Tolerance, autoimmunity & tumour escape mechanism

Level 1, Semester 2

Instructor Information

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Contact	Official email
Prof. Niveen Adel Mohamed El-wakeel	niveen10@gmail.com
Dr.Amany Elmatbouly Elsayed	amanielmatbouly@gmail.com
Dr.Aya Ahmad Elnegery	ayaelnegery@mans.edu.eg
Dr. Nada Hamid Qandeel	nadahamid@mans.edu.eg
Dr. Lamis Mohamed Taha	Lamis_mohamed@mans.edu.eg
Dr. Aya Gamal Borham	ayagamalborham@mans.edu.eg
Dr. Azza Mohamed Mamon	Azzam2010@mans.edu.eg

Learning Outcomes

1. Describe the features of immunological tolerance.

2. Explain the mechanism of immunological tolerance .

3. Define concept of and classify autoimmunity.

4. Explain the theories of autoimmune diseases.

5. Describe diagnosis and treatment of autoimmune diseases.

6. Describe Tumour escape mechanisms

Case scenario

48-year-old woman with minor bleeding symptoms (petechiae, purpura, and some nosebleeds). Blood count and clinical examination were normal, But her platelet counts are 28,000 per microliter, when the lower limit of a normal platelet count would be 150,000 per microliter.

- Mention an immunological mechanism for this case?
- Mention treatment for this patient?

Immunological Tolerance

Definition

- It is the state of unresponsiveness to self-antigens
- When an antigen induces tolerance, it is termed tolerogen .
- Loss of self tolerance leads to autoimmune diseases.

Immunologic features of tolerance

- Tolerance is specific and with immunological memory, it can exist in T-cells, B cells or both .
- Tolerance can be broken naturally (as in autoimmune diseases) or artificially (by X ray irradiation or certain drug treatments)

Mechanisms of tolerance:

A. Clonal deletion:

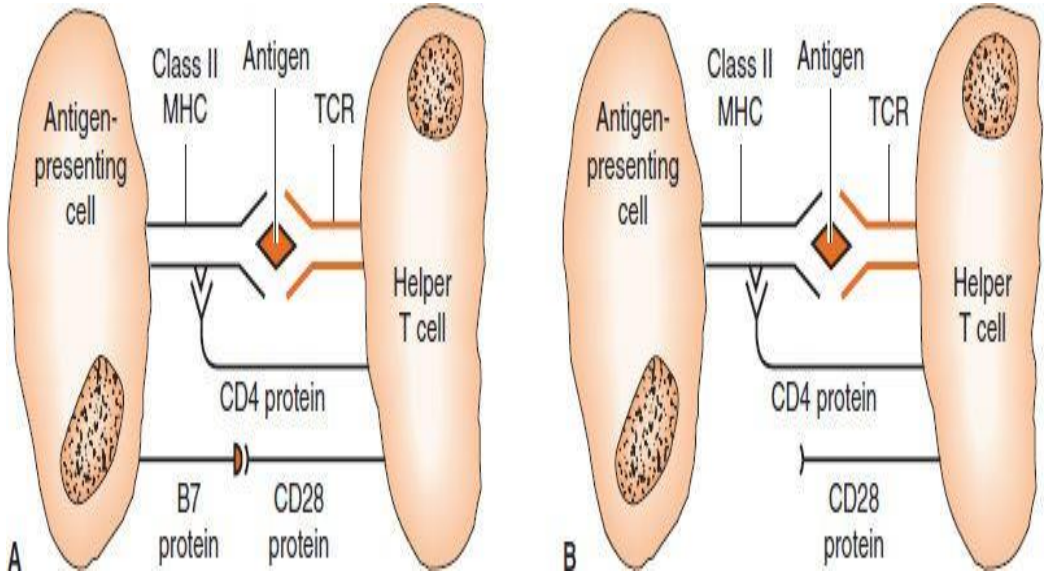
1- Auto-reactive T-cells are eliminated in the thymus following interaction with self-antigen during their differentiation (**negative selection**).

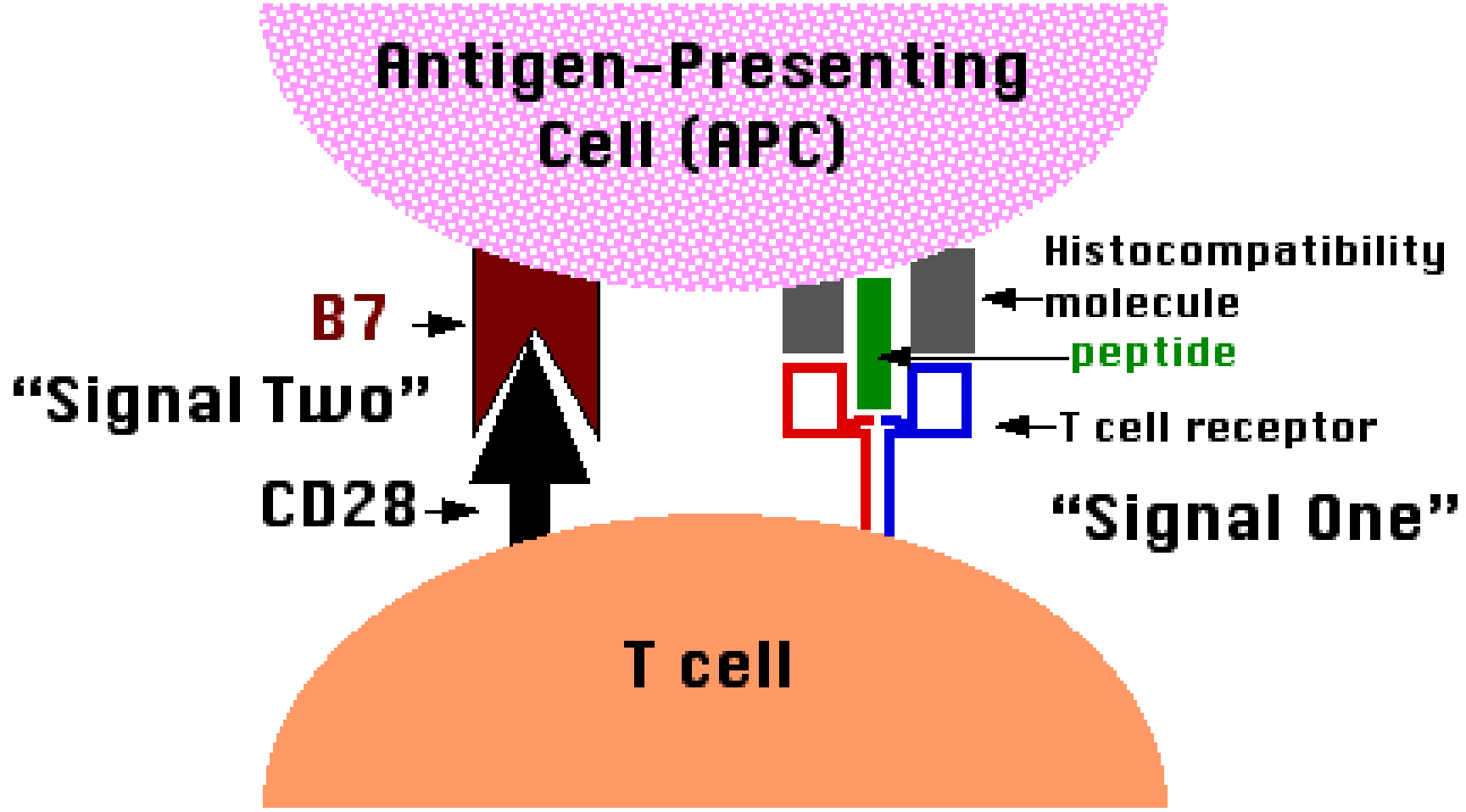
2- B cells develop in the BM and tested for self-reactivity. If immature B cells encounter self-antigen (soluble form or cells) it undergo apoptosis

Mechanisms of tolerance:

B. Clonal anergy:

1-Auto-reactive T cells, when exposed to antigenic peptides which do not possess co-stimulatory molecules (B7-1 or B7-2), become anergic to the antigen.





One method of the "co-stimulation" needed to activate T cells. If the T cell fails to receive "signal two", it dies by apoptosis. (B7 comes in two forms: B7-1 [CD80] and B7-2 [CD86].

- If self-reactive B cells are not deleted in the bone marrow, anergy ensures they remain inactive.

- **B cells require two signals for full activation:**

1. Signal 1: The B cell receptor (BCR) binds to an antigen.
2. Signal 2: A helper T cell provides additional activation signals (via CD40-CD40L interaction and cytokines).

- When immature B cells encounter large amounts of soluble antigen (blood proteins), only Signal 1 occurs, but Signal 2 is missing. This leads to anergy instead of activation.
- B cells when exposed to large amounts of soluble antigen down regulate their surface IgM and become anergic.

Feature	Clonal Deletion	Clonal Anergy
Mechanism	Self-reactive cells are **eliminated** by apoptosis	Self-reactive cells are **functionally inactivated** but remain alive
Affected Cells	Mostly T cells (in the **thymus**) and B cells (in **bone marrow**)	T and B cells in the **periphery** (after leaving central lymphoid organs)

Mechanisms of tolerance:

C. Clonal ignorance :

1-T cells reactive to self-antigen not represented in the thymus will mature and migrate to the periphery, but they may never encounter the appropriate antigen because it is sequestered. Such cells may die out for lack of stimulus

2-Auto-reactive B cells that escape deletion may not find the antigen or the specific helper T-cells and hence are not activated and die out.

Mechanisms of tolerance:

D. Receptor editing:

- B cells which encounter large amounts of soluble Ag bind to it with very low affinity, undergo **DNA recombination and change their specificity.**

E: Suppressor cells (Treg cells) :

- Antigen may induce suppressor T cells, which can suppress immune response

Termination of tolerance :

1. Prolonged absence of exposure to the tolerogen .

2. Treatments which severely damage the immune system (x irradiation).

3. Immunization with cross reactive antigens

Quiz!!!

- Loss of immunological tolerance leads to hypersensitivity reaction (true or false).
- Clonal ignorance means negative selection of auto-reactive T-cells in the thymus (true or false).

Autoimmunity

Definition :

- Failure of the mechanisms of self-tolerance i.e. the ability to discriminate between self/non-self-antigens and the attack of self-tissues by the immune system resulting in tissue injury.
- Both antibodies and autoreactive effector T cells can be involved in the damage in autoimmune diseases

Classification :

A: Organ specific autoimmune diseases:

the immune response is directed against antigen(s) associated with a target organ

- **Endocrine glands :**

1-Hashimoto thyroiditis .

2-Type I diabetes mellitus .

- **Blood :**

1-Autoimmune haemolytic anaemia .

2-Autoimmune thrombocytopenia

Classification

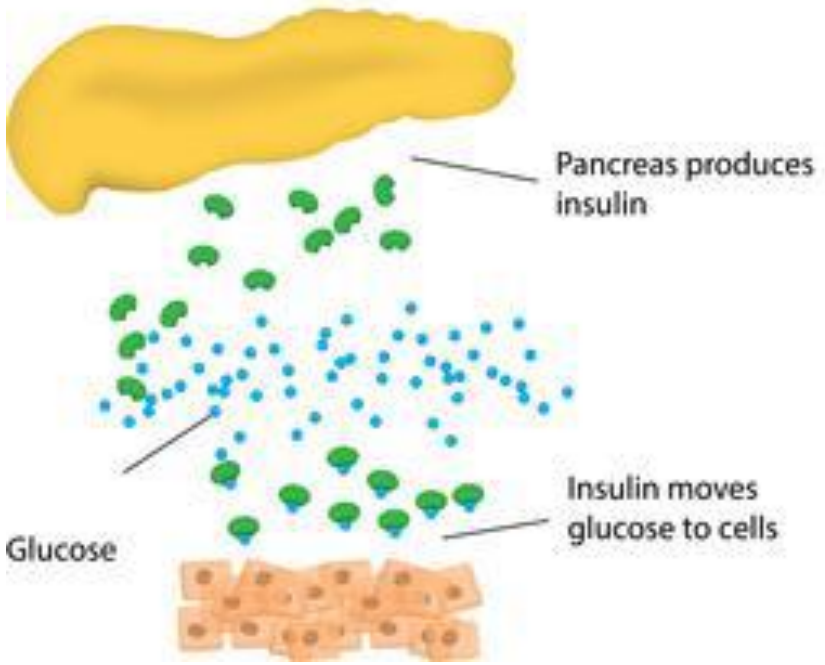
B:Non-organ-specific autoimmune diseases (systemic):

the immune response is directed against an antigen or many antigens throughout the body .

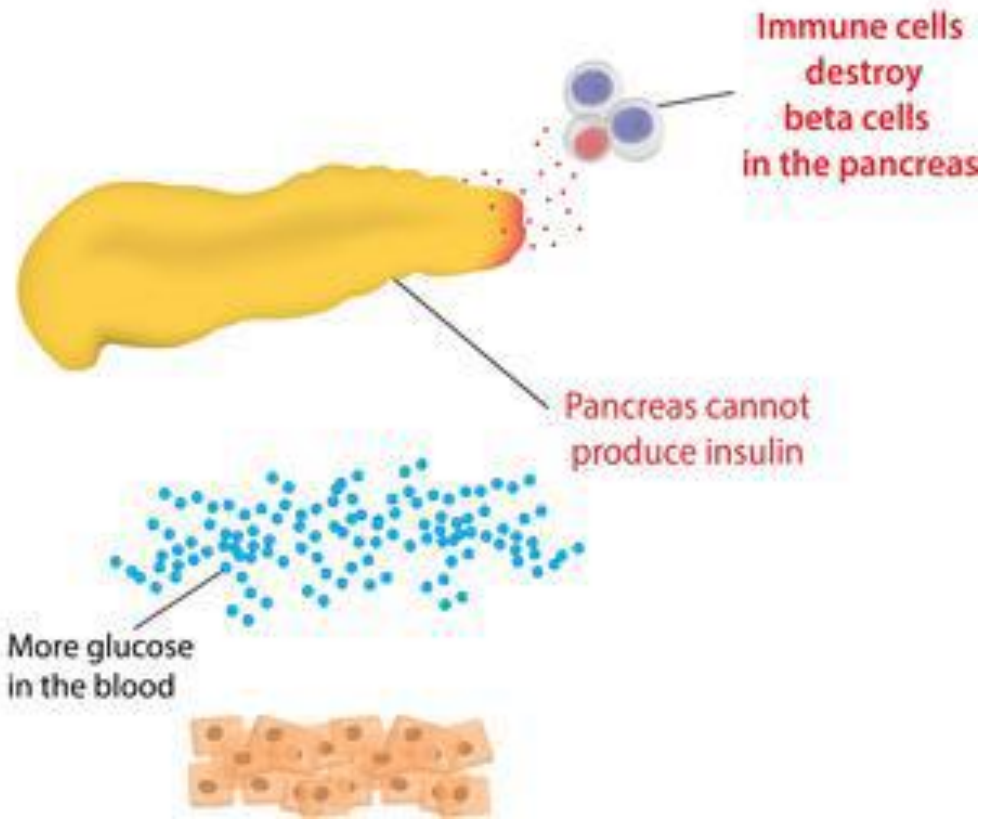
- **1-Rheumatoid arthritis (RA)**
- **2-Systemic lupus erythematosus (SLE).**

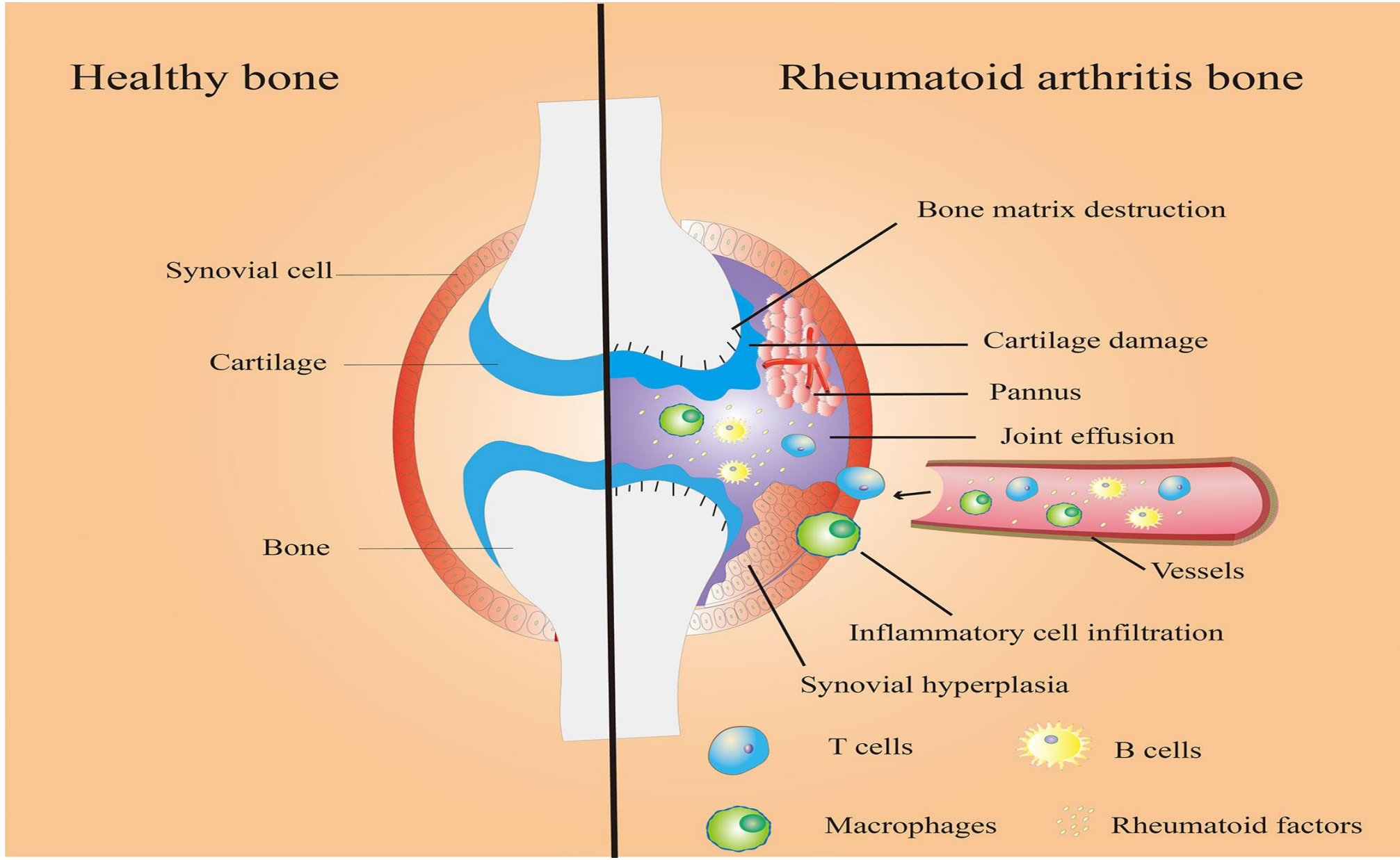
Type 1 Diabetes

Healthy



Diabetic

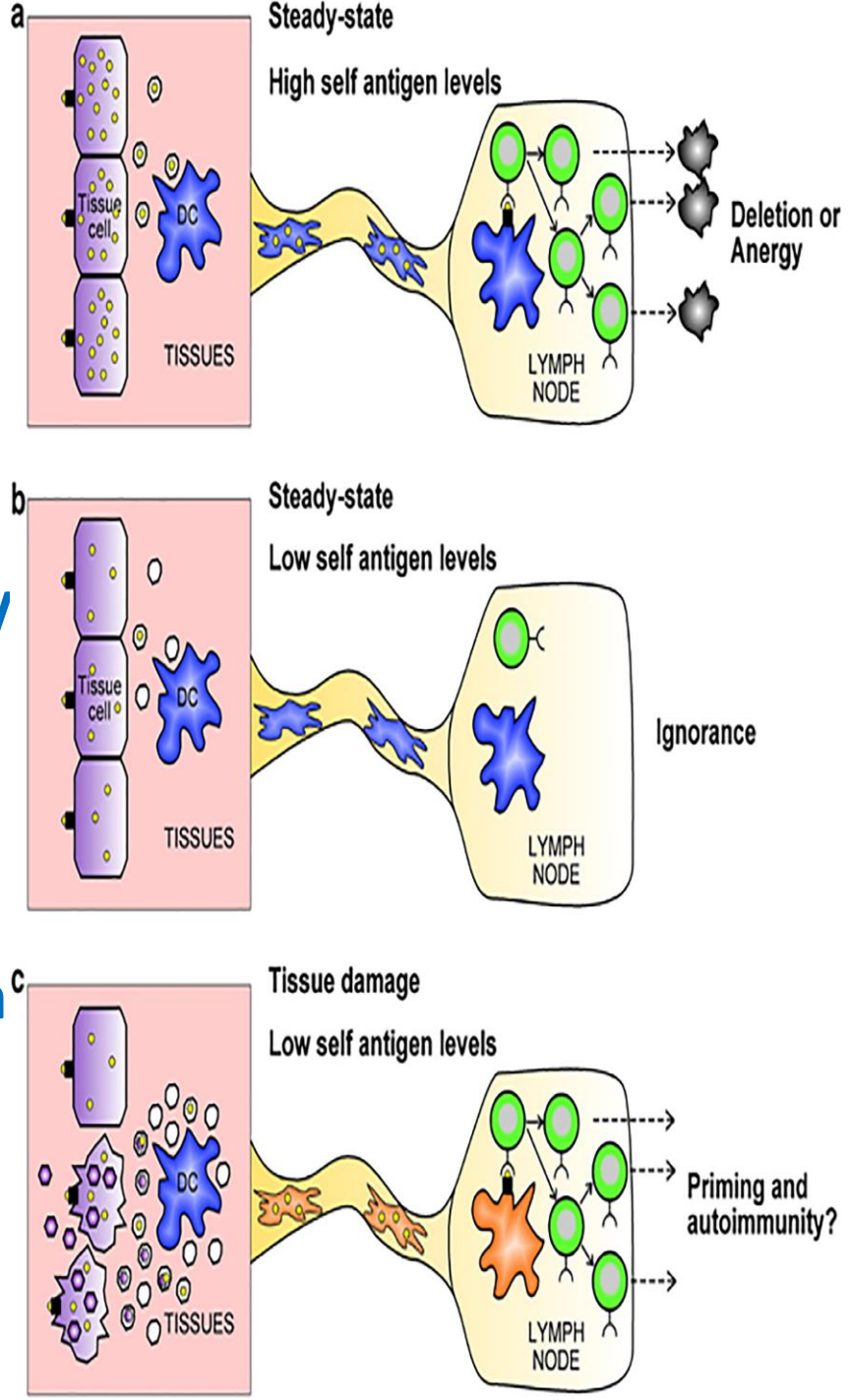



Healthy bone
Rheumatoid arthritis bone
Synovial cell
Cartilage
Bone
Bone matrix destruction
Cartilage damage
Pannus
Joint effusion
Vessels
Inflammatory cell infiltration
Synovial hyperplasia
T cells
B cells
Macrophages
Rheumatoid factors

Aetiology

A. Sequestered antigen :

- Lymphoid cells may not be exposed to some self-antigens during their differentiation, because they may be late-developing antigens or may be confined to specialized organs (e.g., testes, brain, eye).
- A release of antigens from these organs, resulting from accidental traumatic injury or surgery, can result in the initiation of an autoimmune disease.



Aetiology

B. Escape of auto-reactive clones:

- The negative selection in the thymus may not be fully functional to eliminate self-reactive cells .

C: Lack of regulatory T cells:

- Deficiency of T suppressor cells that regulate immune response to self-antigen .

Aetiology

E: Cross reactive antigens :

- Antigens on certain pathogens may have determinants which cross react with self-antigens and an immune response against these determinants may lead to immune response against tissue antigens

Diagnosis of autoimmune diseases :

1-By symptoms

2-By detection of antibodies (and/or T cells) reactive against self-antigens

Treatment of autoimmune diseases :

- Anti-inflammatory (corticosteroid) and immunosuppressive drug therapy .
- Anti-TNF alpha, anti-IL2 receptor antibodies, anti-CD4 antibodies, anti-TCR antibodies, are under trial.

Quiz!!!

- Classify Autoimmune diseases.
- Sequestered antigen means release of antigens from organs as a result from accidental injury, can result in the initiation of an autoimmune disease (true or false).

Escape from immuno-surveillance

Escape from immuno-surveillance

1. Lack or poor expression of MHC antigen.
2. Fail to express co-stimulatory molecules
3. Tumours express a death-inducing ligand known as fas ligand (fasl) which interact with death receptor (fas)expressed on T cells and mediate their cell death by apoptosis.
4. Fail to express neo antigens

Escape from immuno-surveillance

5.Some tumours may secreting products that suppress anti- tumour immune response e.g. transforming growth factor-β which inhibit lymphocytes.

6.Some tumours stimulate the regulatory T cells which suppress T cell response to tumours.

7.Some tumours may shed their unique antigens which block antibodies and T cells from reacting with malignant cells.

Quiz!!!

- Failure of expression of neo antigens can lead to tumour evasion from immune system (true or false)

Case scenario

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References

- Basic Immunology : functions and disorders of the immune system , fifth edition ; Abul K. Abbas, Andrew H. Lichtman and Shiv Pillai
- •Immunology :7th edition ; David Male, Jonathan Brostoff, David Roth and Ivan Roitt


Let's sum
it up...


Questions
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THANK YOU!