Immunology team - 437

1- Mechanisms of Autoimmunity

Objectives :

1. Autoimmunity results from activation of immune response against self antigens.
2. To learn how immunological tolerance (Central & Peripheral) is induced against self antigens for maintaining normal health.
3. To gain understanding of various factors contributing to breakdown of immunological tolerance and development of autoimmunity
4. Gender predilection in autoimmunity is a well known phenomenon and is briefly described.

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).

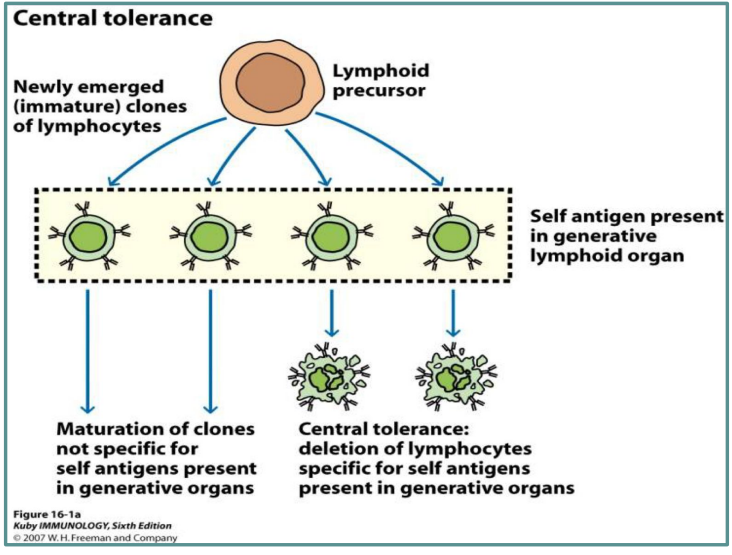
Tolerance to self is acquired by:

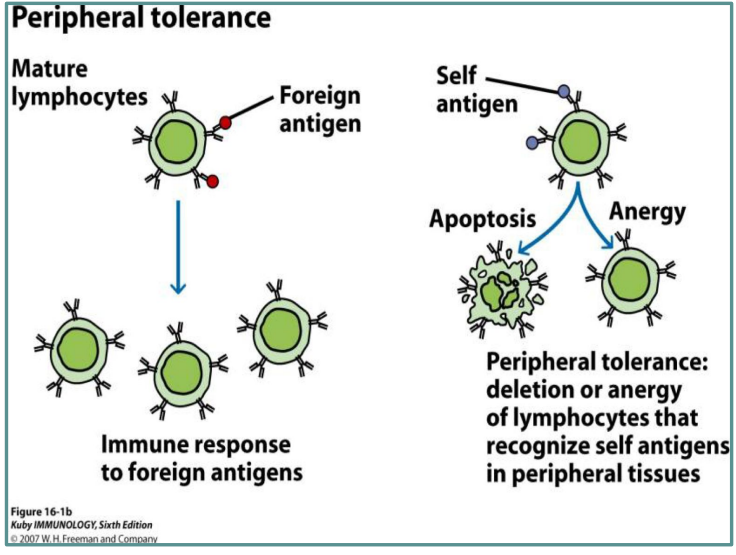
A) **Deletion** (clonal deletion)
OR
B) **Functional inactivation** (clonal anergy) of developing lymphocytes that possess antigenic receptors with high affinity for self- antigens.

Self-Tolerance

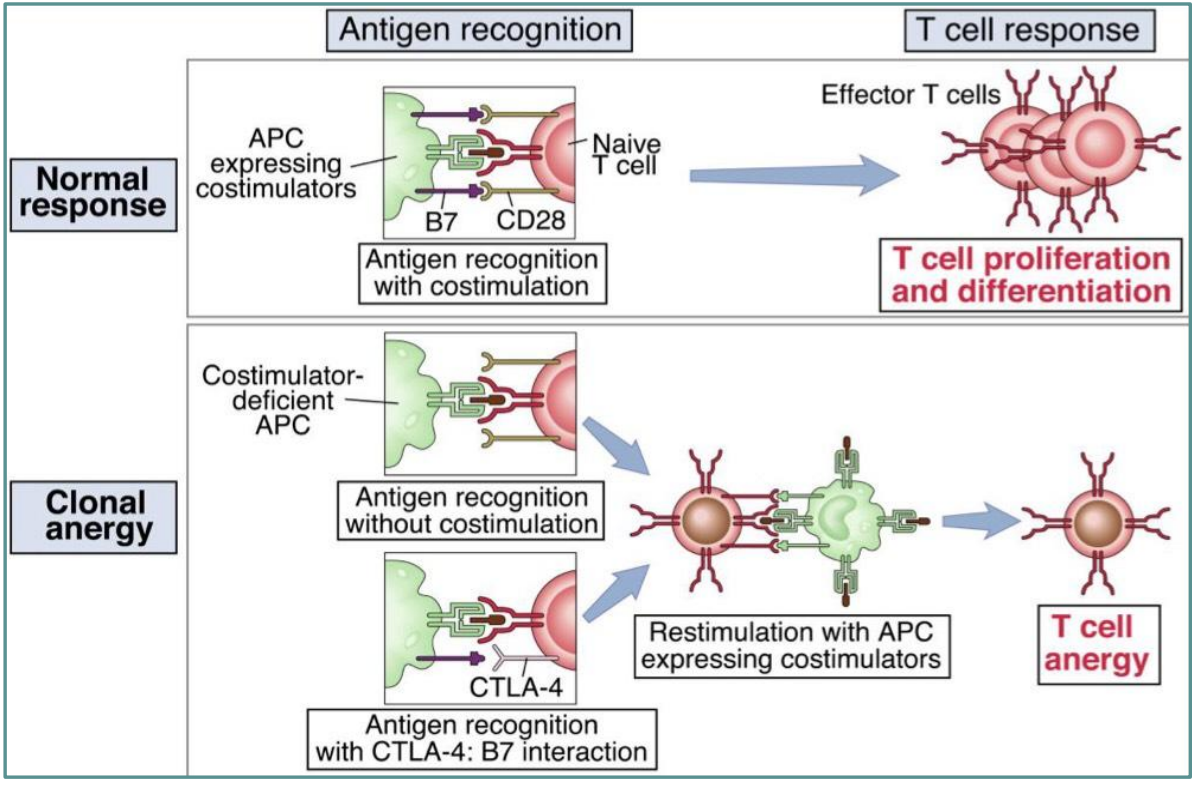
1- **Central Tolerance**
(Thymus & Bone marrow)

2- **Peripheral Tolerance**
(Peripheral tissues)

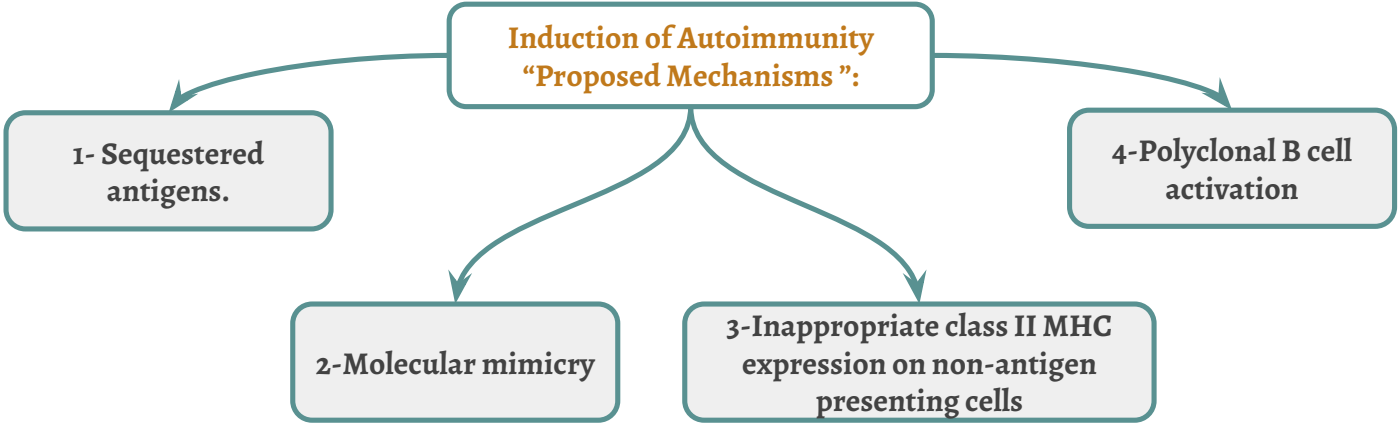




Peripheral Tolerance of T lymphocyte



Failure of Immune Tolerance (Development of Autoimmunity):

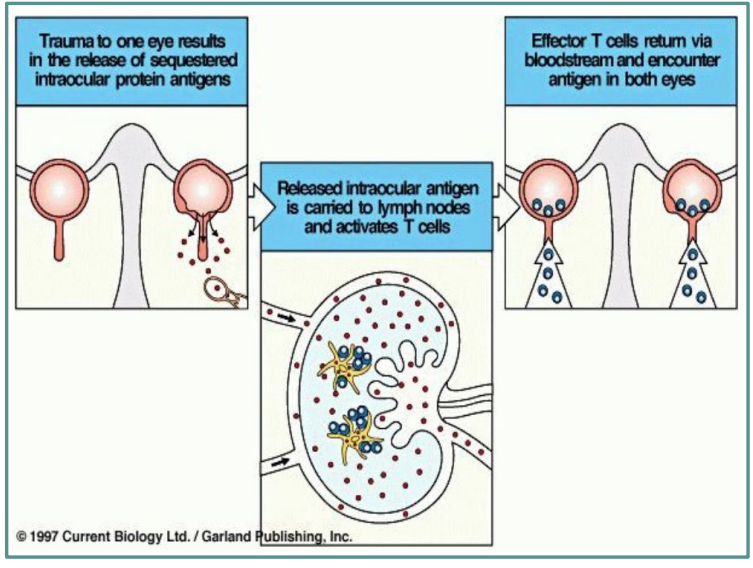


1- Sequestered antigens.

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 :

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



2-Molecular mimicry

(Cross-reacting Antigens) * التشابه الجزيئي*

Dr.notes;

- كلاهما لهما نفس اللاب كوت ف ما يفرق الجسم بينهم ويحدث التنشيط لل T & B cells ضد الجسم
- بمعنى ان اللي أدى الاستجابة المناعية البكتيريا او الفيروس

- 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.

Examples of Molecular Mimicry :

The sequences are similar so a confusion might happen to the cells and cause Molecular Mimicry For your information *Girl's doctor*

MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

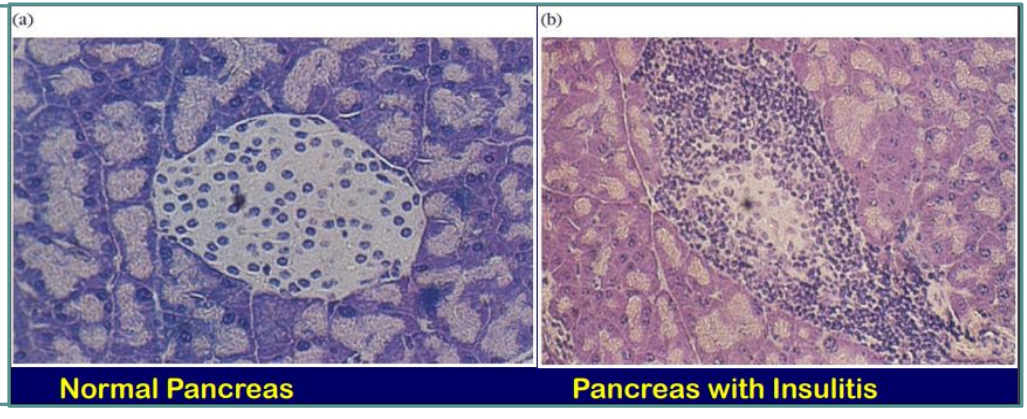
Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	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
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

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

- 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.



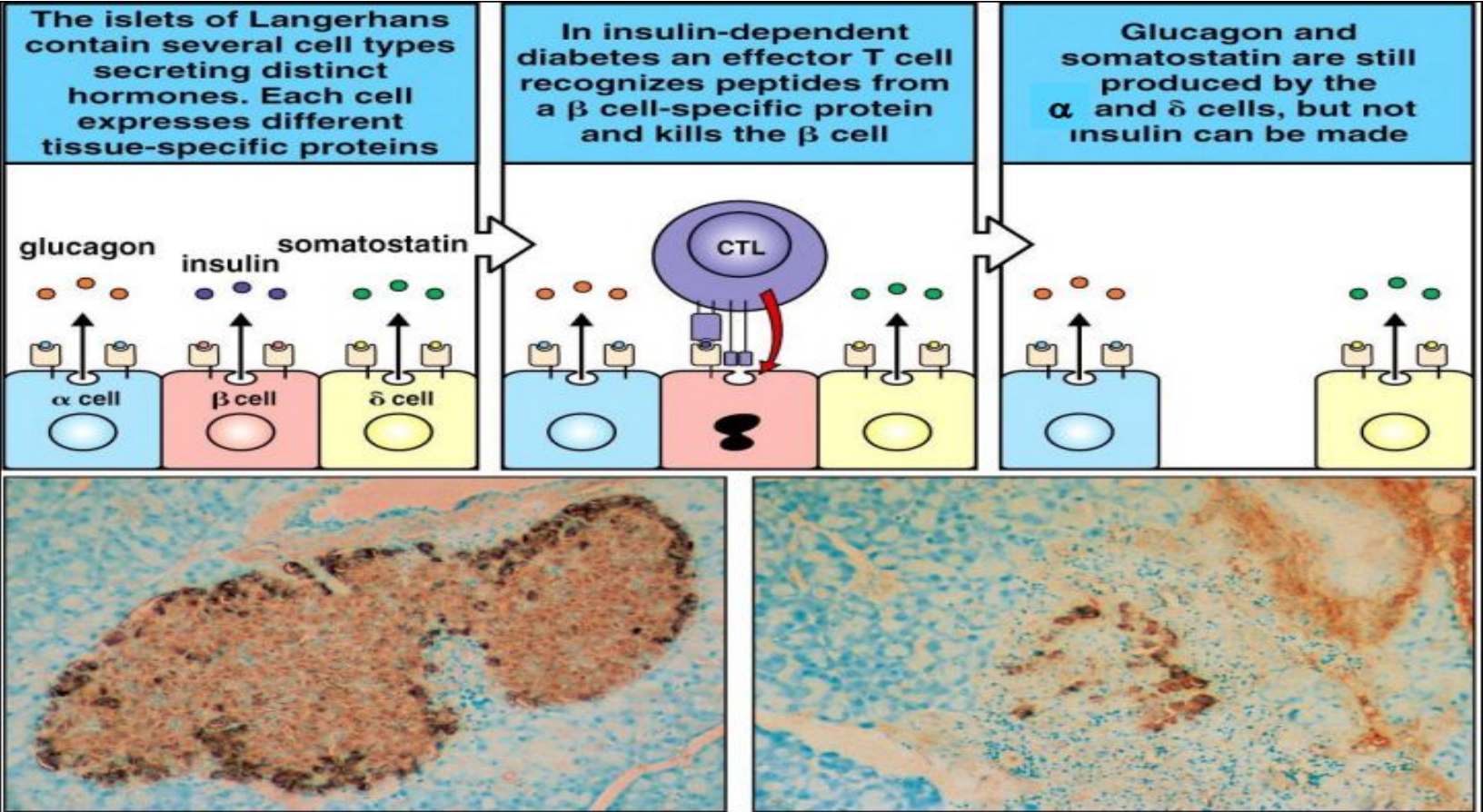


Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

4-Polyclonal B cell activation

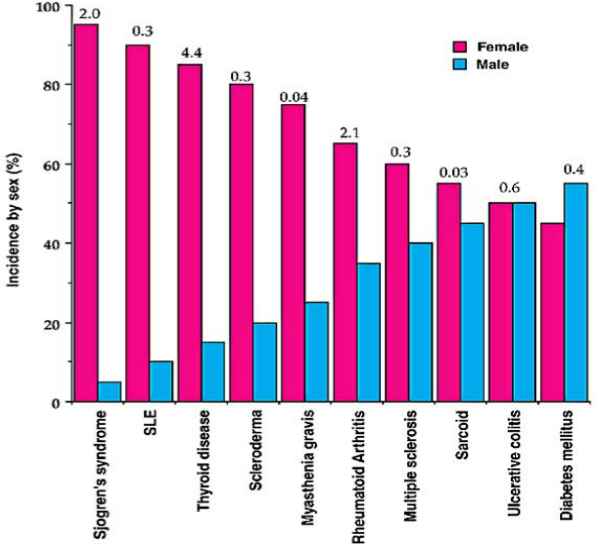
Viruses and bacteria can induce nonspecific polyclonal B cell activation, including:

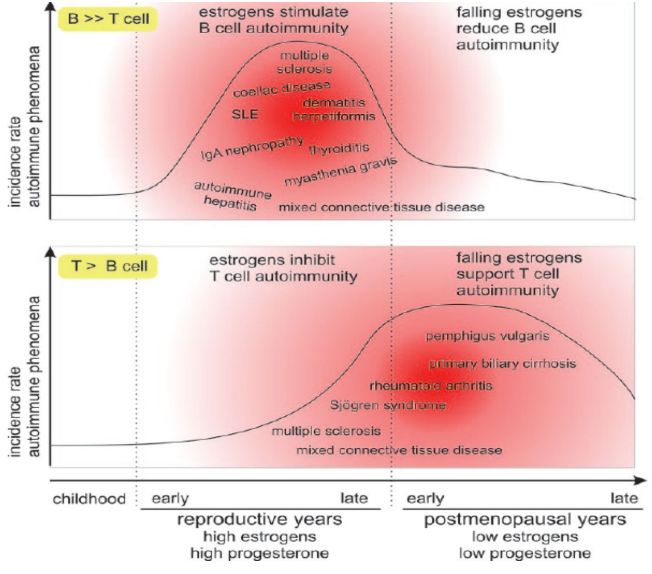
- Certain gram negative bacteria
- Herpes simplex virus.
- Cytomegalovirus.
- Epstein Barr Virus.
- Human immunodeficiency virus (HIV)

- 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

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 either appears or exacerbates during pregnancy.





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.**

MCQ

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

A- antibodies B- immune system

C- T cells D-autoimmunity

2-central tolerance is happening in

A- thymus B- bone marrow

C- both D- neither

3- which of the following the initiating step in a variety of autoimmune diseases

A- Polyclonal B cell activation B- Sequestered antigens

C- Molecular Mimicry D- Inappropriate Expression of Class II MHC

4-which one will not induce self-tolerance.

A- Polyclonal B cell activation B- Sequestered antigens

C- Molecular Mimicry D- Inappropriate Expression of Class II MHC

5-which one occur due to the local production of IFN-γ

A- Polyclonal B cell activation B- Sequestered antigens

C- Molecular Mimicry D- Inappropriate Expression of Class II MHC

6-which of the following induce nonspecific polyclonal B cell activation

A-bacteria B-virus

C-fungus D-a&b

7-About 90% of autoimmune diseases occur in

A-children B-men

C-adult D-women

8-Tolerance to self is acquired by

A-Deletion B-Functional inactivation

C-both D-neither

Answers

1-D

2-C

3-C

4-B

5-D

6-D

7-D

8-C

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٤- العنود المعيثم
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