

Mechanisms of Autoimmunity

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.**

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Life isn't about
getting and
having, it's about
giving and being.

Red = Important Notes gray = Additional Notes Green = Example

Light blue: boys notes Purple: girls notes

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For any questions or suggestions don't hesitate to contact us on Immunology434@gmail.com 😊

Autoimmunity

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

Immune system has evolved to discriminate between:

Self and **Non-self**.

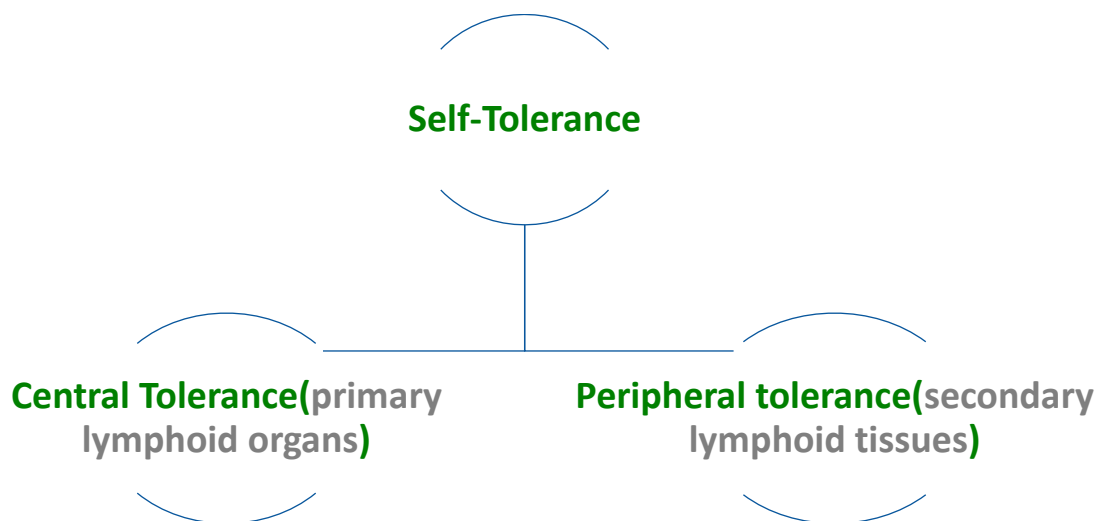
Mediated by auto-reactive **T cells** and auto-reactive **B cells** (auto-antibodies)(Auto-reactive T and B cells are present normally in the body.)

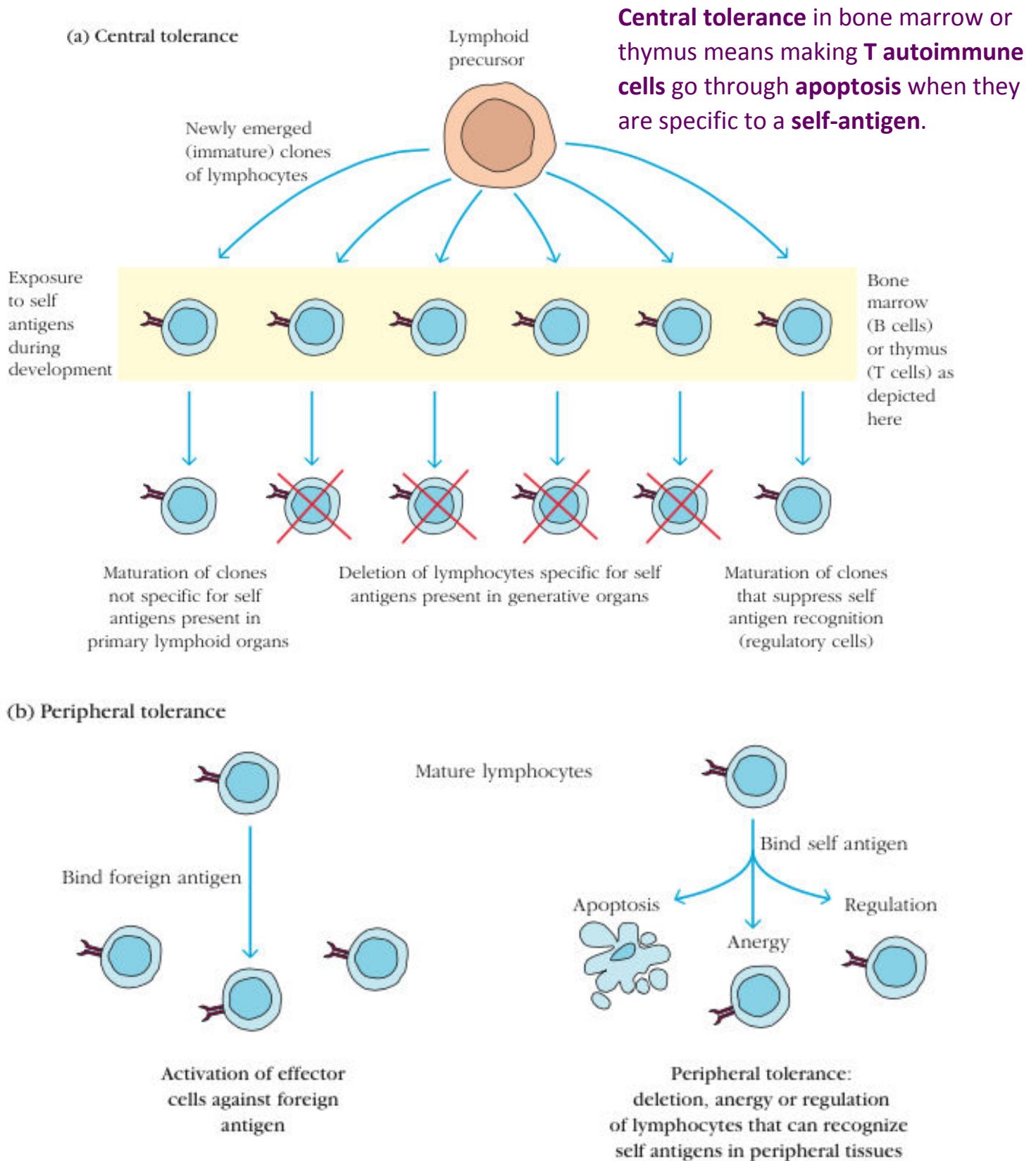
Tolerance to self is acquired by:

- I. **Deletion** (clonal deletion)- (there will be apoptosis and killing of self active clones in the primary lymphoid organs (thymus and bone marrow) and clear it.)

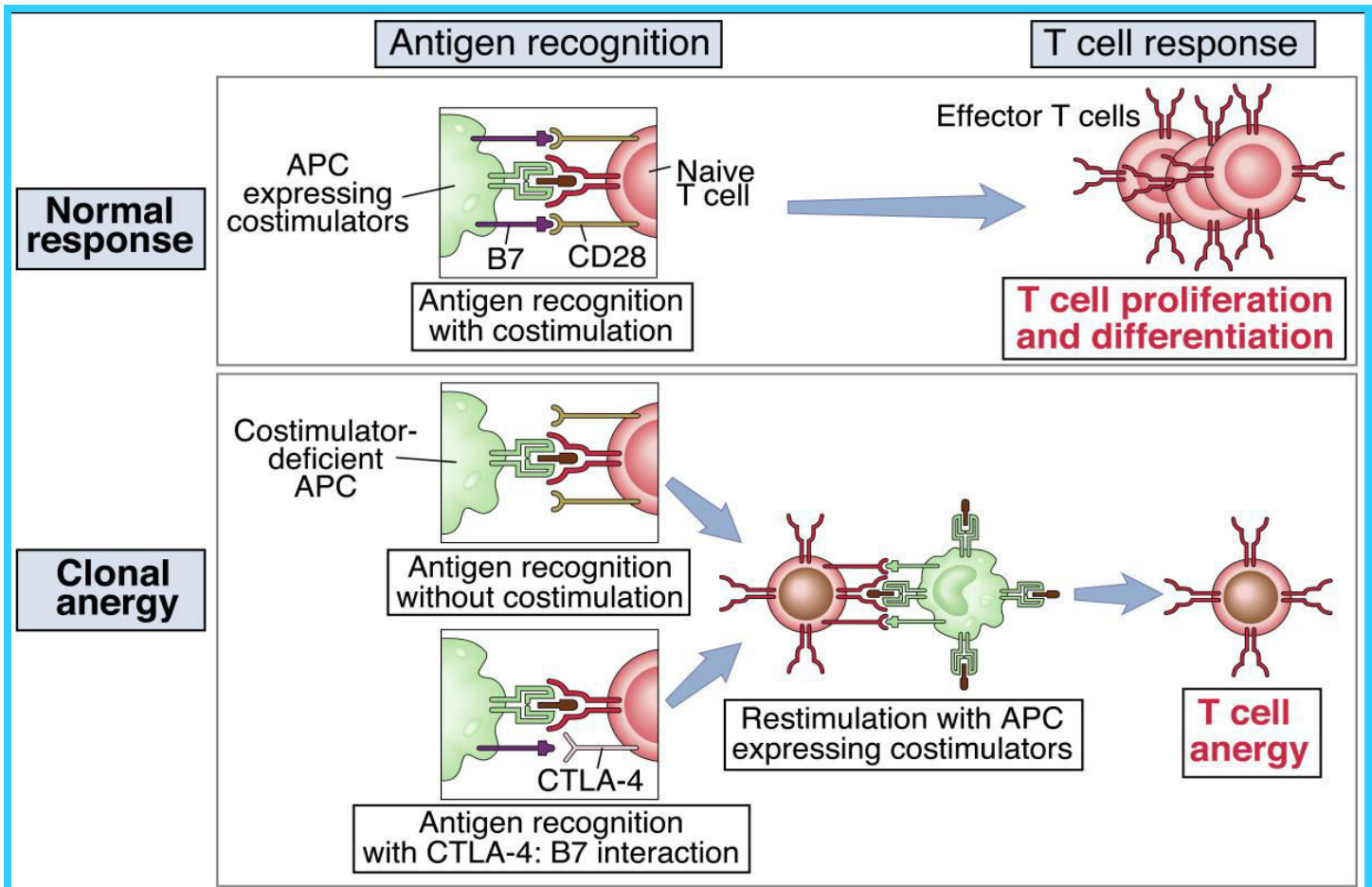
OR

- II. **Functional inactivation** (clonal anergy) of developing lymphocytes that possess antigenic receptors with high affinity for self-antigens. (functional inactivation means if the clones that are reactive with self antigen pass the primary lymphoid organs, there will be switch inactivation and we call in clonal energy)





Peripheral Tolerance of T Lymphocytes



Failure of Immune Tolerance (Development of Autoimmunity)

Failure of tolerance is autoimmunity.

Induction of Autoimmunity "Proposed Mechanisms!"

1-Sequestered antigens.

2-Molecular mimicry.

3-Inappropriate class II MHC expression on none-antigen presenting cells.

4-Polyclonal B cell activation.

1. Sequestered antigens

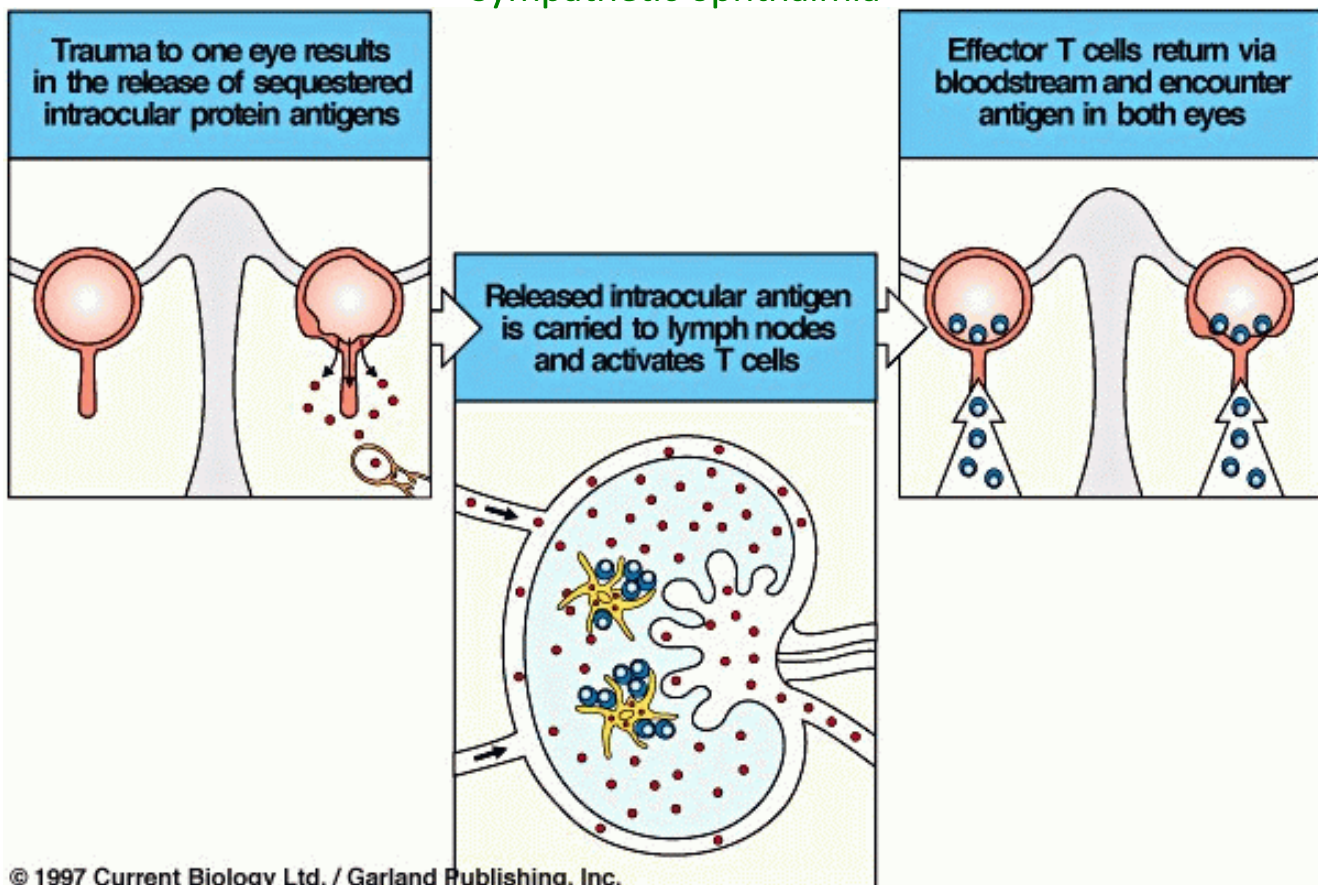
- Some self-antigens are sequestered (hidden) in specialized tissues.
- These are **not seen** by the developing immune system – will not induce self-tolerance.
- Exposure of T cells to these normally sequestered/tissue-specific self-antigens in the periphery results in their activation.

(During the development of immune system in our body these self-antigen will be hidden so the immune system cant recognize it to do tolerance. And because of trauma and infection will appear and will be exposed to our immune system)

○ Examples of Sequestered Antigens

- **Myelin basic protein (MBP)**, associated with MS
- **Sperm-associated antigens** in some individuals following vasectomy
- **Lens and corneal** proteins of the eye following infection or trauma
- **Heart muscle antigens** following myocardial infarction

Sympathetic ophthalmia



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, known as *molecular mimicry*, occurs in a wide variety of organisms.
- Molecular mimicry may be the **initiating step** in a variety of autoimmune diseases.

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.

○ Inappropriate Expression of Class II MHC Molecules

- 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**

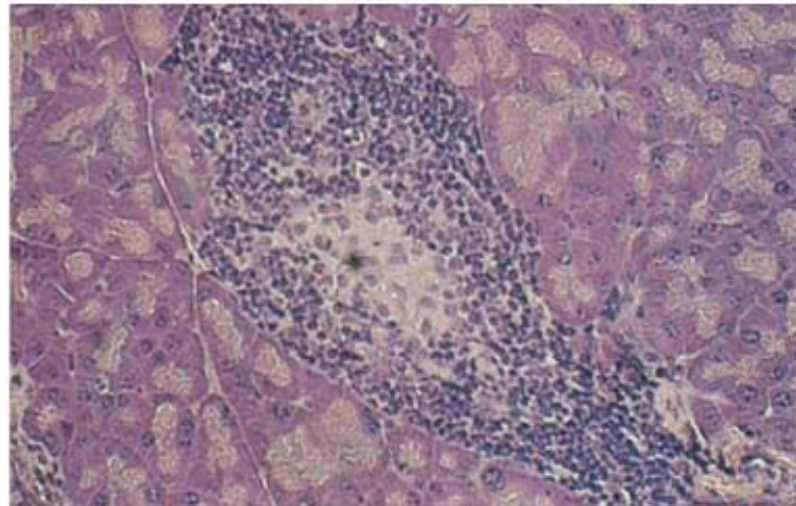
Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II (?)

(a)



Normal Pancreas

(b)



Pancreas with Insulinitis

The theory of **diabetes type I** starts **viral infection** where there is abnormal expression of **MHC II** making it wrongly recognize **B cells** of **pancreas** which has **insulin receptor** that is **similar to a viral antigen** and **killing B cells** making **pancreas unable to produce insulin**.

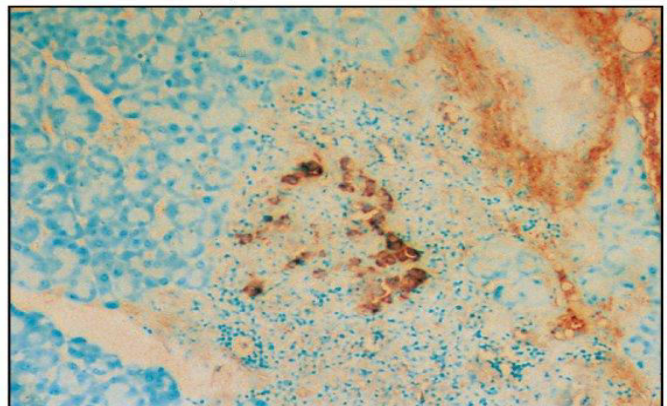
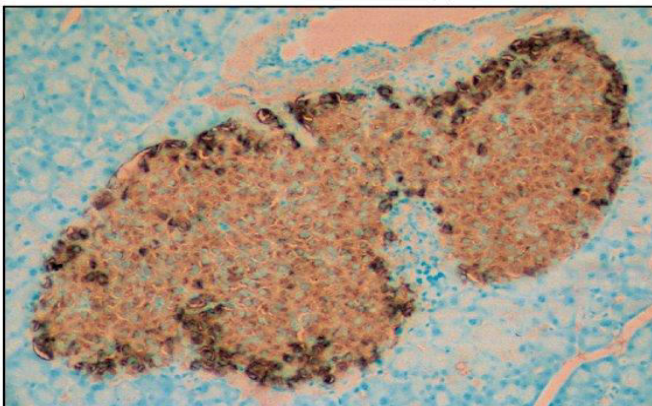
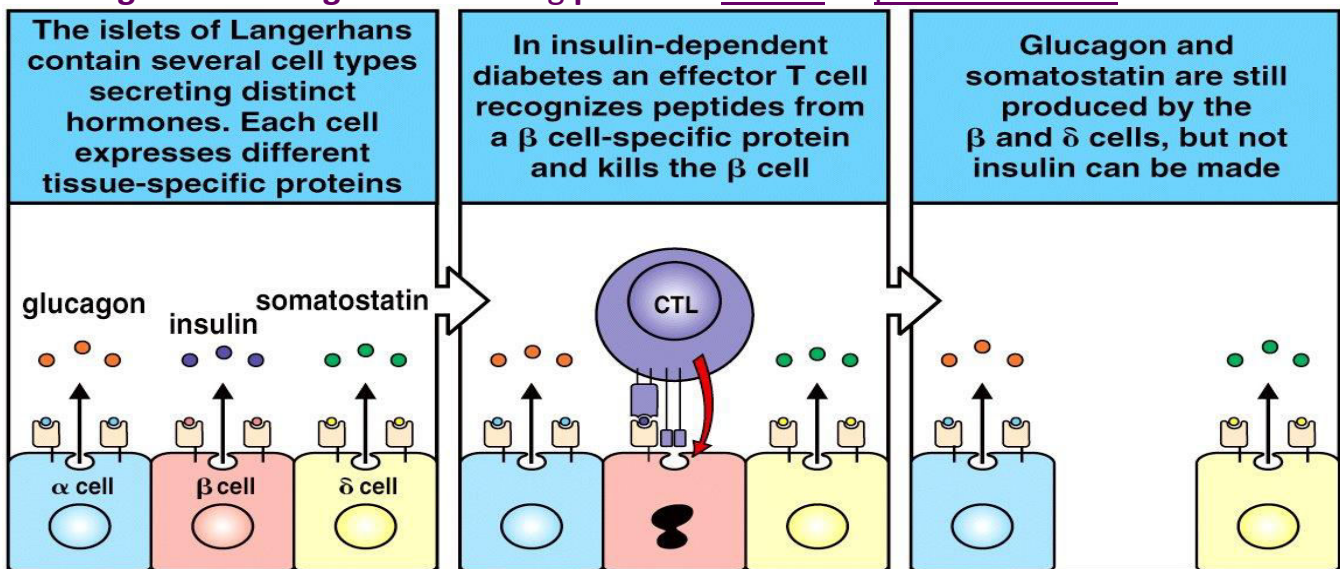


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

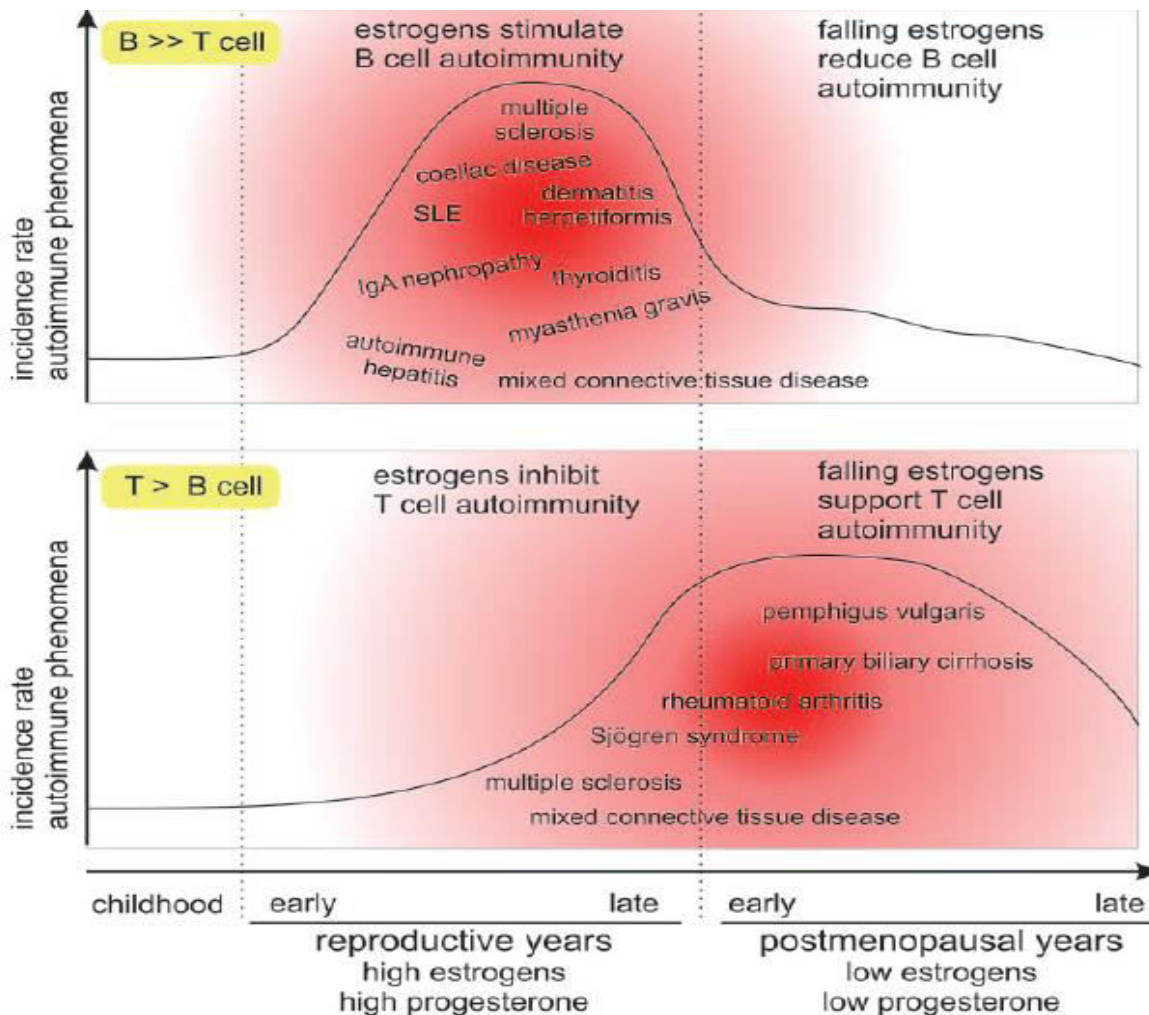
4-Polyclonal B Cell Activation

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

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

○ 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 during pregnancy



Drug Induced Lupus Erythematosus

- **Lupus erythematosus like syndrome develops in patients 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)**
- **Renal and CNS involvement is uncommon**
- **Anti-histone antibodies are frequently present**

Review:

-**Autoimmunity** is a condition that occurs when the immune system mistakenly attacks normal healthy body tissues.

-It is mediated by Auto reactive B and T cells (Auto-antibody)

Our immune system has evolved to differentiate between normal body antigens (self-antigens) and foreign antigens (nonself antigens).

Tolerance to self-antigens is acquired by:

1- (Clonal Deletion)

-Also called Deletion.

-Happens in the environment of the primary lymphoid organs (Thymus and Bone Marrow).

-Normal lymphocytes are allowed to leave the bone marrow and thymus to perform its function, while the autoreactive lymphocytes are not allowed to leave the bone marrow or the thymus and undergo apoptosis.

2- (Clonal Anergy)

-Happens in peripheral tissues (Circulation and tissues)

-Sometimes, autoreactive cells leave the primary lymphoid organs by mistake. This is when functional inactivation happens.

-Anergic cell: a fully mature cell that is inactive.

-It is the inactivation of the functions or the deletion of developing lymphocytes that have receptors with high affinity for self antigens. (If a lymphocyte has receptors for self antigens, it will either lose its immune function or undergo apoptosis).

-It happens in two ways:

A) Antigen recognition without Co-stimulation.

B) Antigen recognition with CTLA-4: B7 interaction.

Induction of Autoimmunity: (how autoimmunity happens)

- 1- **Sequestered antigens:** happens to self-antigens when they are released from their specific tissue. (*due to trauma or infection*)
 - 2- **Molecular Mimicry:** happens when a virus or bacteria having amino acid sequences that are similar or identical to normal host cell components.
 - 3- **Inappropriate expression of class II MHC:** happens when non Antigen Presenting Cells (APC) cell has class II MHC. The result is the presenting of these cells to autoimmune cells leading to its destruction (*due to Interferone Gamma production*).
 - 4- **Polyclonal B Cell activation:** happens when some types of viruses induce the proliferation of B Cells. This leads to the activation of self-reactive B Cells and autoantibody production which could bind and attack self antigens. (*due to infection*)
-

Hormonal Factors.

- 99% of autoimmune diseases occur in females
 - In the reproductive years of a female, it is more common to have B Cell autoimmunity than T Cell autoimmunity. (estrogen stimulates B Cell autoimmunity and inhibits T Cell autoimmunity).
 - In the postmenopausal years, it is more common to have T Cell autoimmunity than B Cell autoimmunity (low estrogen).
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Drug induced Lupus Erythematosus.

- -It happens to patients reviewing certain types of drugs.
- -Associated with the development of Anti-Nuclear Antibodies (an indicator to autoimmune diseases)
- -Renal and CNS involvement is uncommon. (in SLE there is an involvement).
- -Anti-histone antibodies are frequently present.

MCQs:

1) Which ONE of the following is example of sequesterd?

- a. Lens & corneal.
- b. MBP.
- c. Heart muscle antigens.
- d. All of the above.

2) Deletion and anergy of lymphocytes that recognize self-antigens this condition occurs in?

- a) Peripheral tissue
- b) Bone marrow
- c) Foreign antigen
- d) A+B are true.

3) Failure of immune tolerance means?

- a) Development of Autoimmunity
- b) Failure of Autoimmunity
- c) A+B true
- d) None

4) Which ONE of the following occurs in a wide variety of organisms?

- a) Some self antigens
- b) Cross-reaction
- c) sequested antigens
- d) B+C are true

5) Abnormal expression of MCH determinants allows the recognition of these auto antigens by?

- a) Self-reactive T cells
- b) Self-reactive B cells
- c) Auto antibody
- d) B+C are the correct answer

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