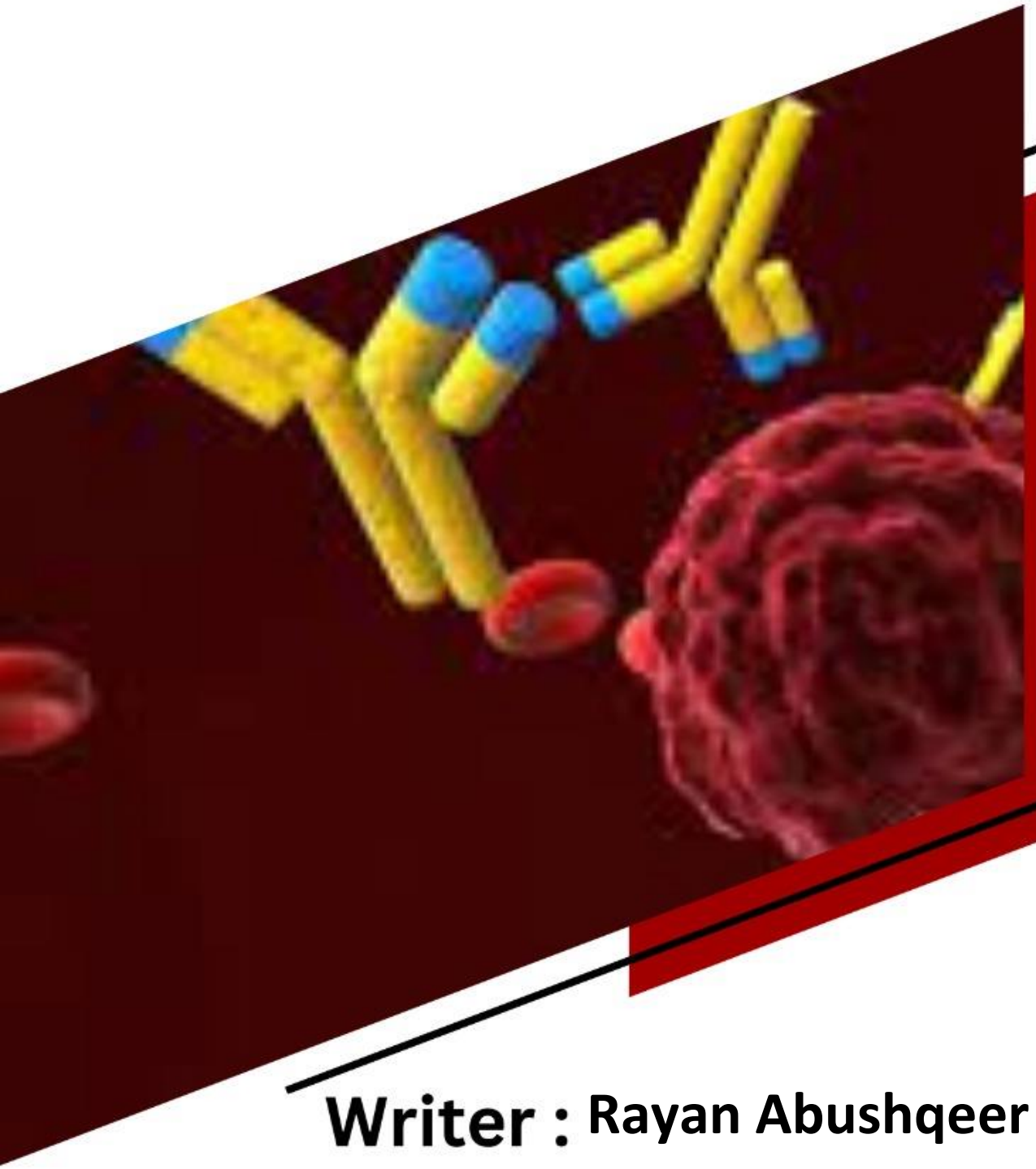
Doctor 021

IMMUNOLOGY

Sheet no. 17



Writer : Rayan Abushqeer

Corrector : Leen abu alreesh

Doctor : Nader Alaridah

IMMUNOLOGICAL TOLERANCE & AUTOIMMUNITY.

Overview:

* Immunological tolerance represents the ability of the immune system to discriminate between self & non-self-antigens.

* The failure of self-antigen tolerance results in immune reactions against self-antigen, (this reactions are called autoimmunity, which leads to autoimmunity diseases).

IMMUNOLOGICAL TOLERANCE

* Immunological tolerance: is a lack of response to antigens that is induced by exposure of lymphocytes to these antigens (meaning that the lymphocytes recognize the antigen but don't initiate any immune response).

* When lymphocytes encounter antigens, they may be:

① activated, leading to an immune response

↪ Antigens that elicit such a response are said to be Immunogenic

② functionally inactivated (anergy) or deleted by apoptosis or surpassed, leading to Tolerance.

↪ Antigens that induce tolerance are said to be tolerogenic

③ in some situations, the 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. it can occur if the antigen:

~ is found in very low quantities

~ is found in Immune Privileged Sites (such as brain, testes, eyes)

NOTE: there are many factors that determine whether the antigen is tolerogenic or immunogenic
For example some antigens could be both tolerogenic & immunogenic depending on:
1- The dose of the antigen
2- Route of administration (for example if we are dealing with vaccines).

* The importance of immunological tolerance:

1) First, self-antigens normally induce tolerance, and failure of self-tolerance is the underlying cause of autoimmune diseases.

2) 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.

~ treat allergic & autoimmune diseases.

~ prevent rejection of organ transplants.

~ prevent immune responses against the products of newly expressed genes or vectors & for stem cell transplantation if the stem donor is genetically different from the recipient.

NOTE: usually we give the patients immunosuppressive drugs if transplantation occurs.

TOLERANCE TYPES

Note: here we are concerned with self-tolerance

*** There are 2 types of tolerance:**

1) Central Tolerance. **2) Peripheral Tolerance.**

Central Tolerance:

*** Occurs in the *central (generative) lymphoid organs*, the bone marrow & thymus.**

↪ **Remember: they are considered sterile sites (meaning that they don't have foreign antigens, only self-antigens)**

*** It is induced when developing lymphocytes encounter the self-antigens during their maturation generative lymphoid organs (meaning that it occurs at the level of *immature lymphocytes*).**

↪ **Remember: that we have positive & negative selection.**

*** As we mentioned, in central lymphoid organs there are only self-antigens, so if the lymphocytes recognize the antigen with high affinity & avidity, this will lead to:**

1) Cell death/deletion by apoptosis (intrinsically or extrinsically)

↪ **Could happen for both B & T lymphocytes.**

2) or Replacement of a self-reactive antigen receptor with a new one (changing the specificity).

↪ **Only for B-cells.**

3) or Development of regulatory T-lymphocytes

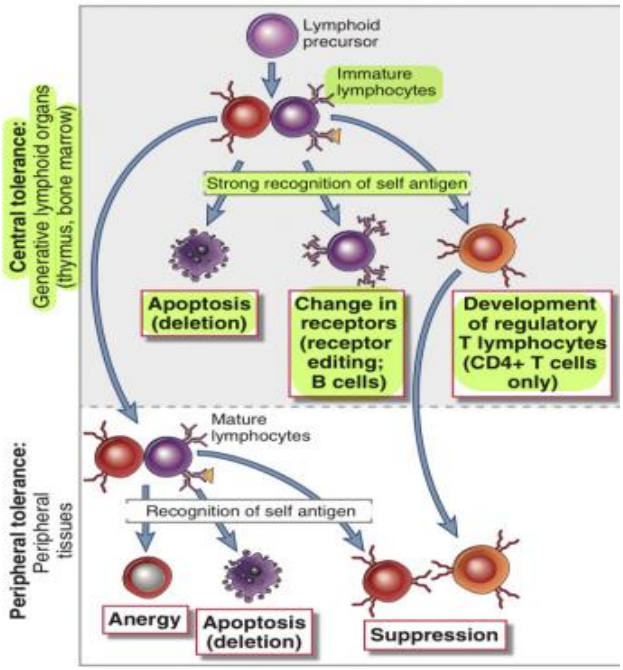
↪ **Only for CD4+ T-cells in the thymus.**

NOTEs:

~ regulatory T-cells (the master regulator of the immune system)

can act on CD4+, NKs, B-cell .

~ regulatory T-cells markers: *1) CD25. 2) transcriptional factor called (FOXP3).*



Peripheral Tolerance:

*** Occurs in the peripheral (secondary) lymphoid organs, the lymph nodes & spleen**

*** Occurs when mature lymphocytes encounter self-antigen in the peripheral(secondary) lymphoid organs.**

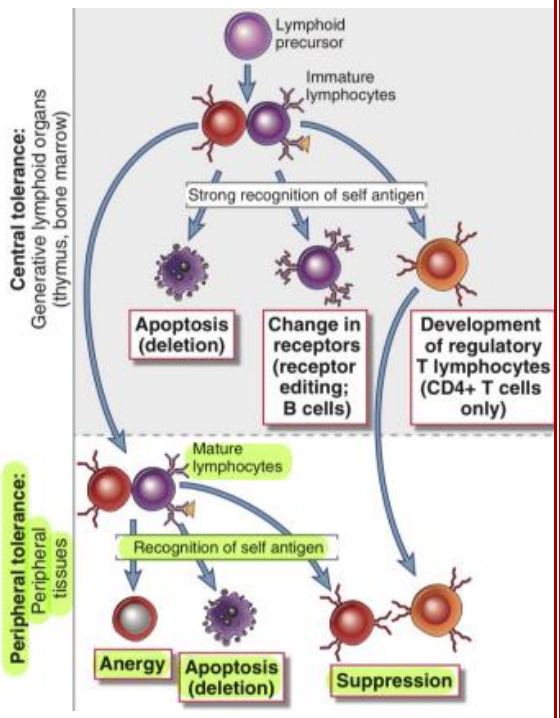
* The recognition of self-antigen leads to:

1) Cell death/deletion by apoptosis (intrinsically or extrinsically)

2) functional unresponsiveness (**anergy**)

↪ In this process, the self-reactive cells do not die but become unresponsive to the antigen

3) Suppression by regulatory T-cells



CENTRAL IMMATURET-LYMPHOCYTES TOLERANCE

*** Again, it occurs at the level of immature T-lymphocytes (specifically double positive & single positive) during their maturation in the thymus.**

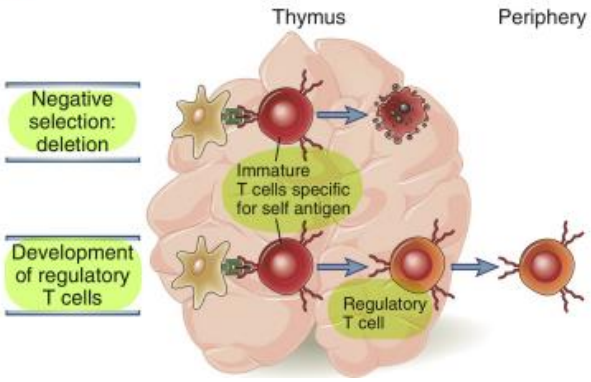
*** Here the antigens are expressed on MHC molecules on thymic-antigen presenting cells. Therefore this process affects both CD4+ & CD8+ lymphocytes.**

* The principles mechanisms of central tolerance in T-lymphocytes are:

1) Death of immature T-cells (negative selection/clonal deletion)
2) or Generation of CD4+ regulatory T cells

↳ regulatory T-cell properties:

1- high expression of FOXP3 as well as CD25
2- secrete IL-10 & TGF-β



*** Immature lymphocytes may interact strongly with an antigen if:**

~ the antigen is present at high concentrations in the thymus.

~ and the lymphocytes express receptors that recognize the antigen with high affinity.

↳ leading to one of the above mechanisms

*** Antigens that induce negative selection may include proteins that are abundant throughout the body, such as plasma proteins and common cellular proteins.**

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

↳ (thymus ال مسؤول انه يعرضها داخل AIRE protein ، periphery ال البعيدة الموجودة في antigns ال)

PERIPHERAL MATURE T-LYMPHOCYTES TOLERANCE

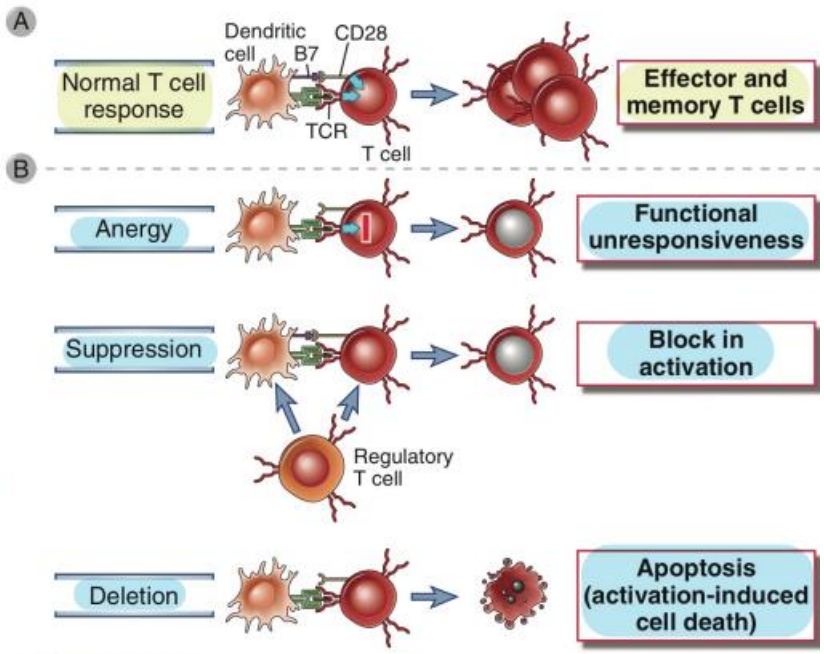
*** Occurs at the level of mature T-lymphocyte when they recognize self-antigens in peripheral tissues & this antigen recognition occurs without adequate co-stimulation, leading to functional inactivation (anergy) or death, or when the self-reactive lymphocytes are suppressed by regulatory T cells.**

* Here the antigen are presented on APCs (mostly dendritic cells)

* Remember, for normal T cell activation, we need 2 signals:

1) the recognition of antigen by the TCR (which provides signal 1)

2) recognition of costimulators, mainly B7-1, by CD28 (signal 2)



* But in peripheral T-lymphocyte tolerance, the principle mechanisms that occur are:

1) functional inactivation (anergy)
2) or death by apoptosis (activates the CASPASEs)
3) or makes self-reactive T cells sensitive to suppression by regulatory T cells

Now, we will talk about each one of them in more details:

Anergy

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

*** There 2 cases lead to Anergy:**

① When T cells recognize antigens without costimulation {signal 1 is exist only}, therefore the TCR complex may:

a) lose its ability to transmit activating signals → signaling blocks → functional inactivation.

b) in some cases activate enzymes called *ubiquitin ligase*, which modify signalling proteins associated with it (TCR complex) by ubiquinate them & target them for intracellular destruction by proteases

↪ modification = ubiquitation

purpose = to target these signalling proteins for proteasome

② When T-lymphocytes recognize self-antigens, they may preferentially engage one of the inhibitory receptors rather than the CD28 family (CD28 family is activating receptor & bind to B7) → leading to inhibition of T-cells → functional inactivation

Examples about inhibitory receptors:

1) Cytotoxic T-Lymphocyte associated Antigen 4 (CTLA-4, or CD152)

2) Programmed Death protein 1 (PD-1)

NOTE: these receptors are expressed on T-cells and bind to the costimulatory ligand (B7)

↪ More clarification:

~ CTLA-4 has a higher affinity than CD28 for B7 ligand, SO if B7 is expressed on the APCs in low levels, the CTLA-4 will bind rather than CD28

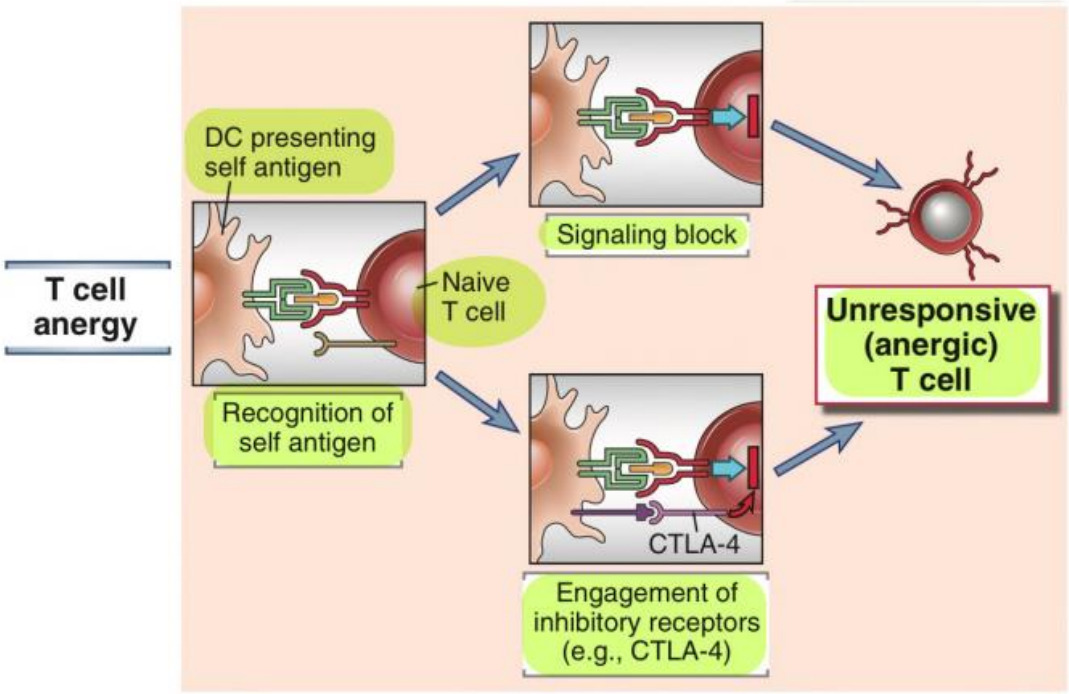
~ BUT, if there are high levels of B7 & above the threshold (as a result of inflammation, infection, danger), the CD28 will bind rather than CTLA-4

~ BUT remember here we are talking about self-antigens, which means they are not dangerous → lo levels of B7 → CTLA-4 bind → inhibition of T-cell

↪ again:

CD28 → activation of T-cell

CTLA-4 or PD-1 → inhibition of T-cell



NOTE: the anergy is a transient state & depends on the conditions that exist, meaning that the anergic T cells could return self-reactive.

REGULATION OF T CELL RESPONSES BY INHIBITORY RECEPTORS:

*** CTLA-4 is expressed transiently on activated CD4+ T cells and constitutively on regulatory T cells.**

*** It functions:**

1) to terminate activation of responding T cells

2) 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 costimulation 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 (notice that the name is programmed death protein, but actually its function is inhibitory & not apoptotic signaling)**

*** 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* mainly in the thymus & some in peripheral lymphoid organs due to recognition of self-antigens & *suppress* the activation of potentially harmful lymphocytes specific for these self-antigens.**

*** Most regulatory T cells:**

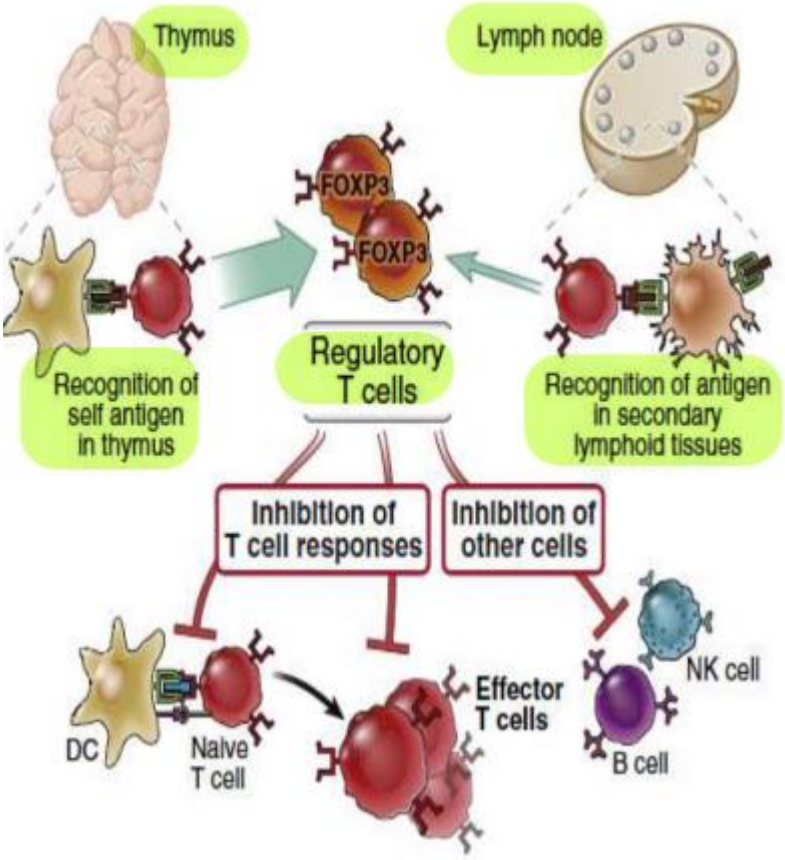
~ are CD4+

~ express high levels of CD25 (Interleukin-2 receptor α chain (IL-2Rα))

~ express a transcription factor called FoxP3

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

NOTE: IL-2 is also needed in T-lymphocyte activation



* REGULATORY T CELLS SUPPRESS IMMUNE RESPONSES BY SEVERAL MECHANISMS:

① Some regulatory cells produce cytokines (e.g., IL-10, TGF-β) that inhibit the activation of lymphocytes, dendritic cells, and macrophages.

② Regulatory cells express CTLA-4, which, may block or remove B7 molecules made by APCs and make these APCs incapable of providing costimulation via CD28 and activating T cells

③ 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.

↪ notice that the IL-2 has dual role:

~ activation of T-lymphocytes

~ suppression of responding T-lymphocytes during its consumption by regulatory T-cells

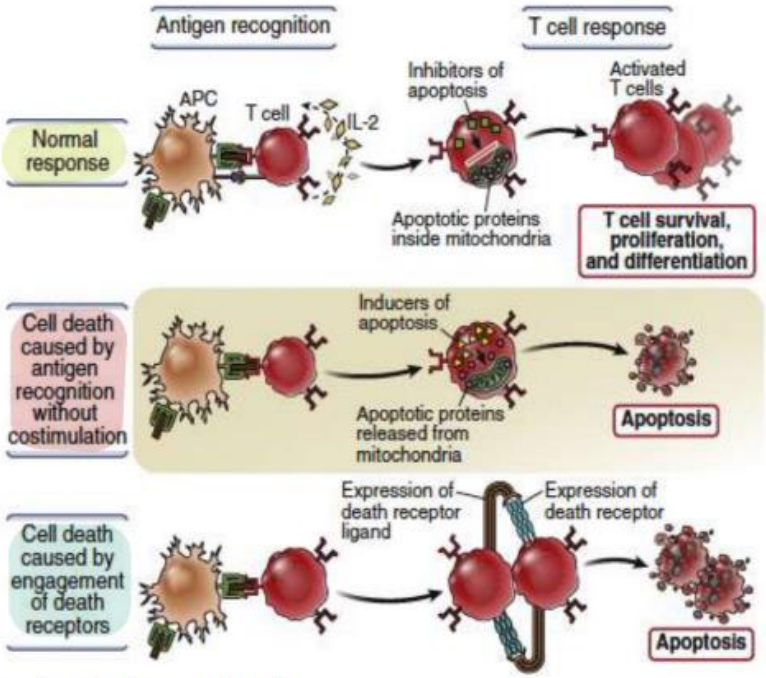
DELETION: APOPTOSIS OF MATURE LYMPHOCYTES

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

* Apoptosis could be intrinsic & extrinsic

* In normal response we have:
- APC that presents the antigen on MHC molecule
- T-cell binds the antigen by TRC (signal 1)
- B7-CD28 interaction (signal 2)
- IL-2 is abundant

all these lead to cell activation → proliferation → differentiation into effector & memory T cell



NOTE: all the time, there are in the T-cell pro-apoptotic & anti-apoptotic molecules (the difference in their synthesis cause different response)

↪ more anti-apoptotic → activation
more pro-apoptotic → death

* In apoptosis, we have 2 pathways:

① Intrinsic pathway happens when there's an imbalance between pro-apoptotic (BAK and BAX) and anti- apoptotic (Bcl-2 and Bcl-XL) proteins

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

NOTE: absence of signal 2 (costimulation) is the stimulator for the production of pro-apoptotic molecules.

② Extrinsic pathway , happens when Fas ligand bind to Fas Receptor (on the apoptotic cell)

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).

Now, let's talk about B-cells Tolerance:

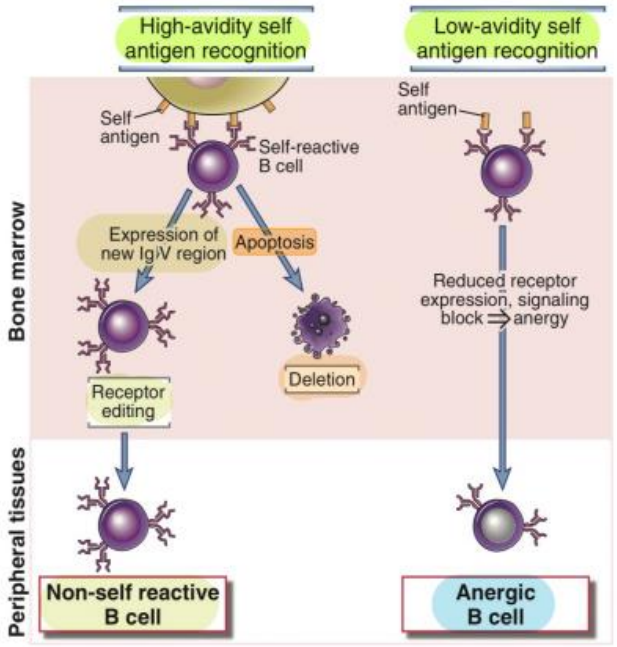
CENTRAL TOLERANCE IN IMMATURE B LYMPHOCYTES

* 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)

1) Receptor editing:

Some immature B cells that recognize self antigens in the bone marrow may reexpress RAG genes (RAG-1 & RAG-2), resume immunoglobulin (Ig) light-chain gene recombination, and express a new Ig light chain (if it was kappa, it is converted to lambda & vice versa)

↪ This new light chain associates with the previously expressed Ig heavy chain (notice that we don't do isotype switching) to produce a new antigen receptor that may no longer be specific for the self antigen



2) 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

3) 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)

NOTE: B-cell tolerance is more far from perfect as most autoimmune diseases are related to antibodies.

PERIPHERAL TOLERANCE IN MMATURE B LYMPHOCYTES

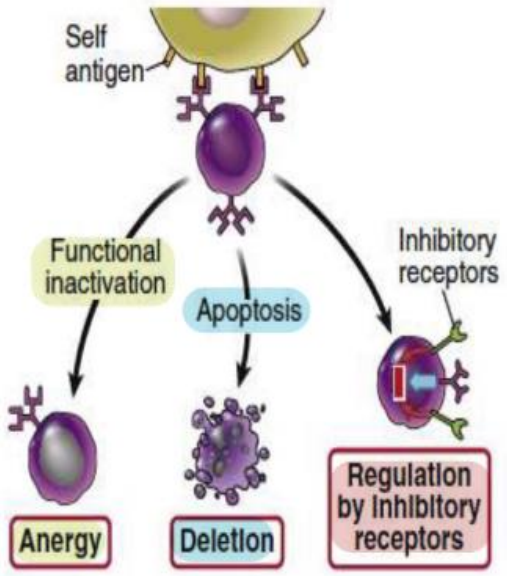
*** Mature B lymphocytes that encounter self-antigens in peripheral lymphoid tissues become incapable of responding to that antigen by:**

1) Anergy:
~ remember that it depends on the costimulatory signals

2) Apoptosis (extrinsic or intrinsic)
~ but it mainly extrinsic in B-cells
because ↪ B cells express high levels of Fas (when they don't sense danger) and are killed by FasL-expressing T cells

3) Suppression by regulatory T-cell

NOTE: the doctor did not talk about the inhibitory receptors



TOLERANCE TO COMMENSAL MICROBES AND FETAL ANTIGENS

*** Commensal Microbes:**

~ 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

~ There are many theories explain why, some of them:

1) Physical barrier (epithelial barrier is found between them & immune circulation)

2) The presence of high numbers of T-regulatory cells i the intestines

3) High levels of IL-10 in the intestines

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

↪ the recurrent abortions could be caused by the abnormal immune response to the fetus antigens

AUTOIMMUNITY

* Autoimmunity is defined as an immune response against self (autologous) antigens (failure of self-tolerance)

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

* It is an important cause of autoimmune diseases, estimated to affect 2% to 5% of the population in developed countries

↪ the prevalence of several autoimmune diseases is increasing (as a result of our life style & also Hygiene theory could explain this increasing)

* Different autoimmune diseases may be:

1) organ-specific, affecting only one or a few organs

2) or systemic, with widespread tissue injury and clinical manifestations

* A cautionary note: in many cases, diseases associated with ***uncontrolled*** immune responses (sometimes, infections lead to exaggerated responses that cause collateral damage) are called autoimmune without formal evidence that the responses are directed against self-antigens

↪ so you should differentiate between the uncontrolled immune & autoimmune disease (uncontrolled immune response is not an autoimmune disease)

↪ uncontrolled → non-self antigen
autoimmune → self-antigen

PATHOGENESIS

* Autoimmunity is a multifactorial process (meaning that depends on many factors)

The principal factors in the development of autoimmunity are:

1) The inheritance of susceptibility genes (Genetic factors)

2) Environmental triggers, such as infections (Environmental factors)

Roles of the Genetic factors

* Inherited risk for most autoimmune diseases is attributable to multiple gene loci, of which the largest contribution is made by MHC genes (but it could be non-MHC genes)

* Roles of MHC genes in autoimmunity (mostly is MHC2):

~ Notice that the presence of the gene only increases the risk and not necessarily means the presence of the disease (we call this: **genetic predisposition**)

~ MHC molecules are encoded by HLA gene

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

~ Type 1 diabetes: antibodies as well as auto reactive T-cells attack the Langerhans cells found in the pancreas

~ Pemphigus vulgaris: it is a skin disease characterized by chronic recurrent bluster formation (because the patients develop antibodies against Desmosomes (type of the tight junction in the epithelium).

*** Roles of non-MHC genes in autoimmunity:**

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

~ They are not strong as the polymorphism in MHC genes.

Protein tyrosine phosphatases non-receptor type (PTPN) → Rheumatoid Arthritis (RA)

Nucleotide oligomerization domain (NOD) → Crohn's disease

AS: ankylosing spondylitis

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

~ CTLA-4 are the checkpoint

~ Autosomal dominance means that 1 allele is enough to cause the disease

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

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.

There are some other factors that trigger autoimmune diseases such as: exposure to sunlight is a trigger for patients with SLE disease (systemic lupus erythematosus) or some drugs such as procainamide that cause spreading of antigens or introducing new antigen (the body recognize self-antigen as foreign antigen) which lead to immune response.

*the majority of autoimmune diseases occur in females, we still don't know why, but it is thought that hormonal effect(estrogen, progesterone) is the reason ,but there's still no valid evidence why AI chance in women is higher.(بتزيد احتمالية الاصابة كمان وقت الحمل)

ROLE OF INFECTIONS

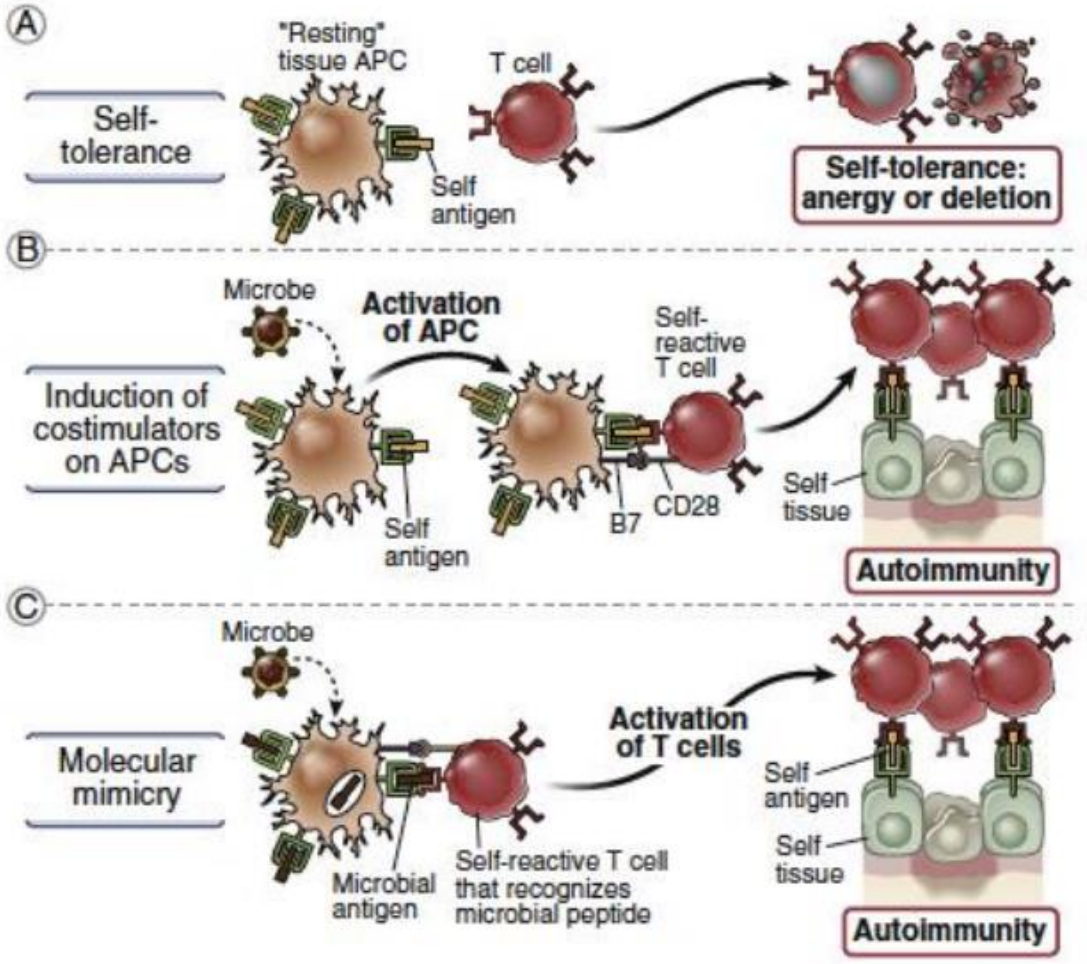
• An infection of a tissue may induce a local innate immune response, which may lead to increased production of co-stimulators and cytokines by tissue APCs. These activated tissue APCs may be able to stimulate self-reactive T cells that encounter self-antigens in the tissue. In other words, infection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

Explanation of the role of tissue infection: if a microbe (bacteria, virus) caused inflammation there will be higher expression of B7, therefore there'll be higher probability of B7 engagement with CD28 thus, strengthen the co-stimulatory signal resulting in more activation of self-reactive T cells which become more reactant to self-antigens.

• 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.

Example of molecular mimicry: infection caused by –group A beta hemolytic streptococci- which causes pharyngitis , people who get this infection will recover in few days ,but 2 weeks after the recovery they may develop rheumatic fever(why? Because this bacteria has a protein called M protein which looks a lot like myosin in cardiac muscle so after the immune response against M protein from the streptococci, antibodies will start attacking cardiac muscle resulting in rheumatic fever).

MECHANISMS BY WHICH MICROBES MAY PROMOTE AUTOIMMUNITY.



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