MED439
KING SAUD UNIVERSITY

Mechanisms of autoimmunity

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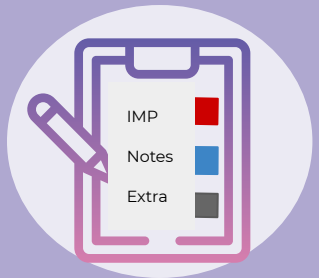
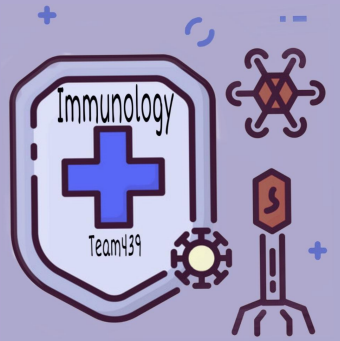




Objectives

1- Autoimmunity results from activation of immune response against self antigens.

2- To learn how immunological tolerance (central and peripheral) is induced against self antigens for maintaining normal health.

3- To gain understanding of various factors contributing to the breakdown of immunological tolerance and development of autoimmunity.

4- Gender predilection in autoimmunity is a well-known phenomenon and is briefly described.

The original lecture has too many pictures without explanation
So we apologize if our notes were a lot.

Tolerance

Immune system has evolved to discriminate *differentiate* between
Self and Non-self By
" immunological TOLERANCE":
Unresponsiveness to an self-antigen.
So Body tolerated **not** to do immune response against self-antigen.

"Clonal" because lymphocytes get activated and start to proliferate so deletion will be for almost a colony

Self Tolerance is **acquired by:**

1 A) Deletion (clonal deletion)
Able to delete itself (bad guys are deleted)

2 B) Functional inactivation (clonal **anergy**).

Loss of function or "Freeze" > cannot kill or delete self antigen.

Anergy:
absence of an immune response to an antigen.

Applied to developing lymphocytes that posses antigenic receptors with high affinity for self-antigen.
Notice antigenic receptor >if it high affinity to self antigen > applies one of self tolerance (delete or inactivate)

Lymphocytes يشيك فيها على سلامة Checkpoints التولرنس عنده نفس
Secondary ومره في Primary lymphoid organs مره تكون في

Self tolerance:

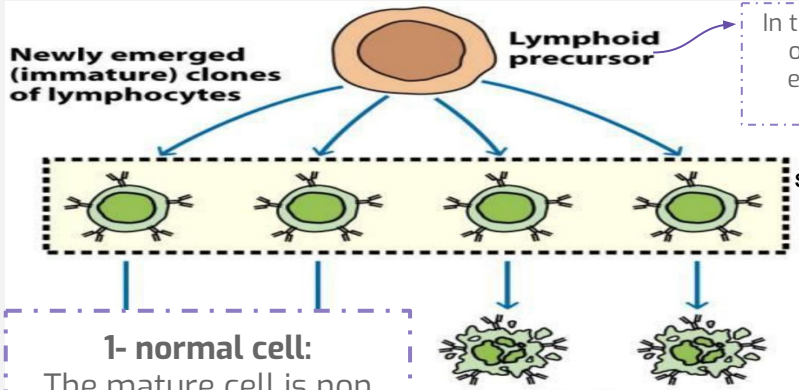
Central tolerance

Peripheral tolerance
Next slide

1- Central tolerance mechanism

Occur in:
primary (generative) lymphoid organs
Thymus & Bone marrow.

we have lymphoid precursor which will differentiate into either T or B cell After differentiation there are 2 possibilities :



1- normal cell:
The mature cell is non specific for self antigens (Educated cell) -i.e **it does not attack self antigens**- it will be allowed to leave the bone marrow or thymus.

2- abnormal cell:
The mature cell is specific for self antigens (Autoreactive cell) -i.e **it will attack self antigens**- it won't be allowed to leave, and the cell will undergo **apoptosis (clonal deletion).**

Self tolerance

Central tolerance

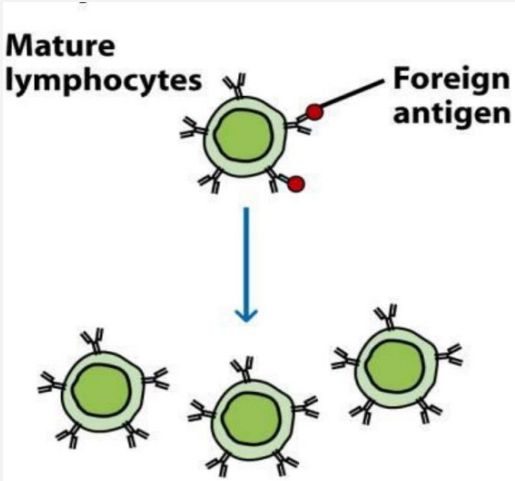
Peripheral tolerance

2-peripheral tolerance mechanism

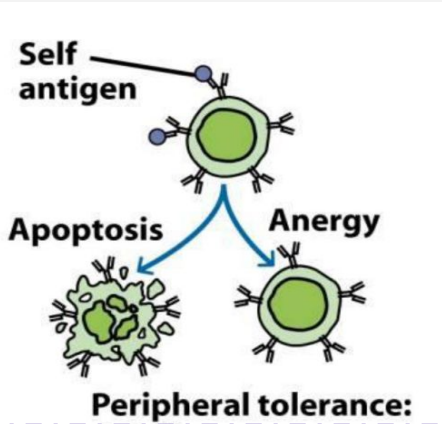
Occur in secondary lymphoid organs
it's the second checkpoint after central tolerance, so its involve deleting or anergic for **escaped autoreactive** lymphocytes.

Note:
Central tolerance by:
deletion only.

Peripheral tolerance by:
(deletion or Anergy)



-Normal mature lymphocyte will conduct an immune response when binding to foreign antigen.



Peripheral tolerance:

-Abnormal mature lymphocyte which recognize self-antigens will undergo **apoptosis (clonal deletion) or functional inactivation (clonal anergy)** when binding to self-antigen.

Peripheral Tolerance of T Lymphocytes (Anergy)

Anergy:The deactivation of an autoreactive T-cell

Binding of MHC class II located on the surface of an APC to TCR (T-cell receptor) on T-cell.

1st signal

(**Co**stimulatory signal): Binding of B7 located on APC with CD28 on T-cell.

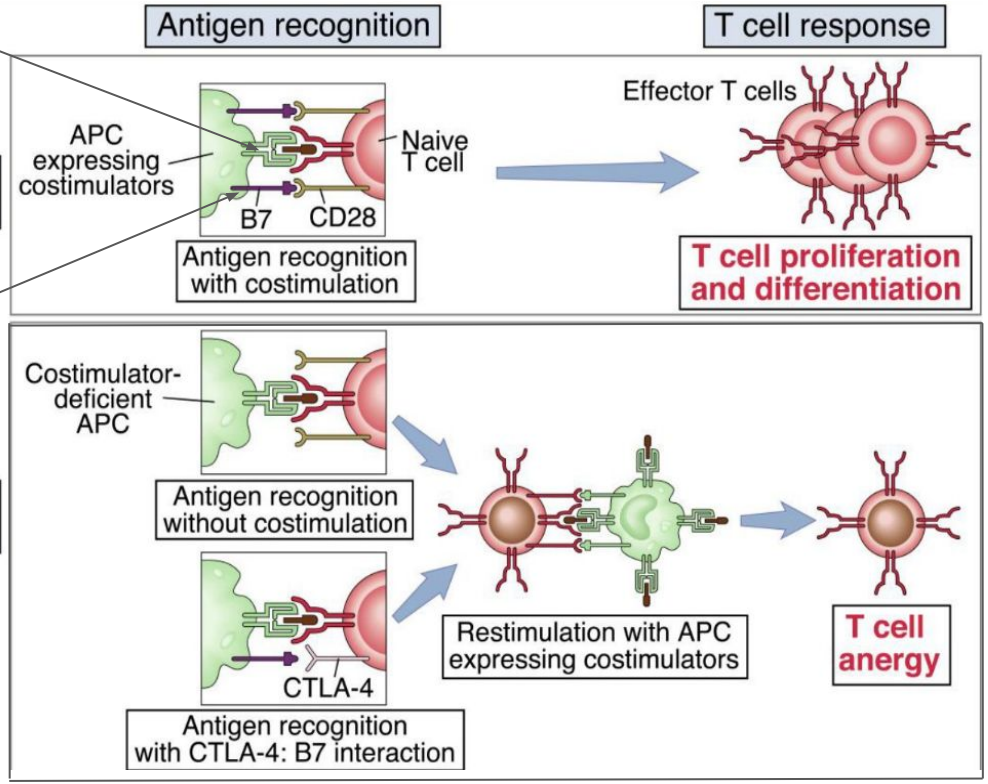
2nd signal

Normal response

Clonal anergy

The first signal is present but it get deactivated because the second signal:
Either lack of CD28+B7
Or CTLA-4+B7 binding
CTLA-4:inhibits T-cell.

that results in inactivating T-cell or as called “clonal anergy”



What happens in SELF TOLERANCE failure ?

Autoimmunity

Auto: self Immunity: immune response

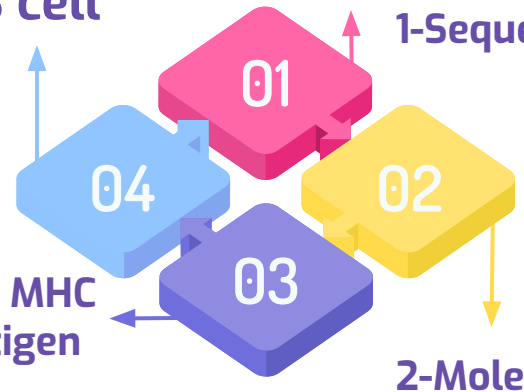
In **autoimmunity** the immune system mistakenly attacks and destroys healthy body tissue. this attack is Mediated by auto-reactive T cells and auto-reactive B cells that produces (auto-antibodies).

*attack Non-self is the desirable response, Attack self antigen is autoimmune response.

*Autoimmunity is strongly associated with hypersensitive Type 2 and Type 3.

discriminating between Self and Non-self antigens is one of the major criteria in adaptive immunity.
These lymphocyte called auto-reactive which mean: A lymphocyte that reacts with autoantigens.

Induction of autoimmunity



1-Sequestered antigens

2-Molecular mimicry

3-Inappropriate class II MHC expression on non-antigen presenting cells

4-Polyclonal B cell activation

1. Sequestered antigens

major development is from birth till 1 year old

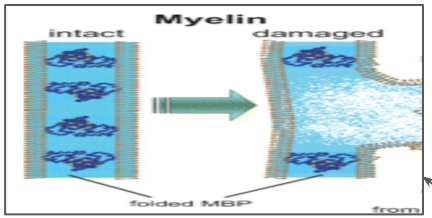
خلال تطور جهاز المناعة وتعرفه على الجسم يكون فيه اماكن في الجسم ما يقدر يدخلها وبالتالي ال antigens داخل هذه الاماكن ما تكون ضمن قائمة ال antigens اللي اعتبرها الجهاز جزء من الجسم, بالتالي عند حدوث trauma او عملية جراحية او اي شيء يؤدي الى خروج هذه ال antigens من المناطق اللي ما تعرف عليها الجهاز وترتبط ب lymphocyte فهي ما راح تسوي self-tolerance بل يعتبرها جسم غريب ويهاجمها **مع إنها جزء من الجسم.**

- Some self-antigens are sequestered (hidden) in specialized tissues.
- These are not seen by the developing immune system, thus it will not induce self- tolerance.
- Exposure of T cells to these normally sequestered tissue-specific self-antigens in the periphery results in their activation.

01 Heart muscle antigens following myocardial infarction.

Sperm-associated antigens in some individuals following vasectomy*. 02

03 Lens and corneal proteins of the eye following infection or trauma. (explained next slide).



Myelin basic protein (MBP) associated with MS** 04

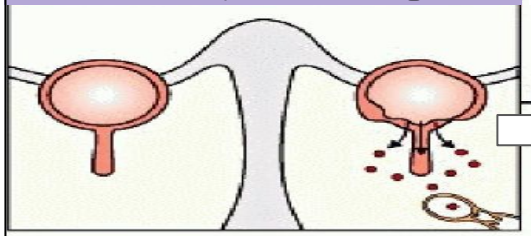
*vasectomy: the surgical cutting and sealing of part of each vas deferens, typically as a means of sterilization.

**MS stands for Multiple sclerosis.

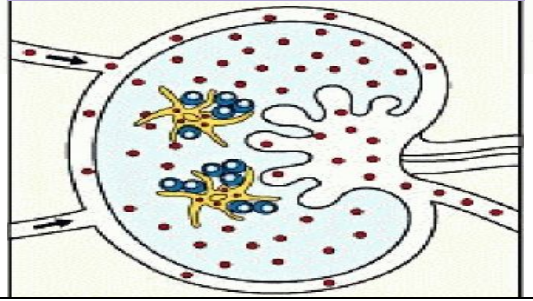
Cont.

Sympathetic ophthalmia

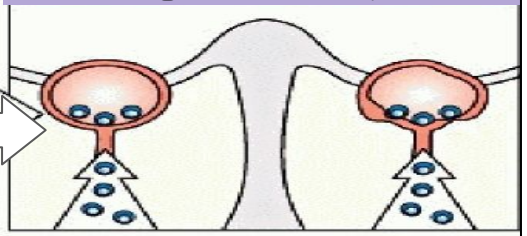
Trauma to one eye results in the release of sequestered intraocular protein antigens.



Released intraocular antigen is carried to lymph nodes by dendritic cells and presented to T-cells to be activated.



Effector T cells return via bloodstream and encounter antigen in both eyes.



2. Molecular Mimicry (Cross-reacting Antigens)

- Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components. (so T cell will think that the normal antigen is foreign body "cross react" ! Then will destroy it).

- This phenomenon, known as molecular mimicry, occurs in a wide variety of organisms.

- Molecular mimicry may be the initiating step in a variety of autoimmune diseases.

So here we see that each infectious organism shares one of the human host proteins in the sequence
E.g Poliovirus VP2 (S T T K E S R G T T)
Acetylcholine receptor (T V I K E S R G T K)

MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K

3. Inappropriate Expression of Class II MHC Molecules

- Class II MHC ordinarily expressed on antigen presenting cells, such as macrophages, dendritic cells and B cells. *MCH II is exclusive for APC.

- Abnormal expression of MHC determinants allows the recognition of these auto-antigens by self-reactive T cells.

Normal condition: APCs phagocytose the foreign body > present the antigen on its surface for T-cells.
Autoimmune: Any cell that express MHC class II (except APCs) will present its antigens (which is considered part of the body) for the lymphocyte when it binds to it >> it will attack the cells.

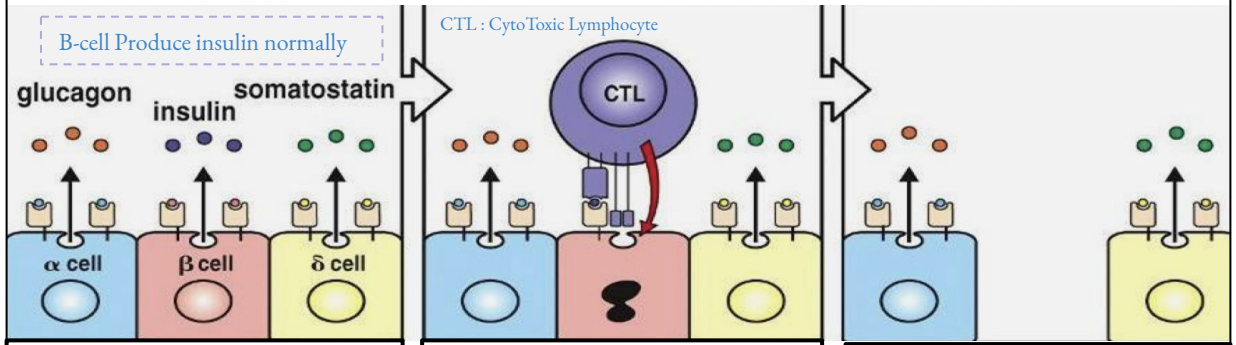
- This may occur due to the local production of IFN-γ, which is known to increase class II MHC expression on a variety of cells.

- The inducer of IFN-γ under these circumstances could be a viral infection.

3. Inappropriate Expression of Class II MHC Molecules

Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II

Dr's explanation:
1- B cell will be attached
2- express MHC II, because it's nucleotide it already has MHC I
3- by CTL , T helper 1 (recognize self antigen), interact with B cell that was exposed by MCH I&II
4-attacked by lymphocytes and abortion for the B cell functions

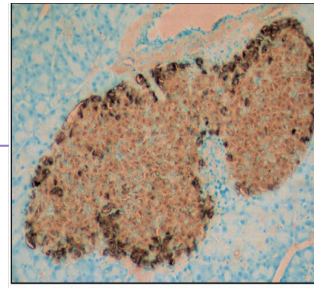


The islets of langerhans:* Group of pancreatic cells secreting insulin and glucagon* contain several cell types secreting distinct hormones. Each cell expresses different tissue specific proteins

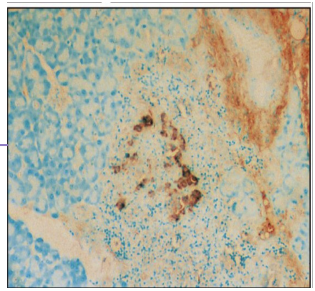
In insulin-dependent diabetes an effector T cell recognizes peptides from a **β** cell-specific and kills the **β** cell.

Glucagon and somatostatin are still produced by ***α*** cell and ***γ*** Cell respectfully , will continue being produced,this leads to type I diabetes.

Normal pancreas



Pancreas with insulitis (destruction by T cell)



4. Polyclonal B Cell Activation

1

Viruses and bacteria induce nonspecific polyclonal B cell activation, <u>including:</u>

-Certain gram negative bacteria
-Herpes simplex virus.
-Epstein Barr Virus
-Cytomegalovirus
-HIV

Able to activate large amount of B cells (to become plasma cell then produce antibodies).

2

These viruses and bacteria induce the proliferation of numerous clones of B cells to secrete IgM in the absence of a requirement for CD4 T cell help.

3

Polyclonal activation leads to the activation of self-reactive B cells and **autoantibody production.**

4

Patients with infectious mononucleosis (caused by EBV) and AIDS (HIV) have a variety of auto-antibodies

hormonal factors

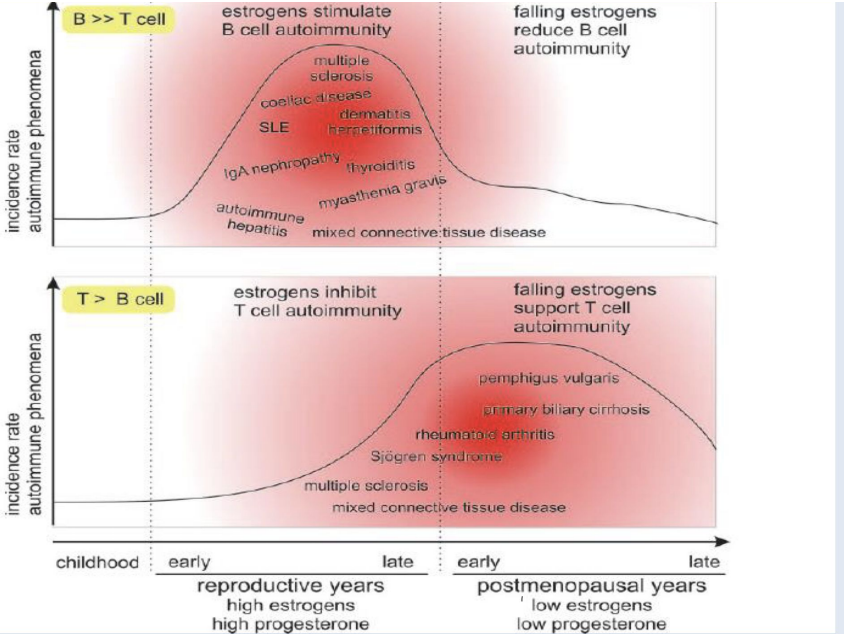
In animal models estrogen can induce B cells to enhance formation of anti-DNA antibodies.

- About 90% of autoimmune diseases occur in women – cause not known-.

- High estrogen levels (pre-menopause):
  - Stimulate **B-cell** autoimmunity (e.g higher chance to appear or exacerbate SLE*during pregnancy when the estrogen level is high).
  - Inhibit T-cell autoimmunity.

- Low estrogen levels (post-menopause):
  - Inhibit B-cell autoimmunity.
  - Stimulate **T-cell** autoimmunity (e.g. higher chance to get rheumatoid arthritis).

SLE: Systemic lupus erythematosus (مرض الذئبة الحمراء)



-Diabetes occurs more in male than female .
-Both males and females have the same chance to develop (Ulcerative colitis)

Drug Induced Lupus Erythematosus

This was found in boys slides only

Induced drugs :

Lupus erythematosus like syndrome develops inpatients receiving a variety of drugs such as:

- Hydralazine (used for hypertension)
- Procainamide (antiarrhythmic)
- Isoniazid
  - Used in cases of TB
- Penicillin (antibiotic)

Treatment

Immunological therapy

- Many are associated with the development of anti-nuclear antibodies (ANAs). (general Test)
  - ANAs are screening tools for autoimmunity.
- Renal and CNS involvement is uncommon.
- Anti-histone antibodies are frequently present in this condition.

Take Home Messages :

- Normal healthy state is maintained by immunological tolerance against self antigens at central and peripheral levels
- An Autoimmune diseases result from the breakdown of immunological tolerance to self antigens
- Certain autoimmune diseases exhibit strong association with female gender

Quiz

Q Bank Questions :

Question 1: the mature cell that is specific for self antigens is also called:
A- Educated cell. **B-** Agglutinogen **C-** Endothelial cell **D-** Autoreactive cell
Question 2: Which of the following mediates autoimmunity:
A- T-lymphocyte **B-** B-lymphocyte **C-** Autoantibody **D-** Neutrophils
Question 3: Which of the following induce nonspecific polyclonal b cell
A - Herpesvirus **B-** Adenovirus **C-** HBV **D-** Epstein Barr Virus
Question 4: Which of the following drugs is used to treat cardiac arrhythmias?
A - Penicillin **B-** Procaine **C-** Procainamide **D- Go Study Pharma!!!**
Question 5: Inappropriate expression on mhc occurs in
A - Dendritic Cells **B-** Macrophages **C-** Islet cells **D-** RBCs

1:D
2:C
3:D
4:C
5:C

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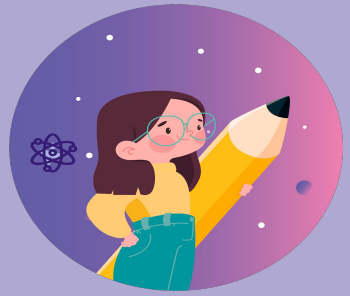

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editing file
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