TOLERANCE

what happens when a lymphocyte is exposed to an antigen, and meets that antigen, which is specific to that lymphocyte ?

1. **Activation** ... i.e produce an immune response
2. **inactivation** .. i.e tolerance
3. **Ignorance** .. when the concentration of the Ag is too small it would be ignored. here the lymphocyte stills alive, it I still present .. it might die after few weeks if they were not stimulated by an Ag (coz they have limited life , but if they don't die and meets the antigen again it produces an immune response and cause autoimmunity.

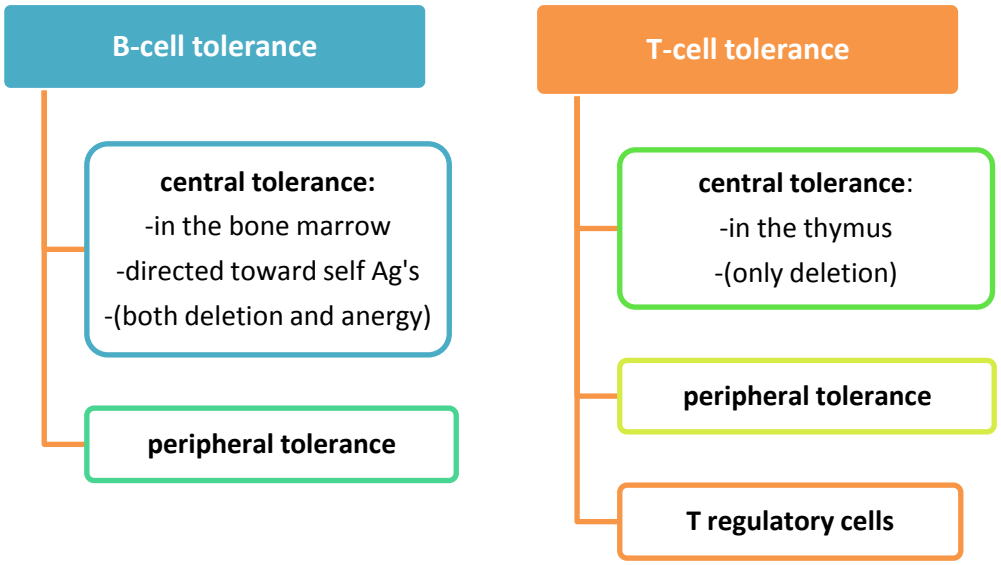
Tolerance: a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response

- in majority of cases what really happens is either activation or inactivation.

-If an immature lymphocyte encountered an Ag it will be turned off :
either deleted by giving a signal to die by apoptosis, or the signal is going to produce Anergy; which means that the cell is still alive, but it can't interact with Ag. It is useless even though it has not died yet. It will eventually die and nothing will happen.

we know that tolerance should be toward our own proteins in order to recognize the self from non-self , but also tolerance could occur with foreign proteins. what happens actually is that when the lymphocyte recognizes the Ag it won't produce immune response and it will suppress other cells from mounting an immune response.

we'll talk about:



Central tolerance

Rule: stimulation of the receptor of the B or T cell at the immature stage will lead to their death.

A. T-cell central tolerance:

- ✓ positive selection in the thymus has nothing to do with tolerance .in positive selection we choose cells that may be useful for us.
- ✓ tolerance is based on negative selection. in the medulla; T-cells that recognize self Ag in conjunction with MHC I or II with high affinity are going to be deleted, so by this we remove cells that are potentially reacting with our own proteins.
- ✓ Low affinity lymphocytes are called conventional lymphocytes.
- ✓ also in the medulla: there's AIRE gene in the medullary epithelial cells. it manufactures self proteins as many as possible, because not every protein in our body goes to the thymus. if this gene is mutated or is deficient the person will have multiple autoimmune diseases and endocrinopathies .
  ex: insulin is not present in the thymus but it is manufactured by this gene, and offer them to the lymphocytes. That doesn't mean that everything made outside the thymus is going to be made by this gene, so some of the T-lymphocytes that exit the thymus is still autoimmune, and they are removed by the mean of peripheral tolerance .
  *Central tolerance is directed against our own antigens.
  *Peripheral tolerance is directed against our own antigens, and it can be directed against foreign antigens.

SO; in central tolerance: self reactive lymphocytes are deleted.

- ✓ if the interaction between t-cells and MHC is low, the cell is allowed to mature
- ✓ if the interaction is medium --> we get T regulatory cells that go to the periphery to regulate the immune response and prevent autoimmunity.

B. B-cell central tolerance

Central Tolerance happen in the bone marrow

the immature B-cell has IgM only on its surface. if the immature B-cell meets our own Ag it's going to be inactivated in 2 ways:

1. if the Ag is multivalent and cross links the BCR's together , the cell will be given a sign to be deleted by apoptosis
2. if the Ag is soluble, it'll be given a signal to become ***anergy*** (anergy: the cell is not dead but is unable to be stimulated anymore. so they circulate in the blood but can't be stimulated and produce a response, and eventually after few weeks it'll die) they come out to the periphery and die.

Some cells that go to the periphery are going to be self reactive and die by the means of peripheral tolerance .

peripheral tolerance

A. T-cell peripheral tolerance:

1) Recognition of the Antigen without co-stimulation.
   when the T-cell binds to an Ag , it must have both 1^{st} and $2^{nd(co\text{-}stimulatory)}$ signals. the absence of the 2^{nd} signal makes the cell **anergic** (can't be activated anymore and die after few weeks) rather than activated.
2) sometimes we get odd\abnormal Ag presentation. a T-cell might present Ag's to another T-cell, if this happens there will be inactivation . this is known as **Aveto cell** (the odd APC , i.e the T-cell).
3) there's a theory says that the affinity plays a role. if the affinity between the TCR and the APC is *high* then we get tolerance. low affinity leads to activation
4) **the microinvironment :**
   - too much IL-2 at the time of stimulation(or repeated stimulation of IL-2) leads to inactivation of the cell rather than activation.
   - CTLA-4 appearance on the surface of the cell produces inactivation. what determines whether CD28 or CTLA-4 will bind to B7? it actually depends on the density of B7 on APC. too many B7=CD28 will bind . few B7=CTLA-4
5) **FAS**. repeated activation of T-cell produces FAS, then it binds to FAS ligand which leads to killing of the cell rather than activation.

SO; all of these will produce tolerance, reduce the immune response and avoid any damage to our tissues.

B. B-cell peropheral tolerance

- what's really important in B-cell tolerance is the lack of co-stimulation by TH cells. if there's no T helper cells u get no activation of B-cells. (that's in case of T-dependent B-cells)
- in case of T-independent B-cells, we also have tolerance but we don't exactly how it happens. e.g: if you have blood group A, you don't produce Anti-A Ab. so you're tolerant but we don't know how.

T regulatory cells

There old name: suppressor cells.

They are T-lymphocytes that are produced from median affinity thymocytes.

Are of 2 main types:

1) **Natural regulatory cells (NRT cells)**: come from the thymus and are identified by few markers:
    a. $CD4^+$ (like many other T-cells)
    b. $CD25^+$. it's the α chain of the IL-2 receptor. unlike the resting T-cells which express this chain upon activation to make a complete functional IL-2 receptor. We only have beta and gamma receptors in all resting cells, and the third chain(alpha- CD25) is expressed upon activation.
    These T-Reg cells already have 3 chains in the receptor when they exit the thymus.
    c. FOXp3. this's a transcription marker that transmit signals inside the cell , but its function is not known. (FOXp3 is member of the fork-head transcription factor family)
    d. they express CTLA-4 constitutively on their surface when they come out from the thymus, they don't need to wait for 3-4 days for expressing it (i.e always have CTLA-4)
    Other cells : at the beginning we have CD28, and 3-4 days after activation we will get CTLA-4

now these natural T-reg go to the periphery and their TCR recognize Ag's with MHC II molecules on the APC and suppress other cells from producing immune response against Ag's (ya3ni they react with the Ag specifically , but all other cells are suppressed)
so we will get tolerance for this Ag. The cell is not aggressive , it wont cause an immune response . it will suppress other cells that may interact with this antigen either by contact or by interleukins
tolerance is Antigen specific, same as the immune response.So , natural T-reg is specific to that, but their effect is not , it suppress all T-lymphocytes that are around, probably through contact and non inflammatory cytokines, like IL-10 and TGF-β.

2) **Induced T_{reg} cells (iT_{Reg}):** come from the conventional T-cells outside the thymus by the influence of the suppressor cytokines (IL-10 & TGF-β) produced by natural T-reg.
    - they're $CD4^+$, $CD25^-$
    - they're of 2 kinds:

T regulatory 1 cells (TR1)	TH3
- in peripheral - Produce IL-10 - same function as NRT cells by producing tolerance, preventing autoimmunity and shut off immune responses	- in GIT in the mucosa . - produce alot of TGF-β Reduce the reactions toward the antigens , we don't want to initiate immune response against anything we eat, and this is called : Oral tolerance. Ex: they fed some animals an antigen , and then they injected them with that antigen but they didn't develop an immune response; this mean that they have got tolerance against that antigen. so the way we administer the antigen is important. Also the dose is important, high doses cause tolerance. -Remember: immunogenic antigen should be in optimal conc. -new immune deviation can be regarded as a form of tolerance, because you deviate from activated form. - to switch to IgA and damp any unnecessary immune reactions. It is not a very inflammatory AB. It works on tolerance of antigens(neutralizing them).

NOTE

we said tolerance can happen with foreign Ag ... is this dangerous ?
yes, some bacteria become chronic because they maybe use the T_{reg} cells for their own benefit (like: mycobacteria and leshmania)

Good luck
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