IMMUNOLOGY

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The activation of helper T lymphocyte

As you know T helper cells are T lymphocytes which means : they express CD4 and TCR which recognizes antigens attached to MHC II , also these displayed antigens are of the exogenous type which means that they have to be processed first by the APCs which are the macrophages in this instance.

So the TH cells move around and come in contact with the APCs (macrophages and dendritic cells) and binds to them temporarily by means of adhesive molecules :

- the first one is the **LFA-1** (lymphocyte function associated adhesive molecule) that interacts with its receptor on the APCs which is **ICAM-1** (intercellular adhesive molecule 1) .

- the second one is **CD2** (previously called **LFA-2**) , and its receptor on the APCs is **LFA-3** , they can also attach to RBCs since these also have LFA-3 on their surface

CD2 are markers present on the T lymphocytes and the NK cells

Now this temporary adhesion that's not very strong allows the TCR of the TH cell to inspect the antigen that is presented by the APC by MHC II, so if it is a self-antigen nothing will happen and the two cells will separate.

Now when it inspects and recognizes a foreign antigen, the process of activation starts.

Now the signal is not transmitted through the TCR, it's transmitted through **CD3** , and this is known as the *first signal*.

Consequently there's increased adhesion between the CD2 and LFA-3 , LFA-1 and ICAM and the cells won't separate till there's full activation of the T-cell.

Taking place at the same time, the **CD4** will attach to the **Beta** chain of the MHC II (this is another kind of adhesion) , the CD4 also signals to the inside of the cell, so we have signals coming from the CD3 and CD4 .

We need a second signal in order to activate the T lymphocyte, because one signal alone will cause **ANERGY** and no activation**.**

This second signal comes from **B7** which is present on the surface of the APC, and its ligand on the T cell is known as **CD28**.

After receiving the two signals, T cell activation means: gene activation which will cause the production of cytokines, expressing molecules on the surface and cell proliferation forming a lymphoblast which will divide to form a clone, this clone as you know has the same specificity as the mother cell.

This activation process needs interleukin 2 **(IL-2)** which mediates the proliferation and division of the helper T-cell.

So we have the first signal then the co-stimulation from the second signal followed by producing IL-2.

IL-2 receptor is composed of 3 chains: alpha which is known as CD25 (as you remember we said that this is present on the T regulatory cells and not on other cells), beta and gamma.

now the cells start producing IL-2 and also IL-2 receptors (autocrine action)

IL-2 also acts on other adjacent cells as a growth factor on Cytotoxic T cells, B cells and NK cells (paracrine action).

It also has endocrine effect.

IL-1 , IL-6 , TNF produce fever by affecting the hypothalamus (endocrine effect.

As we said it will proliferate forming a clone, this clone will develop into 2 variants:

1 - **effector helper T cells**: they help other cells in the immune system, they have a limited life span (maybe several weeks) then they will die off once finishing their job.

2 - **memory cells**: these go into a resting stage (this is NOT a naive cell anymore because it had been activated previously) , we can differentiate between the resting stage of the memory T cell and the naive one by cell markers , in this case it is the **CD45** (known as the common leukocyte antigen because it's present on all WBCs) , this CD45 has different

isomers: the naive cell has **CD45 RA isomer**, the resting memory cell has **CD45 RO isomer**.

CD45 is also involved in signaling to the inside of the cell.

Now the memory cells will go to a secondary lymphoid tissue and stay at the resting stage there, they are very long lived; some of them may stay alive for 20 years or even more, so if you become exposed to the same antigen again, the response of T-cells will be stronger and faster.

After the activation some of these helper T cells, some will be concerned with **cell mediated immunity** and others will be concerned with **humoral immunity (antibody production)**.

The cell mediated immunity will involve cytotoxic T-cells, NK cells, macrophages, neutrophils etc these will either phagocytose the cell or kill it, that's the reason behind naming it cell mediated immunity.

When the macrophage is activated by the ingested bacteria through the TLR (toll like receptor), they need some help from the TH cell because some bacteria (like Listeria monocytogenes and TB) are very resistant to killing by the lyzosomes although being phagocytosed. The only way of eliminating these intracellular pathogens is by activating the phagocytes, we activate them either by direct contact or by producing cytokines.

We have on the surface of the T helper cell the **CD40 ligand** and equivalent to it on the macrophages there is **CD40**, so the ligation between these two will cause activation of the macrophages.

We also have the production of cytokines from CD4 cells mainly **interferon gamma** which is also involved in cell mediated immunity.

we talked about interferons previously and said that there are non-specific cytokines (part of the innate immunity), as in the case of interferon alpha and beta which are produced by macrophages, fibroblasts and a variety of cells, and they will produce an antiviral state, in fact, the main inducer of interferon alpha and beta are viral infections, they will act on the cell itself or on other cells preventing viral multiplication.

Interferon gamma is part of the **acquired immunity** because it is produced by the T lymphocytes upon activation, and it will mediate cell mediated immunity by:

1- activating neutrophils by increasing their respiratory burst; producing free oxygen radicals and nitric oxide which will kill the resistant bacteria which hasn't been killed by the hydrolytic enzymes in the lysosomes.

2- promoting the actions of cytotoxic T cells and NK cells making them more capable of killing.

3- they also work on APCs and endothelial cells inducing more expression of MHC I and II molecules and more adhesion molecules which is better for the immune response.

Remember that macrophages normally by themselves express very little MHC II, in opposite to dendretic cells which express lots of MHC II (they are professional :))

These cells - that secrete interferon gamma and are concerned with the cell mediated type - will be known as **TH1** cells, the naïve T-cells that haven't been activated are called **TH0** cells.

The other cell will be known as **TH2** cells which are concerned with humoral immunity, as you expect: their action will be mainly on the B lymphocytes.

Now this is known as immune deviation: once you activate a CD4 it can either be TH1 deviated or TH2 deviated, the reason behind one deviation over the other is the antigen nature and certain cytokines, for example: activated APCs (macrophages or dendretic cells) will produce **IL-12** under the effect of the ingested material which will work on the T cell and deviates it towards TH1 cell as expected.

NKT cells share markers with NK cells like : CD16 , CD56, NK1.1, NKG2D

If the deviation is toward TH2 cell we another cytokine which is **IL-4**, this IL-4 comes from the helper T cells themselves especially the TH2. But how did the TH2 cells got activated to start with if it already came from the helpr t-cell? so there is a theory claiming that the first TH2 cells are produced by the NKT cells, as you remember these cells recognize antigens (glycolipids in general) presented on **CD1** and not by MHC molecules, then it will activate the CD4, thus producing IL-4.

The activated TH is gonna take IL-4 and deviate towards TH2 variant of helper T-cells.

As a general rule: Extracellular pathogens like helminthes tend to deviate the variant toward becoming TH2 cell since they can be affected by antibodies, while intracellular pathogens like viruses tend to do the opposite, deviating it to the TH1 variant since antibodies are useless for intracellular pathogens so we need the cell mediated immunity.

So TH2 secretes IL-4 which is a growth factor for B-cells so it promotes the proliferation and the secretion of antibodies by B lymphocytes, also it may take part in isotype switching, for example switching to the IgE immunoglobulin which is under the effect of IL-4, they can also work on mast cells promoting histamine release.

as you remember T regulatory cells are either induced or natural

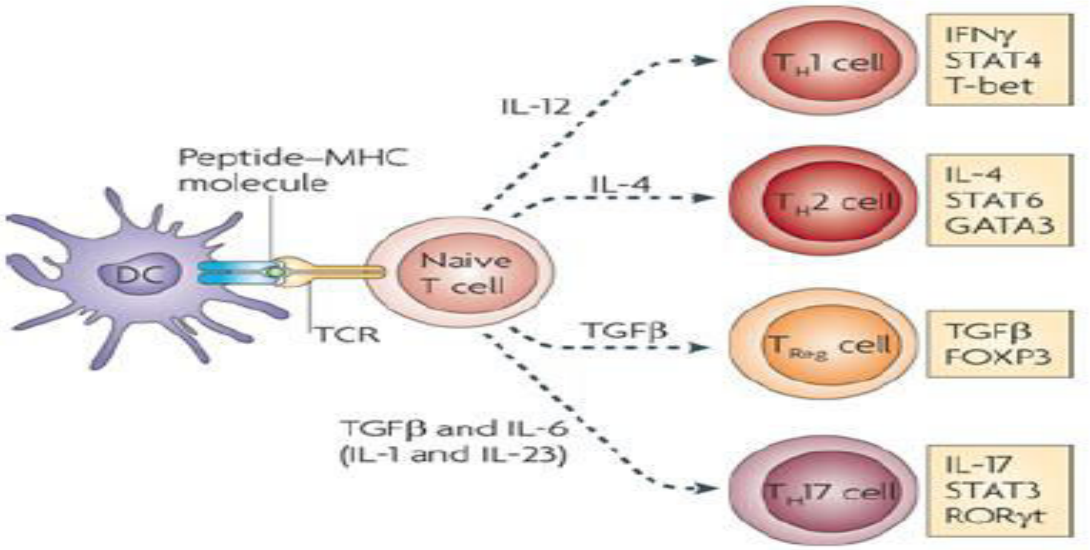
There's also TH3 cell which is a suppressor cell, it has nothing to do with activation! Some people say it's the induced T regulatory cells, these are involved in the suppression of the immune system and are present in the submucosa of the GI tract.

We also have TH17: this is an inflammatory cell which is very effective in immune response and it's also implicated in the development of autoimmune diseases.

We previously talked about leishmania if you remember and said that we could have cutaneous leishmaniasis or diffuse cutaneous leishmaniasis where it spreads, well this depends on the immune response that the body elicits. For example if the cells have been deviated towards the TH1 response, you will find that the disease is confined to one side (this is cutaneous leishmaniasis) : the cell mediated will kill the intracellular parasite. But if the deviation was to the TH2 response you will get the diffuse variant of the disease, you will have a lot of antibodies but because they are inside the macrophages it will not affect them

Now after the end of activation of the T cell so that you don't get over activation and to reduce the immune response (this is part of the regulation), the T cell will express **CTLA-4** (cytotoxic lymphocyte antigen 4), this molecule is similar to CD28, and it's capable of binding to B7

molecule, but this signal is of the suppressor type not of the activating one, so this is a negative response .



Activation of cytotoxic T cell

As you already know, these cells recognize antigens which are attached to MHC I, so essentially the virus can affect any cell in the body, and parts of the virus can be displayed on MHC I in which it can be recognized by the TCR of the cytotoxic T cell, but these infected cells can't activate the CTLs because they don't have the ability to provide a second signal, so this is not effective.

The cell which can present the antigen AND provide the second signal to the CTLs is the dendretic cell, these can take foreign antigens from the environment including the virus which will multiply inside and be presented on MHC II through the endogenous pathway.

In the case on macrophages the antigen was exogenous, here it's endogenous.

after binding the mechanism of activation is similar to TH cells, as the signal is transmitted to by CD3 then increased adhesion of the ICAM with LFA-1 , CD2 (marker for T-cells and NK cells) with LFA-3 , BUT here we have CD8 instead of CD4 which attaches to the **alpha 3 domain of the alpha** chain of MHC I , the second signal is provided by B7 and CD28 .

So again: normal cells can provide the first signal but not the second signal, and the result is abortive immune response rather than activation.

After activation the CD8 cell will proliferate forming a clone, some of these cells will become effector cells; killing all viral infected cells, and the other becoming memory cells.

These effector cells in this instance are long lived (known as armed CTLs) so they will inspect different cells that have MHC I and when it encounters a cell that is presenting the viral antigen on its MHC I it will kill it .

The killing action happens by injecting perforins and granzymes in the cell which activate the process of apoptosis, also it can induce apoptosis of other cells by binding of Fas- ligand which is present on the surface of the CTLs with Fas- receptor which is expressed on the infected cells, this is also how you kill intracellular pathogens.

Also IL-2 (autocrine growth factor) is necessary in the proliferation and production of the clone, which comes from the CTLs themselves (very little amount), but it's debatable whether this amount is sufficient or not, some people say that this cytokine comes from activating TH cells by presenting the antigen on MHC II of the dendretic cells, now these TH cells secrete IL-2 and affects CTLs in a paracrine fashion as well as themselves.

dedications to : Q , ali khresat , 3laa shaban , abu alia