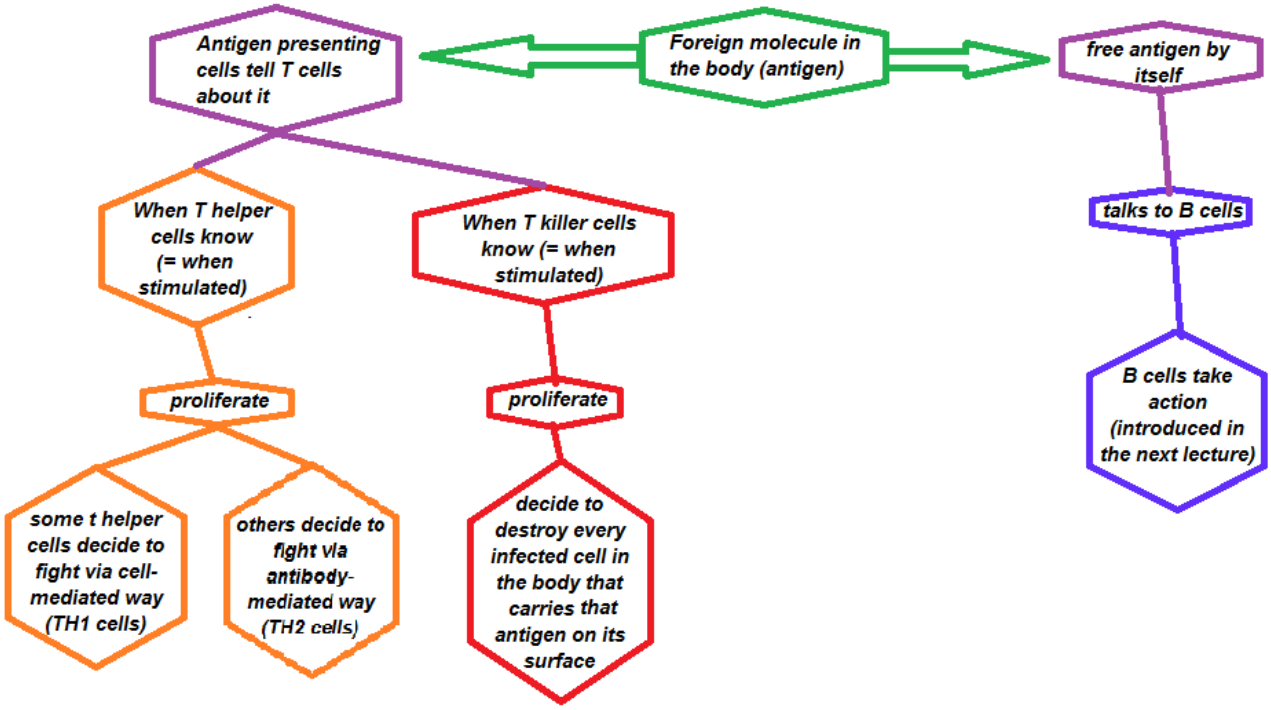
Immune response

This overview figure summarizes simply how our body responds to foreign molecules that enter to it.



It's highly recommended to watch Dr Najeeb's lecture that's titled "T Helper cells and B cells" on YouTube, it covers most of this topic and makes this sheet more easily imaginable.

The doctor recalled some features of the following cells:

- T cells mature in the thymus have T cell receptors which consist of alpha and beta chains, and there's a small subset which are gamma and delta receptors and these are equivalent to CDRB16.
- NK T cells (1-5%) are in the periphery, have TCR and markers for NK cells (NK1.1)
- T regulator cells will be known later.

Immune response by T helper cells (CD4 cells) activation

We start with T helper cells because these cells have a primary role in helping everything in immune response.

1. *Contact between T helper cells and antigen presenting cells (APCs):*

T helper cells are always circulating so meetings between them and APCs are at random; it might be difficult because the number of helper cells that are specific for certain antigen is only a few! So the best remedy for this is to set a meeting place; that's why we have lymph nodes, spleen and other secondary lymphoid tissues that drain the areas from which the antigens can enter.

Antigens are presented when pathogens are taken up either by resident dendritic and phagocytic cells present in the lymphoid tissues or sometimes antigens can be brought to these areas by the cells themselves, like cells of Langerhans that take the antigens from under the skin and migrate until they go to the regional lymph node where they meet T helper cells.

So: by T cells circulating + by APCs migrating = we make sure that there's a sort of meeting in order to get the immune response occurring.

Now, why is the meeting needed? These cells as they go by one another they try to inspect each other i.e. the helper cell has to see whether there's something wrong that the APC has on its surface or no.

In order to get, this time is needed! This occurs by adhesion between the cells through molecules like integrins or intercellular adhesion molecules, these are the ones that are responsible for bringing those 2 cells close enough for some time.

▲Some integrins between T cells and APCs are:

1- LFA1 (lymphocyte function associated molecule 1, it's a beta 2 integrin) interacts with ICAM (intercellular adhesion molecules).

2- CD2 on T cells (a marker on T cells and NK cells, it was previously called LFA2) interacts with LFA molecule 3 on the APCs.

This is the **immune surveillance theory** نظرية الرقابة المناعية that the contact which lasts for some time gives the helper T cell the chance to go around and inspect the MHC class 2 molecules of the APC to see if there is something wrong on them or not.

If the MHC II molecule has self peptide, this means the APC has nothing wrong with it so the 2 cells will separate and the lymphocyte will go to its way.

If the MHC II molecule has non-self (foreign) antigen, the lymphocyte recognizes it and the adhesion becomes more intense to make sure that the cells don't separate and stay together.

2. ***Then, signaling between T helper cells and APCs and stimulation occur:***

At the same time the adhesion increases between the two cells, signaling increases too in order to activate them.

▲Remember that: the ligand for CD4 is the beta 2 chain of MHC II molecule (its receptor) meanwhile CD8 has a receptor on the alpha 3 domain of MHC I molecule and that's why they interact together.

The first signal between APC and helper cell is gonna be transmitted through the TCR to say that there is something wrong and start activating T cell, transmission of signals to the inside of the cell occurs through CD3 molecule because TCR itself doesn't signal too much. A little bit of signaling comes along CD4. All this is the first signal.

▲Note that: in the immune response it was found that one signal on a sole is not enough to activate T cells. In fact if a T cell received a primary signal only, instead of being activated it will become allergic or it will go into apoptosis. So T cells always need a **secondary signal** to finish the job, thus called **co-stimulatory signal** too.

Secondary signal between APC and T helper cell occurs along a molecule known as **B7** on APC and **CD28** on the surface of T cell. Indeed there are two kinds of B7 molecules*: B7.1* (known as CD8.80) and *B7.2* (known as CD8.86).

▲Again, co-stimulation is important in tolerance because if T cell is actually stimulated by APC without 2ry stimulation, activation won't occur and the cell will be allergic or undergoes deletion by apoptosis.

There's another interaction between the APC and T helper cell: APC has a molecule on its surface which is known as CD40 and it has a ligand present on T cell known as CD40 ligand or CD40L.

▲Note that: through these interconnections APC is also activated and made more active! So the interaction actually is mutual. Thinking about dendritic cells, macrophages and B cells as APCs: dendritic cells are prototype of APC because usually these cells have already MHC II molecules on them i.e. constitutively expressed. Macrophages in general don't express MHC II molecules on their surface nor do the B cells so expressing MHC II molecules has to be induced to become very good at presentation and induction occurs under the influence of many causes like phagocytosed bacteria itself, or even cytokines coming from helper T cell (INFɣ), or interaction between CD40 ligand and CD40.

It's believed that naïve cells are usually activated by dendritic cells whereas macrophages may activate memory cells but not naïve cells. So the excellent APCs are the dendritic cells, and macrophages can easily activate memory cells because they are already stimulated.

▲How can we differentiate between memory cells and naïve cells?

CD45R**A** molecules are present on n**a**ïve cells, but CD45R**O** are present on mem**o**ry cells.

3. ***After stimulation, proliferation takes place:***

One of the earliest things that happen after stimulation of the T cells is the production of cytokine **IL2** (this is a growth factor for the helper T cells, it also acts on NK cells and on B cells as growth factor. Cytokines have multiple functions that overlap and have multiple sources, and many redundancies that are discussed later)

IL2 acts on T cells as an autocrine. At the time it's secreted, its receptors on naïve T helper cells are not there yet but once activated, receptors will eventually appear. As a result, IL2 goes to the receptor and influences the growth of T cells (IL2 causes the cell to swell up, become bigger, and produce a clone of effector and memory cells.

▲Effector cells produce cytokines, but this lasts for short time only and has to be shut off! One of the factors that influence the duration of immune response is the short half-life of the effector cells.

A while after stimulation, T cells then start producing the **CTLA4** (cytotoxic T lymphocyte antigen number 4) on their surface and this is very similar to CD28 so the ligands gonna be B7 but here the effect on T cell is the opposite; instead of turning on and activation of proliferation, it has a negative influence that stop the cell from carrying on its function and it will eventually die. So the balance between positive and negative inputs stops immunity from working forever.

4. ***finally, produced cells drive 2 different ways of defense (immune deviation):***

The produced cells can be of 2 kinds (of 2 varieties) depending on the environment and the substances that are present around at the time of stimulation. We know that we have humoral and cell mediated immunity, in fact these two are driven by 2 separate sets of activated T lymphocytes:

1- The ones that induce *cell-mediated* immune response are known as **TH1 cells**.
2- The ones that produce *humoral or antibody-mediated* immune response are known as **TH2 cells.**

Naïve cells are sometimes referred to as TH0 or THº; because they are not activated yet. But once they are activated they have to be either TH1 or TH2 and this is what's known as **immune deviation.**

These two immune responses produce separate kinds of cytokines and these actually produce different functions. They are antagonistic that the TH1 suppresses the TH2 and the TH2 suppresses the TH1, for example:

- T helper 1 cells produce INFɣ, this is the main cytokine that's produced in cell-mediated immune response and it suppresses antibody-mediated immune response.
    - ✓ Some of its effects on macrophages are that it stimulates expression of more MHC II molecules and more B7 molecules, and promotes respiratory burst (when bacteria can't be digested in lysosomes so free oxygen radicals and nitrogen peroxides can kill it).
    - ✓ Some of its effects on NK cells are that it promotes antibody-dependent cell-mediated cytotoxicity (ADCC) and promotes production of granzymes and perforins and so on.

So in general INFɣ promotes cell-mediated immunity and also suppresses TH2 cells i.e. suppresses production antibodies.

- T helper 2 cells produce lots of IL-4, this is really responsible for production of the antibodies and responsible for switching to IgE.

T helper 2 cells produce IL-5, which promotes the growth of the eosinophils.
T helper 2 cells produce IL-6 and TGF-ß (transforming growth factor-ß), involved in switching to IgA.

But, how different responses are driven? Why after activation of CD4 helper T cells some of them become TH1 and others become TH2?

1- That depends on the **antigen**. If the antigen is a parasite or allergic, usually the immune deviation goes towards the TH2. If it is bacteria or proteins that are specifically intracellular organisms, deviation goes towards TH1. So the antigen actually plays a role.

2- But the main determinant that's responsible is the **cytokines** that happen to be present at that time. For example: IL-12 which is mainly produced by APCs, deviation is gonna be towards TH-1 response. In the case of TH-2 response, IL-4 is needed for the deviation.
▲But IL-4 is a product of TH2 cells, then how it's needed to stimulate it at the same time? We can't deviate T helper cells towards TH2 cells unless IL-4 is there, but it's produced by them so how can we use IL-4 which is mainly a product of B cells to activate T cells that should be activated before B cell is? The answer in this case is **NK T cells.** NK T cells play a role in recognizing antigen in conjunction with non classical MHC molecules, remember that they

are CD4 cells yet have the markers of NK cells. So it's actually the TCR on NK cells that recognizes antigens on the CD1 (CD1 has got too much globulin in it and it's similar to MHC-I but not really the same; alpha chains are different.) CD-1 represents lipids (glycolipids) and doesn't actually display protein peptides.
So NK cells produce the IL-4 first.

Immune response by T killer cells (CD8 cells) activation

1. *Contact between T Killer cells and antigen presenting cells (APCs):*

CD8 T cells have TCRs which recognize MHC I molecules and antigens. It's found that these cells will be stimulated by endogenous antigens so the dendritic cells either are treated as infected with the viruses or they have taken up the antigen.

▲The dendritic cells are not really true phagocytic cells, they actually take up molecules by pinocytosis/endocytosis and connect them to MHC I molecules so represent the antigen.

2. *Then, signaling between T Killer cells and APCs and stimulation occur:*

It's the same story as T helper cells that after recognition, CD8 attaches to the alpha 3 domain of the alpha chain of MHC I molecule. And transmission of signal to the inside of CD8 cell happens by CD3.

The second signal is provided by the same set of molecules: CD28 on CD8 cell interacts with B7 on the APC which is the dendritic cell.

3. *After stimulation, proliferation takes place:*

There will be production of IL-2 which has a receptor on T killer cell, and then proliferation starts.

▲A theory says that IL-2 is mainly produced by CD4 cells and the amount produced by CD8 cells is not enough. So activation of CD4 cells is needed to produce IL-2 in order to help CD8 cells. If we believe this theory, APCs activate both cytotoxic T cells (through MHC-I molecules) and helper T cells (through MHC-II molecules) at the same time. By this IL-2 is produced in large amounts, and will work on CD8 T cells in a paracrine fashion and work on CD4 T cells in an autocrine one.

4. finally, cytotoxic T cells attack:

After stimulation, clones of T killer cells are produced with some becoming memory cells and others becoming effector cells. Now the effector cells are known as armed or primed cells and will be directed towards any cell in the body that happens to have MHC I molecules with the antigen that produced them (virus for example).

▲Note that: infected body cells with viruses display the viral antigens with MHC-1 molecules on their surface, yet they can't stimulate naïve cytotoxic cells because they lack secondary signal (they don't have B7 on the surface). These cells when they meet with cytotoxic T cells they just tell them "look there's something wrong!" but without being able to activate them.

Back to active cytotoxic T cells, they end up going round and inspect every cell's MHC-1 molecules with viral antigens on them, and inject granzymes and kill them. Once it kills an infected cell it moves to the next and so on until the infection is under control.