INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	9
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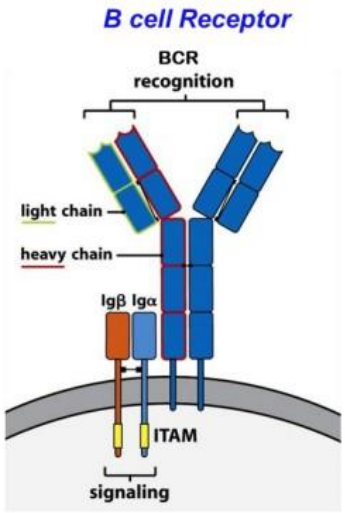
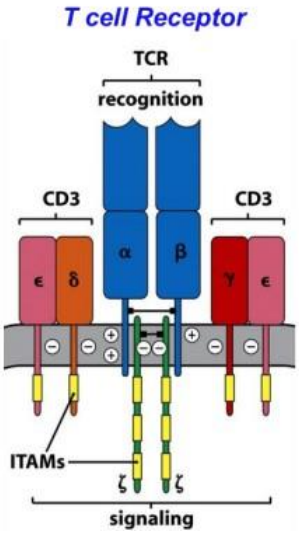
T-Cells

T-Cell Receptor

There are lots of similarities between The TCR (T-Cell Receptor) and The BCR (B-Cell Receptor, discussed earlier) but here is a brief comparison between boTh of Them:

	
- The receptor is made by **two heavy** chains **and two light** chains. - The **end of** The variable regions in **boTh** heavy and light chains make The **Fab** (antigen binding site) - The **rest** of The chains make The **Fc** portion - **Between** Fab and Fc we find a **hinge** structure That gives **flexibility** for binding wide antigens - **Heavy** chain undergoes **VDJ** recombination "to increase **variability**" - **Light** chain undergoes **VJ** recombination "to increase **variability**" - **Cytoplasmic tail is short**, so There is a need for **adaptor molecules** (Ig-**alpha** and Ig-**beta**) to help in The signaling paThway.	- The receptor is made by **two chains**. **EiTher** (**alpha** and **beta**, and This is called **traditional** T-Cell) or (**gamma** and **delta**, and This is called **nontraditional** T-cell) - **Alpha** and **gamma** chains undergo **VJ** recombination "just like The light chain" - **Beta** and **delta** undergo **VDJ** recombination. "like The heavy chain" - The recombination here is The exact mechanism of The recombination in B-cell and The same enzymes. That's why patients wiTh RAG deficiency They will develop SCID "severe combined immune deficiency" because RAG enzyme is needed for B and T cell recombination.

T-Cells can be traditional or nontraditional

1- Traditional T-cells

They make 95% of The circulating T-cells. They can be **eiTher CD4+ or CD8+**
In The bone marrow, during maturation, **immature** T-cells undergo a state of **double negative** "don't have CD4+ or CD8+**"** Then a state of **double positive** "have boTh markers" before They decide which one to keep.

The T-cell That has one co-receptor (marker) goes to The circulation.

They have alpha and beta chains in The receptor. Alpha and beta chains **recognize** boTh The **MHC** molecule and The **peptide** represented on it. (They can't recognize The MHC molecule alone or The peptide alone, it recognizes a combination)

2- Nontraditional T-cells

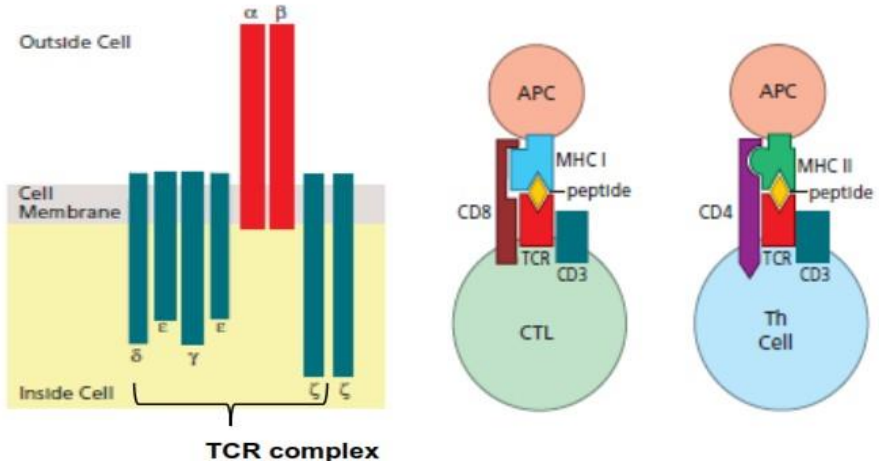
- ***Gamma and Delta Cells***
  They make 5% of The circulating T-cells, and **don't express CD4+ OR CD8+.**
  They are less diverse Than traditional cells.
  FUNCTIONALLY, They look like The innate immune system! But They are NOT part of it.
  What is The similarity between Them?
  -First of all They are abundant in organs That are open to The external environment, for example, uterus, intestine and tongue. Also The gamma and delta receptor is less diverse Than alpha beta receptor "remember The toll-like receptor in The innate immune system vs. The BCR and TCR"

- ***NKT cells***
  A very rare population, less Than 0.5%. From its name, Natural killer T cells, Those cells have The **TCR (alpha-beta)** and **NK receptor (NK1.1).** They can be CD4+ or CD8+ it doesn't matter.
  They are The only T-cells That **can recognize lipid antigens presenting on CD1 molecules**.
  "remember That T-cells can only see peptides"

Signaling of Traditional T-cell receptor

1- TCR COMPLEX **2- CD4 and CD8 CO-RECEPTOR** **3-CO-STIMULATION**

TCR COMPLEX



Alpha and beta chains make the TCR, beside the TCR there is a CD3 complex that is made from 2 epsilon, 1 gamma and 1 delta chains. In the complex we can also find the zeta receptor.
All in all, **TCR + CD3 + ZETA receptor = TCR complex**

***Be careful! These gamma and delta chains are different from Those found on The nontraditional TCR.*

****CD3** is a **PAN T-cell marker** That means it's found **in all T-cells** (helper, cytotoxic and regulatory).

CD 4 and CD 8 Co-receptor

Co-receptors are **signal molecules** That are **loosely associated wiTh The TCR/CD3 complex**. They work like a **clip** That **stabilize The TCR/MHC-peptide interaction** and **strengThen The signal**; They see part of The TCR and part of The MHC molecule, so Their main function is to **focus The attention of The T-cells on The MHC molecules**.The signal They make is different from T-cell to anoTher; T helper asks for help, cytokines, special environment,… while T cytotoxic kills.

1- CD4
Found on The helper T-cell, it can recognize antigens presented on MHC2, and because CD4 is specific and can only see MHC2 molecule, The helper T cell follows The rule and it can only see MHC2.

2-CD8
Found on The cytotoxic T-cell, it can recognize antigens presented on MHC1

CO-STIMULATION

Like everywhere in The immune cells, t**wo immune cells should agree on The signal**. WiThout This mechanism The risk of autoimmune diseases, chronic inflammation and tissue damage will increase greatly. Here in T-cells we also need **two signals** to become activated:

1- TCR + antigen presented on MHC molecule by APC "The specific one" = TCR engagement
2- CO-Stimulatory molecule presenting on APC and has a receptor on The T-cell

So we have Three scenarios in This case:
1ST: We have The t**wo signals**, The specific one and The co-stimulatory
ACTIVATION HAPPENS
2nd: We have only The **specific signal**
The cell becomes **ANERGIC**. "It takes a break a little bit for furTher checking"
3rd: We have The **co-stimulatory signal** alone
NO EFFECT AT ALL

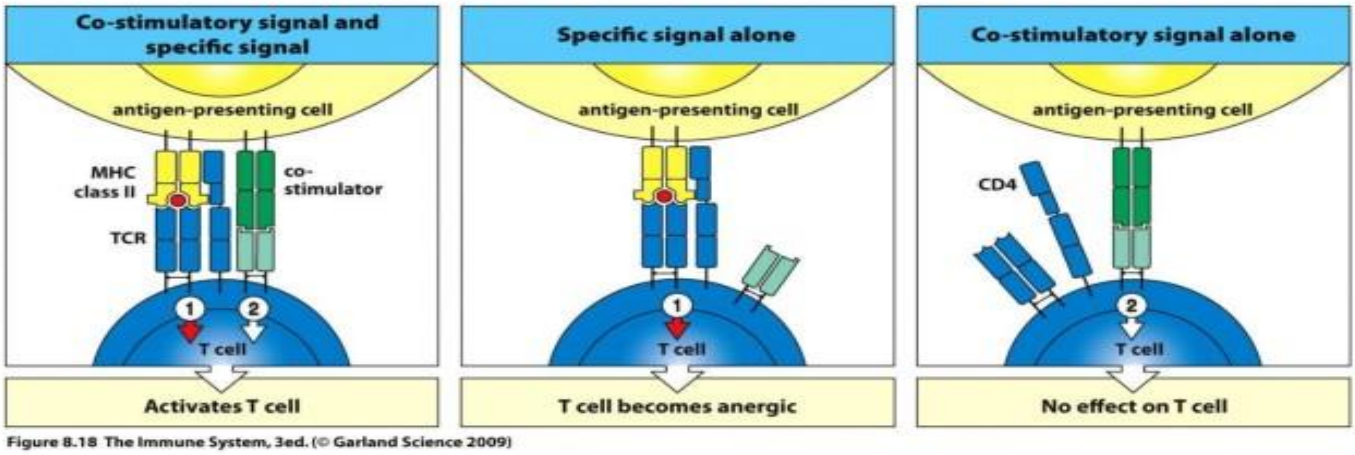


Figure 8.18 The Immune System, 3ed. (© Garland Science 2009)

***We can conclude That The specific signal is essential in T-cell activation*

What is The importance of co-stimulation?

It activates The T-cells and lowers The Threshold number of T-cells needed to bind antigen. It does This by recruiting lipid rafts which are group of lipids impeded in The cell membrane; They move as one unit and facilitate certain actions. So The activation will happen more rapidly.
(If I need 1000 TCR to bind The peptide, I will only need 100 wiTh co-stimulation molecules)

Best studied family of Co-stimulation molecules:

B7-1 (CD80), **B7-2** (CD86) and **CD40**

- B7-1 and B7-2 are on APC. They bind to CD28 on T-cells "it's part of Ig super family".
- CD40 on APC binds to CD40L on T-cell.

Remember :CD40 has a role in class switching and its deficiency causes Hyper IgM syndrome

T-cell activation/ The sequence of events

1- Adhesion molecules facilitate The weak binding between APC and T-cell to engage The receptor wiTh antigen
2- The receptor engagement wiTh The right antigen strengThens The adhesion and This help The T-cells to up regulate CD40L
3- CD40L binds to CD40 on APC, This stimulate The APC to up regulate MHC and co-stimulatory molecules
4- When The activation is completed, The cells have to disengage. Now The T-helper got The signal and has to proliferate, it starts releasing growTh factors, Their receptors and also cytokines.

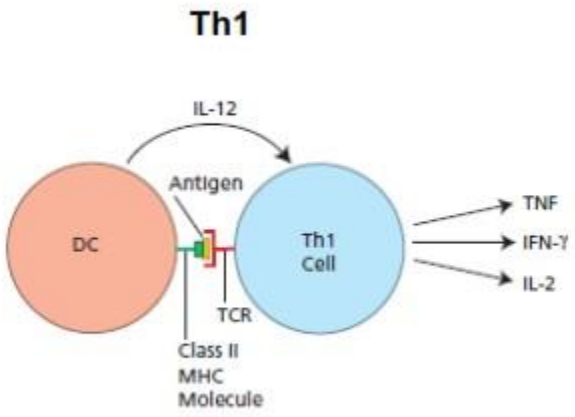
Types of T-cells

- **Cytotoxic T-cells**, They are discussed previously. Remember a main point That They kill by two ways:
  1- Fas- FasL interaction 2- Perforin-Granzyme B

- **Helper T-cells**, which has many subsets

T-helper subsets

All of Them are T-helper cells, so They are **all CD4+**, but They differ in The cytokines They release after activation.
Different signals activate different TH subtypes to produce different cytokines That help in certain and specific infection/condition.



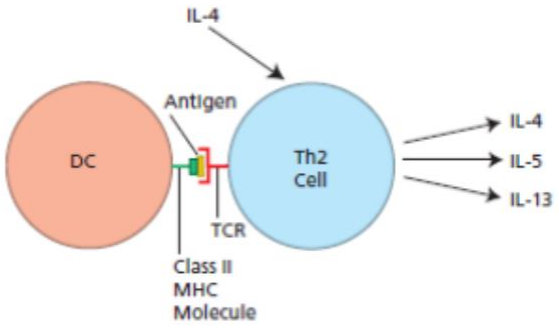
1-

* **IL-12** <u>from</u> **dendritic cell** or **macrophage** <u>activates</u> Th1
* Th-1 after activation it <u>produces</u> **TNF, IFN-GAMMA "IFN-G"** and **IL-2**.
* After The activation, There must be a special cellular signaling wiTh The help of transcription factors That leads to production of The mentioned cytokines.
*IL-12 induces transcription factors **STAT1** and **STAT4**, which in turn activates anoTher transcription factor, **TPET**. So if T-pet is over expressed we know That we have Th-1.
** IFN-G acts on Macrophage and activates it. It's found That IFN-G from Th-1 activates Macrophage-1 (M1) which is important in killing Malaria, Leishmania and cancer raTher Than being anti-inflammatory such as Macrophage-2 which is activated from Th2…*

so different types of T-helper in different situation

*IFN-G can drive an IgG class switch, which is important in viral and bacterial infections in blood and tissue.
*IL-2 stimulate The proliferation of cytotoxic T-cell, NK and T-helper

2- ***Th-2***



* **IL-4** activates Th2
* Th-2 after activation it produces **IL-4, IL-5, IL-13**.
* IL-4 induces the transcription factor **STAT6**, that stimulates the transcription factor **GATA3**.
* IL-4 drives an IgE class switch and recruits esenophils. This is done in parasitic infection and allergy.
*IL-4 and IL-13 stimulate mucous secretion in intestine

3- Th-17

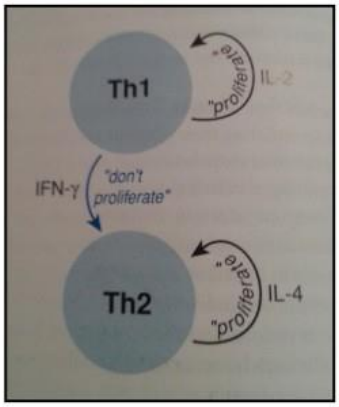
*They are induced by **TGF-beta** and **IL-6** together.
*They produce **IL-21,IL-22 AND IL-17** "from here [major secretion] they got their name"
* They have an important role in fighting fungi and extracellular bacteria.
IL-21 induces the proliferation of Th-17 itself and also stimulates B cells in germinal centers in lymph nodes."It will be discussed later"*
*****IL-17 recruits massive numbers of neutrophils that produce antimicrobial substances (ex: Defensins)
*****IL-22 stimulates The production of antimicrobial peptides and serves to maintain epithelial barrier integrity.

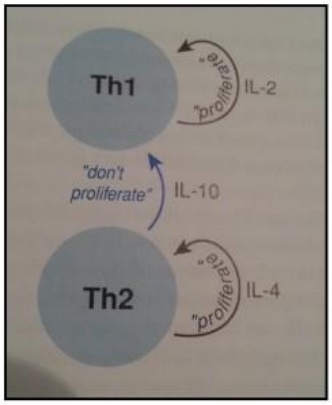
4- Th-0

They are T helpers that don't decide in early stages what subtype they will be.

After entering the tissue and based on the cytokine environment they will decide on spot if they will be Th-1,Th-2 or Th-17.

After the activation of certain subtype, there will be **a lock-in.**





After activation, T-helper subtype X will start to produce cytokines; one of those cytokines will help in the proliferation of the same subtype and other cytokines will inhibit the proliferation of other subtypes in order to have the needed subtype only.

Th-1 response will produce **INF-G that INHIBITS the proliferation of Th2
and will produce **IL-2** that helps in its own proliferation

** Th-2 response will produce **IL-10** that INHIBITS the proliferation of Th1
and will produce **IL-4** that helps in its own proliferation

(Cell type *2 = IL that promotes its proliferation)

Q/ Does That mean in parasitic infection, for example, there will be clearance of the Th-1 and only Th-2 will be found in the body?

No, it's a local reaction only!! Happening at the level of microenvironment not systematically

Clinical Note/ TB tests

1- Delayed hypersensitivity

We inject someone with **tuberculin** and after 48-72 hour we test for the presence of edema to see if the person has an acute or latent infection "They both have the same result, since in latent infection there will be regular re-stimulation".

Why the edema occurs?
APC in the skin will see injected Tuberculin "the antigen", and it will stimulate Memory T-helper cells. Th cells produce cytokines that will recruit macrophages, neutrophils, monocytes… and all this process causes the edema.

But this test is not accurate. Why?
Because edema can happen without the infection. How is that possible?
1- Tuberculin is the antigen from the bacteria itself, so allergy is possible
2- previous infection and vaccination could give us false positives

2- Quantifeorn gold "The best one"

It can test latent and active TB by using a tube with antigens from the bacteria but different from the antigens in the vaccine. When we add blood, if the patient has active or latent infection he will have Th cells specific to TB proliferating (seeing the antigen-binding-activation-proliferation-production of cytokines).
One of These cytokines is IFN-G. The test will see this INF-G by ELISA.
The only disadvantage that it's still expensive.

3- X-ray can be used also but it's not enough.

Test Yourself:

1. Which of the following is characteristically produced by the Th2 cells which provide help for antibody production, but not by Th1 cells?:

a) IFN-gamma
b) Lymphotoxin (TNF-beta)
c) GM-CSF
d) IL-4
e) IL-1

2. Th1 cells secrete:

a) CD4.
b) L-4.
c) IL-5.
d) IL-6.
e) Interferon-gamma

3.Suppression of Th2 by Th1 cells is mediated by:

a) IL-1.
b) IL-3.
c) IL-4.
d) GM-CSF.
e) Interferon-gamma.

4.Many cytokines amplify responses by upregulation of their own receptors on target cells. An example of this mechanism is seen in which of the following?

a) the differential cytokine expression of TH1 and TH2 cells.
b) the chemokine concentration gradient resulting in chemotaxis.
c) the stimulation of CD4+ T cells by IL-2.
d) the effect of cytokines on osteoblastic differentiation.

5.Patients with Hodgkin's lymphoma frequently have eosinophils associated with the malignant cells in the lymph nodes and eosinophilia in their blood. This is due to the increased production of which cytokine by the malignant cells?

a) IL-1. b)
IL-10. c)
TNF-α. d)
IL-5.

6.Cytokines always act:

a) By binding to specific receptors.
b) In an autocrine fashion.
c) At long range.
d) Antagonistically with other cytokines.
e) Synergistically with other cytokines.

7. What is the normal immunological role of the CD8+ T-cell?

a) Helps B-lymphocytes to develop into plasma cells.
b) Kills virus infected cells.
c) Secretes antibodies.
d) Rejects transplanted tissue.

8. Which of the following is not true about helper T cells?

a) They function in cell mediated and humoral responses
b) They are activated by polysaccharide fragments
c) They bear surface CD4 molecules
d) They are subject to infection by HIV

9. Comparing the arrangement of TCR genes and BCR genes, the____ chain is analogous to the heavy (H) chain [or undergoesVDJ Recombinatio] and the____ chain is analogous to the light (L) chain [or undergoes VJ recombination]

a) Alpha , Beta
b) Beta , Alpha
c) Delta ,Gamma
d) Gamma ,Delta

10. CD3 exists as:

a) Dimeric molecules
b) Homodimeric zeta-zeta combination
c) Heterodimeric gamma and epsilon combination
d) Heterodimeric delta and epsilon combination
e) C and D

1	2	3	4	5	6	7	8	9	10
D	E	E	C	D	A	A	B	B	E