SHEET NO. 16

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

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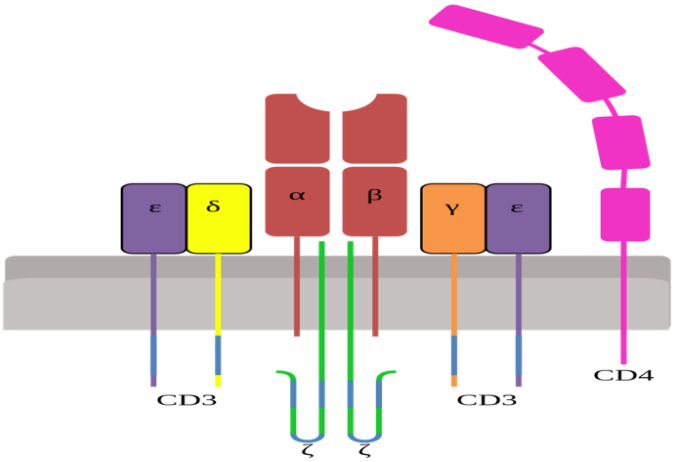
Th1, Th2 activation & Co-stimulation

Before we get into this, let's do a small review about the T-cell receptor that is bound in this case here. It's always bound to cd3, cd3 acts as a signal transmission conductor to conduct or transmit the signal from the T cell when it's occupied by its unique antigen and then send the signal down to the nucleus what happens in the nucleus briefly : the signal will turn on IL-2 production for activation of the cd4 cell and other cells. (more about this in the next lec.)



Type of Cells	Surface Proteins
Helper T cells	CD4, TCR, CD28
Cytotoxic T cells	CD8, TCR
B cells	IgM, B7
Macrophages[2]	Class II MHC
Natural killer cells	Receptors for class I MHC
All cells other than mature red cells[3]	Class I MHC

You can review this table!

Now lets get started,

We will talk about this new concept ,that we touched on it briefly, as we said that cd4 lymphocytes perform their regulatory function and we said that they can activate cd8 cells which is the **IL-2 pathway** or **the cellular pathway** to make the cytotoxic cells activated while the other pathway is to go towards the **humoral pathway** to activate b cells to become plasma cells that produce antibodies.

- T-cells could either be **regulatory cells (helper cells)** or as **effector cells (Cytotoxic)**.
- The regulatory role of CD4 helper cells is mediated by signal proteins **(interleukins)**. For example, helper T cells make :
  - (1) interleukin (IL)-2, which activates CD4 and CD8 cells
  - (2) IL-4, which help B cells make antibodies, especially IgE
  - (3) gamma interferon, which enhances killing by macrophages.

- T cell progenitor cells differentiate from the **outer layer of cortical epithelial thymus** cells (nurse cells), T cell progenitors differentiate under the influence of **Thymic hormones** (Thymosins and thymopoietins) into T-cell subpopulations that are characterized by their surface proteins (CD3, CD4, and CD8).

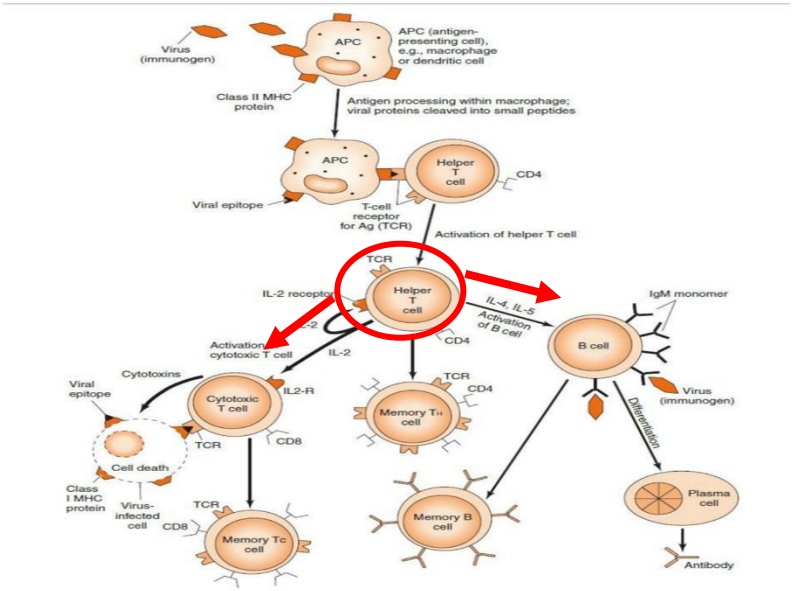
- CD3 is present on the surface of **ALL T-cells** and is associated with antigen receptors (TCR). The CD3 is a complex of **five transmembrane proteins**, its main function is the transmission of signals from outside the membrane to within the cell (hence the transmembrane part!)
- As it is associated with the antigen receptor (TCR) the signal transmitted is that the TCR is occupied (ON). (One of the CD3 transmembrane proteins, **the zeta chain**, is linked to a tyrosine kinase called fyn, which is involved with signal transduction).
- Second messengers further transmit the signal.
- CD4 is a **single transmembrane protein**, whereas CD8 is made up of **two transmembrane proteins**. (Lck kinase is a possible way for their signal transmission).
- T cells are subdivided into two major categories based on whether they have CD4 or CD8 proteins on their surface, when they mature they have one of them, but not both.
- CD4 lymphocytes perform their regulatory functions in the following manner:

(1) they help activate CD8 T-cells to become activated cytotoxic T cells
(2) They help activate B cells to develop into antibody-producing plasma cells
(3) they help macrophages effect delayed hypersensitivity (e.g., limit infection by Mycobacterium tuberculosis).

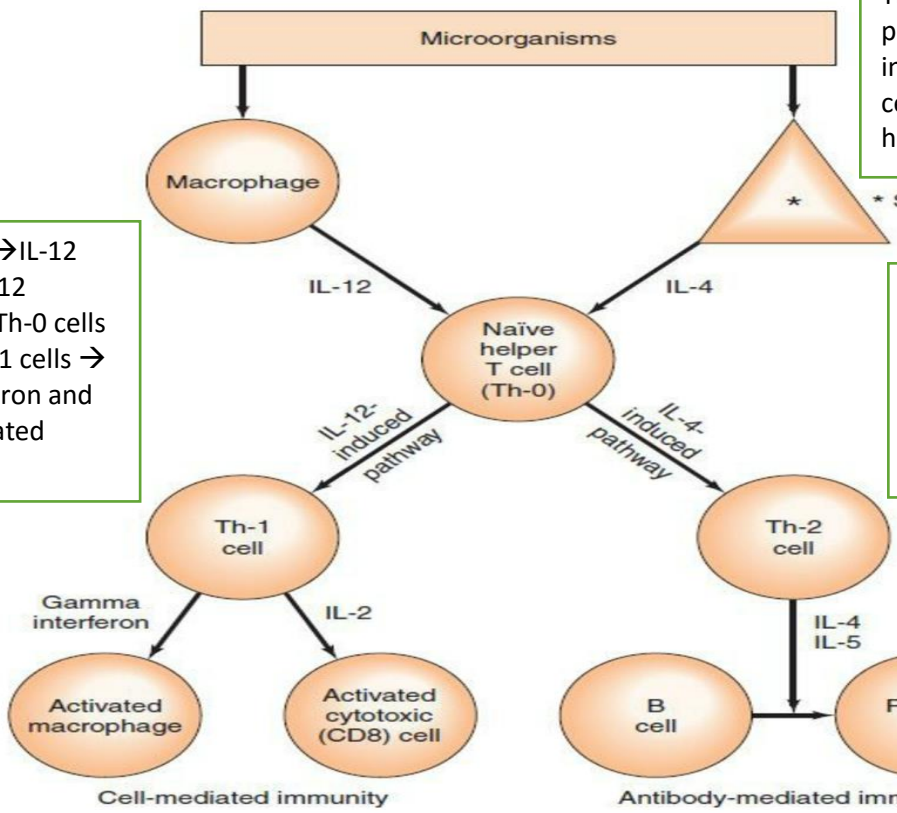
- ✓ The first two functions are carried out by two different subpopulations of CD4 cells.
- ✓ The first function is carried out by **Th-1 CD4 cells** help activate **cytotoxic T cells** by producing **IL-2** and help initiate the delayed hypersensitivity response (the third function) by producing primarily IL-2 and gamma interferon
- ✓ The second function is carried out by **Th-2 cells**, which help activate **B-cells** by producing primarily **IL-4** and **IL-5**.
- ✓ However, the role of Th1 cells (e.g., gamma interferon), also affects B cells to class switch from **IgM to IgG** by producing cytokines which produce two subclasses of IgG (IgG 1 & IgG 3) that are very effective in opsonization of bacteria.

* the first and third function by the cellular function reformed by the th1 cells and by producing primarily a signal **IL-2 for the first function** and **gamma interferon for the third function.**

* the humoral response is carried out by th2 cd4 cells which help activate b cells by producing primarily as we know **IL-4 & 5**. The role of Th1 cells when they produce gamma interferon also affects b-cells to **class switch** as well for T-dependent response, it will help the b cells to switch **from IgM to IgG and others** and we will see how that works later .Between cellular & humoral there's a balance in which each side try to shift towards themselves.



The core picture here shows Th2 response (right branch) & Th1 response (left)



The human cell that produces the IL-4, which induces naïve helper T cells to become Th-2 cells, has not been identified

Ingested bugs→IL-12 produced→IL-12 induces naïve Th-0 cells to become Th-1 cells → gamma interferon and IL-2 (cell mediated immunity)

IL-4 induces naïve Th-0 cells to become Th-2 cells→ production of IL-4 and IL-5→ activation of B cells to become plasma cells (antibody immunity)

More about Th1 & Th2,

In the above figure, a macrophage has ingested a bug it will produce some **IL-12**, here the macrophage will convert a **Th0, which** is a naïve T-helper**,** to either of the two populations. Now the macrophage through **pattern recognition molecules** has deemed this bug to be for example a cellular bug ,let's say virus or whatever, it requires **cytotoxic response** it will produce **IL-12**, IL-12 will go to the naive helper t cell and in the normal situation our naive t cells or our naive Th0 cells will always become **th1** cells in the case of **intracellular antigens such viruses**.

About the antibodies against this bug, another cell (unknown other than macrophage) will stimulate the Th0 naïve cells toward humoral immunity. The mediator is **IL-4** that would push towards the **th2** response so that's what we have here that's how we push each cell to the right response according to our needs.

Now the question is that can you produce both a **th1** response and a **th2** response at the **same time?**

the answer would be **No!** It's a commitment ,the cell is always committed towards one of the populations. So, you cannot mount both responses, once the cell take a route it will become permanently committed towards it.

How about making the question bigger, can you mount **th1** response and a **th2** response **against the same bug**?

Yes! (the same microbe could have many antigens)

so, the 1st question was: can I mount th1 response and a th2 response against the same antigen? No, this is a commitment that the antigen can make an antigenic response of **either IL-12 or IL-4 pathway, it's committed to only one of them**. On the other hand, the

virus itself will have different antigens, so you might process different parts and you might mount slightly a th2 response against a certain antigen and maybe a dominant th1 response against another antigen.

- The balance between th1 & th2 is provided by the production of IL-12 from macrophages. **IL-12** increases the number of **Th-1** cells (cell mediated), enhancing host defenses against organisms that are controlled by a delayed hypersensitivity response.
- Interferon from Th1 cells also inhibits the production of Th2 cells, tipping the scale further towards Th1 response. **Th1 = IL-12 (stimulatory to Th1) + Interferon (inhibitory to Th2)**
- IL-10, produced by Th-2 cells, inhibits IL-12 production by macrophages and drives the system toward an antibody response and away from a cell-mediated response (towards Th2).
- CD4 cells make up about 65% of peripheral T cells and predominate in the thymic medulla, tonsils, and blood. **Th2 = IL-4 (stimulatory to Th2) + IL10 (inhibitory to Th1)**

So, there is a balance between th1 and th2 cells, this balance is provided by the production of **IL-12** try to **push all these naive undecided T-cells towards the cellular response** th1. And as we work on the th1 side, we will inhibit the other side with the interferon. The opposite happens on the th2 response, which is stimulated by the **IL-4** and **IL-10** which is a **well-documented inhibitory interleukin**, it will try to inhibit the other side the th1 response.

[10:40]

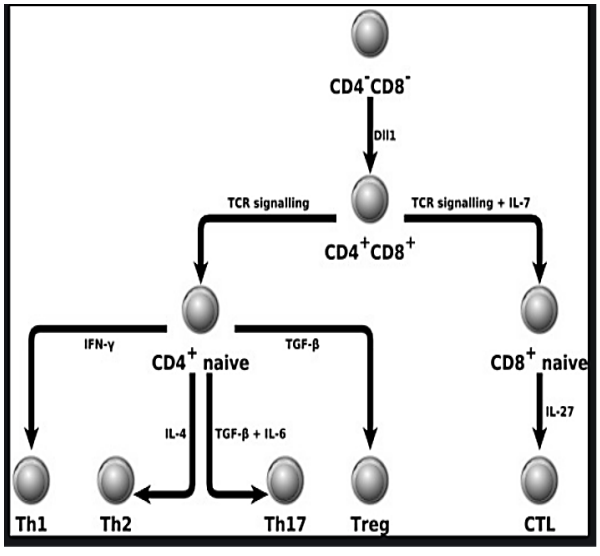
TABLE 58–4 Comparison of Th-1 Cells and Th-2 Cells

Property	Th-1 Cells	Th-2 Cells
Produces IL-2 and gamma interferon	Yes	No
Produces IL-4, IL-5, IL-6, and IL-10	No	Yes
Enhances cell-mediated immunity and delayed hypersensitivity primarily	Yes	No
Enhances antibody production primarily	No	Yes
Stimulated by IL-12	Yes	No
Stimulated by IL-4	No	Yes

- Here is a comparison between th1 and th2 (table)

- IL-4,5,6 are all stimulatory for Th2 and IL-10 inhibits Th1.

so this is another diagram where maturation is added, when cells are maturing they become **double positive** then you have a **single negative cd8 naive cell** and a **single negative cd4 naive cell** these can go to either pathway of **interleukin-12** for **th1** or **interleukin-4** for **th2** with their inhibitory signals as INF-ɣ and IL-10 . There's another sub population called the **th17** response primarily in the gut. **cd8 naive cell is active with IL-27, TGF-β** activate **T- regulatory** cells which we will mention later.



Remember this from lecture 1?

Antibody-Mediated Immunity (B Cells)	Cell-Mediated Immunity (T Cells)
1. Host defense against infection (opsonize bacteria, neutralize toxins and viruses)	1. Host defense against infection (especially *M. tuberculosis*, fungi, and virus-infected cells)
2. Allergy (hypersensitivity) (e.g., hay fever, anaphylactic shock)	2. Allergy (hypersensitivity) (e.g., poison oak)
3. Autoimmunity	3. Graft and tumor rejection
	4. Regulation of antibody response (help and suppression)

We all know that antibody mediated b-cell immunity will mount our defense against infection by opsonizing bacteria, neutralize toxins and viruses, they mediate types of allergy (hypersensitivity) and the autoimmune reaction against your own cells
now about the cell mediated response against intracellular infection upon bacteria or fungi for example **tuberculosis**, **viruses** or whatever, and then we have type four hypersensitivity, we also have graft and tumor rejection mediated by **MHC1**, and then regulation of antibody response absolutely by the **cd4 cells.**

Types of Hypersensitivity,

Type	Name	Mechanism	Disease examples
Type I	Immediate hypersensitivity	IgE-mediated degranulation of mast cells following antigen binding and cross-linking of IgE	Allergic asthma, allergic rhinitis, anaphylaxis
Type II	Antibody-mediated hypersensitivity	IgM/IgG antibody:antigen interactions on target cell surfaces	Drug-induced thrombocytopenia, myasthenia gravis, Graves disease, haemolytic anaemia of newborn
Type III	Immune complex-mediated hypersensitivity	Immune complex formation and deposition in tissues leading to local or systemic inflammatory reactions	Rheumatoid arthritis, SLE, ~~Goodpasture's syndrome~~, Arthus reaction, serum sickness
Type IV	Delayed-type hypersensitivity	Sensitized T_H1 cells activated to release cytokines upon binding to antigen, resulting in macrophage and cytotoxic T cell accumulation	Contact dermatitis, chronic transplant rejection

Goodpasture's should be in group 2 not 3

We'll take small details about them (فكرة مبدئية) (we will discuss them in a separate lec.)
Lets range them by how immediate they cause disease or how often they cause their sensitivity or symptoms >> type 1 **immediate** & type 4 **delayed**, first three **types use antibodies**, last type **uses T-cells** that activate macrophages which are the actors.

- ✓ type 1 => immediate **degranulation** /use IgE /cause **immediate anaphylaxis** and **allergies** when something comes to contact with the allergen.
- ✓ type 2 => antibodies is produced over time / they bind the cell and causes the cell to be destroyed /over time as you destroy more and more target cells they fail in their function and you have the symptoms / is IgM and IgG /direct action on cells /need time .

* Note on Types 1+2: 1. IgE granulation and symptoms are because of **histamine**.
2. IgM & IgG lead to some diseases as drugs induced thrombocytopenia that's when you are destroying your platelets, myasthenia gravis disease you are destroying these acetylcholine receptors , Graves disease you are targeting the thyroid , hemolytic anemia of newborn you are targeting red blood cells, so in all these cases you have produced **antibodies against target cells from your body**.

- ✓ type 3 => is a little different, you have antibodies again but these antibodies bind to their antigen and then you have these **immune complexes** are formed, they are large they bind to each other and then they start to precipitate specially in places where blood flow is slow such as around the joints, so they cause Rheumatoid arthritis ,SLE, etc. It can be quick.
- ✓ Type 4 => sensitized **th1 cells** activate cytokines resulting in macrophage and cytotoxic T-cell accumulation which is the normal cellular response carried by your th1 cells basically. It's also called the **delayed hypersensitive reaction** because it can be made against certain allergens in contact dermatitis, for example if someone wears a copper ring and then with time they develop a reaction against it, so that why it's delayed not like type 1 when you are immediately hypersensitive to substances.

[19:20]

Back to the normal situation,

- To mount a protective immune response against a specific microbe requires the **appropriate subpopulation** (i.e., either Th-1 or Th-2 cells) to play a dominant role in the response.
- For example, if an individual is infected with *M. tuberculosis* then **Th-2** cells are the major responders. Humoral immunity shouldn't be activated here and if so it's not protective against *M. tuberculosis*, and the patient will suffer severe tuberculosis (why?).

This individual with TB needs cellular response, instead this he made th2 response to TB with antibodies, antibodies will not really be effective so he will develop major infection. Humoral immunity isn't protective here because TB as we know is an **intracellular pathogen.**

- Similarly, if an individual is infected with *Streptococcus pneumoniae* and **Th-1** cells are the major responders, then humoral immunity will not be stimulated and the patient will have **severe pneumococcal disease**. (why?)

Here we have an individual who is infected with *S.pnuemonia*, which is a **capsulated** organism, I need to make antibody against this capsule so I can neutralize it, but the individual

made th1 response (cellular response) instead of antibody response. *S.pneumonia* does not infect cells it does not go inside cells so the th1 response will not be helpful, again the individual will have a severe infection.

- Precisely what component of a microbe activates either Th-1 or Th-2 cells is unknown.
- *M. tuberculosis* is a well-studied and well-known example of how the response is stimulated.
- It was found that a specific lipoprotein on the surface of that bacterium interacts with a specific Toll-like receptor **(TLR)** present on the surface of the **macrophage**, the interaction of the lipoprotein and the macrophage's TLR induces the production of IL-12. (so this is before the bacteria enters cells, it is now detected before entry by macrophages)
- (remember Toll like receptors, part of innate immunity, how cells such as macrophages and dendritic cell use pathogen associated patterns to detect microbes and engulf them)
- IL-12 is the stimulatory signal that drives the differentiation of undifferentiated (naïve) helper T cells to go down the **Th-1** type of differentiation which drives a **cell-mediated (delayed hypersensitivity)** response against the organism which is here the correct response.

Incorrect response: If a person produces **th2** response when activating TLRs towards this pathogen, he will die and he was less likely to reproduce. So that's why over time we all develop a TLRs that respond to this pathogen by Th-1 response not Th-2 (people who develop an incorrect response will absolutely die and have no chance to transmit this error to next generations). This is known as the ***evolutionary pressure*** that moves us towards th1 response method.

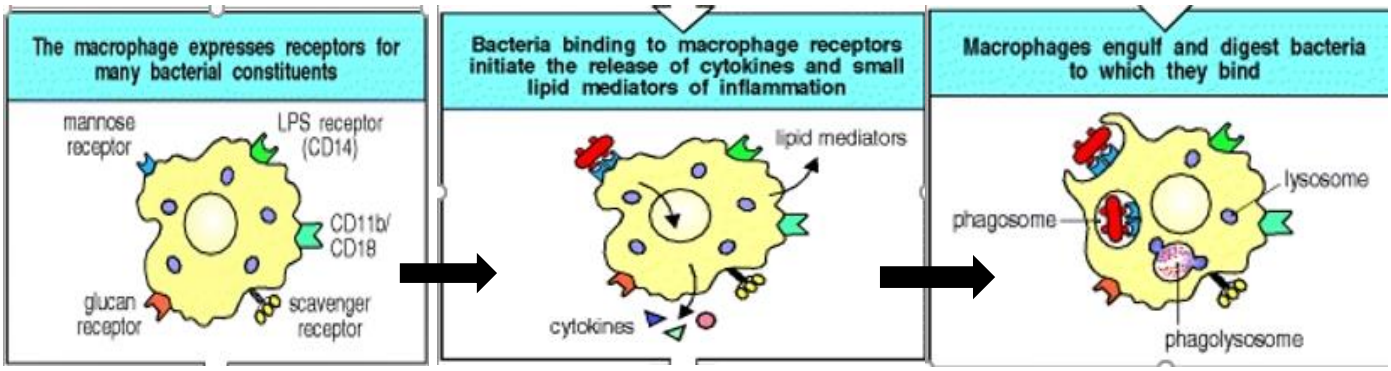
T-Helper 17,

- Another subpopulation of CD4 cells that differentiate into yet another subpopulation of immune responders (called Th-17), they have been shown to have a significant role in the **mucosal immunity** of the gastrointestinal (GI) tract (this will include the mucosa of the mouth!).
- The reason these cells are different , is that they are producing IL-17 **instead of gamma interferon** (that is usually produced by Th1 cells, or IL-4 from Th-2 cells)
- The function of IL-17 is as a signal that recruits neutrophils to the site of **bacterial** infections.
- What do neutrophils do? How?

they are present **from mouth to anus** all throughout the GI, they recruit **neutrophils** to any site of bacterial invasion to the mucosa and neutrophils would **come and clear up these bugs**. They are recruiters for neutrophils to clear up infection.

The following figure shows how macrophages drive cells towards a specific response, you have **mannose binding receptors**, **Lps receptor** , **scavenger receptors** ,**glucan receptor** and others. All of them will tell us which interleukin we're going to send ? where ? and whether we're going to try to produce a th1 response or not ?

So let's say bacteria binding to macrophage receptor initiate the release of the cytokines which affect the macrophage itself and then at the same time the macrophage will engulf and digest the bacteria so it can go and present it to the t cells after they are committed to their subpopulation.



So how we found the significance of these cells th17 ?

- we found that HIV SELECTIVLEY targets these cells, which creates an almost total loss of function of Th-17 cells.
- It was shown that those patients have a high rate of blood infection caused by colonic (gut) bacteria such as *Escherichia coli* and *Klebsiella* (the gut is not protecting them from the penetration of these bacteria into the blood). This is how we discovered this subpopulation of CD4 cells.
- In a similar fashion, IL-17 was found to also contribute to our immunity against some **fungal infections** (*chronic mucocutaneous candidiasis*).

HIV selectively targets th17 response, these patients have high rate of invasion of gut bacteria into their blood, they develop **blood infections** caused by gut bacterium, they also have reduced immunity against fungal infections in **esophagus or in the mouth** and again this is due to the reduction of the IL-17 cd4 population.

CD8 Cells,

- As was discussed before, CD8 lymphocytes are cellular responders (effectors), which respond as cytotoxic cells against other cells (virus-infected cell, tumor and allograft cells they are called their **target cells**).
- The way they kill these cells is by either release perforins (the bullets) that poke **holes** in the membranes of the target cells, or by forcing these cells to **undergo apoptosis**.
- CD8 cells constitute about **35% of all peripheral T-cells**, that are usually found mainly in the **bone marrow** and **gut lymphoid tissue**.

Question about tumor cells: if you could train a cd4 cell or a cd8 cell to produce a response against a mutated protein produced by a tumor cell, will you cure that cancer?
this is one of the basis of the immune therapy for cancer that if you allow your cells to produce cd8 response (cytotoxic response) and cd4 activation against cancer cell, you will cure cancer or you will at least start fighting it reducing the size of the tumor, you might also overcome the entire cancer, so what happens is that **cancer cells they prevent cd4 cells from being activated against them ,and we can stop this using immune therapy by which we**

produce an antibody that activates these inactivated cells. (more info when we talk about co-stimulation)

A table about signature cytokines produced by either of the subsets of the cd4 cells:

TABLE 58–5 Signature Cytokine Produced by Subsets of CD4-Positive Helper T Cells

Subset of CD4-Positive Helper T Cells	Signature Cytokine	Function of Cytokine
Th-1 cells	Gamma interferon	Activates macrophages to kill intracellular microbes
Th-2 cells	Interleukin-4 (IL-4)	Stimulates development of Th-2 cells; enhances class switching to IgE
Th-17 cells	Interleukin-17 (IL-17)	Recruits neutrophils to site of infection

- th1 cells will produce gamma interferon to activate macrophages interleukin 2 again for cd8 cells
- your th2 cells would produce IL-4 and then enhance switching to IgE
- th17 will produce IL-17 to recruit neutrophils to side of interaction.

[27:30]

Activation of T-cells,

- To activate **helper T cells**, an antigen presenting cell must posses **MHC-II** complex, which carries (as a complex) an antigen, which the T-cell receptor is able to recognize. (antigen presenting cells are usually macrophages and dendritic cells, but there are others).
- The activation of **cytotoxic T cells** on the other hand requires antigen presentation from cells on **MHC-I**, that is complexed with an antigen recognizable by the cytotoxic CD8 cell TCR.
- APCs have both class I and class II proteins on their surface.
- The first step in the activation of helper T cells is the uptake of the foreign protein-antigen, microbe- by the APC. This microbe or protein is then digested within the APC into smaller parts –processing into small peptides for example-, and these unique small peptides are then complexed with **MHC-II** proteins and presented on the outside of the cell for a **CD4** cell (using its TCR) to recognize it.

Here's a mathematical formula to help memorize them:

the rule of eight: CD4 cells interact with class II (4 × 2 = 8), and CD8 cells interact with class I (8 × 1 = 8).

Now one may ask that if a macrophage is infected by a virus and it doesn't produce mhc-1, will a natural killer cell kill it? **Yes**, it doesn't matter if it's a microphage or anything else, if you're not producing a mhc1 I'm going to kill you. so that's one mechanism where we can **"police the police itself"**.

- T cells are usually harbored in lymph nodes, while at the same time the antigen is being encountered in mucosal surfaces where APC are present under these epithelial surfaces. ***How do these APCs recruit the T cells from such distance****?*
- An APC when it carries the antigen on its surface, it will produce a **specific receptor on its surface** (which indicates it is currently presenting an antigen), this receptor is reactive to the **chemokine CCR7**.
- The chemokine signal of CCR7 is being produced all the time (like a radio wave, seen as a gradient of CCR7, highest in the lymph node and gets lower and lower away from the lymph node) from T cells in the lymph node at all times, **once the correct radio (the receptor on the APC) is produced it will start to migrate to the NEAREST signal** -lymph node- going from low concentrations of CCR7 (away) to higher concentrations gradually (towards the NEAREST lymph node).

✓ having a receptor indicates that APC is currently presenting. Think like this : I'm an APC ,I'm not carrying antigen & not presenting anything soo **I don't put the helmet of ccr7 on my head**. While I'm in the mucosa I found an antigen and presented it, therefore **I'll put on this helmet which listens to the waves coming from T-cells** (ccr7 signals) that's how the it will find its way towards the nearest lymph node.

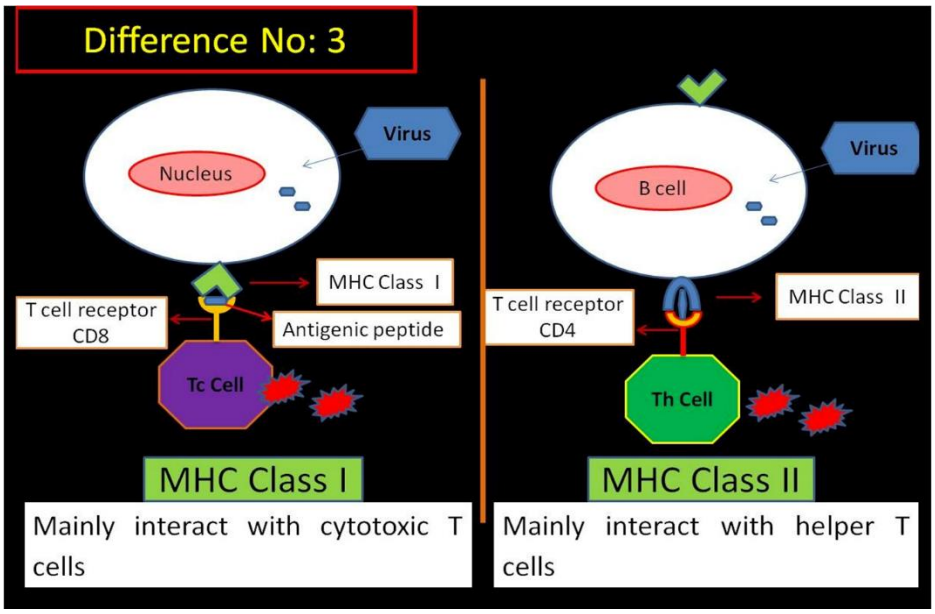
- As for the activation of cytotoxic T cells, this happens when the APC itself is infected with a virus, the virus within the cell is now producing foreign proteins which are presented on the surface with an MHC-I protein which activates the CD8 cells to perform cytotoxic function.
- The same happens when a **piece of a dying infected cells is presented to CD8 cells on MHC-I proteins** (also viral antigens are being presented on MHC-I protein).
- A Non-APC cell will also present viral antigens on its surface on an MHC-I complex (all nucleated cells have MHC-I)

The T-Cell Receptor & MHC ,

- Polymorphism of MHC proteins is needed in order to enable them to bind many different types of antigens to be recognized by TCR (if **all MHC proteins were exactly alike, they will only bind a small portion of antigen peptides**).
- This polymorphism is achieved by having many **different alleles** within the class I and class II MHC genes.
- MHC-I and MHC-II proteins **can only present peptides** and they are unable to present any other type of molecule.
- As mentioned previously, MHC proteins present peptides from foreign and self-sources, and to direct the immune response towards **responding** only to MHC proteins that are presenting foreign proteins, the T cells must be correctly trained in the thymus (**negative and positive selection**) as to only release the ones that recognize non self MHC complexes and delete the ones that recognize self-proteins.

❖ meaning we are not deleting cells that present self-peptides on their MHC proteins but deleting the cells-T cells- that would incorrectly respond to this self-signal.

- ✓ We need the polymorphism for **t cell receptor** and polymorphism for the **antibodies**, so this polymorphism is achieved by having many different genes ,**I take randomly one of each gene pool and I get a different result each time.**
- ✓ T-cells must be correctly trained in the thymus as to not react to our own peptides



so that's the same picture that we saw in the in the beginning so there's nothing new here it's just a reminder

Co-stimulation Is Required to Activate T Cells we need two signals,

- The first signal is the initial activation of the T cell by the interaction between the MHC complex protein with an antigen that is specific and interacts with that TCR.
- It is an important observation that the CD4 protein on the surface of these T cells functions in stabilizing the connection between TCR and MHC protein on the surface of the APC.
- Other proteins also serve to stabilize the contact between the two cells (APC and T cell)
  - **lymphocyte function-associated antigen 1** [LFA-1] protein 2 on CD4 or CD8 T cells binds with **intracellular adhesion molecule 1** [ICAM-1] protein on the surface of APCs this is how the connection is established, which is then further strengthened by CD4

Now the concept of **stimulation** is required to activate T-cells, everything that we said so far still stands but we'll add another thing, it's important to know that if you ever activate a **cd4** cell you will undergo **clonal proliferation** and then you will start activating cd8 cells under down the line or b-cells down the line, so you have to be **absolutely sure before you activate your cd4 cell**. There are other proteins that also serve to stabilize the contact between these two and this will get us towards **the co-stimulatory signal.**

- A second signal, co-stimulatory signal is also required to complete the activation
- B7 protein on the APC must interact with CD28 protein on the **helper T cell** to proceed with the costimulatory signal.

- If the secondary co-stimulation occurs, only then that IL-2 is produced by the helper T cell
- ***The production of IL-2 is the vital step that produces activated helper T cells*** that can regulate the immune response in Th-1 or Th-2 manner and produce memory cells.
- If this costimulatory signal does not occur a state of **Anergy** occurs (unresponsiveness). This **unresponsiveness** will only be specific to that epitope.
- Production of the costimulatory protein depends on activation of the Toll-like receptor on the APC surface.
- This is yet **another defense mechanism** against an immune response towards self-proteins, there is no B7 production for self-proteins however, foreign antigens can induce the production of B7.

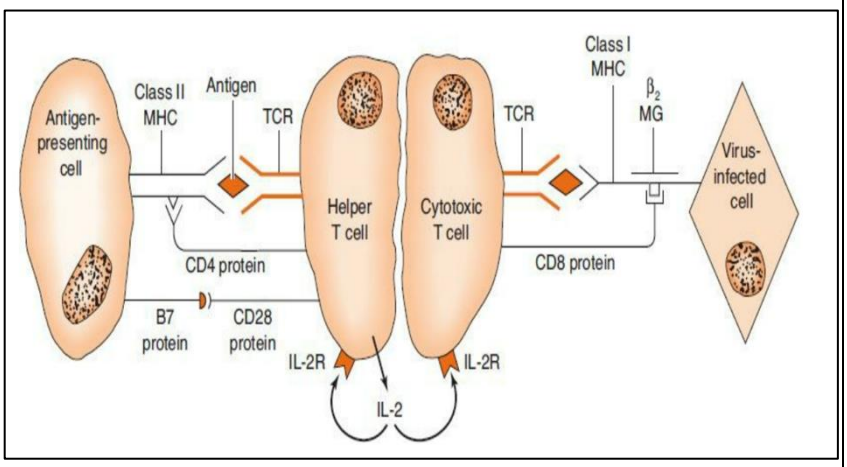
✓ let's talk now about the actual **second co-stimulator signal** it's **the b7 protein on the APC** will bind & interact with the **cd28 on the side of the helper t cell** to proceed with the co-stimulatory signal.

✓ If I found that TCR is correctly bound & MHC2 is correctly bound and then I did my **lymphocyte function associated antigen** and then I stabilized the signal with cd4 >> if all this has occurred then my second signal will proceed with b7 protein , **if you have both the first signal that is the occupation of the t cell receptor by the antigen plus the co-stimulatory signal both together will move the cell towards activation** ,once it's activated it will undergo proliferation and making memory cells .

✓ you can **never undo** this activation. If the cell had anergy, we I need to use help to **reactivate this by producing the co-stimulatory signal.**

✓ The defense mechanism of ensuring the appropriate response works by confirming the stimulation by this co-stimulatory signal, it will vastly reduce any future activation after the thymus of cd4 cells against your own cell proteins

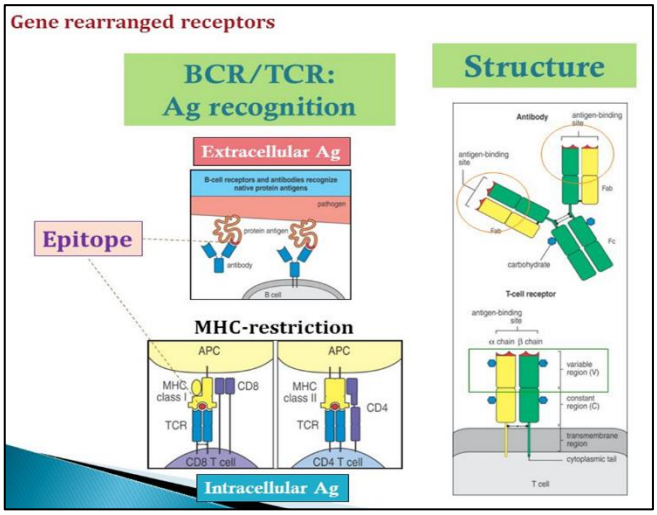
[36:38]

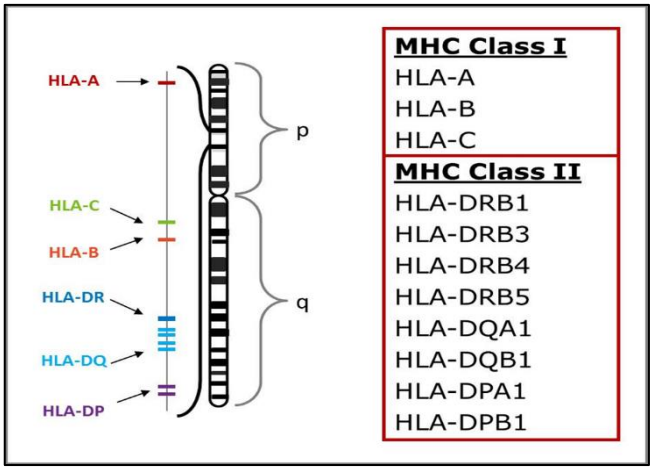


- On the left: APC presenting antigen with MHC-II → TCR specifically recognizes antigen→CD4 helper cell is activated and produces IL-2 which will only occur if the B7 protein binds the CD28 protein on the T cell. CD4 protein helps stabilize the connection between the cells.
- On the Right: A virus-infected cell uses its MHC-I to present viral antigen--> viral antigen recognized by TCR (it is specific to that antigen)→IL-2 produced by the helper T-cell activates this CD8 cell to kill the viral infected cell.→ CD8 protein helps stabilize the interaction between the two cells.
- Class II MHC protein consists of two polypeptides, both of which are encoded by genes in the human leukocyte antigen (HLA) locus, whereas Class I MHC protein has only one

of its polypeptide encoded by the HLA locus and β2 - microglobulin (β2 MG), which is encoded somewhere else.

In the above figure, we have the APC, MHCII, b7 protein and the antigen, as we said cd4 cell **stabilizing the connection** ,this is our first signal and there is our second signal it's promoted by **TLR and b7 protein with cd28** ,when T-cell is activated it produces **IL-2** which **activates itself and then activates the cd8cell** , cd8 will look for a virus infected cell that is producing or showing the same antigen on MHC1 and then **kill this virus infected cell.**





Polymorphism & MHC, TCR, BCR

How do I have polymorphism for the MHC complex protein, the t cell receptor and b cell receptor?

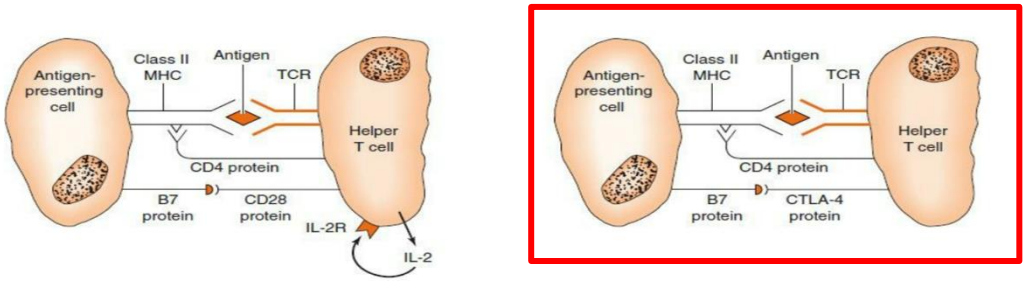
- the idea is that we have a pool of genes that we draw from and then we make different kinds of these molecules.
- **the least polymorphic is mhc-1** there's **only three genes** but you either have any of those three genes so the matching here will be easier.
- Mhc-2 I have more genes about **eight genes**, they are all present on different sites in the chromosome.
- Whereas B-cell receptor is an antibody that has a heavy & light chains and each have an antigen binding site and each part of the chains have a pool of genes that I need to draw from, these receptors are **the most polymorphic** because they're antibodies , there're many kinds of different unique antigens about billion different antibodies against different antigens and they're obviously still counting ,so this this will be the most polymorphic

Turn Off Helper T-cell,

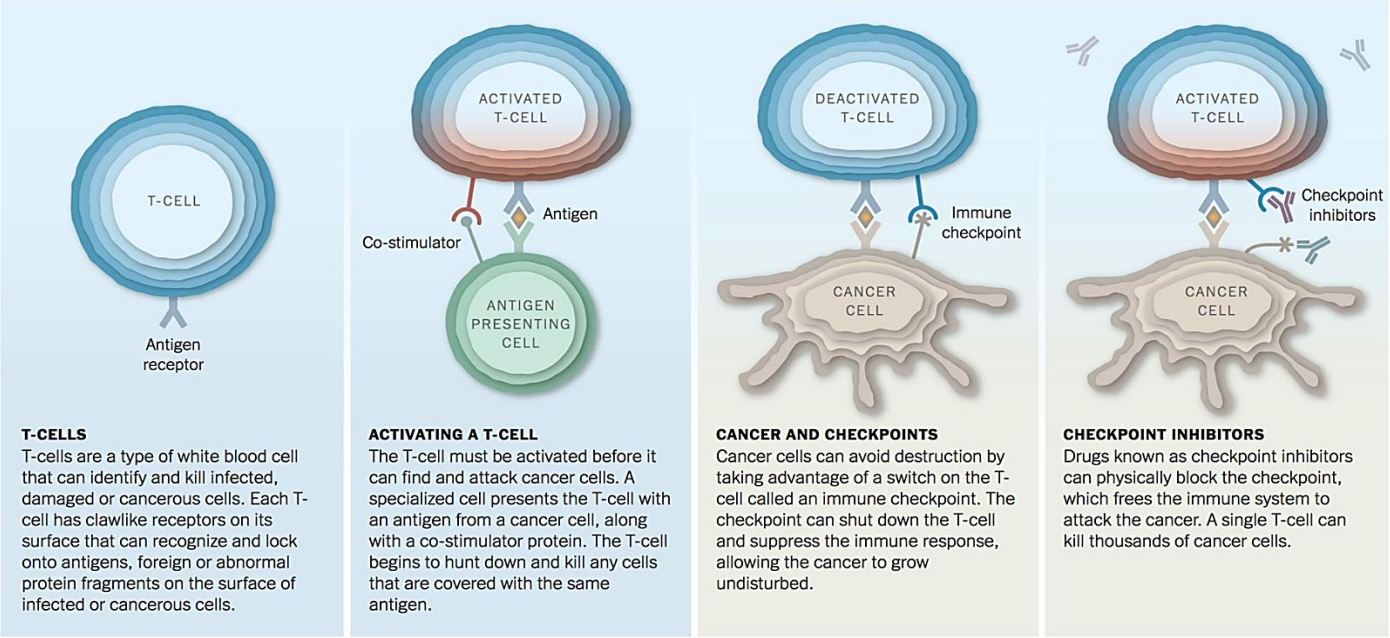
- To turn off these helper T- Cells, a different protein called **cytotoxic T lymphocyte antigen-4 (CTLA-4)** appears on the T-cell surface and **binds to B7** and displaces the bound CD28.
- Now the co stimulatory signal is no longer working and thus CTLA-4 inhibits T-cell activation (IL-2 is now not produced due to the lack of the costimulatory signal).
- This is a regulatory mechanism to control the T cells and create a balance between on and off status.
- If this OFF switch is not present (mutant T cells that do not have CTLA-4) cannot be deactivated and cause autoimmune reactions.

- The use of CTLA-4 protein is shown to reduce the rejection of organ transplants in experimental animals (remember it is a cellular response).

If I want to intentionally cause anergy for example to reduce **auto autoimmune** reaction or I want to produce Anergy and turn off these cells by preventing co-stimulation using **CTLA-4**. So I put CTLA-4 to turn them off & I remove CTLA-4 to turn them back on.
We use CTLA-4 to **reduce rejection of organ transplant**, the activation against the graft will be further delayed



So now that we have covered the co-stimulatory signal , we will get back to cancer cells & immunotherapy of cancer, so in the normal way you have this t cell with an antigen receptor and is waiting for its APC >> then it presents the antigen >> it co-stimulates it to become an activated t cell >> an activated t cell if it is active against a cancer cell it will kill it.
But cancer cell is clever it can avoid destruction by taking advantages of this co-stimulatory checkpoint and they shut down the t cell using something similar as CTLA-4 >> it will deactivate the t cell >> the t-cell will not come and bind to it and even if it binds to it ,it will not do anything.
To solve this, we will go and make an antibody that binds this inhibitory protein on cancer cell so we prevent it from inhibiting the t cell ,so these two will not bind to each other and this t cell will remain active and then it will act on the cancer cell. These are the drugs of **immune therapy**, however, we have a problem here we need an antibody for each different kind of immune checkpoint that each cancer cell is producing so it's not something that you can use for all cancers.



- Agonists of **CTLA4** are used coupled with Ig (in the form of **antibodies**) to reduce immunity and are in trials to treat immune disorders such as Rheumatoid arthritis and renal transplants in specific patients (with EBV virus).
- Ig Fc fragment provides resistance against degradation, resulting in increased plasma levels of CTLA-4 for a longer duration than CTLA-4 alone
- Antagonists of CTLA4 (enhancers of cellular immunity) are used to increase immunity, this is in trials to be used as a potential therapy to reduce the tolerance of immune system to tumor cells and thus help mount a response against them
- Antagonists to CTLA-4 can be in the form of antibodies, that would inactivate CTLA4 and thus improve the immune response **against some human cancer cells and cause the cancer to regress**.
- So the antibody is an inhibitor of an inhibitor of the immune response.
- Another inhibitory protein on the surface of T cells has also been described (**PD-1** (**programmed cell death-1**)).

When PD-1 interacts with its ligand (PDL-1) on the surface of APCs, such as dendritic cells and macrophages, the immune response is inhibited-similar to CTLA-4. Similarly, antibodies against PD-1 enhance the immune response and are effective against some cancers, as shown in recent trials

Things that prevent inactivation are used to increase immunity as a potential therapy and to reduce tolerance to tumor cells. [45:32]

* Blue is for what the doctor said, black is for slides and timing is in red