Th1/Th2 Regulation

The immune response is either deviated toward Th1 or Th2 and the products of each one actually antagonize one another for example IFN-γ which is produced from Th1 Suppresses the proliferation of Th2 and so do IL4 and IL10 which are produced by Th2

IFNγ suppresses the proliferation of eosinophils and mast cells while IL-3,IL-4,IL-5,IL-6 activate them and so on *please check the figures In the handout no. 6*

So Th1 regulates Th2 and vice versa.

Activation of B cell :

It can be activated by :

1. T dependent Ags (proteins)
2. T independent Ags (lipids and polysaccharides)

T Cell-Dependant B Cell Activation

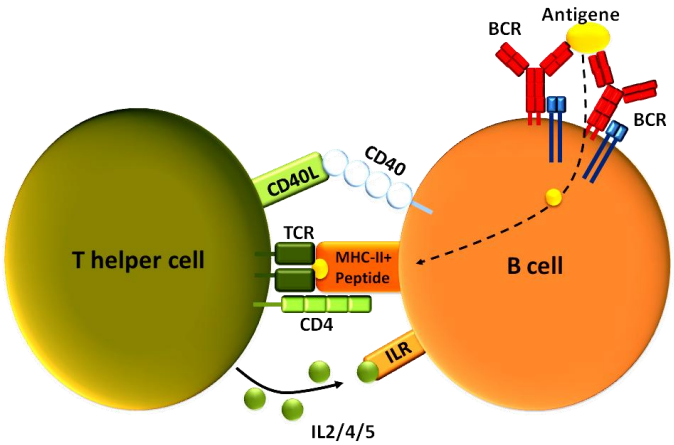
BCR[1]:

- Immunoglobulin (IgM) + Two Chains (Igα + Igβ).
- Able to recognize antigens in its native form.
- You need **two** adjacent BCRs engaged so that you can get initial activation or two IgMs that have been **cross-linked** by the antigen so that will give you the **first** signal.
- We *always* need a second signal when activating B lymphocytes. This signal is provided by a **trimolecular complex** present on B cells.
- To be technical, the second signal is provided by the antigen which activates complements through the **alternative pathway** and their products will be deposited on the activating particle (CR2 will attach to C3d on the antigen

Trimolecular complex is composed of CD19 (*Marker of B cells and present **only** on them*), CD81 and CD21 (*Complement receptor 2; present on few cells like follicular dendritic cells, parietal cells and cervical cells, also present on EBV).*

CR1 is present everywhere and serves as a receptor for C3b.

Due to the presence of CR1 on RBCs, they have the function of clearing out immune complexes around the body by delivering them to the macrophages in the spleen.



[1] Beta Cell Receptor
EBV = Epstein-Barr Virus

for example), only now can a second signal be produced.

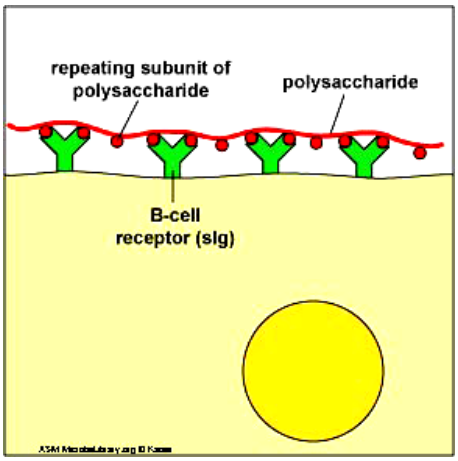
- Second signal is not really enough because this is a T-dependent antigen.
- Antigen *and* its receptors are internalized inside the B cell and broken down in the lysosomes into peptides.
- These peptides are displayed on the surface of the B cell in conjunction with MHC Class II molecule.
- The story now continues as before since the B cell has become an APC with CD40L interacting with CD40 on B cells. This will be recognized by the TCR.
    - CD40 is very important in isotype switching.
    - We know this because there is a disease with absence of CD40L and we get cells that produce IgM which never switch to anything else. Hence, it's called Hyper IgM Syndrome (There is no IgA or IgG or anything else)
- The signal will go through CD3, at the same time there will be junction between B7 and CD28 providing a second signal.
- This CD4 T cell will produce IL-2 and IL receptor and now it will be ready to produce cytokines for B cell.
- We will produce cytokines (A Th2 response because the B cells is going to produce antibodies) so we will get production of IL-4, IL-5 and IL-6 which will further promote the growth of B cell and maturation.
- B cell is known to produce antibodies, first one being IgM and their isotype switching depends on the cytokines produce by Helper T Cells e.g. IL-4 switches to IgE[2], TGF-β (Produced by cells in the GIT) is concerned with switching to IgA (Doesn't induce much inflammation but good at neutralizing viruses, toxins and bacteria).

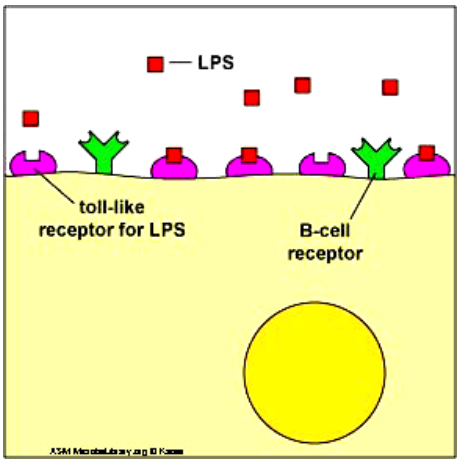
Why do we need to put a carrier on Haptens?

If a B cell recognizes an epitope on a hapten, the antigen will be internalized so the hapten and the carrier will be internalized and then they will be conjugate . The hapten can't actually produce peptides inside the B cell for antigen presentation (Reason why haptens are not really immunogenic) but the carrier gets broken down and its peptides are displayed on the surface of MHC Class II molecule for the T cell.

The recognition of the B cell is done by the hapten but the presentation of peptides is by the carrier. The carrier is immunogenic and can be recognized by another B cell which can produce antibodies against the carrier so the B cell response in the human body is polyclonal because it can produce antibodies against multiple epitopes (Each antigen can have more than one epitope).

[2] IFNg switches to IgG but it's not very well documented.





T-Independent Antigens

Can be of two kinds (*If you expose B cells to either one of them, you will find that many clones of cells are expanded and many Abs are being produced*):

1. Polysaccharides with repeating units of sugars
    a. Because they have repeating similar units, they can cross-links many BCRs and by doing so, they can activate the cells.
    b. Activated B cells will not have memory cells and will only produce IgM which is of low affinity.
    Eg : group A and B in blood grouping
2. Polyclonal activators of B Cells e.g. LPS (*Polyclonal non-specific[3] activator*)
    Also here we don't have switching of Igs so there are no memory cells produced

Regulation of Immune Response

1. **Removal of Antigen**: Antigens produce the immune response and their presence is what compels the response to go on so once they're removed, the driving force for the reaction is gone and the response can subside.
2. **Effecter elements (***Plasma cells, cytotoxic effecter cells and complement system***) of the response are short-lived**.

3.CTLA-4

After 2 or 3 days of activating T helper cells, they will express CTLA-4 on their surfaces and this is very similar to CD28 so the ligand for it is going to be B7 but this happens usually to find the effect is a negative one rather than a positive one because when it's expressed, it inhibits B7 and can suppress activation of helper T cells.

4.IL-2

Too much of a good thing is a bad thing.

[3] Activates cells haphazardly and produces antibodies without actually seeing them.

Very good promoter of proliferation and growth of helper T cells but excessive exposure to high levels of IL-2 production would cause the cell to shut off in an attempt to suppress immune response.

5-Fas

Receptor which can be detected on T -cells which have been activated for quite a while. FasL is its ligand and it's present on other T cells.

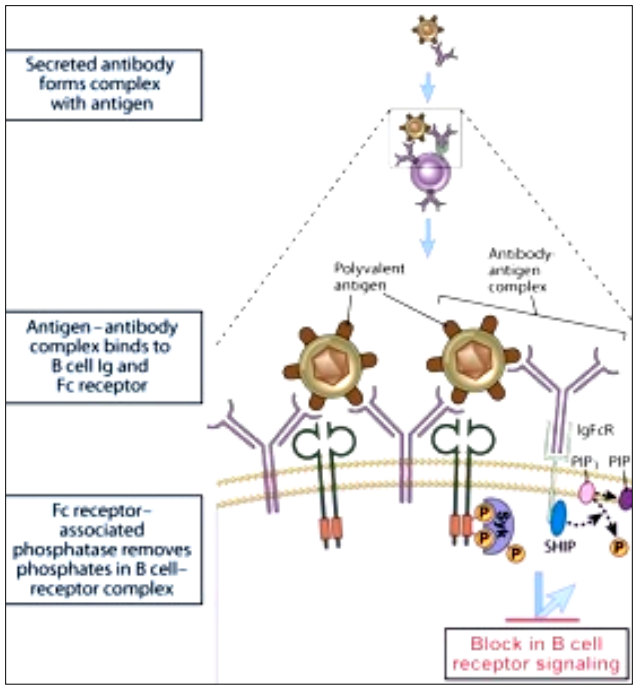
When the ligand attaches to its receptor, it sends apoptotic signals to the cell. This is another way of controlling the immune response.

Sometimes the same cell produces Fas and expresses it's ligand as if the cell is committing a suicide !

Antibody Feedback

Present on B cells which have Igs as cell receptors and they also have Fc receptors.

During the immune response, we produce antibodies and they're specific for antigens. We can actually join the immune complex to the B cell in two places so the antigen can engage an IgM receptor on the surface and the Fc receptor can engage theirs so the Fc receptor can be cross-linked to IgM through the antigen and immune complex of the immunoglobulin. When this happens, the cell is actually shut off, cannot be activated.



So when you have produced a lot of antibodies which are enough to interact with the present antigens, no more B cells are needed so you need to shut them off.

I deeply apologize for the delay, mistakes and possible confusions in this sheet.

Best of luck on the exam.