Cellular and Molecular Immunology

Module1: Introduction

Lecture 1: Introduction

The term immunity comes from the Latin word immunitas, means protection from legal prosecution. Immunity refers to protection from disease and other pathogens. The cells and molecules responsible for immunity are called **immune system** and their efforts in regards to any etiological agent are called **immune responses**. Normally the immune responses are elicited against the foreign substances but occasionally to the self molecules and are referred as autoimmune responses. **Immunology** is a branch of life-science which deals with the cellular and molecular events occurring in the body after encounters of micro-organisms and other foreign substances.

The history of immunology is quite old. In ancient China, people often used skin lesions of patients recovered from small pox to cure small pox in young children. The first successful record of vaccination came from the work of Edward Jenner's efficacious vaccination against smallpox. Jenner observed that milkmaid who had recovered from cowpox never showed any symptom of smallpox. Following this observation he inoculated the cowpox pustules into the arm of a young boy who later did not show full progressive smallpox symptoms. Small pox was the first disease that was eradicated worldwide by vaccination.

Recently the science of immunology has grown up by the advent of new molecular biology tools. Our current understanding of the human and animal immune system and its functions has remarkably improved. Advances such as recombinant DNA technology, immunohistochemistry, monoclonal antibody production and x-ray crystallography have changed the immunology to a broader area. The development of techniques to produce transgenic and knockout mice has also played a great role to understand many complex immunological pathways.

1.1Innate and adaptive immunity

Defense against microbes includes an early response action called **innate immunity** and a later response called as **adaptive immunity.** Innate immunity is also called **natural or native** immunity and provides first line of defense against any microbial infection in human body. It usually involves many cellular and biochemical events that react to microbes and their products in order to clear them from the body. The main components of innate immune system are

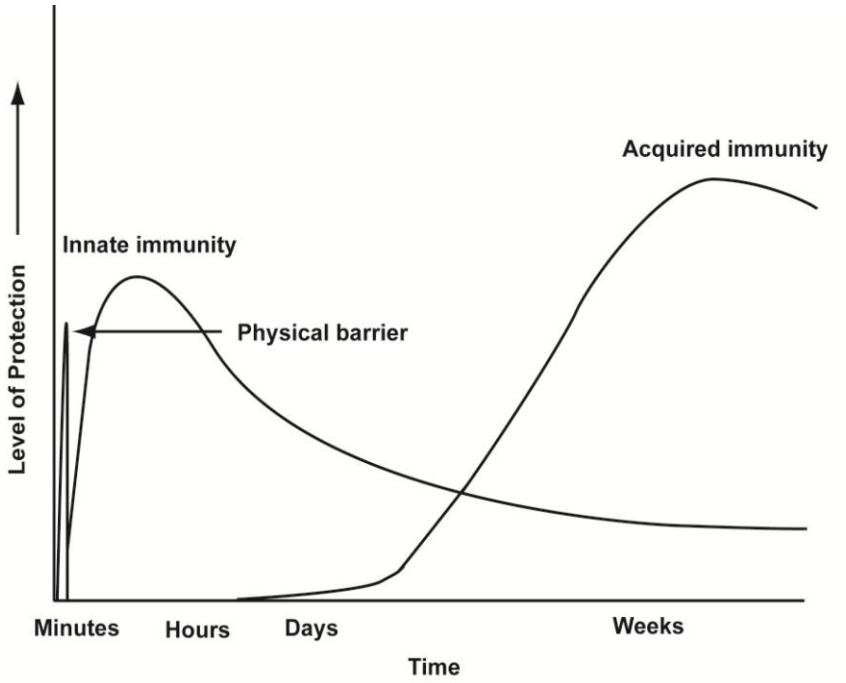
1) Barriers – skin and outer epithelial surface.
2) Scavenger cells – neutrophils, macrophages, dendritic cell and natural killer cells.
3) Complement system
4) Cytokines
5) Chemical mediators of inflammation

Microbial agents and pathogens contain some molecules over their surface that act as foreign substance for the body and are collectively called as **pathogen associated molecular pattern** (PAMP). PAMP's are recognized by specific proteins and biochemical molecules produced by cells of innate immunity and these recognition molecules are called as **pattern recognition receptors**. The innate immune responses are produced against the specific structures present over the microbes and are common to many of them. Thus, they cannot distinguish the minute differences among microbes.

In contrast, adaptive immunity is stimulated by constant exposure of infectious agents. The most characteristic feature of adaptive immunity is **memory** against the repetitive exposure of same pathogen. Furthermore, it has a capacity to distinguish between fine differences among microbes and hence also called as **specific immunity**. As specific immunity is gathered by constant exposure to the foreign agent, it is better termed as **acquired immunity**. The central components of adaptive immunity are

1) Lymphocytes and their secreted products e.g. **antibodies**
2) Foreign substances that trigger specific immune responses and are identified by lymphocytes or antibodies are called as **antigens**.

Figure1.1 Graph showing the relation between innate and acquired immunity:



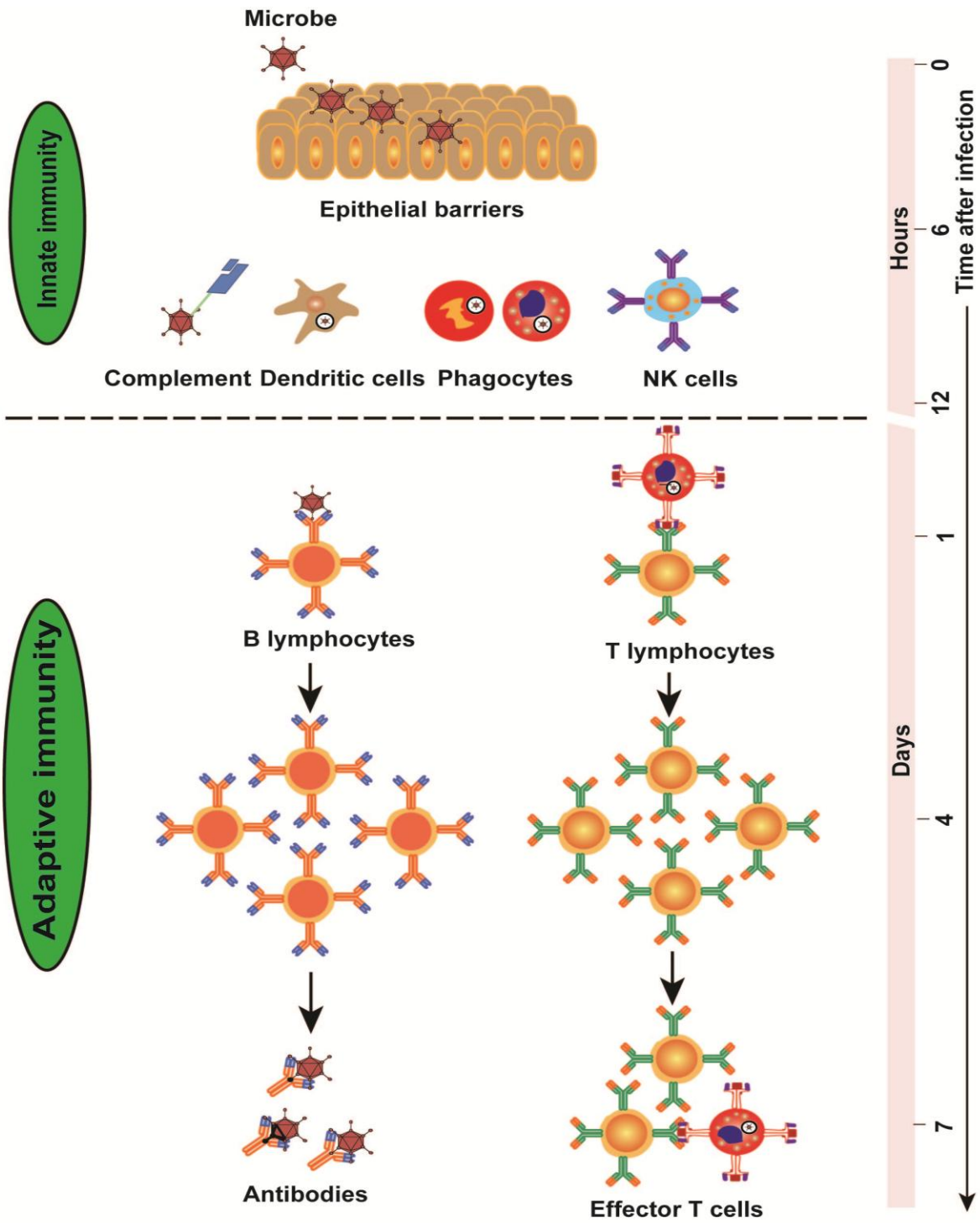
Almost all the higher organisms have well developed mechanisms for defending against the microorganisms. Innate and adaptive system work together as they are the components of host integrated system. However there are many microbes that have developed and adapted to resist the innate immunity and hence more robust mechanisms are required for their expulsion. Innate and adaptive immune systems are interlinked; stimulation of anyone against the foreign substances instigates the other and hence functions cooperatively.

Table 1.1 common features of innate and adaptive immunity:

Features	Innate	Adaptive
Specificity	Molecules present in a group of related microbes	Microbes and nonmicrobial molecules
Memory	No	Yes
Diversity	Narrow	Wide
Reactivity against self	No	No
Part of innate and adaptive system		
Barrier	Skin, epithelial surface	Lymphocyte and antibodies
Proteins	Complements	Antibodies
Cells	Phagocytes	Lymphocytes

The mechanism of innate immunity provides an initial defense against the infection. Adaptive immune responses develop later and consist of lymphocytes.

Figure 1.2 Innate and adaptive immunity:



Lecture 2: Properties of Immune system

2.1 Cells of the immune system

Cells of the immune system are present as circulating cells in the blood and lymph. They are distributed to almost every organ and tissue of the animal body. Their distributions upon exposure to an external agent or pathogens are utmost important in the generation of effective immune response. At beginning, the immune system must respond to the entering pathogen followed by an adaptive immune response by specific lymphocyte. Finally, the cells of adaptive immune response destroy the pathogens by the effector cells.

Followings are the major cells of immune system

2.1.1 Macrophages and Phagocytes- They are present in virtually every tissue and organ of the body and respond instantaneously to the entering pathogens. The job of phagocytic cells involves recruitment of cells at the site of infection, ingestion, and destruction of the pathogens.

2.1.2 Neutrophils- These are the granulocytes present in the blood stream and are the first line of the defense in the body. They are the most abundant cells present in the blood stream. They are about 12-15 µm in diameter with projection on their surface. The nucleus of neutrophils contains 3-5 lobes (polymorphonuclear cells). The cytoplasm of the neutrophils contains the granules that are filled with enzymes like lysozyme, collagenase, and elastase. They are stained with neutral dyes and produced in the bone marrow. The production of neutrophils is stimulated by granulocyte colony stimulating factors (G-CSF). On an average about 10^{11} cells/day are produced in a normal human individual. Usually neutrophils are recruited at the site of infection immediately following the invasion of the foreign substance, if not they undergo apoptosis and get cleared from the circulation. The other two granulocytes present in the blood are basophils and eosinophils which are stained by basic (hematoxylin) and acidic (eosin) dye, respectively.

2.1.3 Mononuclear phagocytes- They play a central role in the innate and adaptive immune system. They are formed by precursor hematopoietic cells and are called monocytes. They are about 10-15 µm in diameter and have bean shaped nuclei. Once enter into the circulation they are called macrophages. The major function of macrophage includes following

1. To ingest and kill the microbes.
2. To ingest and clear dead cells and unused cells.
3. They secrete cytokines upon activation.
4. They serve as antigen presenting cells to display the antigens to the T lymphocyte.
5. They also help in angiogenesis (formation of blood vessels).

2.1.4 Mast cells- These are derived from bone marrow cells and contain histamine and other chemical mediators of allergic diseases. Mast cells express the receptors for IgE and IgG antibodies. They also provides defense against helminth infection.

2.1.5 Basophils- They are structurally and functionally similar to mast cells and mediate allergic conditions. The granules of basophils contain acidic proteins which bind to basic dyes (hematoxylin)

2.1.6 Eosinophils- They are granulocytes present in the blood and contains the enzyme required to damage the cell wall of the parasite. The granules of the eosinophils contain the basic proteins which bind to acidic dye (eosin).

2.1.7 Dendritic cells- They are the specialized antigen presenting cells which captures the microbes and microbial antigens, and transport them to lymphoid tissues to be recognized by lymphocytes. They activate the naive T cells and form a bridge between innate and adaptive immune response. They are widely distributed into many organs and epithelial surface. Plasmacytoid dendritic cells are the subpopulation of dendritic cells involved in the recognition of the virus infected cells.

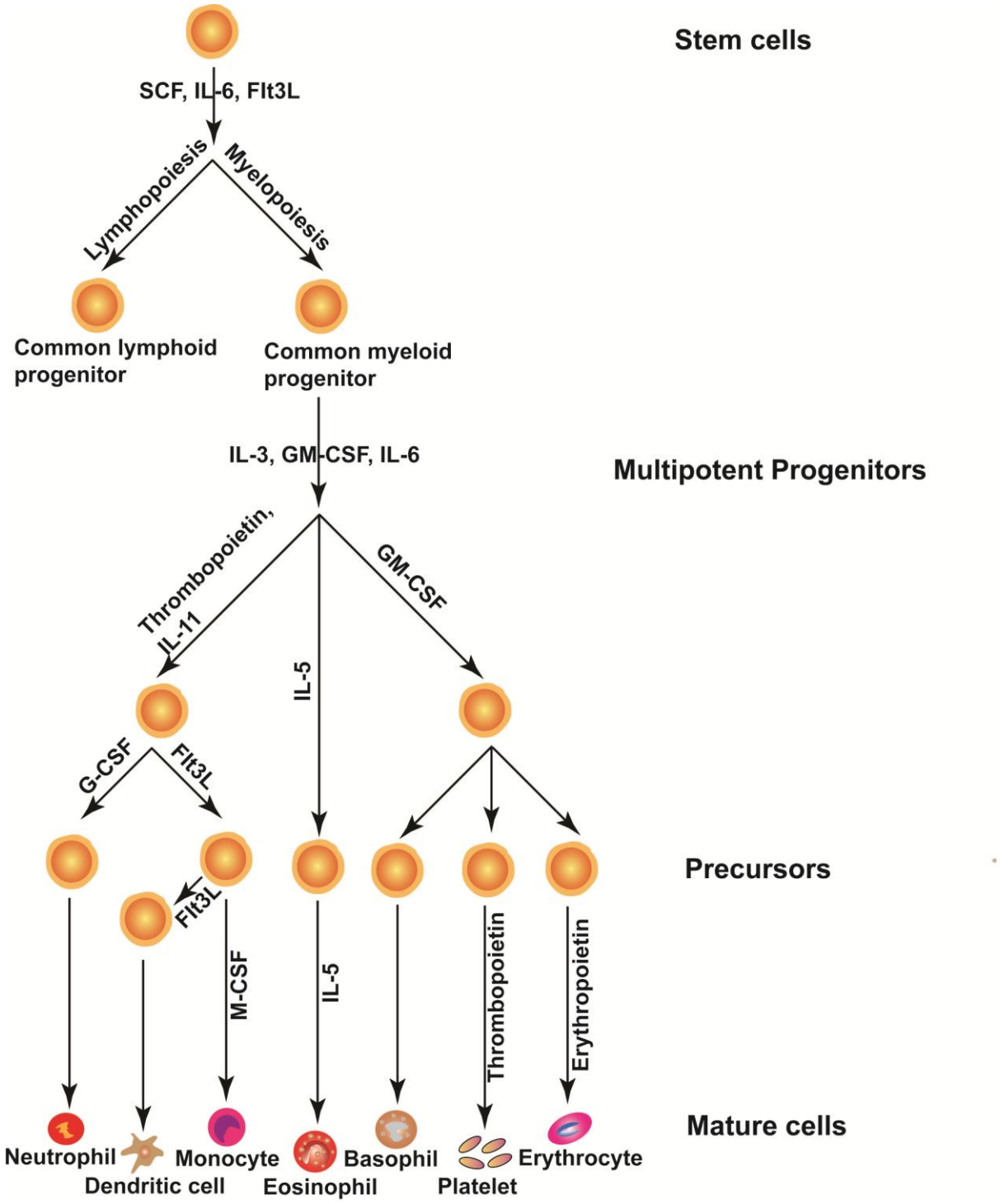
2.1.8 Naïve lymphocytes- The lymphocytes that are not previously encountered with antigens are called as Naïve lymphocytes. They trigger the adaptive immune response after encountering with the antigen.

2.1.9 Lymphocytes- These are the cells of the adaptive immune system. There are two subsets of the lymphocytes.

a) B lymphocyte- Involved in the production of the antibodies (bursa of Fabricius derived lymphocyte). The two major subsets of the B lymphocytes are follicular B cells and marginal B cells.
b) T lymphocyte- Involved in the production of cellular immune response (Thymus derived lymphocyte). The two major subsets of the T lymphocytes are CD4+ and CD8+ cells.

2.1.10 Effector and memory lymphocytes- They circulate through the normal blood stream and are responsible for systemic immunity against a particular pathogen. The memory cells are important for providing protection against second exposure of the antigens. They are produced in the body during their first encounter with the antigen and expand following their repeated exposure.

Figure 2.1 Overview of hematopoiesis:



2.2 Anatomy of lymphoid tissues and organs

In order to properly activate the immune system following antigen-antibody interaction, the immune cells need to be localized to a specific area where they properly express the receptors for Ag recognition and attain maturity. **Bone marrow** and **thymus** are the **central** or **primary** lymphoid organs which produce B and T lymphocytes, respectively. B and T lymphocytes are produced in the primary lymphoid organs and complete its functional maturation in the **peripheral** or **secondary** lymphoid organs such as **spleen** and **lymph node**. Two important functions shared by the primary lymphoid organs are to

i) Provide growth factors required for maturation of lymphocytes.

ii) Present self antigens for recognition and selection of maturing lymphocytes.

2.2.1 Bone marrow

Bone marrow is the major site for the generation of circulating RBC, granulocyte, monocytes and B cells. All the cells are formed in the bone marrow by the process of **hematopoiesis** by hematopoietic stem cells (HSC) during fetal stage. HSCs give rise to the common lymphoid and common myeloid progenitor cells under the influence of interleukin-6 (IL-6), stem cell factor (SCF), and fms-like tyrosine kinase receptor-3 ligand (Flt3L). The common lymphoid progenitor is the source of T cells, B cells, and natural killer (NK) cells. Majority of the B cell maturation takes place in the bone marrow, but the final maturation completes in the secondary lymphoid organs (spleen). T cell maturation occurs entirely in the thymus while NK cell maturation occurs entirely in the bone marrow. The common myeloid progenitors give rise to the lineages of erythroid, granulocytic, megakaryocytic, and monocytic cells, which give rise to mature red blood cells, granulocytes (neutrophils, eosinophils, and basophils), platelets, and monocytes, respectively. Monocytic lineage give arise to dendritic cells.

2.2.2 Thymus

The thymus gland is the site for the maturation of T lymphocytes. It is situated in the anterior side of mediastinum and bilobed in shape. The thymus is divided into outer cortex which is densely filled with T lymphocyte and inner medulla which are sparse in lymphocyte population. Interleukin- 7, secreted by the cortical cells is responsible for the

development of T lymphocytes. Medulla of thymus contains Hassall's corpuscles which are supposed to be the remnants of the degenerating epithelial cells.

2.2.3 Lymphatic system

This consists of specialized vessels which drain fluids from tissues and lymph node into the blood circulation. The skin, epithelial cells, and lymphatic capillaries absorb the fluid called lymph, present in the tissue spaces and drain it into the blood vessels. The lymphatic system collects the microbial antigens from the entry point and delivers it to the lymph node to activate the adaptive immune response. The antigens are captured and transported to the lymphoid organs during their initial encounter. Antigens are displayed by the antigen presenting cells in the lymphoid tissue and presented to the lymphocytes.

a) **Lymph nodes** are the organs that carry the lymph and help in the activation of adaptive immune response. The segregation of B and T lymphocyte depends on the cytokines secreted by the lymph node.

b) **Spleen**

   Spleen is also called as grave yard of red blood cells. It is made up of **red pulp** which is full of blood cells and **white pulp** rich in lymphocyte. The white pulp helps to stimulate adaptive immune response against blood borne antigens. The white pulp area is divided into T cell and B cell zone. The T cell zone is also the resident area for mature dendritic cells which activates the naïve T cells upon antigen stimulation. Follicular dendritic cells reside in the B cell zone and activate the humoral immune response.

2.2.4 Other lymphoid tissues

Skin, gastrointestinal mucosa, and respiratory epithelium mucosa have their own lymph nodes. The lymphoid tissues associated with the gastrointestinal tract are called **gut associated lymphoid tissues** (GALT) while bronchial mucosa associated lymphatic tissues are called **mucosa associated lymphoid tissues** (MALT).

2.3 Cytokines and chemical mediators of immune system

Cytokines are the proteins secreted by different cell types and are the regulators of cell cycle and various aspects of innate and adaptive immunity. On an average human genome contains more than 180 genes that encode different kinds of cytokines. The nomenclature of cytokines is mostly based on their biological activity (e.g. interferon). By analogy many cytokines which were thought to be made by leucocytes are called as **interleukins**. The productions of cytokines are transient and are not stored for long period of time. Once needed, they are synthesized and secreted out for their biological effect and degraded rapidly upon completion of their assigned job. Cytokines are **pleiotropic** in nature which means one cytokine can do multiple biological actions. Cytokines may be **redundant** which means many cytokines can do similar kind of biological activity.

Many cytokines act close of their production, either on the same cell called **autocrine** or to the nearby cells called **paracrine** action. Cytokines may enter into the circulation from their site of production to act on distant organ; the property is called as **endocrine** action.

Lecture 3: Innate immune system (Part I)

Innate immunity is the first line of defense against any invading pathogen. Innate immune system is remarkably conserved among animals, plants and insects, suggesting common source of origin and their diversion during the course of evolution. Families of receptors called Toll like receptors are found in every form of life from insects up to mammals. Major signal transduction pathway that activates the Toll-like receptors in mammals are called NF-κB pathway.

3.1 Important functions of innate immunity

Controls and eliminates the infection at the entry point itself.

Eliminate the infected cells and correct the damage by tissue repair.

Stimulates adaptive immune response

3.2 Immune response to microbes

The early innate immune response is the first check point for any microbe that enters the body through different portals (skin, blood, aerosol and mucous membrane). If pathogen enters successfully inside the body the innate immune response counter attacks the pathogens. The major way of innate immunity interventions are inflammation and antiviral defense.

3.2.1 Inflammation

Inflammation is the migration of leukocytes, plasma proteins, and blood to the area of breach. They are recruited to the site of injury and destroy the evading pathogens by the help of cytokines and phagocytic cells (neutrophils, macrophages, monocytes). The mechanism of killing may involve formation of free oxygen and nitrogen radical by the phagocytes. The effect of inflammation in the body has some cardinal features which are described as rubor, calor, dolor, tumor, and functio laesa.

Rubor- Redness (because of increased blood supply).

Calor-Heat ((because of increased blood supply).

Dolor- Pain (because of the P substance produced following the secretion of cytokines).

Tumor- swelling (due to accumulation of fluid).

Functio laesa - Loss of function.

3.2.2 Antiviral defense

These are the responses against viral infection and are mediated by cytokines and natural killer cells. Pathogens which are able to survive against inflammation and antiviral defense in turns enter into blood circulation. Blood contains another important component of innate immunity called complements. The pathogens are destroyed by typical classical and alternate pathways of the complement system (lecture 4). The innate immune responses many time fails to eradicate the pathogens. In those cases the immune system is evolved with more robust and powerful cells and antibodies of adaptive immune system.

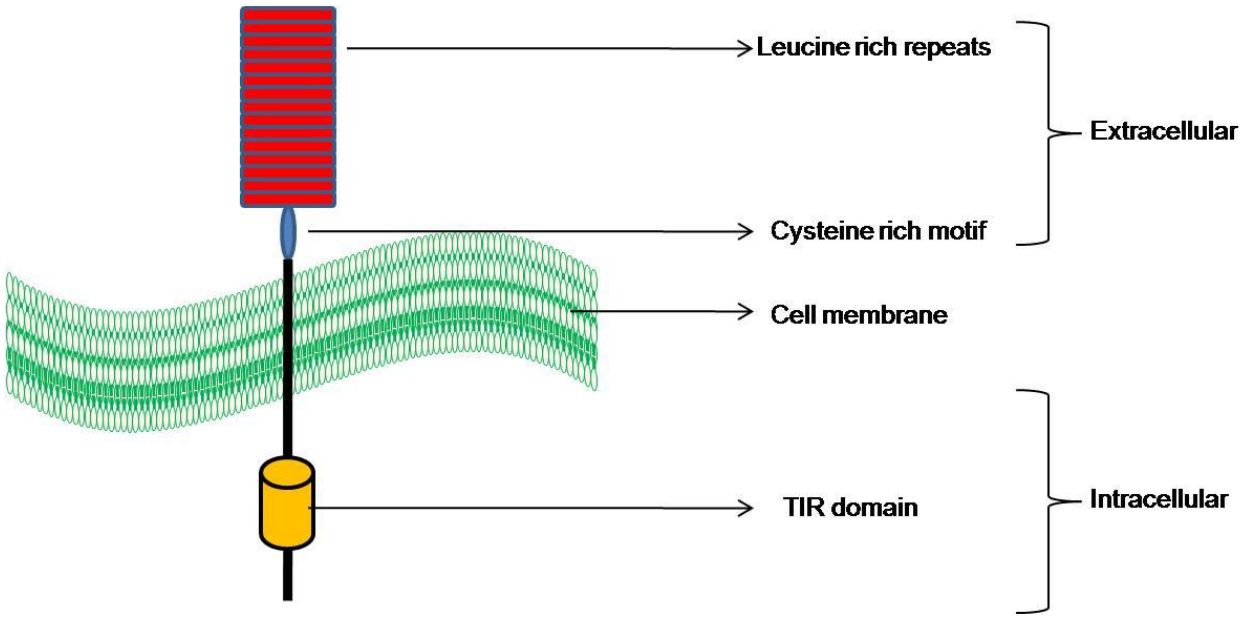
3.3 Recognition system of innate immunity

Innate immune system recognizes the structures present on the microbial pathogens and are collectively called **pathogen associated molecular pattern** (PAMP). Similarly innate immune system also recognizes the molecules produced by the damaged cell and are collectively called **damage associated molecular pattern** (DAMP). The PAMP and DAMP are collectively called **pattern recognition receptors**. The receptors for innate immune system are developed at the level of germline (adaptive are generated by somatic recombination). The innate immunity does not react with the normal and healthy cells.

3.4 Toll like receptors

Toll like receptors (TLRs) are the families of PAMP expressed in many cell types and are involved in the recognition of various kind of antigens. The gene for TLR was first discovered in Drosophila. There are nine different kinds of TLRs (TLR1-9) each recognizing different antigenic molecules. TLR contains leucine repeats and cysteine rich motif at their extracellular domain while intracellular domain contains toll IL-1 receptor (TIR). The extracellular part of TLR is involved in ligand binding while the intracellular domains are involved in the downstream signaling cascade.

Figure 3.1 Structure of Toll like receptor:



TLRs are found in the cell surface as well as inside the cells and hence are able to recognize a wide variety of antigens. TLR-1, -2, -4, -5 and -6 are expressed over the surface of plasma membrane while TLR-3, -7, -8, and -9 are expressed inside endosomal membrane (Figure 3.2). Different TLRs can recognize different antigens as listed below.

TLR-1 Bacterial lipoprotein

TLR-2 Bacterial peptidoglycans

TLR-3 Double stranded RNA

TLR-4 Lipopolysaccharides

TLR-5 Bacterial flagella

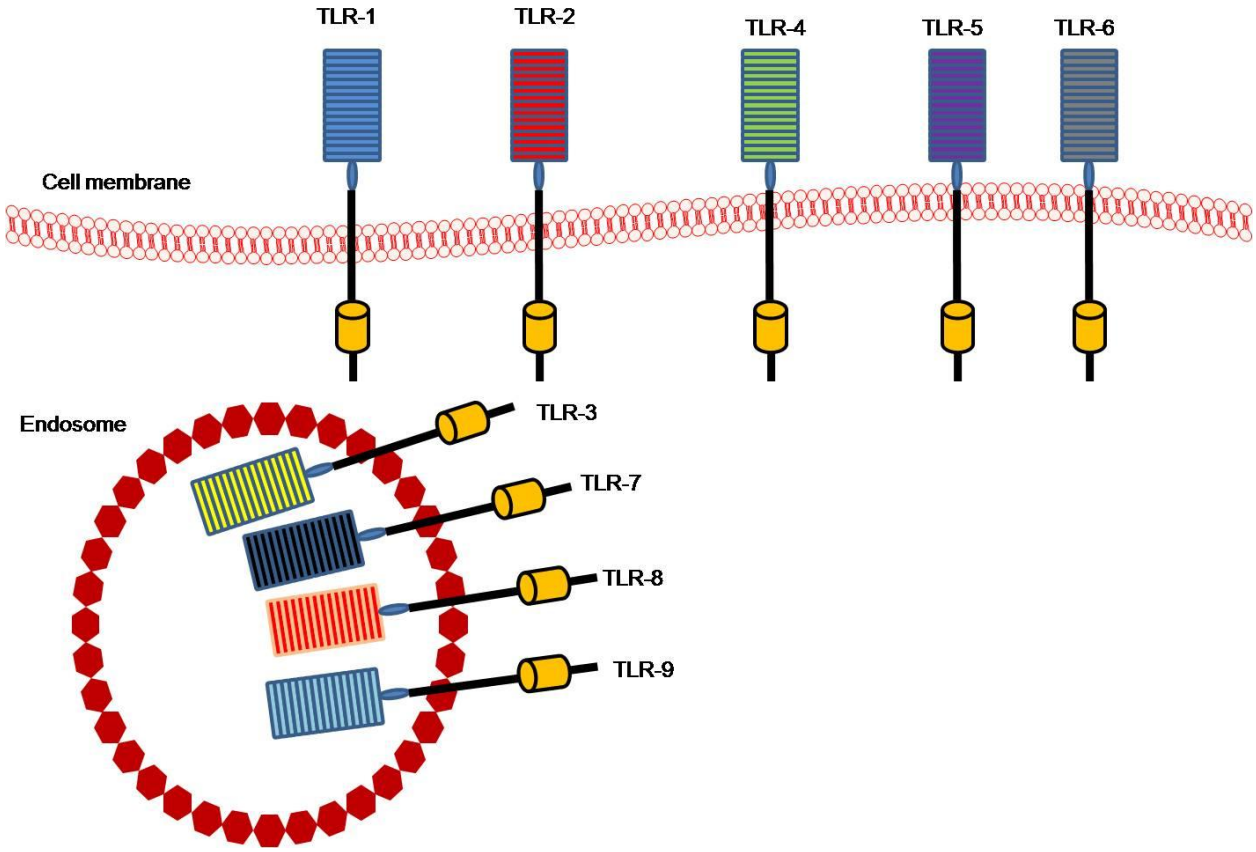
TLR-6 Bacterial lipoprotein

TLR-7 Single stranded RNA

TLR-8 Single stranded RNA

TLR-9 CpG DNA

Figure 3.2 Location of Toll like receptor:



Signaling pathway of TLR activation begins with the ligand binding either on the cell surface or in the endosome. The binding of ligand to TLR leads to dimerization of the TLR which further recruits the adaptor proteins such as MyD88. The adaptor proteins then activate the transcription factor such as NF-κβ, activation protein-1, interferon response factor-3 (IRF-3) and IRF-7. NF-κβ and activation protein-1stimulates the production of inflammatory cytokines (TNF and IL-1) while IRF-3 and -7 promote the production of type-I interferon.

Lecture 4: Innate immune system (Part II)

4.1 Receptors for PAMPs and DAMPs present in cytosol

In addition to membrane bound TLR many receptors are present in the cytosol which can sense the invading antigenic structures.

Nucleotide oligomerization domain (NOD) like receptors present in the cytosol is specialized to sense PAMP and DAMP and recruit the chemical mediators of inflammation. NOD1 can sense invading gram negative bacteria while NOD2 can recognize the muramyl dipeptide from both gram positive and negative bacteria.

Retinoic acid-inducible gene-I (RIG-I) like receptors are another sensors present in the cytosol which are specific against viral RNA and induce the production of type I interferon.

Carbohydrates present on the surface of microbes are recognized by **C-type lectin** receptors and facilitate their phagocytosis. Similarly, **mannose receptors** are also playing an important role in sensing the carbohydrate entity present over the surface of many microorganisms. Another group of receptor called **dendritic cell-associated C type lectin-1**(Dectin-1) and dectin-2 are important sensors of fungal antigens.

In addition, many cell types express different receptors involved in the phagocytosis of the antigens. **Scavenger receptors** present over the surface of macrophages senses specifically the oxidized lipoproteins from bacterial cell. **N-formyl met-leu-phe receptors** are expressed over the surface of neutrophils and macrophages and are involved in the recognition of the N formylmethionyl residues of bacterial origin.

4.2 Cellular components of innate immune system

Many different cellular components are involved in the proper functioning of the body innate immune system.

4.2.1 Epithelial cells

Epithelial cells over the skin surface are the physical barriers for the invading pathogens. Epithelial cells produce antimicrobial substances such as **defensins** and **cathelicidins** which also hinder the entry of pathogens. Epithelial barriers include skin, gastrointestinal and respiratory mucosa. Intraepithelial T lymphocytes present in the skin and gastrointestinal tract can respond to the encountering pathogens.

4.2.2 Phagocytes

Macrophages and neutrophils are the first line of defense against the pathogens and are specialized in phagocytic function. Usually phagocytic cells are involved in killing of the microbes and secretion of cytokines that mediate the inflammatory response.

4.2.3 Dendritic cells

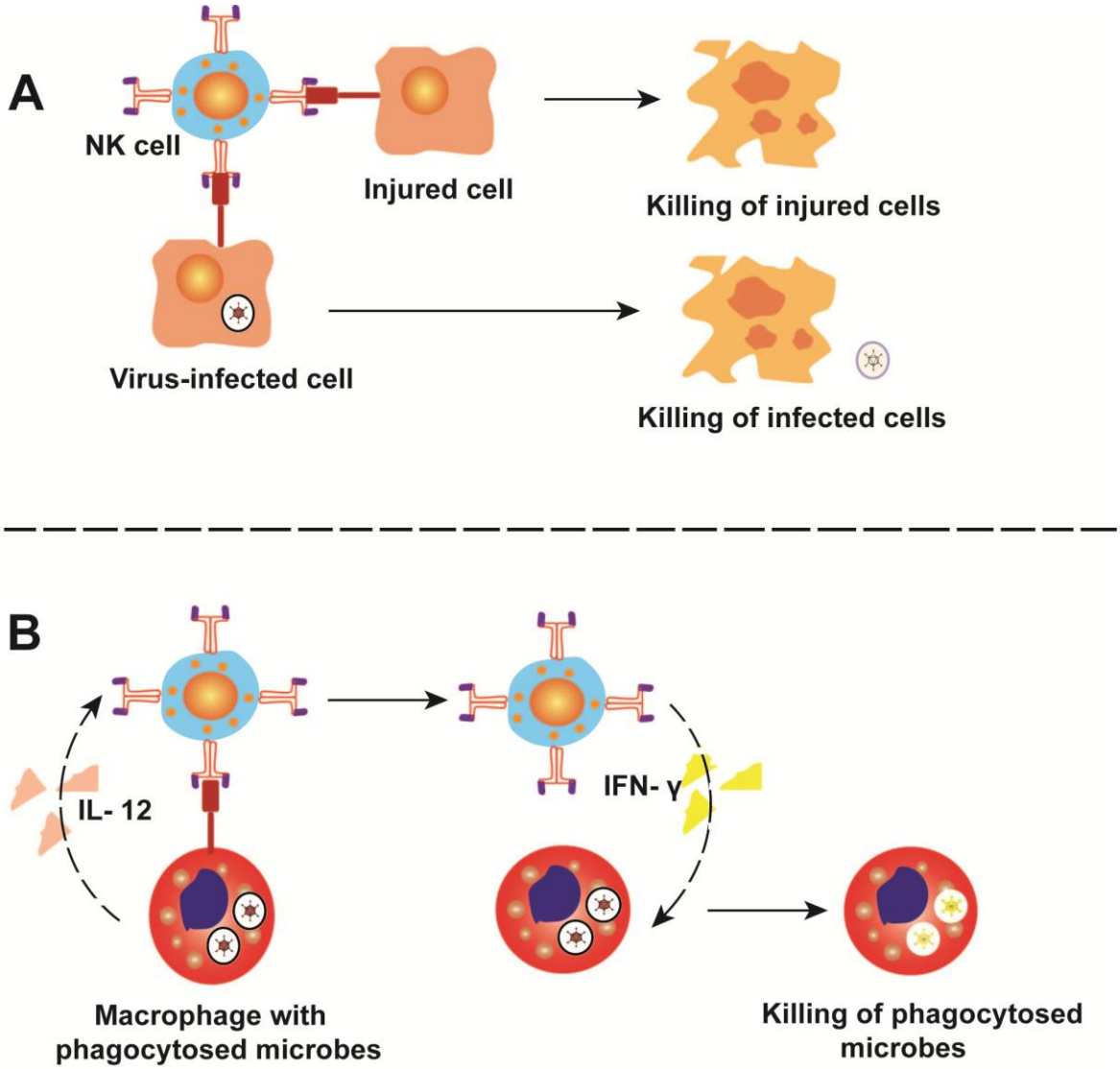
They are one of the most important components of the innate immune system. Their role of presenting the antigens to the cells of adaptive immune system makes it unique among the others. They express variety of TLRs, PAMPs and DAMPs for the recognition of the pathogens and present it to the naïve T lymphocytes to trigger the adaptive immune response.

4.2.4 Natural killer cells

Many natural killer (NK) cells express the **inhibitory receptors** that recognizes the MHC class I molecules. Inhibitory receptors contain a unique structure in their cytoplasmic tail called **immunoreceptor tyrosine-based inhibition motif** (ITIM), which blocks the signaling pathways of the activating receptors. Activating receptor of NK cells contains **immunoreceptor tyrosine-based activation motif** (ITAM), which promotes the infected cell killing and cytokine secretion. NK cells contains a unique CD molecule called CD16 over their surface that has an affinity towards microbial bound IgG molecules, the phenomenon is called **antibody-dependent cell-mediated cytotoxicity**.

NK cells recognize the ligands of infected cells or cells undergoing stress and kill the host cells. This helps in the elimination of infection and also unwanted cell population in the human body. IL-12 is produced by the macrophages that phagocytize the microbial antigens, the NK cells secretes interferon-γ in response to IL-12 and kill the phagocytized pathogen.

Figure 4.1 Natural killer cell mediate innate immune response:



4.3 Soluble components of innate immune system

The soluble components of innate immune system bind with the microbes and help in their phagocytosis by the cells of innate immunity. They may sometimes involve in direct killing of the pathogens by promoting the inflammatory response.

4.3.1 Complement system

This system consists of many plasma proteins that help in opsonization of the microbial antigens to promote the recruitment of phagocytic cells. It involves a cascade in which an inactive zymogen is converted into active proteases and many proteolytic products.

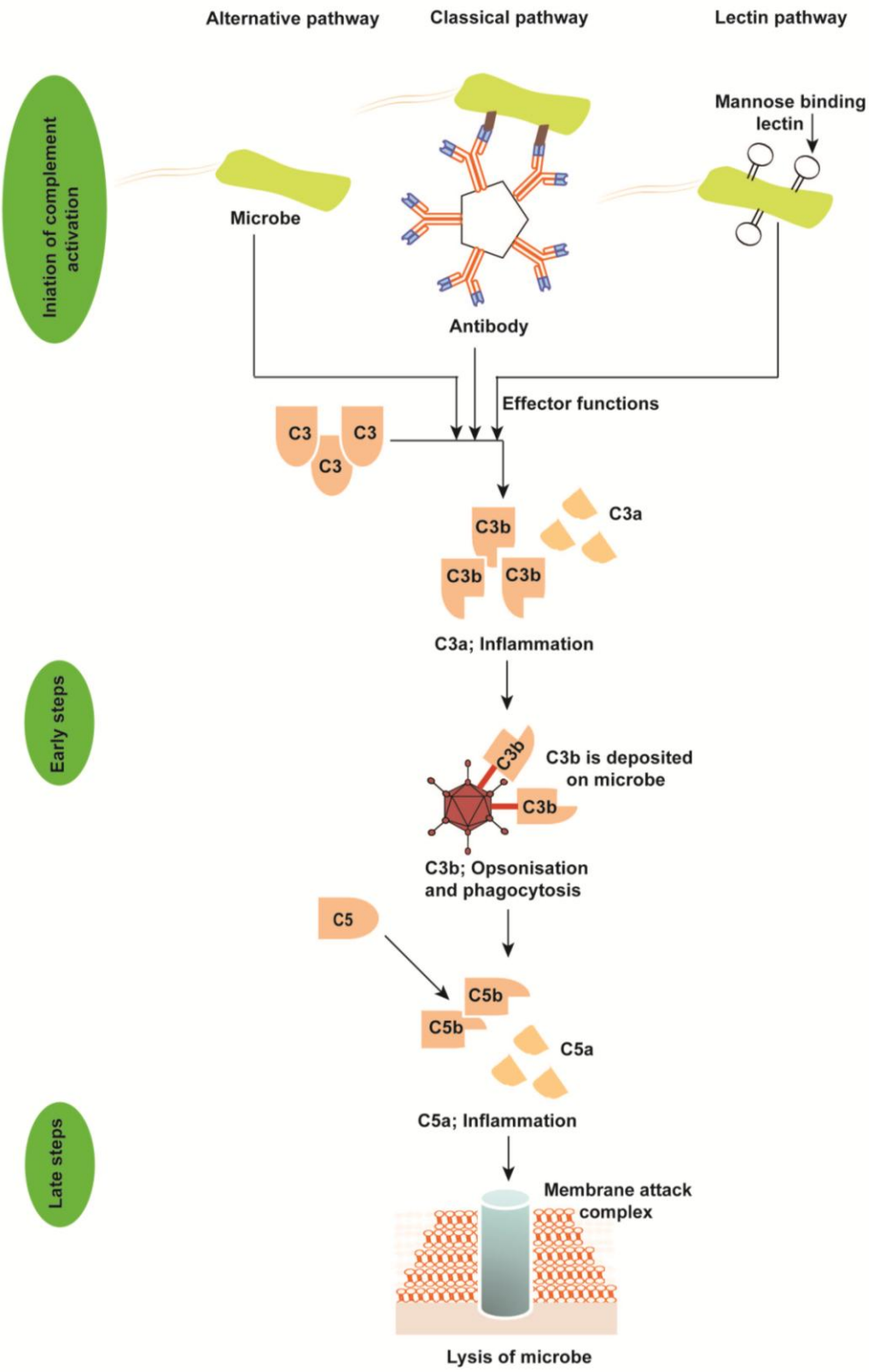
First step in the activation of complement system is the recognition of the foreign substance and that occurs by three different pathways

1. Classical pathway
2. Alternate pathway
3. Lectin pathway

Classical pathway was named as it was discovered first and uses the plasma protein C1q to detect antibody bound over the surface of microbes. Following the binding, C1q starts the cascade (figure 4.2) which leads to lysis of the microbes. **Alternate pathway** is triggered with a protein called C3 which recognizes the lipopolysaccharides present in the bacterial cell. **Lectin pathway** is triggered by the mannose binding lectin that recognizes the mannose residues present in the microbes.

Recognition of antigens by any of these pathways converts C3 into C3a and C3b with the help of C3 convertase. C3b binds with the microbial antigen while C3a stimulates the release of inflammatory cytokines. C3b activates the C5 convertase to convert C5 into C5a and C5b. C5a is a chemoattractant while C5b initiates the formation of complex with other complement proteins C6, C7, C8, and C9. This sequential cascade leads to formation of **membrane attack complex** which causes lysis of the cell.

Figure 4.2 Complement system pathways:



Lecture 5: Adaptive immune system (Part I)

Adaptive immune responses are of two types

Humoral immune response

Cell mediated immune response

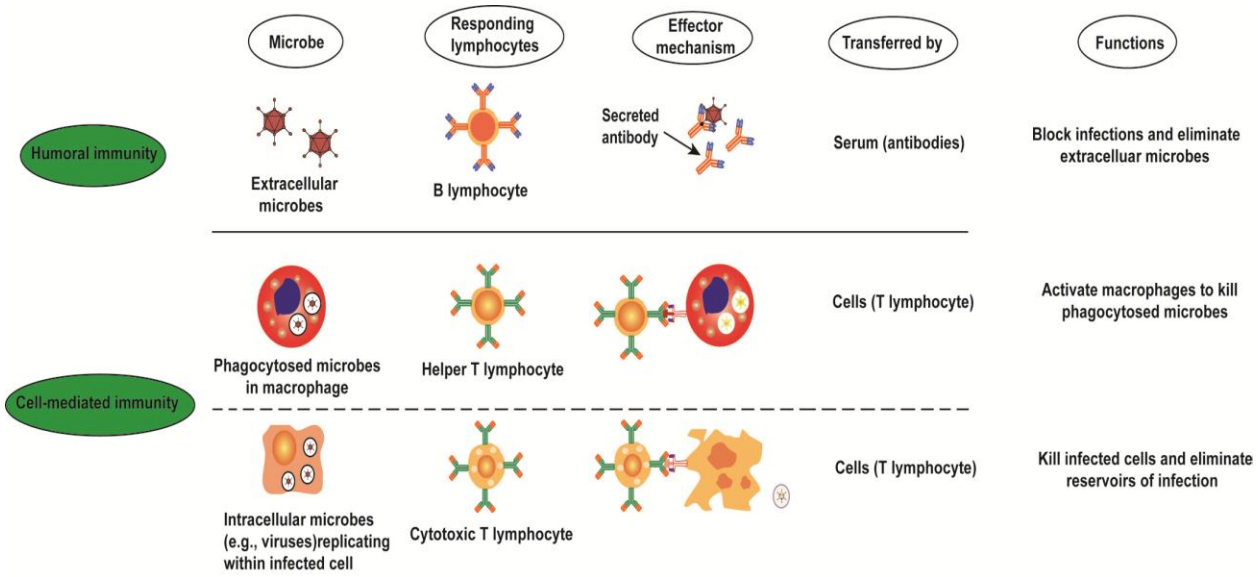
5.1 Humoral immune response

Humoral immune responses are mediated by the antibodies which are produced by activated B cells. Antibodies recognize the microbial antigen, neutralize the infectivity, and target the microbes to other effector system for degradation. Humoral immunity is the major type of immune response against extracellular microbes and toxins because the secreted form of the antibody can easily bind and eliminate the microbes and toxins. Occasionally antibodies may bind to the microbes to promote their phagocytosis in order to eliminate the infection.

5.2 Cell mediated immune response

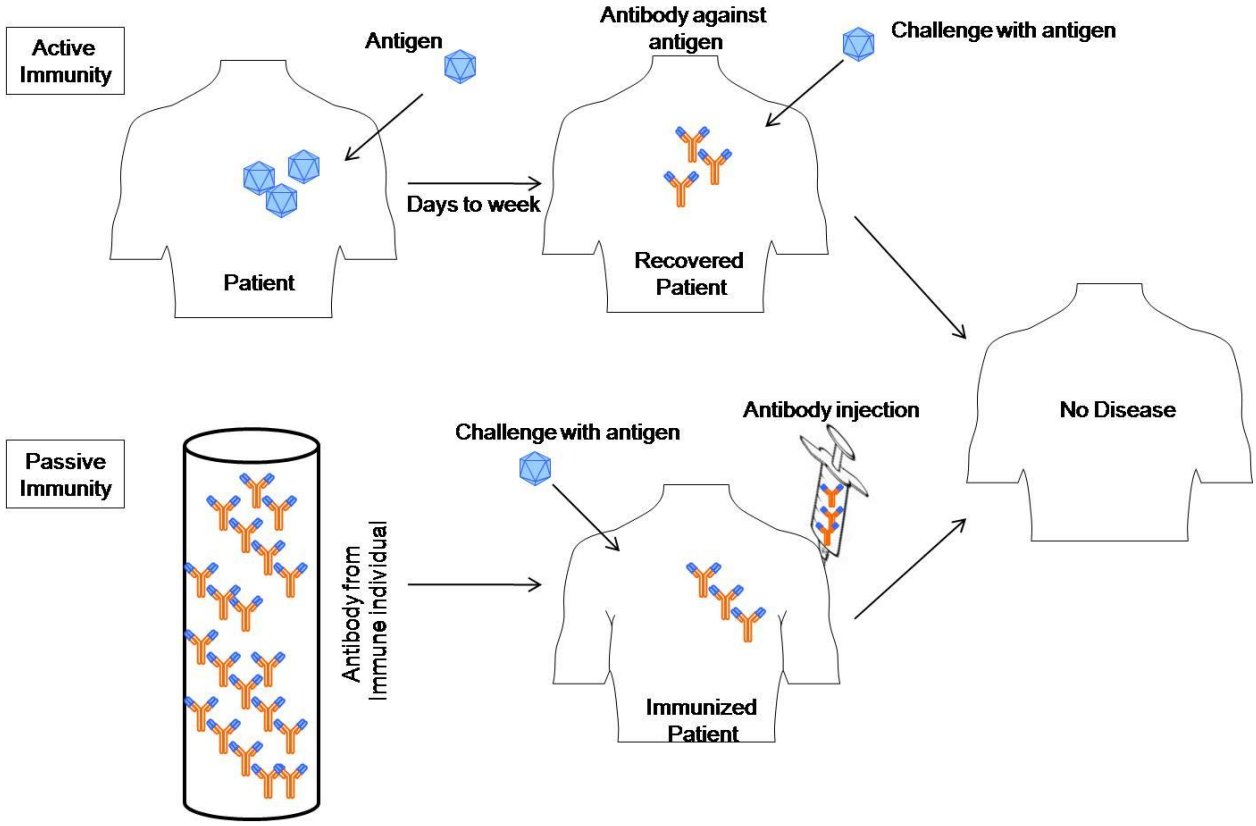
This is also called cellular immunity, and is mediated by T lymphocytes. Cell mediated immunity plays an important role against intracellular microbes, viruses, and some intracellular bacteria. The cellular immunity promotes the destruction of microbes by direct killing or phagocytosis of the infected cells.

Figure 5.1 Schematic representation of humoral and cell mediated immunity:



Immunity against a pathogen is usually induced by the exposure of microbial antigen to the host and is called **active immunity**. Immunity can also be transferred by serum or lymphocyte from an immunized individual to a diseased individual and is called **passive immunity**. Passive immunization is a rapid way to transfer the immunity in the absence of active immunity. Passive immunization against toxin and venoms is a life saving treatment in many lethal conditions (Tetanus toxoid, snake antivenom).

Figure 5.2 Schematic representation of active and passive immunity:



The first concept of humoral immunity was given by **Emil von Behring** and **Shibasabro Kitasato**; they showed for the first time that serum transferred from a recovered diphtheria patient protected the recipient from active diphtheria infection. The active ingredients are called antitoxins because they nullify the effect of toxins. They won the noble prize for their landmark discovery. Paul Ehrlich coined the term **antibodies** for the proteins present in the serum and showed that it is capable to bind and neutralize the toxins. The substances that induce the production of antibodies are called **antigens**. The definition of the antigen changed in due course of time with the modern discoveries. The antigens are defined as substances that bind to a specific lymphocyte with or without further production of antibody. However the substances that induce the production of antibodies are called **immunogens** in modern immunology world.

The cellular theory of immunity started with the work of **Elie Metchnikoff**, who first demonstrated the phenomenon of phagocytosis. Another remarkable finding was put

forth by Almroth Wright, who showed that the factors present in the serum can coat the bacteria and help them to phagocytize by the cells of the immune system, the process known as **opsonization**.

5.3 Feature of adaptive immunity

The adaptive immunity has some fundamental properties.

5.3.1 Specificity

The adaptive immunity is specific to a particular antigen, which means specific antibodies are produced against a particular antigen. The structures present over the antigen that stimulate the production of antibodies are called **antigenic determinants** or **epitopes**. Minute differences exist among lymphocytes that express membrane receptors which are able to distinguish fine differences present on the epitopes. The specificity of immune system leads to a huge population of lymphocytes that are antigenically specific and are called **lymphocyte repertoire.**

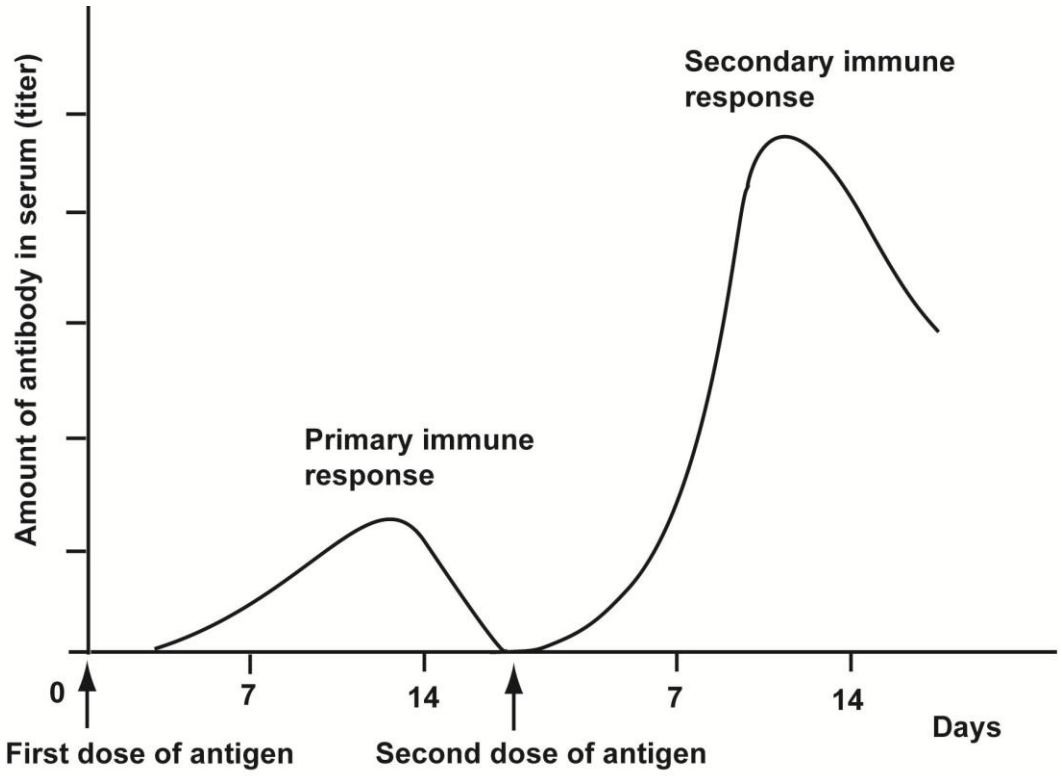
5.3.2 Diversity

The ability of lymphocyte repertoire to recognize a wide variety of antigens is called diversity. In fact lymphocyte repertoire that contains receptors for different antigen contributes to a large population of extremely diverse lymphocyte clones.

5.3.3 Memory

The ability of the immune system to remember the antigens and respond again to the same upon exposure is called immunological memory. The immune response against the second exposure of the same antigen or subsequent exposure is usually rapid and larger than the primary immune response (figure 5.2).

Figure 5.3 Memory response of the adaptive immune system:



Immunologic memory forms because of long-lived memory cells generated upon each exposure of an antigen and are specific for that antigen. The memory cells produced following second exposure are more efficient in eliminating the antigen as compared to the primary immune response.

5.3.4 Nonreactivity to self antigens

A unique and remarkable property of immune system is to respond and eliminate any foreign antigen (Non self), while not producing any harmful effect against the own antigen (self). It is sometimes called as **tolerance** towards the self antigen. Any deviation from the above in which immune system starts reacting towards the self antigen leads to a condition what we call as **autoimmune diseases**.

5.3.5 Specialization

Both humoral and cellular immune system responds to the foreign pathogens in a different way. The responses are different against extracellular and intracellular pathogens. Each type of response is unique for a particular type of pathogen and is specialized to perform specific functions.

5.3.6 Clonal expansion

It is another unique property of immune system in which the lymphocyte starts producing similar kind of cells upon exposure to an antigen in order to eliminate the pathogen more effectively and more rapidly. The cells formed after clonal expansion has similar surface markers and responds to similar kind of antigen.

5.3.7 Homeostasis

Every process in the body has a regulatory mechanism. The immune responses are produced against an antigen or pathogen upon entry inside the body and wane following the clearance of antigen. This is done in order to maintain homeostasis mechanism inside the body. Any deviation from the homeostasis leads to an immunological disease condition.

Lecture 6: Adaptive immune system (Part II)

6.1 Cells of the adaptive immune system

Major cells of the adaptive immune system includes following.

Lymphocytes

Antigen presenting cells

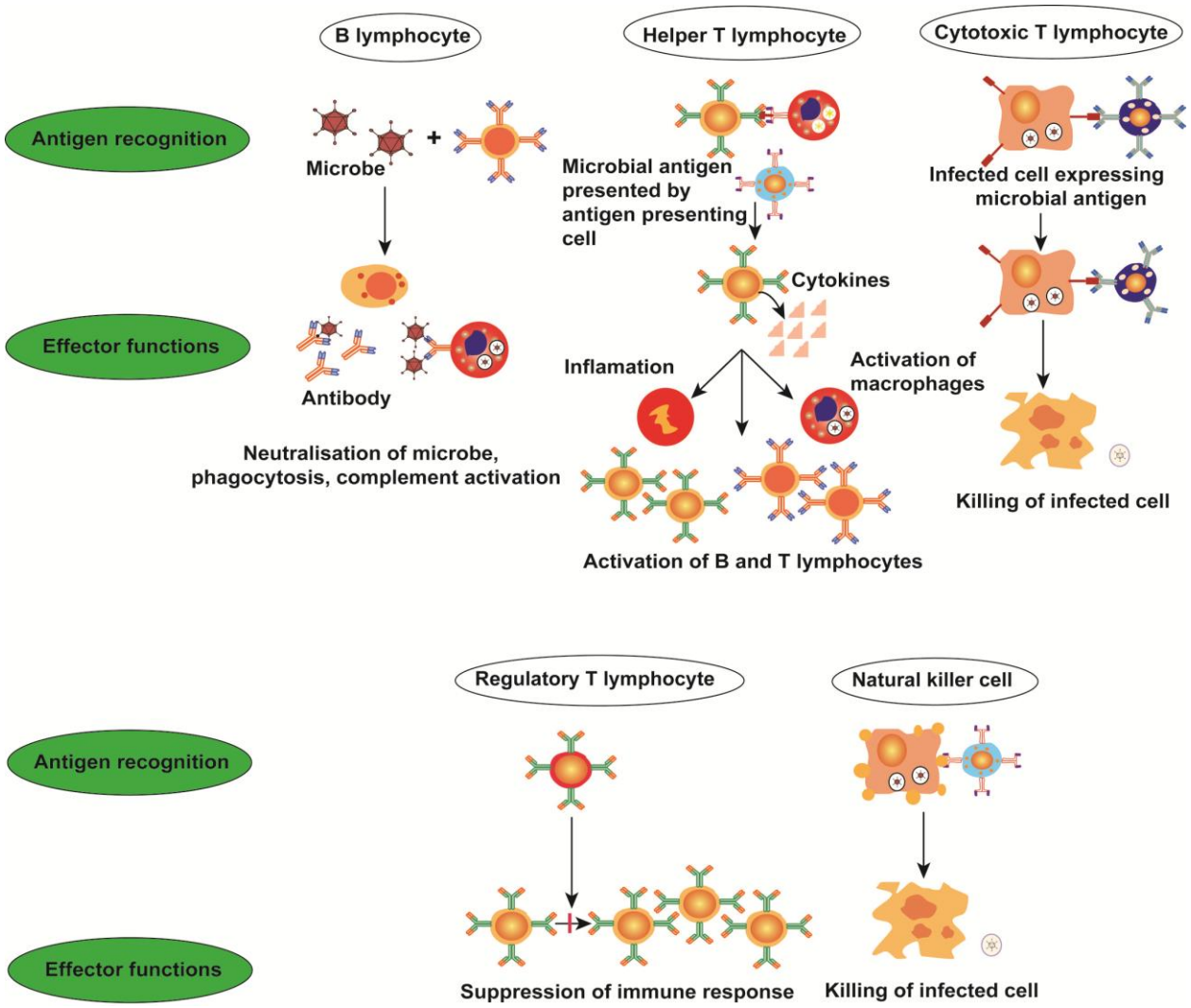
Effector cells

Lymphocytes are the main cells which can recognize the antigen and produce an antibody in order to eliminate the antigens. They are considered as a mediator of both humoral and cellular immunity. **B lymphocytes** are the only cells in the body capable of producing antibodies. B lymphocytes recognize the extracellular antigens and are differentiated into the plasma cells. **T lymphocytes** recognize the intracellular antigens and they either help in their phagocytosis or direct killing of the infected cells. T lymphocytes are activated by the antigen loaded over the major histocompatibility complex (MHC) molecules, which are expressed on the surfaces of other cells. T lymphocytes are divided into different subsets which are specific for certain specialized functions. **Helper T cells** are the subsets of T lymphocyte that secretes the cytokines and help in the proliferation and activation of T lymphocyte. Helper T cells also activate the B cells (to secret the antibody), macrophages and other leucocytes by the virtue of the cytokines. **Cytotoxic T lymphocytes** kill the cells infected by viruses or other intracellular pathogens. **Regulatory T cells** help to reduce or inhibit the immune response and are negative regulators of immune system. **Natural killer cells** are involved in the innate immunity against viruses or other intracellular pathogens. Different classes of lymphocytes can be identified and differentiated by the expression of their surface receptors called cluster of differentiation (CD).

Antigen-presenting cells are mostly the dendritic cells which capture the antigens, transport it to the lymphoid organs and present the antigens to naïve lymphocytes in order to activate the immune response.

Effector cells of the immune system mainly include activated T lymphocytes, mononuclear phagocytes, and other leukocytes. Effector cells are required to complete the immune cascade, i.e. to eliminate the microbes.

Figure 6.1 Lymphocyte classes:



6.2 Different stages of adaptive immune response

Steps of adaptive immune response follow a cascade orchestrated by the antibodies and the cells of the adaptive immune system.

Step 1 Capture and display of antigens

Step 2 Recognition of antigen by lymphocytes

Step 3 Activation of T lymphocytes

Step 4 Activation of B lymphocytes

Step 5 Production of memory cells

6.2.1 Capture and display of antigens

Dendritic cells present in the epithelial body surfaces and connective tissues are the major antigen presenting cells. They display the antigens to the CD4+ T cells to activate the antibody mediated (humoral) immune response and CD8+ T cells to activate cell mediated immune response. The antigen presenting cells contain a specialized structure over their surface called the MHC molecules that helps in the display of antigenic peptides to the cells of immune system (discussed in later chapters). Pathogens entering into lymph nodes and spleen are displayed by the antigen presenting cells to the B and T lymphocytes.

6.2.2 Recognition of antigen by lymphocytes

Lymphocyte specific for an antigen is activated upon encountering with antigen presenting cells loaded with an antigenic peptide. The concept of activation of lymphocyte is called **clonal selection theory**. The theory was put forth first by **Neils Jerne** and explained further by **Burnet**. This theory says that antigen specific clones of lymphocytes exist even before the exposure of antigens and a large number of clones are generated during lymphocytic maturation to diversify the recognition of microbial antigens.

6.2.3 Activation of T lymphocytes

Activated T helper cells proliferate and differentiate into effector cells with the help of cytokines. Interleukin-2, secreted by T-helper cells modulate the clonal expansion of activated T lymphocytes. The effector cells help in killing the pathogen by phagocytosis.

Activated cytotoxic T cells kill the intracellular pathogens in the cytoplasm of infected cells. Alternatively, cytotoxic T cells eliminate the infection by phagocytosis of the infected cells.

6.2.4 Activation of B lymphocytes

B cells are activated with the help of CD4+ T lymphocyte and differentiated into antibody secreting plasma cells. Usually lipids and carbohydrate antigens stimulate the production of IgM class of antibody while protein antigens can induce IgG, IgA, IgE type of immunoglobulins. The production of different form of antibodies requires class switching of the surface immunoglobulin present over the B cells. Antibodies bind and prevent the pathogens, thus “neutralizing” the pathogens and block their ability to infect host cells. IgA antibodies specifically act on the mucosal surface of the gastrointestinal and respiratory tract and neutralize the invading pathogens. IgG antibodies coat pathogens and target them for phagocytosis while IgM can activate the complement pathway.

6.2.5 Production of memory cells

Initial activation of T lymphocyte produces the long-lived memory cells that survive for many days following infection. Memory cells respond much faster than the naïve lymphocytes. Generations of long lasting memory cells are the major target for vaccine design against microbial pathogens.