LYMPHOCYTES

Where are T cells located?

T cells exist in different places depending on the point in the cell cycle. Tcells start in your bone marrow, mature in your thymus and eventually relocate to your lymph tissue or bloodstream.

1. Bone marrow: T cells start in the spongy tissue inside your bone called marrow. Like all blood cells, they start as hematopoietic stem cells. These cells have the potential to develop into any type of blood cell.

2. Thymus: T cells move to an organ called your thymus (located in your upper mid-chest) to mature. At this stage, the immature T cells are called thymocytes. Your thymus is like boot camp for T cells.Once inside, T cells go through testing to be sure they can bind correctly to MHC and won't attack your body's healthy cells. They also receive the right receptor, either CD4 (helper T cells) or CD 8

3. Lymph tissue and bloodstream: Fully mature T cells travel to tissue and organs in your lymph system, such as your spleen, tonsils and lymphnodes.

Lymphocytes consist of T cells, B cells, and natural killer cells (NK).

Lymphoid cells represent about 20% of the total leukocytes population in the adult circulation. Many mature lymphoid cells are long-lived, and may persist as a memory cells for several years, or even for the live time of the individual.

LYMPHOCYTES CAN BE IDENTIFIED BY CHARACTERISTIC MARKERS

Lymphocytes and other leukocytes express different surface molecules witch can be used for distinguishing cell population. A systemic nomenclature called the CD system has been developed, in which the term CD refers to (cluster of designation).
These different cell surface molecules are detected with specific monoclonal antibodies, each of these molecules are given CD number. Molecular markers can be further defined according to the information they offer about the cell. For example;

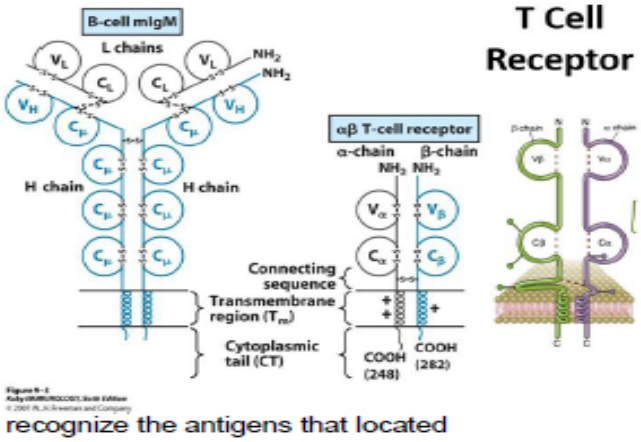
A. Lineage markers are exclusive to a particular cell line, e.g., CD3, which is found only on T cells.

B. Maturation markers are transiently expressed during cell differentiation, e.g., CD1, which is only found on cells developing in thymus and is not present on peripheral T cells.

C. Activation markers. e.g., low affinity T-cell growth factor receptor (IL-2 receptor, CD 25), which is only expressed when the cell is stimulated with antigen.

►T cell receptor can recognize the antigen that located on the MHC

► you can see here the differences and similarities B/W BCR and TCR .
For example , the T cells and B cells have two regions (constant and variable) .



►BCR composed of 4 chains :
1- 2 heavy
2- 2 light

►TCR composed of 2 chains :
1- α chain
2- β chain
each of them contain variable and constant regions .

►the variable region of the α chain and β chain can recognize the antigens that located on the MHC .

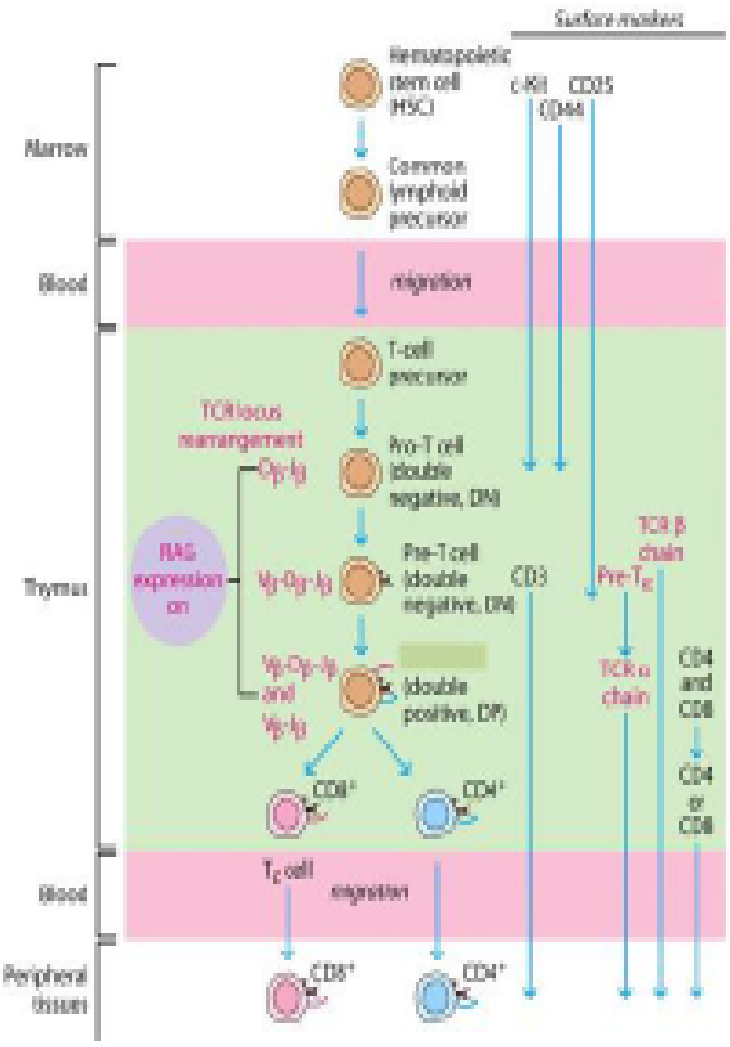
►each chain has :
1- extracellular domain
2- intermembrane domain
3- intracellular domain

►the intracellular domain is very short , and it can't induce any signal into the cell after recognition the antigen.
Because that the TCR needs another molecule to induce the signal to the cell , and this molecule is CD3 (also called **CD3 zeta chain**), which is a co-receptor and it composed of 6 chains :
1- two epslion chains
2- One gamma chain
3- Delta chain
4- Two zeta chains

►there are two types of T cells according to the type of the TCR ;
1- α β T cells
2- μ delta T cells
►90-99% of T cells in our body are α β T cells , and small group of T cells are μ delta T cells about 1-10% .
►the TCR on the α β T cells are very variable but the TCR on the μ delta T cells are not very variable .
► μ delta T cells are more regulatory cells in our body .
►most of the α β T cells are :
1- CD4+
2- CD8+
►there are two types of T cells according to CD4+ and CD8+ :
1- T helper cells
2- Cytotoxic cells

Development of T cells

► T cells develop from hematopoletic stem cells in bone marrow.
Then these stem cells will migrate to the thymus through the blood.
The thymus is the place for development of T cells.



► In the thymus , there are different stages of development of T cells :

1- **The first stage** : here the T cells is pro-generator T cells (which derived from T cell precursor or thymocytes)and they are <u>double negativeT cells</u> (because there are no CD4+ or CD8+ on their surfaces), then these cells will differentiate into pre-generator T cells.

   In the pro-generator T cells , the D-J recombination will occur , and after the recombination will complete.

   Pro-generator T cell can produce β chain (the recombination will start from here), which express on the surface of pro-generator T cells in association with surrogate TCR-α chain (they are present also in the development of BCR).

2- **Second stage** : here we have <u>double positive T cells</u> (means , these cells can express CD4+ and CD8+ on their surfaces).

3- **Third stage**: here we have single positive T cells, some of these will become CD4 and some of them will become CD8 .

4- **Then the mature T cells will leave the thymus and migrate to the circulation to recognize the antigen to be activated .**

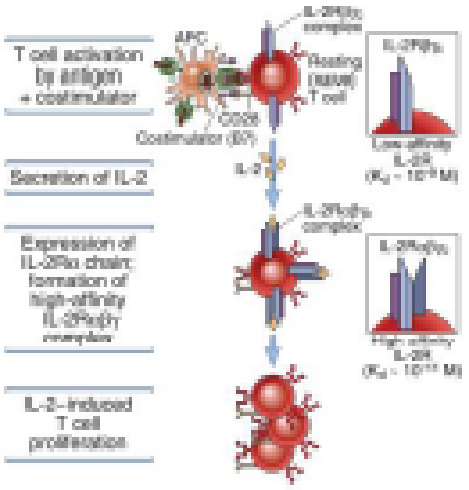
► during the development of T cells , the rearrangement of genes occurs in variable region .

► Interleukin-2 is an important cytokine that can activated the T cells and also it ahs an autocrine functions.

► there are two forms of interleukin -2 receptors ;

1- **low affinity interleukin-2 receptor:** which is composed of β, and μ chains
2- **high affinity interleukin-2 receptor:** which is composed of α , β, and μ chains .

Naive T cells express the low affinity IL-2 receptor



► cytokines can promote their functions by binding to the receptors .

► before recognition of antigens , T cells or B cells are called naive T cells or naive B cells .

► naive T cell have low affinity interleukin-2 receptors .

► after activation of T cells , T cells can express high affinity receptors .

► so , naive T cells have low affinity interleukin-2 receptors .
Activated T cells have high affinity interleukin-2 receptors

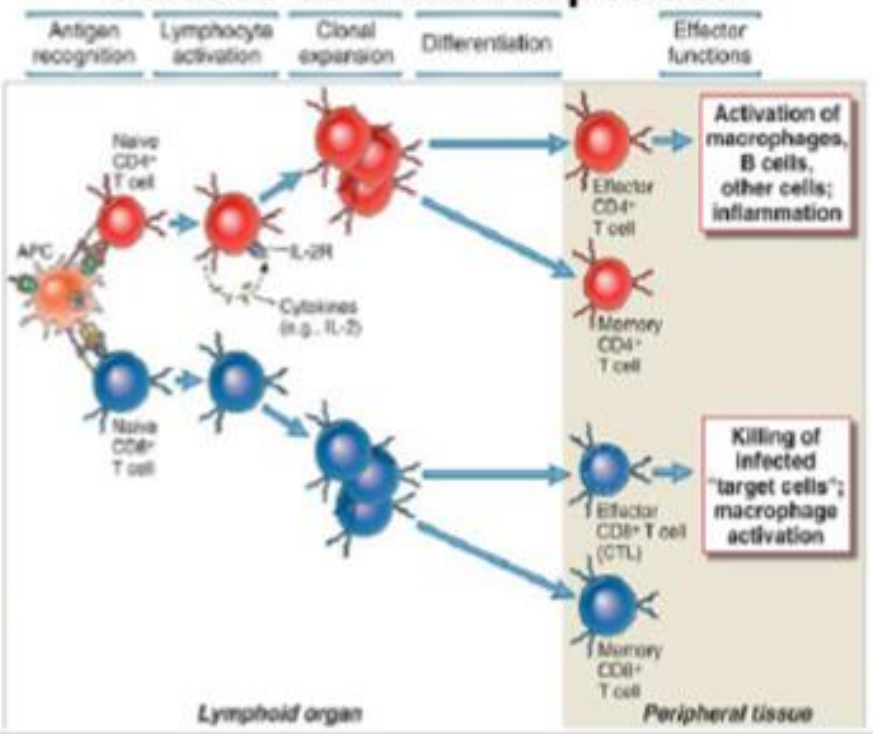
► in this slide you can see different phases of development .
After recognition , part of the development of T cells will occur in the thymus .

► after recognition ,the activation phase of the development will start .

► naive T cells can develop into:

1- effector T cells
2- memory T cells

Phases of T cell responses



► before development of naive T cells into effector and memory T cells , we have a phase called **clonal expansion phase** (proliferation of T cells) , because in each colony of T cells , there are a low number of T cells , and this low number is not sufficient for having a functional response for infection or other responses , that's why before development of naive T cells , they should be proliferate to increase the number of T cells in each colony, then the naive T cells can develop into effector and memory T cells .

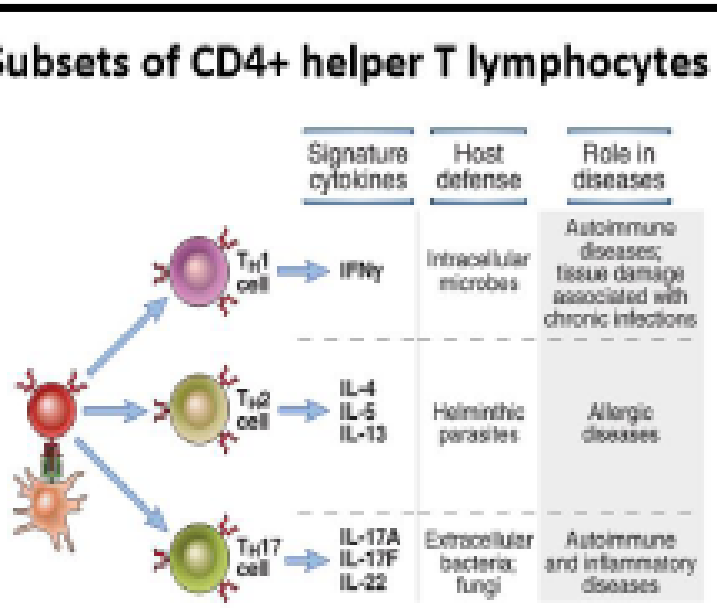
► the effector type of CD4+ T cells is called T helper cells .
T helper cells have many types :

1- TH1
2- TH2
3- TH17

And these types can produce different types of cytokines , for example , the TH1 have CD4+ on their surfaces and they can produce IFn-μ .

TH2 have CD4+ on their surfaces and they can produce Interleukin-4 , Interleukin-5 and Interleukin-13

TH17 have CD4+ on their surfaces and they can produce Interleukin-17A , Interleukin-17F and Interleukin-22 .



These types of T helper cells have different functions , for example , TH1 response to the intracellular microbes , and they will activated the macrophages cells by INF-μ to kill these microbes

TH2 response to parasite and including in allergic disease because they can produce Interleukin-4 that is very important in allergic disease

The cell surface molecules (markers) exist as a number of different families.

A. The **immunoglobulin superfamily** contains molecules whose structural characteristic are similar to those of the immunoglobulins. This family includes CD2, CD3, CD4, CD8, murine Thy-1, and many more.

B. The integrin family consists of heterodimeric molecules containing α and β chains. There are a number of integrin subfamilies; all members of a particular subfamily share a common β chain, but each has a unique α chain. One subfamily the β**2 integrins** uses CD18 as the β chain. This chain can be associated with CD11a, CD11b, or CD11c; these combinations make up the lymphocyte function antigen LFA-1, Mac-1 (CR3) and p150, 95 (CR4) surface molecules respectively and are commonly found on leukocytes. The second subfamily, the β**1 integrins** has CD29 as the β chain, again associated with various other polypeptides, and includes the VLA (very late activation) markers.

C. Selectin (E, L, and P), expressed on leukocytes (L), or activated endothelial cells (E and P). They have lectin like specificity for a variety of sugars expressed on heavily glycosylated membrane glycoproteins.

D. Proteoglycans typically CD44, which can bind to components of extracellular matrix.

Lymphocytes are morphologically heterogeneous

Lymphocytes show several variations in the size (6-10 μm) and morphology. These variations are seen in the:

A. Nuclear to cytoplasmic ratio (N: C ratio).

B. The nuclear shape.

C. The presence or absence of azurophilic granules.

T cells can be distinguished by their different antigen receptors.

There are two defined T-cell receptors.

TCR-2 is a heterodimer of two disulphide-linked polypeptides (α andβ); and

TCR-1 is structurally similar but consists of γ and δ polypeptides.

Both receptors are associated with five polypeptides, the CD3 complex, to give the T-cell receptor complex (TCR-CD3 complex). Approximately 90-95 %

of blood T cells express TCR-2 (α,β), and the remaining 5-10 % are TCR-1+ (γ,δ)

PHYSICAL STRUCTURES OF T CELL RECEPTOR (TCR) GENES

At the gene level, the TCR genes α, γ, β, and δ are organized into separate gene segments designated variable (V), diversified (D), joining (J), and constant (C) regions.

The α, and γ genes only have the V, J, and C segments, while the β, and δ genes have all four segments.

There are more than one V, D, J, and C within each gene locus, with the V and J segments having the highest number; the numbers of each gene segment are different in mice and human.

As in the case of B cells, a unique feature in T cell development is the generation of T cells, each with a specific TCR that recognizes a specific peptide antigen.

While B cells recognize conformational epitopes, the TCR expressed on T cells recognizes antigenic peptides that are associated with the major histocompatibility complex (MHC) that are presented by antigen-presenting cells (APC).

The generation of T cells, each cell with a unique TCR specificity, is achieved by cutting an d joining regions of various gene segments encoding the TCR.

The process is known as gene rearrangement and is executed by the products of two separate genes, the recombination activation genes 1 and 2 (RAG-1, RAG-2) **.**

Figure 1

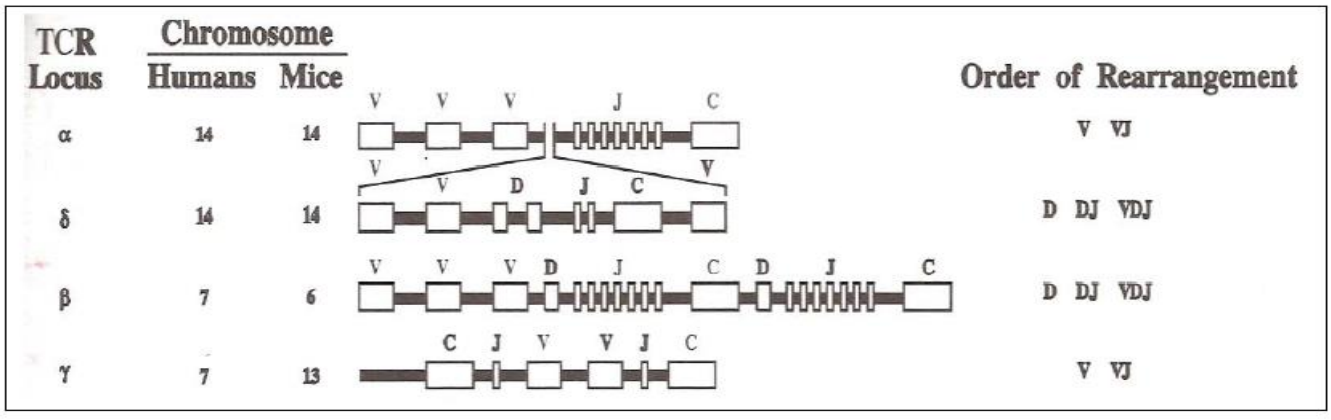


Figure-1 Organization of the T cell receptor α, δ, β, and γ chain genes in humans and mice. In the α and γ chains, the order of rearrangement is VJ since there are no D segments. In contrast, the order of rearrangement is D to J and DJ to V forming VDJ in the β, and δ T cell receptor chain genes.

TCR - cells are further distinguished by their expression of CD4 or CD8

TCR-2+ T cells can be subdivided into two distinct non-overlapping populations: a subset which carries the CD4 marker (MHC class II receptor) and mainly '**help**' or '**induce**' immune responses (**TH**), and the other subset which express the CD8 marker (MHC class I receptor) and it is predominantly cytotoxic (**TC**) The expression of either CD4 or CD8 determine the type of cells that the T cell will react to, because T cells carries CD4 will recognize the antigens associated with MHC class II, and T cells which carries the CD8 marker will recognize the antigens associated with the MHC class I. Most TCR-1+ cells do not express either the CD4 or the CD8 marker, although a few of them may be CD8+

CD4 AND CD8 CO-RECEPTORS

The two proteins α, and β, are used by T cells for antigen recognition; and four more, γ, δ, ζ, and ε, to use for signaling. Killer T cells and helper T cells perform two very different functions, and they "look at" two different molecules, class I or class II MHC, to get their cues. After all, it wouldn't be so great if a CTL got confused, recognized as class II-peptide complex on APCs, and killed that cell. So here's where CD4 and CD8 come in. CTLs generally express CD8 and Th cells usually express CD4, and these co-receptor molecules are designed to clip onto either class I MHC (CD8) or class II MHC molecules (CD4), and strengthen the adhesion between the Tcell and the APC **(Figure-3)**. So CD4 and CD8 co-receptors function to focus the attention of CTLs and Th cells on the proper MHC molecule. But there is more to the story, because it turns out that CD4 and CD8 are signaling molecules just l like the CD3 complex of proteins. Both CD4 and CD8 have tails that extend through the cell wall and into the interior (cytoplasm) of the cell, and both of these tails have the right characteristics to signal. In addition, because CD4 is a single protein and CD8 is composed of two different proteins, the signals that these co-receptors send are likely to be quite different, perhaps as different as "help" and "kill". In contrast to the CD3 molecules, which are glued rather tightly to the αβ T cells receptor on the cell surface, the CD4 and CD8 co-receptors usually, are only loosely associated with the TCR/CD3 proteins. The latest thinking is that the MHC molecule on the APC actually functions as a "clamp" that brings together the TCR/CD3 complex and the jCD4 or CD8 molecule on the surface of the T cell, and that this clustering of TCR/CD3 with CD4 or CD8 greatly amplifies the signal sent by the TCR.

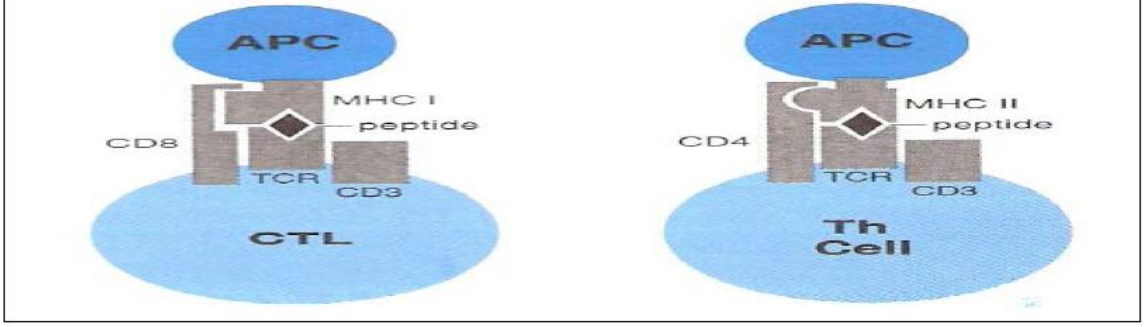


Figure-3 CD4 and CD8 co-receptor

The functional subsets of TCR-2+ CD4+ cells

On the basis of function, CD4+ cells can be subdivided into two sets of cells.

A. CD4+ cells which positively influence the response of T cells and B cells (the helper cell function) are CD29+.All the cells of this population also express the CD45R0 (leukocyte common antigen). Thus this population will carry the CD4+ CD29+ CD45R0 markers and they are helper T cells.

B. CD4+ cells that induce the suppressor/cytotoxic functions of CD8+ cells (the suppressor/inducer function), these cells also carry CD45RA marker.
The CD45RA and CD45R0 TH cells have been found to be 'naive' and memory cells respectively. But a current opinion holds that the expression of CD45R0/CD29 by CD4+ cells is more relevant to the state of activation of the cell.

TCR-2+ CD4+ lymphocytes can also be classified on the basis of the cytokine secretion

The TH cells can be divided into two sets of cells depending on the cytokine secretions.
TH1 subset secretes IL-2 and IFNγ and the TH2 subset produces IL-4, IL-5, IL-6, and IL-10.
TH1 cells mediate several functions associated with the cytotoxicity and local inflammatory reactions. Generally these cells are important for combating **intracellular pathogens** including **viruses, bacteria and parasites.**
TH2 cells are more effective at stimulating the B cells to proliferate and produce antibodies, the therefore function primarily to protect against free-living microorganisms (humoral immunity).

There are subsets of CD8+ cells (expresses MHC class I receptors)

CD8+ (cytotoxic) T cells can be subdivided into specific functional subsets according to a number of criteria and using a variety of monoclonal antibodies. One subset expresses CD28 molecules and **produces** IL-2 in response to activation signals. Another subsets **respond** to (**but does not produce**) IL-2 and **expresses** the heterodimeric CD11b /CD18 molecule (**CR3**).
Cells of the first subset show a distinct **Gall body**, whereas cells of the second subset show **LGL** morphology.

Activation markers on lymphocytes

These activation markers include;

♦ Adhesion molecules (allow efficient interaction with other cells).

♦ Receptors for growth and differentiation factors (required for continued proliferation and maturation). For example,

IL-2 receptor which expressed following T cell **activation** is composed of three subunits. Resting T cells have the β unit (a low-affinity receptor of 55 kDa (CD25), and the γ unit. On activation the α subunit (70 kDa) is induced resulting in heterotrimeric high affinity IL-2 receptor. The **gp39 (CD71**) is a receptor for transferrin, it transiently expressed on the activated T cell, and it is important for **proliferation**.

Class II MHC molecules are present on human T cell as a **late activation marker**. **CD29** is expressed on the T cells and the memory cells as a **very late activation marker.**

Activation markers on B cells include the **high affinity IL-2R**, and other receptors for growth and differentiation

factors such as **IL-3, IL-4, IL-5, and IL-6**. **CD71** (transferrin receptor), and elevated level of **class II MHC**

molecules are also expressed.

CD23 (FcεRII, a low-affinity IgE receptor) drives B cells into proliferation.

CD38 is present on plasma cell.

How do T cells work in the immune system?

T cells work once they're activated. Several steps have to happen before T cell activation:

1. A cell called an antigen-presenting cell (APC) locates evidence of the intruder and attaches it to a structure called major histocompatibility complex (MHC). This step is important because T cells can't recognize evidence of an intruder unless it's attached to MHC.

2. The T cell binds to the MHC. There are two types of MHC. One fi tseach type of T cell. The CD8 receptor on a cytotoxic T cell can only bind to MHC-1. The CD4 receptor on a helper T cell can only bind toMHC-II.

3. Once the T cell binds with all the matching parts, it activates. The binding is important because it ensures that the T cell is the right one to filter the intruder.

An activated cytotoxic T cell kills infected cells or cancer cells. Anactivated helper T cell sends signals that tell other immune cells what actions to take to fi ght the intruder.

What are the different types of T cells?

There are two main types of T cells:

1. **Cytotoxic T cells:** Cytotoxic T cells are also called CD8+ cells because they have a CD8 receptor on their membranes. These cells get their name from "cyto," which means cell, and "toxic," which means poisonous or harmful. Cytotoxic T cells kill cells infected with viruses and bacteria, and they also destroy tumor cells.
2. **Helper T cells:** Helper T cells are also called CD4+ cells because they have a CD4 receptor on their membranes. Unlike cytotoxic T cells, helper T cells don't kill cells directly. Instead, they send signals that tell other cells in your immune system how to coordinate an attack against invaders. Helper T cells signal cytotoxic T cells, B cells and another type of white blood cell called a macrophage.

Although they're not considered one of the main T cell types, regulatory T cells (suppressor cells) play an essential role in your immune system. These cells reduce the activity of other T cells when necessary. They can prevent T cells from attacking your body's healthy cells.

What are the common conditions and disorders that affect T cells?

Several types of

1. **Autoimmune diseases and immunodeficiency disorders**

can affect your T cells. With autoimmune diseases, your immune system malfunctions and attacks your healthy cells. Immunodeficiency disorders may be inherited or acquired, but they involve having a weakened immune system.

Conditions that can affect your T cells include

2. **Acute lymphocytic leukemia**

A type of cancer that starts in yourblood and bone marrow.

3. **Chronic T-cell leukemia (T-cell prolymphocytic leukemia)**

A blood cancer that starts in your T cells that can affect your bone marrow, blood and lymph nodes.

4. **HIV** A virus that attacks your white blood cells (especially your CD4+T cells) and potentially leads to AIDS.
5. **Job syndrome**

A rare immune system disorder that causes repeatinfections.

6. **Severe combined immunodefi ciency (SCID)**

A group of rare genetic disorders that involves a weakened immune system resulting from problems with T-cells and other lymphocytes.

7. **Thymic aplasia**

A condition in which you're born with an underdeveloped thymus.

8. **Wiskott-Aldrich syndrome**

A rare genetic condition that involves immune system issues, including atypical white blood cells.