Immunology Team

Mechanisms of Autoimmunity

First Lecture

Musculoskeletal Block

431

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

Autoimmunity

Immune system has evolved to discriminate between **Self and Non-self**

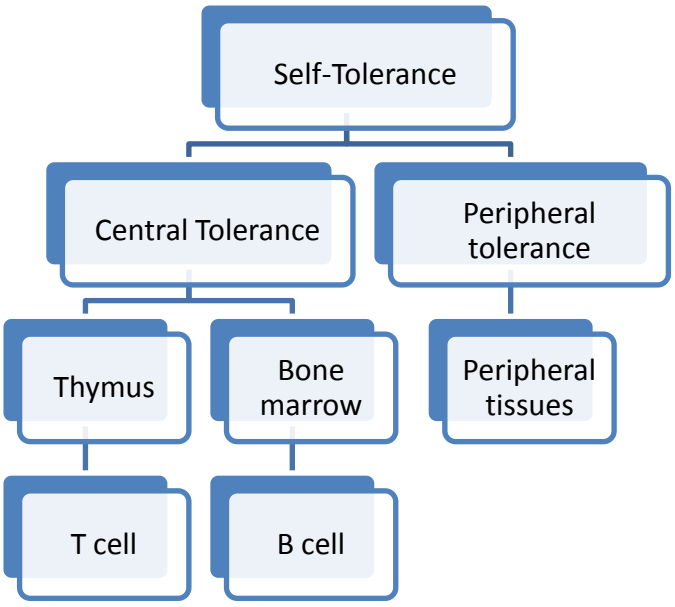
Mediated by auto-reactive T cells and auto-reactive B cells (auto-antibodies)

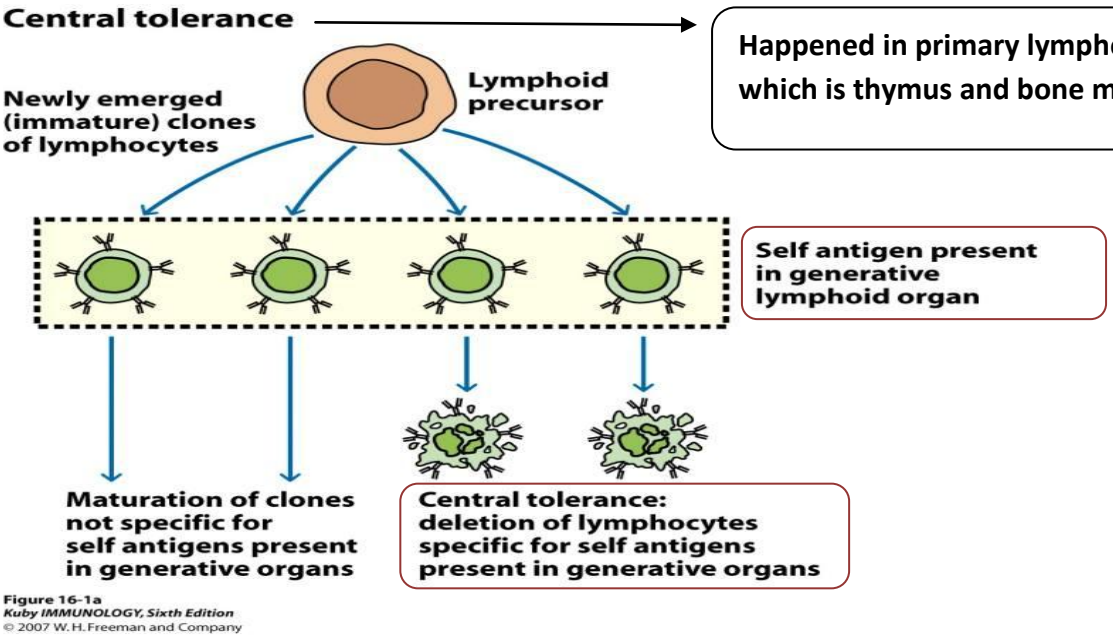
Tolerance → is the process by which the immune system does not attack an antigen

Tolerance to self is acquired by:

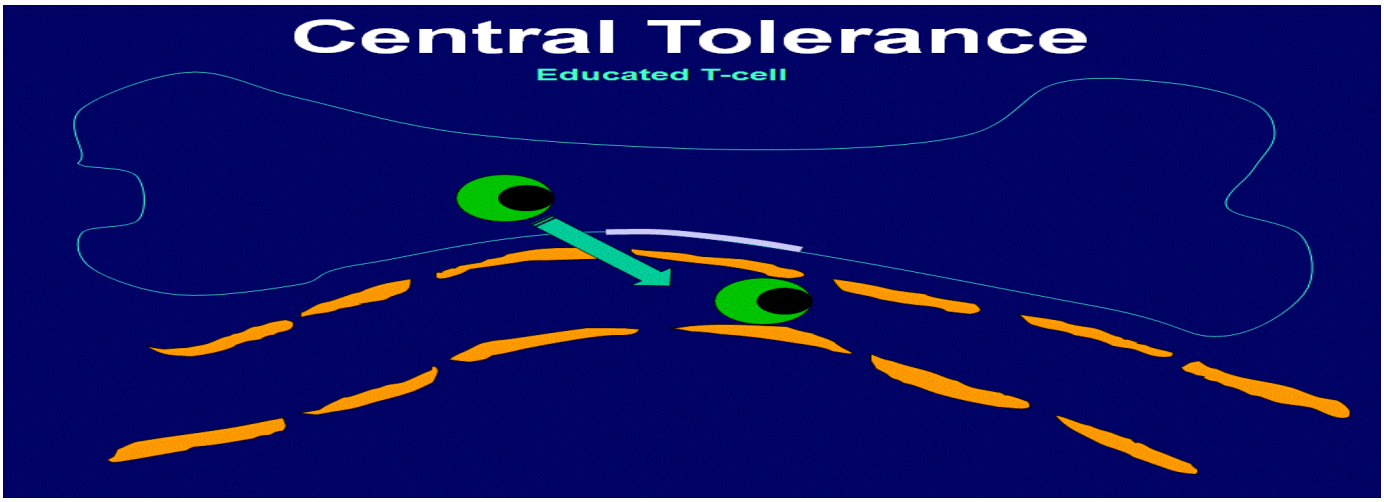
A) Deletion (clonal deletion) → clonal deletion : any cell , whether it's in the thymus gland (T-cells) or in the bone marrow (B-cells), that may react against self antigens will be deleted in the central tissue of the thymus or of the bone → (they are not allowed to pass to the blood because if they pass to the blood they will cause autoimmune process)

B) Functional inactivation (clonal anergy), of developing lymphocytes that possess antigenic receptors with high affinity for self-antigens. → Anergy = losing response

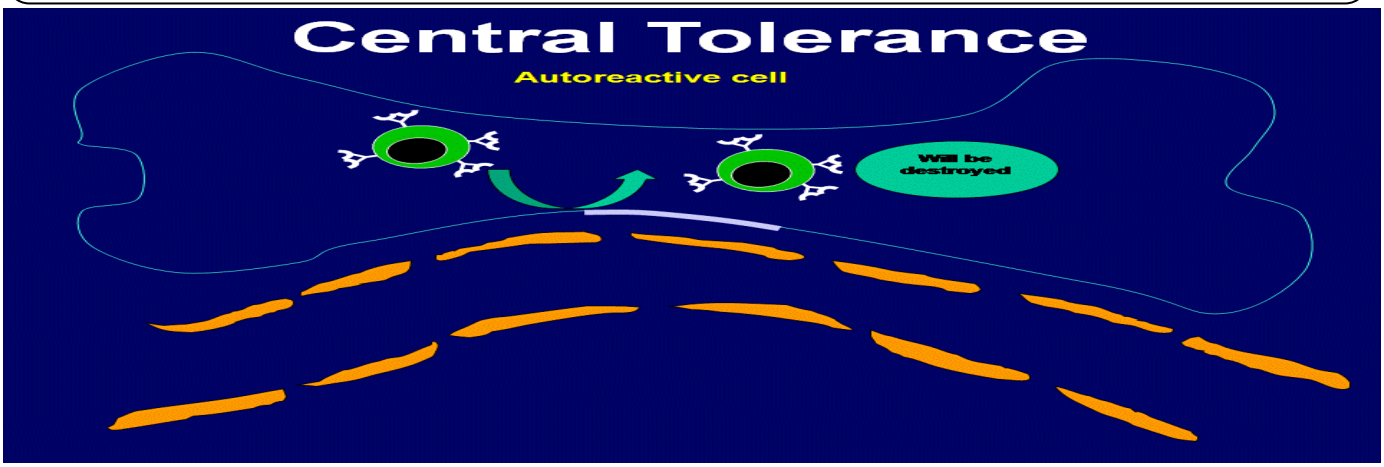




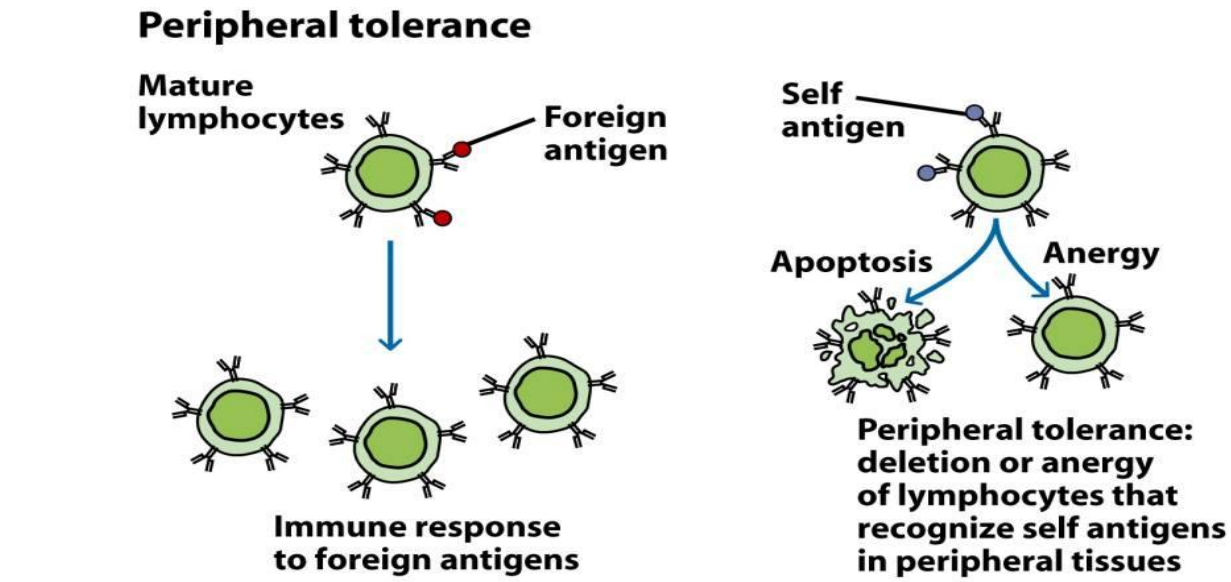
Happened in primary lymphoid organ which is thymus and bone marrow .

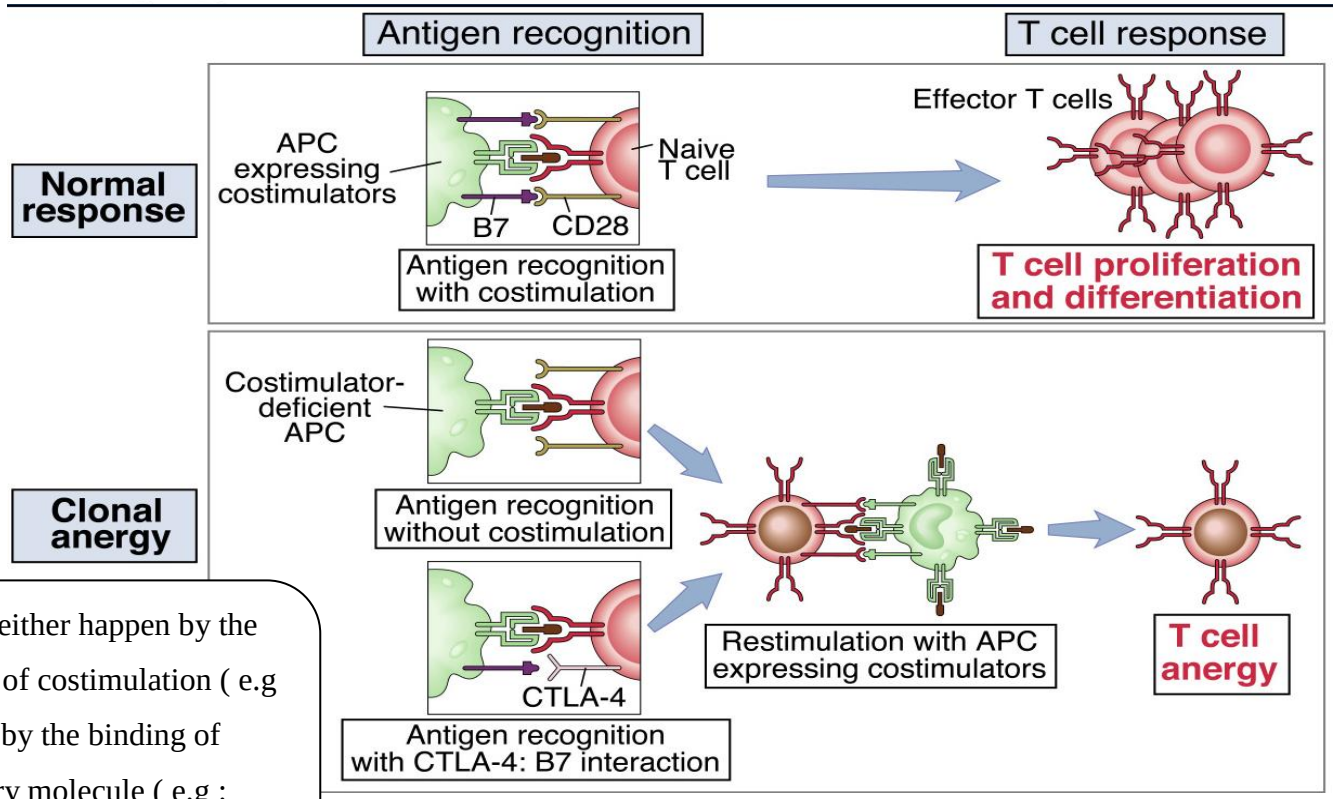


This a cell that don't react with self- antigen. So , it will be allowed to pass through to the circulation to be mature and start functioning .

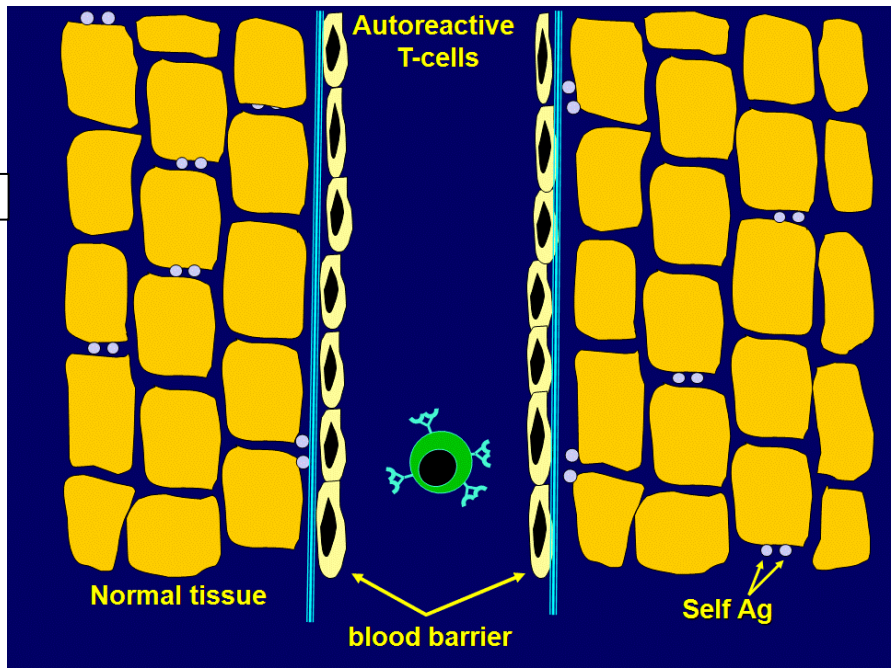


This cell has been react with self antigen .So, it will not be allowed to pass through to the circulation because if it's pass It will cause autoimmunity. So , it will be destroyed in the thymus or bone marrow.





Anergy either happen by the absence of costimulation (e.g : B7) or by the binding of inhibitory molecule (e.g : CTLA-4)



The Blood barrier doesn't allow the autoreactive T-cell to pass through the blood vessel to normal tissue which contain self-antigen .because if it pass it will cause autoimmunity.

Failure of Immune Tolerance (Development of Autoimmunity)

Induction of Autoimmunity
"Proposed Mechanisms!"

- Sequestered antigens
- Molecular mimicry
- Inappropriate class II MHC expression on none-antigen presenting cells
- Polyclonal B cell activation

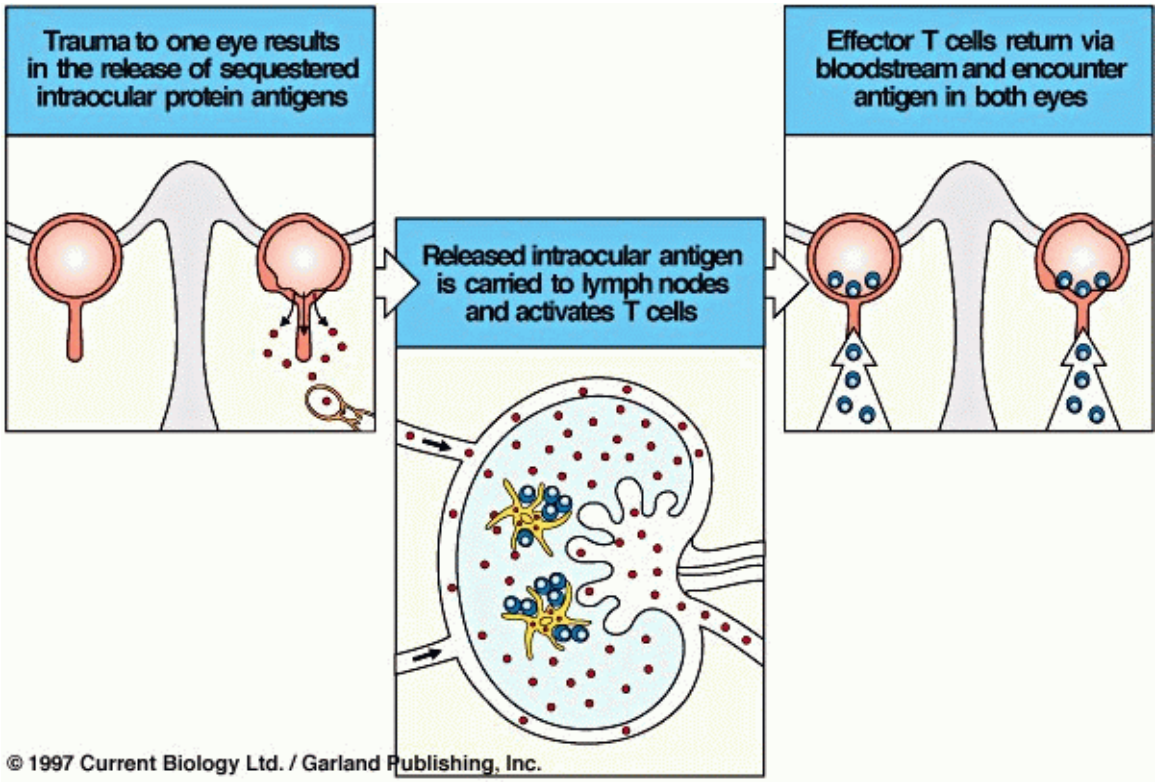
Sequestered antigens

- 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

MS = ***multiple sclerosis*** / MBP present in the central nervous system

- **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



Molecular Mimicry (Cross-reacting Antigens)

Many of autoimmune disorders are due to mimicry molecule

- **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.

TABLE 20-3 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

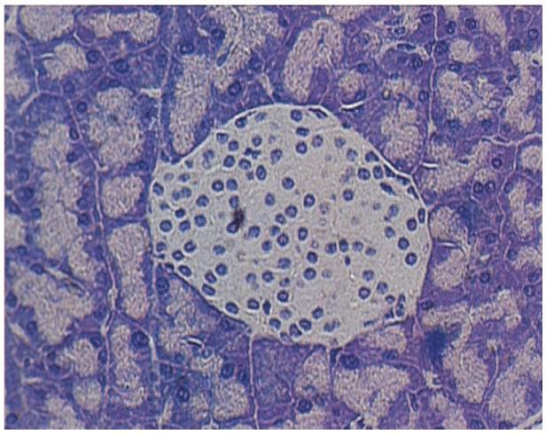
Inappropriate Expression of Class II MHC Molecules

- 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-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**.

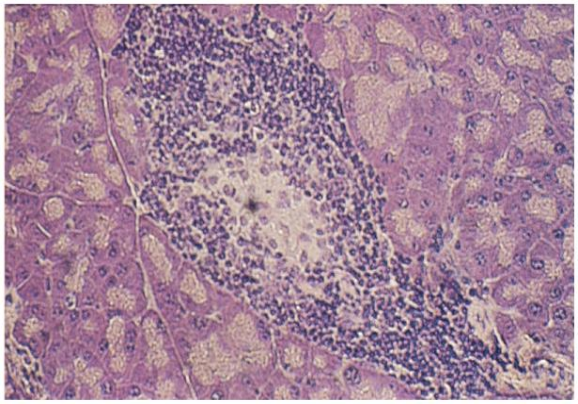
Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II

(a)



Normal Pancreas

(b)



Pancreas with Insulitis

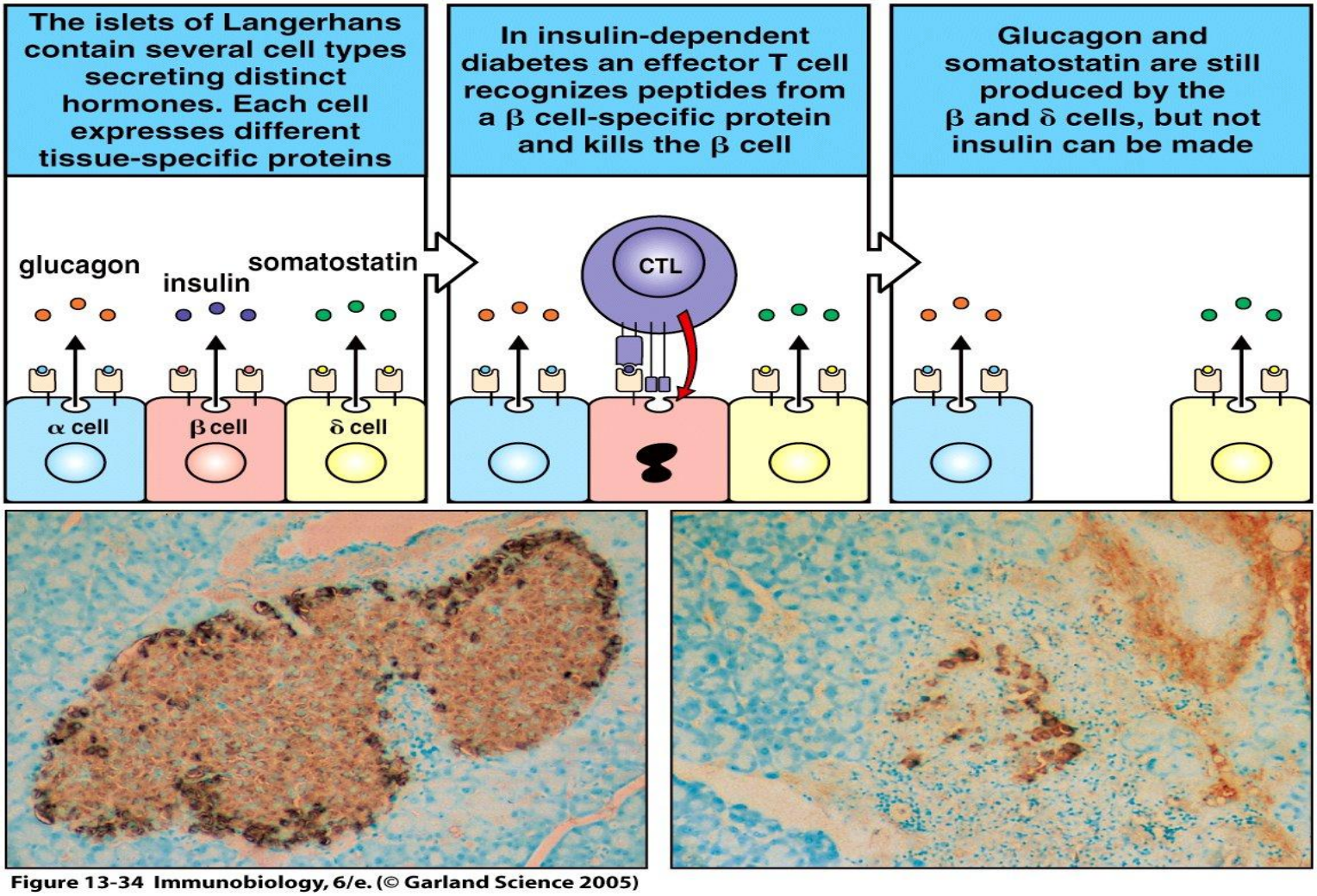


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

Polyclonal B Cell Activation

Polyclonal B-cell activation = Excessive activation of B-cell producing large number of antibodies which are not specific to any antigen

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)

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.

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

There is a **theory** that says " the cause because of estrogen and progesterone in female "

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

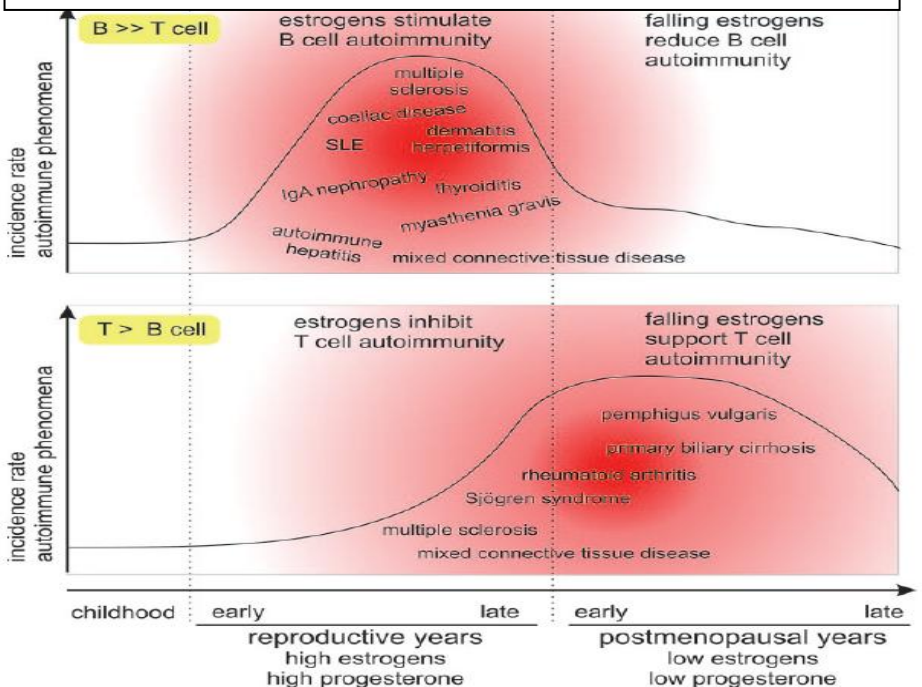
In animal models estrogen can induce B cells to enhance formation of anti-DNA antibodies

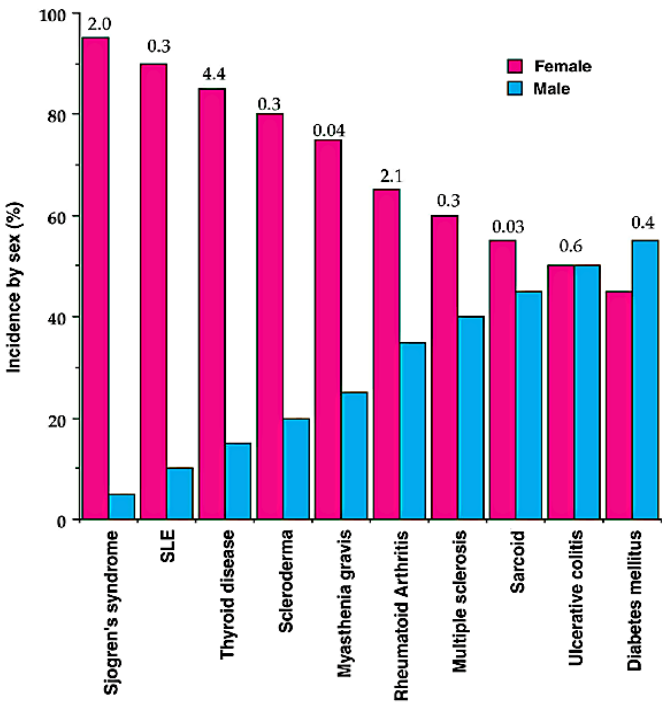
SLE either appears or exacerbates during pregnancy

SLE = Systemic Lupus Erythematosus

SLE becomes more severe in pregnancy , due to the changes in the hormones levels

Diagram demonstrate the affect of hormones to T &B cells inhibiting or stimulating





Drug Induced Lupus Erythematosus

- Lupus erythematosus like syndrome develops inpatients 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

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