Sheet 17

Immunology

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Corrected by | – – –

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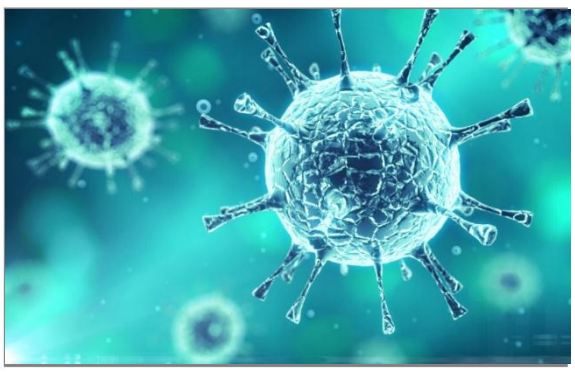
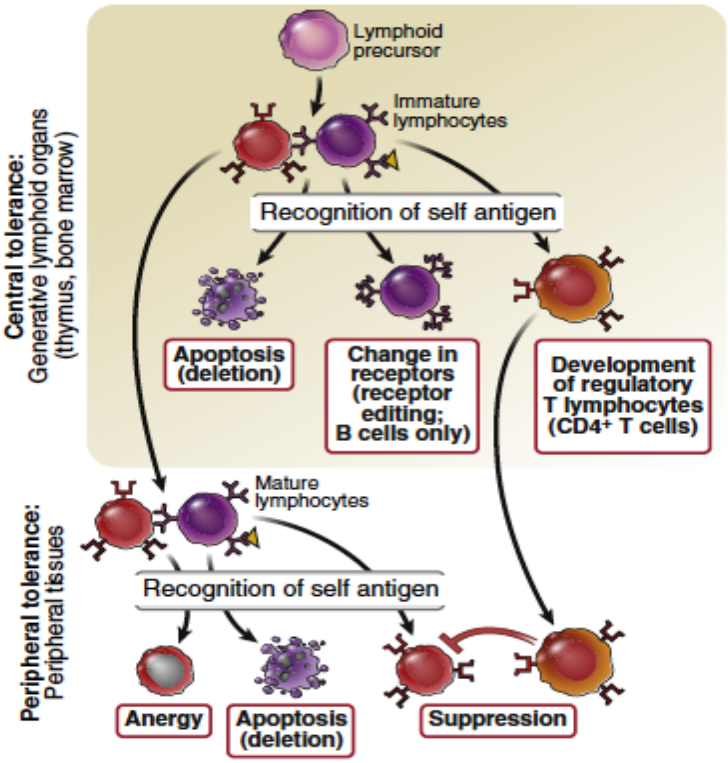


Immunological Tolerance(IT) and Autoimmunity(AI)

- We will start with the definition of IT , which is the ability of the immune system to discriminate between self and non-self antigens , that's it , when your body doesn't make antibodies against self antigens , it's said to be tolerant. When it does so , AI will develop as we'll see later.
- Another definition for IT is the lack of immunological response to an antigen , induced by the exposure of lymphocytes to this antigen previously.
- *There're some terms that you should be familiar with :-*
  - Immunogenic antigen : An antigen that elicits an immune response (bacterial antigens for example).
  - Tolerogenic antigen : An antigen that induces tolerance , where the lymphocytes become functionally inactive or they're killed.
  - Immunological Ignorance : As the term implicates , here the lymphocytes IGNORE the presence of the antigen. This phenomenon is seen in Immune Privileged Sites (IPSs) such as Brain , Testes and Eyes. You should notice that these areas are physically separated from antigens (ie; there's no Lymphatic drainage) and the idea behind this separation is to protect these IPSs from damage.
- IT is an important subject because (1) its failure is the underlying cause of AI , also , if it's well studied , there'll be (2) production of IT against specific antigens and thus prevention of unwanted immune responses as in cases of transplantation .(3) Another application of this is "Gene therapy" where we prevent immune responses against newly expressed genes.
- There're two types of IT :- Central IT (In central lymphoid organs , ie; BM and Thymus) and Peripheral IT (In peripheral lymphoid organs).

*** Remember that Central tolerance isn't perfect as some cells can escape. Another difference between central and peripheral tolerance is that the earlier occurs at the level of immature lymphocytes.



- This scheme is very important as it summarizes what happens.
- In the upper part of the diagram you see the central tolerance , it occurs at the level of immature lymphocytes that recognize self antigens , they either *(1) Die by apoptosis , (2) Change in receptors*** , *(3) Development of regulatory T lymphocytes (CD4+ T cells)* or *(4) Anergy for B cells ONLY***

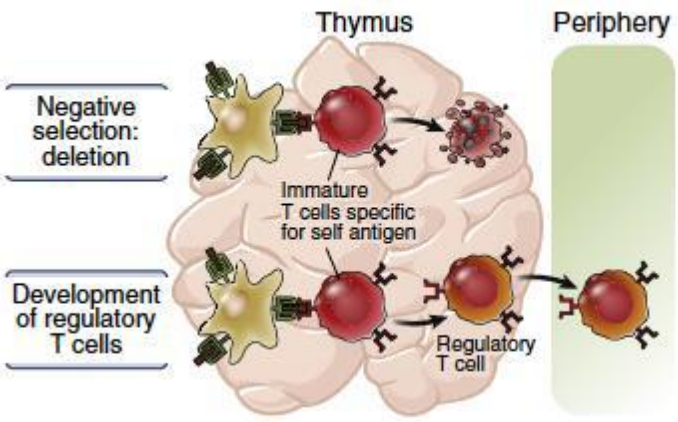
  ** The change in receptors happens ONLY in B cells through what's called *Receptor editing*. During which B cells increase the expression of Recombinant Activating Genes (RAGs) and they change their LIGHT chain , in order not to die by apoptosis (During –ve selection) and this is the most common method in removing self reactive B cells.

** Anergy is known as Long-standing functional unresponsiveness , ie ; lymphocytes are viable but they're non-functional , I'll will talk about it in more details later on.

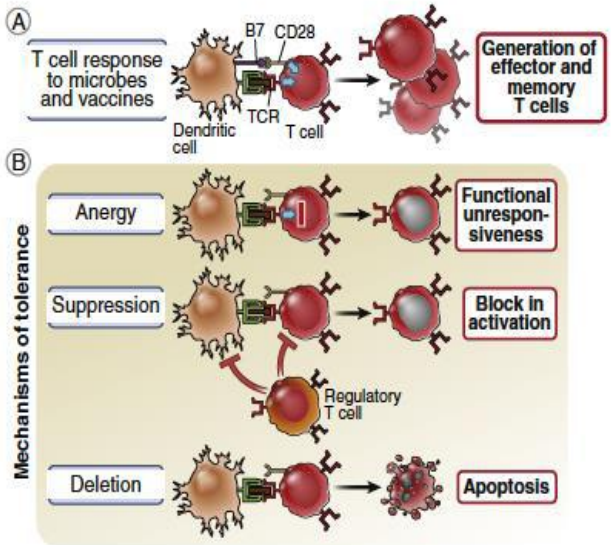
- In the lower part of the diagram you see the peripheral tolerance where self reactive MATURE lymphocytes have multiple fates :

  (1) Anergy for BOTH B and T cells , (2) Apoptosis or (3) Suppression by Regulatory T cells.

- ***Central T lymphocytes Tolerance(CTLT):-***
  - If you refer to the diagram you'll see that the principal mechanisms for CTLT are Apoptosis or Development to CD4+ Reg. Cells.
  - Remember that self antigens play a vital role in –ve selection of T cells.
  - These antigens are triggered (Expressed in the thymus) by AIRE (AutoImmune REgulator) protein.
  - This process happens in the thymus for T cells.



- ***Preipheral T lymphocytes Tolerance (PTLT):-***
  - If you refer to the diagram you can see that the mechanisms for PTLT are Anergy , Death or Suppression by CD4+ Reg. Cells.



- ***Anergy :-***
  - As I said before , Anergy is … ?
  - To understand this , let me remind you that a Naive lymphocyte needs two signals in order to become activated :
    (1) The binding of the antigen to its receptor on the lymphocyte (whether it's present on MHC for T cells or Free for B cells)
    (2) Co-stimulatory signal , which is achieved by the binding of B7 protein on APCs with its receptor on the lymphocyte , CD28. This binding should be strong in order to activate the lymphocyte.
  - If the Co signal is weak , the first signal will lose its ability to transmit activating signals , and sometimes , the first signal will activate some enzymes (eg; ubiquitin ligases) that target signaling proteins for intracellular degradation by proteases.
  - Also if the binding is weak , T cells preferentially engage one of the inhibitory CD28 receptors family , for example , Cytotoxic T Lymphocyte associated Antigen 4 (CTLA-4 or CD152) or Programmed Death protein 1 (PD-1). In these cases the signal is converted from B7-CD28 activation to either B7-CTLA4 inhibitory or B7-PD1 which induces apoptosis.

** The process by which T cells determine whether they'll express CTLA-4 or PD-1 is complicated and not well understood.

- ***Immune Suppression by Regulatory T cells:-***
  - Regulatory cells as we said before , either develop in the thymus or in the periphery after their recognition of self antigens and the function of these cells is to regulate immune responses.
  - When flow cytometry is done , these cells are CD4+ , express high levels of CD25 and FoxP3 , which is a transcription factor.
  - CD25 is an IL-2 receptor , remember that IL-2 is an important cytokine for T cells activation and proliferation (ie; T cells also express CD25).

- There're many mechanisms by which T Reg cells suppress immune responses , of them are :
  1- Production of some cytokines (eg; IL-10 and TGF-B) which are inhibitory cytokines for lymphocytes , DCs and Macrophages.
  2- Expression of CTLA-4 and PD-1 which bind to B7 molecule , thus reducing its bioavailability (The Co signal will be missed).
  3- Also , highly expressed IL-2R (CD25) reduces IL-2 levels.

- ***Deletion (Apoptosis) :-***
  - When the lymphocytes recognize self antigens , pathways of production of pro-apoptotic proteins and receptors are activated.
  - Let me remind you of the two pathways of apoptosis :-
    ⇨ Intrinsic pathway , happens when there's an imbalance between pro-apoptotic (BAK and BAX) and anti- apoptotic (BCL-2 and BCL-XL) proteins , this is followed by the leakage of Cyt C form mitochondria which inturn activates caspases.
    ⇨ Extrinsic pathway , happens when Fas ligand bind to Fas Receptor (On the apoptotic cell) , this binding activates caspases.
- Now let's talk about ***Central B Lymphocyte Tolerance:-***
  - If you refer to the diagram in page 2 , you can see that the mechanisms for CBLT are Apoptosis , Receptor Editing or Anergy.
  - We've previously talked about Receptor editing but let's talk about it again. Self reactive B cells can escape death by apoptosis by altering their receptors (increasing the expression of RAG and changing their light chain structure) , this aids in the formation of a new receptor that might not react with self antigens.
- ***Peripheral B Lymphocyte Tolerance :-***
  - If you refer to the diagram in page 2 , you can see that the mechanisms for PBLT are Apoptosis , Suppression by T Reg cells or Anergy.

- **Now one can ask , why we don't have immune responses against Normal Flora ? and why pregnant women don't have immune responses against Fetal Antigens??**
  - The answer for these questions is Tolerance, but the exact mechanism is unknown , an acceptable theory states that T Reg cells carry up this process.
  - Notice that in the second question , if Tolerance is abscent , GVHD will develop , because mother's T cells will fight Fetus's antigens causing serious problems.

- ***AutoImmunity :-***
  - We already know that AI is an immune response against self antigens . AI is of two types , organ-specific affecting only one or few organs , or systemic affecting multiple tissues
  - As I previously mentioned , AI results when Tolerance fails to occur.
  - **NOTE** :- AI differs from Uncontrolled immunity , in the latter , there's an antigen that elicits a strong immune response (Super Antigen) as seen in Mycobacterium TB's granuloma.
  - **Pathogenesis of AI:-**
    - ⇨ First of all , you should know that AI is a multifactorial process , it depends on Genetic factors , Environmental factors and failure of tolerance to occur (Interaction between these factors produces AI).
    - ⇨ Genetic Factors are attributed to multiple gene loci , most commonly MHC genes (MHC Loci).

Disease	MHC allele	Relative risk
Ankylosing spondylitis	HLA-B27	90
Rheumatoid arthritis	HLA-DRB1*01/*04/*10	4-12
Type 1 diabetes mellitus	HLA-DRB1*0301/0401	35
Pemphigus vulgaris	HLA-DR4	14

⇨ Notice that the presence of the gene only increases the risk and not necessarily means the presence of the disease.

⇨ Other non-HLA polymorphisms :-

A

Genes that may contribute to genetically complex autoimmune diseases		
Gene(s)	Disease association	Mechanism
PTPN22	RA, several others	Abnormal tyrosine phosphatase regulation of T cell selection and activation?
NOD2	Crohn's disease	Defective resistance or abnormal responses to intestinal microbes?
IL23R	IBD, PS, AS	Component of IL-23 receptor; role in generation and maintenance of Th17 cells
CTLA4	T1D, RA	Impaired inhibitory checkpoint and regulatory T cell function
CD25 (IL-2Rα)	MS, type 1 diabetes, others	Abnormalities in effector and/or regulatory T cells?
C2, C4 (Complement proteins)	SLE	Defects in clearance of immune complexes or in B cell tolerance?
FCGRIIB (FCγRIIB)	SLE	Defective feedback inhibition of B cells

⇨ The Dr. just read the highlighted parts.

⇨ Single gene defects that cause AI (Mendelian diseases) :-

B

Single-gene defects that cause autoimmunity (mendelian diseases)		
Gene(s)	Disease association	Mechanism
AIRE	Autoimmune polyendocrine syndrome (APS-1)	Reduced expression of peripheral tissue antigens in the thymus, leading to defective elimination of self-reactive T cells
CTLA4	Autosomal dominant immune dysregulation syndrome	Impaired inhibitory checkpoint and regulatory T cell function leading to loss of B and T cell homeostasis
FOXP3	Immune dysregulation, X-linked polyendocrinopathy and enteropathy (IPEX)	Deficiency of regulatory T cells
FAS	Autoimmune lymphoproliferative syndrome (ALPS)	Defective apoptosis of self-reactive T and B cells in the periphery

⇨ This table is very important , the doctor read it and I think that it's required to know its info.

⇨ AIRE gene defects are AR.

- ***Here are some required slides, but the dr didn't add anything , he just read them.***

Role of Infections and Other Environmental Influences

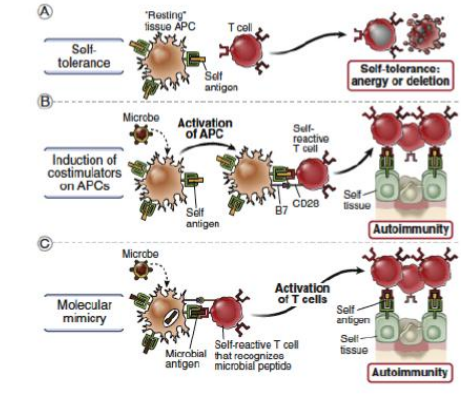
- **Infections may activate self-reactive lymphocytes, thereby triggering the development of autoimmune diseases.** Clinicians have recognized for many years that the clinical manifestations of autoimmunity sometimes are preceded by infectious prodromes. This association between infections and autoimmune tissue injury has been formally established in animal models.

Role of Infections

- An infection of a tissue may induce a local innate immune response, which may lead to increased production of co-stimulators and cytokines by tissue APCs. These activated tissue APCs may be able to stimulate self-reactive T cells that encounter self antigens in the tissue. In other words, infection may break T cell tolerance and promote the activation of self-reactive lymphocytes.

- Some infectious microbes may produce peptide antigens that are similar to, and cross-react with, self antigens. Immune responses to these microbial peptides may result in an immune attack against self antigens. Such cross-reactions between microbial and self antigens are termed **molecular mimicry.**

Mechanisms by which microbes may promote autoimmunity.



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- Don’t hesitate to ask about any miss understood concept. Your Sincerely.