SHEET NO.

IMMUNOLOGY

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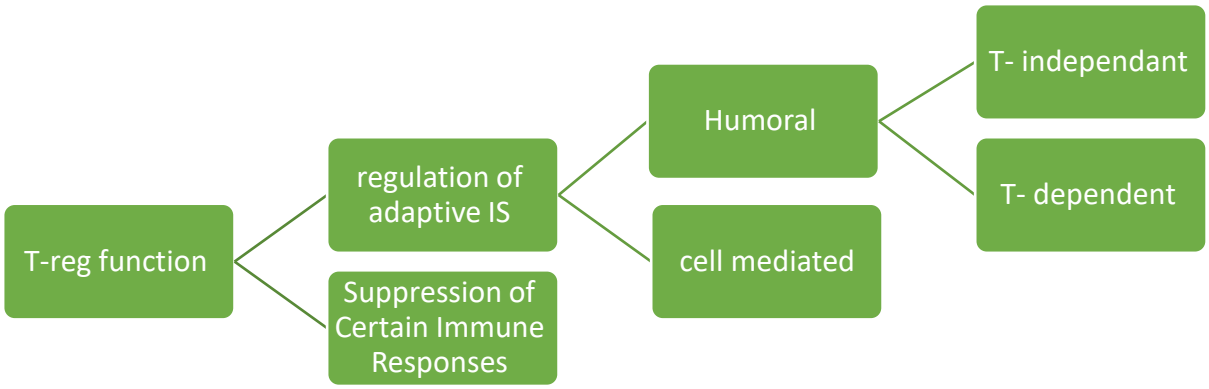
Regulatory T cell function, B cells and APCs



The T cell is the main player in the regulation of adaptive immune response, in both its arms (Humoral and cell mediated):

humoral (Antibody production):

1- T cell dependent response:

helper T cells are required to **directly** activate the specific **B cell** to differentiate into a **plasma** (AB producing cell).

2- T cell independent producers of antibodies:

- to produce antibodies to certain **atypical** antigens **(such as bacterial capsular polysaccharides that are multivalent)** can attach to antibodies at more than one side and thus cause cross linking such antigens (along with haptens, although with a slightly different mechanism) .
- macromolecules that have repeating nature (being multivalent) can activate B cells without needing activation from T helper cells by cross-links the IgM antigen receptors on the B cell surface.

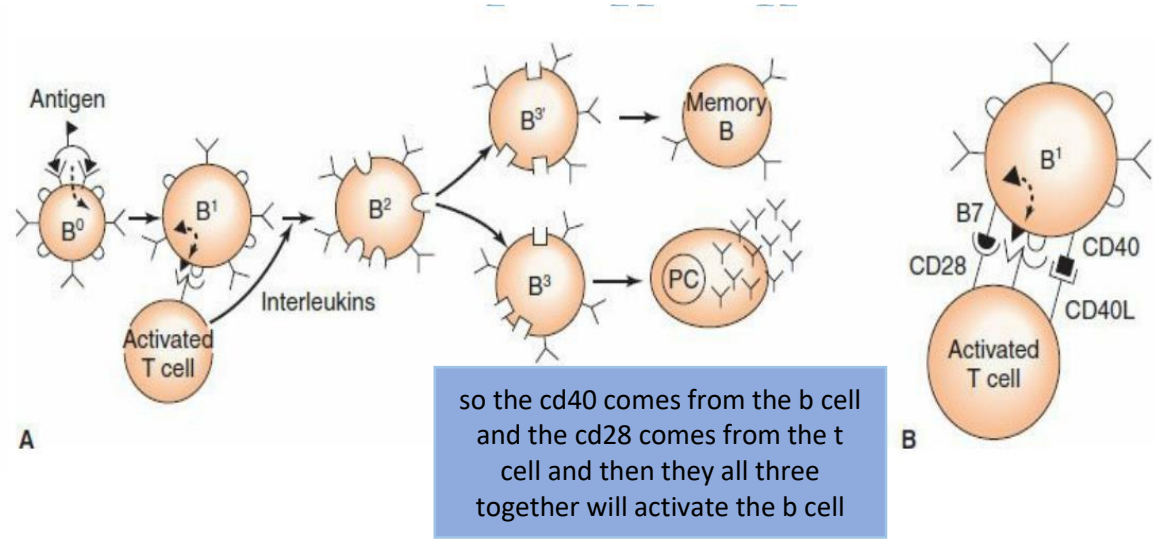
Ex: (Polysaccharides, DNA, RNA, many lipids)

Now let's talk more about T-dependent and independent response:

1-T cell dependent Antibody production:

a) the antigen attaching to **IgM** or **IgD** on the surface of the B cell.
b) antigen is internalized within the B cell, the epitope is the linked to the MHC-II complex and presented on the surface of the APC to the helper T cell
c) the interaction with the receptor on the helper T cell, (along with a costimulatory signal is given by the B7 protein with T cell CD28 protein) the helper T cell is then stimulated to produce interleukins (e.g., IL-2, IL4, and IL-5).
d) These interle ukins (IL2, IL4,IL5) stimulate the B cell to divide and differentiate into many antibody-producing plasma cells.

IL-4 and IL-5 induce "class switching" from IgM (ACUTE phase) to other classes: IgG, IgA, and IgE (chronic phase).



so the cd40 comes from the b cell and the cd28 comes from the t cell and then they all three together will activate the b cell

FIGURE 58–7 **A:** B-cell activation by helper T cells. B^0 is a resting B cell to which a multivalent antigen is attaching to monomer IgM receptors (Y). The antigen is internalized, and a fragment (▲) is returned to the surface in conjunction with a class II molecule (□). A receptor on an activated T cell recognizes the complex on the B-cell surface, and the T cell produces interleukins that induce the B^1 cell to form B^2 and B^3 cells, which then differentiate into antibody-producing (e.g., pentamer IgM) plasma cells (PC). Memory B cells are also produced. **B:** Inducible protein B7 (◒) on the B cell must interact with CD28 protein on the helper T cell in order for the helper T cell to be fully activated, and CD40L (CD40 ligand) on the helper T cell must interact with CD40 on the B cell for the B cell to be activated and synthesize the full range of antibodies. (Modified and reproduced with permission

- **There is a 3rd signal** (similar to co activation with B7 CD28) between a now fully activated T cell (CD40 Ligand), this protein interacts with RESTING B cells (CD40) , which helps them differentiate into antibody producing plasma cells.
- Other proteins on the surface of B and T cells serve to strengthen the interaction between them helper T cell and the antigen-presenting B cell (CD28 and B7 protein in last figure and others).

2-T cell independent Antibody production:

This is in part similar to hapten and the hypersensitivity reaction following it in that **it bypasses the need for T cell**, and cause activation for **non-peptide** molecules however, unlike the hypersensitivity reaction to haptens, T cell independent activation of these molecules comes with **two main differences:**

1) these molecules are not usually small, but instead are 1)**large molecules** that are 2)**not peptide** based (can't be presented on MHC-II to B cells) and thus they must 3)**CROSS LINK the IgM on the B cells** to activate them, once they are active.

2) they cause full activation and antibody production without the need to present the antigen to the T cell and cause a loop of activation, but rather start producing antibodies right away.
(remember carrier protein in haptens causes T cells to activate the B cell to produce Antibodies).

There are two types of antigens produce a T cell independent B cell activation:

1) B cell mitogens:

molecules that cause proliferation of B cells and production of **polyclonal antibodies** (sometimes monoclonal at low concentrations). are they will produce varying response.

The activation occurs due to reaction between these molecules and toll like receptors on these B cells. (do you notice the link between innate immunity?)
EX: Bacterial DNA, LPS , endotoxin (all they are not peptides)

NOTE: polyclonal antibodies means that we have different clones of the same antibody, but they are not identical 100% like mono clonal antibody

2) Large macromolecules that cause **cross linking** of a critical number of IgM on the B cell surface of only **MATURE B cells**.

Ex: Bacterial capsules, DNA, RNA
remember they are made of the same molecule cross linked over and over to form a macromolecule

- immature B cells (those in young children) produce an anergy response.

- this is why UNCONJUGATED vaccines do not elicit a response in children or why children are more susceptible to infections with capsulated bacteria

- Children have less mature IgM on the surface of their B cells, we need to help them by including the T cell independent loop (to present the antigen to T cells to help activate the B cells faster), that's why do we conjugate vaccines, **HOW?**

We conjugate a weak immunogen protein like (capsule) to a known strong immunogen like(typhoid toxoid).

Discussion point: will there be any T cell DEPENDANT activation here? Can it be responsible for side effects of vaccines? Or improve its efficacy? **Yes**

Differences between T cell dependent and independent responses:

1-In T cell dependent response, all classes of antibody are produced at first (IgG, IgM, IgA, etc.), but in **T cell independent response**, where primarily IgM is produced.

This is because T cells are responsible for Ig class switching through their lymphokines (which they will produce with the T cell dependent response).

in T cell dependent I get the license from the beginning not like independent that you must wait to class switch; I want to find a hapten or a thing and conjugate it to a protein and then find the cell to get my activation license

2-only the T-cell dependent response generates memory B cells, therefor there is no secondary antibody production in T cell independent response (which mean it is usually faster responding but keeps no memory Antibody production).

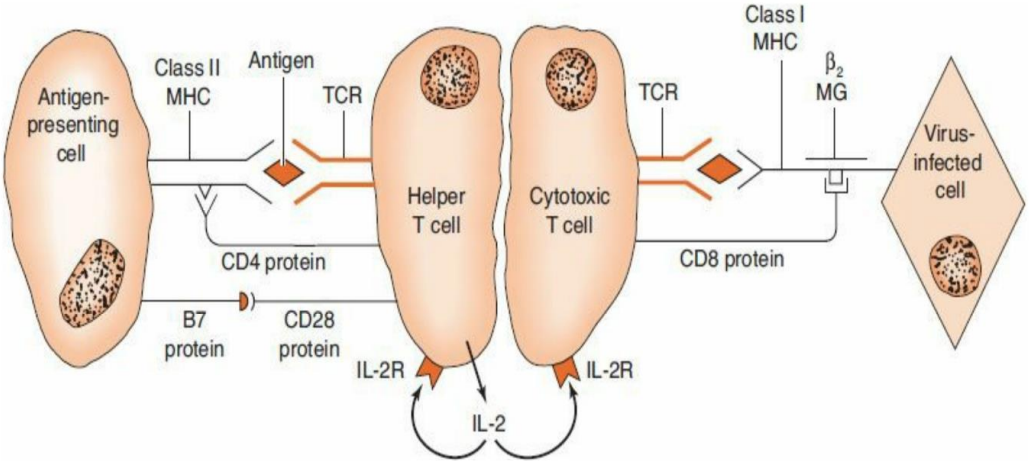
عشان هيك الـ independent
أقرب لـ adaptive من الـ innate

T-cell–independent response is the main response to bacterial capsular polysaccharides, why? because these molecules are not processed and presented by APCs and hence do not activate helper T cells. The reason for this is that polysaccharides do not bind to class II MHC proteins, whereas peptide antigens do (see later).

Cell-Mediated Immunity

Reminder: the regulatory function for cell mediated immunity is similar to direct T cell dependent activation:

APC process antigen present it on MHC-2 and then bind to helper CD4 T cell, this is followed by co stimulation and then IL-2 production form the CD4 helper T cell which stimulates the specific helper and cytotoxic T cells to grow.



Suppression of Certain Immune Responses

Regulatory T cells (a subset of T cells) (TR) act as inhibitors for effector functions of CD4 (helper) and CD8 (cytotoxic) T cells.

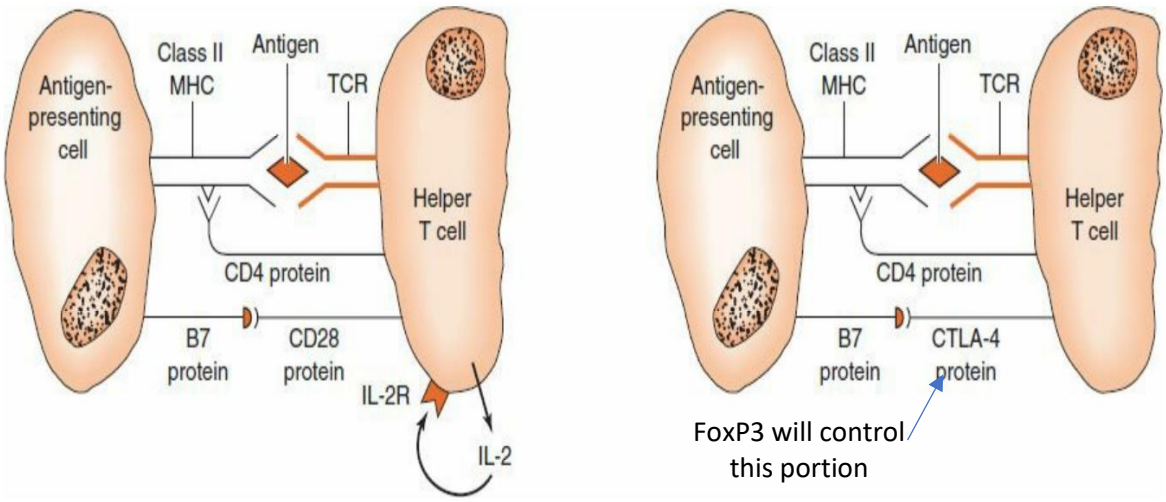
• These cells are also called suppressor T cells.

• TR cells are 5% to 10% of the CD4-positive cells and are characterized by possessing the CD25marker.

• These TR cells also produce a protein that regulates transcription of other various genes (called **FoxP3**).

• Inhibitory TR cells (which express FoxP3) are the ones that produce CTLA-4.

• In people where TR cells do not express FoxP3, so they are not able to express CTLA-4, those individuals are predisposed to autoimmune diseases such as: SLE (Systemic lupus) and a rare X-linked disease characterized by **polyendocrinopathy** and **enteropathy (IPEX**).



•Regulation of T cells is extremely important, if an imbalance in numbers or ratio/activity between CD4 and CD8 cells happens, normal immune response is impaired (suppressed) as seen in three examples below:

Example 1: lepromatous leprosy

In lepromatous leprosy there is uncontrolled multiplication of *Mycobacterium leprae* (intracellular organism, similar to *Mycobacterium tuberculosis* it needs a delayed hypersensitivity reaction and recruitment of macrophages).

But a lack of delayed hypersensitivity (Type 4) to *M. leprae* antigen and a lack of cellular immunity to that organism plus an excess of CD8 cells in lesions, all contribute to the uncontrolled growth.

⇒ you have a lot of CD8 cells that are not doing anything in these legions so removal of some CD8 cells can restore cellular immunity in such patients and limit *M. leprae* multiplication.

Example 2: AIDS

in normal individuals the ratio of CD4: CD8 cells is (>1.5), however in **acquired immunodeficiency syndrome (AIDS)**, the normal ratio of CD4: CD8 is greatly reduced (CD4 cell count falls below 200 = from HIV to AIDS, so as CD4 cells are targeted and destroyed by HIV, CD8 cells numbers increase, creating further imbalance-loss of T helper activity and increase in suppressor activity).

⇒ This imbalance is the cause of the susceptibility to opportunistic infections and certain tumors in AIDS patients.

Example 3: (HBV Adenovirus and CMV)

•An important mechanism of the host response to infection is the increased expression of class I and class II MHC proteins which is induced by various cytokines (**gamma interferon especially**).

•Having more MHC means more antigen presentation and more vigorous (highly controlled) immune reaction.

•Some viruses (HBV Adenovirus and CMV) suppress this increase in MHC (MHC-I to be exact, why?) during infection, making the control mechanism more loose and allowing them to escape more easily. **"they're trying to mask their presence inside the cells**"

B CELLS

B cells perform two important functions:

1) They differentiate into plasma cells and produce antibodies
2) They can present antigens to helper T cells

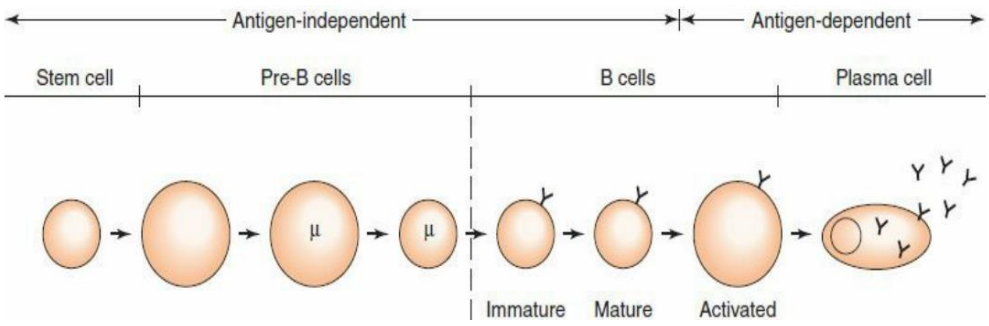


FIGURE 58–8 Maturation of B cells. B cells arise from stem cells and differentiate into pre–B cells expressing μ heavy chains in the cytoplasm and then into B cells expressing monomer IgM on the surface. This occurs independent of antigen. Activation of B cells and differentiation into plasma cells is dependent on antigen. Cells to the left of the vertical dotted line do not have IgM on their surface, whereas B cells, to the right of the vertical line, do have IgM. μ, mu heavy chains in cytoplasm; Y, IgM. (Modified and reproduced with permission from Stites DP, Terr A, eds. *Basic & Clinical Immunology*. 7th ed. Originally published by Appleton & Lange. Copyright 1991 McGraw-Hill.)

it's important to know that an activated b cell requires antigen (it is antigen dependent to be activated) whereas an immature one is not antigen dependent it just keeps maturing its surface receptor so between mature to activate it, i need an antigen, otherwise it keeps just maturing on its own.

- Pre-B cells differentiate into immature B cells (with IgM on the surface without the need of antigen presentation) , they even mature to naïve mature B cells, without the need of antigen presentation, they only proliferate and become **active** once antigen is presented to them(or through T cell independent activation).

  HOWEVER, you do need a certain protein for pre–B cells to differentiate into B cells(immature), a **signal transduction protein** called Bruton's tyrosine kinase is required.

- If Bruton's kinase is mutated this causes X-linked agammaglobulinemia in which immunoglobulins (e.g., IgM, IgG) are not made and B cells are absent.

  ⇒ so, if you don't have this protein kinase which is the signal required to differentiation of PRE-B cells into immature B cells, then you will never have mature b cells and you'll never be able to activate b cells.

  ⇒ Severe infections caused by **pyogenic bacteria** occur in these patients.
  (this bacteria usually needs antibody production to be cleared, like capsulated bacteria)

- B cells display surface IgM, which serves as a receptor for antigens.

  • This surface IgM is a monomer (1 piece or 1 molecule), in contrast to circulating IgM, which is a pentamer(5 IgMs in one), a pentameris too large and doesn't cross the placenta, **thus the baby is usually protected by IgG, and then igA from the milk** .

  • The monomeric IgM on the surface has an extra transmembrane domain that anchors the protein (basically IgM with a membrane attachment module) in the cell membrane that is not present in the circulating pentameric form of IgM.

  • Surface IgD on some B cells may also be an antigen receptor.

- Pre–B cells are found in the bone marrow, whereas B cells circulate in the bloodstream.

  • The mature lymphocytes have a relatively short lifespan (weeks at most), this is compensated by high production of B lymphocytes about 10^9 B cells are produced each day -about 30% of the recirculating pool of small lymphocytes-
  (remember these aren't necessarily active yet).

  within **lymph nodes** ⇨ they are located in **germinal centers**
  within the **spleen** ⇨ they are found in the **white pulp.**
  also found in the **gut-associated lymphoid tissue (GALT)** ⇨ **Peyer's patches**

Clonal Selection

How are antibodies made selectively for each antigen?

the current theory which is most accepted: (an antigen basically waits to be picked up by a B cell that is already selected a variability in its IgM receptor that accepts this antigen this is called **clonal selection**, the clone of that IgM carrying B cell will be selected since it has the correct IgM and thus it proliferates sort of like positive selection

- **Each individual has a large pool of B lymphocytes (about 10^7).**
- **Each immunologically responsive B cell bears a surface receptor (either IgM or IgD) that can react with one antigen** (or closely related group of antigens-this is basically how cross reactivity occurs, when an antigen of a bacteria like GAS is similar to a self-antigen).
- **It is estimated that there are at least 10 million different specificities.**

There is a library for antibodies in a certain university, this library contains different types of different antibodies in humans (up to a billion) different antibodies, each one of them interacts with a different antigen

So basically →An antigen "key" will interact with the B lymphocyte that shows the best "fit" or "lock" with its immunoglobulin surface receptor.

→After the antigen binds, the B cell is stimulated to **proliferate and form a clone of cells**, this is similar to T cell activation with end result of gene activation to produce **IL-2**.

→Once these B cells are selected, they will become plasma cells and secrete the antibody specific for the antigen.

- Plasma cells synthesize the immunoglobulins with the same **antigenic specificity (i.e., they have the same heavy chain and the same light chain)** as those carried by the selected B cell.
- If class switching from IgM to IgG for example is to occur, **only the heavy chain is changed, and the specificity remains the same.**

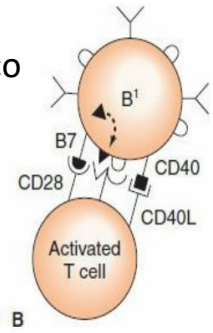
•This is all similar to clonal selection with T cell →*The antigen that interacts with the specific TCR on the surface of either a CD4-positive or a CD8-positive* T cell will select this specificity of the antigen and produce clones of the T cell that are specific to this antigen.

Activation of B Cells

The process of activation of B cells, occurs in the following manner:

1. a multivalent antigen binds to surface IgM (or IgD) and cross link a critical number of those surface antigen.
2. The Ig aggregate (combine together in a clump) and form patches which they further combine together to form a cap on one pole of the B cell.
3. Endocytosis of the capped Ig material ensues and the antigen on these Ig is then processed within the B cell to reveal epitopes which then appear on the surface of the B cell in **conjunction with class II MHC proteins**.
4. This complex is recognized by a helper T cell with a receptor for the antigen on its surface (so now I need a B cell specific to that antigen and then a T cell as well)
5. The T cell now produces various interleukins (IL-2, IL-4, and IL-5) that stimulate the growth and differentiation of the B cell.

As mentioned, now the only thing remaining is to have the two other co stimulatory signals :



1) CD28 on the T cell must interact with B7 on the B cell

2) CD40L on the T cell must interact with CD40 on the B cell.

The CD28-B7 interaction is required for:
activation of the T cell to produce interleukins-prevent anergy which will prevent IL-4 and IL-5 production and thus no activation of the B cell.
the CD40L-CD40 interaction is required for:
class switching from IgM to other immunoglobulin classes, such as IgG and IgA, to occur.

Hyper-IgM syndrome: is a syndrome caused when CD40L is mutated and no class switching occurs ⇒ high IgM, no IgA or IgG ⇒ severe PYOGENIC infections.

Effector Functions of B Cells/Plasma Cells

• The end result of the activation process is the production of many plasma cells that produce large amounts of immunoglobulins specific for the epitope.

• Plasma cells secrete thousands of **IDENTICAL antibody** molecules per second for a few days and then die.

• Some activated B cells form memory cells, which can remain quiescent for long periods but are capable of being activated rapidly upon re-exposure to antigen.

• Most memory B cells have surface IgG that serves as the antigen receptor, but some have IgM.

•Memory T cells secrete interleukins that enhance antibody production by the memory B cells.

•The presence of these cells explains the rapid appearance of antibody in the secondary response.

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