Cell- Mediated Immunity

The cell-mediated and Humoral branches of the immune system assume different roles in protecting the host. The effectors of the humoral branch are antibodies which is highly specific molecules on the surfaces of cells that can bind and neutralize antigens in the extracellular spaces…. ***Cell-mediated immunity*** is an immune response that independent antibody but dependent on the recognition of antigen by T cells to eliminate intracellular pathogens, It's type IV hypersensitivity reaction.

Cells contribute to cell- mediated immune response:

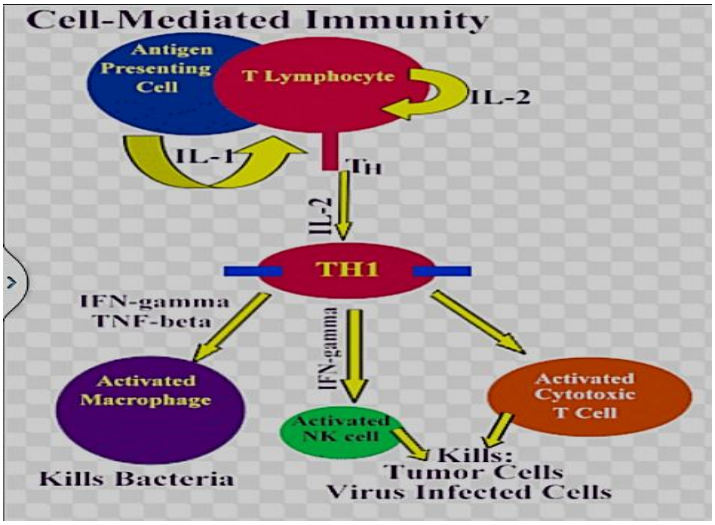
A. Antigen – specific cells:

- $CD8^+$ Cytotoxic T- lymphocytes (Tc cells or CTLs);
- Cytokine- secreting $CD4^+$ T_H cells mediated delayed type hypersensitivity (DTH)

B. Antigen – nonspecific cells:

- NK cells;
- DC;
- Non-lymphoid cell types…Macrophages, neutrophils and eosinophils.

However, activation of cells to carry out killer functions requires cooperation of different cell types (cooperation of Cellular and humoral immunity), cells such as Mq, NK, neutrophil and eosinophil can use antibodies to recognize and presented Ag for killing and in the same time chemotactic peptides generated by the activation of complement in response to Ag-Ab complexes can contribute to assembling cells required for a cell- mediated response.



"Cells contribute to cell- mediated immune response"

T- Helper cells ($CD4^+$):

T- cell maturation, activation and differentiation:

In most cases, both the maturation of progenitor T cells in thymus and the activation of mature T- cells in the periphery are influenced by involvement of MHC molecules. Progenitor T- cells begin to migrate to the thymus from the early sites of hematopoiesis in the eighth or ninth week of gestation in humans. In the thymus, developing T- cells known as thymocytes, proliferate and differentiate along developmental pathways that generate functionally distinct subpopulations of mature T- cell. The final stage in the maturation of most T cells proceed along two developmental pathways, which generate functionally distinct **$CD4^+$** and **$CD8^+$** subpopulations that exhibit class II and class I MHC restricted, respectively.

Generally, T- cell activation is initiated by interaction of the T- cell receptors (TCR-CD3) complex with a processed antigenic peptide bound to either a class I ($CD8^+$ cells) or class II ($CD4^+$ cells) MHC molecule on the surface of an antigen presenting cell. Interaction of a T- cell with Ag initiates a cascade of biochemical events that induces the resting T cell to enter the cell cycle, proliferation and differentiation into memory cells and effector cells.

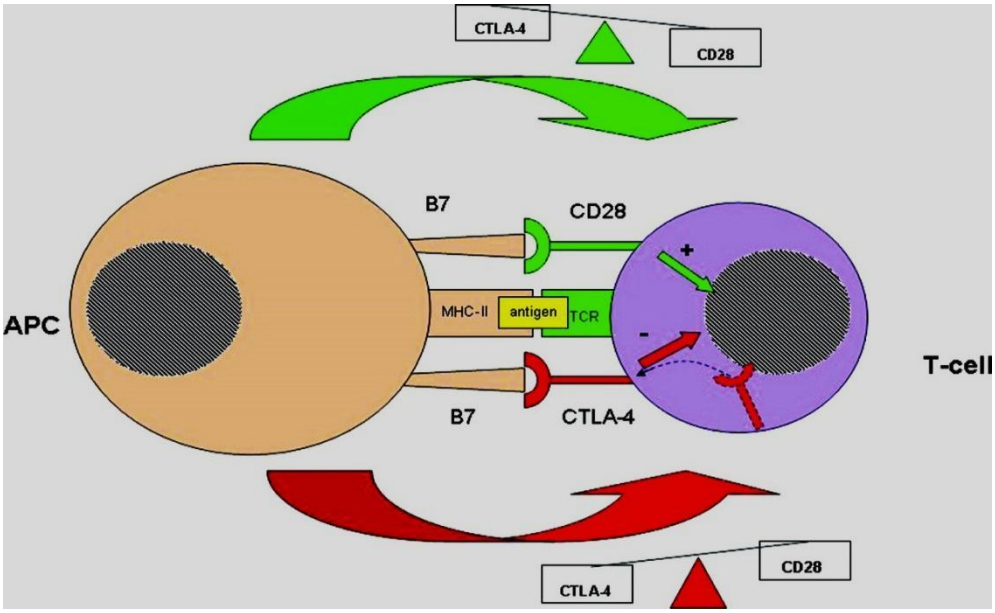
Activation of T_H- cell:

T_H- cell activation requires a costimulatory signal provided by antigen- presenting cells (APCs):

Signal 1…. The initial signal is generated by interaction of an antigenic peptide with the TCR- CD3 complex.

Signal 2…. A subsequent antigen- nonspecific costimulatory signal, is provided primarily by interactions between CD28 on the T- cell and members of the B7 family on the antigen- presenting cell. There are two related form of B7: B7-1 and B7- 2, these are members of the immunoglobulin superfamily and both B7 molecules are constitutively expressed on dendritic cells and induced on activated macrophages and activated B cells. The ligands for B7 molecules are CD28 and CTLA-4 (also known as CD125), both of which expressed on the T- cell membrane as disulfide linked homodimers, they are also members of the immunoglobulin superfamily.

As described these signals of T_H- cell activation trigger entry of the T cell into the G_1 phase of the cell cycle and at the same time induce transcription of gene for IL-2 and high affinity IL-2 receptor (CD25) production, secretion of IL-2 and it's subsequent binding to the high – affinity IL-2 receptor induces naïve T- cell to proliferate and differentiate generate a clone of progeny cells which differentiate into memory or effector T- cell population. The effector T- cells carry out specialized functions as $CD8^+$ and $CD4^+$.



Interaction of B7 family members on APCs with CD28 delivers the costimulatory signal, while engagement of the closely related CTLA-4 (CD152) molecule with B7 produces an inhibitory signal and down regulates the activation of the T- cell……..

T- cell receptor:

T- cell receptor is differs from B- cell antigen binding receptor in important ways, it is membrane bound and does not appear in soluble form as B- cell receptor. the antigen – binding interaction of T- cell receptors is weaker than that of antibodies and requiring more sensitive assays, finally most T- cell receptors are specific not for antigen alone but for antigen combined with (MHC) this attribute, called self- MHC restriction.

T- cell receptor is associated on the membrane with a multicomponent signal transducing complex CD3 whose function is similar to that of the Ig- α/ Ig- β complex of the B- cell receptor.

The molecule responsible for T- cell specificity is a heterodimer composed of either α and β or γ and δ chains. The α and β TCR like the antibody is characterized by high degree of specificity and consider a signature molecule of the adaptive immune system, By contrast to γ and δ TCR function in a manner more consistent with innate immunity. The domain structure of αβ and γδ TCR heterodimers are strikingly similar to those of immunoglobulins. They are classified as members of immunoglobulin superfamily. Each chain in a TCR has two domains containing an interaction disulfide bound that spans 60 – 75 amino acids, the amino terminal domain in both chains exhibits marked sequence variation but the sequences is conserved in each chain. Finally, each TCR chain contains a short cytoplasmic tail of five to 12 amino acids at the carboxyl-terminal end.

Finally, T- cell can be subdivided into two populations according to their expression of CD4 or CD8 membrane molecules. CD4 T- cells recognize antigen that combined with class II MHC molecules and function largely as helper cells, whereas CD8 T- cells recognize antigen that is combined with class I MHC molecules and function largely as cytotoxic cells.

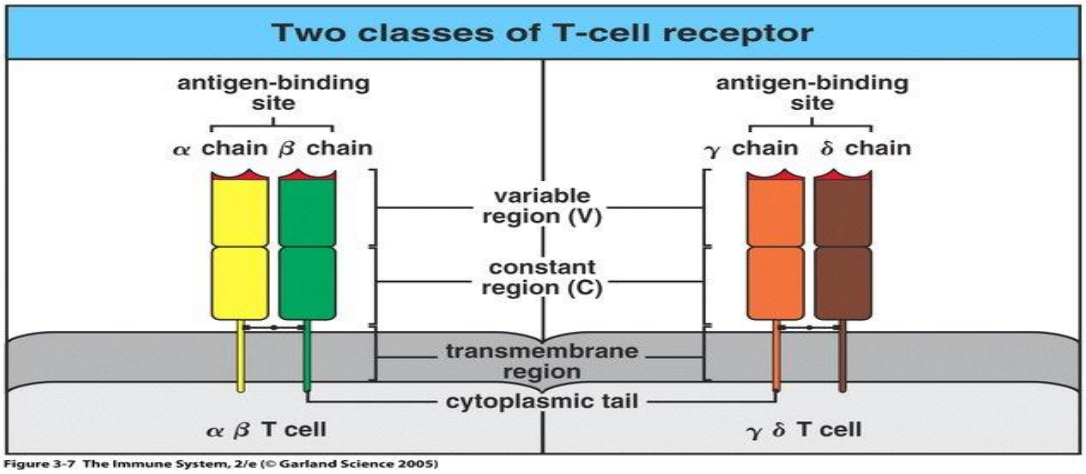


Figure 3-7 The Immune System, 2/e (© Garland Science 2005)

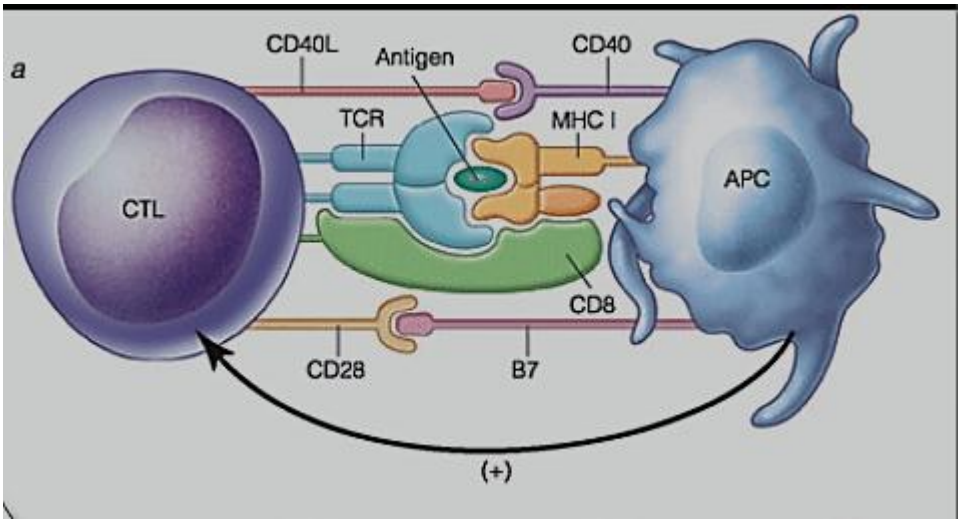
Cytotoxic T cells ($CD8^+$):

Effector cytotoxic T lymphocytes or CTLs generated from CTL precursor CTL-Ps (Naïve Tc cell) which are in capable of killing target cells. In general CTLs are $CD8^+$ and therefor class I MHC restricted. These effector cells have lytic capability in the recognition and elimination of altered cells (e.g. virus- infected cells and tumor cells) and genetically different cells in graft rejection reactions.

Activation of functional CTLs from CTL-Ps:

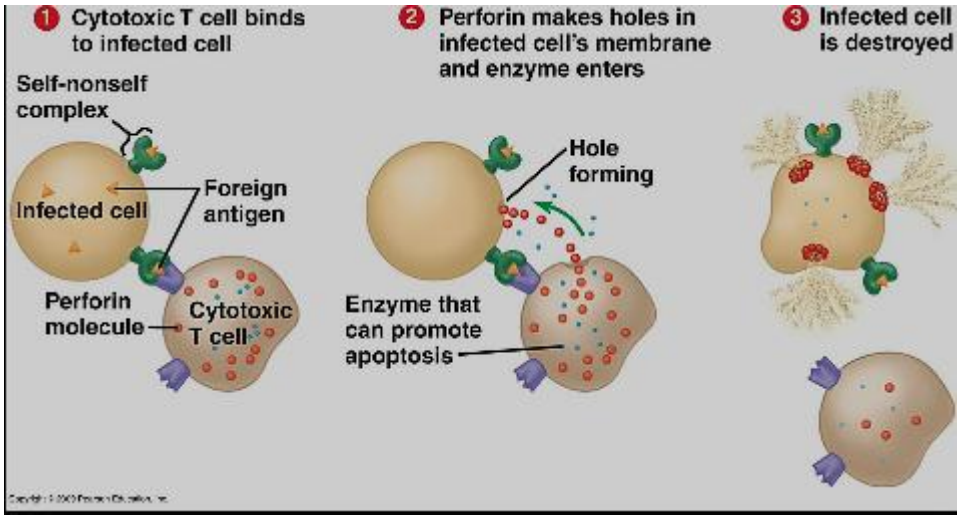
Activation of functional CTLs from CTL-Ps is appears to require at least three sequential signals:

1. An antigen – specific signal transmitted by T cell receptor upon recognition of peptide- class I MHC molecule complex on Antigen presenting cell APC;
2. A costimulatory signal transmitted by the CD28- B7 interaction (CD28 on CTL-Ps surface and B7 on APC surface (virus infected dendritic cell);
3. A signal induced by the interaction of IL-2 with the high – affinity IL-2 receptors, resulting in proliferation and differentiation of CTL-Ps into effector CTLs.



Stages in CTL- mediated killing of target cells:

The effector phase of a CTL- mediated response involves a carefully orchestrated sequence of events that beings with the binding of the target cell by the attacking cells, the primary events in CTL- mediated death are **conjugate formation**, **membrane attack**, **CTL dissociation** and **target cell destruction**. When T- cell receptors on a CTL interact with processed antigen – class I MHC complexes on a appropriate target cell leading to formation of a CTL-target-cell conjugate. The Golgi stacks and granules in the CTL reposition toward the point of contact with the target cell and the granule's contents released by exocytosis. Within several minutes by a Ca^{+2} – dependent…. Energy-requiring step in which the CTL programs the target cell for death. The CTL then dissociates from the target cell and bind another and recycled. Within a variable period (up to few hours) after CTL dissociation, the target cell dies by apoptosis (Fas/FasL pathway). Electron microscopy reveals presence of intracellular electron – dense storage granules in CTLs called perforin and granzymes (fragmentins).



Natural killer cells:

The cells which are named natural killer (NK) cells for their non specific cytotoxicity make up 5 – 10% of the circulating lymphocyte population, derived from bone marrow. These cells are involved in immune defenses against viruses, intracellular pathogens and tumors. Because NK cells produce a number of immunologically important cytokines they play contributing roles in immune regulation and influence both innate and adaptive immunity.in particular interferon- gamma (IFNγ production by NK cells can effect the participation of Mq in innate immunity by activation of their phagocytic and microbial activities).

Receptors of NK cells:

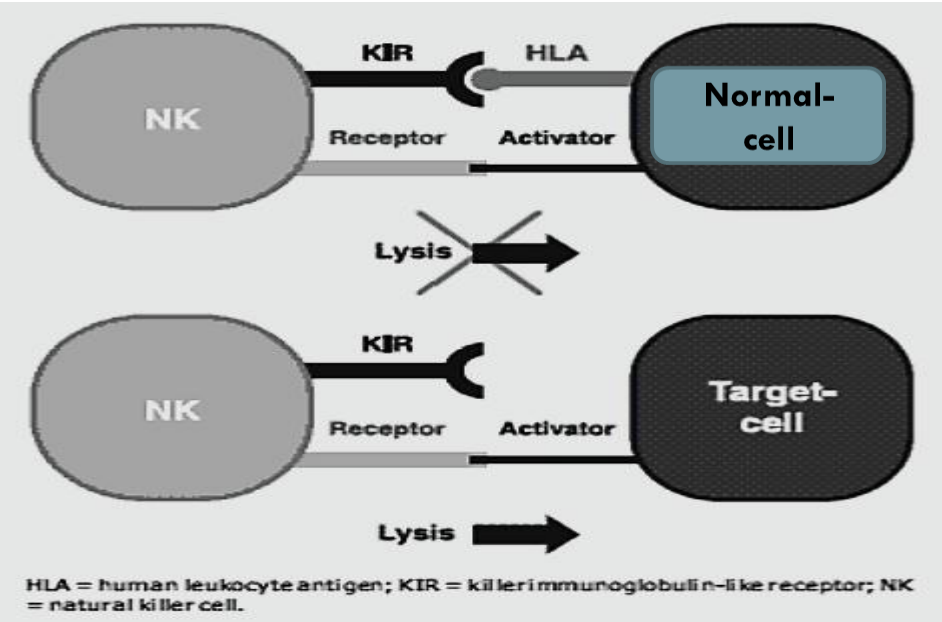
Because NK cells do not express antigen-specific receptors, the mechanism by which these cells recognized altered self cells and distinguish them from normal body cells baffled immunologists for years. NK cells turned out to employ two different categories of receptors: one that delivers inhibition signals to NK cells and another that delivers activation signals.

The receptors of NK cells fall into two general categories based on their structural characteristics:

A. **Lectins- like receptor:** a group of proteins that bind to specific carbohydrates, it's activation receptor.

B. **Immunoglobulins- like receptor:** members of the immunoglobulin superfamily include the killer- cell immunoglobulin- like receptors (KIR) which bind to HLA-B or HLA-C molecules, it's inhibitory receptor.

In the opposing- signals model of NK- cell regulation, activating receptors engage ligands on the surface of a targeted tumorous and virus- infected cells. Recognition of these determinants by activating receptors would signal NK cells to kill the target cells. Killing signals can be overridden by signals from inhibitory receptors. The inhibitory receptors provide a signal that overrides activation signals when these inhibitory receptors detect normal level of MHC class I expression on potential target cells. This prevents the death of target cell. Because MHC class I expression is often decreased on altered self cells, the killing signal predominated leading to their destruction.



HLA = human leukocyte antigen; KIR = killer immunoglobulin–like receptor; NK = natural killer cell.

Killing by NK cells:

Natural killer cells appear to kill tumor cells and virus infected cells by processes similar to those employed by CTLs. NK cells bear FasL on their surface and readily induce death in Fas- bearing target cells. NK cells are constitutively cytotoxic and always have perforin and granzymes granules in their cytoplasm unlike CTLs which must be activated before granules appear. After an NK cell adheres to a target cell, degranulation occurs with release at the junction between interacting cells. Perforin and granzymes play the same roles in NK- mediated killing of target cells by apoptosis as they do in the CTL-mediated killing process.

NK cells are involved in the early response to infection with certain viruses and intracellular bacteria. NK activity is stimulated by IFN-α, IFN-β and IL- 12 in the coarse of viral infection the level of these cytokines rapidly rises. NK cells are the first line of defense against virus infection, controlling viral replication during the time required for activation, proliferation and differentiation of CTL-P cells into functional CTLs.

Superantigens

Superantigens are viral or bacterial proteins that bind simultaneously to the V_β domain of a T- cell receptor and to the α chain of a class II MHC molecule. Cross – linkage of a T- cell receptor and class II MHC molecule by either type of superantigen produces an activating signal that induces T- cell activation and proliferation. There are exogenous and endogenous antigen, exogenous antigens are soluble secreted bacterial proteins, including various exotoxins. Endogenous superantigens are membrane – embedded proteins produced by certain viruses, these viral proteins called minor lymphocyte-simulating (Mls) determinants.