Immune response refers to the highly coordinated reaction of the cells of immune system and their products. It has two arms .

-Humeral or Antibody-mediated Immune Response (AMI)

- It provides protection to the host by secreting *antibodies*; that can bind and neutralize microbial antigens circulating free or present on the surface of the host cells and in the extracellular spaces, but have no role against intracellular antigens. If antibodies were the only agents of immune response, pathogens that manage to evade them by being in the intracellular environment would have escaped the immune response. Nevertheless, this is not the case.

-Cell-mediated Immune Response (CMI)

- It plays a crucial role in providing protection against intracellular microbes as well as tumor cells. Although CMI is mainly T cell mediated (especially cytotoxic T cells); however, various other effector cells such as natural killer (NK) cells, macrophages, granulocytes are also components of CMI.

-CMI and AMI are Interdependent

- CMI and AMI cannot work individually, but they are highly dependent on each other .Cytokines released from T cells stimulate B cells to produce antibodies. Similarly, many effector cells of CMI such as macrophages and NK cells use antibodies as receptors to recognize the target cells for killing.

-CMI also regulates the humoral immunity by releasing cytokines from activated T cells that stimulate the B cells to transform into antibody secreting plasma cells.

-There are certain initial events that must take place before the induction of either CMI or AMI. These events are common to both CMI and AMI, and they occur irrespective of the type of immune response that will follow. These events include:

1. Antigen presentation to helper T cells

2. Activation and differentiation of helper T cells into either TH1 or TH2 subsets.

3-Helper T (TH) cells are the central key that regulate the type of immune response that is going to occur.

4-Activated helper T cells differentiate into either TH1 or TH2 subsets.

5-Induction of TH1 cells secrete cytokines that stimulate cell mediated response, whereas if TH2 cells are differentiated, they secrete certain cytokines that in turn induce the B cells to produce antibodies.

Antigen-presenting Cells (APCs)

- Although antigen presentation refers to presentation of antigenic peptide to both TH (helper T cells) and TC (cytotoxic T cells) by complexing with MHC-II and I respectively; however, antigen-presenting cells (APCs) in strict sense implies only to those cells (e.g. dendritic cell, macrophage, etc.) that present the antigenic peptide along with MHC class II to TH cells.

- Cells presenting antigenic peptides along with MHC class I molecules to TC cells are not included under APCs.These cells are usually virus infected cells or tumor cells.They are often referred to as **target cells** as the activated TC cells cause lysis of these cells.

-Dendritic cells, macrophages and B cells are the major APCs and are called **professional APCs**. There are some other non-professional cells that can occasionally present antigens to helper T cells .

Antigen Processing Pathways

For induction of immune response (both CMI and AMI),antigens must be presented to TH cells. In addition, for CMI induction, antigen presentation to TC cells is essential. Two well defined pathways are used by the immune system for this purpose. They differ from each other in their mechanism and target antigen, as described below

1. **Cytosolic pathway:** Here, the endogenous (intracellular)antigens such as viral antigens and tumor antigens are processed and presented along with MHC class I molecules to CD8 T cells

2. **Endocytic pathway:** In this pathway, the exogenous antigens (extracellular microbes and their products,e.g. toxins) are processed and complexed with MHC class II molecules and presented to TH cells. The cells involved in endocytic pathway include the APCs such as macrophages, dendritic cells and B cells.

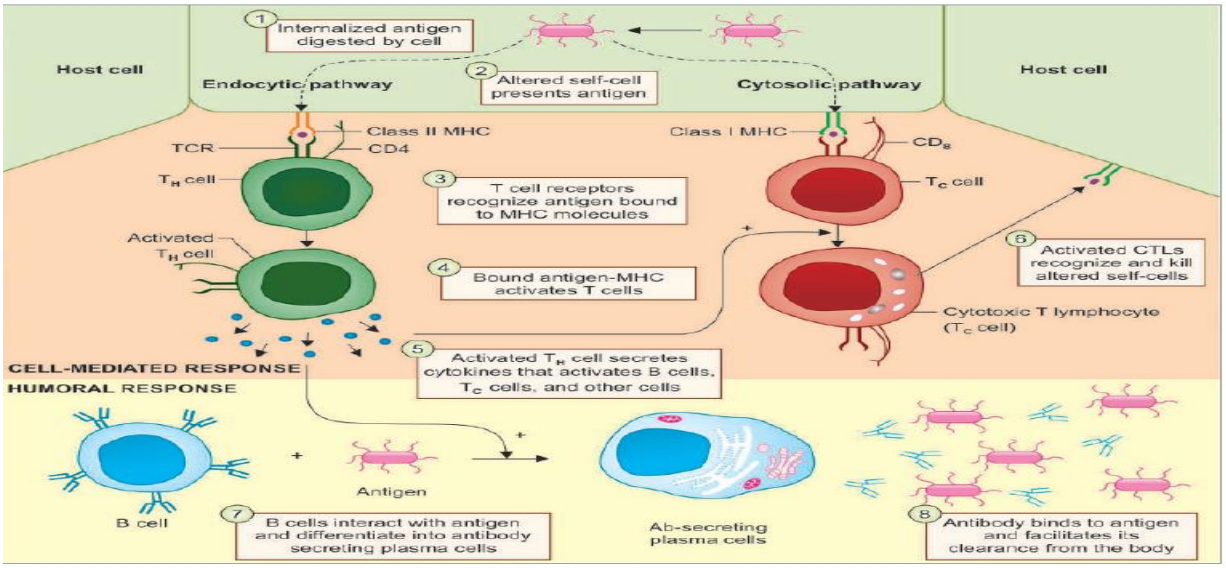

Fig. 15.1: Overview of immune response.
Abbreviations: MHC, major histocompatibility complex; CTL, cytotoxic T lymphocyte; Ab, antibody.

T CELLS

- T cells perform several important functions, which can be divided into two main categories, namely, **regulatory** and **effector.** The regulatory functions are mediated primarily by **helper** (CD4-positive) T cells, which produce **interleukins** -. For example, helper T cells make (1) interleukin (IL2), which activates CD4 and CD8 cells; (2) IL-4, which help B cells make antibodies, especially IgE; and (3) gamma interferon, which enhances killing by macrophages. The effector functions are carried out primarily by cytotoxic (CD8-positive) T cells, which kill virus infected cells, tumor cells, and allografts.

-cells constitute 70–80% of blood lymphocytes. Unlike B cells, they do not have microvilli on their surface. They bear specialized surface receptors called T cell receptors (TCR).

-T Cell Receptor :The T cell receptors (TCR) of T cells are equivalent to the surface immunoglobulins (B cell receptors) of the B cells. Their main function is antigen recognition. Unlike B cell receptor which binds to antigen directly, TCR does not recognize antigen by itself. It can only respond to an antigen which is processed and presented by the antigen presenting cells, such as macrophages.

TCR–CD3 Complex

-Most T cell receptors (95%) comprise of two chains (α and β) which in turn have three regions—(1) extracellular domain, (2) transmembrane domain, and (3) cytoplasmic tail

-About 5% of TCRs do not have α/β chains, instead they bear γ/δ chains.TCR is active only when both the chains (α and β) complex with CD3 molecule.

-The **variable region** of α and β chains of TCR bind to the presented antigens. They are polymorphic in nature. Rearrangement of α and β genes during T cell development can produce large number of different combinations of TCRs. Each TCR is capable of recognizing a particular epitope of an antigen.

-Following binding of antigen to α and β chains of TCR, a signal is generated that is transmitted through the CD3 complex leading to activation of T cells.

TABLE 58–2 Cell Surface Proteins That Play an Important Role in the Immune Response[1]

Type of Cells	Surface Proteins
Helper T cells	CD4, TCR, CD28
Cytotoxic T cells	CD8, TCR
B cells	IgM, B7
Macrophages[2]	Class II MHC
Natural killer cells	Receptors for class I MHC
All cells other than mature red cells[3]	Class I MHC

gM = immunoglobulin M; MHC = major histocompatibility complex; TCR = T-cell ntigen receptor.

-T Cell Development

-The major events of T cell maturation take place in thymus,in contrast to bone marrow for B cells.

-. The progenitor T cells are originated from the bone marrow (or liver in fetal life) and then migrate to thymus through bloodstream

- Developing T cells in the thymus (collectively called as thymocytes) pass through series of stages that are marked by characteristic changes in their cell surface markers . **Most of the development events take place in the cortex of thymus, under the influence of thymic stromal cells which secrete thymic hormones and lymphopoietic growth factor IL-7.**

-The sequence of events of T cell development is as follows

1. **Double negative (DN) T cells:** T cell precursors after entering into the thymus transform into double negative T cells (CD4– CD8–). These cells are so called because, they do not express the surface markers of mature T cells, i.e. CD4 and CD8 molecules. DN T cells first express CD3 molecule and then undergo further development

- Five percent of T cell precursors carrying TCR γδ develop into mature γδ T cells

- The remaining (95%) of the cells express TCR αβ and subsequently express both CD4 and CD8 molecules to become double positive (DP) T cells.

2 . **Double positive (DP) T cells (CD4+ CD8+):** They are immature T cells, carrying both CD4 and CD8 molecules on their surface. They further undergo one of the following fate:

a. **Positive selection:** The 5% of DP T cells, whose αβ receptors are capable of recognizing their MHC molecules are positively selected. This results in MHC restriction.

b. **Death by neglect:** Majority of DP cells (95%) fail positive selection because they do not specifically recognize their MHC molecules

c. **Negative selection:** The survived cells that undergo positive selection (5%) are MHC restricted. However, some of these surviving cells (2–5%) react to the selfantigens and therefore, they are selected to be killed by apoptosis and removed (negatively selection)

-The remaining double positive T cells (2–5%) having αβ type TCR selectively shut off the expression of either CD4 or CD8 molecules and eventually become single positive mature T cells (CD4+/CD8– or CD4–/CD8+).

3- **Mature T cells** (e.g. CD4+ helper T cells and CD8+ cytotoxic T cells) acquire thymus specific antigens, then are released into the circulation and migrate to the peripheral lymphoid organs where they respond to the antigenic stimulus.

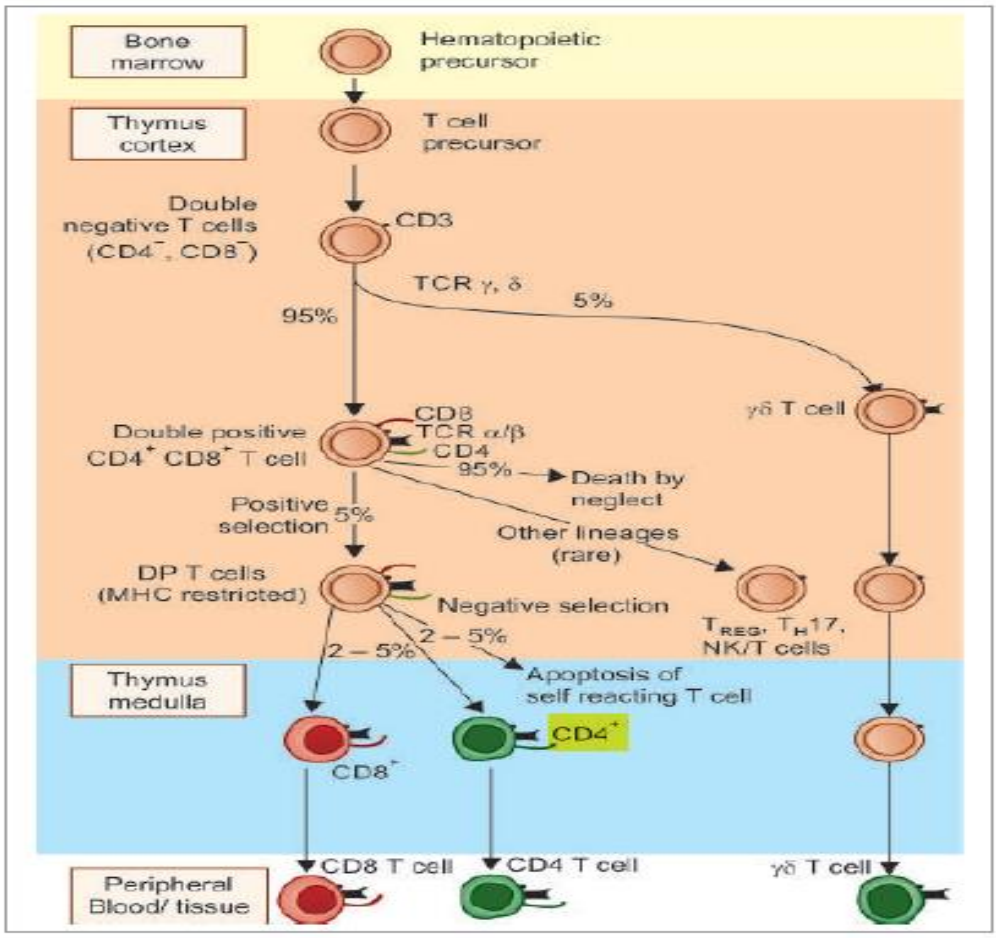

Fig. 14.6: T cell development.

Types of T Cells

-Effector T Cells

There are two types of effector T cells—(1) CD4+ helper T cells and (2) CD8+ cytotoxic T cell.

1. **Helper T cells:** Helper T cells (TH) possess CD4 molecules as surface receptors. They recognize the antigenic peptides that are processed by antigen presenting cells and presented along with MHC-II molecules (major histocompatibility complex)

- Following antigenic stimulus, the helper T cells differentiate into either of the two types of cells— (1) TH1 and (2) TH2 subset; each secrete specific cytokines which modulate the cellular and humoral immune responses respectively .

- **TH17 cells:** Recently a third subset of T helper cells called TH17 cell has been discovered. It produces IL-17 and IL-22, and is primarily involved in recruiting neutrophils. They contribute to the pathogenesis of

many autoimmune inflammatory diseases such as rheumatoid arthritis and others.

2. **Cytotoxic T cells:** In contrast to TH cells, cytotoxic T cells (TC) possess CD8 molecules and recognize the intracellular antigens (e.g. viral antigens or tumor antigens) that are processed by any nucleated cells and presented along with MHC-I. In general, TC cells are involved in destruction of virus infected cells and tumor cells.

Rare Subtypes of T Cells

1. **Regulatory T cells (TREG cells):** The TREG cells (formerly known as suppressor T cells) are a subpopulation of T cells which regulate the immune system

-They provide tolerance to self-antigens (known as peripheral tolerance), and thus prevent the development of autoimmune disease

-Surface markers: TREG cells possess surface markers such as CD4, CD25 and Foxp3 (a forkhead family .transcription factor). Deficiency of Foxp 3 receptors leads to a severe form of autoimmune disease known as **I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy **X**-linked (**IPEX**) **syndrome**.

2. γδ **T cells:** γδ T cells represent a small subset of T cells (5%) that possess a distinct TCR composed of γ and δ chains; instead of α/β chains. They lack both CD4 and CD8 molecules,. They differ from the conventional αβ T cells by the fact that they do not require antigen processing and MHC presentation of peptides

- They are part of innate immunity as the γδ receptors exhibit limited diversity for the antigen,. They are usually found in the gut mucosa, within a population of lymphocytes known as IELs

-The function of γδ T cells is not known, they may encounter the lipid antigens that enter through the intestinal mucosa.

- γβT cells are predominantly found in the lamina propria of the gut and are thought to assist in protection against microorganisms entering through epithelium at mucosal surfaces. Their range of response to antigens is limited. These cells have been found to be active toward mycobacterial antigens and heat shock proteins, and they have the ability to secrete cytokines like their αß counterparts. Generally, γβ cells lack CD4 and CD8 (double-negative cells), although some γβ cells do express CD8. Some γβ T cells can function in the absence of MHC molecules.

TABLE 58–3 Main Functions of Helper T cells

Main Functions	Cytokine That Mediates That Function
Activates the antigen-specific helper T cell to produce a clone of these cells	IL-2
Activates cytotoxic T cells	IL-2
Activates B cells	IL-4 and IL-5
Activates macrophages	Gamma interferon

IL = interleukin.

Table I-8-2. Summary of Cytotoxic T-Cell Markers and Function

Cell	CD Markers	MHC class I	Effector Mechanisms
CTL	CD8, CD3, TCR, CD2	Yes	Perforin, granzymes, cytokines

Natural Killer T Cells

The term natural killer T (NKT) cell was first used in mice to define a subset of T cells that express NK cell–associated marker NK (CD161). These cells recognize an APC molecule (CD1) that presents self and foreign lipids and glycolipids, recognized through a relatively nonpolymorphic αß-TCR.Recognition of these antigens does not require CD4 or CD8 coreceptor for activation. NKT cells are able to produce large quantities of INF-g or IL-4 as well as multiple other cytokines and chemokines.

-Dysfunction or deficiency in NKT cells has been linked to the development of autoimmune diseases (such as diabetes or atherosclerosis), progression to asthma, and development of certain cancers. Of interest, a potent agonist for cell activation of NKT cells is α galactosylceramide, which is now being examined for broad-based use in development as a vaccine adjuvant.