# Mechanism of Autoimmunity

## Musculoskeletal block

First lecture

Brought to you by:

Bayan Al-Amr
Abrar Al-Faifi
Muath Alsabih

## Objectives:

- ☑ Autoimmunity results from activation of immune response against self-antigens.
- ☑ To learn how immunological tolerance (central and peripheral) is induced against self-antigens for maintaining normal health.
- ☑ To gain understanding of various factors contributing to the breakdown of immunological tolerance and development of autoimmunity.
- ☑ Gender predilection in autoimmunity is a well-known phenomenon and is briefly described.

## Note:

Black: Slides

Orange: Explanation

Purple: Extra

Red: Important

## Autoimmunity:

A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue.

هو مرض قصور خلايا الجهاز المناعي عن التعرف على خلايا الجسم فتهاجم خلايا وانسجة الجسم للجسم نفسه

In other words, it is the condition that occurs when immune system can't distinguish تمييز between self and non-self.

Remember the characteristics of adaptive immunity:
1-long term.
2-memory.
3- Specific ( can distinguish between self and non-self(foreign antigen) in order to protect the body).

Mediated by: 1- Auto reactive T-cells.
2-Auto reactive B-cells (Auto- antibodies).

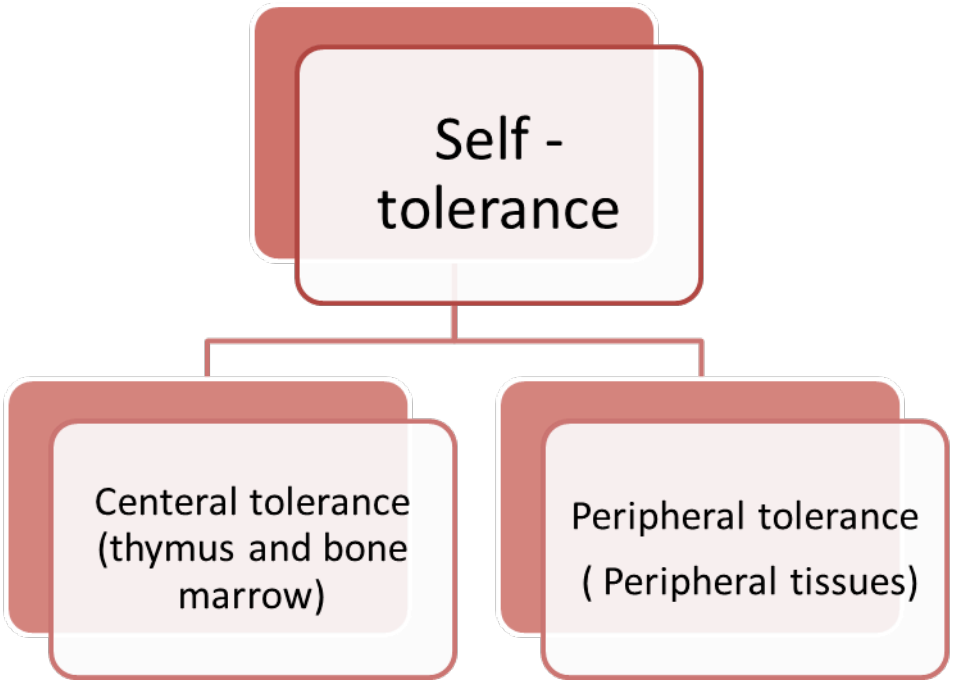
Tolerance: is the process by which the immune system does not attack an antigen.

## Tolerance to self is acquired by:

- Deletion (clonal deletion) within primary (central) lymphoid organs (bone marrow and thymus).

- Functional inactivation (clonal anergy) of developing lymphocytes that possess تملك antigenic receptors with high affinity for self-antigens. (Occurs when the auto reactive T-cells for example are capable of crossing the primary lymphoid organs).

Anergy = losing response



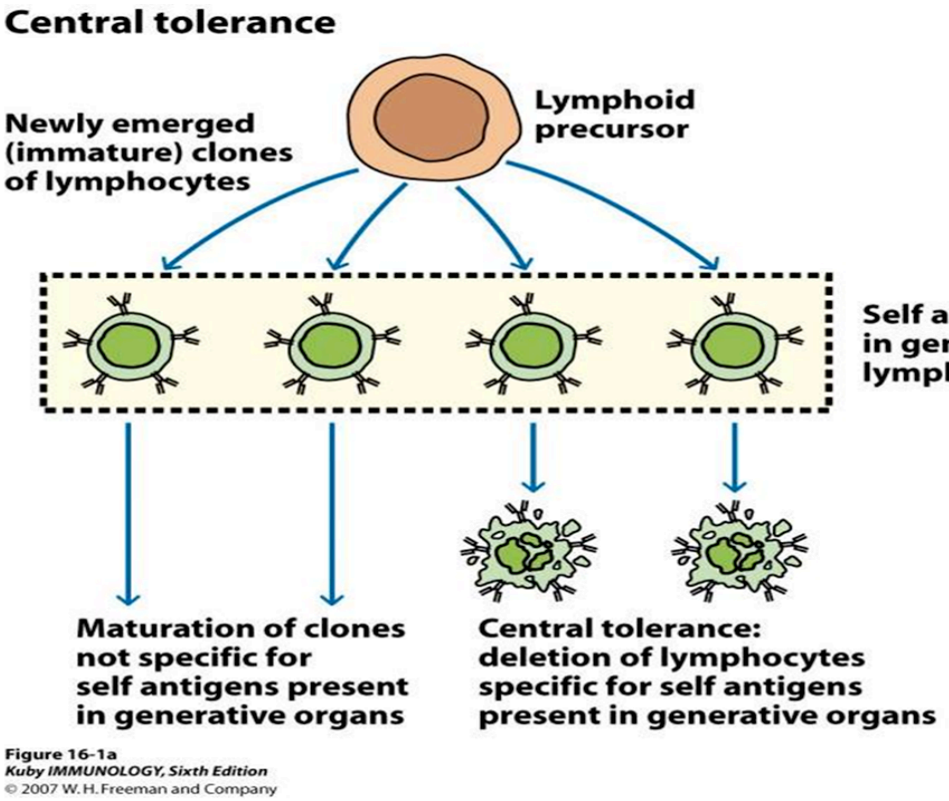
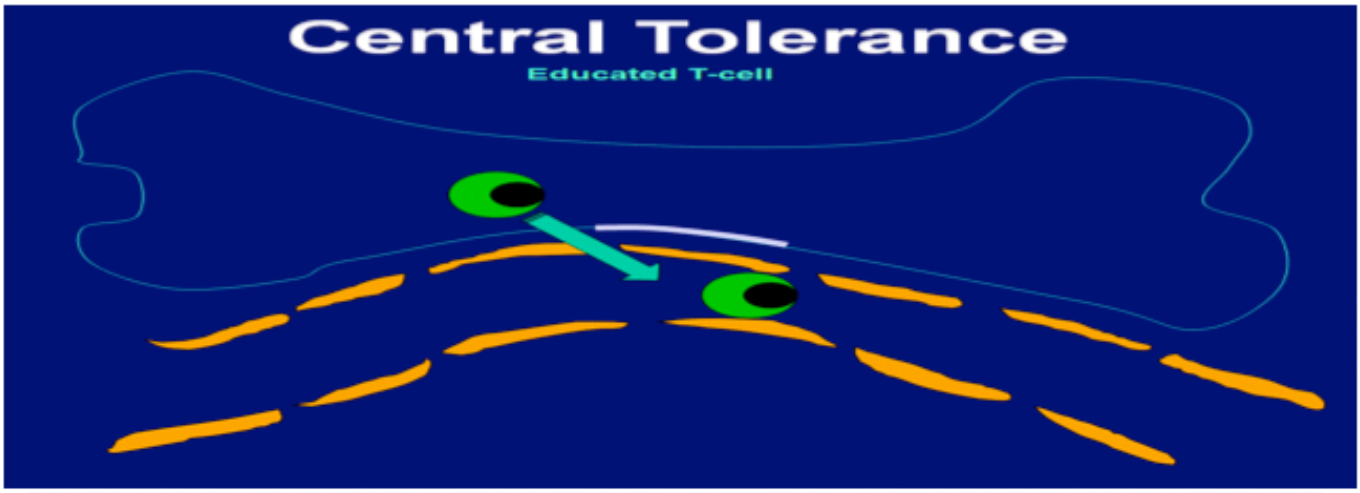




Figure 16-1a
*Kuby IMMUNOLOGY, Sixth Edition*


A case of autoimmunity where deletion (apoptosis) will happen within the primary lymphoid organs.

**Note**: there is no disease here, it is only a process showing how healthy immune system works against self-antigens.




This a cell that don't react with self- antigen. So , it will be allowed to pass through to the circulation to be mature and start functioning .


This cell has been react with self antigen .So, it will not be allowed to pass through to the circulation because if it's pass It will cause autoimmunity. So , it will be destroyed in the thymus or bone marrow.

Peripheral tolerance occurs when the cells (clones) exit from the primary lymphoid organs, due to a failure in the central tolerance.

So the cells will undergo apoptosis or anergy (which is like switching off the mature T-lymphocytes that recognize a self-antigen in a peripheral organ).

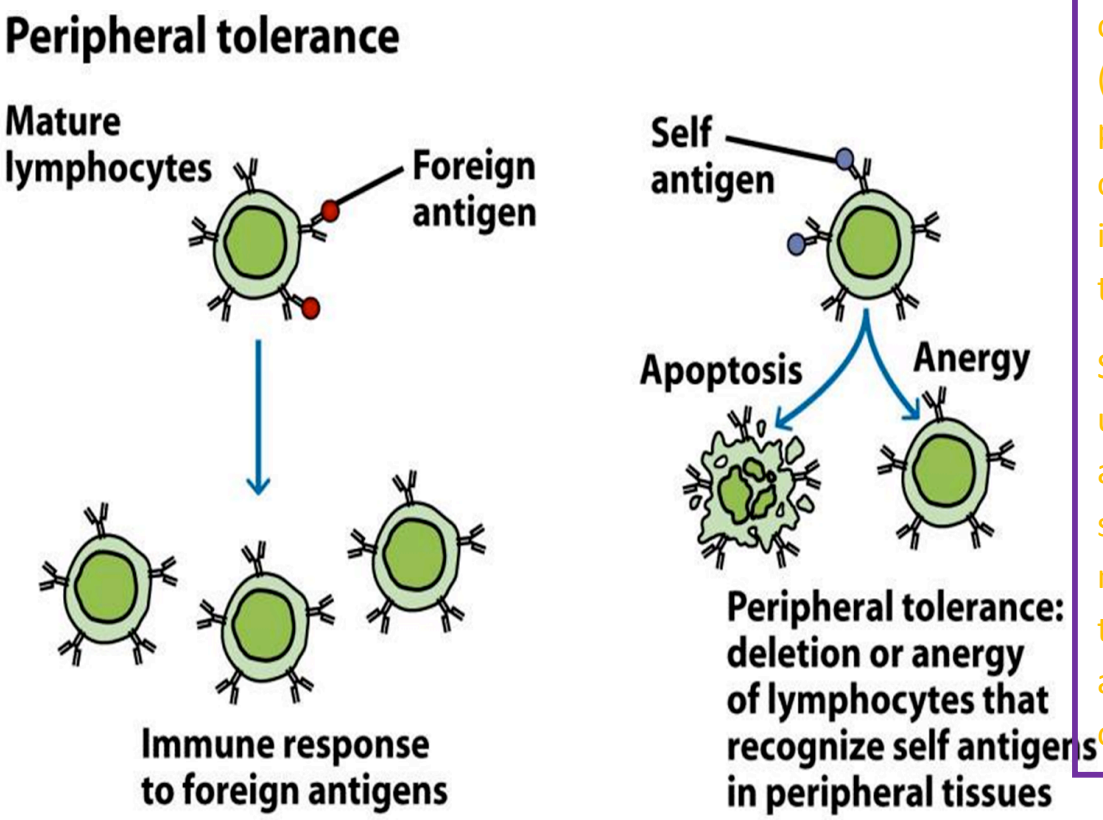
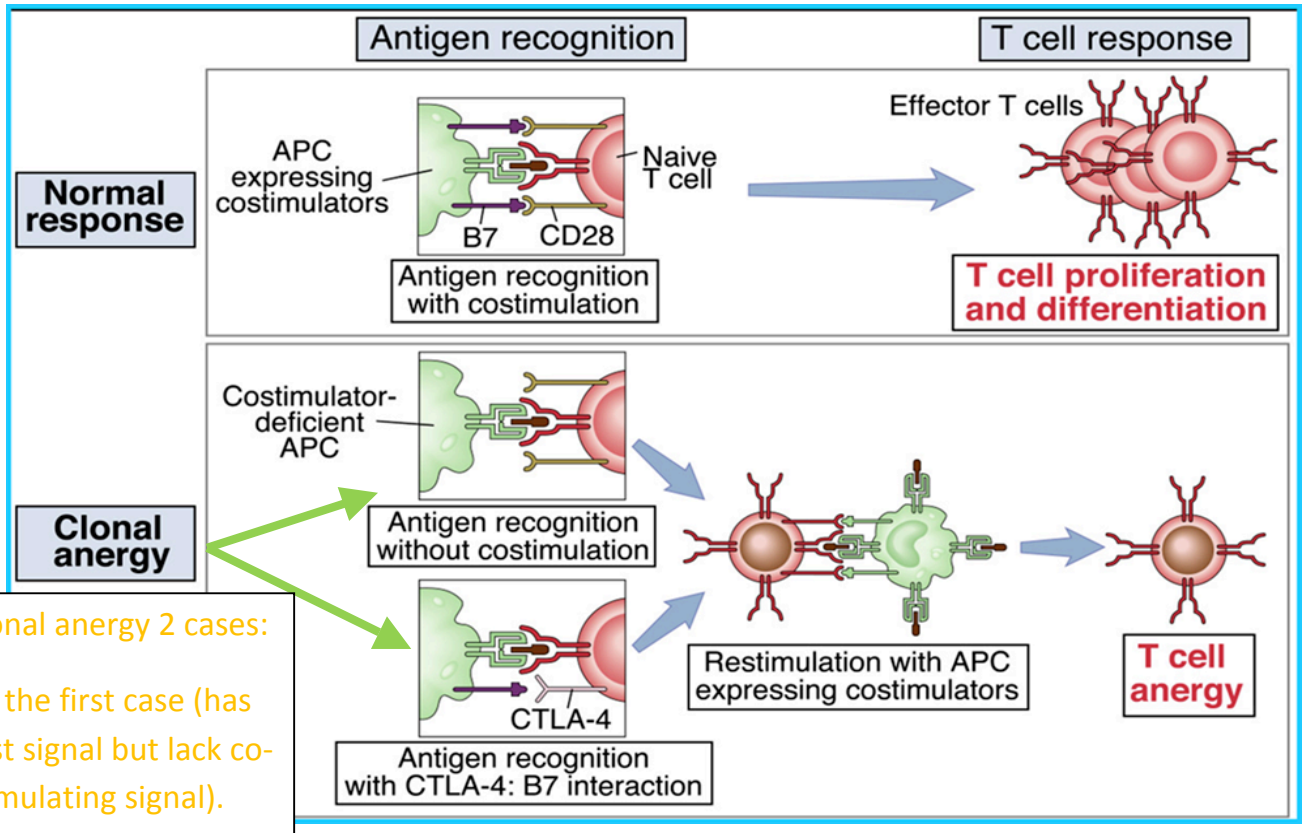
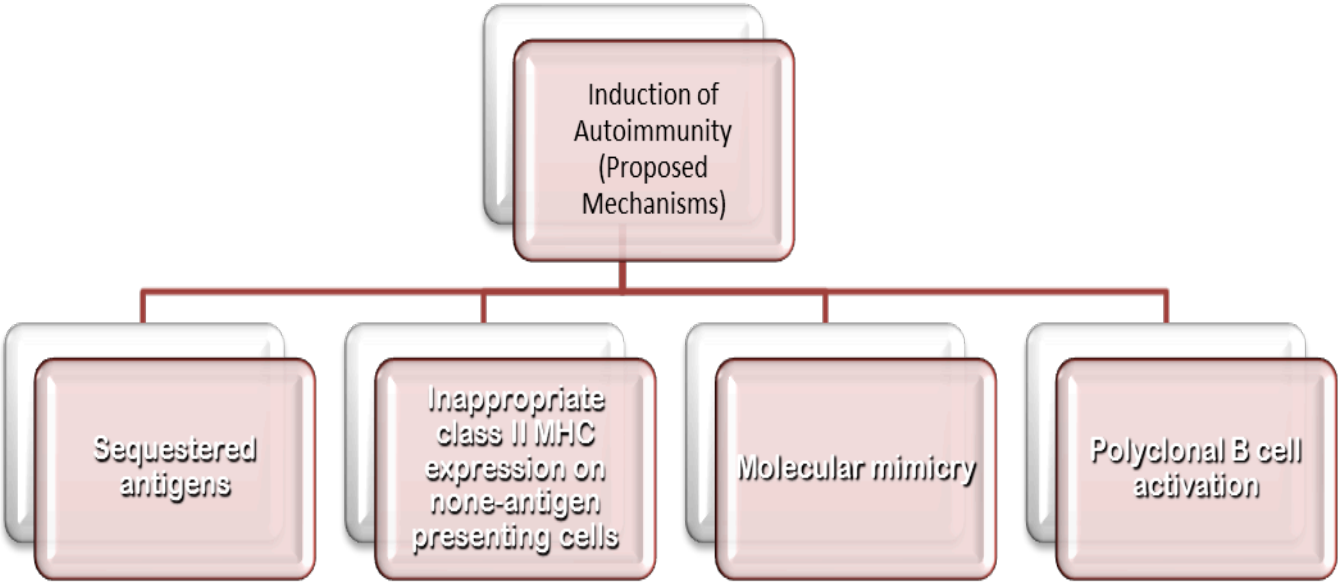



Figure 16-1b
*Kuby IMMUNOLOGY, Sixth Edition*

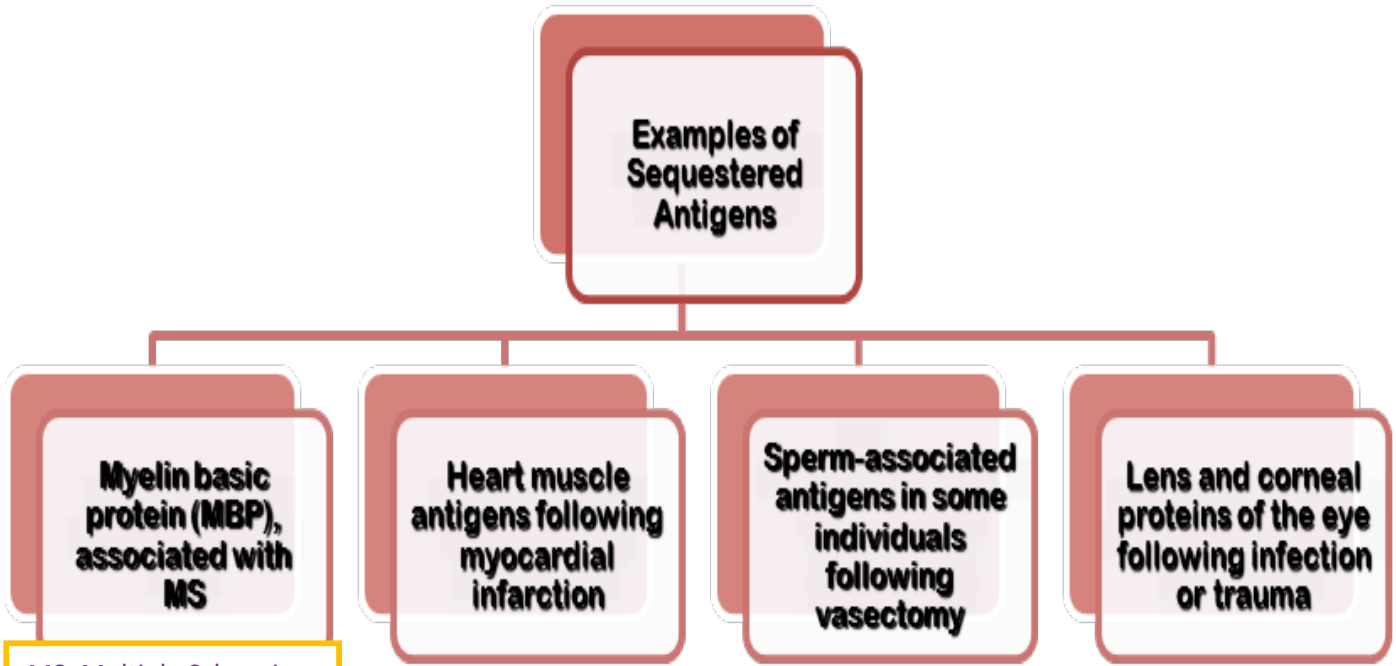

Clonal anergy 2 cases:

-In the first case (has first signal but lack co-stimulating signal).



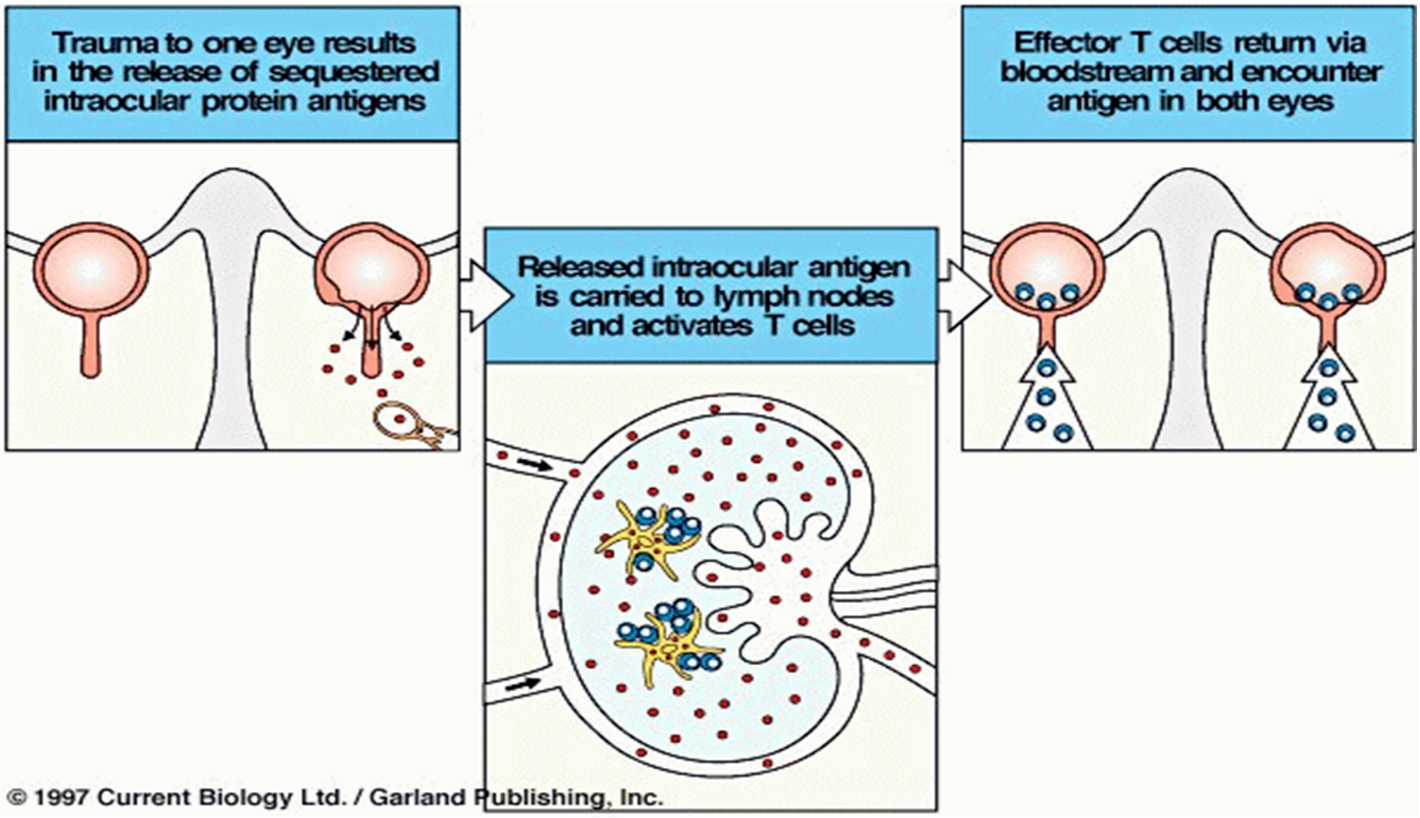

### 1- Sequestered antigens:

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




MS: Multiple Sclerosis (autoimmune disease of the nervous system.

## Sympathetic ophthalmia التهاب العينين




- 2- Molecular Mimicry (Cross-reacting Antigens):
  - Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components.
  - This phenomenon الظاهرة, known as molecular mimicry, occurs in a wide variety of organisms.
  - Molecular mimicry may be the initiating step in a variety of autoimmune diseases

**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 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 |
| Measles virus P3 | 31 | E I S D N L G Q E |
| Myelin basic protein | 61 | E I S F K L G Q E |

For example:

In the case of Rabies virus glycoprotein, my body is going to secrete antibodies or t-cells (according to the reaction) they are supposed to attack rabies virus but instead they **may attack** insulin receptor because of the similarity in the sequence of amino acids.

(This may occur but not always remember it is purpose mechanism)

### ○ 3- Inappropriate Expression of Class II MHC Molecules:

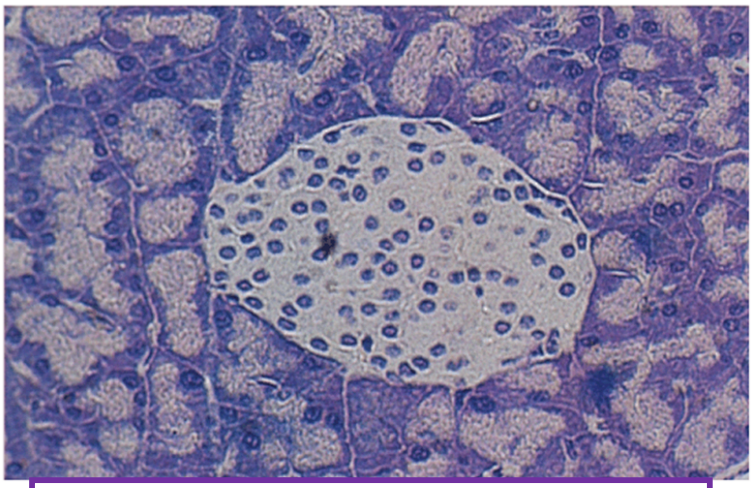
- Class II MHC ordinarily expressed on antigen presenting cells, such as macrophages, dendritic cells and B cells.
- Abnormal expression of MHC determinants allows the recognition of these auto-antigens by self-reactive T cells.
- This may occur due to the local production of IFN-gamma, which is known to increase class II MHC expression on a variety of cells.
- The inducer of IFN-gamma under these circumstances الظروف could be a viral infection.

- 4- Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II (?)

  MHC 1: expressed by nucleated cells. (In this case normal)

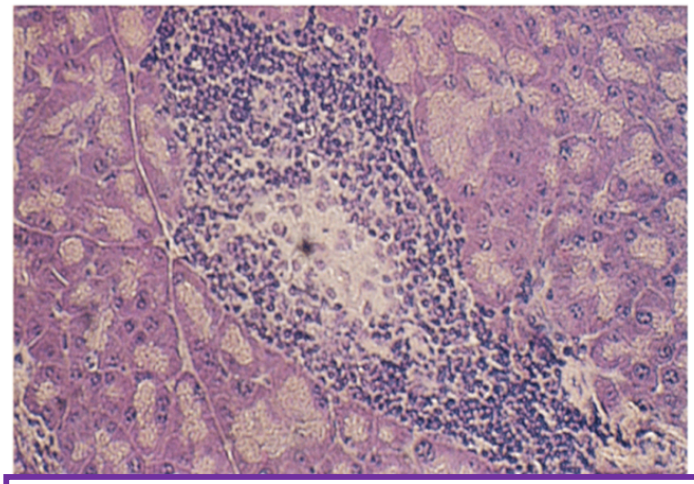
  MHC 2: expressed by APC. (In this case abnormal because beta cells are not antigen presenting cells).

(a)



MHC class one only (normal pancreas)

(b)



MHC Class 1 and MHC class 2 (pancreas with insulitis)

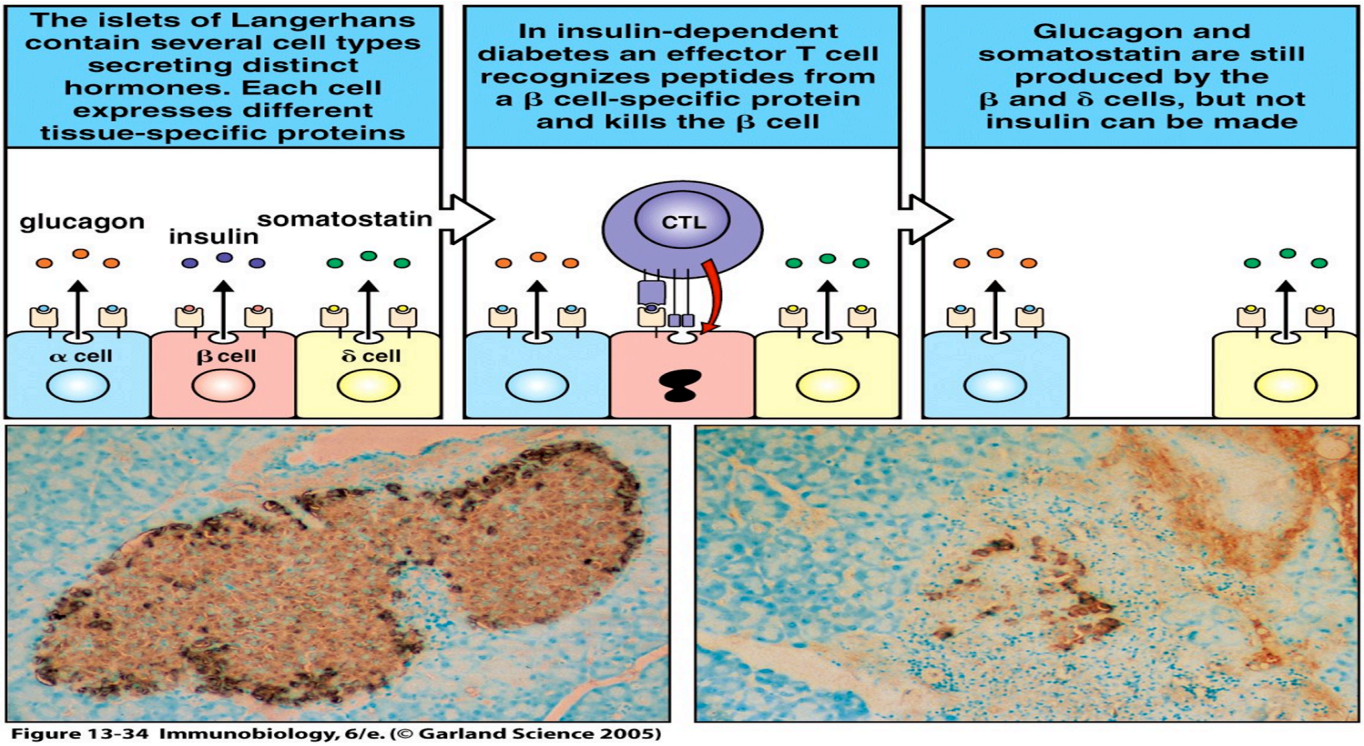



Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

- Polyclonal B Cell Activation:

• Viruses and bacteria can induce nonspecific polyclonal B cell activation, including:

- Certain gram negative bacteria
- Herpes simplex virus.
- Cytomegalovirus
- Epstein Barr Virus (EBV)
- Human immunodeficiency virus (HIV)

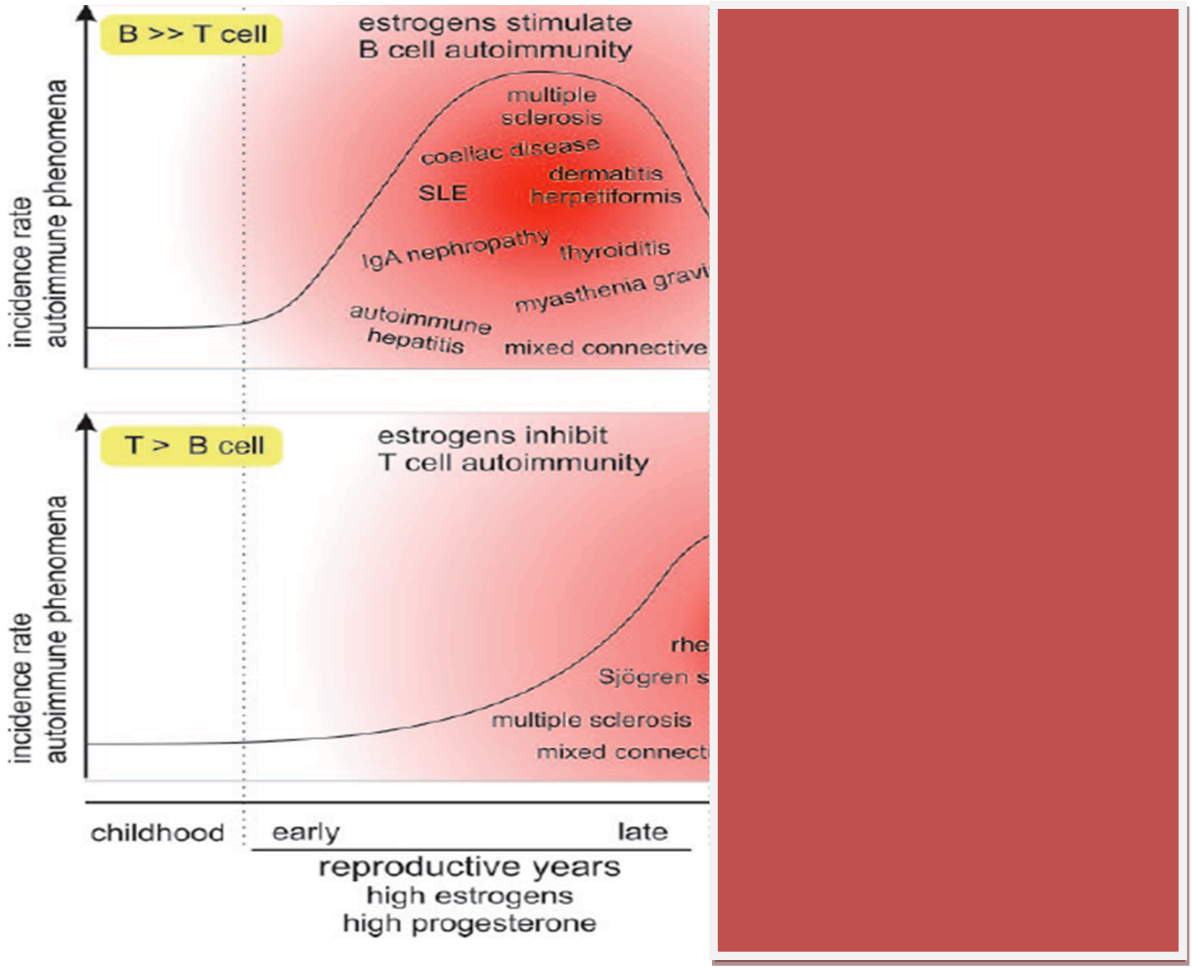
• These viruses induce the proliferation of numerous clones of B cells to secrete IgM in the absence of a requirement for CD4 T cell help.(Normally antibodies are secreted by the help of T-helper cells CD4).

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

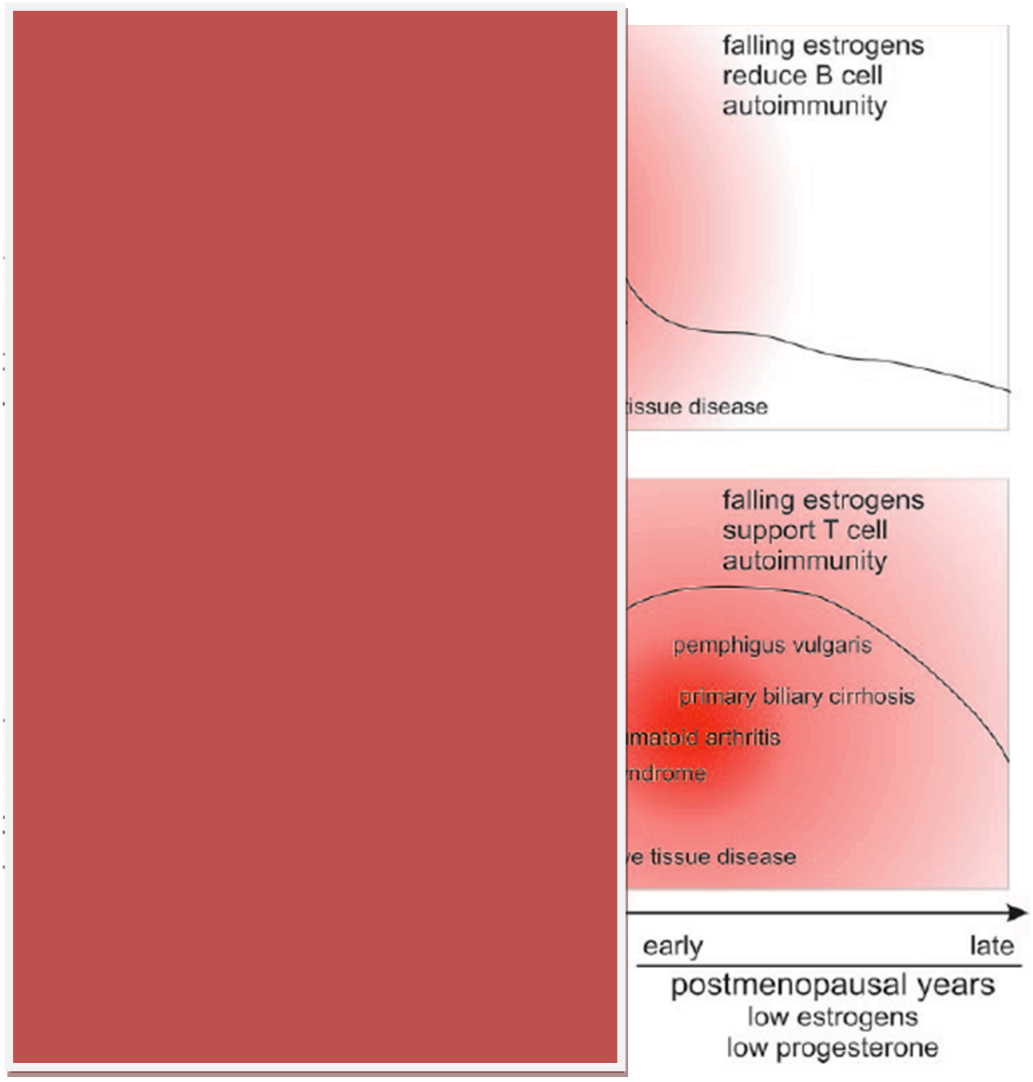
• Patients with infectious mononucleosis (caused by EBV) and AIDS (HIV) have a variety of auto-antibodies.

- Hormonal Factors:

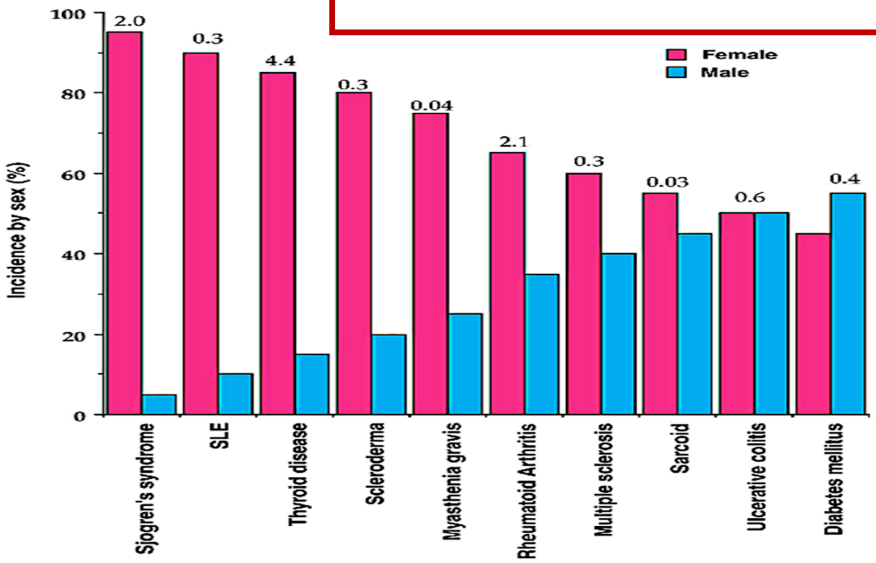
- About 90% of autoimmune diseases occur in women – cause not known.
- In animal models estrogen can induce B cells to enhance formation of anti-DNA antibodies.
- SLE either appears or exacerbates يتفاقم during pregnancy.




The production of estrogen will stimulate B cell autoimmunity and inhibits T cell autoimmunity.




Low estrogen will reduce B cell autoimmunity and support T cell autoimmunity.



- Drug Induced Lupus Erythematosus:

- Lupus erythematosus like syndrome develops inpatients المرضى المنومين receiving a variety of drugs such as
- Hydralazine (used for hypertension)
- Procainamide
- Isoniazid
- Penicillin
- Many are associated with the development of anti-nuclear antibodies (ANAs) they are used in laboratory to diagnose an immune disease (indicator in the circulation).
- Renal and CNS involvement is uncommon
- Anti-histone antibodies are frequently present

- Take home message:

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

لا تنسونا من دعواتكم