. Explain the graft rejection mechanism with suitable labelled diagram.
9. What is immunosuppressive therapy. Explain the two major types of the same.
10. Define the immunological tolerance highlighting the central and peripheral tolerance.

14.8 ANSWERS

Self Assessment Questions

1. i) Benign tumor.
iii) (c).
iii) (d).
iv) (a).
2. i) Epidermal growth factor and Platelet-derived growth factor.
ii) Proto oncogene, DNA binding protein.
iii) Tumor-suppressor genes.

- iv) Activation.
 - v) Mutation.
 - vi) Erythroleukemia in chicken.
 - vii) p53.
 - viii) bcl-2.
- 3.
- i) α -fetoprotein (AFP).
 - ii) FP & CEA.
 - iii) (a).
 - iv) Carcinoembryonic antigen (CEA).
 - v) Tumor specific antigens.
- 4.
- i) One of the mechanisms by which the immune system is thought to control tumor growth is by actively recognizing and removing newly transformed cells is referred to as immunosurveillance.
 - ii) By immunoediting, the immune system engages in both positive (pro-tumor) and negative (anti-tumor) actions that help to make the foundations of the tumor, by determining the cells fate in order to be eliminated or not.
 - iii) Recombination Activating 2 (RAG2).
 - iv) Self-cells.
 - v) Interferon-gamma (IFN- γ).
- 5.
- i) Immune escape.
 - ii) Cytotoxic T Lymphocyte (CTL).
 - iii) HER2.
 - iv) Humanized.
 - v) Cytotoxic T Lymphocytes.
- 6.
- i) Micronutrients, macronutrients.
 - ii) Peyer's patches.
 - iii) Vitamin D.
- 7.
- i) Transplantation.
 - ii) Xenograft.
 - iii) Microcytotoxicity.
 - iv) Mixed Lymphocyte Reaction (MLR).

- v) Class I MHC molecules.
- vi) Antigen presenting cells (APCs).
- 8. i) Immunosuppressive.
- ii) Autoimmune diseases.
- iii) Placenta.

Terminal Questions

1. Refer to Sub Section 14.1.2.
2. Refer to Sub Section 14.1.3.
3. Refer to Sub Section 14.1.4.1 and 14.1.4.2.
4. Refer to Sub Section 14.1.5.
5. Refer to Sub Section 14.1.7.
6. Refer to Sub Section 14.2.2 and 14.2.4.
7. Refer to Sub Section 14.3.1.
8. Refer to Sub Section 14.3.4.
9. Refer to Sub Section 14.3.5.
10. Refer to Sub Section 14.4, 14.4.1, 14.4.2.

UNIT 15

VACCINES

Structure

15.1	Introduction	Concerns and Difficulties with Vaccination
	Objectives	
15.2	The History of Vaccination	Composition of Vaccine
15.3	Immune System	The Herd Immunity Imperative
	The Function of the Immune System	15.5 Clinical Evaluation of Vaccine
	Innate and Adaptive Immunity	15.6 Government Schemes for Vaccination
	Active and Passive Immunization	15.7 Vaccine Hesitancy
15.4	Overview of Vaccine	15.8 Summary
	How Vaccine Works	15.9 Terminal Questions
	Types of Vaccines	15.10 Answers
	Advantages and Disadvantages of Vaccines	

15.1 INTRODUCTION

The administration of a vaccine to help the immune system develop protection from disease is called vaccination. Vaccines stimulate the body's immune system and help prevent sickness from an infectious agent. The word "vaccine" originates from the Latin word "*Variolaevaccinae* (cowpox). Vaccines can be produced by the biological preparations, produced from the disease-causing organisms which may be in a weakened, live, or killed state, or may be a part of the organism (DNA/proteins) or toxins released by them. Edward Jenner in 1798 demonstrated that smallpox is preventable in humans. When a large population has been vaccinated it results in herd immunity. The effectiveness of vaccination has been established worldwide as the most cost-effective method of preventing infectious diseases. The prevalence of several diseases such as measles, diphtheria, mumps, pertussis (whooping cough), rubella (German measles), poliomyelitis, and tetanus has decreased

dramatically as vaccination has become more common. Not even a single naturally acquired smallpox case has been reported anywhere in the world, since October 1977. Similarly, polio cases have decreased globally by over 99% since 1988, from an estimated more than 350000 cases to 22 reported cases in 2017 as recorded by World Health Organization (WHO). This reduction is the result of the global effort of vaccination to eradicate the disease and so far, only 3 countries in the world (Pakistan, Afghanistan and Nigeria) have not stopped transmission of polio (WHO). Vaccines are administered in liquid form of injection, either through oral or through intranasal routes. Generally, in today's language, the term vaccination and immunization have a similar meaning. This is different from inoculation, which uses unattenuated live pathogens. Vaccination efforts have been met with refusal on scientific, ethical, political, medical safety, and religious grounds.

Objectives

After studying this unit you should be able to:

- ❖ explain how the immune system works for the protection of our body.
- ❖ describe vaccination and explain the mechanism of vaccines.
- ❖ list the types of vaccines and describe the formulation, function and advantages/disadvantages of each type of vaccine.
- ❖ enumerate the different vaccination programmes started by the government for the proper administration of the vaccine in India.

15.2 THE HISTORY OF VACCINATION

Vaccine development begins with basic research. Smallpox was the first disease that people tried to prevent through inoculation. In the 16th century in China, dried pustules of smallpox were administered from a sick to a healthy individual to prevent the healthy individual from developing the disease. This practice of inoculation of dried pustules is called variolation. The first vaccine was developed for Smallpox. The smallpox vaccine was invented by an English physician Edward Jenner. In 1798, in England, he published the results of his experiments on "vaccination", the practice of the inoculation of cowpox virus (nearly related to the human smallpox virus), *Variolaevaccinae*, to prevent smallpox in humans. The practice became broadly popularized.

At the end of the 19th century, the concept of vaccination to other diseases was applied by Louis Pasteur. He demonstrated, how the virulent nature of pathogens could be weakened (or attenuated) in the laboratory. He showed the effectiveness of vaccines against chicken cholera and anthrax in animals followed by the development of vaccine against rabies for humans in 1885.

Daniel Elmer Salmon and Theobald Smith, in 1886 in the US, showed that vaccines could not only be produced just from live organisms, but also from killed pathogens. Their discovery leads to the subsequent development of inactivated vaccines against several human diseases.

In the early 20th century, it was found that there were some diseases that were caused not by bacteria themselves, but by the toxins produced by them. Inactivated toxins are depicted like vaccines as they protect against these toxins-induced diseases. Such vaccines are called toxoids.

Till the end of the 20th century, a flow of experiments led to the development of numerous new methods of producing vaccines such as development of genetically modified organisms, by conjugation of polysaccharides to carrier proteins, and by the assembly of virus-like particles.

SAQ 1

Answer the following in one word:

- i) Name the first disease against which the vaccine was introduced?
- ii) Which scientist created the world's first vaccine?
- iii) Who developed a vaccine against rabies for humans in 1885?
- iv) The practice of inoculation of dried pustules is called

15.3 IMMUNE SYSTEM

The immune system is composed of various organs, cells, and proteins. It plays an important role in protecting our body from pathogens, harmful substances, and cell changes that could make us ill.

The importance of the immune system can be noticed when it becomes weak or stop functioning properly and can't defend our body against the aggressive germs resulting in illness. Micro-organisms that our body has never encountered before are also likely to make us ill. Some microorganisms can occasionally make us ill in a lifetime viz. chickenpox.

15.3.1 The Function of the Immune System

Immune system provides a defense mechanism to our body to tackle the harmful effects caused by the disease-causing micro-organisms or any other antigen. The main functions of the body's immune system are as follows:

- It fights against the disease-causing microorganisms (pathogens) like viruses, bacteria, parasites or fungi.
- It recognizes and neutralizes harmful substances from the environment that our body may encounter.
- It fights against disease-caused due to mutations occurring in the genome of an individual resulting in cancer.

How is the Immune System Activated?

If the body do not recognize anything as its own is called as antigen, can activate the immune system. Examples of antigens are the surface proteins of bacteria, fungi and viruses. A series of processes against that antigen is triggered when they bind to the special receptors on the immune cells (immune system cells). On first encounter with an antigen, body stores information about the pathogen and the mechanism to fight against it. On a subsequent encounter with the same antigen, it recognizes it easily and starts to fight against it in a much faster way compared to the first encounter.

The body's own cells also have surface proteins but they usually don't trigger the immune response. It's rare when the immune system mistakenly recognizes the body's own cells as foreign cells and attack the healthy and harmless cells of the body. If such a mistake occurs in our body then it is called an autoimmune response.

15.3.2 Innate and Adaptive Immunity

Innate immunity (also called natural or native immunity) provides the early line of defense against pathogens. It consists of biochemical and cellular defense mechanisms that are present even before infection and it responds rapidly to infections.

Adaptive immunity (also called acquired or specific immunity) system recognizes and reacts to a large number of microbial and non-microbial substances. Adaptive immunity can distinguish different antigens, which is known as specificity, and the ability to respond more vigorously to repeated exposures to the same antigen, known as memory. The unique components of adaptive immunity are cells known as lymphocytes and their secreted products like antibodies (Fig. 15.1). The major differences between innate and adaptive immunity are listed in table 15.1.

Table 15.1: Difference between innate and adaptive immunity.

INNATE IMMUNITY	ADAPTIVE IMMUNITY
Non- specific	Specific
Antigen independent	Antigen dependent
Predominates in early stages of infection	Predominates in the middle and late stage of infection
Maximum response in hours	Maximum response in days
Response to repeat infection is identical to the primary response	Response to repeat infection is much more rapid than the primary response
No immunologic memory	Immunologic memory develops

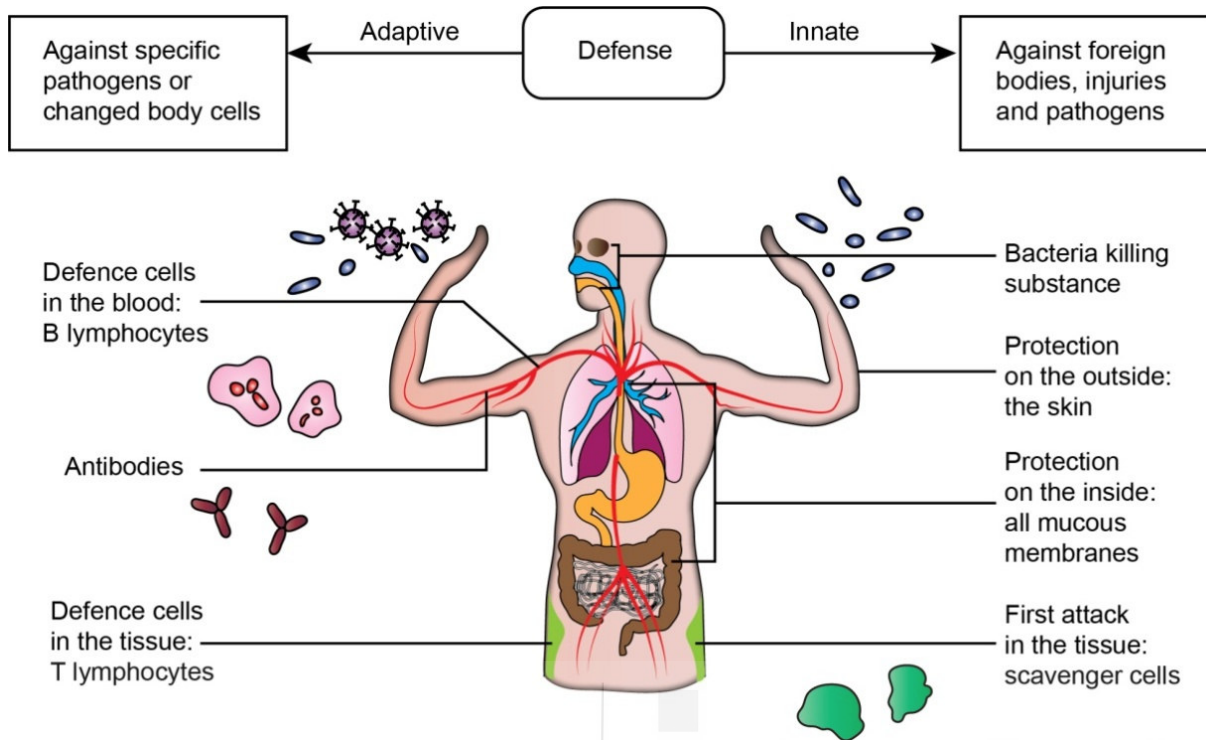


Fig. 15.1: Innate and adaptive immune system. The adaptive immune system works against specific pathogens or changed body cells. The innate immune system works against foreign bodies, injuries and pathogens.

15.3.3 Active and Passive Immunization

By the process of immunization, a person develops immunity against the infectious disease. Immunity against infectious microorganisms can be attained by active or passive immunization.

Passive Immunity

When an antibody or antitoxin produced by an individual gets transferred to another is called as **Passive immunity**. Although the protection against an infection is immediate but temporary because the antibodies degrade within a short span of few days or weeks, and the recipient is no longer protected.

A well known example of passive immunity is the antibodies received by an infant from the mother. A full-term infant has the same type of antibodies as the mother because IgG antibodies are carried across the placenta mainly during the last 1–2 months of pregnancy. The infant gets protection from certain diseases because of these antibodies within few months after the birth. Maternal antibodies against diphtheria, tetanus, streptococci, rubella, mumps, and poliovirus all are passively acquired by the developing fetus. Infant acquires passive immunity from milk and colostrum, the source of maternal antibodies. Passive immunity can also be acquired through the transfusion of blood products.

Although passive immunization is considered an effective treatment, it should be used with care because of the certain risks associated with the injection of preformed antibodies. If the antibody is produced in another species, for example horse, the receiver can mount a strong response to the isotypic determinants of the foreign antibody which can cause serious complications.

Active Immunity

An active immunity is the person's own immunity that imparts protection. The antigen stimulates the immune system to produce antibodies and cellular immunity. The active immunity usually lasts for many years, often for a lifetime in comparison to passive immunity, which is temporary. Active immunization elicits protective immunity and immunologic memory.

Active immunity is acquired by surviving infection with the disease-causing organism. Once recovered from infectious diseases, the patient will have lifelong immunity to that disease (except disease, such as malaria). The protection lasts for many years even for a lifetime. This perseverance of protection for many years after the infection is known as **immunologic memory**. B cells called as memory B-cells are formed on exposure to the antigen that keep circulating in the blood and reside in the bone marrow for a long time. These memory cells replicate and act quickly to establish protection on re-exposure to the same antigen (Fig 15.2). The main difference between active and passive immunity are listed in table 15.2.

Vaccination is another way to acquire active immunity. Vaccines consist of antigens that resembles the natural infection causing organism but the recipient does not acquire disease and its potential complications as the infection causing organism is attenuated or inactivated. Hence, it has the capability to stimulate the immune system to produce an immune response that is similar to the one produced by the natural infection. However, with vaccination, active immunization by different vaccines has played a crucial role in the reduction of mortality from infectious diseases, especially in children.

Factors that can influence the immune response during vaccination are the nature and dose of antigen, the presence of maternal antibody, the route of administration of the vaccine, and the presence of an adjuvant (e.g., aluminum-containing material added to improve the immunogenicity of the vaccine). The immune response may also be affected by certain host factors, such as age, nutrition, genetics, and coexisting disease.

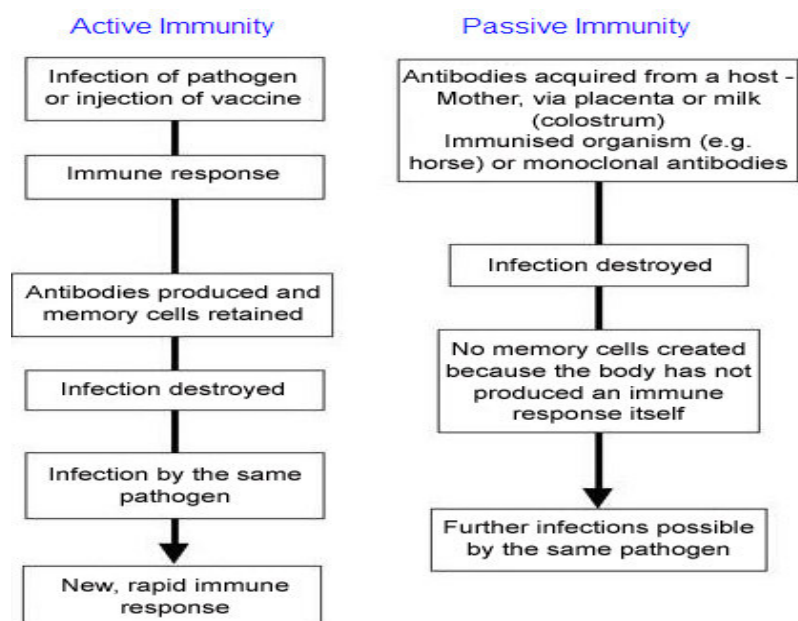


Fig 15.2: A flowchart representing the function of active and passive immunity.

Table 15.2: Difference between and passive immunity.

ACTIVE IMMUNITY	PASSIVE IMMUNITY
Produced by the body's own immune system in response to antigen	Received passively by the host, no involvement of immune system
Take time in the production of specific antibodies and cells	Provides instant protection, no time lag
Usually protects for a longer period of time	Protects for a short period of time.
Not applicable in immune deficient individual	Applicable in immune deficient individual

Immunity can be achieved either by natural processes (usually by transfer from mother to fetus through placenta or by the previous infection by the organism) or by artificial methods like the injection of antibodies or vaccines. (Fig.15.3).

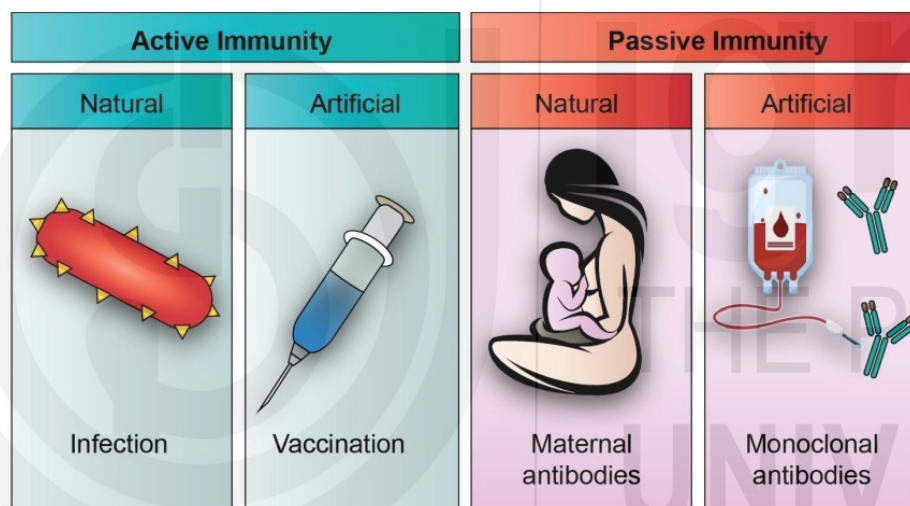


Fig. 15.3: Figure depicting the natural and artificial forms of active and passive immunity.

SAQ 2

Read the following statements and write True (T) or False (F).

- Immunity that an infant receives from the mother is a form of active immunity.
- Protection produced by person's own immune system is active immunity.
- Innate immunity is antigen independent.
- Adaptive immunity predominates in early stages of infection.
- Transfusion of blood products is an example of passive immunity.
- Active immunization elicits immunologic memory.

15.4 OVERVIEW OF VACCINE

A vaccine delivers active acquired immunity against the pathogens. A vaccine is typically constituted of an antigen that is alike to a disease-causing microorganism and is often made from attenuated or killed forms of the pathogen, its toxins made up of surface proteins or polysaccharides, or its DNA. These antigens are recognized as a threat by the body's immune system and hence gets stimulated resulting in the destruction of the infection causing organism. Also, it may recognize and destroy any of the same microorganisms or associated antigen in the future on subsequent encounter.

15.4.1 How Vaccine Works

Vaccines develop immunity by imitating or copying an infection. To achieve immunity, certain molecules from the pathogen or whole pathogen (inactivated /attenuated) are introduced into the body to trigger an immune response. This imitating infection never causes illness, but it causes the immune system to produce T-lymphocytes and antibodies. Minor symptoms can be observed after vaccination, such as fever. Such symptoms are normal and expected as the body builds immunity against the pathogens. Once the imitation infection disappears, the body is left with a supply of “memory” T-lymphocytes, and B-lymphocytes which will memorize how to counter the disease in the future. If the same pathogen reappears, the immune system will recognize the antigens immediately and stops it from spreading and causing the sickness (Fig. 15.4).

HOW VACCINE WORKS

Vaccine work by imitating a bacteria or virus using either mRNA or a dead or weakened version of a virus or bacteria



The vaccine activates the body's Immune system. It trains the body to recognize and fight virus or bacteria



When the body encounters the real –dead virus, it is primed and ready to fight for the body's health

Fig. 15.4: Mode of vaccine action.

15.4.2 Types of Vaccines

Based on their formulation there are different types of vaccines which include: whole organism vaccines (attenuated / inactivated), purified macromolecules as vaccines, recombinant vaccines, DNA vaccines and multivalent subunit vaccines (Fig. 15.5).

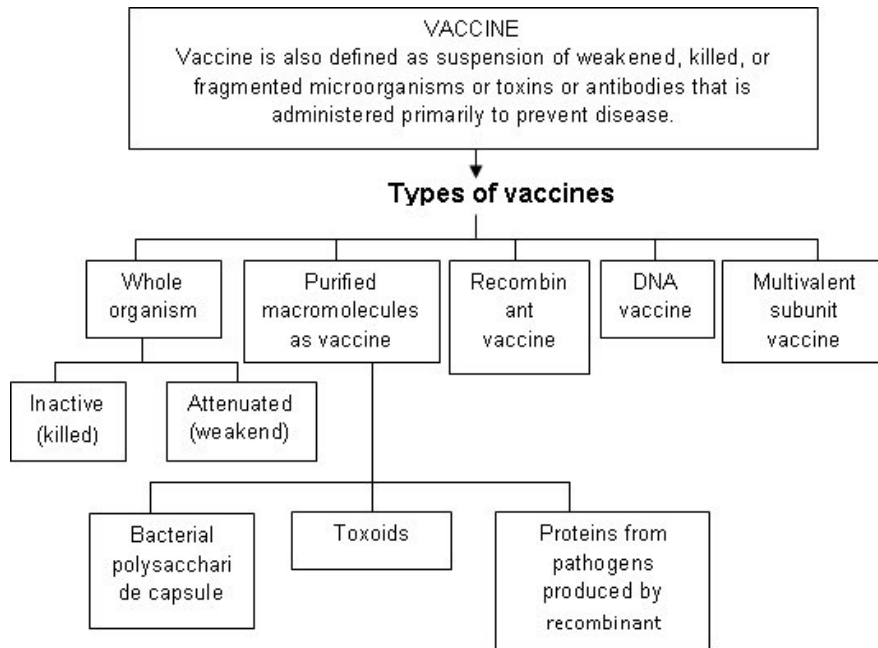


Fig. 15.5: Flow chart showing the different types of vaccines.

1. **Whole-Organisms Vaccines:** Many of the current vaccines used for humans which are effective against viral and bacterial diseases, consist of whole microorganisms that are either inactivated (killed) or attenuated (live but avirulent). Such vaccines are known as whole-organism vaccines.

Live Attenuated Vaccines: In these sorts of immunizations, a more fragile, asymptomatic (attenuated) type of the microorganism is brought into the body. The feeble microorganism loses its capacity to spread and cause ailment, but the immune system will still learn to recognize this antigen on future encounter and response by the immune system.

- **Advantages:** The live attenuated vaccines can result in lifelong immunity with just one or two doses as the vaccines introduces the actual live pathogens into the body and strongly stimulates the immune system.
- **Disadvantages:** The vaccines usually require the continuous maintenance of the appropriate temperature range to avoid the inactivity of the vaccine due to the death of the organism. These vaccines are not given to the people with compromised immune systems, undergoing chemotherapy or HIV treatment as it comprises of the live attenuated pathogens and also to avoid the risk of the pathogen to get stronger in order to cause any sickness.
- **Specific Vaccines:**
 - Measles
 - Mumps
 - Rubella (MMR combined vaccine)
 - Varicella (chickenpox)

- Influenza (nasal spray)
- Rotavirus

2. Inactivated Vaccines: In these vaccines, the specific micro-organism is killed by heat or chemicals, and the same is introduced into the body where the immune system can still recognise it as an antigen and can prepare itself to fight the live versions of the micro-organism on future encounter.

- **Advantages:** As these vaccines comprise of killed pathogens, these vaccines can be freeze dried and easily stored. They are also safer, as there is no risk of the micro-organism to mutate back into its disease-causing form.
- **Disadvantages:** As the micro-organism is dead, it cannot mimic the simulation of its own actual, live attenuated form. Hence, it often takes several doses and "booster shots" to train the body to defend itself.
- **Specific Vaccines:**
 - Polio (IPV)
 - Hepatitis A
 - Rabies

Refer to Fig. 15.5 for different types of vaccine and table 15.3 for comparison between the inactivated and attenuated vaccines.

Table 15.3: A Comparison of Inactivated (Killed) and Attenuated (Live) Vaccines.

Major Characteristic	Inactivated Vaccine	Attenuated Vaccine
Booster shots	Multiple boosters require	Only a single booster
Production	Virulent microorganisms are inactivated by chemicals or irradiation	Virulent microorganisms are grown under extreme conditions or passed through different hosts until avirulent
Reversion tendency	None	May revert to a virulent form
Stability	Very stable	Less stable
Type of immunity induced	Only Humoral	Both Humoral and cell-mediated
Source: Adapted from Goldsby, T. J. Kindt, and B. A. Osborne, Kuby Immunology. 2000, New York: W. H. Freeman.		

Whole Organism Vaccines can also be problematic. Whole-organism vaccines fail to protect from some disease-causing organisms. Attenuated vaccines that do work can also cause full-fledged illness in individuals with compromised immune systems viz. AIDS patients, cancer patients undergoing chemotherapy, and elderly people. There are possibilities that the mutation in an attenuated virus may revert to its virulent form, as observed in some monkeys vaccinated with an attenuated simian form of the AIDS virus. The risk of reversion to virulence in the case of a very lethal disease is unbearable. Since these vaccines are composed of whole pathogens, they retain molecules that are not involved in evoking immunity which leads to another big drawback of whole organism vaccines. Whole organism vaccines can trigger allergic or other disruptive reactions because of the unavoidable byproducts of the manufacturing process. Refer to Fig. 15.6 for the formulation of the inactive and attenuated vaccine.

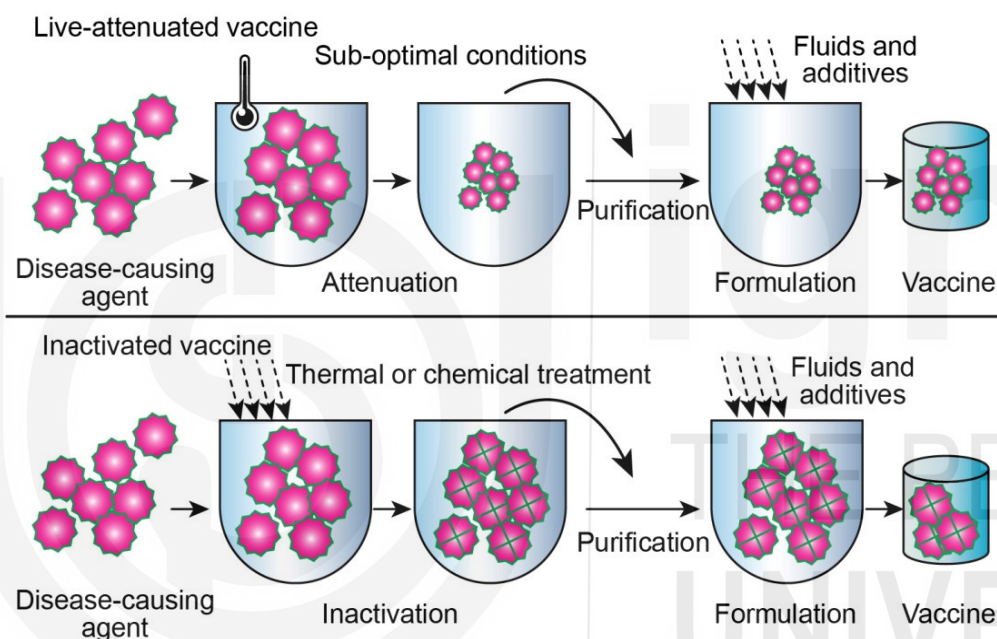


Fig. 15.6: Formulation of the inactive and attenuated vaccine.

3. **Purified Macromolecules as Vaccine:** Vaccines that consist of specific, purified macromolecules derived from disease-causing microorganisms can be the safer option in comparison to the risks associated with attenuated or inactivated vaccines. Currently, there are three forms of such vaccines: inactivated exotoxins, capsular polysaccharides, and recombinant microbial antigens.

- i) **Bacterial Polysaccharide capsules are used as vaccines:** The antiphagocytic properties of the hydrophilic polysaccharide capsule of a few bacteria make those bacteria virulent. When the capsule is coated with antibodies and/or complement, it greatly increases the phagocytic ability of macrophages and neutrophils to phagocytose such pathogens. Such findings provide the rationale for vaccines consisting of purified polysaccharide capsules, for example, the current vaccine for *Streptococcus pneumoniae*, which causes pneumococcal pneumonia, constitutes 23 antigenically different capsular polysaccharides.

There is one limitation of polysaccharide vaccines which is their inability to activate TH cells.

- ii) **Toxoids Manufactured From Bacterial Toxins:** Some bacterial pathogens, produce exotoxins for example bacteria causing diphtheria and tetanus. Many of the disease symptoms that result from infection are produced by these exotoxins. The vaccines of diphtheria and tetanus can be made by purifying the exotoxins produced by these bacteria and then inactivating the toxin with formaldehyde to form a toxoid. Vaccination with the toxoid consists of anti-toxoid antibodies, which also bind to the toxin and neutralize its effects (Fig. 15.7).

• **Specific vaccines:**

- Diphtheria
- Tetanus

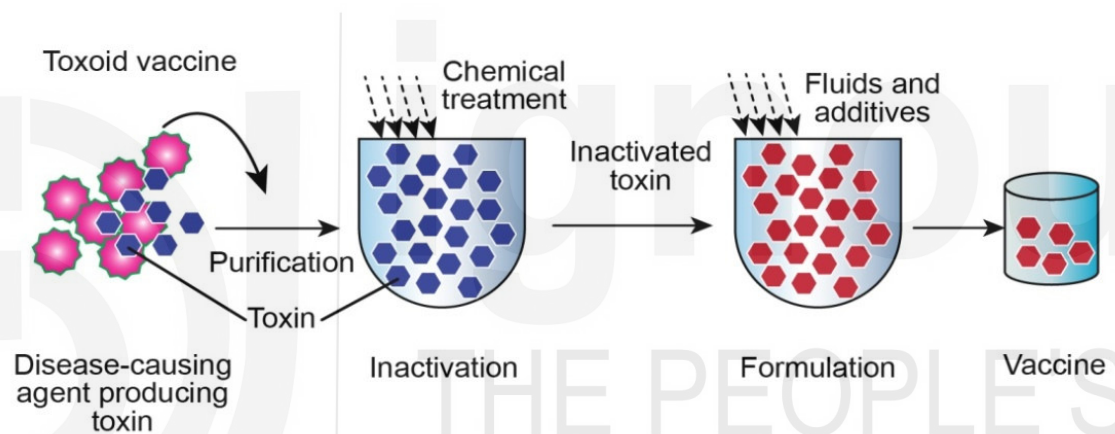


Fig. 15.7: Formulation of Toxoid vaccine.

- iii) **Proteins from Pathogens Produced by Recombinant Technique:** Numerous genes have been cloned and expressed in bacterial, yeast, insect, or mammalian based expression systems that encode different surface antigens from disease causing organisms successfully. These expressed antigens are used for vaccine development. Example: Hepatitis B vaccine.

4. **Recombinant Vaccines:** Recombinant vaccines are very different in structure from whole organism vaccines. The recombinant DNA technology is used to produce a recombinant vaccine. This involves inserting the DNA encoding an antigen (such as a bacterial surface protein) is cloned in an expression vector such as non-virulent viruses or bacteria which serve as vectors. The purified gene product of the pathogen (antigenic proteins) can stimulate an immune response. . . Many microorganisms have been used in the production of recombinant-vector vaccines. For example adenovirus, vaccinia virus, canarypox virus, attenuated poliovirus and attenuated strains of *Salmonella* and *Mycobacterium*. Recombinant vector vaccines for HIV, rabies, and measles are currently being developed. Refer to Fig. 15.8 for formulation of recombinant vaccine.

Recombinant Sub-Unit Vaccine

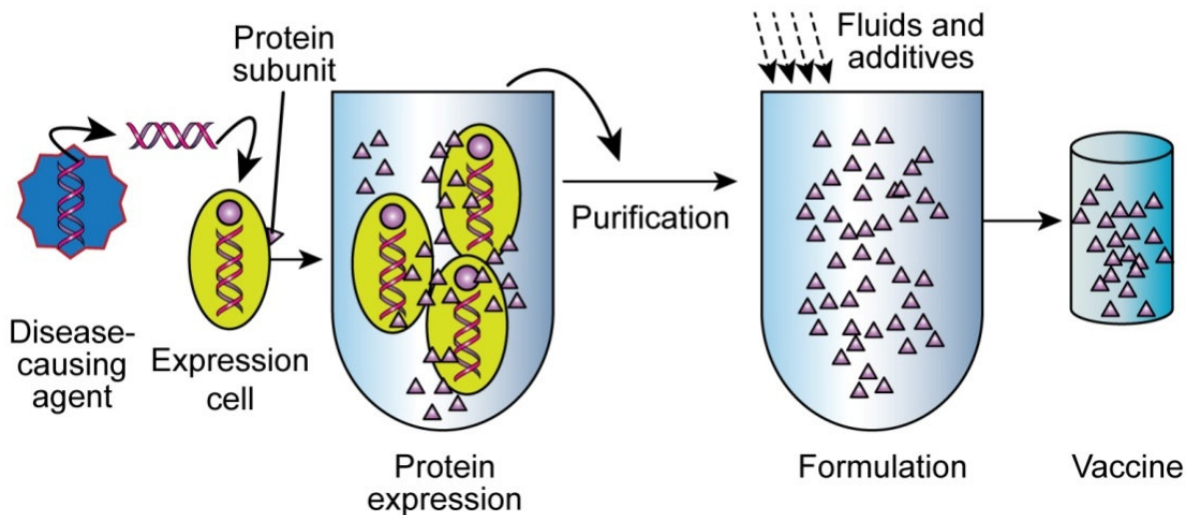


Fig. 15.8: Formulation of recombinant vaccine.

5. **DNA Vaccines:** DNA vaccine is a more complicated vaccine that emerged recently. A DNA vaccine elicits protective immunity against a disease-causing microorganism by activating both humoral and cellular immune responses. Memory cells are generated. Plasmid DNA which encodes antigenic proteins is directly injected into the muscle of the recipient. DNA is taken up by the muscle cells and the encoded protein antigen is expressed, leading to both a humoral antibody response and a cell-mediated response. The DNA either integrates into the chromosomal DNA or is maintained in an episomal form for long periods (Fig. 15.9).

There are many advantages of DNA vaccines over many of the existing vaccines. These includes:

- i) There is no denaturation or modification of encoded proteins, as it is expressed into the host in its natural form. Therefore, the immune response is directed to the antigen exactly as it is expressed by the pathogen.
- ii) Both humoral and cell-mediated immunity are activated by DNA vaccines. To elicit both types of immune response with non-DNA vaccines, immunization with a live attenuated preparation is required, which may introduce additional elements of risk.
- iii) As DNA vaccines cause prolonged expression of the antigen, it generates momentous immunological memory.
- iv) The controlled low temperature is not required for the handling and storage of the plasmid DNA, which greatly lowers the cost and complexity of the delivery.

- **Specific Vaccines:** DNA vaccines for influenza and herpes are currently in human testing phases.

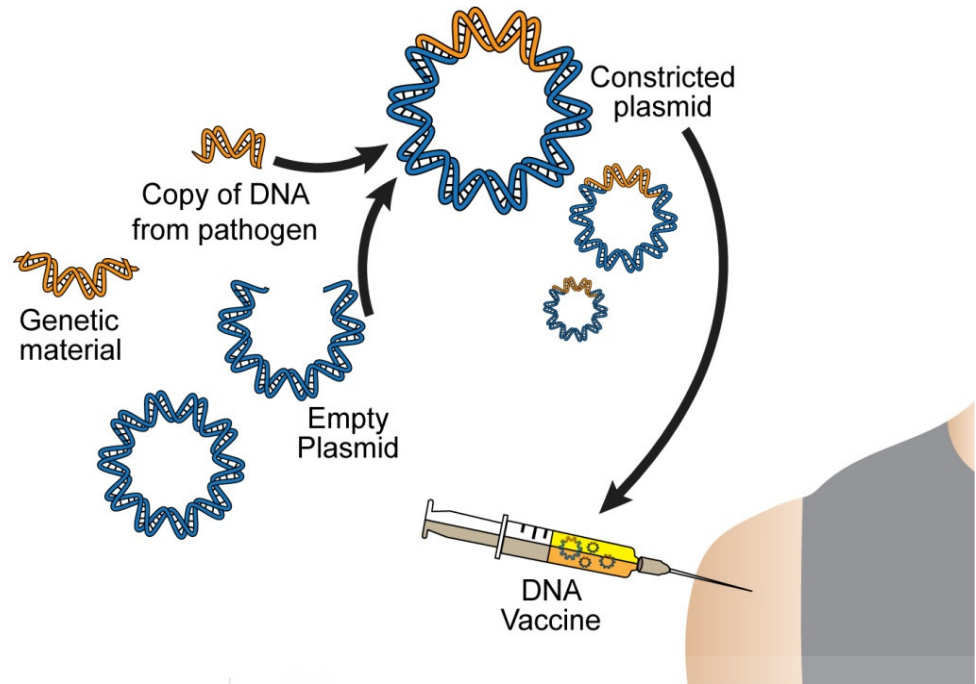


Fig.15.9: Figure showing the formulation of DNA vaccine.

6. **Multivalent Subunit Vaccines:** Some of the above vaccines elicit only humoral immune responses but are less likely to elicit cell-mediated response. There is a need for a method for producing synthetic peptide vaccines that contain both immunodominant B-cell and T-cell epitopes. Several cutting-edge techniques are being applied for the development of multivalent vaccines that can present numerous copies of a given peptide or a mixture of peptides to the immune system.

- **Advantages:** As only a part of the original pathogen is injected into the body, there is a least chance of an adverse reaction in the patient.
- **Disadvantages:** To recognize and separate the best antigens in the microbe for preparing the vaccine is not always possible. Only a few vaccines can be produced in this way.
- **Specific Vaccines:**
 - Hepatitis B
 - Influenza
 - *Haemophilus Influenzae* Type B (Hib)
 - Pertussis (part of DTaP combined immunization)
 - Pneumococcal
 - Human *Papillomavirus* (HPV)
 - Meningococcal

Few Vaccine-preventable diseases, their types and year of development are listed in table 15.4.

Table 15.4: Vaccine-Preventable Diseases, Vaccine Type, and Year of Vaccine Development *Developed in Japan; **Urabe Am9 strain developed in Japan; ***Several Japanese vaccine strains.

Vaccine - preventable disease	Type of disease	Most common severe disease outcome	Type of vaccine	Year of vaccine development
Smallpox	Viral	Disfiguring, sometimes fatal	Live attenuated	1798
Rabies	Viral	Always fatal	Inactivated	1885
			Inactivated (cell culture)	1976
Typhoid	Bacterial	Intestinal hemorrhage and perforations, encephalitis, psychosis, abscesses of internal organs, sometimes fatal	Inactive	1886
			Live attenuated	1983
			Polysaccharide	1994
			Protein conjugate	2008
Cholera	Bacterial	Life-threatening dehydration, electrolyte imbalance, sometimes fatal	Inactivated (Injectable)	1886
			Inactivated and recombinant protein (oral)	1991
			Inactivated (oral)	1997
Plague	Bacterial	Seizures, coma, internal bleeding, fatal in four days if not treated	Inactivated	1997
Diphtheria	Bacterial	Choking, heart and kidney failure, facial or swelling or respiratory paralysis, sometimes fatal	Toxoid	1923
Tetanus	Bacterial	Severe muscle spasms and bone fractures, lockjaw, respiratory distress, sometimes fatal	Toxoid	1926
Pertusis	Bacterial	Choking in young infants, rib fractures, hernias, incontinence, ruptured blood vessels, sometimes fatal	Inactivated	1914
			Purified protein	1981
Tuberculosis	Bacterial	Coughing blood, abscesses of internal organs or bone, meningitis, sometimes fatal	Live attenuated	1921

Yellow fever	Viral	Life-threatening pneumonia, worsening of coronary heart disease, extreme muscular fatigue or aches, high fever, sometimes fatal	Live attenuated	1936
Polio	Viral	Respiratory paralysis, life-long paralysis of limb(s), skeletal deformity, sometimes fatal	Inactivated	1955
			Live attenuated	1962
Pneumococcal	Bacterial	Pneumonia, meningitis, ear infections, infections of bone and heart muscle, sometimes fatal	23-valent polysaccharide	1983
			protein conjugate	2000
Measles	Viral	Diarrhea and severe weight loss in infants, convulsions, pneumonia, ear and brain infections, ulcerations of the eye, sometimes fatal	Live attenuated	1963
Mumps	Viral	Loss of male fertility, loss of pregnancy, meningitis, pancreatitis, brain infection, deafness	Inactivated	1948
			Live attenuated**	1967
Rubella	Viral	incurable congenital malformations, arthritis	Live attenuated***	1969
Varicella (chickenpox)	Viral	stroke in children, skin infections, pneumonia, liver damage, kidney and heart diseases, brain infections, incurable congenital malformations	Live attenuated*	1974
Herpes Zoster	Viral	persistent pain, eye diseases and paralysis and blindness, hearing loss, vertigo, meningitis or brain infections	Live attenuated	2005
Japanese encephalitis	Viral	coma, deafness, loss of feeling, emotional disturbances, sometimes fatal	Inactivated*	1935
			Live attenuated	1988
Rotavirus	Viral	severe dehydration, sometimes fatal	Live attenuated	2006

Tick-borne encephalitis	Viral	permanent neuropsychiatric effects, sometimes fatal	Inactivated	1937
Hepatitis A	Viral	protracted illness and loss of productivity, liver failure, sometimes fatal	Inactivated	1995
Meningococcal	Bacterial	permanent brain damage	Polysaccharide	1971 (US Army) (1981 tetravalent US)
		permanent brain damage	Protein conjugate	1999 (conj C); 2005 (tetravalent)
Haemophilus influenzae type b	Bacterial	meningitis, pneumonia, skin, bone and throat infections, arthritis, sometimes fatal	Polysaccharide	1985
			Protein conjugate	1987
Hepatitis B	Viral	liver failure, cirrhosis, liver cancer, sometimes fatal	Plasma derived	1981
			Recombinant protein	1986
Anthrax	Bacterial	blood poisoning, vomiting blood, sometimes fatal	Protein	1954
Human Papillomavirus	Viral	genital and cervical and oral cancers, genital warts, sometimes fatal	Recombinant protein	2006

15.4.3 Advantages and Disadvantages of Vaccines

Advantages

1. One of the most important advantages of vaccination is the prevention of disease. Many diseases like cowpox, whooping cough, polio, and various types of fevers have been prevented due to mass scale vaccination.
2. Many life-threatening diseases from the human race have been completely eradicated due to vaccination programs that have been carried out broadly.
3. Adoption of vaccination is an economically beneficial task compared to spending the money otherwise for getting medical attention and buying medication.

Disadvantages

The disadvantages of each type of vaccine are already mentioned in the text above. The general disadvantages are given below:

1. New born babies are most susceptible to the infection if their mothers have received vaccines intravenously against diseases. Babies can easily contract diseases such as hepatitis if their mothers have been using such vaccination.
2. Natural immunity lasts longer compared to the artificial immunity that can compromise the ability of the body to defend itself for a long time. For instance, contracting chickenpox can give long lasting resistance against the disease as the antibodies will be suitably evolved to safeguard the body against the genuine infection.
3. There is the risk of the introduction of harmful and toxic chemicals in the body along with vaccine. Few individuals can be very sensitive to these chemicals and may show reaction against the same. The chemicals include:
 - Mercury is a toxic substance that is very dangerous to people.
 - Aluminum has been associated with Alzheimer's disease, dementia and seizures.
 - The simian virus 40 (SV-40) are traceable to the monkey tissue that is used in making the polio vaccine and the same is associated with tumors that are prevalent in children.
 - Formaldehyde is a chemical widely known for causing cancer.

15.4.4 Concerns and Difficulties with Vaccination

- A). Vaccine development has been very difficult for some viruses because of different reasons including:
 - i) Failure to develop attenuated strains. This could be because the virus does not grow well in culture, or because the genes which are required for virulence are also required for the survival of the virus.
 - ii) Inactivated virus is not effective at eliciting an immune response to the native virus. This would occur if the inactivation process changes the structure of the viral antigens.
 - iii) If purified viral proteins do not induce neutralizing antibodies or are not immunogenic. In some cases, they may even be immunosuppressive.
 - iv) The virus rapidly change their genome due to mutation which leads to antigenic drift and/or shifts, so that antigenically distinct strains are constantly arising.

- B). The timing of vaccination is critical because of the presence of maternal Abs obtained either through the placenta to the fetus or from the colostrum. Too high titer of maternal Ab at the time of vaccination will neutralize the immunogen (viral Ag) before an immune response can be elicited. The titer of maternal Ab varies from virus to virus and animal to animal that is why most animals are vaccinated several times.
- C). Moreover, vaccination doesn't help once an animal is already infected, especially with chronic diseases. So there is a need of developing other strategies for treating viral diseases, which is to develop anti-viral drugs.

15.4.5 Composition of Vaccine

In addition to the bulk antigen that is the main ingredient of a vaccine, vaccines are formulated (mixed) with other fluids (such as water or saline), additives or preservatives, and sometimes adjuvants. All together, these ingredients are called excipients. The excipients ensure the quality and potency of the vaccine over its shelf-life. Vaccines are always formulated to be both safe and immunogenic when injected into humans. Vaccines are usually formulated as liquids, but may be lyophilized (freeze-dried) for reconstitution immediately before the time of injection.

15.4.6 The Herd Immunity Imperative

Vaccination secures an individual, yet additionally ensure whole population. At the point when significant number of individuals are inoculated, openings for an episode of sickness become so low that even individuals who aren't vaccinated are likewise advantage. Basically, an infection causing microorganism essentially will not have enough qualified hosts to set up sickness and will ultimately cease to exist totally without duplicating. This phenomenon is known as "herd immunity" or "community immunity," and it eliminating the devastating diseases, even without the need of vaccination of the every individual of a population (Fig. 15.10).

Since few individuals of the population may not be vaccinated due to various reasons such as infants, young children, the elderly, people with severe allergies, pregnant women, or people with compromised immune systems, Herd immunity help these individuals to remain safe because disease causing organism is unable to multiply and cannot get a chance to spread the disease in the whole population.

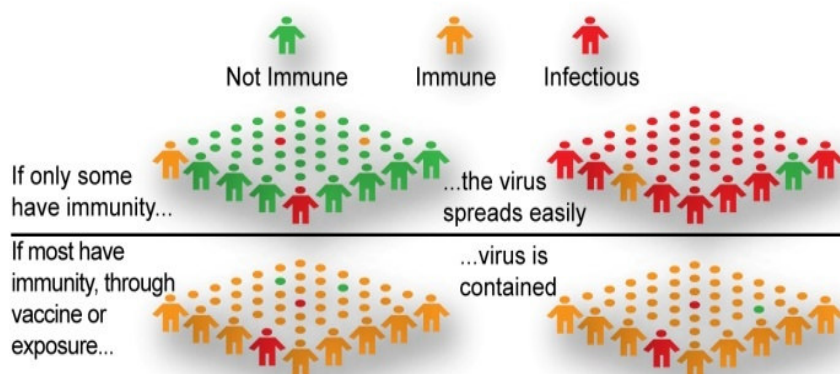


Fig. 15.10: The illustration depicts the herd immunity.

SAQ 3

Match the following disease with its specific types of vaccines.

Diseases	Types of Vaccines
i) Diphtheria	a) Inactive
ii) Small pox	b) Polysaccharide
iii) Hepatitis A	c) Toxoid
iv) Meningococcal	d) Recombinant proteins
v) Hepatitis B	e) Live attenuated

15.5 CLINICAL EVALUATION OF VACCINE**Clinical Evaluation**

A good vaccine must meet the basic criteria of safety, purity, potency, and efficacy. After the product has completed preclinical studies which usually involve animal models and the sponsor is considering clinical trials in humans, an Investigational New Drug (IND) application is submitted to the Food and Drug Administration (FDA).

In Phase I trials short term involves a small number of subjects. Phase I trials are short-term studies and are designed primarily to assess the safety of the candidate vaccine and its ability to induce an immune response (immunogenicity). These studies are usually conducted in individuals at low risk of acquiring natural infection

After the successful completion of phase I trials, phase II trials are conducted, which involve up to hundreds of subjects. For a treatable pathogen, trials can be conducted in susceptible adults under controlled conditions to observe the ability of the vaccine to confer protection against experimental challenge

The results of phase I and phase II studies can provide the information necessary to proceed with phase III trial. Phase III trials involve hundreds to thousands of individuals that are at risk for acquiring the infection or disease.

After a product is licensed phase IV trials may be conducted, as part of post marketing surveillance. Phase IV trials provide information about the safety and effectiveness of the vaccine in the general population, usually under normal (nonstudy) conditions (Table 15.5).

Various types of COVID-19 vaccines:

- **mRNA vaccines** contain material from the COVID-19 causing virus that gives our immune system the instructions to make a protein that is harmless and is unique to the COVID-19 causing virus. The genetic material from the vaccine is destroyed after our cells make copies of the protein. Our immune system prepares our body for

future defense after recognizing the protein of the virus that causes COVID-19 as an antigen and build T-lymphocytes and B-lymphocytes.

- **Protein subunit vaccines** include harmless proteins of the COVID-19 causing virus instead of the entire micro-organism. After vaccination, our recognises the protein as an antigen and develops T-lymphocytes and antibodies that are set up the cells of the body to fight the virus that causes COVID-19 if any individual is infected later on.
- **Vector vaccines** contain a modified version of a different COVID-19 causing virus. Inside the shell of the genetically engineered virus, there is material from the COVID-19 causing virus which is called a “viral vector.” When the viral vector is inside our cells, the hereditary material gives cells the instruction to make a protein that is specific to the virus that causes COVID-19. Utilizing these information, our cells make duplicates of the protein. This prompts our immune system to construct T-lymphocytes and B-lymphocytes that will recall how to fight that infection if any individual is contaminated later on.

Table 15.5: Stages of vaccine trial.

Phase	No of subjects	Purpose
I	5 to 50	Assess safety, immunogenicity, and optimize dose schedule
II	25 to 1,000	Expand safely, immunogenicity, and optimize dose schedule
III	More than 1000	Assess safety
IV	100,000 to millions	Assess safety and effectiveness under Item conditions and detect rare adverse events
SOURCE: Adapted from <i>The Jordan Report</i> , National Institute of Allergy and Infectious Diseases, 1992.		

SAQ 4

How many subjects are there in each phase of the vaccine trial?

15.6 GOVERNMENT SCHEMES FOR VACCINATION

By the Ministry of Health and Family Welfare, Government of India in 1978, introduced an immunization programme called as ‘Expanded Programme of Immunization’ (EPI). After few years in 1985, the programme was modified as ‘Universal Immunization Programme’ (UIP) was carried out in a phased manner to cover all regions in the country by 1989-90 with the one of the

biggest wellbeing program on the world. Although, operational since long time, UIP has covered just 65% of kids for immunization in the first year of their life.

During vaccination under UIP/national immunization programme, Government of India, provides free of cost immunization against vaccine-preventable diseases include diphtheria, pertussis, tetanus, polio, measles, a severe form of childhood tuberculosis, hepatitis B, meningitis and pneumonia (*Hemophilus influenza* type B infections), Japanese encephalitis (JE) in JE endemic districts. New vaccines such as rotavirus vaccine, IPV, adult JE vaccine, pneumococcal conjugate vaccine (PCV) and measles-rubella (MR) played a major role for the same

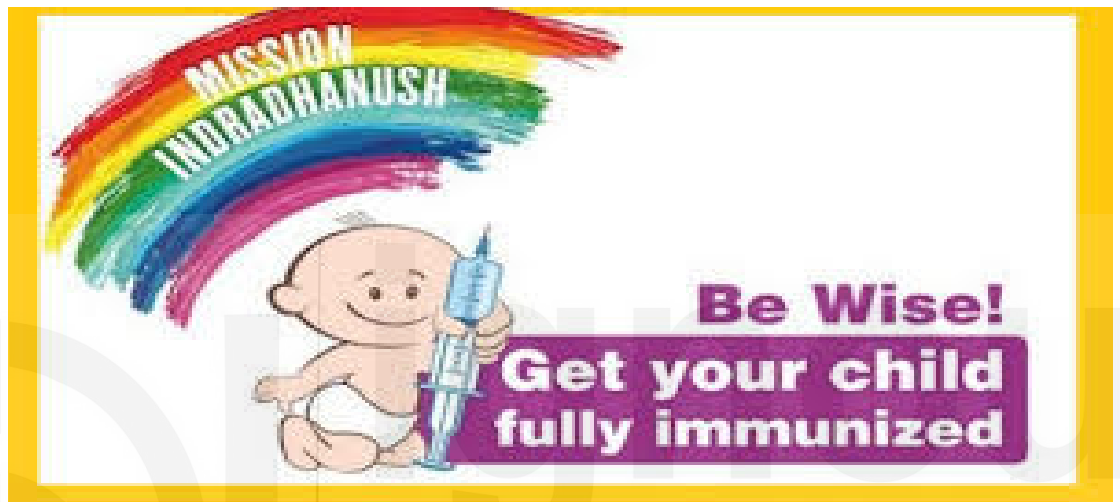


Fig. 15.11: Mission Indradhanush.

Mission Indradhanush: Government of India introduced “Mission Indradhanush” in December 2014 to escalate and once again stimulate the program at a fast speed and to accomplish full immunization of all kids and pregnant ladies. The fundamental objective is to guarantee complete vaccination of kids of two years old and pregnant ladies with every single available vaccine. Till August 2017 four phases of Mission Indradhanush have completed the vaccination of more than 2.53 crore children and 68 lakh pregnant women (Fig. 15.11).

Intensified Mission Indradhanush (IMI): To further strengthen the immunization programme, on October 8, 2017, Prime Minister of India introduced the Intensified Mission Indradhanush (IMI). The focus of IMI programmer is to improve vaccination coverage in high-need regions and urban communities to guarantee full vaccination to over 90% by December 2018.

Intensified Mission Indradhanush 2.0 (IMI2.0): To boost up the routine immunization speed up the vaccination process of children and pregnant women in the identified districts and blocks in the country, the Indian Government has introduced Intensified Mission Indradhanush 2.0 by December 2019-March 2020. The IMI 2.0 aims to achieve the targets of full vaccination coverage in 272 districts in 27 states and at the block level (652 blocks) in Uttar Pradesh and Bihar among hard-to-reach and tribal populations.

15.7 VACCINE HESITANCY

According to the World Health Organization, 'vaccine hesitancy' is one of the 10 threats to global health which highlights that overcoming 'vaccine hesitancy' can reduce the global spread of measles infection. Vaccine Hesitancy is defined as "reluctance or refusal to vaccinate despite the availability of vaccines" and is influenced by factors such as complacency, convenience, and confidence. These are called three Cs of vaccine hesitancy (Fig. 15.12).



Fig. 15.12: A cartoon depicting Vaccine Hesitancy.

SAQ 5

What are factors influence vaccine hesitancy?

Vaccines are very effective in eliminating many infectious diseases and in declining the mortality rates in children. There are vaccines against many infectious diseases, but there are still a few diseases against which vaccines are not developed or are unsuccessful like AIDS, cancer and COVID 19 disease, etc. For some diseases, such as AIDS, vaccine development is challenging because HIV escapes the body's natural immune response. So, there is an urgent need for the successful development of vaccines against such diseases, which requires more advanced techniques.

15.8 SUMMARY

- The vaccine is also defined as a suspension of weakened, killed, or fragmented microorganisms or toxins or antibodies or lymphocytes that is administered primarily to prevent disease.
- The first vaccine was the smallpox vaccine which was invented by Edward Jenner.
- Immunity can be induced by passive or active immunization a) Short-term passive immunization is induced by transfer of preformed antibodies. b) Infection or inoculation achieves long-term active immunization. A state of immunity can be induced by passive or active immunization a) Short-term passive immunization is induced by the transfer of preformed antibodies. b) Infection achieves long-term active immunization.

- Three types of vaccines are currently used in humans: attenuated (avirulent) microorganisms, inactivated (killed) microorganisms, and purified macromolecules.
- Protein components of pathogens that are expressed in cell culture may be effective vaccines
- Recombinant vectors, including viruses or bacteria, which are engineered to carry genes from infectious microorganisms, increase cell-mediated immunity to the encoded antigens.
- Plasmid DNA encoding a protein antigen from a pathogen can act as an effective vaccine inducing both humoral and cell-mediated immunity.
- Government of India has introduced many schemes for the implementation of the vaccine in India with full efficiency. The schemes include Mission Indradhanush, Intensified Mission Indradhanush, and Intensified Mission Indradhanush 2.0.
- Reluctance or refusal to vaccinate despite the availability of vaccines is known as Vaccine Hesitancy.

15.9 TERMINAL QUESTIONS

1. What is vaccination?
2. Differentiate between active and passive immunity.
3. Define herd immunity.
4. Explain DNA vaccine.
5. Based on formulation how many types of vaccines are there and give the example of major preventable diseases of each?
6. Mention the advantages and disadvantages of vaccines?
7. What are the goals of Mission Indradhanush, Intensified Mission Indradhanush and Intensified Mission Indradhanush 2.0?
8. Define vaccine hesitancy?

15.10 ANSWERS

Self Assessment Questions

1. i) Small pox, ii) Edward Jenner, iii) Louis Pasteur, iv) Variolation.
2. i) F, ii) T, iii) T, iv) F, v) T, vi) T.
3. i) c, ii) e, iii) a, iv) b, v) d.

4. Phase I 5-50
Phase II 25-1000
Phase III more than 1000
Phase IV 100,000 to millions
5. Complacency, Convenience and Confidence

Terminal Questions

1. Vaccination is the process whereby a person is made immune or resistant to an infectious disease, by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection or disease.
2. Refer to Table 15.2, Section 15.3.3.
3. Herd immunity is when a large part of the population is immune to a specific disease. When enough people are immunized, opportunities for an outbreak of disease become so low even people who aren't immunized get the benefit.
4. A DNA vaccine uses a gene from a virus or bacteria to stimulate the immune system. Plasmid DNA which encodes antigenic proteins is directly injected into the muscle of the recipient. DNA is taken up by the muscle cells and the encoded protein antigen is expressed, leading to both a humoral antibody response and a cell-mediated response.
5. Whole organism vaccine

inactivated	Rabies
live attenuated	Smallpox
Purified macromolecules	
Polysaccharide	<i>Pneumococcal pneumonia</i>
Toxoid	Tetanus
Protein conjugate	<i>Haemophilus influenza</i> , type II
Recombinant vaccine	Hepatitis B
DNA vaccine	DNA vaccines for influenza and herpes are currently in human testing.
Subunit vaccines	Influenza

6. Refer to Section 4.3.
7. Mission Indradhanush: The main goal of Mission Indradhanush is to ensure complete vaccination with all available vaccines for children up to two years of age and pregnant women.

Intensified Mission Indradhanush: to reach each and every child up to two years of age and all those pregnant women who have been left uncovered under the routine immunization programme/UIP.

Intensified Mission Idradhanush 2.0: The goal of IMI 2.0 is to achieve targets of full vaccination coverage in 272 districts in 27 states and at the block level (652 blocks) in Uttar Pradesh and Bihar among hard-to-reach and tribal populations.

8. Vaccine Hesitancy is defined as “reluctance or refusal to vaccinate despite the availability of vaccines”



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Acknowledgement of Figures

Fig. 13.1: M.R. Ngasainao, Self drawn

Fig. 13.2: *M.R. Ngasainao – Self drawn*

Fig. 13.3: *M.R. Ngasainao – Self drawn*

Fig. 13.4: *M.R. Ngasainao – Self drawn*

Table 13.1: *Self prepared M.R. Ngasainao*

Fig. 15.1: <https://www.informedhealth.org>

Fig. 15.6: Basic Concept of Vaccination, Vaccine Factbook, 2012.
<http://www.pharma-jp.org>

Fig. 15.7: Basic Concept of Vaccination, Vaccine Factbook, 2012.
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Fig. 15.8: Basic Concept of Vaccination, Vaccine Factbook, 2012.
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Fig. 15.9: <https://www.businessindustryreports.com>

Fig. 15.11: <https://www.nhp.gov.in/mission-indradhanush1>

Fig. 15.12 vajiramias.com/current-affairs/vaccine-hesitancy/5d8306a01d5def2711d433db/.

Fig. 15.17: vajiramias.com/current-affairs/vaccine-hesitancy/5d8306a01d5def2711d433db/).

GLOSSARY

- Abzyme** : A monoclonal that has catalytic activity.
- Active immunity** : Adaptive immunity that is induced by natural exposure to a pathogen or by **vaccination**.
- Acute phase protein** : One of a group of serum proteins that increase in concentration in response to inflammation. Some **complement** components and **interferons** are acute phase proteins.
- Adaptive immunity** : Host defenses that are mediated by B cells and T cells following exposure to antigen and that exhibit specificity, diversity, memory, and self-nonself discrimination.
- Adjuvants** : Factors that are added to a vaccine mixture to enhance the immune response to antigen by activating innate immune cells. Dead mycobacterium were among the original adjuvants, but more refined preparation include alum, cytokines, and/or lipids.
- Autoimmunity** : An abnormal immune response against self antigens.
- Carcinoma** : Tumor arising from endodermal or ectodermal tissue (e.g., skin or epithelium) Most cancers (>80%) are carcinomas.
- Cell adhesion molecules (CAMs)** : A group of cell surface molecules that mediate intercellular adhesion. Most belong to one of four protein families: the **integrins**, **selectins**, mucin-like proteins, and **immunoglobulin superfamily**.
- Cross-reactivity** : Ability of a particular antibody or T-cell receptor to react with two or more antigens that possess a common epitope.
- Cross-tolerance** : The induction of CD8⁺ T cell tolerance to an antigen processed and presented via cross-presentation.
- Early B-cell factor (EBF)** : A transcription factor that is essential for early B-cell development. It is necessary for the expression of RAG.
- Endogenous pathway** : Intracellular route taken by antigen that is processed for presentation by MHC class I, typically associated with proteins generated in the cytosol.
- Haplotype** : The set of **alleles** of linked genes present on one parental chromosome; commonly used in reference to the **MHC** genes.

Herd immunity	: When the majority of the population is immune to an infectious agent, thus significantly reducing the pathogen reservoir due to the low chance of a susceptible individual contacting and infected individual.
Hypersensitivity	: Exaggerated immune response that causes damage to the individual. Immediate hypersensitivity (types I, II, and III) is mediated by antibody or immune complexes, and delayed-type hypersensitivity (type IV) is mediated by T _H cells.
Idiotypic	: The set of antigenic determinants (idiotopes) characterizing a unique antibody or T-cell receptor.
Immunoglobulin (Ig)	: Protein consisting of two identical heavy chains and two identical light chains, that recognize a particular epitope on an antigen and facilitates clearance of that antigen. There are 5 types: IgA, IgI, IgE, IgG, and IgM. Also called antibody .
Intravital (Ii) chain	: Component of the class II MHC protein that shows no genetic polymorphism. The Ii chain stabilizes the class II molecule before it has acquired an antigenic peptide.
Kappa (k) light chain	: One of the two types of immunoglobulin light chains that join with heavy chains to form the B cell receptor and antibody heterodimer. Lambda (λ) is the other type.
Leukotrienes	: Several lipid mediators of inflammation and type I hypersensitivity, also called slow reactive substance of anaphylaxis (SRS-A). They are metabolic products of arachidonic acid.
Lymph	: Interstitial fluid derived from blood plasma that contains a variety of small and large molecules, lymphocytes, and some other cells. It circulates through the lymphatic vessels.
Lymphoma	: A cancer of lymphoid cells that tends to proliferate as a solid tumor.
Mucosal-associated lymphoid tissue (MALT)	: Lymphoid tissue situated along the mucous membranes that line the digestive, respiratory, and urogenital tracts.
Mutational hot spots	: DNA sequences that are particularly susceptible to somatic hypermutation. Found in the variable regions of the immunoglobulin heavy and light chains.
Myeloma	: A malignant tumor arising from cells of the bone marrow, specifically B cells.

- Nod-like receptors (NLR)** : Family of cytosolic pattern-recognition receptors with nuclear-binding/oligomerization and leucine-rich repeat domains; they have a nuclear-binding domain.
- Passive immunity** : Temporary adaptive immunity conferred by the transfer of immune products, such as antibody (antiserum), from an immune individual to a nonimmune one. See also **active immunity**.
- Pathogen** : A disease-causing infectious agent.
- Phagocytes** : Cells with the capacity internalize and degrade microbes or particulate antigens; neutrophils and monocytes are the main phagocytes.
- Plasmin** : A serine protease formed by cleavage of plasminogen. Its major function is the hydrolysis of fibrin.
- Pre-B-cell receptor** : A complex of the Ig α , Ig β heterodimer with membrane-bound Ig consisting of the μ heavy chain bound to the **surrogate light chain** Vpre-B/ λ 5.
- Pre-B cell (precursor B cell)** : The stage of B-cell development that follows the pro-B- stage. Pre B-cells produce cytoplasmic μ heavy chains and most display the **pre-B-cell receptor**.
- Pseudogene** : Nucleotide sequence that is a stable component of the genome but is incapable of being expressed. Pseudogenes are thought to have been derived by mutation of ancestral active genes.
- Retrovirus** : A type of RNA virus that uses a reverse transcriptase to produce a DNA copy of its RNA genome. HIV, which causes AIDS, and HTLV, which causes adult T-cell leukemia, are both retroviruses.
- T-cell receptor (TCR)** : Antigen-binding molecule expressed on the surface of T cells and associated with the **CD3** molecule. TCRs are heterodimeric, consisting of either an α and β chain or a γ and δ chain.
- T-dependent (TI) response** : An antibody response elicited by a T-dependent antigen.
- T-independent (TI) response** : An antibody response elicited by a T-independent antigen.
- Thymus** : A primary lymphoid organ, in the thoracic cavity, where T-cell maturation takes place.
- TI interferons** : A group of cytokines belonging to the Interferon family of cytokines that mediates anti-viral effects. Type I interferons are released by many different cell types and are considered part of the innate immune system.

Type II hypersensitivity	: A pathologic immune reaction to non-infectious antigens mediated by IgG and IgM, which recruit complement or cytotoxic cells. It underlies blood transfusion reactions, Rh factor responses, and some hemolytic anemias.
Type II interferon	: A cytokine belonging to the interferon family that is normally secreted by activated T cells. Also known as Interferon γ .
Type III hypersensitivity	: A pathologic immune reaction to non-infectious antigens mediated by antibody-antigen immune complexes. It underlies damage associated with several disorders, including rheumatoid arthritis and systemic lupus erythematosus.
Type IV hypersensitivity	: A pathologic immune reaction to non-infectious antigen mediated by T cells. It underlies the response to poison ivy.
Vaccine	: A preparation of immunogenic material used to induce immunity against pathogenic organisms.
Variable (V) region	: Amino-terminal portions of immunoglobulin and T-cell receptor chains that are highly variable and responsible for the antigenic specificity of these molecules.
Variable (V₁)	: The variable region of an antibody light chain .
Viral load	: Concentration of virus in blood plasma; usually reported as copies of viral genome per unit volume of plasma.