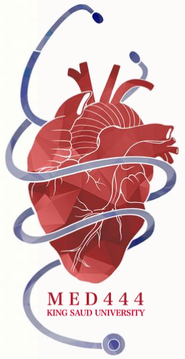







# Mechanisms of Autoimmunity

MSK Block | Immunology

Color index:

Main text

Important

Girls slides

Boys slides

Doctor's notes

Extra

# Objectives

01 **Autoimmunity results from activation of immune response against self antigens.**

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

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

04 **Gender predilection in autoimmunity is a well known phenomenon and is briefly described.**

*Reference: Kuby Immunology 7th Edition 2013*
*Chapter 16 Pages 517-520 & 531-534*

# Autoimmunity المناعة الذاتية

ادعوا لـ د. محمد بالرحمة

**Autoimmunity:** A condition that occurs when the immune system *'adaptive immunity'* mistakenly attacks and destroys healthy body tissue.

- Immune system has evolved to discriminate (differentiate) between Self antigens (e.g hormones, receptors, etc) and Non-self antigens (e.g microorganisms, etc).
- Mediated by auto-reactive T cells and auto-reactive B cells (auto-antibodies).

(Auto-reactive cells: immune cells acting against body's own cells or tissues)

***Dr. Note:*** **Tolerance** is the prevention of an immune response against self antigen, normal mechanism.

- Tolerance to self antigen is acquired by (how the immune system deal with auto-reactive cells?):

◄ *Deletion (clonal deletion):* ***Dr. Note:*** the removal through apoptosis of B cells and T cells that have expressed receptors for self antigens before developing into mature cells, It can happen for mature and immature immune cells.

◄ *Functional inactivation (clonal anergy):* of developing mature lymphocytes that possess (own) antigenic receptors with high affinity for self-antigens.

(anergy: lymphocyte is functionally inactivated following an antigen encounter, but remains alive)

**Self-tolerance:** the ability of the immune system to recognize self-produced antigens as a non-threat while making an immune response to foreign substances. This balance is critical to normal physiological function and overall health.

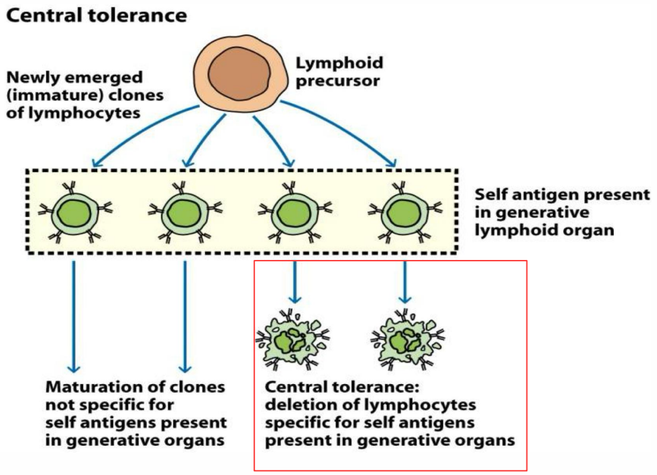
# Mechanisms of Self-Tolerance

## Central tolerance

Just Deletion

### Thymus and Bone marrow

Immature lymphocyte



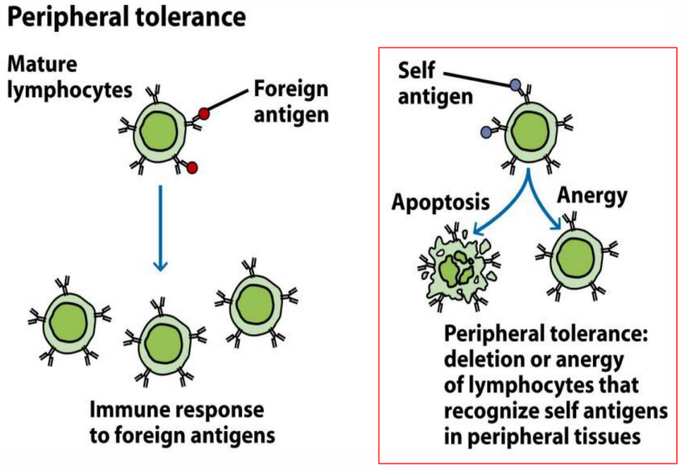

## Peripheral tolerance

Deletion & Anergy

### Peripheral tissues

(lymph node - spleen - liver)

Mature lymphocyte



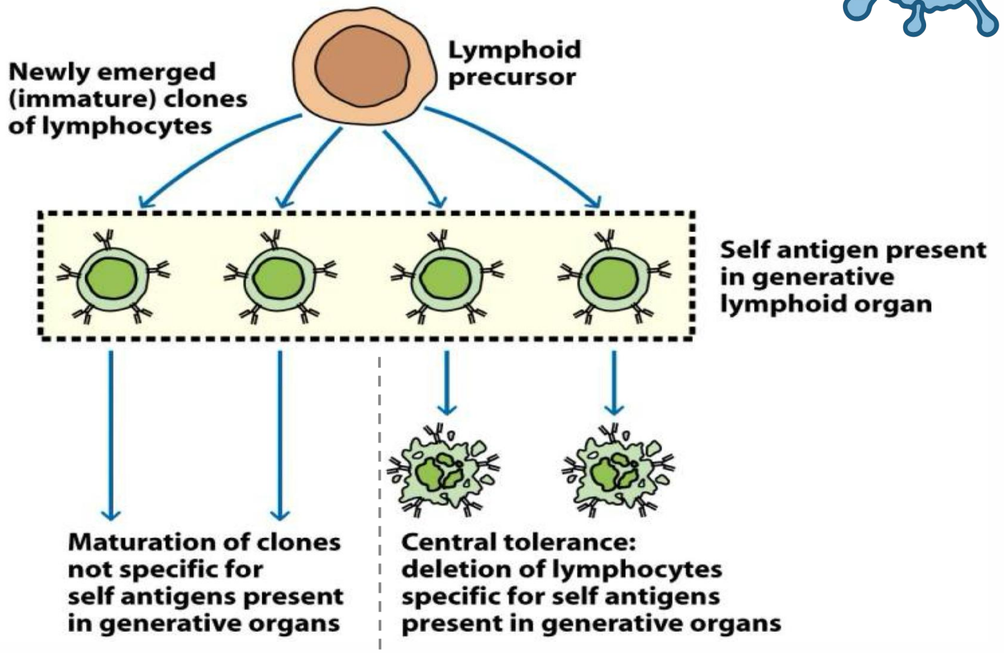
# Central tolerance

Normal mechanism.

Occurs in primary (generative) lymphoid organs: Thymus and Bone marrow.

Immature cells will undergo **deletion (apoptosis)** only.

Lymphoid precursor (Lymphoid stem cell) will differentiate into either **T** or **B** cell.




**Normal cells**

mature cells are non-specific for self-antigens

They do not attack self-antigens and will be allowed to leave the bone marrow or thymus to the circulation.

**Abnormal cells**

mature cells are specific for self antigens (auto-reactive).

They will attack self-antigens, won't be allowed to leave to the circulation, and will undergo (clonal deletion).

But some of them could escape, due to a failure in the central tolerance. and they will be dealt with in peripheral lymphoid organs.

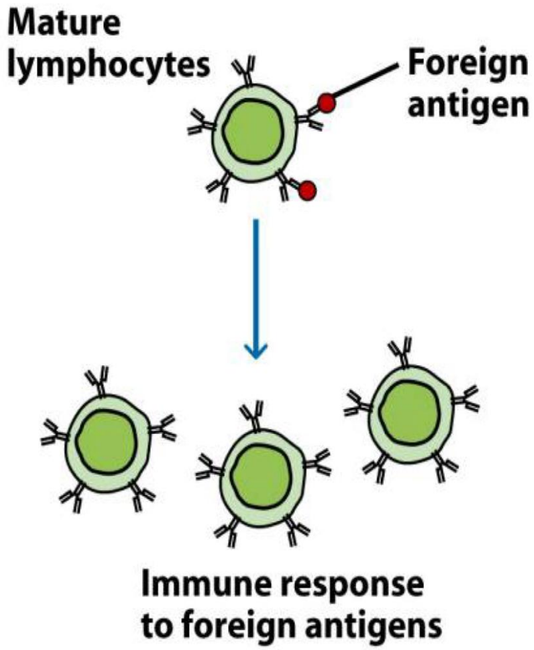
# Peripheral tolerance

Normal mechanism.

Occurs in secondary lymphoid organs.

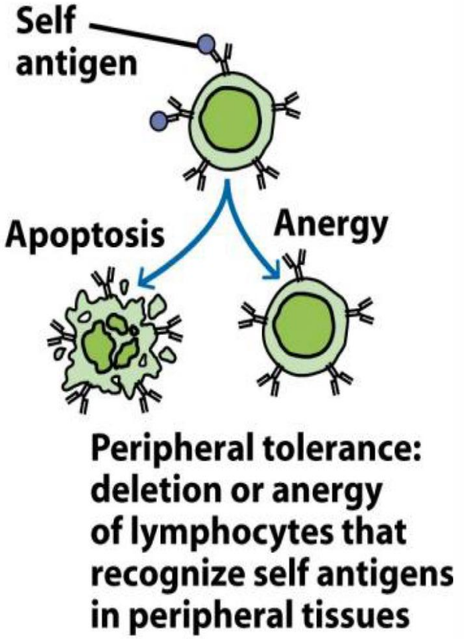
Mature cells that escape from the central mechanisms will undergo **deletion** (**apoptosis**) or **Functional inactivation** (**anergy**).

When self-reactive cells escape into the periphery, peripheral tolerance ensures that they are **deleted** or become **anergic** (functionally unresponsive to antigen).




**Normal cells**

mature lymphocytes will conduct an immune response when binding to a foreign antigen.




**Abnormal cells**

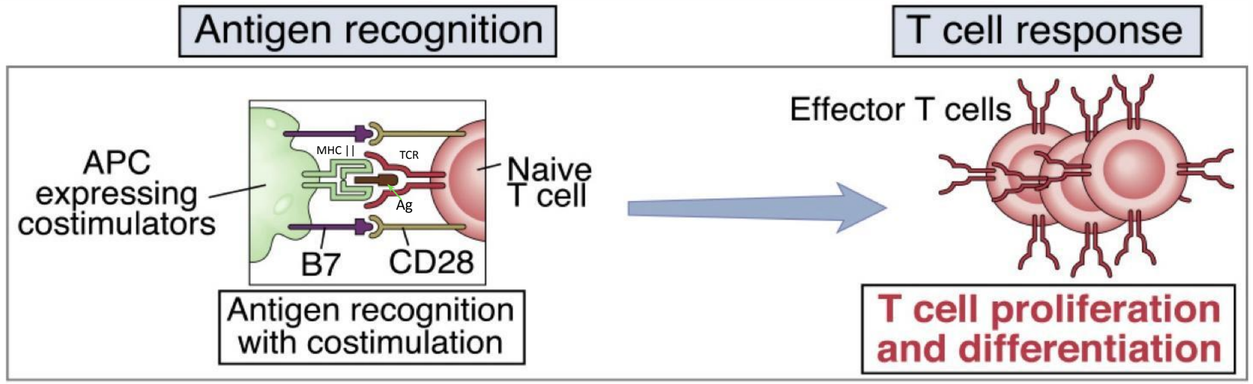
mature lymphocytes which recognise self antigens will undergo apoptosis (clonal deletion) or functional inactivation (clonal anergy).

# Peripheral tolerance of T Lymphocytes

Antigen presenting cell (APC) presents **foreign antigen** to Naive T cell.
- *1st signal:* Binding of **MHC II** (on APC) to **TCR** (T cell receptor)
- *2nd signal (Costimulatory Signal):* Binding of **B7** (on APC) with **CD28** (on T cell)

Lead to Activation of T cell and stimulate their differentiation.

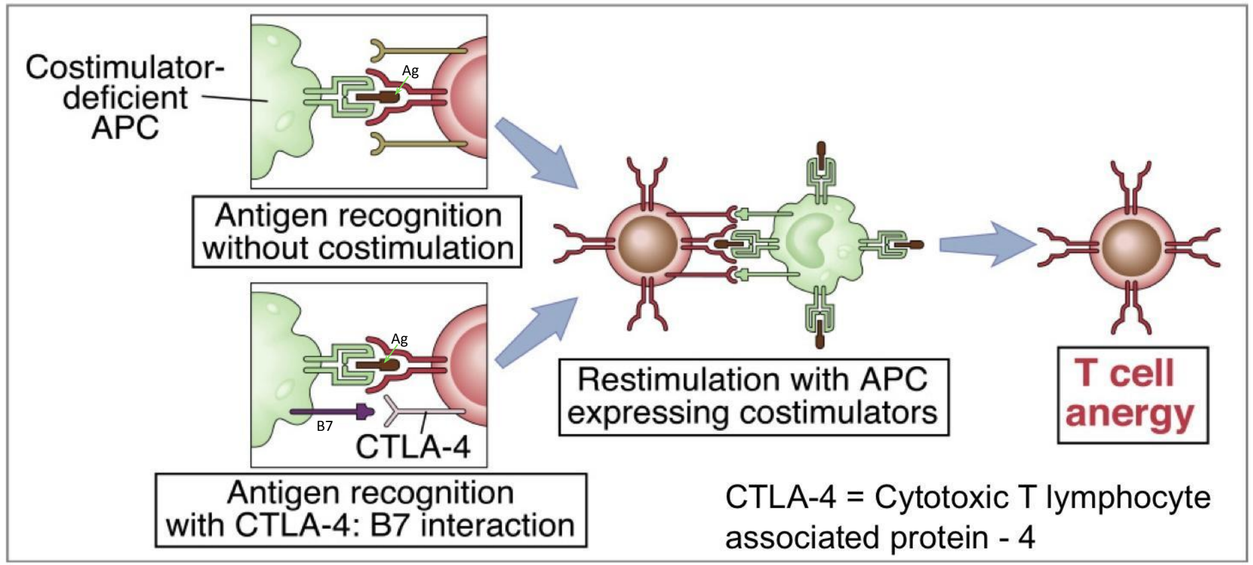
**Normal response**




Antigen presenting cell (APC) presents **self antigen** to Naive T cell.
- *1st signal:* deactivated
- Absence of *2nd signal*
- No costimulation
- Binding of **B7** (on APC) with **CTLA-4** cytotoxic T-Lymphocyte associated protein-4 (on T cell).

Lead to Deactivation of T cell (Anergy).

**Clonal anergy**



Extra slide

# Self-Tolerance Summary

| | Central tolerance | Peripheral tolerance |
|---|---|---|
| **Features** | Inactivation of cells required for initiation of an immune response | Inhibition of expression of the immune response |
| **Site** | Primary lymphoid organs | Secondary lymphoid tissue |
| **B cell participation** | Immature B cells | Mature B cells |
| **T cell participation** | Immature T cells | Mature T cells |
| **Mechanisms** | Clonal deletion | Clonal deletion and Clonal anergy |
| **Function** | Eliminates potentially self reactive Lymphocytes | Maintains unresponsiveness to self Antigens |

# Failure of Immune Tolerance

Can result in: (Development of Autoimmunity)

Failure of central tolerance —> Failure of peripheral tolerance —> Autoimmune diseases

If the attack on **non-self antigen** is the normal (desirable) response

But if the attack on **self antigen** is autoimmune response

---

## Induction of Autoimmunity

"Proposed Mechanisms!"

**01**

Sequestered antigens

**02**

Molecular mimicry

(Cross reaction antigen)

**03**

Inappropriate class II MHC expression on none-antigen presenting cells

**04**

Polyclonal B cell activation

# 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 of T cells to these normally sequestered / tissue-specific self antigens in the periphery results in their activation.

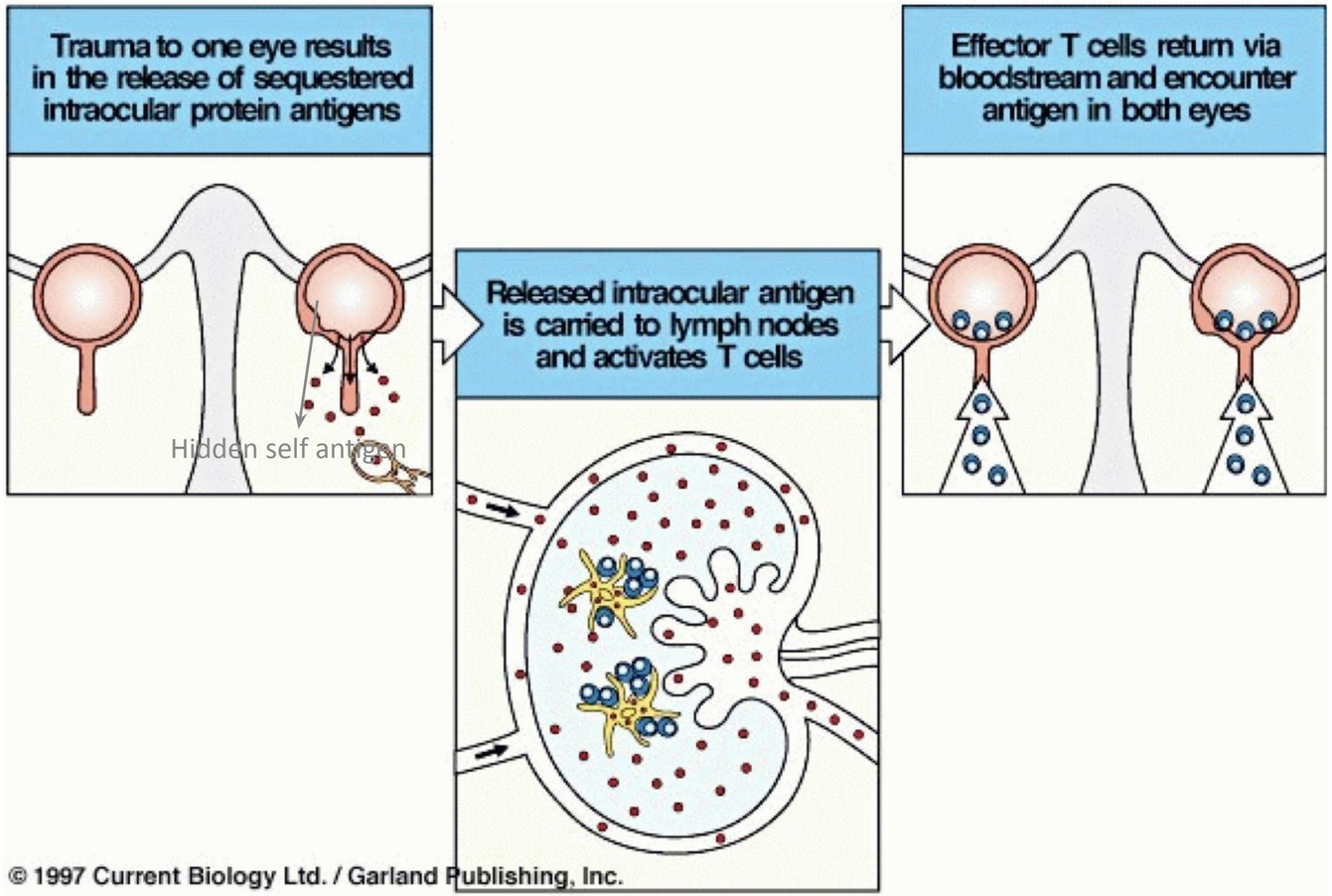
**Examples of Sequestered Antigens:**

- Myelin basic protein (MBP), associated with Multiple Sclerosis (MS).
- Sperm-associated antigens in some individuals following vasectomy استئصال الأسهر
- Lens and corneal proteins of the eye following infection or trauma —> the patient loses his vision gradually
- Heart muscle antigens following myocardial infarction.

***Team 442:*** Example If a child was taken from his biological parents from birth and after 7 years he got back to them they will see him as a strange person even though he got the same DNA.
The same thing happened in our body, there are area where the self antigens are hidden from our developing immune system, by trauma or infection this antigen get exposed, and our immune system recognise it **as foreign antigen** (because the developing immune system didn't see that self antigen because it was hidden)

# 1- Sequestered antigens

## (Sympathetic ophthalmia)




***Team 435:*** If one eye is ruptured by a blow or other trauma, an autoimmune response to eye proteins can occur, although this happens rarely, once the response is induced it often attacks both eyes (bilateral)

# 2- Molecular Mimicry (Cross-reacting Antigens)

Examples of molecular mimicry:

You don't have to memorize it —>

**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 |

- Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components.
- 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

***Team 443:*** The antibody didn't initially target the self antigen but it was against the virus and because of the similar structure in part of virus and the other part of normal tissue it lead to cross-reacting between auto-antibodies and normal tissue

# 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 .

  ***Normal condition:*** APCs phagocytose the foreign body —> present the antigen on its surface for T-cells

  ***Autoimmune condition:*** 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-gamma, which is known to increase class II MHC expression on a variety of cells.
- The inducer of IFN-gamma under these circumstances could be a viral infection.

***MCQ:***
The viral infection induces the secretion of IFN-gamma, example of:
**A-** hidden antigen
**B-** molecular mimicry
**C-** inappropriate expression of MHC II

# 3- Inappropriate Expression of Class II MHC Molecules

**For example:**

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

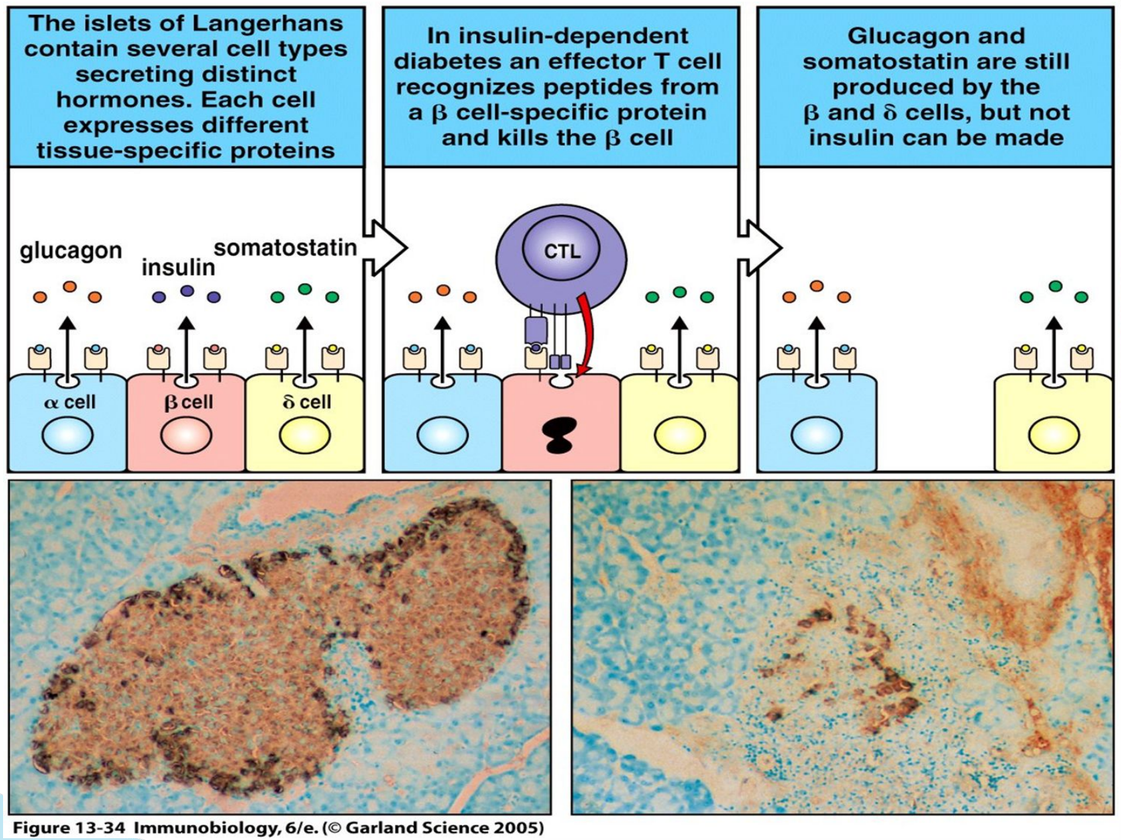
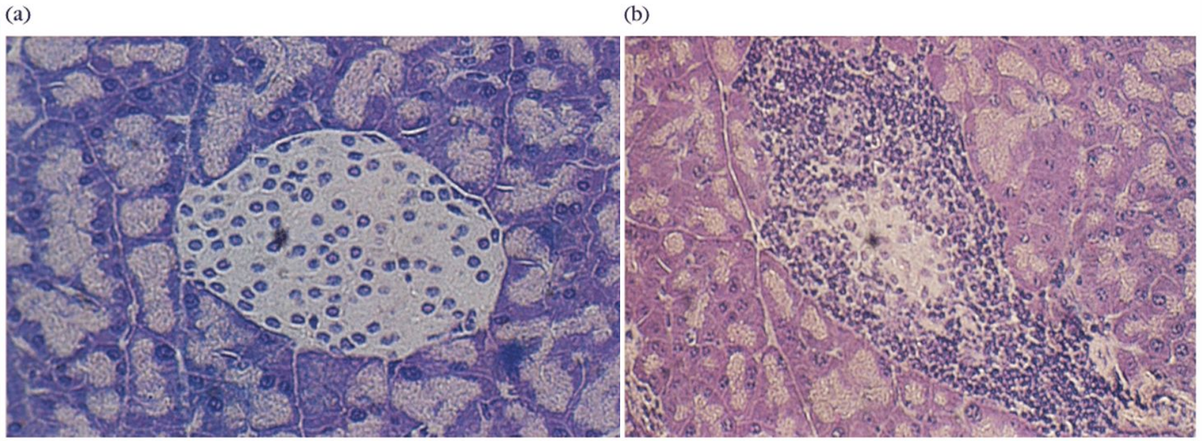



Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)




Normal Pancreas

Pancreas with insulitis

***Dr's explanation:*** (thanks to ***team 439***):

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.

# 4- Polyclonal B Cell Activation

1

Viruses and bacteria can induce nonspecific polyclonal B cell activation, including:
- Certain gram negative bacteria
- Herpes Simplex virus - Cytomegalovirus
- Epstein Barr Virus - (HIV)

2

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.

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.

***MCQ:***
HIV, example of:
**A-** polyclonal B cell

# Hormonal Factors

1

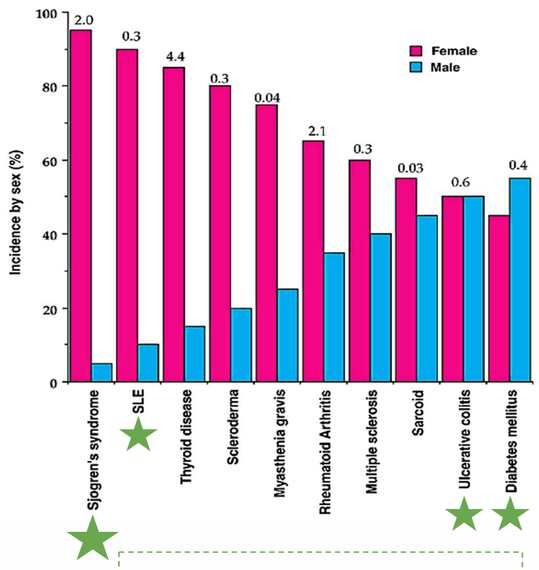
About 90% of autoimmune diseases occur in women – cause not known.

2

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

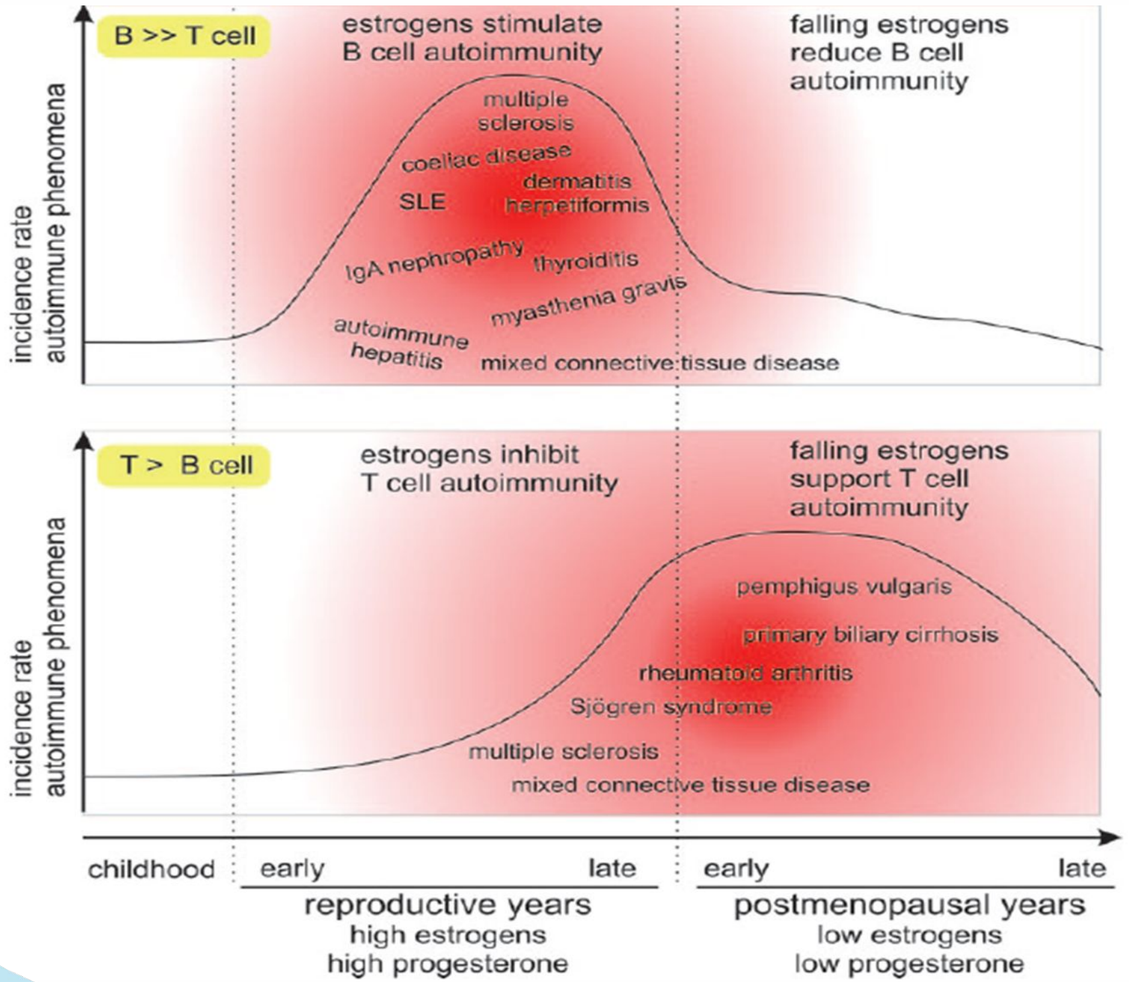
3

SLE (Systemic lupus erythematosus) either appears or exacerbates during pregnancy.




You need to know who's more affected

# Hormonal Factors




1

**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

2

**Low estrogen levels (post-menopause):**

-Inhibit B-cell autoimmunity

-Stimulate T-cell autoimmunity (e.g. higher chance to get rheumatoid arthritis)

# Drug Induced Lupus Erythematosus

**Lupus erythematosus like syndrome** develops in patients receiving a variety of drugs (immunosuppressants) such as:

| | | | |
|---|---|---|---|
| **Hydralazine** (used for hypertension) | **Penicillin** | **Isoniazid** | **Procainamide** |

Many are associated with the development of anti-nuclear antibodies (ANAs)

(An ANA test check to see if you have an autoimmune disorder)

Renal and CNS involvement is uncommon

Anti-histone antibodies are frequently present

***Dr. Note:*** You need to differentiate between real SLE and drug induced:

- Both have +ve ANA
- real SLE: involvement of renal and CNS
- Drug induced: No involvement of renal and CNS, +ve antihistone antibodies

# Take home message

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

# MCQs

**1- Peripheral tolerance differs from central tolerance by:**

**A.** It's required by functional inactivation

**B.** It takes place in the primary lymphoid organs

**C.** It's limited only to antibodies mediated response

**D.** It's limited only to cellular mediated response

**2- Which of the following is an example of Sequestered antigens?**

**A.** Diabetes mellitus

**B.** Myocardial infarction

**C.** Hepatitis

**D.** Tuberculosis

**3- The Central tolerance occurs in?**

**A.** Thymus

**B.** Liver

**C.** Kidney

**D.** Heart

**4- What is one of the effects of High Estrogen levels on autoimmunity?**

**A.** inhibits T cell autoimmunity

**B.** inhibits B cell autoimmunity

**C.** stimulates T cell autoimmunity

**D.** inhibits both T and B cell autoimmunity

**5- Type I diabetes is an example of which one of the following mechanisms of autoimmunity?**

**A.** Sequestered antigens

**B.** Molecular mimicry

**C.** Inappropriate class II MHC expression

**D.** Polyclonal B cell activation

1-A 2-B 3-A 4-A 5-C

# MEET THE TEAM

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