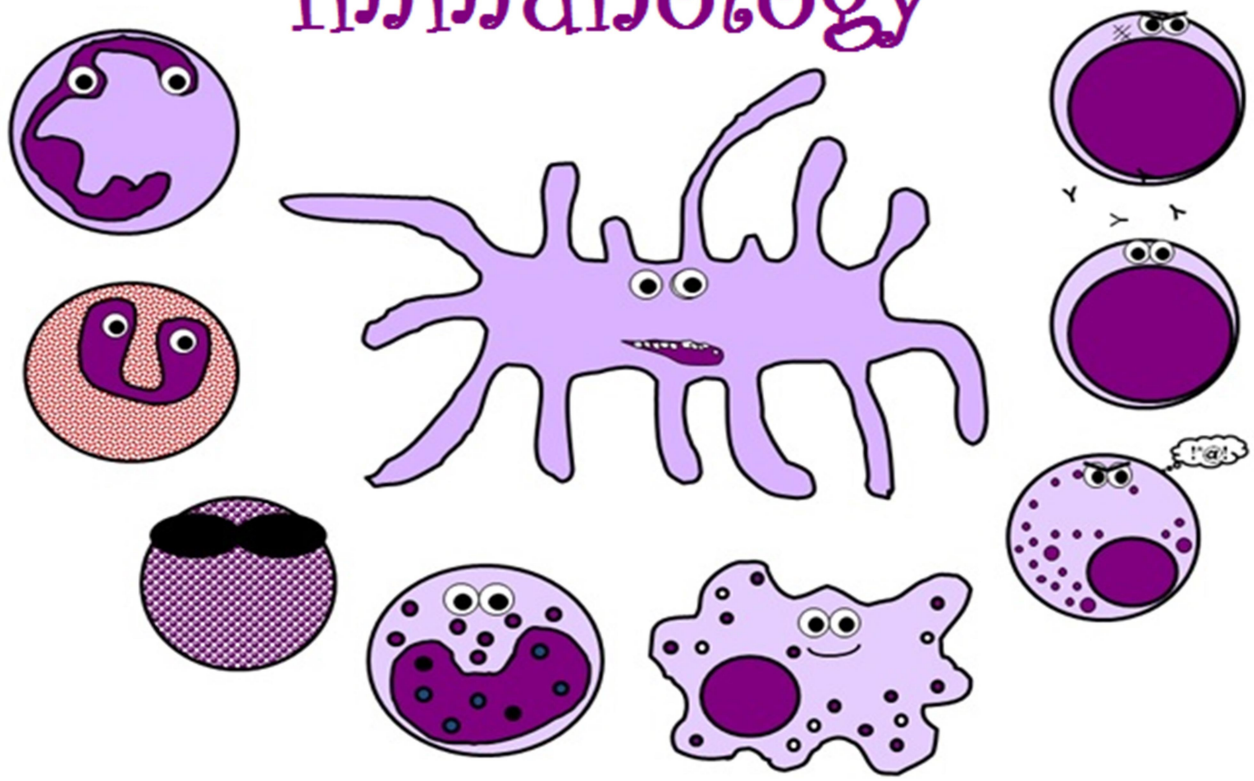
Immunology



Sheet Slides

Number: 12

Subject: Restraining the immune system

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Restraining the immune system

Over view:

In previous lectures, we focused on the activation of the immune system; how to activate *the innate immune system* such as; **Macrophages** activated by IFN-gamma. Also, we talked about **dendritic cells** as *antigen presenting cells*. Additionally, we discussed *the adaptive immune system*; **T-cells** that rely on antigen presenting cells to get activated and **B-cells** that bind to antigens and get co-stimulation from **T-helper cells** to be able to secrete antibodies.

General idea of Restraining the immune system:

In immunology, we need sometimes to restrain the immune system *whenever is not needed and there is no any purpose to activate* such as in: GI tract including the intestines, the commensal bacteria and probiotics. Moreover, we need to restrain the immune system *to stop the strong immune reaction* against for example a microorganism after finishing its work and killing that microorganism because if the immunological response is maintained, this will lead to **hyper-inflammation** that will be associated with *tissue destruction* and an *increase in the susceptibility to develop diseases* such as atherosclerosis or even with its maintenance it'll lead to autoimmune diseases.

Intestines and commensal bacteria. Presence of commensal bacteria is essential for our bodies since they *compete the pathogenic bacteria and preserve the integrity of the gut* hence; it is advised to take probiotics and yogurt. They are also responsible *of degrading certain carbohydrate components to simple structures and alleviating the symptoms related to malabsorption.*

Mechanisms of restraining the immune system in intestines.

In the intestines (small intestine or large intestine), there are certain mechanisms to protect us from activation of unnecessary immune responses: (1) *mucus layer* which acts as a barrier that reduces the interaction between the bacteria present in the gut and the immune mechanisms present inside the cells. (2) *Plasma cells* that are usually recruited at that area due to microenvironment secrete **IgA immunoglobulins** "which are dimers; each one is made up by two immunoglobulins" which are present at the mucus region to prevent the entrance of microorganisms. (3) Presence of *peyer's patches, B-cells, T-cells and dendritic cells*. These dendritic cells express CD103 "$CD103^+$ DC_s" and are able to activate a certain type of **T- helper cells (T-regulatory cells "T_{Reg}")** which regulate the immune response and **suppress** it. (4) *The epithelial cells* secrete cytokines such as: **TGF-beta** which plays an important role in the differentiation of T-regulatory cells. (5) *Macrophages* secrete anti-inflammatory cytokines mostly **IL-10**.

Note: as you can see the environment is pushing -to some extent- toward the immunosuppressant effect.

(Refer to figure 1-12 and the left side of figure 2-12).

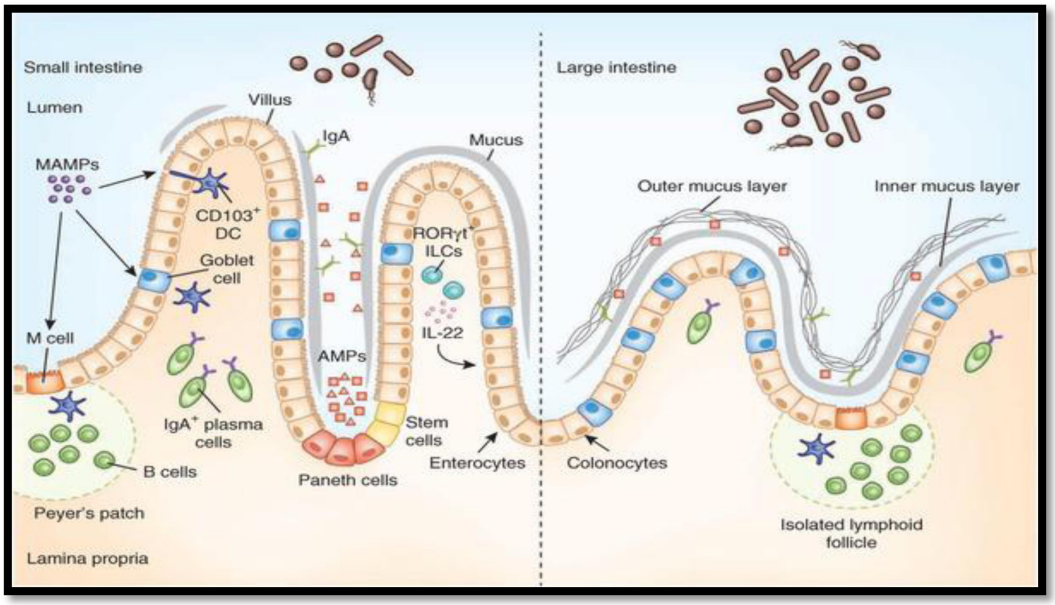

Figure1-12: mechanisms in intestines to restrain the immune response.

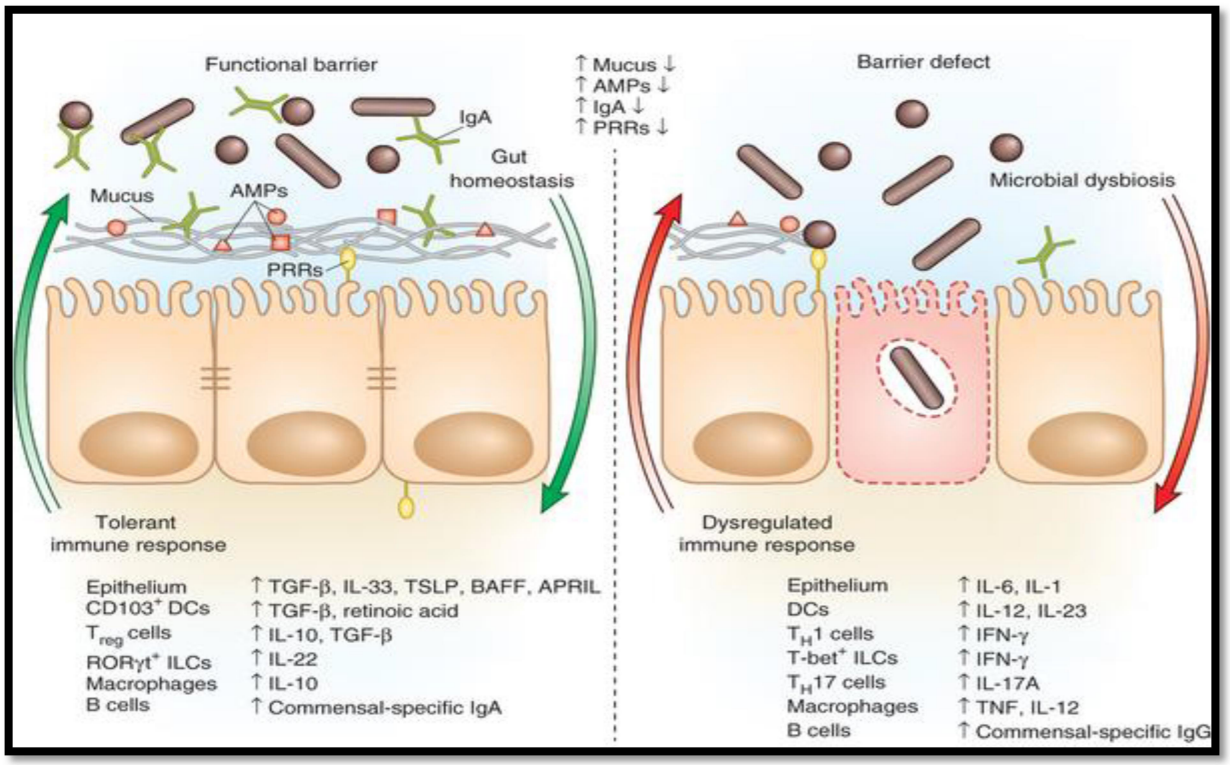

Figure 2-12: represents tolerant immune response (left side) and dysregulated immune response (right side).

Dysregulated immune response in intestines:(Refer to figure 2-12, right side)

In certain conditions in which the barrier is defect such as in presence of pathogenic bacteria and autoimmune diseases including inflammatory bowel disease (ulcerative colitis and crohn disease), *pro-inflammatory profile* occurs. This profile is manifested by: (1) *epithelium* which starts to secrete **IL-6 and IL-1**. (2) Presence of *dendritic cells* (DCs) which secrete **IL-12 and IL-23** (pro-inflammatory cytokines) unlike tolerant immune response in which CD 103^{+} DC**s** are present. (3) *T-helper1 cells* (compared to T_{Reg} in the resting case) which secrete **IFN-gamma** that activates macrophages. (4) *Macrophages* which secrete **TNF and IL-12.** (5) *B-cells, due* to this pro-inflammatory profile, induce class-switch into **IgG immunoglobulins** that have the ability of opsonization and recruitment of immune cells unlike IgA which is a bad opsonin.

Subtypes of T-helper cells (CD4 cells). There are subtypes of T-helper cells which express CD4 and each of them has a specific transcription factor which is involved predominantly: (1) *T_{H1} cells* promote pro-inflammatory pathway by secreting **IFN-gamma and TNF-alpha** and predominantly over-express **T-bet** transcription factor. T_{H1} cells promote macrophage activation and inflammation thus they are involved in resolving certain types of infection such as: Leishmmania and also in cancers. (2) *T_{H2} cells* express **GATA3** transcription factor and secrete **IL-4, IL-5 and IL-13**. These cells are involved in allergic and helminth responses, so T_{H2} cells are predominantly found in asthma. Actually, scientists try to improve asthmatic patients through pushing immune system profile from T_{H2} profile into T_{H1} profile. (3) *T_{H17} cells* express **ROR-gamma-t** and secrete **IL-17 and IL-22** (pro-inflammatory cytokines). These cells are important in fungal infection. (4) *T-follicular helper cells* (FH) are found in germinal centers and involved in B-cell activation. These cells express **BCL-6** transcription factor. (5*) Cytolytic $CD4^+$ T-cells* have **granzyme B, perforin and FASL** and express **EOMES** transcription factor. (6) *Induced regulatory T-cells (T_{Reg})* are stimulated by **TGF-beta** (which is present in gut environment, and plays a major role "with IL-2" in the differentiation of T cells from virgin Tcells to T_{reg}) and **IL-2**. These cells express predominantly **FOXP3** transcription factor and secrete **IL-10** which is anti-inflammatory cytokine thus suppression of inflammatory responses occurs. (Refer to figure 3-12)

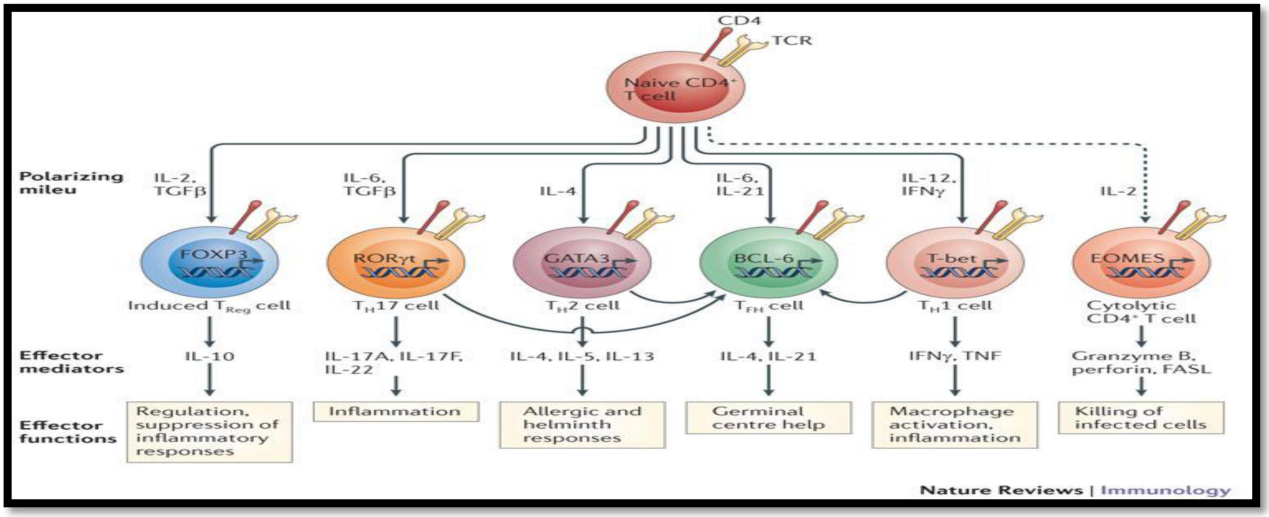

Figure (3-12): represents the subtypes of T-helper cell.

Inducible T-regulatory cells (iTregs):

Inducible means that dendritic cells induce the stimulation of these cells by antigen presentation through MHC II and the induction is completed through TGF-beta. (Refer to figure 4-12). They secrete both TFG-beta and IL-10.

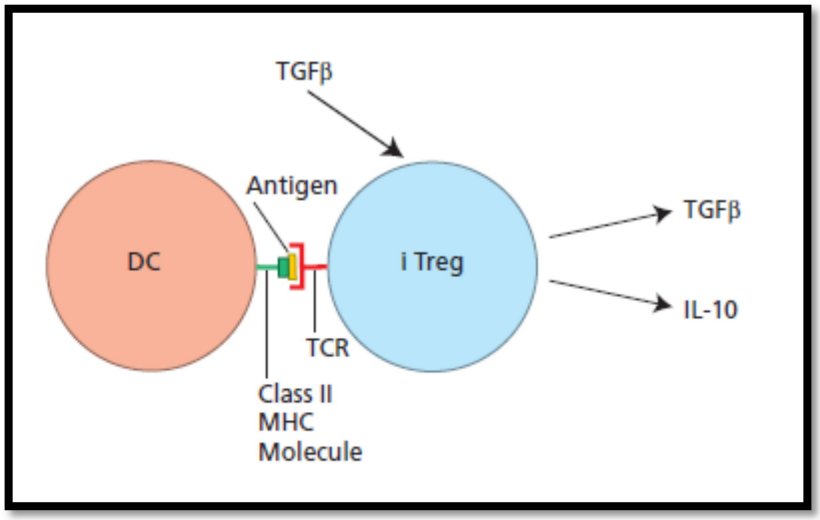

Figure 4-12: represents the induction process of iTregs. *(There are naturally occurring Tregs that are created as Tregs, without induction, in tissues).*

Deactivating the system:

There are two mechanisms mentioned in the lecture to deactivate the immune response: (1) *As foreign antigen is eliminated*, the level of activation of both the innate and adaptive systems decreases since the presence of that foreign antigen is the basis of immune system activation. (2) *Binding of B7 molecules (costimulatory molecules) found on APCs to CTLA-4 receptors on T-cell, inactivates the immune response*; in immune reaction APC presents an antigen on MCH molecule then the co-stimulation happens through binding B7 molecule to CD28 on virgin T cell, so the activation of T- cell occurs, and as these activated T-cells are going on they start to

express a receptor called CTLA-4 which has higher much affinity to B7 compared to CD28. Consequently, at this moment most of B7 molecules are bound to CTLA-4 for two reasons: (a) Higher number of CTLA-4 molecules on the surface of experienced T- cells compared to CD28. (b) Much higher affinity of CTLA-4 molecules to bind B7 compared to CD28. Finally, this binding gives a signal to T-cell to be inactivated.

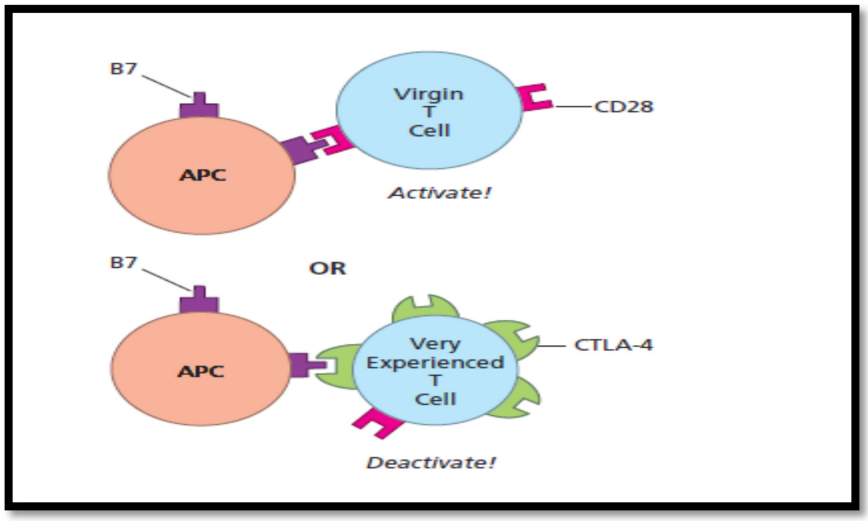

Figure (5-12): represents deactivation of T-cell through CTLA-4 molecule. (There are other inhibitory receptors on the surface of activated T-cells exist such as: programmed Death-1 (PD-1)).

Are inhibitory receptors good or bad? Inhibitory receptors can be: (1) good in terms of ending immune response and avoiding autoimmune diseases. (2) bad in cancer control and cause treatment failure; previously, cancer treatment "Immunotherapy" through stimulation of T-cells was not successful because immunologists at that time were not aware about CTLA-4 nor PD-1 receptors and their inhibition on T-cells but recently, after identifying these receptors immunologists are able to design a monoclonal antibodies (Ipilimumab) against CTLA-4 thus inhibition of the inhibitory effect results in stimulation in presence of CD28. There are many types of cancer which can be treated by this way such as: melanoma, small cell (and non-small cell) lung cancer and prostate cancer.

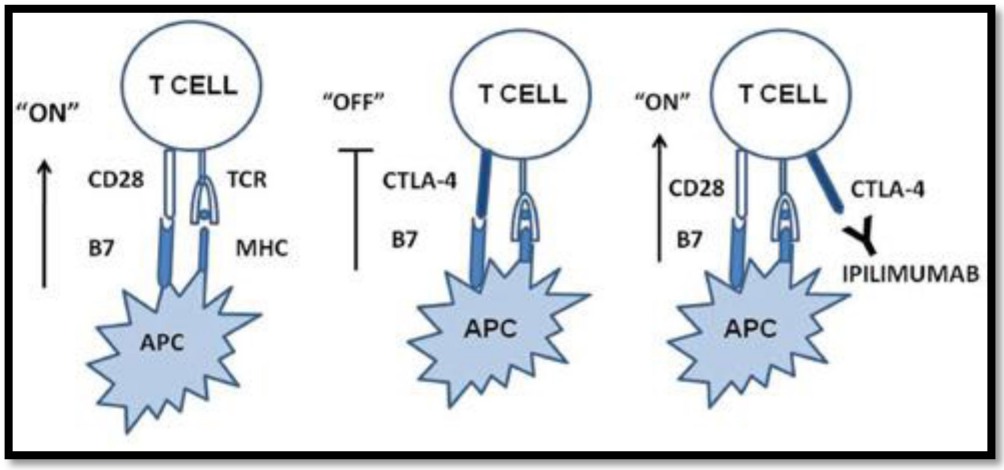

Figure (6-12): represents CTLA-4 targeted immunotherapy using monoclonal antibodies to stop the inhibitory effect of CTLA-4.

PD-1 inhibitory receptors. PD-1 receptors are expressed on the surface of T-cell and the ligands of these receptors are highly expressed by tumor cells so, the binding will result in deactivation of T-cell and consequently, tumor cells will avoid the killing. Also here, immunologists developed antibodies against both PD-1 and PD-1 ligand to treat certain types of cancer as shown in figure (7-12).

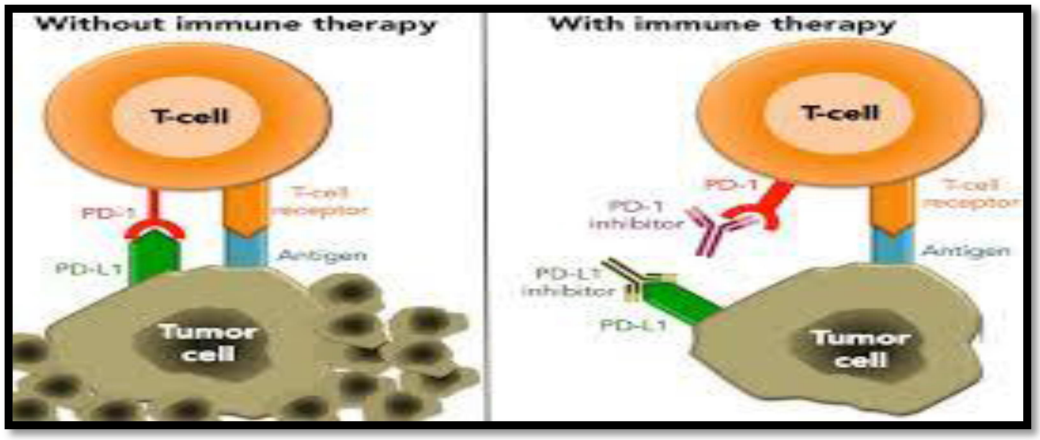

Figure (7-12): represents PD-1 targeted immunotherapy.*(This treatment is associated with developing autoimmunity by the patient as an adverse effect).*

Life is short ! :

Neutrophils live for few days only; we don't need neutrophils to live more because they are very aggressive cells and once they are recruited at the site of inflammation they start to release reactive oxygen species which are harmful to tissues.

Half-life of natural killer (NK) cells is about a week which is short, so less NK means less IFN-gamma is produced and less macrophage activation. (Remember that NK cells has the license to kill without any help from other immune cells)

Dendritic cells also live for a short period of time reaching a week after arriving to lymph node which means less APC activity and less T-helper and B-cell activity (fewer antibodies are produced).

Plasma cells die after about 5 days and antibodies have a short life too (IgG has the longest half-life which equals 3 weeks, compared to others "3-5 days").

So, you can notice that most of immune cells have a short life and this is important in the context of ***restraining the immune system***; immune response can end relatively fast and invader-specific antibodies drop fast.

Exhaustion:

Although NK, DCs and plasma cells have a short life, T-cells do not, they actually live long. ***The strong question*** is:" How do we get rid of the big number of activated T-cells?"

The elimination of the big number of activated T-cells is mediated through *Activation-Induced Cell death (AICD)* in which activated T-cells are actually sensitive to FASL-FAS interaction, so they can help each other commit suicide (apoptosis).

Note: Fas and FasL are expressed by activated T cells.

Remember: this mechanism is also activated by cytotoxic T cells.

AICD eliminates T-cells which have been ***repeatedly*** activated (not once get activated) and makes room for new T-cells that can protect us from the next microbes which might try to harm us.

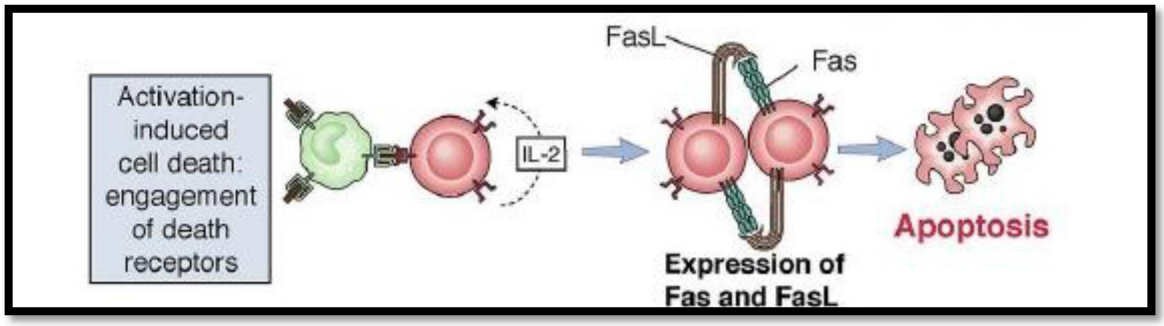

Figure (8-12): represents AICD in which FASL on an activated T-cell binds to FAS on another activated T-cell and consequently, both of these two cells will undergo apoptosis.(mutations in Fas or FasL genes will result in accumulation of unnecessary T-cells, B-cells, Autoreactive T-cells .. result in autoimmunity "next case study ALPS")

Summary:

- The immune system uses several tolerogenic mechanisms to avoid unnecessary stimulation of the immune system. Ex: $T\text{-}_{Regs}$ which express FOXP3 transcription factor and secrete IL-10.
- Disappearance of foreign antigen upon end of infection is the first step to end an immune response (gradual decline of the immune response…).
- The short life of many immune components helps end an immune response quickly ex: Neutrophils, NK cells, and plasma cells.
- The presence of negative immune regulators help inactivate T cells Ex: CTLA-4 and PD-1.
- Exhaustion and killing by AICD helps eliminate ***repetitively*** activated T cells.
- All of the above help reset the system to be ready for the next attack!

As Einstein says: "Logic will get you from A to B. Imagination will take you everywhere"