Sheet n.

Doctor 22

فريق طوفان الاقصى

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Small disclaimer:

A good thing to mention before we start this lecture is that most of what will be discussed is filled with 'unknowns', meaning that there are many pieces of scientific information regarding immunological tolerance which are incomplete. GOOD LUCK!

Immunological Tolerance and Autoimmunity

OVERVIEW:

Immunological Tolerance is defined in simpler words as: Self and Non-Self discrimination, the immune system should not target self-antigens and tissue but rather foreign antigens such as microbes or even cancer cells.

Failure in Immunological Tolerance causes Autoimmunity.

- **Immunological tolerance is a lack of response to antigens that is induced by exposure of lymphocytes to these antigens.**

- **Antigens that elicit such a response are said to be immunogenic.**

When lymphocytes encounter their cognate antigen (epitopes), there are multiple options for their fate. One of them is, if the conditions are suitable (we'll talk about these conditions later), the lymphocyte would undergo activation, differentiation, proliferation, and causes for an immune response. Antigens that do this are called "Immunogenic antigens"

- **The lymphocytes may be functionally inactivated or killed, resulting in tolerance; antigens that induce tolerance are said to be Tolerogenic.**

Another option for the fate of the lymphocyte after encountering an antigen is lacking in response (in methods we'll discuss later), antigens that elicit this lack of response are called "Tolerogenic Antigens." Note that antigens presented to lymphocytes in embryonic life are mostly Tolerogenic.

- **In some situations, the antigen-specific lymphocytes may not react in any way; this phenomenon has been called immunological ignorance, implying that the lymphocytes simply ignore the presence of the antigen.**

There's another phenomenon called "Immunological Ignorance" which could be confused with Tolerance. In this case, the self-reactive lymphocytes exist within the human body, however, they ignore the presence of the antigen because of, for example, an anatomical barrier existing between the two. Most notable barriers are the Blood-Brain Barrier (BBB), Blood-Testis Barrier (BTB), Blood-Retina Barrier (BRB), these sites are called "Immuno-privileged sites." When trauma occurs to these sites, Lymphocytes would migrate to them and immediately mount an immune response to those self-antigens. Conditions such as Orchitis in the Testis and Endophthalmitis in the Eye are the result of this.

IMPORTANCE OF IMMUNOLOGICAL TOLERANCE

- **First, self-antigens normally induce tolerance, and failure of self-tolerance is the underlying cause of autoimmune diseases.**
- **Second, if we learn how to induce tolerance in lymphocytes specific for a particular antigen, we may be able to use this knowledge to prevent or control unwanted immune reactions.**
- **Strategies for inducing tolerance are being tested to treat allergic and autoimmune diseases and to prevent the rejection of organ transplants** (and to treat cancer patients)
- **The same strategies may be valuable in gene therapy to prevent immune responses against the products of newly expressed genes or vectors and even for stem cell transplantation if the stem cell donor is genetically different from the recipient.**

One of these newfound strategies is "Blockade Inhibition," (which will be discussed later in T-Lymphocyte tolerance) which made a breakthrough in treating cancer patients or those with autoimmune diseases.

TOLERANCE TYPES:

- **Immunological tolerance to different self-antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, a process called central tolerance**

Central tolerance induction happens in central lymphoid organs on immature lymphocytes (this is important to know), for T-Lymphocytes, it happens in the Thymus, for B-Lymphocytes, it happens in the Bone Marrow.

- **Or when mature lymphocytes encounter self-antigens in peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance.**

Peripheral Tolerance induction occurs in peripheral tissue or secondary lymphoid organs such as Spleen or Lymph Nodes, and it happens to Mature Lymphocytes (T & B cells).

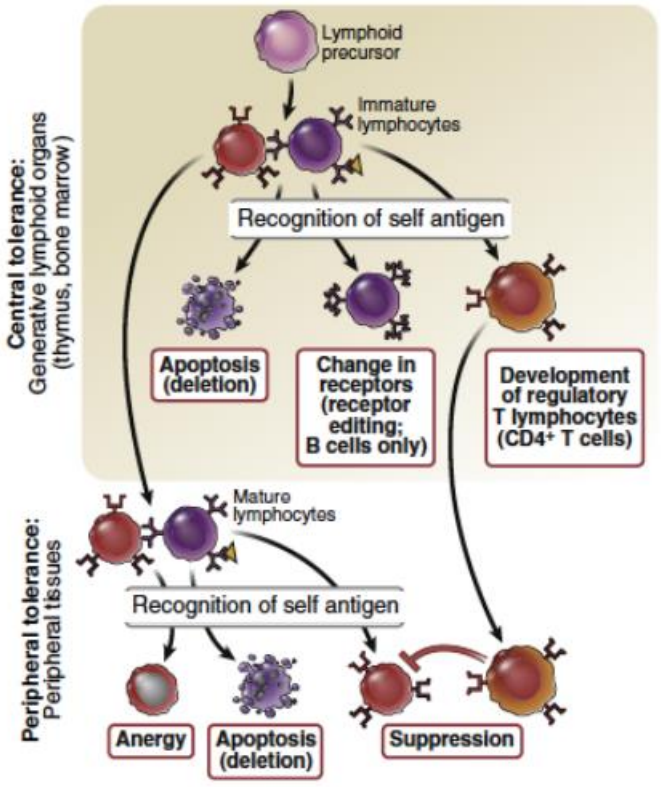
CENTRAL AND PERIPHRAL TOLERANCE:

This figure highlights what we'll talk about in this lecture today.

1- Lymphoid progenitor or precursor cells commit to either becoming B-cells or T-cells.

2- Central tolerance occurs for T-cells in the thymus, and bone marrow to B-cells. If you remember from the lymphocyte development lecture, two things occur here.

A- Positive Selection
B- Negative Selection (deletion)

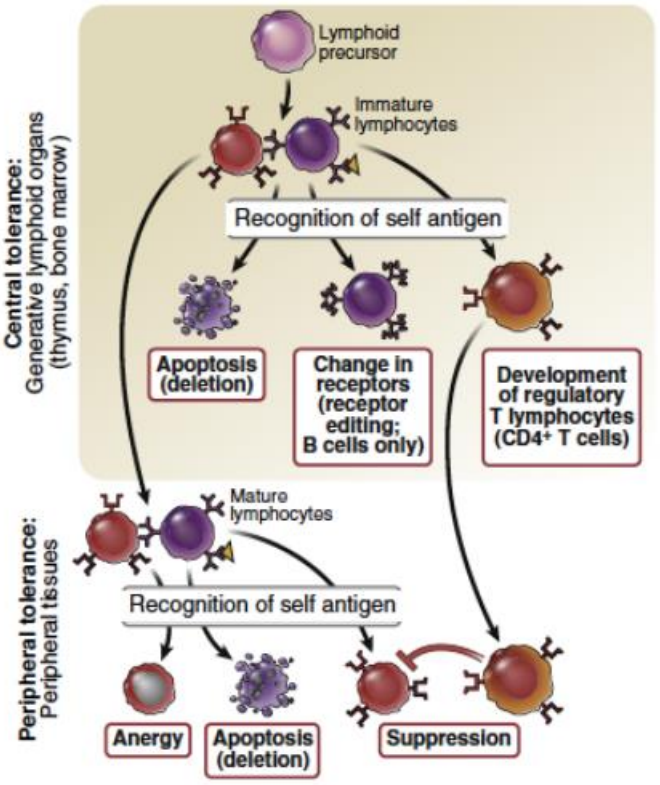


Before deletion occurs after b-cells recognize self-antigens, they can go into an extra step of changing their receptor (receptor editing), only B-Cells have this happen to them (about 50-70% of B-Cells found in circulation have done this step). If the receptor changes and it's still Self-Reactive, the cell would be deleted, if NOT, it would continue its maturation process.

As we said before, receptor editing after self-reaction only occurs in B-Cells. T-Cells however might go into a different pathway than apoptosis and that is becoming T-Regulatory cells which work in suppression of immune response by secreting Anti-Inflammatory cytokines such as IL-10 and TGF-β, notable markers of T-Reg cells are:

1- CD25 (high affinity IL-2α receptor), and 2- FOXP3 (their transcription factor)

3- In the peripheral tissues, self-reactive mature T and B lymphocytes are inhibited through different mechanisms, one is Suppression by T-Reg cells, and they:
   a. Are majorly produced in Central lymphoid organs, some are in Peripheral
   b. Can work on other immune cells
   c. Can be either CD4+(mainly) or CD8+



There's also the Apoptosis pathway (extrinsic and intrinsic, which will be discussed later), and the Anergy pathway, also called "Functional Unresponsiveness,"
The key difference between Apoptosis and Anergy is that in Apoptosis the cell dies, but in Anergy the cell remains alive but is functionally unresponsive to its antigens due to certain conditions, if those conditions are changed to more suitable ones for its survival, it'd come back as a self-reactive lymphocyte.

Don't overwork yourself just yet, this is an overview of each headline in this lecture, we'll go more into depth about every step mentioned.

The next part of this lecture will be divided into the Central & Peripheral tolerance of T-Lymphocytes, and the Central & Peripheral tolerance of B-Lymphocytes

CENTRAL T-LYMPHOCYTE TOLERANCE

- **The principal mechanisms of central tolerance in T cells are death of immature T cells (negative selection) and the generation of CD4+ regulatory T-cells.**

The negative selection occurs after positive selection. If you remember In T-Lymphocyte development, t-cells are first Double Negative (CD4- & CD8-) then

Double Positive (CD4+ & CD8+) and then are Single Positive (CD4+ or CD8+), this process is called Positive Selection which happens through the weak binding of MHC molecules, if it binds to MHC-I with weak affinity-> CD8+, if MHC-II-> CD4+. After this, Negative Selection occurs where Strong binding to self-antigens presented on MHC molecules (whether I or II) causes for its apoptosis.

It's good to note that binding antigens with strong affinity in CENTRAL ORGANS causes for apoptosis, however in peripheral, it is activation. This is because central organs are considered "Sterile" which means that they only contain self-antigens. So any binding antigens within them is considered self-reactive, therefore, their deletion is required.

- **Immature lymphocytes may interact strongly with an antigen if the antigen is present at high concentrations in the thymus and if the lymphocytes express receptors that recognize the antigen with high affinity. Antigens that induce negative selection may include proteins that are abundant throughout the body, such as plasma proteins and common cellular proteins.**

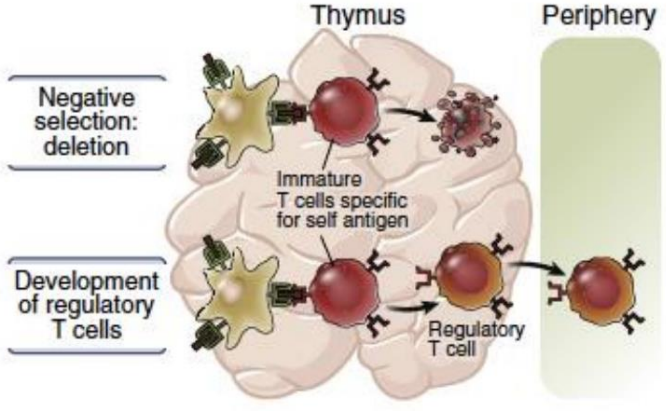
However, not all peripheral antigens are found within the thymus, this is where certain proteins play a role in presenting them such as:

- **A protein called AIRE (autoimmune regulator) is responsible for the thymic expression of peripheral tissue antigens.**

This protein works in presenting those peripheral tissue antigens which aren't exclusively found in the thymus such as plasma proteins and others to developing lymphocytes in thymus. Mutations with this protein cause for certain diseases such as ALPS (Autoimmune Lymphoproliferative Syndrome), which will be discussed later.

This figure shows the two fates of Central T-Lymphocyte tolerance:

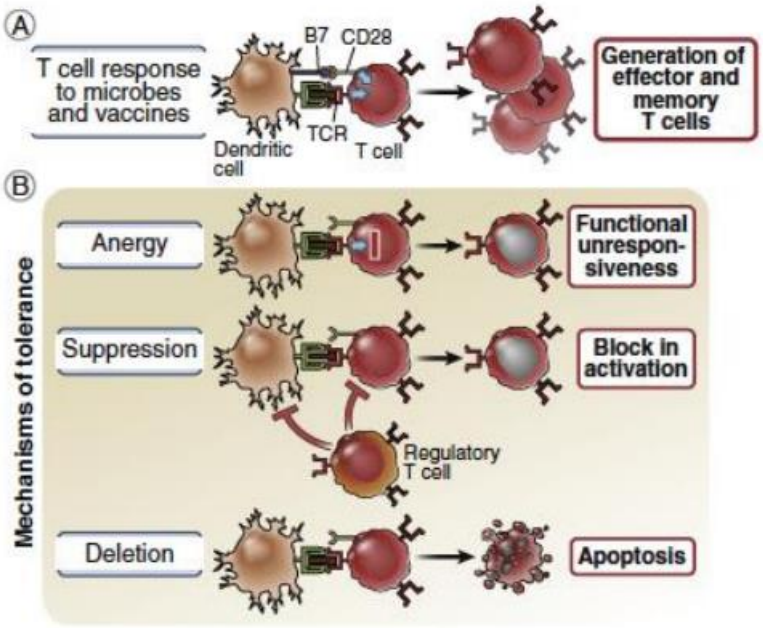
- If immature T-Cells binds their cognate antigen very strongly in the Thymus, which means that it's a self-reactive cell, it would undergo deletion or Apoptosis



- Some of them go into a different pathway which is becoming T-Regulatory cells where they start expressing T-Reg markers such as CD25 & FOXP3 and are able of secreting anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35.

PEREPHRAL T-LYMPHOCYTE TOLERANCE

- **Peripheral tolerance is induced when mature T cells recognize self-antigens in peripheral tissues, leading to functional inactivation (Anergy) or death, or when the self-reactive lymphocytes are suppressed by regulatory T cells.**



- **Antigen recognition without adequate co-stimulation results in T cell Anergy or death, or makes T cells sensitive to suppression by regulatory T cells.**

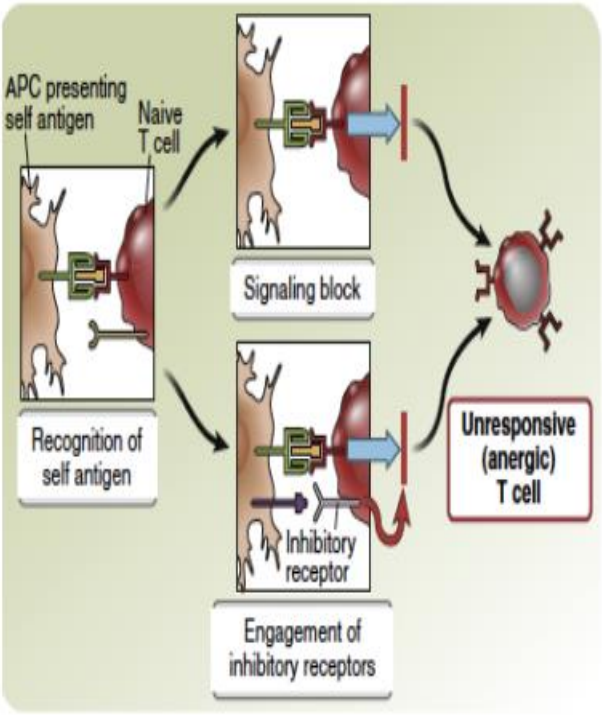
- A- One thing you should always think of when Peripheral tolerance comes to mind is the co-stimulatory signal. We've taken before that we need two signals for T-Cell activation, first the TCR must bind the cognate antigen presented on the MHC molecule, this is Signal #1, the Signal #2 is the binding of the co-stimulatory signal presented on APCs, one of the more notable ones is called B7 (B7-1 is CD80, B7-2 is CD86) and it binds CD28 which is an activating receptor found on T-Cells.

- Another thing that governs T-Cell activation is the ratio between Pro-Apoptotic and Anti-Apoptotic signals, when the Anti-Apoptotic are found more than the Pro-Apoptotic, the cell would survive and allows proliferation and differentiation. This is the normal situation (activation)

- B- However in peripheral tolerance, the first mechanism is Anergy, we can see that the T-Cell is bound to its cognate antigen (Signal #1), and the lymphocyte presented the activation receptor CD28 for the Signal #2, however the APC does not engage the co-stimulatory molecule (B7). In this case, the lymphocyte does not get activated but rather goes into a state of functional unresponsiveness, aka, Anergy.

- The second mechanism that we mentioned is the suppression by T-Reg cells, lymphocytes become sensitive to regulatory signals secreted by T-Reg cells (produced either centrally or peripherally) and get suppressed by them.

- The third mechanism is when the lymphocyte engages with certain receptors which makes the lymphocyte go into deletion. Either in the periphery or Centrally.



ANERGY

- **Anergy in T cells refers to long-lived functional unresponsiveness that is induced when these cells recognize self-antigens.**

- **When T cells recognize antigens without co-stimulation, the TCR complex may lose its ability to transmit activating signals. In some cases, this is related to the activation of enzymes (ubiquitin ligases) that modify signaling proteins and**

target them for intracellular destruction by proteases.

The intracellular cleft may have these ligases or proteases and disrupts the function of signaling, causing functional unresponsiveness or Anergy

- **On recognition of self-antigens, T cells also may preferentially engage one of the inhibitory receptors of the CD28 family, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4, or CD152) or programmed death protein 1 (PD-1).**

"Why would B7 bind to CTLA-4 or PD-1 rather than CD28?"

CTLA-4 and PD-1 have a higher affinity to the B7 molecule than CD28. For example, if B7 was normally expressed at concentration = 100, it would preferentially (prefer) bind to the inhibitory molecules rather than the activating molecule CD28. However, if the conc >100 (the expression of B7 is upregulated by the activation of the innate immune response) -which makes sense, if we have an immune response, we will want more T-Cells activated- the CD28 molecule would bind to it more.

- The Inhibitory receptors are called "Checkpoint Blockade", their discovery made a revolution within the treatment of autoimmune diseases or cancers by creating drugs that target these receptors, whether agonistically or antagonistically.

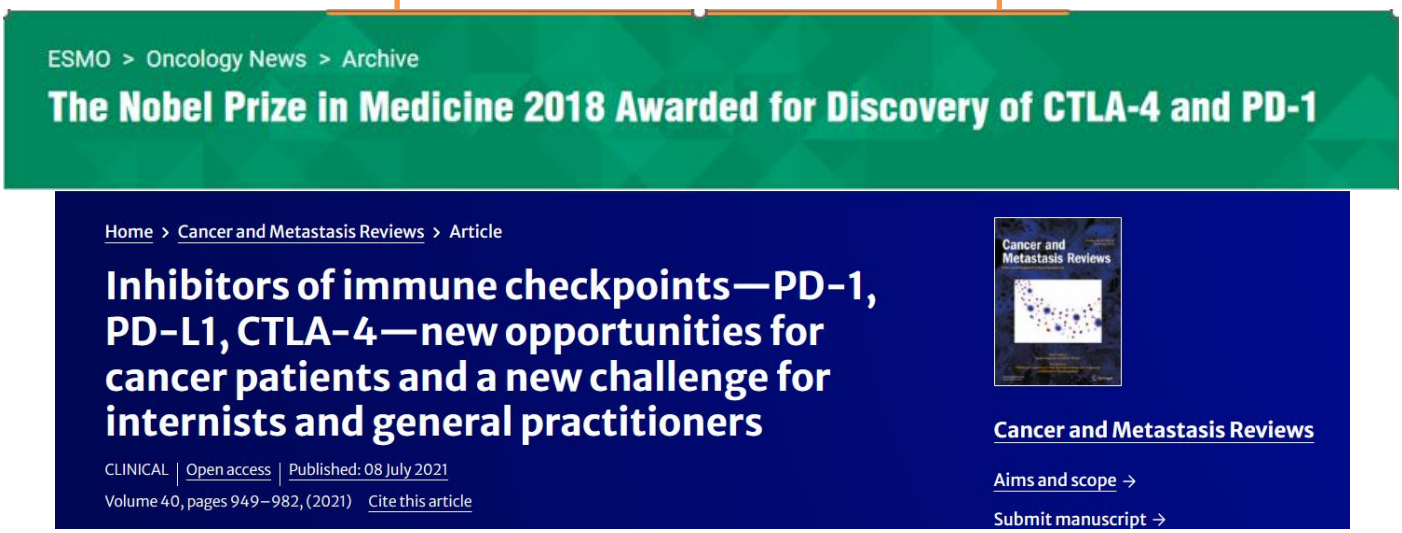
FOCUS HERE MAYBE IT IS AN EXAM QUESTION !!

- Agonists for the inhibitory receptors would cause more inhibition of T-Cells, thereby causing more induction of Tolerance, and it is used in Autoimmune diseases. A popular agonist used for an autoimmune disease called Rheumatic Arthritis is Abatacept (ab-ta-sept)

- Antagonists for the inhibitory receptors would cause stimulation of T-Cells, thereby less tolerance, and this is important in the case of Cancer! In these cases, the immune system cannot see the cancer cells as if they're invisible because it treats them as Self-Antigens, so if we lower the tolerance it'd allow them to see the cancerous cells and tumors. Popular Antagonists are those that end with the suffix "Muab" such as Infliximab, Ipilimumab, and Tremelimumab

We don't know if the drugs are required 😐

Additional information



REGULATION OF T-CELL RESPONSE BY INHIBITORY RECEPTORS

- CTLA-4 is expressed transiently on activated CD4+ T cells and constitutively on regulatory T cells. It functions to terminate activation of responding T cells (and other immune cells) and also mediates the suppressive function of regulatory T cells. CTLA-4 works by blocking and removing B7 molecules from the surface of APCs, thus reducing co-stimulation and preventing the activation of T cells.

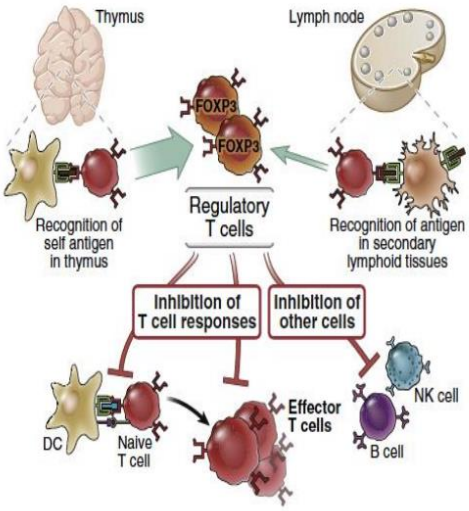
- PD-1 is expressed on CD4+ and CD8+ T cells after antigen stimulation. It has an immunoreceptor tyrosine-based inhibitory motif (ITIM) typical of receptors that deliver inhibitory signals. PD-1 terminates responses of T cells to self-antigens and also to chronic infections, notably virus infections.

IMMUNE SUPPRESSION BY REGULATORY T-CELLS

- Regulatory T cells develop in the thymus (majorly) or peripheral tissues on recognition of self-antigens and suppress the activation of potentially harmful lymphocytes specific for these self-antigens.

- **Most regulatory T cells are CD4+ and express high levels of CD25 (which is IL-2α chain), also express a transcription factor called FoxP3**

- **The survival and function of regulatory T cells are dependent on the cytokine IL-2.**



IL-2 plays a "Dual role", it has a pro-inflammatory role and an anti-inflammatory role:
1- The Pro-Inflammatory role is manifested through IL-2 being considered the "Lymphocyte Growth Factor," for the activation of T-Lymphocytes, the environment must contain a good concentration of IL-2.

2- The Anti-Inflammatory role is used by the T-Reg cells through the IL-2 Receptor (CD25), which works by consuming the IL-2 found in the environment, which leaves not enough IL-2 for the growth of Lymphocytes, which promotes an anti-inflammatory effect. This is called "Consumption Phenomenon."

REGULATORY T CELLS MAY SUPPRESS IMMUNE RESPONSES BY SEVERAL MECHANISMS.

Treg cell inhibit the activation of lymphocyte throw different mechanisms:

• Some regulatory cells produce cytokines (e.g., IL-10, TGF-β, IL-35) that inhibit the activation of lymphocytes, dendritic cells, and macrophages.

• Regulatory cells express CTLA-4(they express it constitutively, not transiently like activated cells) 😁**, which, may block or remove B7 molecules made by APCs and make these APCs incapable of providing costimulation via CD28 and activating T cells.** Which will lead to suppression of APCs**.**

• Regulatory T cells, by virtue of the high level of expression of the IL-2 receptor, may bind and consume this essential T cell growth factor, thus reducing its availability for responding T cells.

DELETION: APOPTOSIS OF MATURE LYMPHOCYTES

Could happen in periphery lymphocytes and for B cells.

There are 2 pathways of apoptosis: extrinsic and intrinsic.

Recognition of self-antigens may trigger pathways of apoptosis that result in elimination (deletion) of the self-reactive lymphocytes.

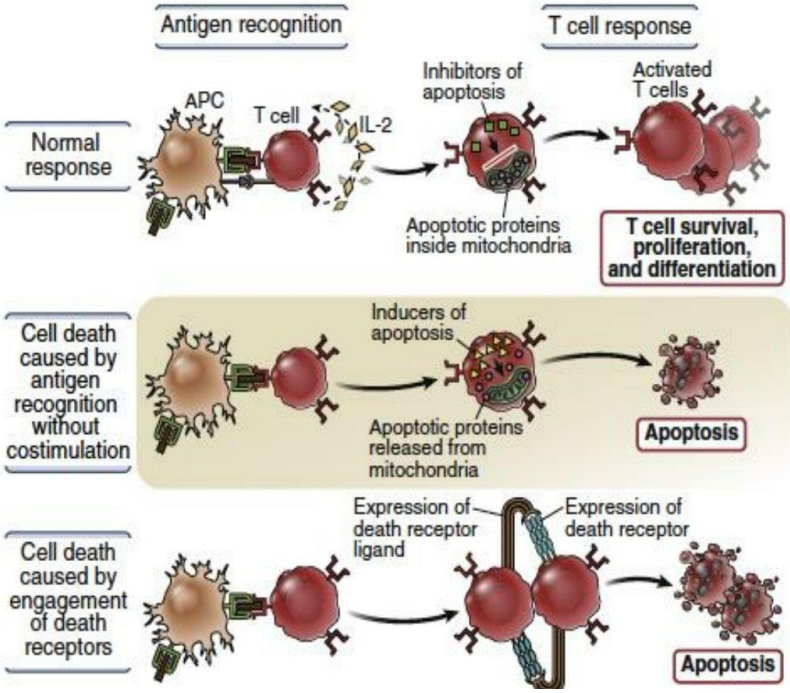
• Antigen recognition induces the production of pro-apoptotic proteins in T cells that induce cell death by causing mitochondrial proteins to leak out and activate caspases, cytosolic enzymes that induce apoptosis.

• Recognition of self-antigens may lead to the coexpression of death receptors and their ligands. This ligand-receptor interaction generates signals through the death receptor that culminate in the activation of caspases and apoptosis (Fas-FasL).

Focus on the picture while reading. **Mechanisms of apoptosis of T lymphocytes:**

1-Normal response: antigen binds with receptor, costimulation is here, IL-2 work as proinflammatory → anti-apoptosis signals get elevated → survival, proliferation, activation.

pro and anti-apoptosis signals are in balance if pro-apoptosis signals get elevated more than anti-apoptosis signals → apoptosis.



2-A- When antigen binds to receptor and there are no costimulatory signals, pro-apoptosis signals will elevate, and this will lead to apoptosis (intrinsic pathway)

2-B- If there is no costimulatory molecule or signal, there would be an engagement of (Fas-FasL), this binding of (Fas-FasL) activate caspases and BAX gene (Bcl-2), cell inter apoptosis and end by death (extrinsic pathway)

B LYMPHOCYTE TOLERANCE

There are central and peripheral tolerance.

• When immature B lymphocytes interact strongly with self-antigens in the bone marrow, the B cells either change their receptor specificity (receptor editing) or are killed (deletion).

Positive selection: if the receptor intact to functioning, then if the receptor reacts with self-antigen with high avidity, it will go deletion, some of them before deletion can do:

• Receptor editing. Some immature B cells that recognize self-antigens in the bone marrow may reexpress RAG genes, resume immunoglobulin (Ig) light-chain gene recombination, and express a new Ig light chain. This new light chain associates with the previously expressed Ig heavy chain to produce a new antigen receptor that may no longer be specific for the self-antigen.

Only happening for B cells → light chain only → variable domain only <--important!

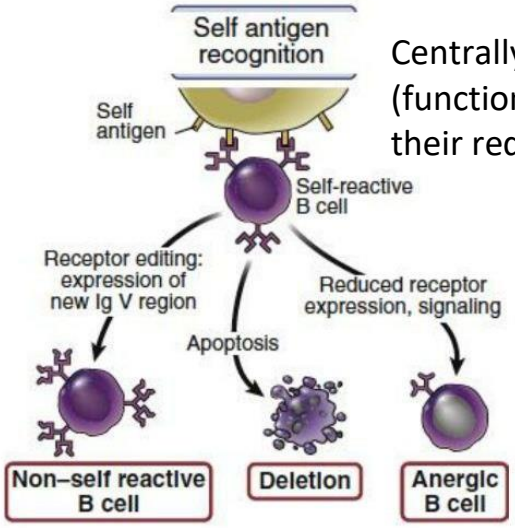
• Deletion. If editing fails, immature B cells that strongly recognize self-antigens receive death signals and die by apoptosis. This process of deletion is similar to negative selection of immature T lymphocytes. As in the T cell compartment, negative selection of B cells eliminates lymphocytes with high-affinity receptors for abundant, and usually widely expressed, cell membrane or soluble self-antigens.

• Anergy. Some self-antigens, such as soluble proteins, may be recognized in the bone marrow with low avidity. B cells specific for these antigens survive, but antigen receptor expression is reduced, and the cells become functionally unresponsive (anergic).

Central tolerance in immature B lymphocytes

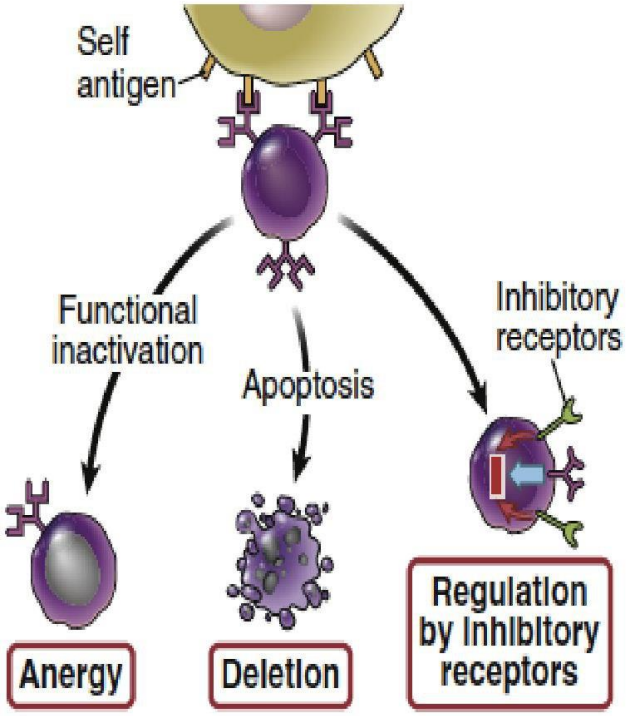
Some cells can undergo receptor editing, if it changes its avidity for self- antigen, it will continue proliferation, if not it will go deletion by apoptosis.

Some cells go deletion without receptor editing.



Centrally B cells can become anergic (functionally unresponsive) through their reduce receptor expression.

PERIPHERAL B CELL TOLERANCE



- **Mature B lymphocytes that encounter self-antigens in peripheral lymphoid tissues become incapable of responding to that antigen.**
- **B cells express high levels of Fas and are killed by FasL-expressing T cells.**

Peripheral B cell tolerance could happen through engagement of Treg cells (they control all immune cells even B cells) these T cells that express CTLA-4 can make engagement → suppression for B cells.

TOLERANCE TO COMMENSAL MICROBES AND FETAL ANTIGENS

With everything we said there are some exceptions, everything is telling you that this is non-self, but the body interacts with it as a self 😱:

• Commensal Microbes(microbiome)reside in the intestinal and respiratory tracts and on the skin, where they serve many essential functions. Mature lymphocytes in these tissues are capable of recognizing the organisms but do not react against them, so the microbes are not eliminated, and harmful inflammation is not triggered.

Some Explanation:

1- inappropriate antigen presentation, why? No one knows 😮 .example: if common pathogen has to react with TLR-2 these microbiomes interact with TLR-5. (Example)

2- They measure the concentration of Treg cells in the intestine and it was high.

3- IL-10, TGF-β, IL-35 concentration is high also

• Paternal antigens expressed in the fetus, which are foreign to the mother, have to be tolerated by the immune system of the pregnant mother.

Some Explanation:

1- The uterus excludes inflammatory cells that are coming from the fetus.

2- Placenta makes inappropriate antigen presentation.

3- Treg cells are found in the uterus.

نقطة بخصوص الموضوع ابيض واسود

- If I inject you with a certain antigen, it will make a certain response, the same antigen but I asked u to drink it, it will not produce any immune response.
- A lot of things play role like natural of the antigen, route of administration, things associated with environment, virulence factor, host…

AUTOIMMUNITY

All this self and non-self-discrimination is called Tolerance, but failure to do so will lead to autoimmunity/hypersensitivity.

• Autoimmunity is defined as an immune response against self (autologous) antigens.

• It is an important cause of disease, estimated to affect 2% to 5% of the population in developed countries, and the prevalence of several autoimmune diseases is increasing.

In developed countries it is higher than in developing countries, why? One of the reasons is hygiene theory.

In developing countries, we are exposed to large number of antigens during the maturation of our immune system while this is not happening in developed countries.

Most of the people affected is women, why? Due to hormonal differences like: progesterone.

• Different autoimmune diseases may be organ-specific, affecting only one or a few organs, or systemic, with widespread tissue injury and clinical manifestations.

• Tissue injury in autoimmune diseases may be caused by antibodies against self-antigens or by T cells reactive with self-antigens.

The majority could be antibody mediated or T cell mediated autoimmune disease.

• A cautionary note is that in many cases, diseases associated with uncontrolled immune responses are called autoimmune without formal evidence that the responses are directed against self antigens.

A lot of diseases cause collateral damage with it because of the inflammation that is happening in response to a pathogen disease, but that doesn't mean this is autoimmune disease.

Autoimmunity is multifactorial, it is not specified with one factor. Factors can include the host, certain polymorphisms, mutations in genes, environmental factors, and infections. For example: SLE can happen in pregnant women (because of progesterone levels) or Sun exposure or even people who take procainamide (cause epitope spreading).

PATHOGENESIS

polymorphism in HLA genes:

• The principal factors in the development of autoimmunity are the inheritance of susceptibility genes and environmental triggers, such as infections .

• Inherited risk for most autoimmune diseases is attributable to multiple gene loci, of which the largest contribution is made by MHC genes.

People who have certain alleles are more prone to develop those autoimmune diseases in comparison with healthy individuals that do not carry those alleles.

MHC=HLA= human leukocyte antigen

In the first example people who have HLA-B27 are ninety time more prone to develop Ankylosing spondylitis in comparison with healthy individuals that do not carry the same allele.

But that doesn't mean that everybody who has this allele will have Ankylosing spondylitis as well as not everybody who has Ankylosing spondylitis will have this allele

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

Relative risk comparison between people who have this allele or not
It is not a causation relationship it is an association relationship.

polymorphism in non- HLA genes:

• Polymorphisms in non-HLA genes are associated with various autoimmune diseases and may contribute to failure of self-tolerance or abnormal activation of lymphocytes.

- In proteins that are associated with innate immune receptors.
- Associated with different autoimmune diseases

RA = Rheumatoid Arthritis

SLE = Systemic Lupus Erythematosus /T1D = Type 1 Diabetes /IBD = Inflammatory Bowel Disease /PS = Psoriasis /MS = multiple sclerosis

ROLES OF NON-MHC GENES IN AUTOIMMUNITY

This is a single gene defect not polymorphism, this enough to cause disease or syndrome.

Mendelian inheritance could be Dominant, Recessive or X-linked.

A

Genes that may contribute to genetically complex autoimmune diseases		
Gene(s)	Disease association	Mechanism
PTPN22	RA, several others SLE and T1D	Abnormal tyrosine phosphatase regulation of T cell selection and activation? During the lymphocyte development
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

ROLE OF INFECTIONS AND OTHER ENVIRONMENTAL INFLUENCES

B

Single-gene defects that cause autoimmunity (mendelian diseases)		
Gene(s)	Disease association	Mechanism
AIRE Autosomal Recessive	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	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

• 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.

Infection develops autoimmune diseases in two ways:

ROLE OF INFECTIONS

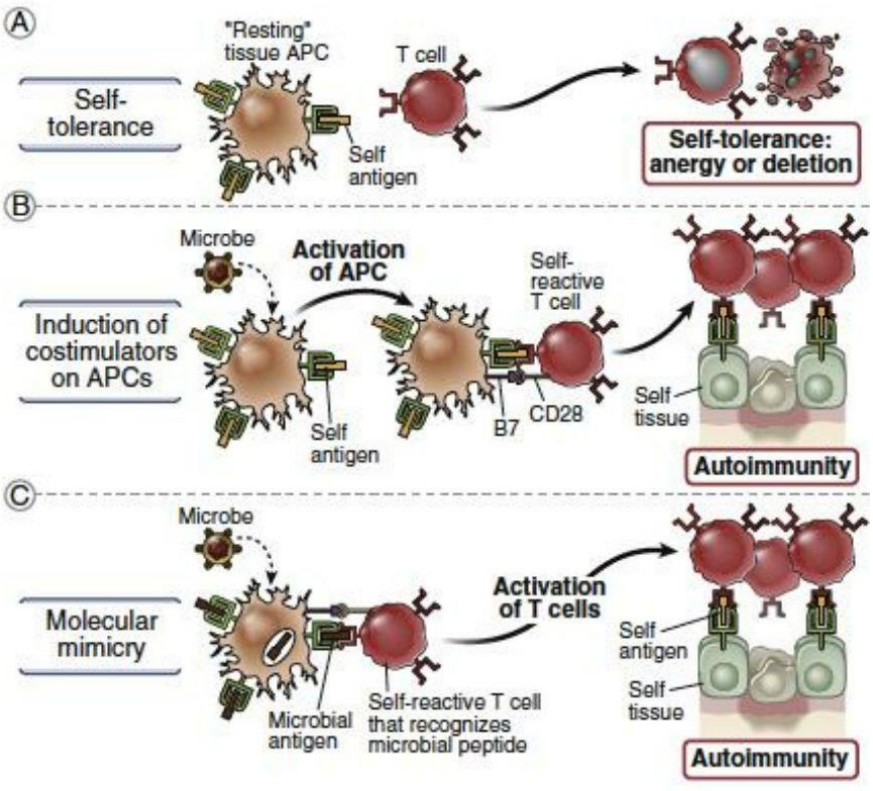
• An infection of a tissue may induce a local innate immune response, which may lead to increased production of co-stimulators and cytokines by tissue APCs. These activated tissue APCs may be able to stimulate self-reactive T cells that encounter self-antigens in the tissue. In other words, infection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

A- no costimulatory signals → anergy or deletion
B- if I have infection → innate immune response → more expression of costimulatory molecule if it was constitutively / expression of costimulatory molecules if it was transiently.
the cell that was non-reactive here it will be self-reactive.

C- Molecular mimicry: well documented in rheumatic



fever, bacteria called (group A streptococcus (GAS), Streptococcus pyogenes, strep throat, all the same my friend) cause pharyngitis in children (abrupt sore throat)

After child get affected with it there is virulence factor called M protein(this protein has more than 100 serotype) and it is highly variable بضل يتغير

After this abrupt onset of sore throat (like 2-3 weeks) our immune system starts to see similar structure of self-proteins like M proteins and starts to attack it. مفكرها الثاني يسعد مساه

Where are these similar proteins found? Heart(causing Myocarditis), synovial joint (polyarthritis), Brain(chorea)

This disease is called "rheumatic fever type 2 hypersensitivity antibody mediated."

This is called molecular mimicry because they are like each other, it starts to attack them.

تم بحمد الله تعالى