INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	13
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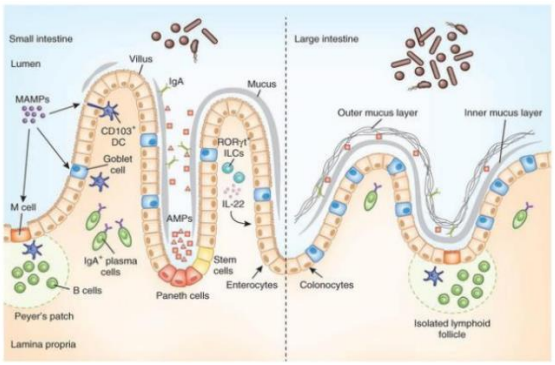
Restraining the immune system

Till now, we have always been talking about activation of the immune system; starting from complement system to the adaptive B and T cell response. This sheet and the following one will talk about different aspect which is the restrainment of the immune system.

We have two main concepts in this lecture:

1- Tolerance to the food and commensal bacteria in the gut- and this is discussed as the intestinal immunity
2- How to stop the already activated immune system?

1- Intestinal Immunity



In the gut only, the number of commensal bacterial cells is 10 times higher than our whole body cells, in other words "we are 90% bacteria regarding number of cells". So how come the immune system doesn't react towards them and elicit an immune response?

We have so many mechanisms in the gut that help in limiting the reaction between the bacteria and the epithelial cells, such as:

1- The **mucous layer**above the epithelial lining in both small and large intestine secreted by goblet cells (It's one thick layer in the small intestine, but two layers in large intestine one is thicker than the other)

2- Presence of **Peyer's patches**, which are a secondary lymphoid tissue that contain cells like Dendritic cells and Lymphocytes such as B-cells that aredifferentiating to plasma cells that secret antibodies.
Dendritic cells here are CD103+,they are known to trigger the differentiation of regulatory T cells that are important in the suppression of the immune response.These cells look like starfish andtheir projections are able to fit in the junction between epithelial cells (without damaging the epithelial) and sense the outer environment in the lumen. Anything abnormal that comes near the epithelial

will be sensed by these dendritic cells.
<u>The differentiated plasma cells</u>undergo class switching to secrete IgA that is transported into the lumen. (we have other subtypes as well but the majority of Abs are IgA)

3- **Paneth cells**: found in the crypts of the villi and they secret antimicrobial peptide (AMP) that kills any bacteria tries to enter and cross the barrier.
"villi increase the surface area to be 200m^2"

4- High numbers of **TGF-beta**, that is important in (1) IgA class switching and (2)Regulatory T cells formation

5- High numbers of **anti-inflammatory cytokines**, such as IL-10

6- Presence of **Retinoic Acid** (Vitamin A) in the payers patches. The retinoic acid is important to DCs to activate certain lymphocytes and drives them to express certain chemokines on the cell surface that is important in the homing of lymphocytes in the gut.
A note from the book: (Since dendritic cells in the gut mucosa are exposed to large amount of dietary vitamin A, these cells preserve large amounts of retinoic acid. When these cells get activated, they activate lymphocytes in the nearby gut lymphoid tissues (payer's patches or mesenteric lymph nodes). During this process of activation, dendritic cells provide signals (which is the preserved retinoic acid) to induce gut-homing chemokine receptors. (These gut-homing chemokine receptors expressed on activated lymphocytes cause these cells to circulate and go toward gut blood vessels to eventually exit and home in the gut lamina propria))

7- The endothelial cells themselves have **Pathogen Recognition Receptors (PRR);**nod-like, toll-like, inflammasome,… and some of these receptors are only expressed on the basolateral surface, so they only interact with the pathogen that tries to cross the epithelium.

All of the mentioned mechanisms will create a tolerant immune response in the gut. And any **problem** happened in any of these mechanisms leads tointeraction between the bacteria and epithelial cells and will elicit a pro-inflammatory response mediated by Th1 and Th17, resulted in the production of certain cytokines such as IL-12 and IFN-Gamma. IFN-G drives the IgG class switch and the production of another inflammatory cytokines, so we have an **exaggerated response** in the gut. And this can be seen in many diseases such as Inflammatory Bowel Disease, Ulcerative Colitis and Celiac disease. The later is an immune response towards gluten, to be more specific towards the Gliadin component in the gluten.

2- Stopping the already activated immune system!

Antigen is picked up by Antigen presenting cell APC, to be presented on MHC molecule. T cells are able to see the MHC-Antigen complex and will trigger the activation of another T cells, B cells, NK, macrophages… all help in eliminating the pathogen or the foreign antigen. After the activation of all these cells eventually we need to control it and stop it! Because if it continues, exaggeratedinflammation, tissue damage and auto-immune diseases are predicted.

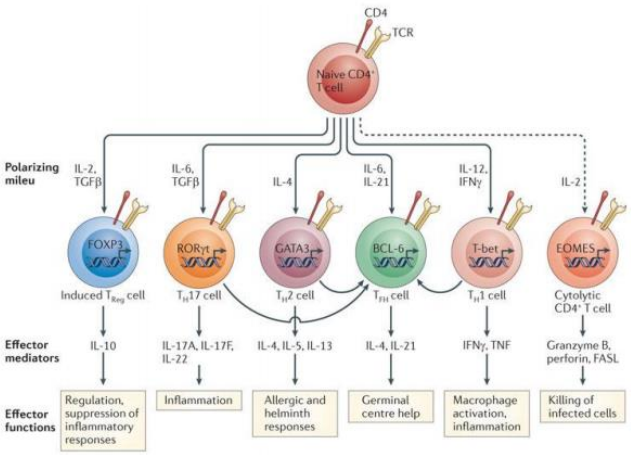
The immune system uses several toleregenic mechanisms to avoid unnecessary stimulation of the immune system; such as:

1- Regulatory T- cell
2- Disappearance of foreign antigen upon end of infection is the first step to end an immune response
3- The presence of negative immune regulators help inactivate T cells ex: CTLA-4 and PD-1
4- The short life of many immune components
5- Exhaustion "of T-cells" and killing by AICD

We will go through them one by one.

1- Regulatory T- cells

*You should now be familiar with this picture; few notes will be mentioned underneath!

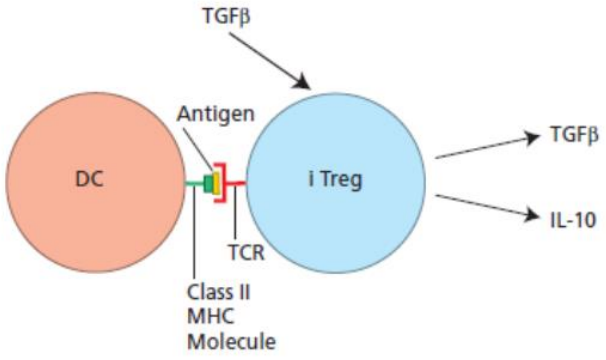


- T helper (CD4+) cells can differentiate into (Th0 - Th1 -Th2 - Th17- REG-T cells).
- Th1 secret IFN-G and TNF "pro-inflammatory cytokines" by the help of the Transcription factor T-bet. IFN-G is a potent activator for macrophages. This subset of T helper cells is important in fighting bacterial infection.
- Th2 secret IL-3, IL-4 and IL-13 by the help of the Transcription factor GATA3. IL-4 drives the IgE class switch. This subset of T helper cells is important in fighting parasitic infection, and allergies in pathological situations.
- Th17 secret IL-17, IL-21 and IL-22 by the help of the Transcription factor ROR-Gamma-t (ROR-Gt).This subset of T helper cells is important in fighting fungal infection.
- Follicular helper T cells (T_{FH}), found inside the germinal centers and secret IL-4 and IL-21.
- Induced regulatory T cells (Induced T_{Reg}), they differentiate in the tissue. The main transcription factor is FOXP3.
  (Remember that we talked about naturally occurring T regulatory cells that mature in the thymus).
- Cytolytic T helper. *(Don't worry about it and don't confuse yourself)*

** In our concept, we are concerned about Induced regulatory T cell, its different than all the other, as other T cells **ACTIVATE** the immune response, while this cell **SUPPRESS.**

** And like any other T cell, these Induced T_{Reg} need **two-key activation system:**

1- Engagementof the TCR with antigen loaded on MHC2
2- Cytokines such as TGF-beta (It helps in the differentiation of Induced $T_{Reg}$and enables them to produce two cytokines, TGF-beta itself and IL-10).
   TGF-beta and IL-10 suppress and control the immune response



2- Disappearance of foreign antigen

Normally, the immune system attack towards the pathogen reducing the number of the antigen. So by the time we are eliminating the antigen, the activation of innate and adaptive immune system will drop, and this is the first step in reducing the immune response!

3- Negative immune regulators (Inhibition receptors)

CTLA-4

- For the activation of T cells we need TCR-antigen + Co-stimulation (B7+CD28)
- Repeated activation to T cells will induce the gene expression of CTLA-4 which has a much higher binding affinity to B7 than CD28; making it harder for the T cell to be reactivated and help shut down the adaptive immune system.
- B7 and CTLA-4 binding causes**INHIBITION**of the T cell.

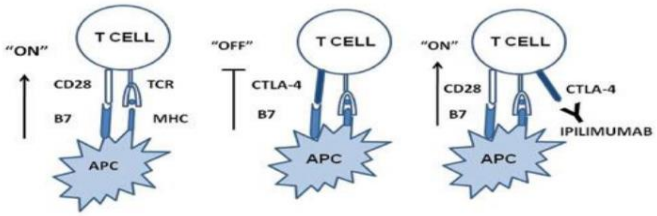
PD-1

PD1 (programmed death-1) is a receptor found on T cells, when it binds to its ligand it shuts down the T cell response.

Q/ Is it good to have inhibitory receptors on T cell?

It's good in ending immune response and preventing autoimmune diseases, but it can be bad in cancer control and lead to treatment failure. (Old treatment focused in inducing the activation of T cells in order to kill the tumor, will be mentioned just in a moment).

****Cancer therapy and CTLA-4 receptors (Immunotherapy vs. cancer)****



Failure of the immunotherapy in treating cancer was a big mystery, as the activated T cells must kill the cancer but this was not the case!
It remains a mystery until the discovery of these inhibitory receptors and the immunotherapy has been introduced after that to treat Melanoma.

So all the idea is simple; the tumor tries to shut down the immune response by engaging the CTLA-4 receptor. And the treatment is done by designing monoclonal antibodies that bind CTLA-4 receptor and suppress them so they are not available anymore for the tumor and this enables the T cell to function and fight the tumor. These drugs are expensive, and one of these is IPILIMUMAB.

Immunotherapy is being used nowadays as treatment for Melanoma, and there are promising results in bladder cancer, prostate cancer, non small cell lung cancer and small cell lung cancer.

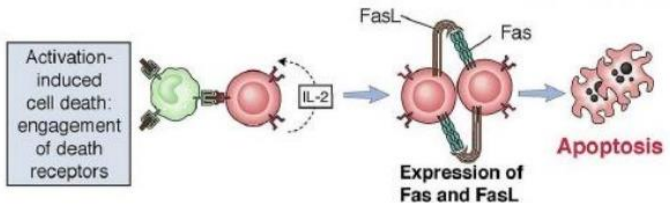
Moreover, many tumors express PD1 ligand and bind PD-1 receptor on T cell and suppress its function. And this is also targeted in treatment such as PD-1 inhibitor and PD-1 ligand inhibitor.*Only if the tumor expresses PD-1 the patient will be a candidate for treatment.*

Note Cancer cells recruit T_{Reg} cells, that will suppress the immune responses elicited by the adaptive and innate immune systems in the cancer environment so it can grow easily!*

4- The short life of many immune components

- Neutrophils: few days, from 1 to 2.
- NK: 1 week, they are the only cells licensed kill with one signal so they can be dangerous!. And because NK cells' half life is short, this leads to reduced IFN-G, which means less macrophage also!
- Dendritic cells(DC): 1 week after arriving to lymph nodes. By reducing DCs, this means less APC, so less B and T cell function!
- Plasma cells: most of them are **short lived** (5 days and they secret large amount of antibodies) and smaller amount of **longed lived**" helps in maintenance of immunization".
- Antibodies themselves have short half life!! The longest for IgG which is 21-23 days.

5- Exhaustion of T cells



Although most of immune cells have short half life, but T cells live long! So there is a need for more complicated mechanisms to control their activity. One of these is **Activation Induced Cell Death (AICD)**. The repeated activation for T cells will up-regulates Fas and FasL and makes the activated T cell very sensitive to Fas-FasL interaction, so they help each other to commit suicide!

(Remember that NKs and CD8+ cells kill their target through Fas-FasL pathway).

AICD eliminates T cells that have been repeatedly activated and makes room for new T cells that can protect us from the next microbe that might cause harm.

Note1: Fas is used also in cytotoxic Tcell and NK to kill their targets.
Note2: the same cell express both fas and fas L
Note3: ALPS, Autoimmune lymphoproliferative syndrome, caused by defective fas-fasL… so T cells cannot die and trigger autoimmune diseases.

All these mechanisms together help control the immune response and reset the system to be ready for the next attack.

And when you become a diamond, you
will see why life had to pressure you.
GOODLUCK