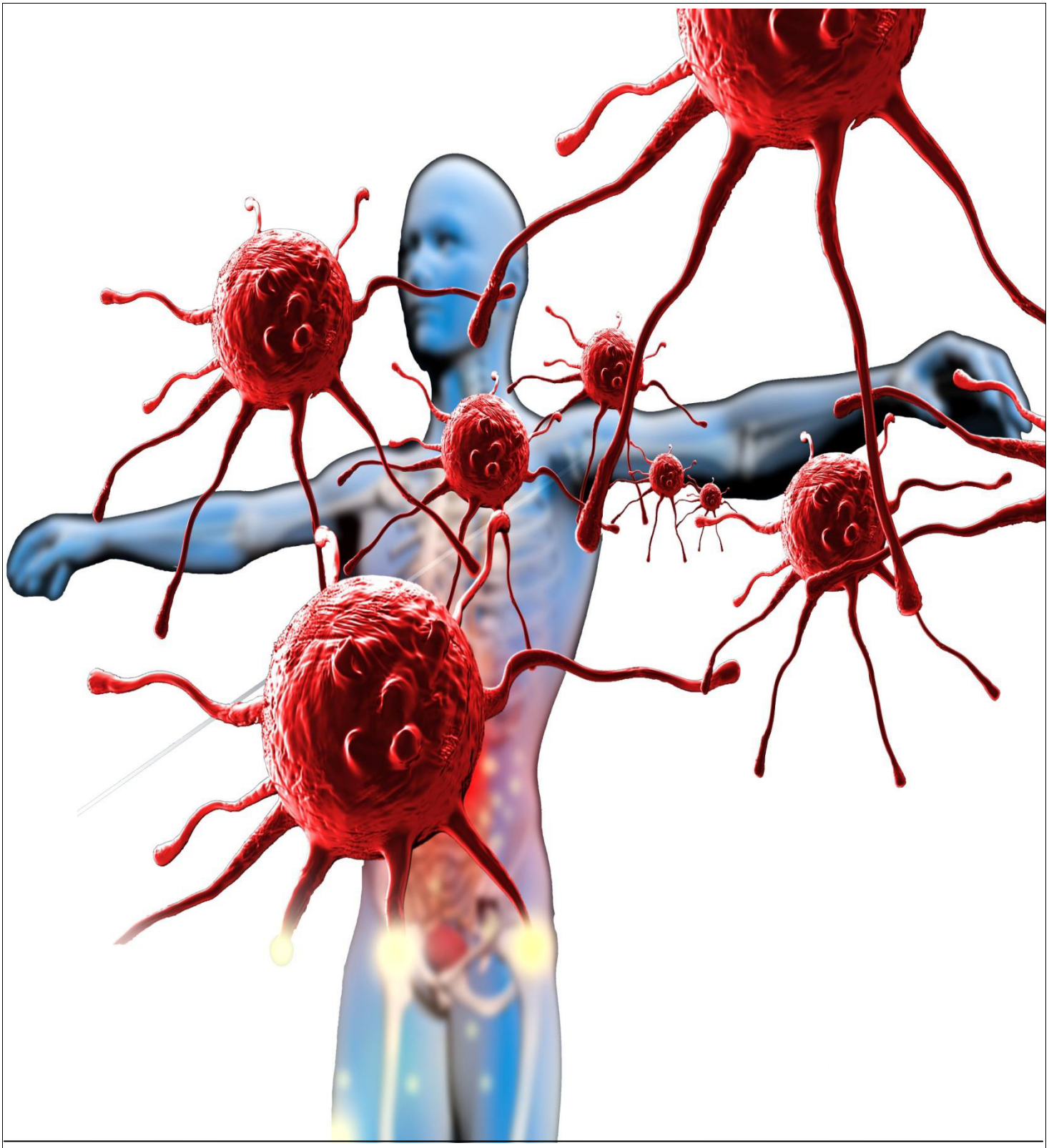

IMMUNOLOGY

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#13

By Mohammed Nawaiseh

Tolerance & Autoimmunity

Tolerance

- When a cell meets an antigen, it won't be activated, it'll be inactivated, or produce certain cytokines that suppress further activations.
- Remember that "Self-tolerance" is very important; the immune system has to recognize the self from non-self antigens. (Normal body can develop tolerance to other antigens other than "self-antigens", but if a body loses the tolerance to self antigens, it will develop Auto-immune disorders.)
- 2 Varieties:
  - **Central Tolerance**: directed mainly toward self-antigens.
    In primary lymphoid tissues where B and T cells mature, they are exposed to self antigens and undergo "**Positive selection**" by Thymic cortical epithelial cells. Remember the developing T cells in the Thymus undergo positive selection in the cortex. Positive selection has nothing to do with tolerance; it only selects the cells that are going to be useful by recognizing the self-antigen on the MHC molecule by its TCR, if a cell doesn't recognize the MHC molecule it will be neglected without signals for maturation, then it undergoes apoptosis (Not actively killed), while the cells that can recognize MHCs will be exposed to activating signals and will mature.
    → Positive selection occurs definitely with double +ve cells.

    Then survived cells travel to the cortico-medullary junction to be trapped by Dendritic cells, Macrophages, and Thymic epithelial medullary cells, where "**Negative selection**" occurs. Negative selection is associated with tolerance; it determines whether a cell is auto-reactive or not, by the affinity recognition between the TCR and the antigen attached to the MHC molecule. If the affinity is high, then the cell is considered to be potentially auto-reactive and is killed actively by apoptosis, eliminated, negatively selected → Central tolerance. Interactions of weak affinity are considered good and cells are allowed to continue maturation, because if you expose them to foreign antigens later on, they probably will interact with them with a higher affinity and will be the effectors of your immune system. Intermediate interactions will indicate that these T cells are special: Natural T-Regulatory Cells, 5-10%, so called due to their formation in the Thymus. These T cells have special markers on their surfaces (some are shared with other T cells, and some are not): CD4, CD25 (the alpha chain of IL2 receptor), then FOXb3 (a transcription factor). They also may express CTLA-4. (A ligand for B7 molecule on Antigen-presenting cells, that gives an inhibitory signal.) N-T-Reg cells produce anti-inflammatory cytokines (IL-10 + TGF-Beta). These regulated cells either interact with other T cells and prevent their activation and send them a message to be killed by direct contact [Imagine a T regulatory cell coming in contact with a T cell that's preparing itself to interact with a self antigen (not previously encountered in the Thymus), the T cell will be prevented from doing so and will die by granzymes-induced apoptosis.], or by the NON-inflammatory cytokines.

Written by Amani Atallah

→ Negative selection as the doctor believes occurs to double +ve cells, but still may occur to single +ve ones as many resources tell.

➔ Although Thymic medullary epithelial cells try to express different normal self proteins of the body (not normally found in the Thymus) through AIRE gene (AutoImmune Regulatory gene), and present them to the maturing T cells to assure that they will be presented on MHCs and the T cells will either tolerate them or be eliminated, still not all self antigens can be presented by this mechanism.

➔ Patients of mutated AIRE gene won't have sufficient Negative Selection + Tolerance, and will develop APS (Autoimmune Poly-enocrinopathy syndrome). *[Not IPEX, the doctor corrected it in the next lecture.]*

- **Peripheral Tolerance:** when a cell becomes tolerant to a self antigen in the periphery because it escaped from central tolerance and has not been exposed to the antigen in the 1ry lymphoid tissue.

-Remember how each cell requires 2 signals in order to be activated, if the 2nd signal is not initiated (no B7 on APCs for example), the cell won't be activated; it'll become anergic or die by apoptosis, and this is the point of peripheral tolerance**.** *[B7 is normally found on cells in small amounts, but if it goes lower, it will allow the inactivatory signals to take place.]*

➔ Some normal mature CD4+ cells can become regulatory cells in the periphery: Induced T Regulatory. These do not carry CD25 on their surfaces initially, and then through their activation, they start to have CD25 and FOXb3 as well. This induction is probably due to the effect of cytokines like: IL-10 + TGF-beta. These cells are selected depending on their affinities to MHC molecules.

➔ The TH3 cells are very similar to the induced T regulatory, but it's unknown if they really belong to one family. they're mainly present in the GIT under the mucosa, and have a marked role in "Oral tolerance"; a type of peripheral tolerance, it is the tolerance to the antigens of the outside that are continuously taken in and it's not proper to fight them (proteins in food). These are taken in by M cells of the GIT and transported to the TH3 + Induced T regulatory cells in the submucosa to accept them. People with allergies to certain types of food may be having something wrong in these T cells. Also the normal flora in your gut continue to produce different antigens that should be tolerated.

➔ If other soluble antigens are injected intravenously (without adjuvants):
- In high doses: T cells will become anergic and won't respond.
-In low repeated doses: Activation of T regulatory cells and their subsequent non-inflammatory IL-10 and TGF-beta occurs→ no response.
[If adjuvants are added, they will release the antigens slowly, and irritate the macrophages to produce more inflammatory signals and molecules.]

Remember that in order for a vaccine to be effective it should be given IM with an adjuvant.

➔ Some areas are said to be "Immuno Privileged";

*The **brain** is isolated from different antigens by the blood-brain barrier and accordingly has no lymphatics or lymphocytes or autoimmune diseases, if you however transport some of the cells of the tissue of the brain to another side in the body, they will be seen as foreign and will be auto-immunologically damaged*

*The cells of the **testes** too do not induce immunologic responses on their own because they are not exposed to the immune system. The sperms also express FAS ligands that induce the apoptosis of any infiltrating T cells.*

➔ This immunological privilege can be broken down in procedures like Vasectomy [The ligation of Vas Deferens in male, making him sterile.] Vasectomy will allow the antigens of sperms to gain access to the circulation and produce an auto-immune response against them. If a patient wants to rejoin the parts of the Vas Deferens, he won't become fertile again because his newly produced sperms will be killed by the immuno system.

*In areas lacking blood vessels as the **eyes**, no immuno cells are present so it's also immuno privileged areas, and like in testes, these cells express FAS ligands. But once an invading injury to the eye happens, the privilege will be lost, and the antigens of these tissues will go to the circulation and induce the formation of autoreactive cells and antibodies. The activated immune system can damage the affected eye and the second non-injured one → Sympathetic Ophthalmeia.*

*The **placenta** is an immuno privileged tissue. Many of the antigens of the baby differ from those of the mother, and that's why the privilege should be maintained so that the mother won't be harmed by the fetal tissues. This explains why trophoblast cells of placenta have no MHC1 molecules on their surface; they can't be rejected by the cytotoxic T cells. But they express non classical MHC molecules (types: E, G, H) to be protected against the killing effect of NK cells by binding the inhibitory NK-G2D receptors.*
