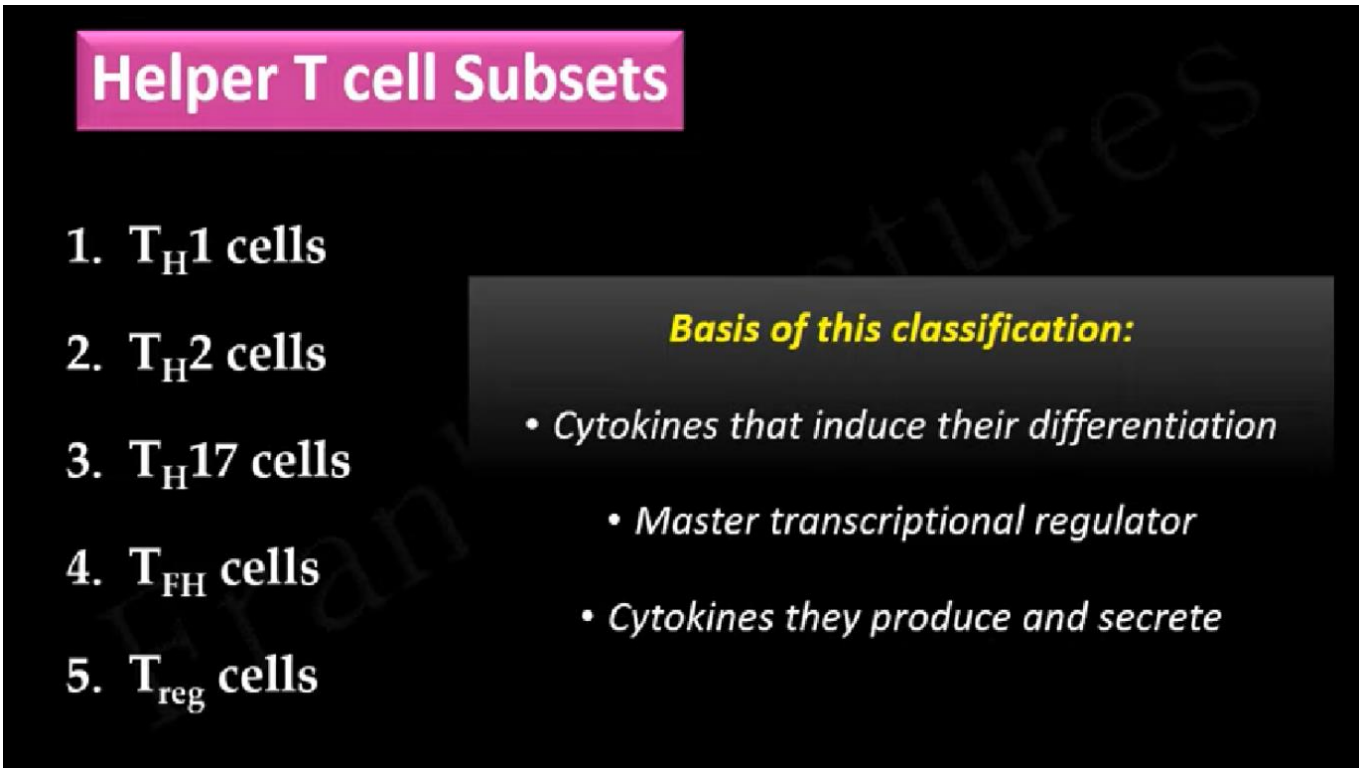
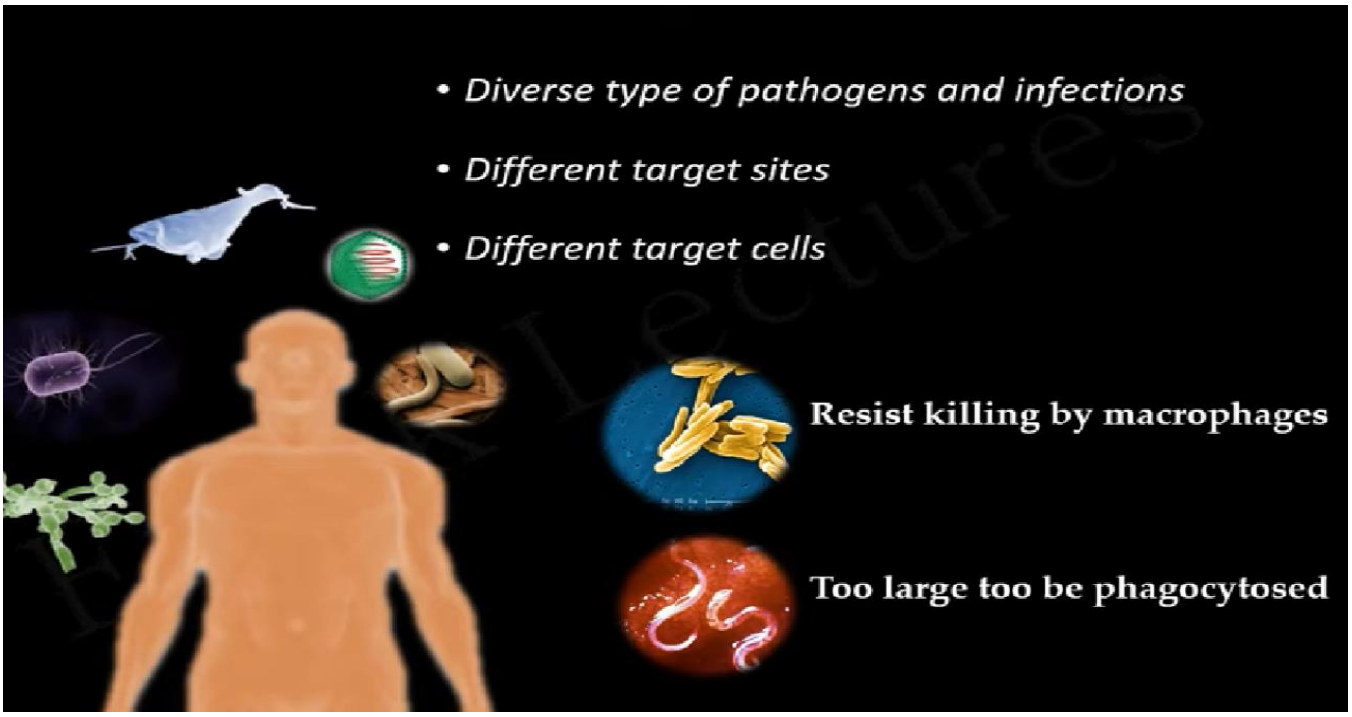
**Lecture 7of Advanced Immunology**
**By Dr Alia Alubadi**

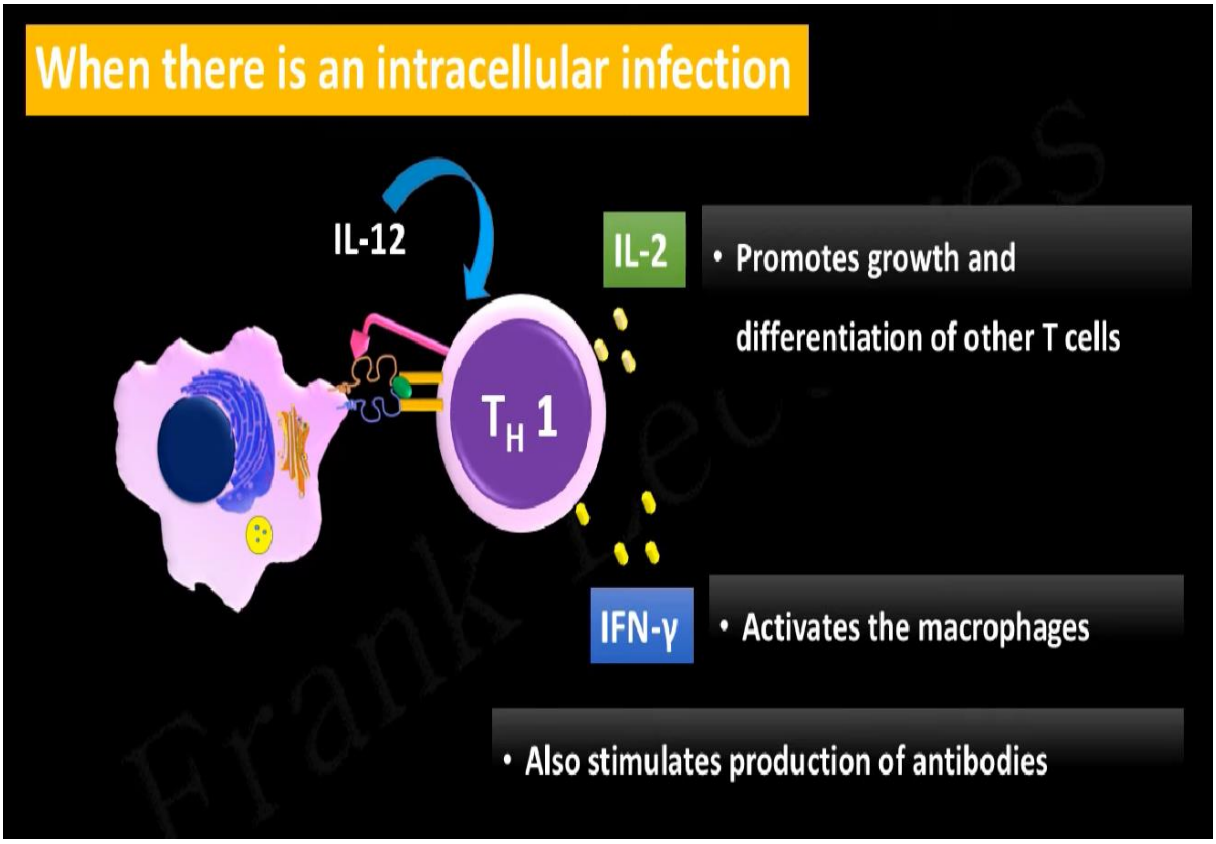


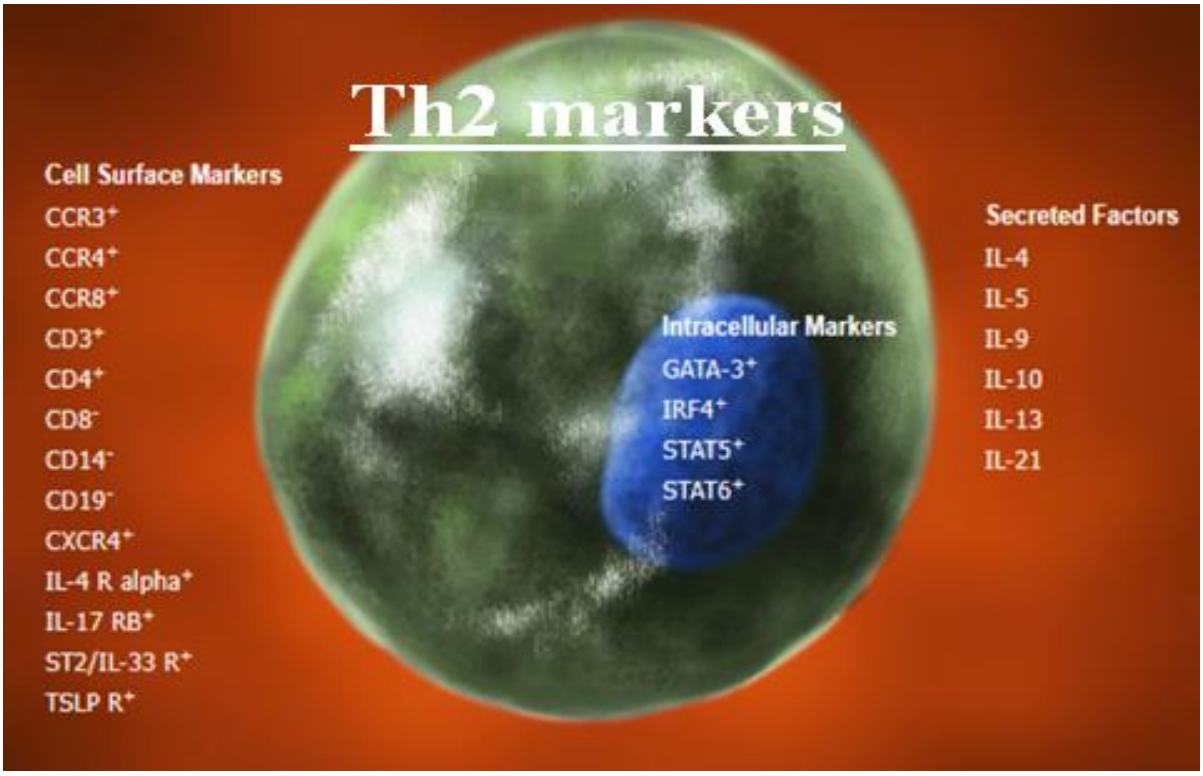




**Th1 and Th2 Cells** are a subset of CD4+ effector T cells, depending on the cytokines they synthesize and secrete, CD4+ helper T cells (Th) can be divided into two subgroups, type I helper T lymphocytes (Thl) and type II helper T cells (Th2). Both types of cells are differentiated from common T cell helper precursor (Thp). Although the differentiation of T cells is affected by **antigen concentration**

**or co-stimulatory molecules, cytokines are the most effective regulators** of Th cell differentiation. In addition, the effects of the **extracellular microenvironment** and **transcription factors** have also played a major role.
Th1 and Th2 cells play an important role in immunity.

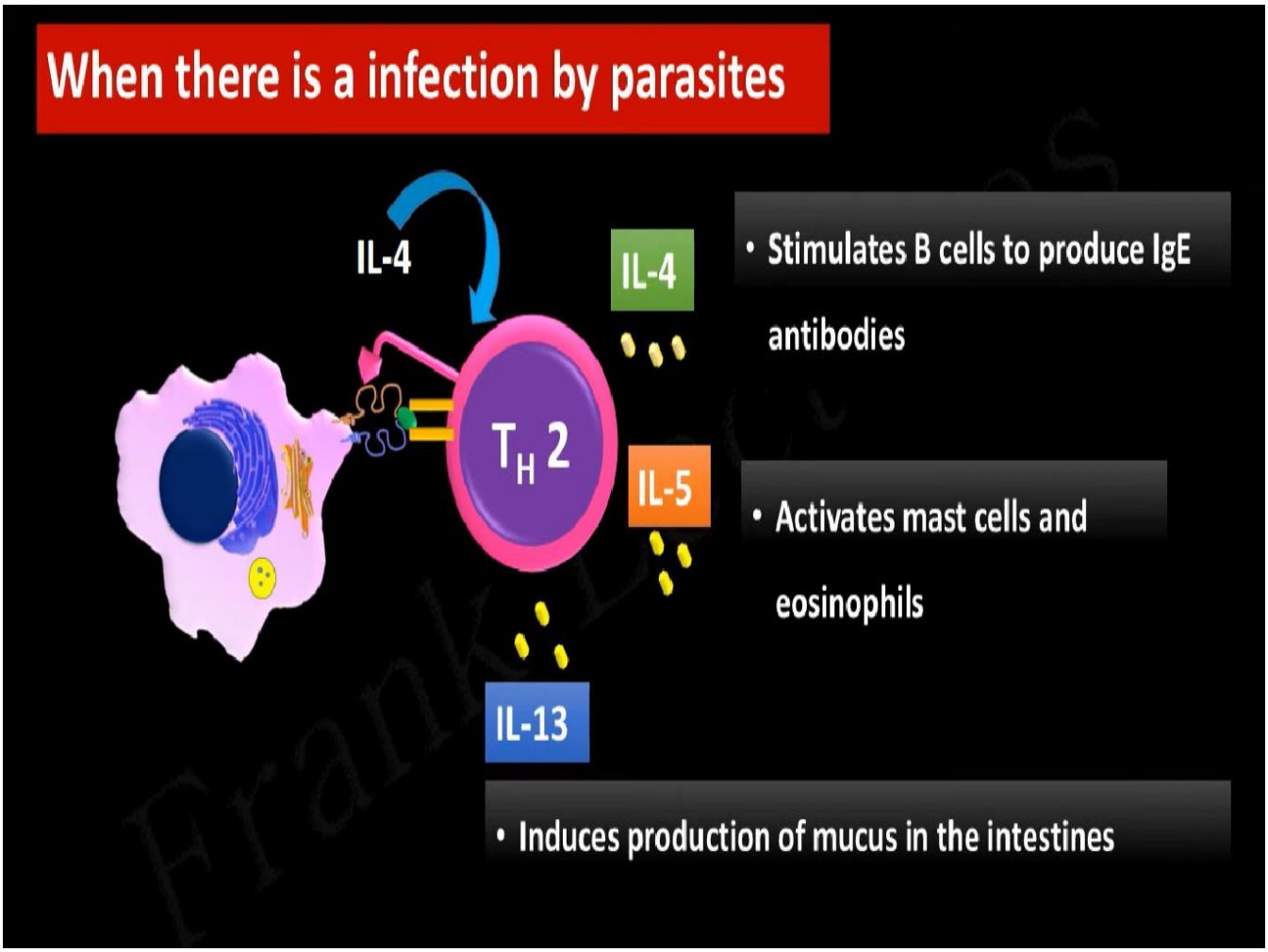

**T helper type 1 (Th1) cells (Th1 cells stimulate the cellular immune response)** that is required for host **defense against intracellular viral and bacterial pathogens**. Th1 cells develop **from activated, naïve CD4+ T cells in the presence of IL-27, IL-12, and IFN-gamma**. They can be distinguished from other CD3+CD4+CD8- T cells based on the cell surface **expression of IL-12 R beta 2, IL-27 R alpha/WSX-1, IFN-gamma R2, IL-18 R, CCR5, and CXCR3**, and the expression of the transcriptional regulators, STAT4 and T-bet, the latter of which is considered to be the master transcriptional regulator required for Th1 cell development. Th1-secreted cytokines induce classical macrophage activation, as well as the activation of natural killer cells and cytotoxic CD8+ T cells. If unregulated, Th1 cells can contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, and type 1 diabetes.

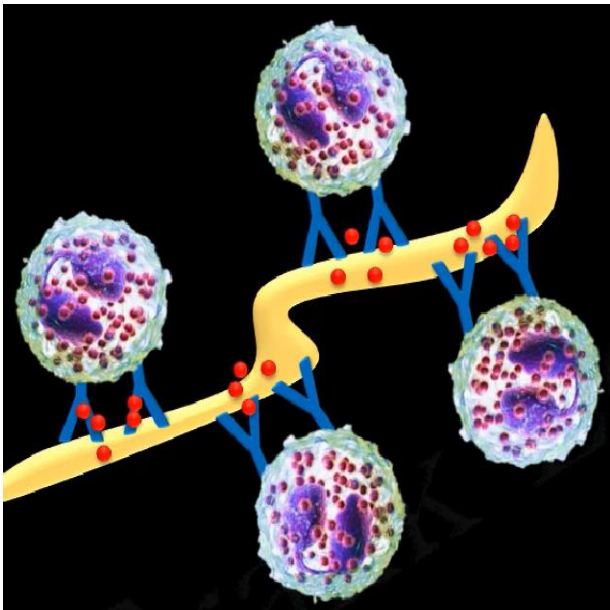



**T helper type 2 (Th2) cells** that **is required for humoral immunity** and is important for host defense **against large extracellular pathogens such as helminths**. Following activation, naïve $CD4^+$ T cells differentiate into Th2 cells **in the presence of IL-4 and either IL-2, IL-7,** or thymic stromal lymphopoietin

(TSLP). Th2 cells are commonly distinguished from other $CD3^+CD4^+CD8^-$ T helper cell subsets based on expression of the cell surface markers CCR3, CCR4, CCR8, CXCR4, and ST2/IL-1 R4, along with the transcriptional regulators, STAT5, STAT6, and GATA-3, the last of which is the master transcriptional regulator required for Th2 cell development. In addition to these markers, **the cytokines commonly secreted by Th2 cells, including IL-4, IL-5, IL-9, IL-13, and IL-17E/IL-25** can also be used to distinguish Th2 cells from other $CD4^+$ effector T cell subsets. Th2-associated cytokines promote **the survival and proliferation of mast cells, induce chemotaxis of mast cells, basophils, and eosinophils**, **regulate the production of IgE antibodies by B cells, and promote alternative macrophage activation.** Unregulated Th2 responses have been associated with the development of atopic diseases such as allergic rhinitis and asthma.



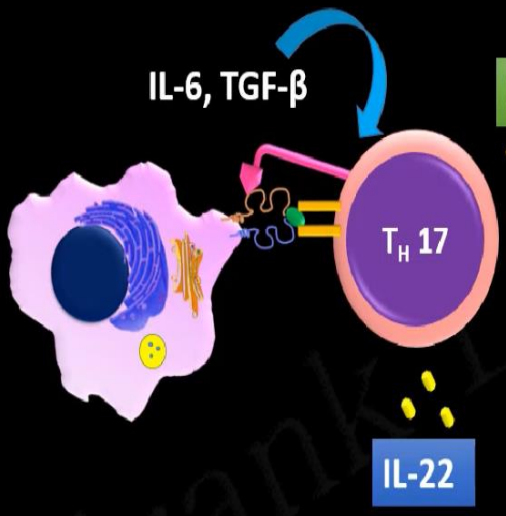


*1.* IgE antibodies coat the surface of the parasite

2. Mast cells and eosinophils bind to the Fc region of these bound antibodies.

3. The enzymes released by degranulation of these cells result in the destruction of parasite.

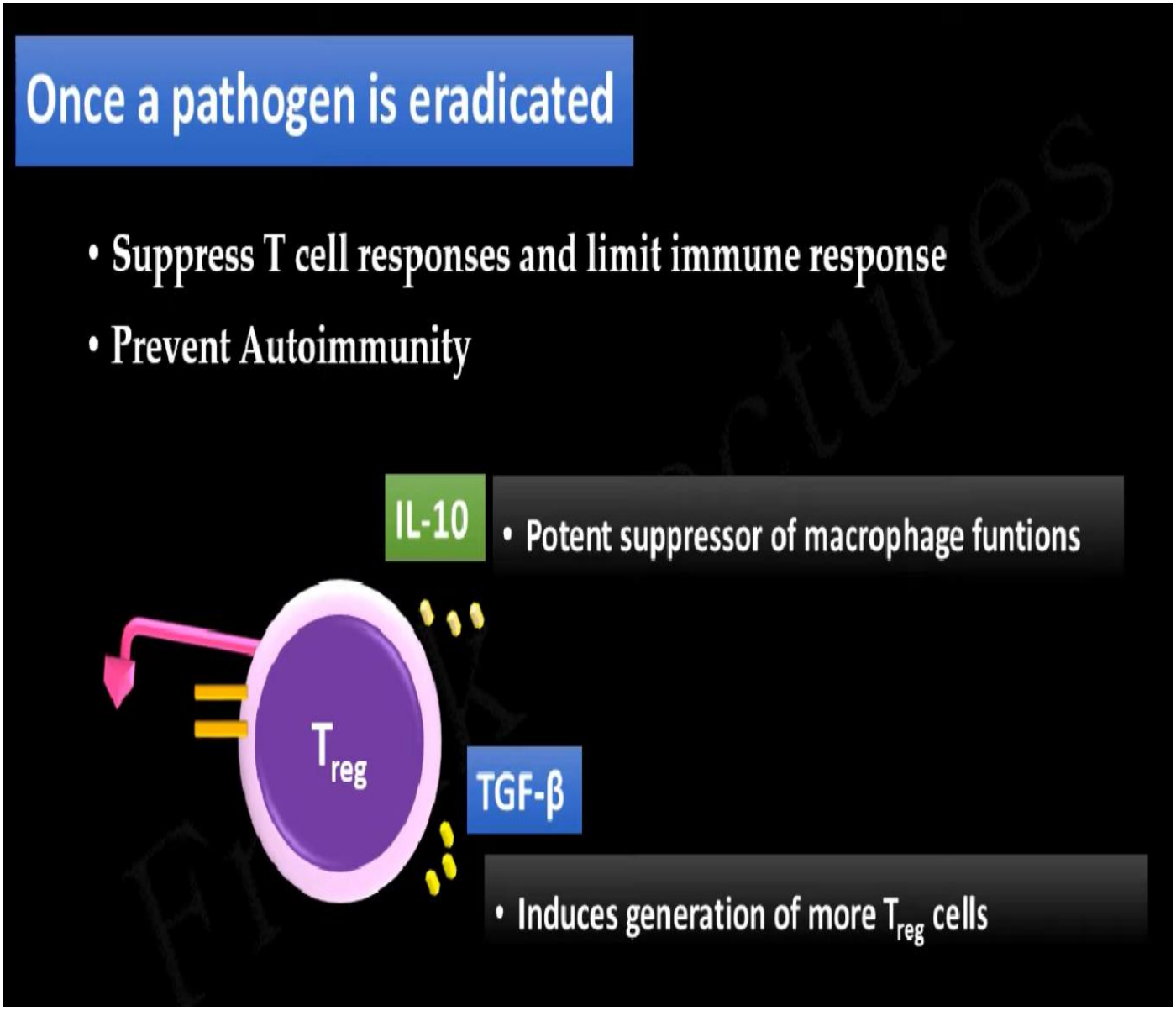
## When there is a infection by fungi or extracellular bacteria



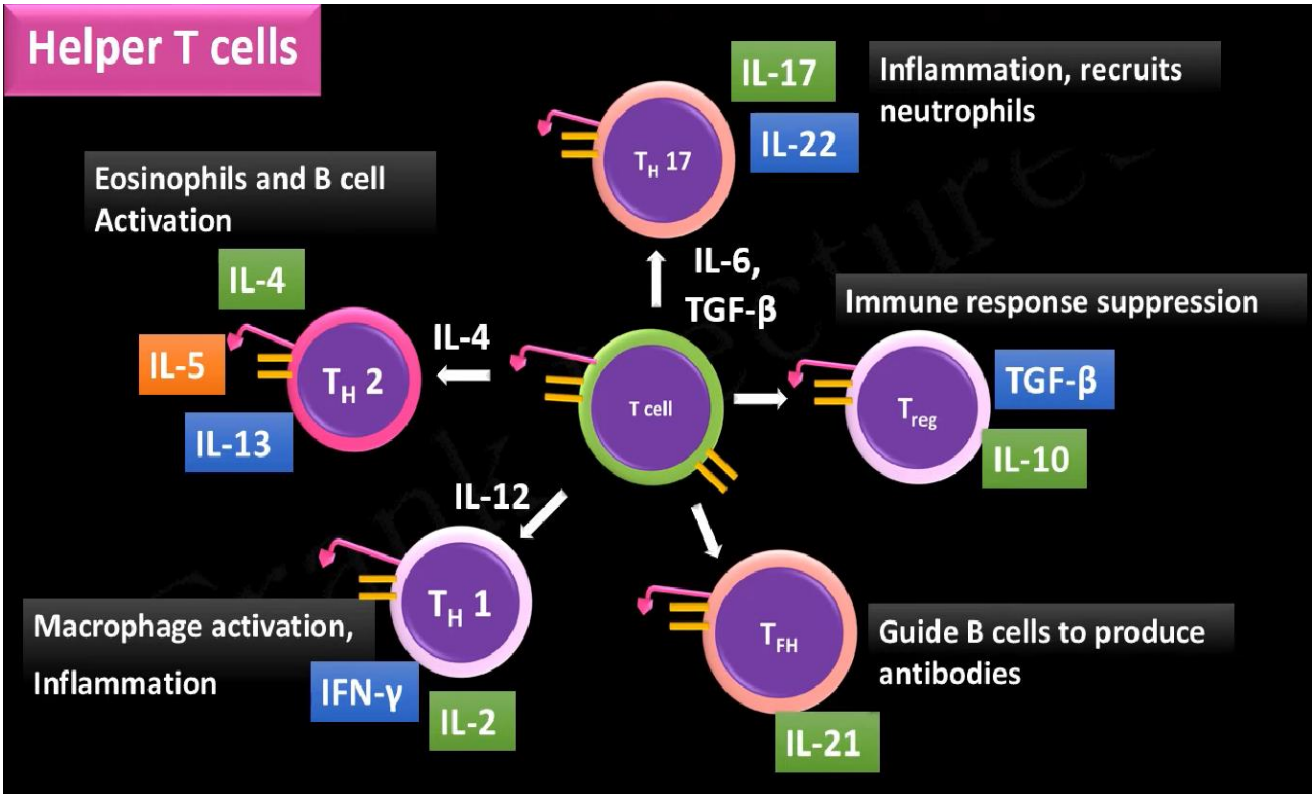

- Recruit neutrophils to the site of infection

- Stimulate epithelial cells to produce antimicrobial peptides


**Regulatory T (Treg)** cells are a subset of **$CD4^+$ T** cells **that is involved in maintaining immune homeostasis and self-tolerance by inhibiting the pro-inflammatory activities of $CD4^+$ and $CD8^+$ effector T cells, natural killer cells, and antigen-presenting cells.** Regulatory T cells develop from activated, naïve $CD4^+$ T cells in **the presence of TGF-beta and IL-2** and several subsets have been described in the literature including naturally occurring $CD4^+CD25^+FoxP3^+$ cells that develop in the thymus (tTregs), peripherally-derived Tregs (pTregs) that are generated from $FoxP3^-$ conventional T cells at sites outside of the thymus, and induced regulatory T cells (iTregs) that are generated *in vitro* by stimulation of mouse conventional T cells with TGF-beta and IL-2. Tregs are most commonly identified as $CD3^+CD4^+CD25^+FoxP3^+$ cells in both mice and humans. Additional cell surface markers include CD39, 5' Nucleotidase/CD73, CTLA-4, GITR, LAG-3, LRRC32, and Neuropilin-1. Tregs can also be identified based on the secretion of immunosuppressive cytokines including TGF-beta, IL-10, and IL-35. While Treg deficiencies or a lack of appropriate Treg activity can contribute to the pathogenesis of inflammatory and autoimmune diseases such as rheumatoid arthritis, type I diabetes, multiple sclerosis, and systemic lupus erythematosus, unregulated Treg activity can also be pathogenic if beneficial, pro-inflammatory immune responses are suppressed.



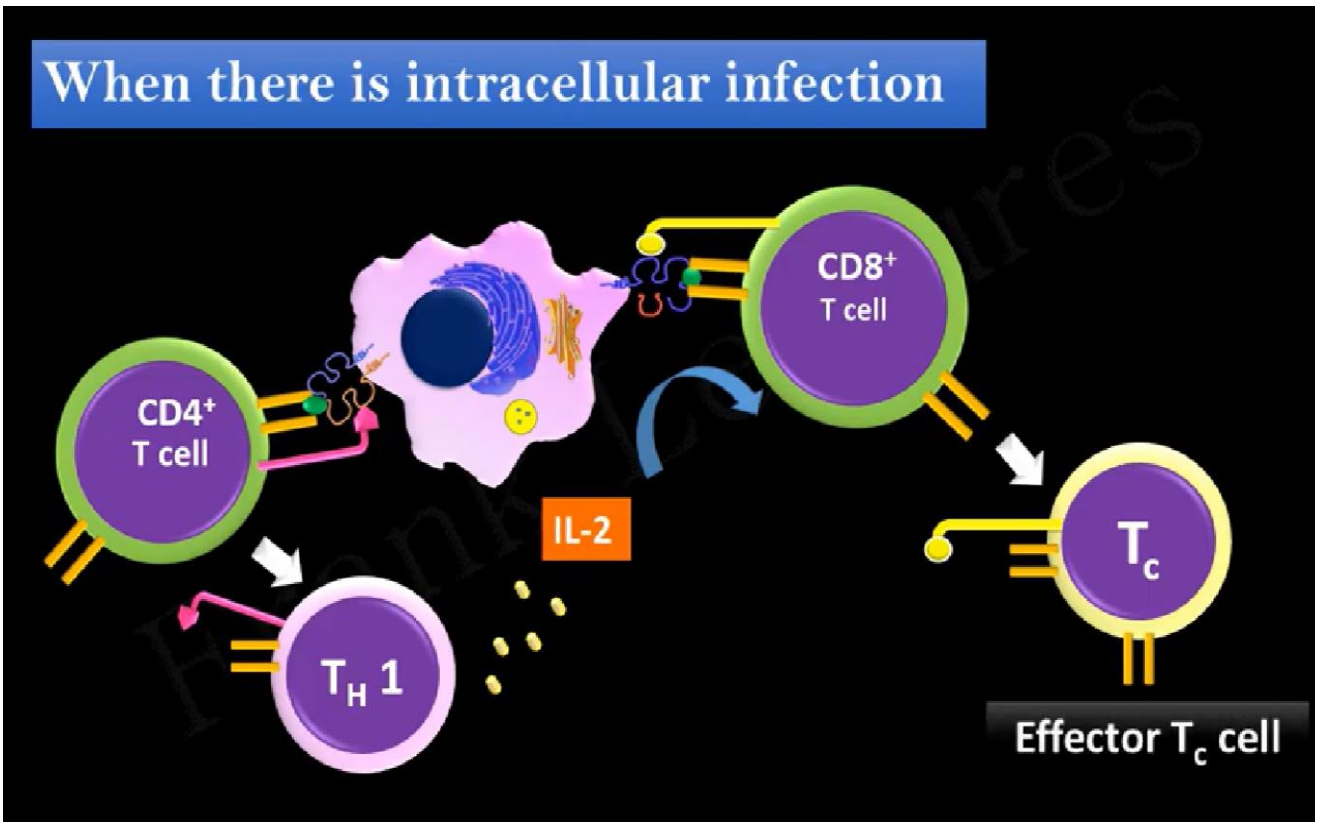

**Under normal circumstances, the differentiation of Thl/Th2 cells is in a balanced** state, and once the balance of Thl/Th2 cells is shifted, it will lead to the occurrence of diseases. **Overexpression of Th2 can lead to inappropriate immune responses, leading to diseases such as allergies and asthma. Overexpression of Th1 or Th17 can lead to autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.**

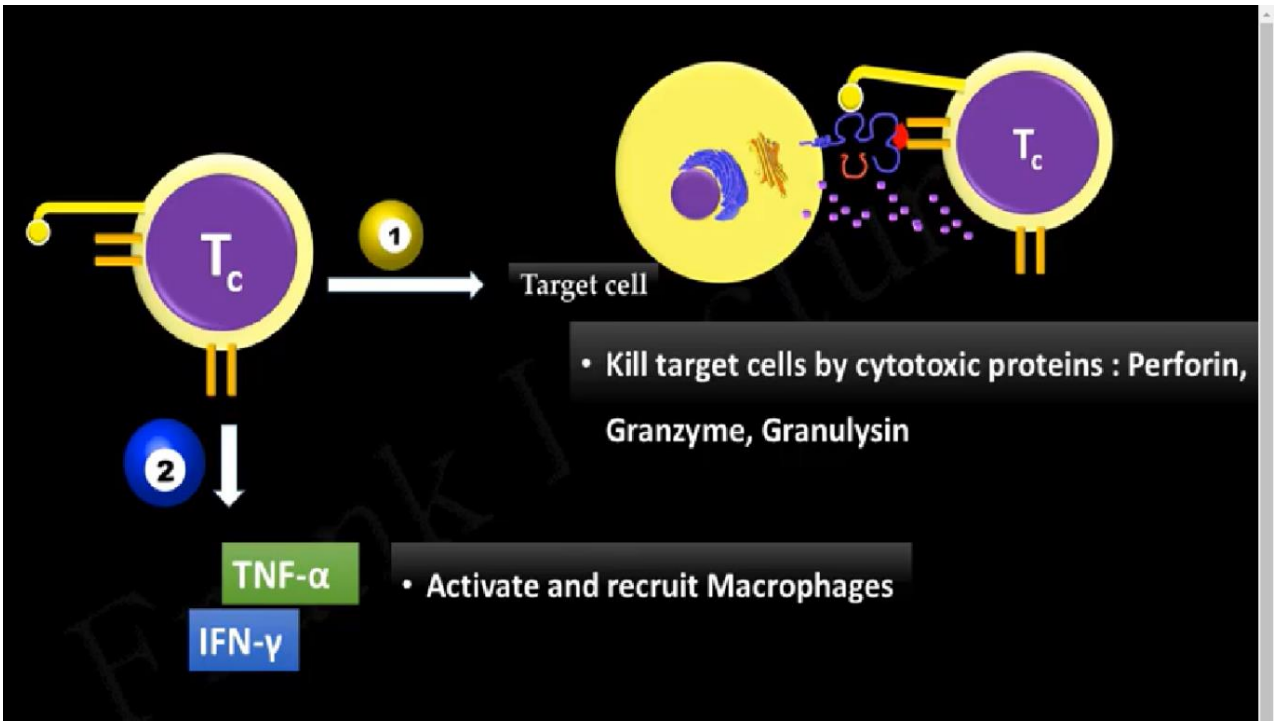


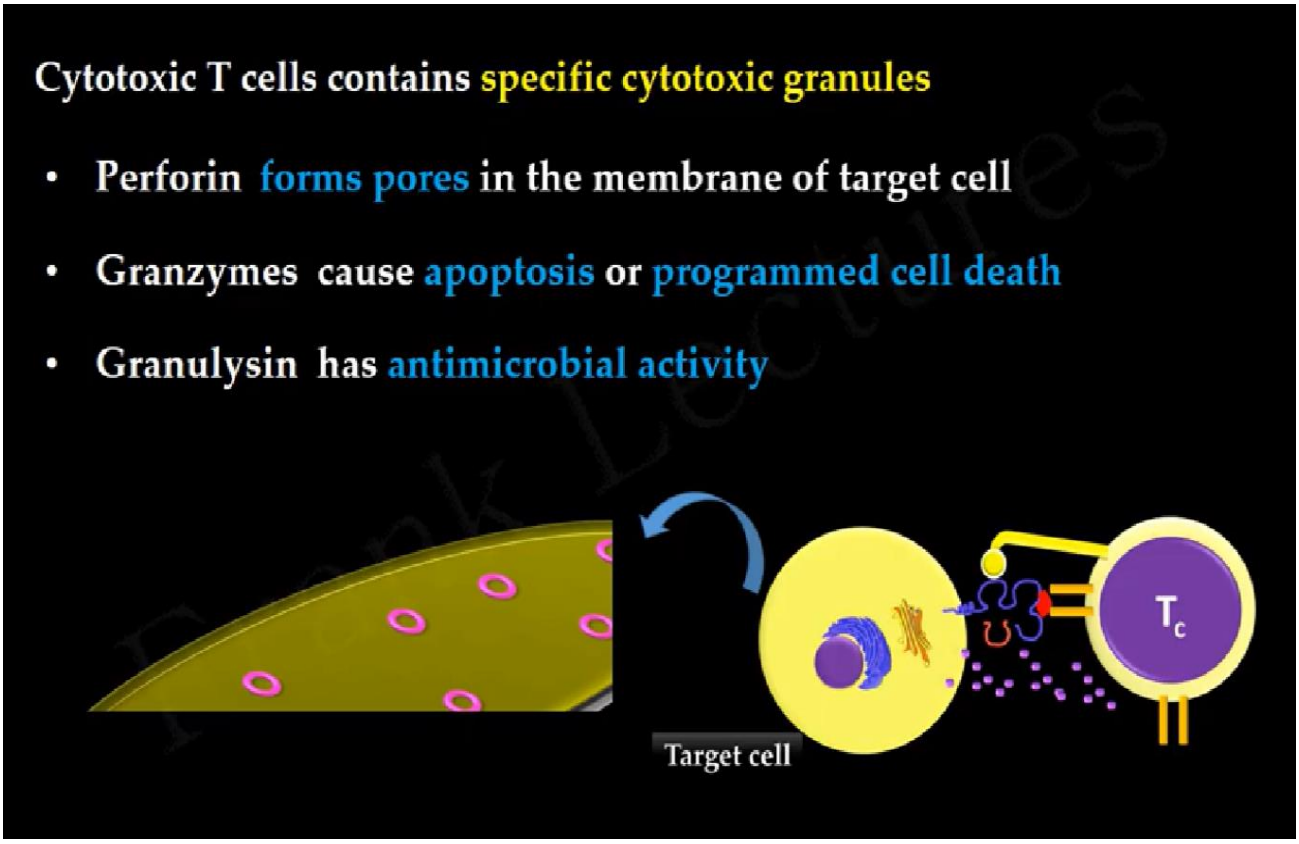

**A cytotoxic T cell is** a T lymphocyte that kills cancer cells, virally infected cells and cells that are under damage. Most T lymphocytes express a subset of surface markers such **as CD8, CD45 and CD54**. **CD28** expresses on the surface of T cells and provide co-stimulatory signals required for T cell activation.

All T cells --> TCR on the surface; TCR's of cytotoxic T's bind to Ag on the surface of the virus-infected eukaryotic cell --> destroy target cell by triggering apoptosis. Cytotoxic T cells can trigger apoptosis by juxtacrine signalling; alternatively, they can use proteins called perforins to make holes in their targets. Then other proteins enter the holes and trigger apoptosis.

**Note complement is similar to perforins but** works **on prokaryotic invaders**; **perforins work on rogue eukaryotic cells**. (This is why grafts fail; foreign cells of graft look like infected (defective) cells and are destroyed.


When there is intracellular infection
CD8+ T cell
CD4+ T cell
IL-2
TH 1
Tc
Effector Tc cell


Tc
1
Target cell
Tc
• Kill target cells by cytotoxic proteins : Perforin, Granzyme, Granulysin
2
TNF-α
IFN-γ
• Activate and recruit Macrophages




**Note : juxtacrine signalling** (or contact-dependent signalling) is a type of cell-cell or cell-extracellular matrix signalling in multicellular organisms that require close contact. Hence, **this stands in contrast to releasing a signalling molecule by diffusion into extracellular space,** the use of long-range conduits like **membrane nanotubes and cytonemes (akin to 'bridges')** or the use of **extracellular vesicles like exosomes or microvesicles (akin to 'boats'**). There are three types of juxtacrine signalling:

A membrane ligand (protein, oligosaccharide, lipid) and a membrane protein of two adjacent cells interact.

A communicating junction links the intracellular compartments of two adjacent cells, allowing **transit of relatively small molecules**.

An extracellular matrix glycoprotein and a membrane protein interact.

**Mature B cells** the **key markers include IgM and CD19**, a protein receptor for antigens. **Activated B cells express CD30**, a regulator of apoptosis. **Plasma B cells lose CD19 expression, but gain CD78**, which is used to quantify these cells.

**Co-stimulation** is a secondary signal which immune cells depend on to activate an immune response in the presence of an antigen-presenting cell.

**Co-stimulatory molecules** are a **heterogeneous group** of cell surface molecules that act to **amplify or counteract the initial activating signals provided to**:-

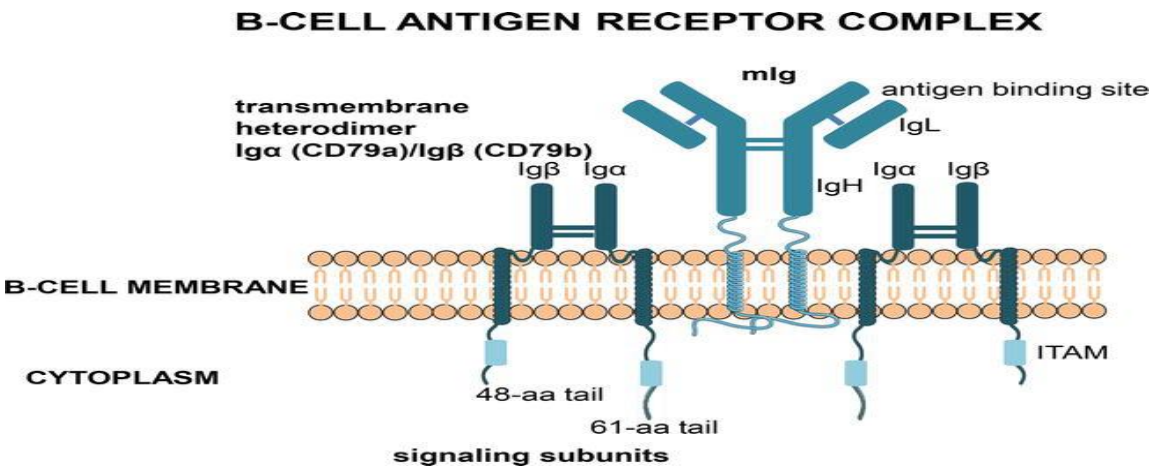
1- T cells require two signals to become fully activated**. A first signal, through APC, presented antigen with MHC to the T cell receptor (TCR) on the membrane**. **A second signal, the co-stimulatory signal, through the interaction between co-stimulatory molecules expressed on the membrane of APC and the T cell.**

The best co-stimulatory molecule expressed by T cells is **CD28,** which interacts with **CD80 (B7.1) and CD86 (B7.2)** on the membrane of APC. Another costimulatory receptor expressed by T cells is ICOS (Inducible Costimulator), which interacts with ICOS-L.

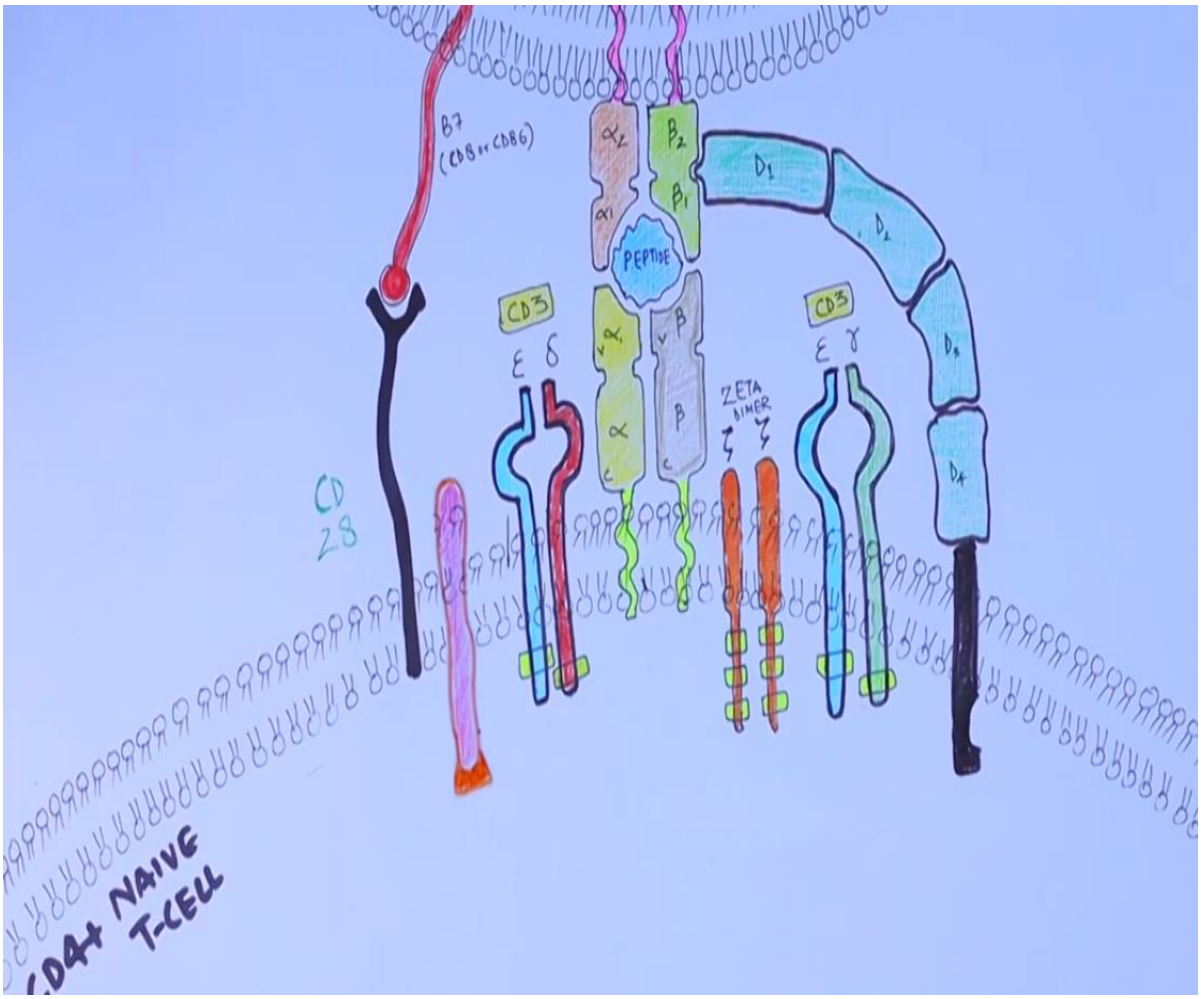
T cell co-stimulation is necessary for **T cell proliferation, differentiation and survival**. Activation of T cells **without co-stimulation may lead to T cell anergy, T cell deletion or the development of immune tolerance.**

2- A- the B cell through binding of TCR of Th2 to the MHC-antigen complex. It is followed by synthesis and presentation of CD40L (CD154) on the Th2 cell, which binds to CD40 on the B cell that leads to stimulating B cell to proliferation.

**B-Co-stimulation** for B cells is provided alternatively by complement receptors. **Complement receptor (CR2)** on mature B cells forms a complex **with CD19** and **CD81**. This complex is called the B cell coreceptor complex for such **sensitivity enhancement to the antigen.**




BCR complex structure. **The BCR complex is composed of a mIg non-covalently bonded to a transmembrane disulfide-linked heterodimer phosphoprotein composed of CD79a (Igα)/CD79b (Igβ). CD, cluster of differentiation; mIg, membrane-bound immunoglobulin.**

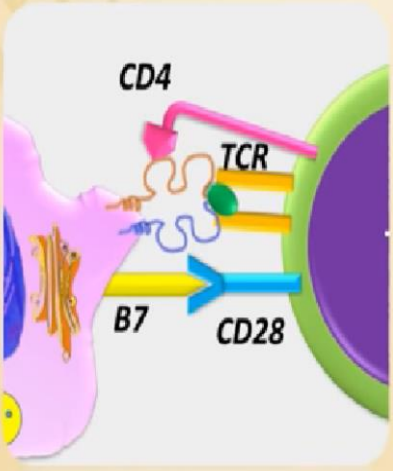


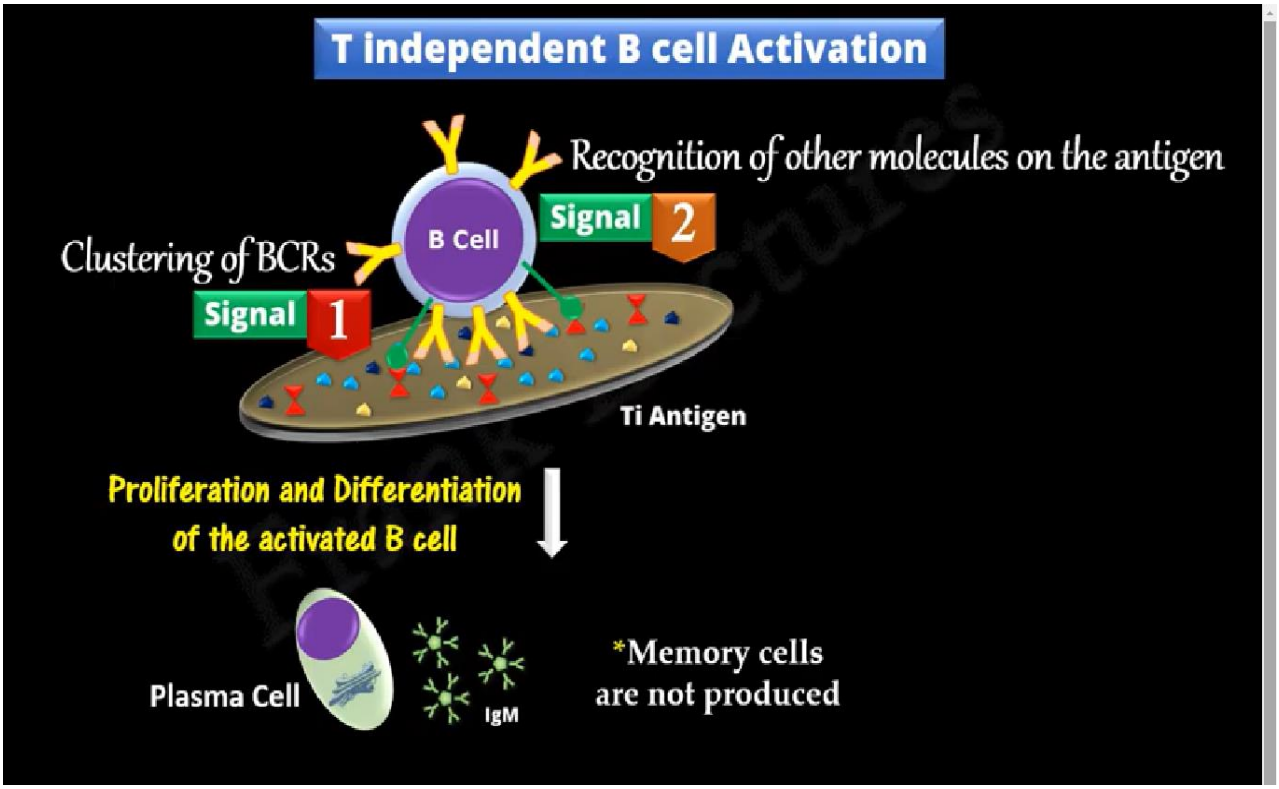
- **SIGNAL 1** — TCR OF T-CELL + MHC II OF APC [HAVING PEPTIDE]
- **SIGNAL 2** — CO-STIMULATION: BY CO-STIMULATORY MOLECULES
  - ⊖ SIGNAL ABSENT → ANERGY
  - CD28 OF T CELL INTERACTS WITH CD80 - B7-1 / CD86 - B7-2 OF APC
- **SIGNAL 3** : CYTOKINE PRODUCTION

# T Cell Activation is a Two Signal Process

**First Signal**: Recognition and binding by TCR and coreceptor CD4 or CD8

**Second Signal**: Costimulation (B7:CD28)



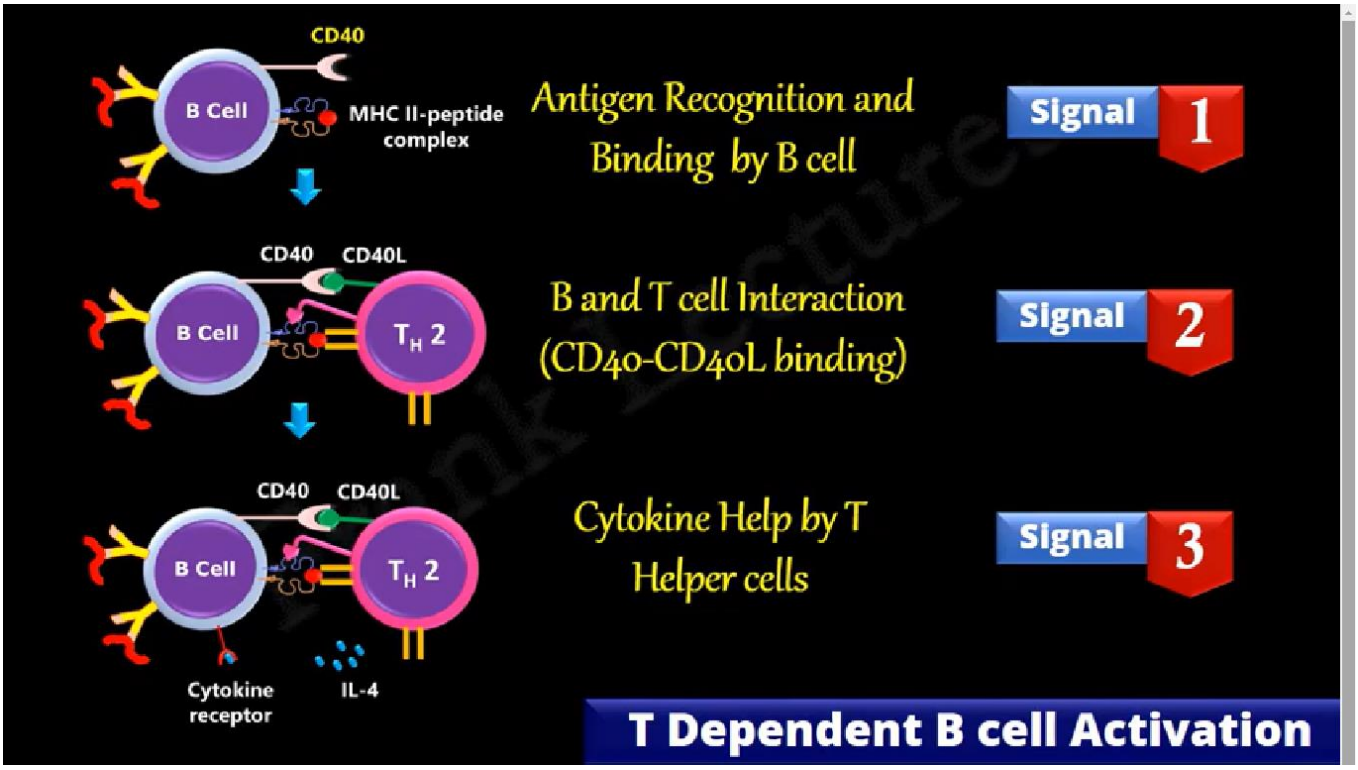



**Most antigens are proteins**

But not present as multiple repeating epitopes.

Thus, clustering of B cell receptors is difficult.

B cell activation requires T cell help.




Major Players in the Immune System:

| | |
|---|---|
| **Cells** | B cells, $T_C$ cells, $T_H$ cells, phagocytic cells, APC's |
| **Secreted Proteins** | Antibodies (Ab or immunoglobulins; 5 classes), Perforin, Cytokines (Interleukins & interferons) |
| **Cell Surface Proteins** | MHC, BCR, TCR, CD4, CD8 |

The chart above summarizes the major players in immunology.
How do T and B cells get activated?

| What's Activated?** | Antigen Presenting/Target Cell | What holds Epitope | Source of Antigen | Result |
|---|---|---|---|---|
| Cytotoxic T | Infected Cell | MHCI | Made in infect. cell | Killing of Target Cell; Mitosis of $T_C$ cell --> clone |
| Helper T | Classic APC (B, macrophage, etc.). | MHCII | From outside APC | Humoral Response as in (1) or (2) below; Mitosis of $T_H$ cell to give clone |

| | | | | |
|---|---|---|---|---|
| | (1) macrophage | MHCII | From outside by Phagocytosis | Activated $T_H$ can go on to activate a B; leads to Ab production by B cell |
| | (2) B | MHCII | From outside by RME | Mutual Activation of $T_H$ and B; Ab production by B cell |

***Note: Activation of lymphocytes also requires appropriate cytokines. $T_H$ cells need IL-1 from the APC's; $T_C$ cells need IL-2 from $T_H$ and B cells need various IL's; class of Ab made by B cell depends on type of IL it gets.*

Why do you need MHC & APC's?

1. T cells are "MHC restricted;" B cells are not

a. B cells recognize plain Ag = Antibodies bind to Ag in plasma or on bacterial/viral surfaces.

b. T cells recognize only Ag that is bound to MHC on (euk.) cell surface.

(1). T cell receptors bind to the variable part of MHC-Ag complex = bind to Ag itself

(2). CD4 or CD8 binds to a constant part of corresponding MHC.

2. Two types of T's recognize (bind to) Ag associated with different MHC's -- this is how T cells tell immune cells and infected (ordinary) cells apart.

a. Cytotoxic T's (CD8+) recognize Ag + MHC I (said to be "MHC I restricted") -- note target must have MHC I and Ag.

b. Helper T's (CD4+) recognize Ag + MHC II (said to be "MHC II-restricted") -- note target must have MHC II and Ag.

T cells recognize their targets (in part) by the type of MHC they have -- infected cells have MHC I and immune cells have MHC II.

**Major features of 2 branches of specific immune system**

| Immune Response Type | Humoral | Cell-Mediated |
|---|---|---|
| Cell involved in Response | B cells | T cells |
| Protein Made by Cell | Antibody (Ab) | T cell receptor (TCR)* |
| Location of Protein | In serum, tears, etc. (released by B cell) or on cell surface. | Always on cell surface (attached to T cell) |
| Protein Recognizes | Free Antigens (Ag) or Ag attached to microbial surfaces | Antigens attached to surfaces of eukaryotic cells |

| | | |
|---|---|---|
| Aide in killing targets | Complement** | perforins |
| Usual targets (for killing) | Microbes, soluble proteins | Infected or cancerous cells (for $T_c$ or CTL) |
| Side Affect | Allergies | Graft rejection |

Notes:
*T cell receptor is NOT the receptor for T cells -- it is the protein **on** the T cells that is the receptor for an antigen. It is the receptor **of** T cells, not the receptor **for** T cells. (By analogy, antibody attached to B cells is sometimes called "the B cell receptor" or BCR instead of antibody. BCR and TCR both act as receptors for antigen -- they allow antigen to trigger the immune response, as explained below. So they are also referred to as B or T cell receptors for antigen.)

** Complement = a series of proteins found in blood. Activation of complement involves a cascade of activations similar to that involved in blood clotting. Complement binds to antibody-antigen complexes attached to microbes and triggers phagocytosis or lysis of the microbe bearing the complex.