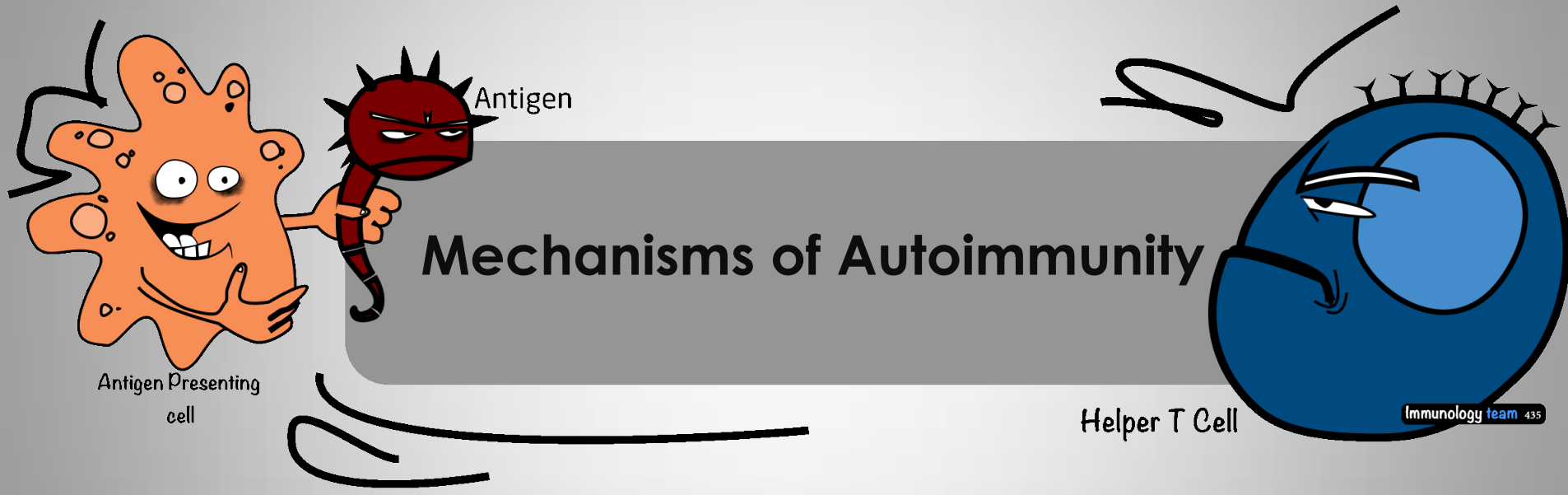


Mechanisms of Autoimmunity

Color index

- Extra explanation

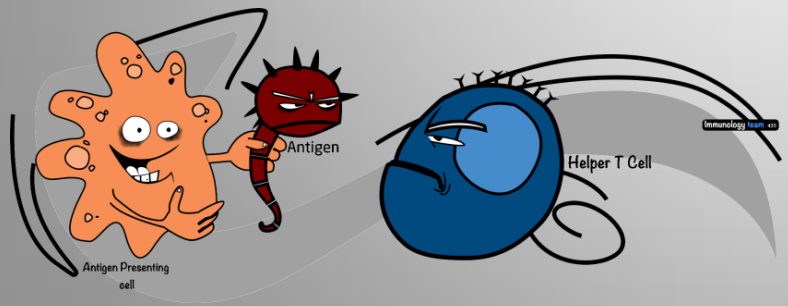
Objectives :

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



Autoimmunity

A condition that occurs when the immune system mistakenly attacks

and

DESTROYS HEALTHY BODY TISSUE

The Immune system has evolved to discriminate between:

Self Ag

Originates **within** the body

e.g. Blood group Ag, MHC Ag

Non-Self Ag

Originate **outside** the body

e.g. Bacteria

This mechanism is mediated by:

Auto-reactive T cells and **Auto-reactive B cells.**

Autoantibodies (antibodies directed at normal cellular components)
Produced by auto-reactive B cells

مثال الجيش لو في واحد منهم هاجم فريقه بيطلعوه او ممكن يحبسوه

Tolerance to self is acquired by:

Deletion

Clonal deletion

Deactivation of auto-reactive T cells and auto-reactive B cells by killing them! (**Apoptosis**)

Functional inactivating

Clonal anergy

Inactivation for those developing lymphocyte which has **high affinity** receptors for **self Ag.**

Anergy: State during which a cell can not become activated by exposure to its Ag.
T & B cells become anergic when exposed to their Ag without costimulatory signal.

* To remember: **A**nergy = **Lack** of **Energy**.

Self tolerance

Central Tolerance

(Thymus & Bone marrow)

Which are the primary lymphoid organs

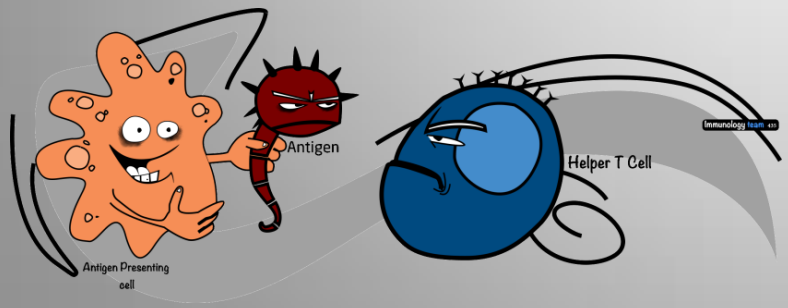
Central tolerance is established by deletion of lymphocytes in primary lymphoid organs (thymus for T cells and bone marrow for B cells) if they possess receptors that can react with self-antigens or by the emergence of regulatory T cells that can inhibit self-reactive cells

Peripheral tolerance

(peripheral tissues)

Which is the secondary lymphoid tissues

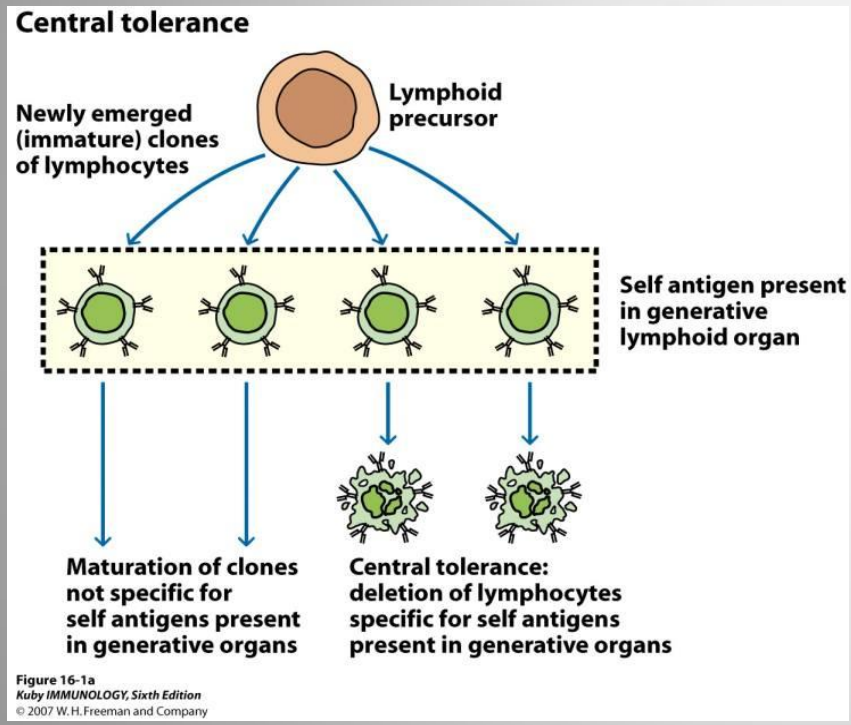
Peripheral tolerance involves deletion, rendering anergic or actively suppressing escaped lymphocytes that possess receptors that react with self-antigens. This process occurs in secondary lymphoid organs.



Tolerance is a good thing , when your tolerance fails you will have an autoimmune disease.

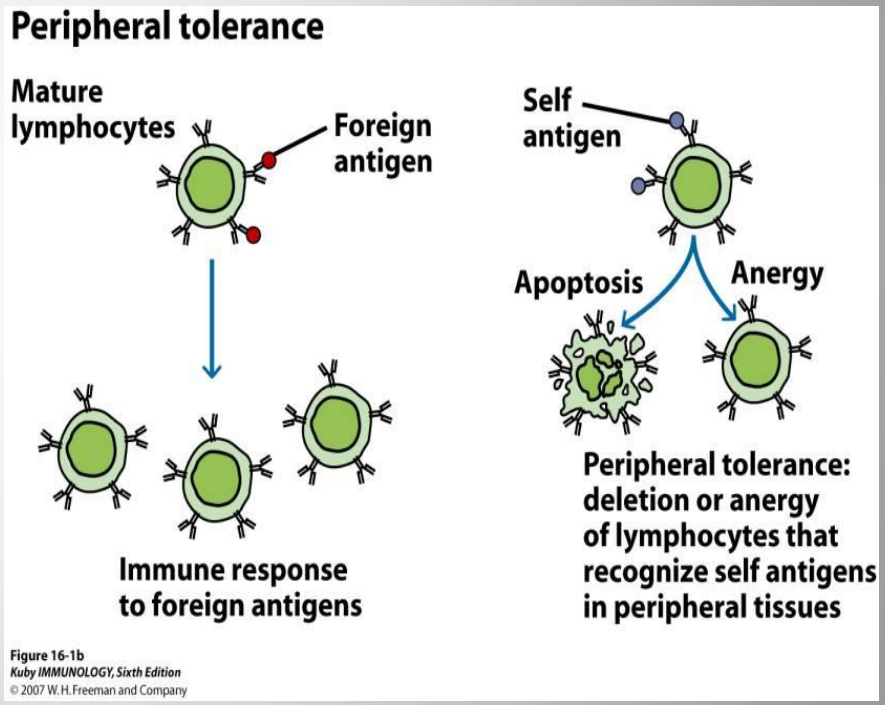
Self tolerance

Central tolerance

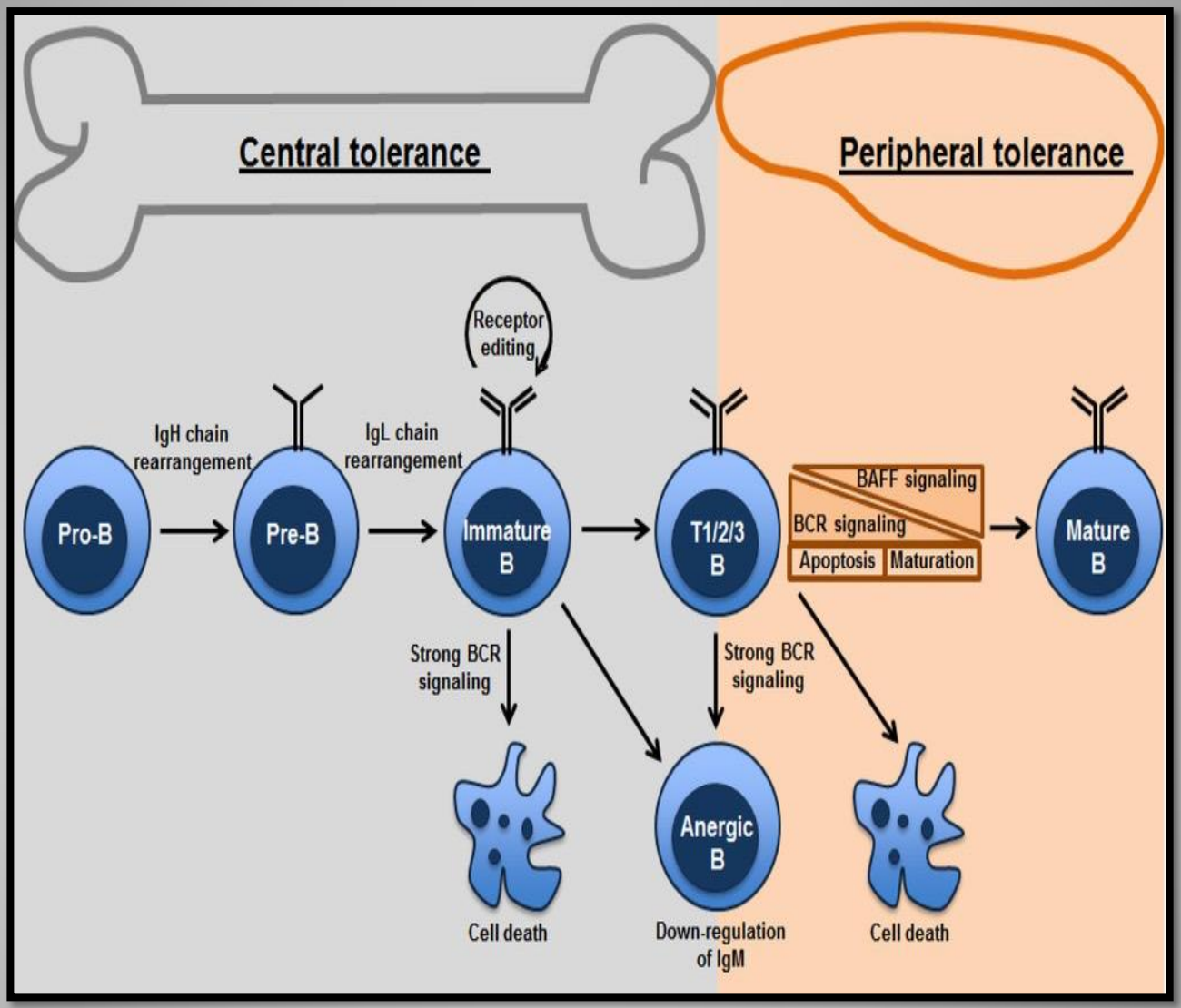


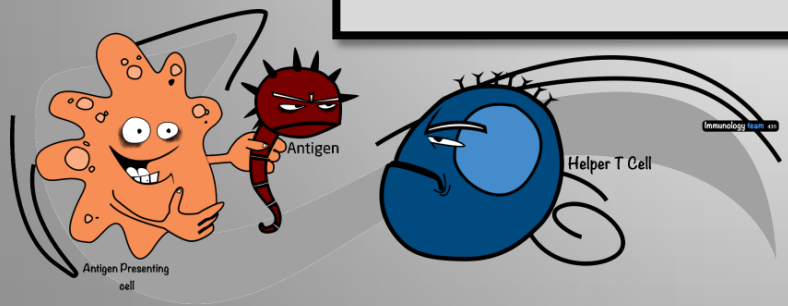
يحدث الليمفاوية تصنيعها انها تتعرف على أنسجة الجسم كأجسام غريبة

Peripheral tolerance



بهاجم الجسم هذه الخلايا في الأجزاء الاخرى من الجهاز المناعي كالطحال او العقد الليمفاوية بالحذف او تعطيل عملها





Extra explanation

Proposed mechanisms that are thought to cause autoimmune disorders :

1)Sequestered antigens

2)Molecular mimicry

3)Inappropriate expression of MCH class II molecule on none-antigen presenting cells

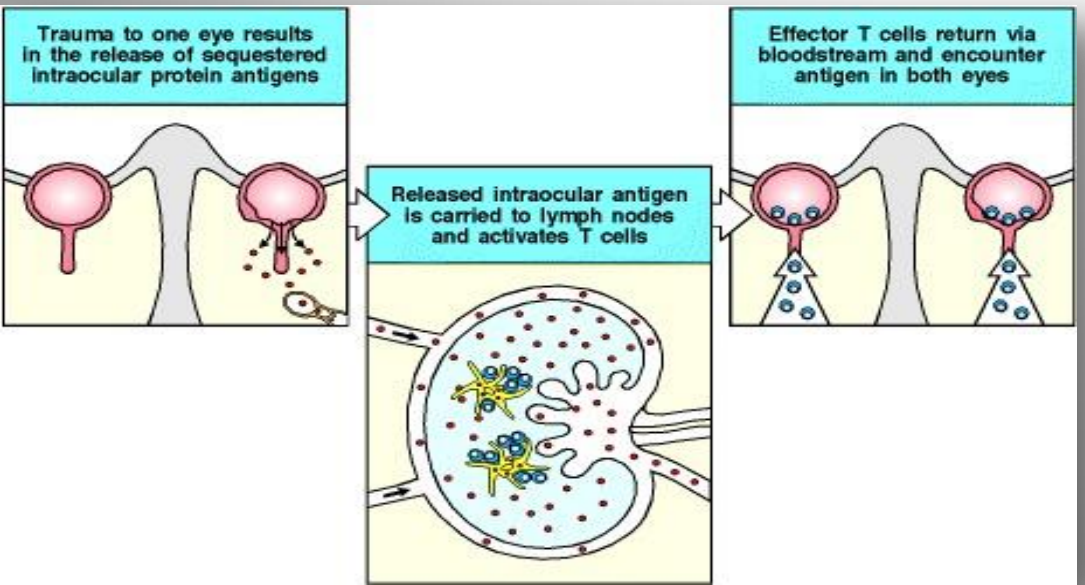
4)Polyclonal B cell activation

1) Sequestered antigens

There is sequestered (hidden) antigens in brain , the lenses of the eye and spermatozoa are isolated from the circulation of the blood and lymph . Therefore they are not in contact with the cells of the immune system (T-cells, B-cells) during a healthy state. But !! When body tissues are damaged by trauma , the hidden antigens are suddenly exposed to the immune system .

Examples

- **Anti-sperm antibodies are known to develop when sperm antigen exposed to B-cells after vasectomy** (A vasectomy is done to prevent fertility in males).
- **Lens protein of the eye enter the circulation as a consequence of crushing injury or surgery.**
- **Myelin basic protein (MBP) hidden by myelin sheath, when it is exposed to T-cells or B-cells it can cause multiple sclerosis.**
- **After myocardial infarction , heart muscle antigens are exposed to T-cells or B-cells.**

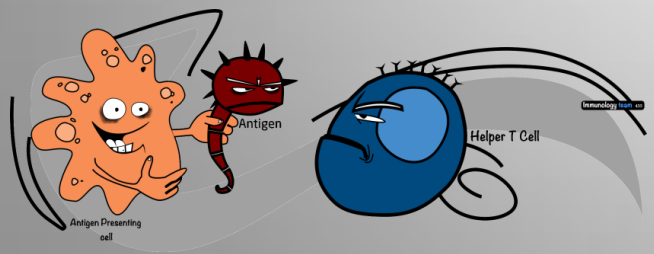


(sympathetic ophthalmia):
If one eye is ruptured by a blow or other trauma, an autoimmune response to eye proteins can occur, although this happens rarely. Once the response is induced, it often attacks both eyes (bilateral).

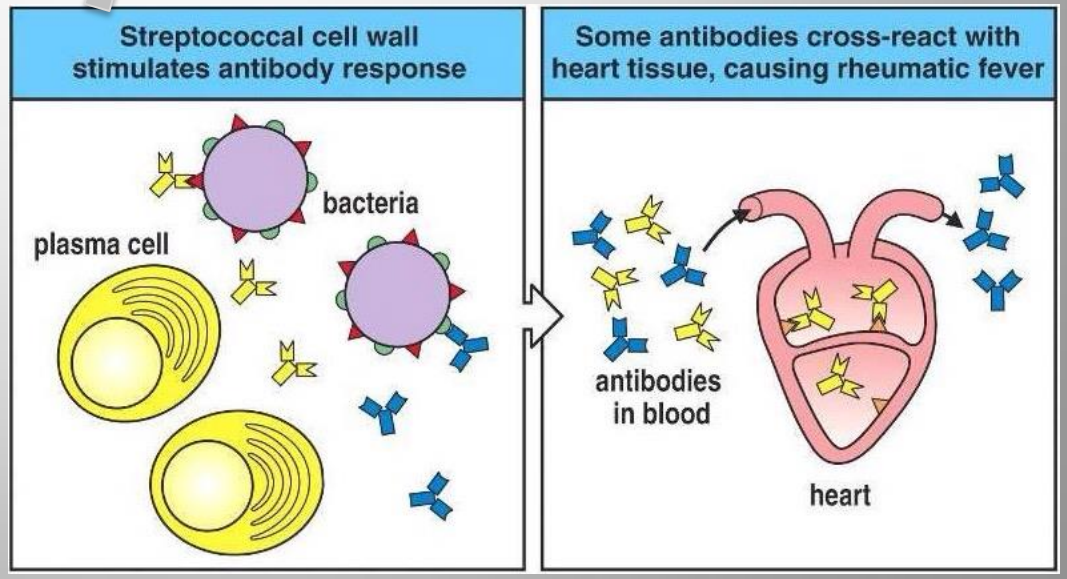
2) Molecular mimicry "Cross-reacting antigens"

It is basically the similarity or identicality between a foreign antigen from either a bacterium or a virus, and a self antigen.
This phenomenon(molecular mimicry) can initiate an autoimmune response in which this confusion is enough to auto-activate B and T cells to fight off the body's own antigens.
Molecular mimicry may be the initiating step in variety of autoimmune diseases

Rheumatic fever:
Is an inflammatory disease that's usually caused by Strep, this is a good example of molecular mimicry in which the Strept's antigens, known as M proteins, closely resemble proteins of heart valves. As your B cells make antibodies against M proteins of the pathogen, these antibodies also attack valves of the heart, resulting in permanent damage of the heart.



Extra !
Just for understanding the idea



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

We took this table from our slides
Check the next slide to understand the idea

Some examples of molecular mimicry

Adenovirus 12 E1B Resembles a Gliadin Causing Celiac disease

Klebsiella pneumoniae nitrogenase Resembles HLA-B27molecule Causing Ankylosing spondylitis

Rabies virus glycoprotein Resembles Insulin receptors

Papilloma virus E2 Resembles Insulin receptors Causing Diabetes Mellitis

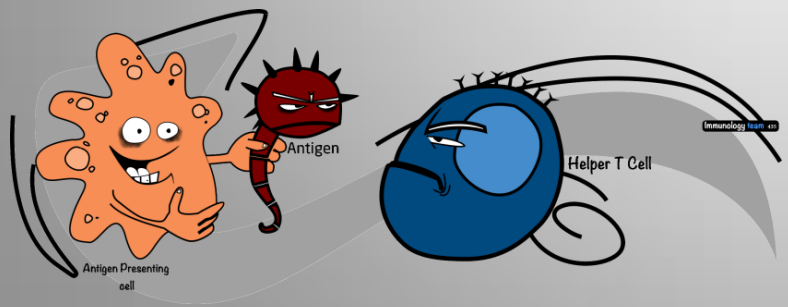
Human cytomegalo virus Resembles HLA-DR molecule

Measeles virus P3 Resembles Myelin basic protein Causing Multiple Scelerosis

Measeles virus P3 Resembles Corticotropin causing Hypoglycemia

Human immunideficiency virus p24 Resembles Human IgG constant region Causing Release of histamine

Poliovirus VP2 Resembles Acetylcholine receptor Causing Myasthenia gravis, paralysis



3) Inappropriate expression of class II MHC molecule

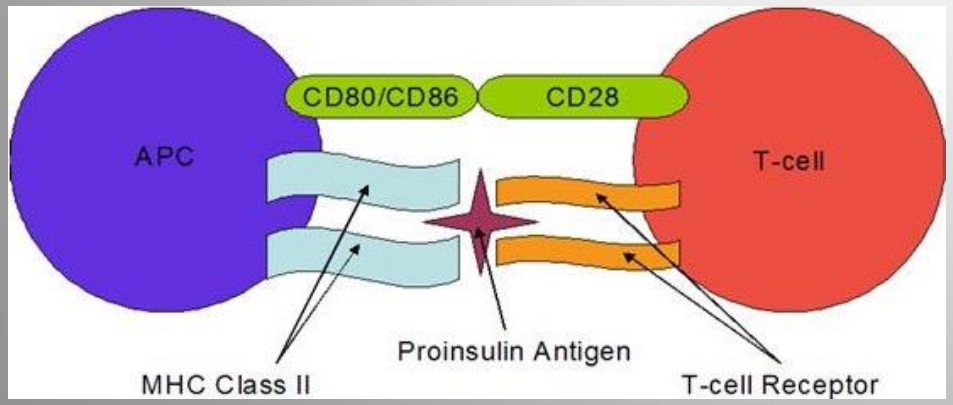
Class II MHC, which is ordinarily expressed on antigen presenting cells is abnormally expressed.
The APC can no longer detect viruses, bacteria and distinguish them from the normal cells in our body!
Therefore, they attack.

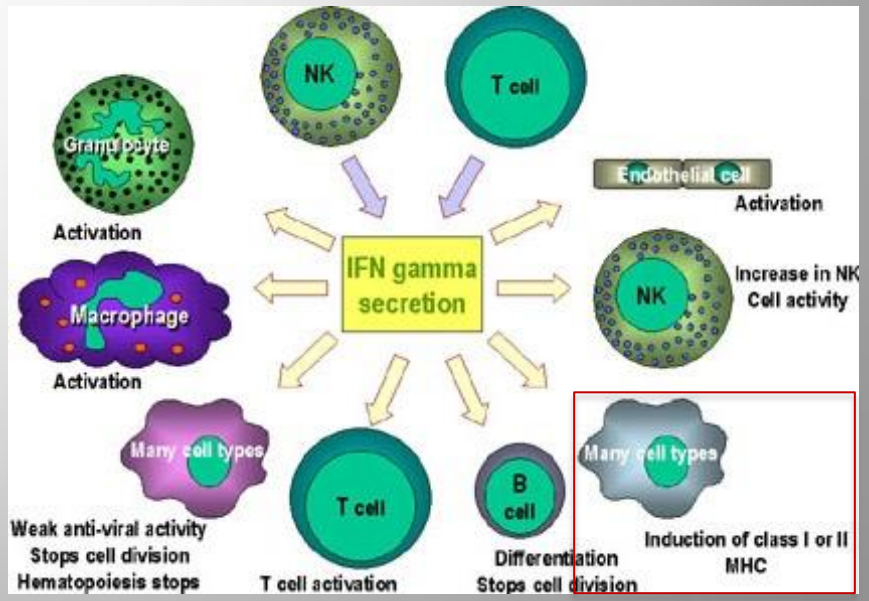
This may occur due to the local production of IFN- γ, which is known to increase class II MHC expression on a variety of cells.
The inducer of IFN- γ under these circumstances could be a viral infection.

Extra !

APC	Location
Monocyte	Peripheral Blood
Macrophage	Tissues
Dendritic cells	Lymphoid tissue
Langerhans cells	Epidermis
B cells	Lymphoid tissue, Blood

Extra explanation!

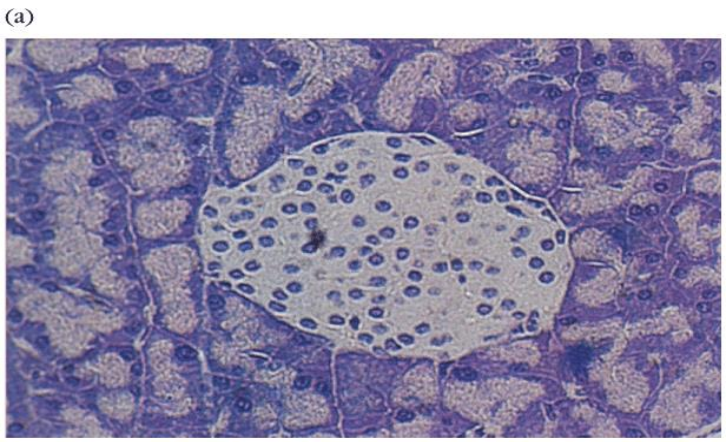




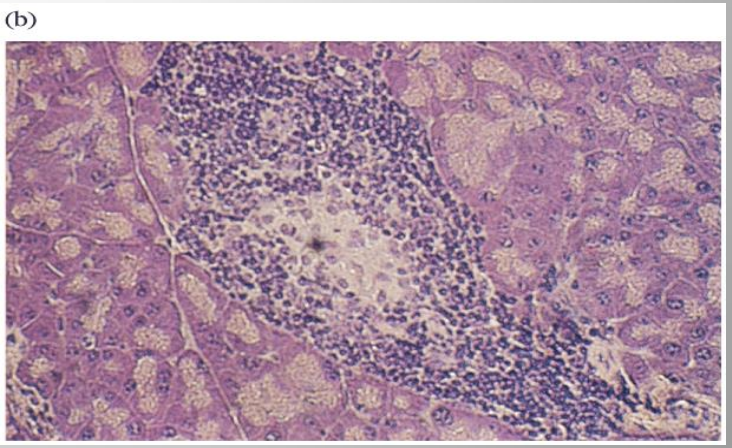
Type I Diabetes: Pancreatic β cells express abnormally high levels of MHC I and MHC II.

Type 1 diabetes is an autoimmune disease. An autoimmune disease results when the body's system for fighting infection (the immune system) turns against a part of the body. In diabetes, the immune system attacks the insulin-producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin. A person who has type 1 diabetes must take insulin daily to live.

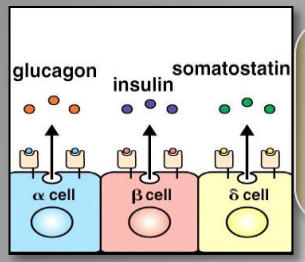
At present, scientists do not know exactly what causes the body's immune system to attack the beta cells, but they believe that autoimmune, genetic, and environmental factors, possibly viruses, are involved. It develops most often in children and young adults, but can appear at any age.



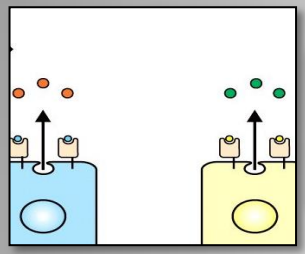
Normal pancreas



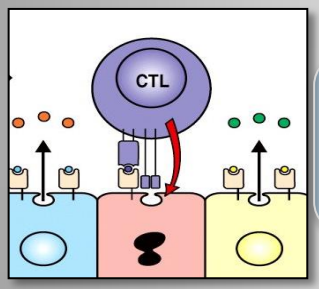
Pancreas with insulitis



*The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins.

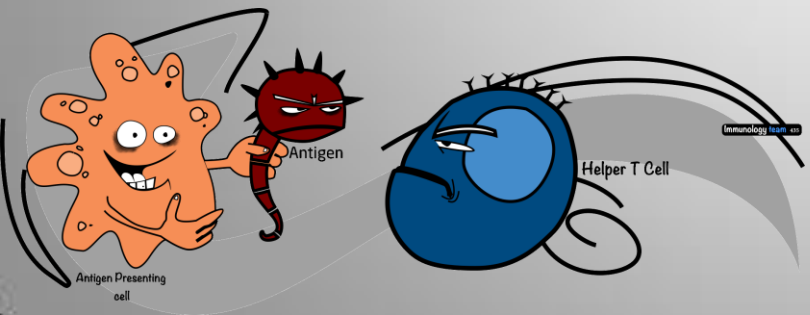


In insulin-dependent diabetes an effector T cell recognizes peptides from a beta cell-specific protein and kills the beta cell.



Glucagon and somatostatin are still produced by the beta and sigma cells, but no insulin can be made.

-**Extra Explanation:** Inappropriate expression of **class II MHC** molecules, which normally expressed only on antigen presenting cells, may serve to sensitize TH cells to peptides derived from the beta cells, allowing activation of B cells or TC cells or sensitization of TH1 against self-antigen. Ultimately, the beta cells are killed and no insulin can be made.



* **the islets of Langerhans** are the regions of the pancreas that contain its endocrine (i.e., hormone-producing) cells.

4) Polyclonal B cell activation

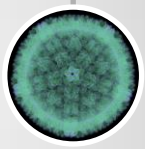
Viruses and bacteria can induce nonspecific polyclonal B cell activation.

Examples:

Certain gram negative bacteria

Herpes simplex virus

Cytomegalovirus



Epstein Barr Virus

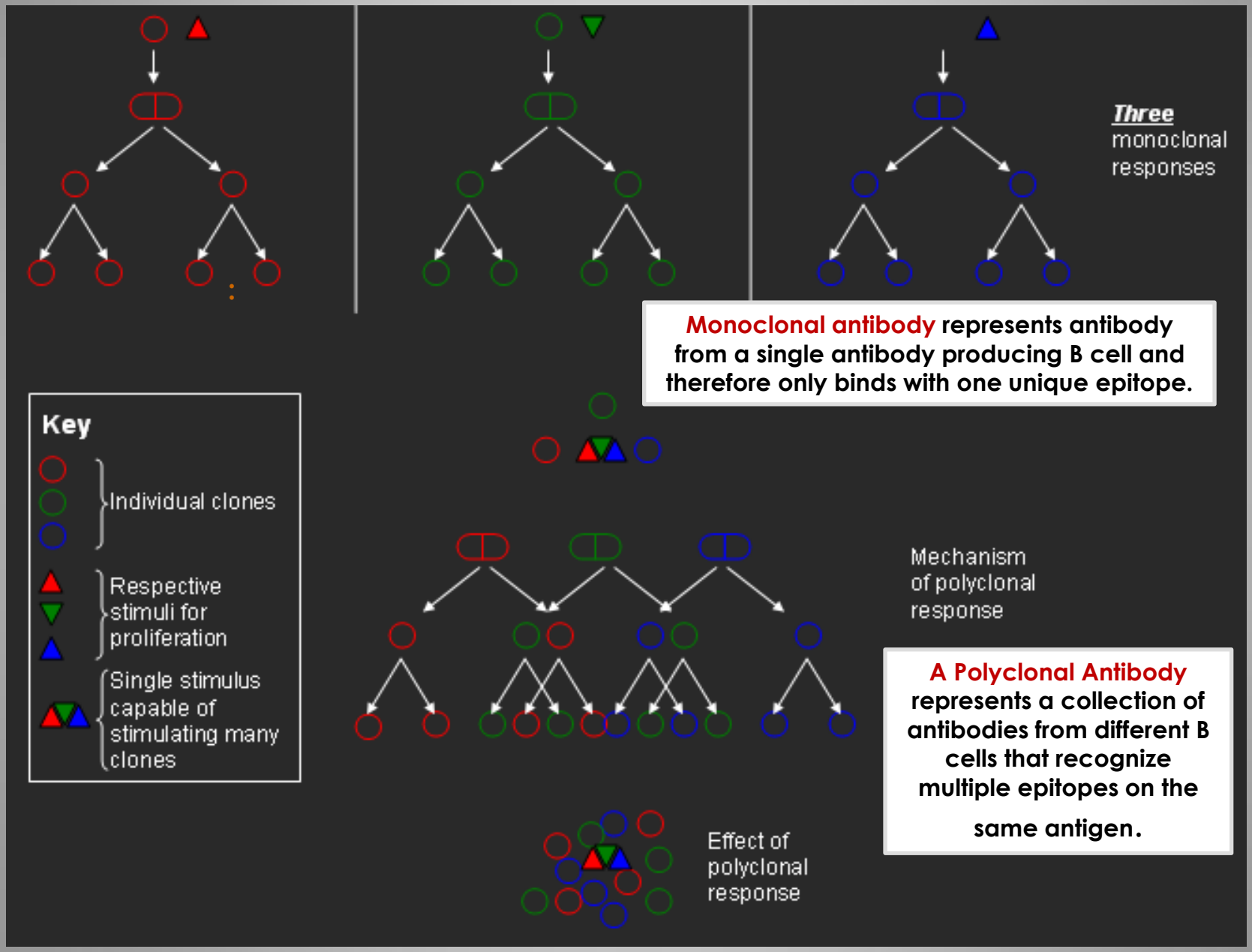
Human immunodeficiency virus

- A number of viruses and bacteria can induce the proliferation of numerous clones of B cells to secrete IgM in the absence of requirement for CD4 T cell

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

Patients with infectious mononucleosis which is caused by EBV a variety of auto-antibodies are produced. Many AIDS patients also show high levels of nonspecific antibody and auto-antibodies to RBC's and platelets

monoclonal B cells activation VS. polyclonal B cells activation:



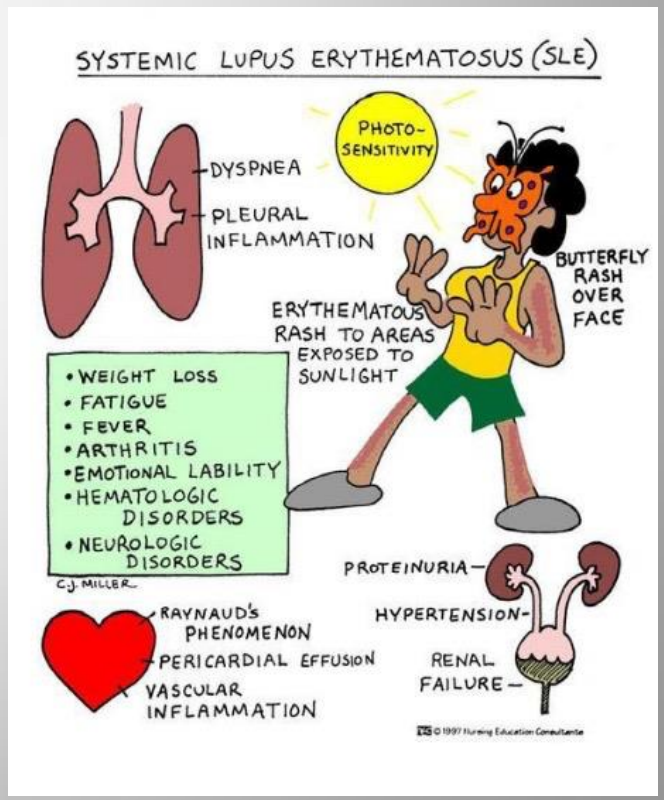
Hormonal factors

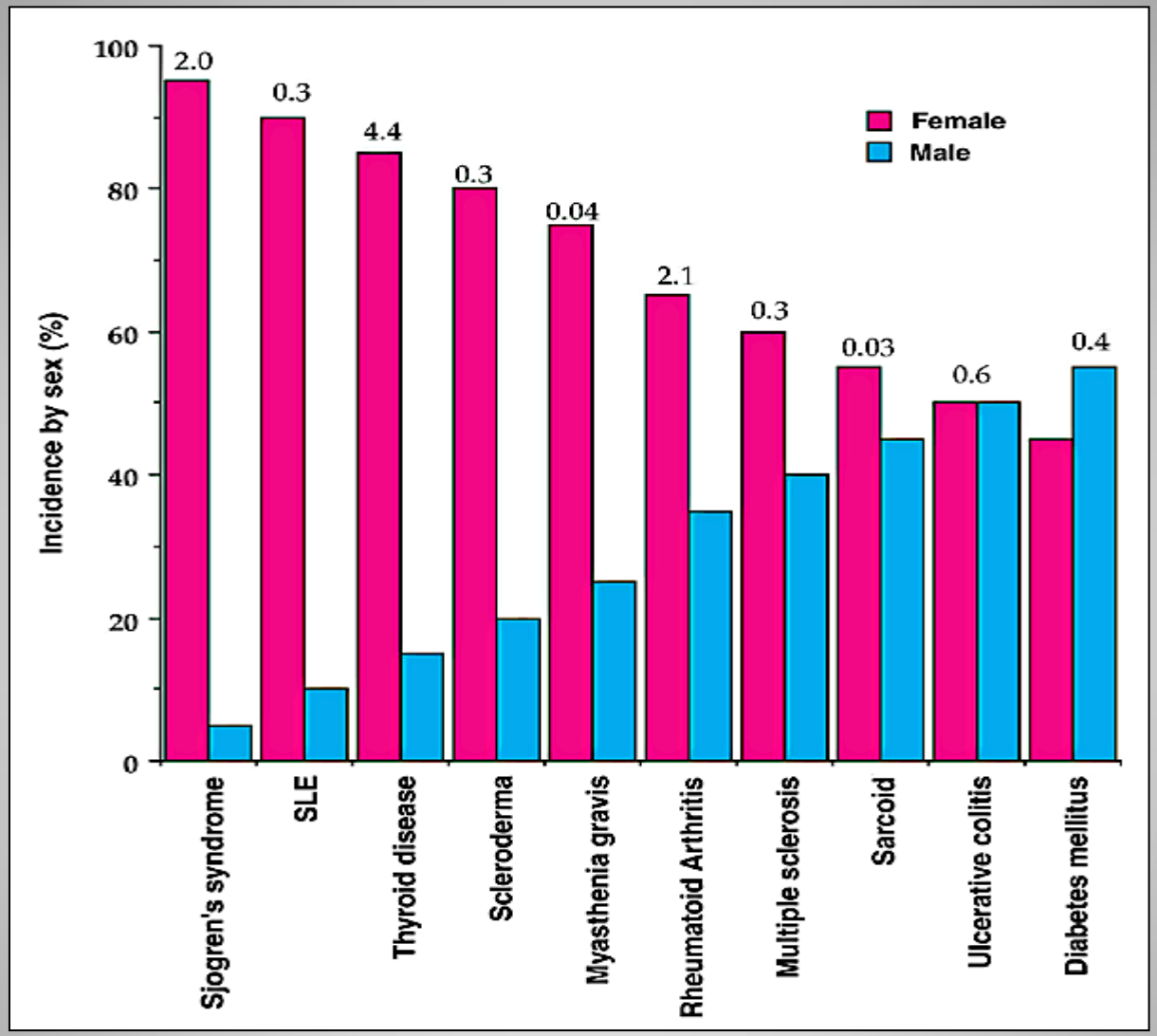
- About 90% of autoimmune diseases occur in women (cause not known)

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

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

-hormones may play a role but not a cause.
- In pregnancy the immune system will be active which will lead to increase the ability of autoimmunity disease, even in the period.





*All **autoimmune diseases** occur in women more than men except diabetes mellitus (DM).*

Estrogen stimulates B cells autoimmunity.

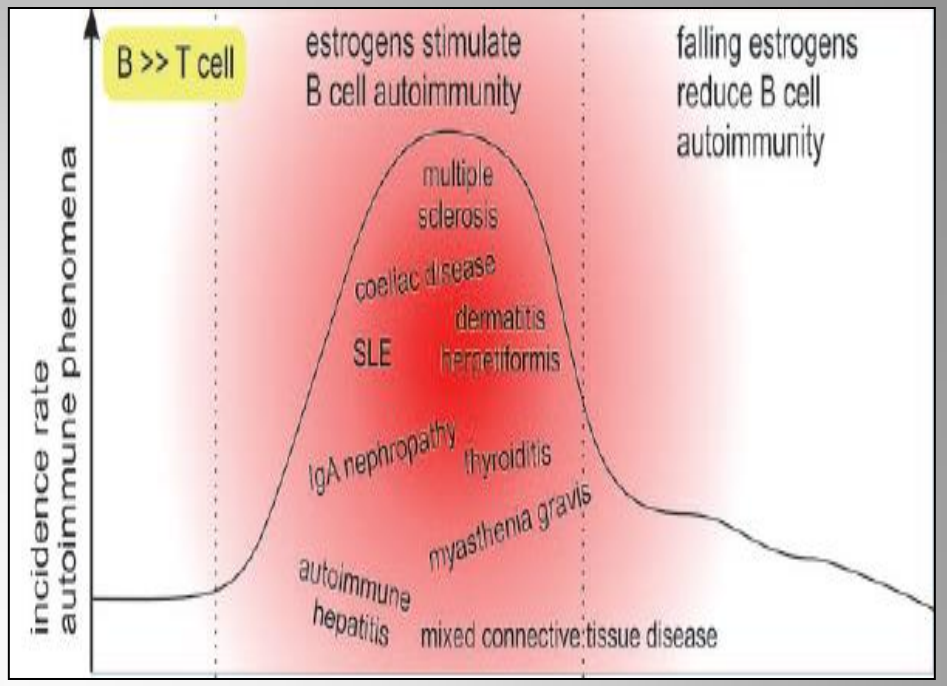
-Falling estrogens reduce B cell autoimmunity.

-Example of autoimmunity disease when B > T cells:

SLE, MS, coeliac disease

coeliac disease:

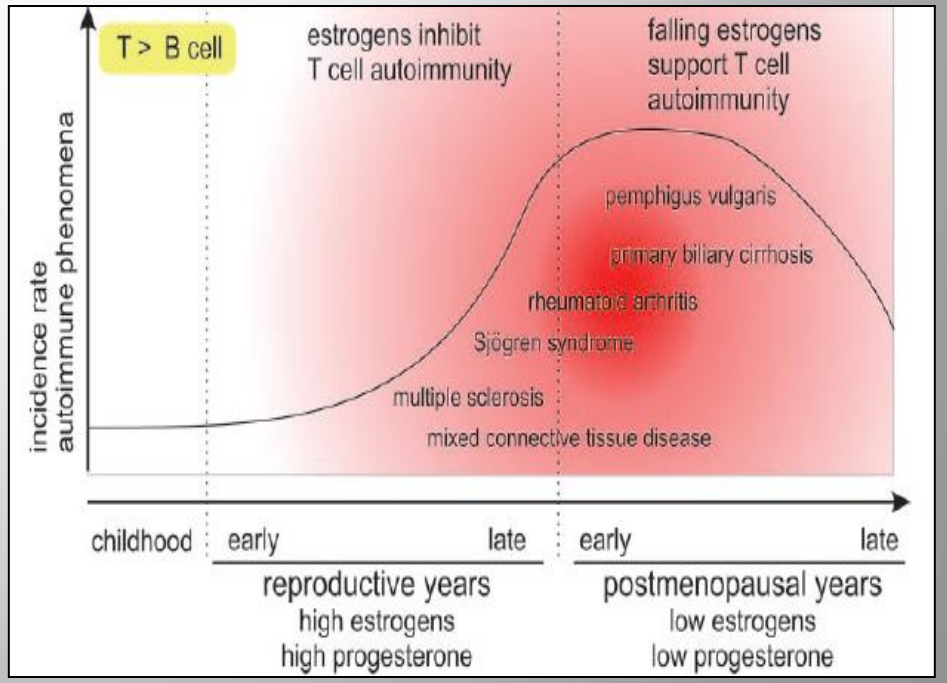
حساسية من القمح ولما الشخص ياكله الجهاز المناعي يبدأ يحارب الجهاز الهضمي



Estrogens inhibit T cells autoimmunity.

-Falling estrogens support T cell autoimmunity.

-Example of autoimmunity disease when T > B cells: diabetes, MS (multiple sclerosis)



Drug induced Lupus erythematous

Lupus erythematosus like syndrome develops in patients receiving variety of drugs many of them associated with development of anti-nuclear antibodies(ANAs)

- Renal and CNS involvement is uncommon
- Anti-histone antibodies are frequently present

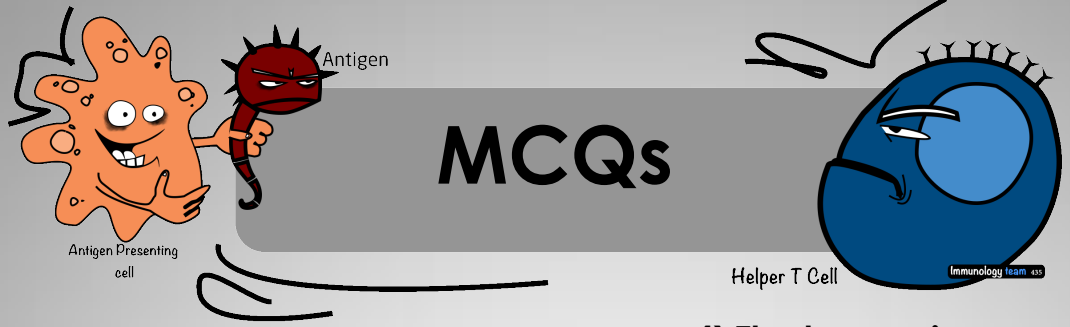
Examples

Hydralazine
Used for hypertension

Procenamide
Used for cardiac arrhythmia

Isoniazid
Antibiotic for tuberculosis

Penicillin
Group of antibiotics



MCQs

1) A patient with type 1 diabetes. His autoimmunity condition is caused by molecular mimicry between ……. and his insulin receptor's proteins.
A- Cytomegalovirus
B- poliovirus
C- papilloma virus
D- Rabies virus glycoprotein
E- both C and D are correct

2) Human cytomegalovirus has similar antigenic determinants as human host's …….
A- HLA-DR molecule
B- HLA-B27 molecule
C- Corticotropin
D- Myelin basic protein
E- Human IgG constant region

3) Which one of these statements is correct regarding type 1 diabetes:
A- it is caused by sequestered antigens.
B- all the islets of Langerhans are affected.
C- beta cells are present but cannot produce insulin.
D- insulin is absent due to the killing of the beta cells.

4) The human immune cells may attack their own …… , because they might mistakenly identify them as measles virus P3.
A- HLA-DR molecule
B- HLA-B27 molecule
C- Corticotropin
D- Myelin basic protein
E- Both C and D are correct

5) AIDS is an autoimmune condition caused by infection with human immunodeficiency virus, HIV has a similar sequence in its 160 molecular residue as ……
A- IgM constant region
B- IgD constant region
C- IgG constant region
D- IgE constant region
E- Both C and D are correct

Answers : 1)E 2)A 3)D 4)E 5)C

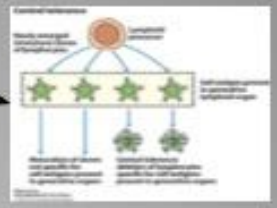
Tolerance to self acquired by

Deletion

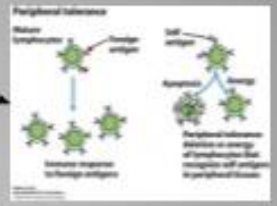
functional inactivation

Self-Tolerance types:

Central Tolerance (Thymus & Bone marrow)



Peripheral tolerance (Peripheral tissues)



Non-self

Self

Induction of Autoimmunity "Proposed Mechanisms!"

Sequestered antigens

- some self-antigens are hidden in specialized tissues
- not seen by the developing immune system → no self-tolerance
- Exposure of T cells to tissue-specific self-antigens in the periphery results in activation.

Examples:

- Myelin basic protein (MBP)
- Sperm-associated antigens
- Lens and corneal proteins of the eye
- Heart muscle antigens

Molecular Mimicry (Cross-reacting Antigens)

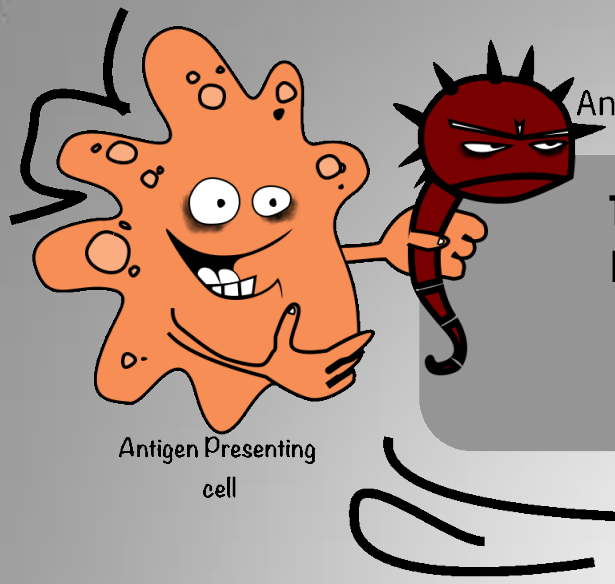
- viruses and bacteria have antigenic determinants = normal host cell components.
- occurs in a wide variety of organisms
- may be the initiating step in a variety of autoimmune diseases.

Inappropriate Expression of Class II MHC Molecules

- Class II MHC ordinarily expressed on antigen presenting cells
- Abnormal expression allows the recognition of auto-antigens by self-reactive T cells.
- may occur due to the local production of IFN-, which increases class II MHC expression on a variety of cells.
- The inducer of IFN- could be a viral infection.

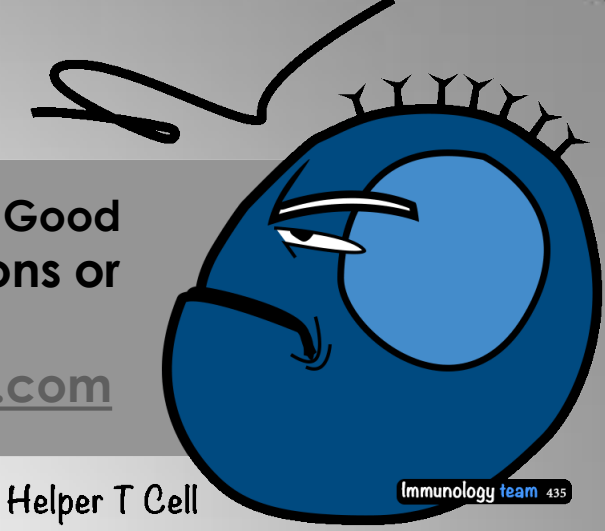
Polyclonal B Cell Activation

- Viruses and bacteria can induce it non-specifically.
- They induce the proliferation of many B cell clones to secrete IgM in the absence CD4 T cell helper that 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.



Thank you for checking our work, Good luck. If you have any suggestions or alterations contact us!

Email Immunology435@gmail.com



- جواهر الحربي
- أثير النشوان
- ربى السعران
- سارة المطوع
- شهد العنزي
- عريب العقيل
- فرح مندوزا
- لينة الشهري
- لولوه الصغير
- ملاك الشريف
- نورة الرميح
- نوف العبدالكريم
- هديل الغرير

- إبراهيم البيشي
- تركي العنزي
- عبدالاله ابو خلف
- عبدالناصر الوابل
- فيصل القحطاني
- ماجد العسبلي
- محمد الفواز
- ناصر المقبل