جامعة الملك سعود
King Saud University

Mechanism of Autoimmunity

Color code:
Important in red
Extra in blue

Immunology
MED438

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KING SAUD UNIVERSITY

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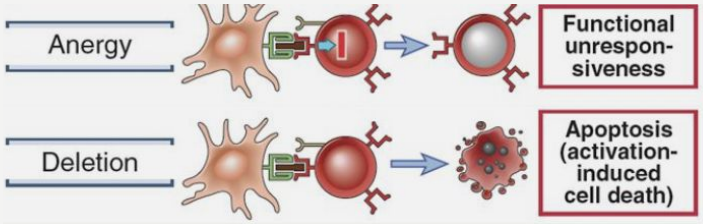
Editing file

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.

Self-Tolerance

- Self-tolerance: The immune system's ability to NOT attack healthy body tissues. (differentiation between self and foreign antigens)
- Acquired by central and/or peripheral tolerance.
- Failure of self-tolerance leads to autoimmune diseases, where autoreactive lymphocytes attack self antigens (healthy body tissues).



"Auto" indicates it attacks the body's own cells

Central Tolerance	Peripheral Tolerance
• In central lymphoid organs (thymus, bone marrow). • Immature autoreactive lymphocytes are stopped from exiting primary lymphoid organs and are broken down there (deletion). • Autoreactive lymphocytes CAN sometimes pass through into the peripheral lymphoid organs.	• In peripheral tissue and secondary lymphoid organs. • Happens when central tolerance fails and autoreactive T cells pass to the periphery. • Either apoptosis (deletion) or anergy (functional deactivation) • Anergy: the deactivation of an autoreactive T-cell through APC binding that either lacks costimulation (CD28+B7) or has CTLA-4+B7 binding. CTLA-4 is a protein receptor that has the opposite effect of CD28. It inhibits T-cell activation.

Autoimmunity Induction

There are 4 proposed (theoretical) mechanisms by which autoimmunity is induced:

1. Sequestered (hidden) Antigens

- Some self antigens are hidden in tissues and are normally not sensed by the immune system (no self-tolerance induced).
- When those self antigens are exposed to T cells (as a result of infection/trauma), an autoimmune reaction occurs.

Examples of sequestered antigens:

- ➢ Myelin Basic Protein (associated w/Multiple Sclerosis)
- ➢ Lens and Corneal Proteins (post eye infection/trauma)
- ➢ Sperm-associated antigens (post vasectomy)
- ➢ Heart muscle antigens (post myocardial Infarction)

Sympathetic Ophthalmia:
Trauma in one eye releases the sequestered intraocular antigens to the Lymph node (activates T cells).
The T cells will then move to the undamaged eye and attack the self-antigens there (autoimmune induction).

Autoimmunity Induction

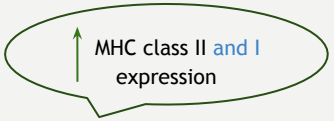
2. Molecular Mimicry

- Viruses and bacteria possess similar/identical antigenic determinants to those of normal cells.
- **Initiating step** in a variety of autoimmune diseases.

Main examples: (no need to memorize, but understand the concept)

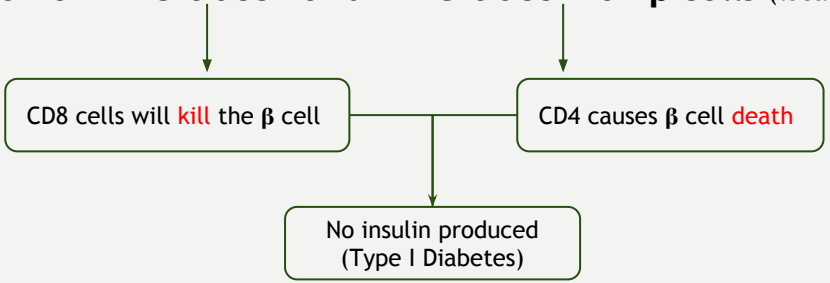
HIV p24	(G V E T T T P S)	Poliovirus VP2	(S T T K E S R G T T)
IgG constant region	(G V E T T T P S)	Ach receptor	(T V I K E S R G T K)

3. Inappropriate Expression of Class II MHC Molecules



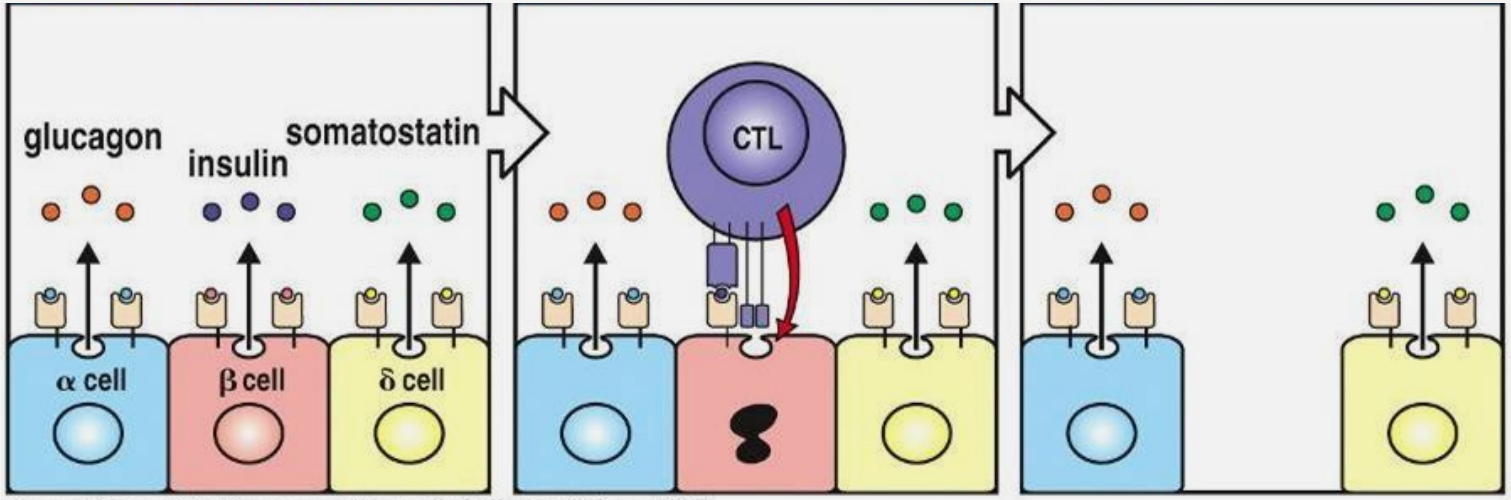
- Abnormal expression of MHC Class II on non-APC cells (e.x. pancreatic β cells) due to IFNγ production (induced by a viral infection) causes self-reactive T cells to destroy them

Type I diabetes (abnormal expression of both MHC classes):
Abnormally high expression of MHC class I and MHC class II on β cells (located in pancreatic/langerhans islets)



Autoimmunity Induction

Type 1 Diabetes (illustration)



A normal islet of langerhans containing several cell types (3 demonstrated), each secreting different hormones and expressing different proteins.

In Type I diabetes (insulin-dependent), an effector T cell attacks and kills the **β** cell because it is abnormally expressing MHC peptides.

Insulin can no longer be produced due to the **β** cell death, while glucagon (*α* cell) and somatostatin (*γ* cell) will continue being produced. This leads to Type I diabetes.

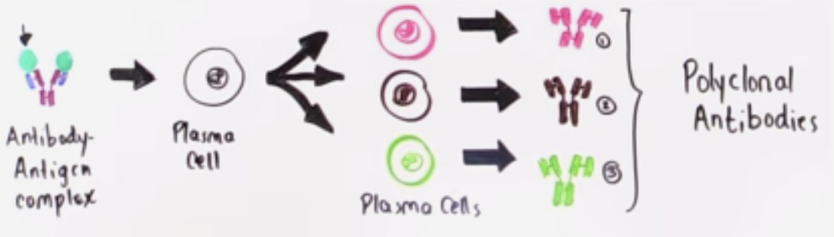
Autoimmunity Induction

4. Polyclonal B Cell Activation

- Happens when a polyclonal B cell (nonspecific) is activated (becomes a plasma cell) by certain viruses and bacteria without the help of T cells (T-independent).
- This self-reactive plasma cell will proliferate and eventually produce polyclonal antibodies (mainly IgM), some of which will be autoantibodies.

Viruses and bacteria that induce the activation of polyclonal B cells are:

- Certain gram negative bacteria
- Herpes simplex virus
- Cytomegalovirus



- Epstein Barr Virus (herpes 4 virus)
- HIV

Cause infectious mononucleosis (glandular fever), an autoimmune disease with a variety of autoantibodies

Click here for a video explaining the concept of "polyclonal" antibodies

Hormonal Factors

- 90% of autoimmune diseases occur more in women.

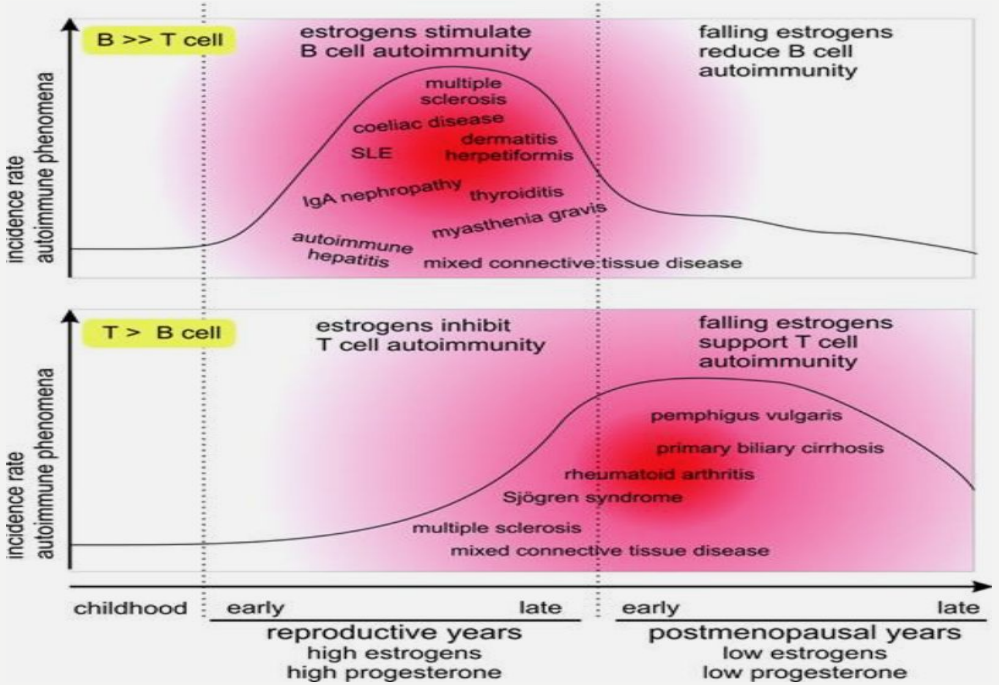
(ulcerative colitis occurs equally in both sexes, while diabetes occurs more in males)

High estrogen levels will induce B-cell maturation, which will lead to the production of anti-DNA antibodies.

- **High estrogen levels (pre-menopause):**
  - Stimulate B-cell autoimmunity (SLE).
  - Inhibit T-cell autoimmunity (rheumatoid arthritis).

- **Low estrogen levels (post-menopause):**
  - Inhibit B-cell autoimmunity.
  - Stimulate T-cell autoimmunity.

- SLE (B-cell autoimmunity) either appears or exacerbates during pregnancy due to hormonal irregularities.



Drug induced Lupus Erythematosus

Autoimmune disease in which the immune system attacks healthy tissues caused by the chronic intake of certain drugs, causing lupus-like symptoms

- Anti-histone antibodies are frequently present, and are used to differentiate between drug induced diseases from others.
- Associated with the development of anti-nuclear antibodies, which are used to diagnose autoantibodies.
- Renal and CNS involvement is uncommon

In short, DILE is a variant of SLE that resolves within days to months after withdrawal of the causing drug(s).

- **Examples:**

➢ Hydralazine (used for hypertension)
➢ Procainamide (antiarrhythmic)
➢ Isoniazid (Anti TB)
➢ Penicillin (antibiotic)

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

Quiz:

1. Which of the following best describes a CD8 T cell antigen recognition process during self-tolerance?

a) MHC Class I-APC + CD28-B7
b) MHC Class II-APC + CTLA4-B7
c) MHC Class II-APC + CD28-B7
d) MHC Class I-APC + CTLA4-B7

2. A 69 y/o man w/type 1 diabetes underwent a heart attack that resulted in the body attacking the heart's α-myosin cells. Which choice fits best as the consequence of the heart attack?

a) Inappropriate MHC Class II expression autoimmune induction
b) Systemic Lupus Erythematosus
c) Sequestered Antigen autoimmune induction
d) Myocardial Infarction

3. Which cytokine has an etiological role in insulin-dependent diabetes?

a) IFNγ
b) TNF-a
c) TNF-b
d) None of the above

4. Which of the following is a characteristic of polyclonal B cell activation?

a) T-dependent
b) Induced by Gram positive bacteria
c) Causes include cytomegalovirus
d) Main antibody is IgG

5. Which of the following patients is most likely to develop a T-cell autoimmunity?

a) A 57 year old woman
b) A 69 year old man
c) A 28 year old woman
d) A 34 year old man

6. What can we use to diagnose autoantibodies?

a) Anti-histone antibodies
b) Anti-nuclear antibodies
c) Immunofluorescence
d) ELISA

1.D 2.C 3.A 4.C 5.A 6.B

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