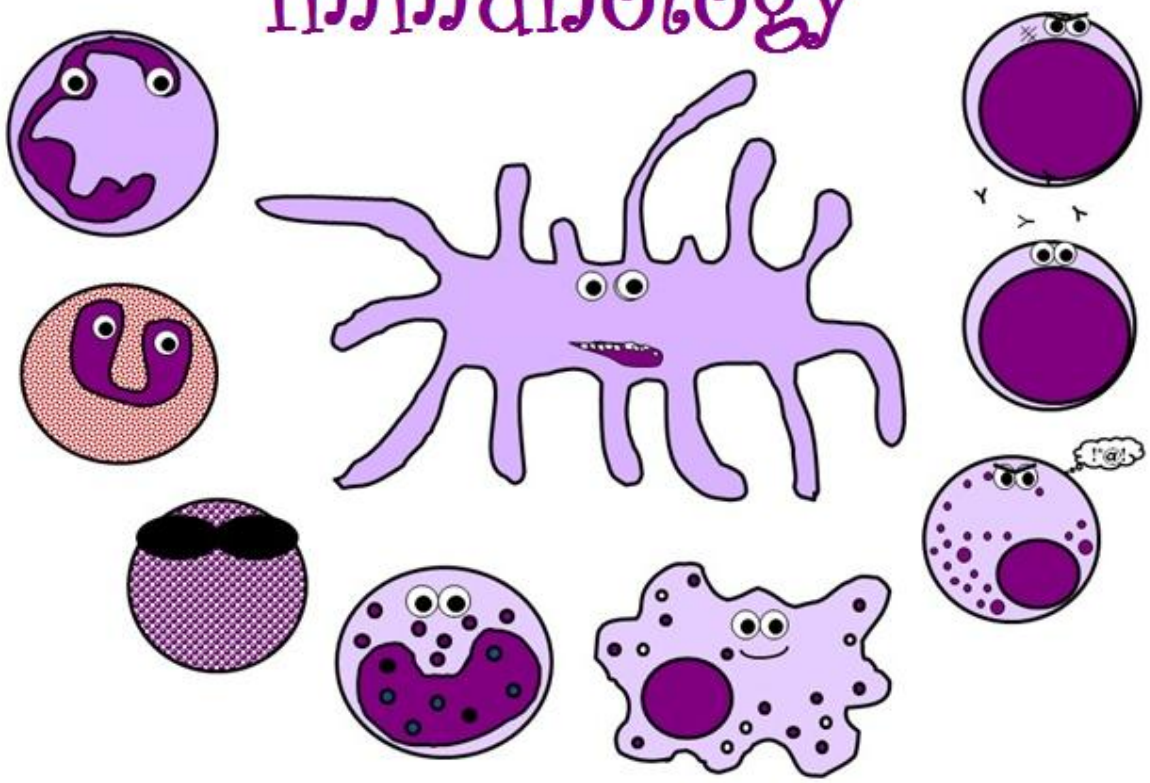
Immunology



Sheet Slides

Number: 8

Subject: Immune Receptors & Signal Transduction

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- This sheet was written according to the record that belongs to section 1.
- The arrangement of some ideas might be not be identical to that of the lectures.

Review

- ✓ The immune system works via two major defense pathways: innate and adaptive.
- ✓ When the innate system fails to eradicate pathogens, signals trigger the activation of the adaptive immune response.
- ✓ Adaptive immunity is provided by T-cells and B-cells.
- ✓ B-cells
    - SIGs are mostly IgM (other clsses like IgG can be present)
    - These cells are capable of immunoglobulin class switching when stimulated by different cytokines.
    - B-cells can act as APCs to help T cells recognize their antigens.
    - B-cells are activated by T-helper cells.

T-Cells VS B-Cells

- T cells are said to be the center of the adaptive immune system. This is due to the involvement of certain types of T-cells in the activation of other cells.
- Despite the fact that B-cells and T-cells have a lot of differences between them, there are many similarities as well, for instance:
    1. Both of them originate from the same stem cells.
    2. The basic steps for activation (discussed later) are basically the same, but they’re mediated by different mediators/regulators.

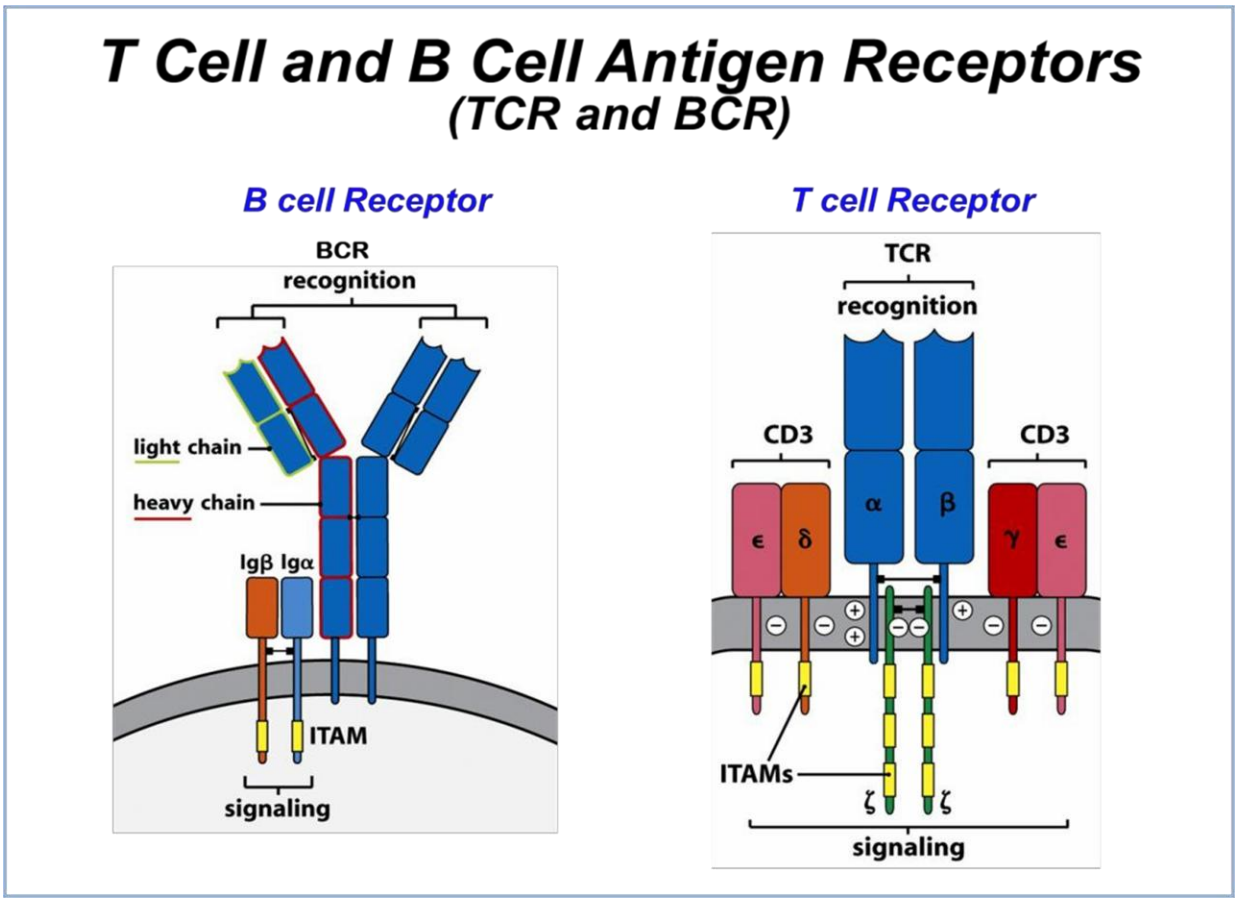
Binding & Signal Transduction

B-Cells	T-Cells
❖ Mediated by SIGs mainly IgM. ❖ IgM can bind the antigen by its surface part, but its cytoplasmic tail is short, so it can't transduce the signal properly. ❖ Signaling is very important to activate the cell. ❖ The signal triggers the release and entrance of transcription factors into the nucleus. ❖ They bind the promoter of the receptor gene which drives gene transcription and formation of mRNA and thus translation into proteins. ❖ These factors upregulate certain genes, and downregulate other genes. This is the base of cell activation.	❖ Have TCR ❖ Cytoplasmic tails of the TCRs are also short. ❖ There are accessory molecules as well, mainly CD3. ❖ There are also other accessory molecules including epsilon, zeta,.. ❖ Work together to send that signal downstream and to activate the cell. ❖ CD3 is called a pan marker (universal marker). ❖ CD3 is present on all T-cells.

➢ **Transducing signals is important for activation of cells. How do B-cells overcome the shortness of the cytoplasmic tail of the IgM?**
- There are accessory molecules to transduce the signal.
- These are Ig alpha and Ig beta.
- They have longer tail and they are capable of signaling and activating transcription factors.

❖ **ITAM molecules (immunoreceptor tyrosine-based activation motif):**
- **Motif** is a site made of amino acids for binding of molecules.
- **"Tyrosin-based"** refers to the fact that it's made of many tyrosine residues, which are sites of phosphorylation.
- Phosphorylation is a key step in signaling because once phosphate groups are seen by proteins, it will be attracted triggering further activation.
- The phosphate group acts as a bait. Serine and threonine are also sites for phosphorylation, but not in ITAM.
- ITIM is similar to ITAM, but its effect is inhibitory.

T-Cell Receptors



- According to the chain forming the receptor, T -Cells can be classified into:
  1. **Traditional T-Cells**
     Their TCRs are made up of alpha and beta chains (<u>HOWEVER, they are different from Ig alpha and Ig beta found in B cells</u>).
  2. **Non-traditional T-Cells**
     Their TCRs are made up of gamma and delta chains.
- In immunology, when we refer to T-cells, we refer to the traditional alpha/beta TCR cells (because they make up around 95% of circulating T-cells).

Traditional T-Cells	Non-traditional T-Cells	NK T-Cells
❖ Have **alpha and beta chains in their TCR.** ❖ These are the cells that **express the CD4 and CD8 as co-receptors.** ❖ The function of TCR is to recognize the antigen peptide bound to the MHC molecule (**both MHC and peptide are required**). ❖ Make up to **95% of circulating T-cells.** ❖ Clinical correlation: In the cases of MHC II deficiency, the T-cell count drops because in order for the cells to survive they need to be able to recognize both antigen and MHC, if this didn't occur cells would die.	❖ Have **delta and gamma chains in their TCR**. ❖ In the beginning of an infection, these cells function by producing interferon gamma (remember that NK cells are also a source of interferon gamma) ❖ Make up to **5% of circulating T-cells**. ❖ They **don't express CD4 or CD8** ❖ Functionally they seem to be more like the innate system. ❖ **Since they work more with the innate system, they respond faster.** ❖ Most abundant in intestines, uterus, and tongue (mostly in sites of contact with foreign pathogens). This means that they have innate immune function. They are less diverse than traditional T-cells so they need to act fast. Traditional T-cells have huge numbers of different TCRs; each TCR is formed to be specific for certain pathogen (antigen). This contributes to diversity. Because non-traditional cells are more like innate cells, and have receptors similar to toll- like receptors that recognize PAMPs (non-specific), they don't need to be diverse.	❖ These are **neither NK nor T-cells.** ❖ However, they have **NK 1 receptor** (normally found on NK) and **alpha-beta TCR**. ❖ They are very few in number (**0.5% of T-cells**).

➢ Why are these important?
- T-cells recognize peptides only. NK T-cells can recognize lipid antigens.
- The immune cells deal with lipid antigens via the B-cells' antibodies.
- The immune system never depends on one type of solution because if this was altered we would have a major problem.
- Peptides are normally presented by MHC. Lipids are presented by CD1 molecules.

- Two steps activation principle:
  - Binding of the TCR to antigen on MHC molecule.
  - Co stimulation present by APC itself.

Signaling of TCR

- Traditional TCR has alpha and beta chains.
- CD3 transmits the signal.
- One antigen binding to one receptor is insufficient to activate the cell. Thus, hundreds are needed**.**
- Clustering of receptors is the base of transmitting the signal to the inside of cell**.**

➢ Why is co-stimulation important?

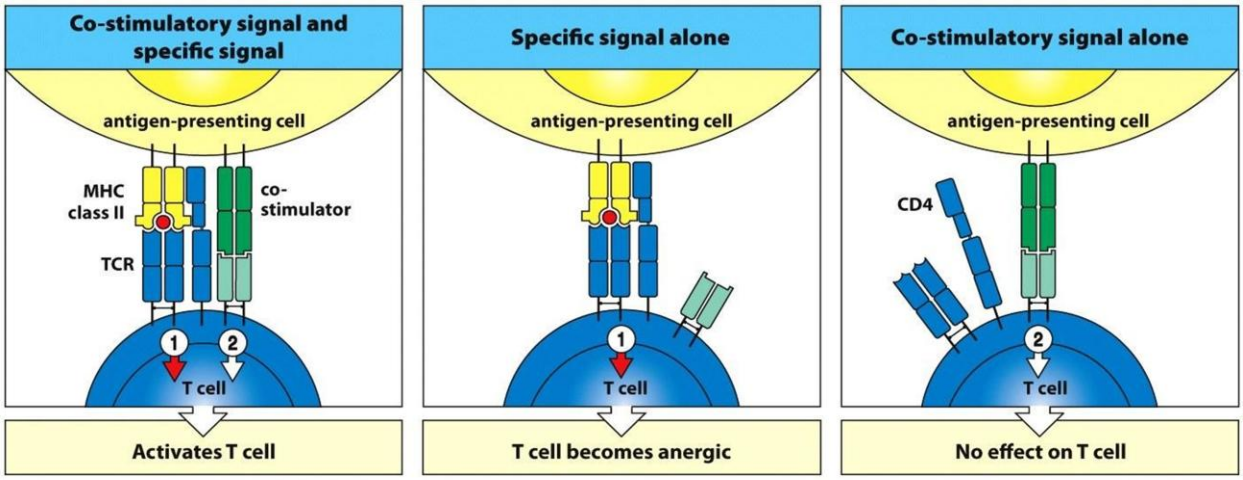


Figure 8.18 The Immune System, 3ed. (© Garland Science 2009)

- The co-stimulatory signal lowers the threshold needed for T-cell activation via TCR.
- Lower number of antigen interactions needed due to increased sensitivity in binding of the few.

Examples:

- Well known families of co-stimulatory molecules presented by the APCs include:
  1. B7 family: B7.1 and B7.2
  2. CD40 family
- These are either present on the APC, or upregulated on the APC.
- They have complementary molecules that bind to on T-cells:
  1. CD28 binds B7.1 and B7.2.
  2. CD40 ligand binds to CD40.

- **How do they work?**
  - They lower the threshold for activation of the cell by increasing the sensitivity for binding of receptors
  - They do this by remobilization of lipid rafts.
  - **Lipid rafts** are areas of the plasma membrane that contain a set of molecules that are needed together to perform a certain function.
  - The plasma membrane is not rigid; it is semi fluid. It was found that molecules that are needed to be together are concentrated in certain areas of the membrane; these are usually found on the inner surface of the membrane facing the cytoplasm. When there is something that triggers their presentation outwards, they move to their site of action.
  - The co-stimulation triggers the remobilization of the lipid raft towards the outer surface to the place where their action is needed.
  - This makes the signaling very effective, increases the sensitivity, and lowers the number of receptors needed for full activation.

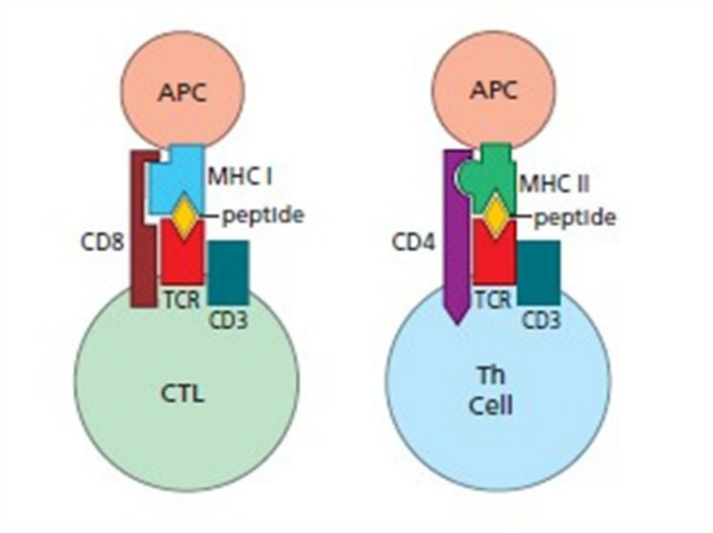
- **What is the result of this signal?**
  - There are different outcomes. It is not just an "on/off" signal.
  - Possible outcomes:
    1. Activation
    2. Inhibition
    3. Death by apoptosis
    4. Anergy

- **Anergy**
  - The **antigen is present** but the **co-stimulation is absent**.
  - Due to certain faults in the system, the APC might present an antigen without the presence of a real attack.
  - A real attack is what drives the cells to send a co-stimulatory signal.
  - To prevent exaggerated or faulty responses, the cells will not be activated.

- **No effect**
  - Binding of the co-stimulatory signal without the binding of TCR to its antigen.
  - There will be no effect because **the cell is not specific for this peptide**.

❖ **Co-receptors**

- These are either CD4 or CD8.
- Present on traditional cells.
- These cells correct the function of TCR; make CD4+ cells bind MHC II more specifically. CD8+ cells bind MHC I.
- They are signaling receptors:
    1. They are loosely bound to the TCR, thus making their binding reversible.
    2. Certain molecules called CLIPs (Class II-associated invariant chain peptides) stabilize this interaction thereby strengthening the signal entering the cell.



❖ Accordingly we have two types based on CD4 and CD8:

1. T-helper cells
    - Activation of T-helper cells triggers the production of cytokines which activates and recruits other cells to the site of infection.
    - They are CD4+
2. Cytotoxic T-cells
    - Cytotoxic T-cell activation triggers killing of other cells directly (virally infected cells and cancer cells)
    - They are CD8+

Cell Activation

1. Recognition and binding:

After the cell recognizes antigen bound to MHC molecules, adhesion molecules allow weak binding between T-cells and antigen presenting cells. This allows the T-cell receptor to be engaged with the antigen presented by the antigen presenting cell.

❖ **Effects :**

- On T-cell:
  Upregulation of the CD40 ligand on the T cell, to prepare the cell for the co-stimulation and binding of the CD40 ligand to the receptor.
  This occurs only after proper binding of the TCR with its antigen.
- On APC:
  This triggers the expression of more MHC and CD20 molecules on APC. This is due to the fact that more MHC molecules are needed to achieve full activation. When dendritic cells are naïve, they have lower MHC molecules; their activation will increase their expression.

❖ This co-stimulation amplifies the TCR binding to their antigen through lipid rafts.
❖ When the activation is complete, the APCs disengage.

2. Proliferation:

- The T-cells need to proliferate and increase in number.
- Clonal expansion: the cell that binds with highest affinity will be increased in number.

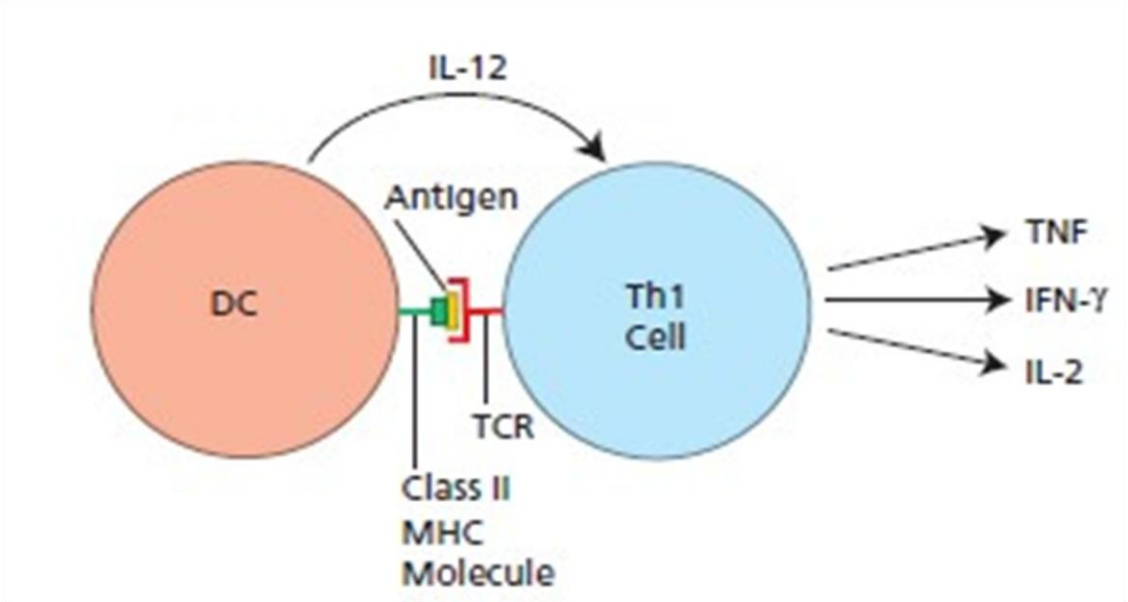
3. Differentiation to: T-helper, T-cytotoxic, etc..

Subclasses of T-helper Cells

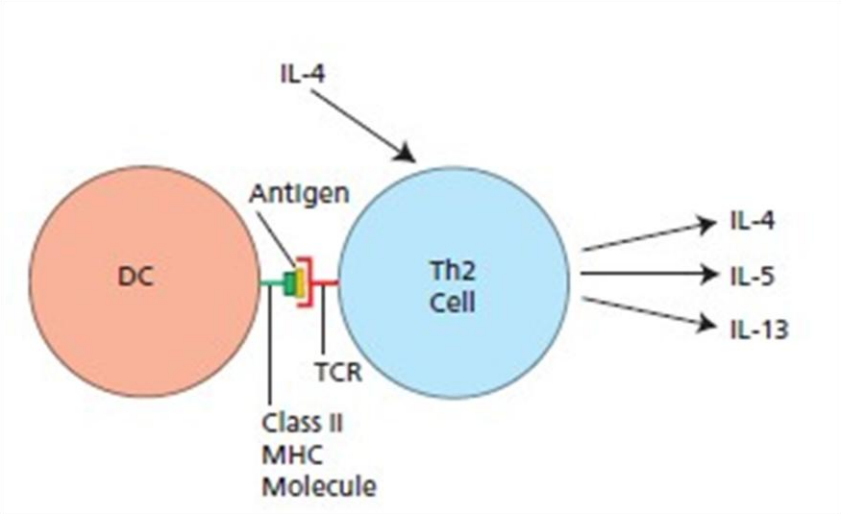
1. T-helper 1 (TH1)
2. T-helper 2 (TH2)
3. T-helper 17 (TH17)
4. T-helper 0 (TH0)

❖ **T-helper 1**

- IL2 triggers its formation.
- It is produced by APCs like macrophages and dendritic cells.
- Featured by a profile of cytokines it produces (these cytokines are somehow profile markers and their presence signifies that the T-helper cell is working).
- Cytokine profile: TNF, IL2, and INF gamma.
- Most of its cytokines are pro-inflammatory.
- INF gamma and TNF are potent macrophage activators.
- Work mostly in leishmania and cancer.
- Clinical correlation: in a certain cancer the activation of TH1 could be a treatment (the treatment could be used to switch from TH2 to TH1).
- TH1 trigger IgG class switch, against viral and bacterial attack.
- IL2: induces proliferation of many cells including the TH1 cells, Cytotoxic T cells, activation of NK cells, fight cancer cells (along with NK cells).

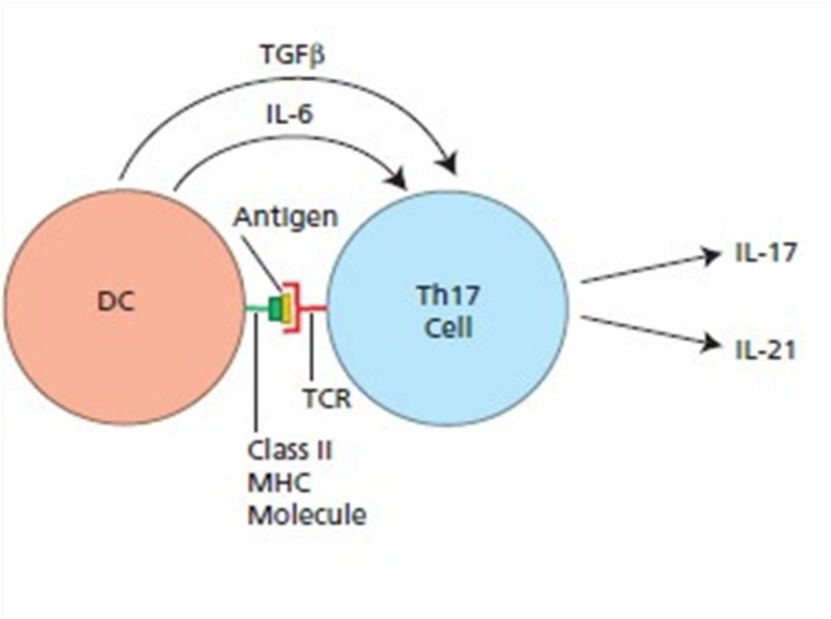


❖ **T-helper 2**



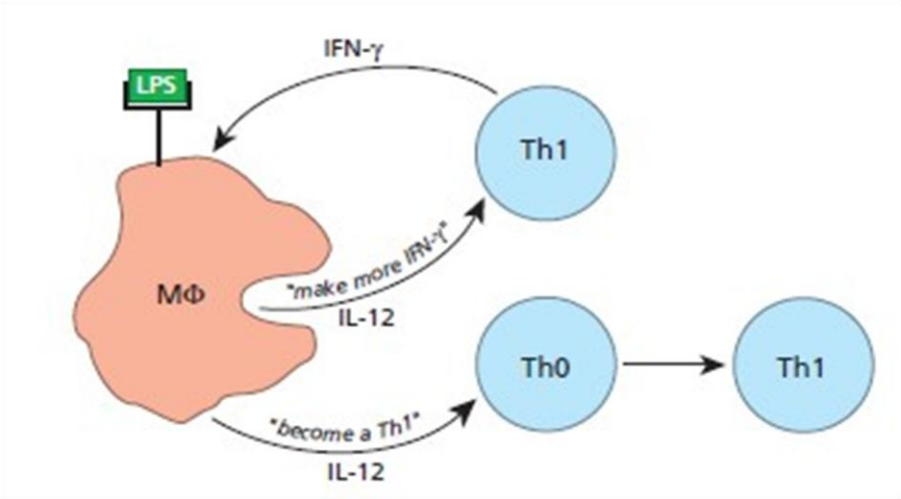
- Cytokine profile: IL4, IL5, and IL13.
- IL4 triggers proliferation of cells, production of other cytokines, recruitment of eosinophils, and IgE class switch.
- IL13 induces mucosal secretion. More mucus secretion means more IgA to combat pathogenic bacteria of the digestive tract.
- TH2 response is crucial for parasitic infection (eosinophils and IgE presence).
- Asthma is also a TH2 response.
- These cytokines could induce cancer.

❖ **T-helper 17**



- The formation of these cells is triggered by: TGF beta, IL6 secreted by APCs.
- Cytokine profile: IL17, IL21, and IL22
- IL17, according to recent findings, recruits neutrophils at the site of infection.
- IL21 and IL22 are important for fighting fungal infections, and extracellular bacteria.
- It is similar to TH1 because it is proinflammatory.
- IL21 triggers proliferation.
- This also triggers IgG class switching (IgG1, IgG2, & IgG3) which fixate complements and trigger opsonization.

❖ **T-helper 0**



- In certain conditions we don't want differentiated TH cells to be produced immediately, we want the cell to go to the site of action to decide what type of TH cell it should differentiate into.
- The APC activate the cell, but it will only differentiate when it comes to the site of action.

❖ **TH response follows the lock-one response:**

- Lock one response means that if it starts as TH1 it will remain TH1.
- They produce INF gamma, activate macrophages, but inhibit TH2.
- This lock is restricted to the site of infection, this means that even if we do a test for the patient, not all of his/her cells will be TH1 or TH2, he/she can have both but at certain sites, only one response.

❖ **Delayed Type Hypersensitivity**

- For example, in areas where TB infection is prominent, they used to do both x-ray for chest and tuberculin test.
- In tuberculin test:
  1. They inject peptides from TB subcutaneously.
  2. These peptides will be taken up by APCs.
  3. If the patient shows positive result this indicates: current infection, previous infection, vaccination, or latent infection.
- The x-ray may falsely show no infection several times.
- The tuberculin test is very old, not accurate, and has many side effects.
- This lead to a new, more effective test called the Quantiferon Gold test.

❖ **Quantiferon Gold Test**

- Cells are isolated from the patient (mainly lymphocytes).
- Cells are mixed with peptides not from vaccination to prevent cross-reactivity with vaccinated patient.
- If there is a previous or active infection the cells will react and produce interferon gamma.
- Measure IFN-γ secreted by TH cells specific to TB by ELISA test.

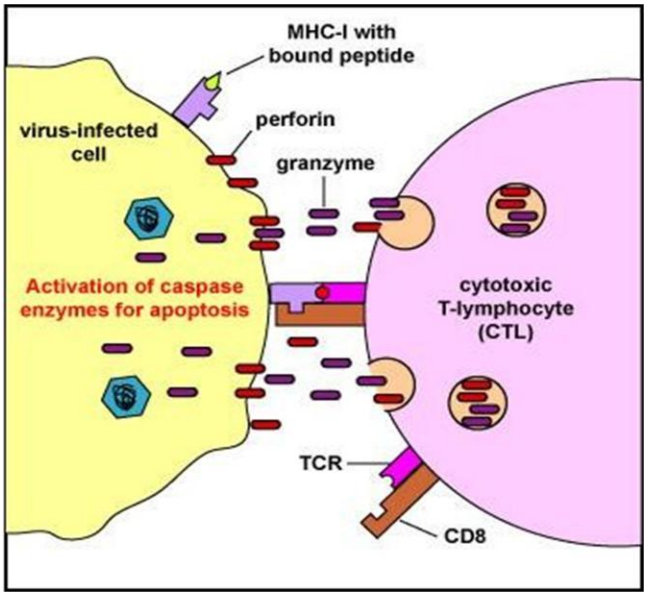
Cytotoxic T-Cells

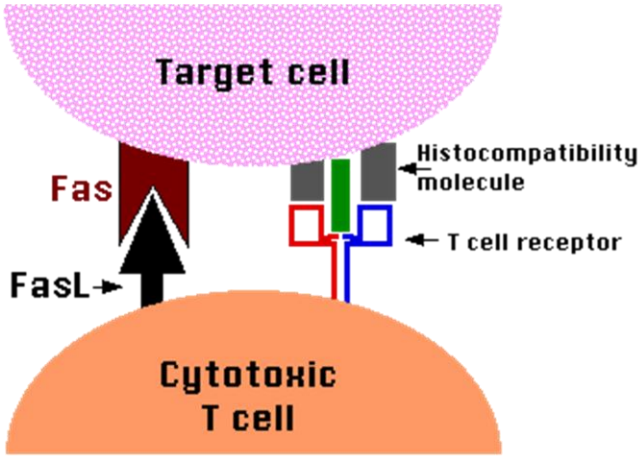
❖ Directly kill virally infected cells as well as cancer cells.
❖ Produce certain mediators, or chemicals in vesicles:
1. Perforins
2. Granzyme b

❖ **Perforins**
Induce pores in the membrane to allow the entry of granzymes.

❖ **Granzymes** activate DNAses (proteins that cut the DNA into smaller pieces called DNA ladder). This triggers apoptosis.

❖ FAS ligands on T-cells interact with FAS molecules (receptors) on infected cells and therefore, induce apoptosis.





One method by which cytotoxic T cells induce their targets (e.g., virus-infected cells) to commit suicide (apoptosis)

A comfort zone is a beautiful place, but nothing ever grows there.

Stop wishing & start doing ;)

Revised and Edited by: Amer Sawalha