

Teaching unit 9

IMMUNOLOGIC TOLERANCE AND AUTOIMMUNITY

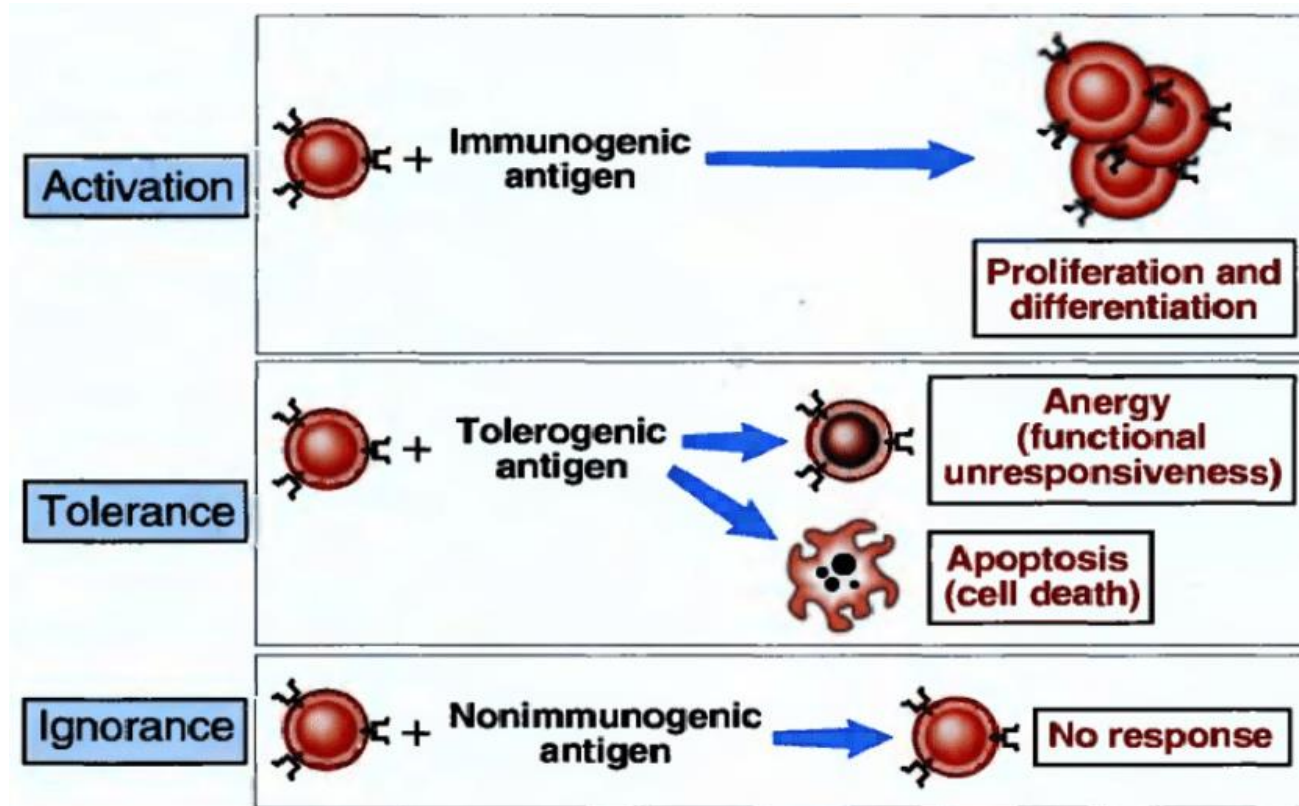
Distinguishing self from foreign in the immune system (immune system recognizes and responds to foreign antigens but not to self antigens)

The failure of self-tolerance results in immune reactions against self (autologous) antigens

Immunologic tolerance is defined as unresponsiveness to a specific antigen that is induced by exposure to that antigen.

Autotolerance is non-reactivity to self-antigens, that is, tolerance to self antigens.

There are three possible outcomes of the encounter between lymphocytes and a specific antigen:



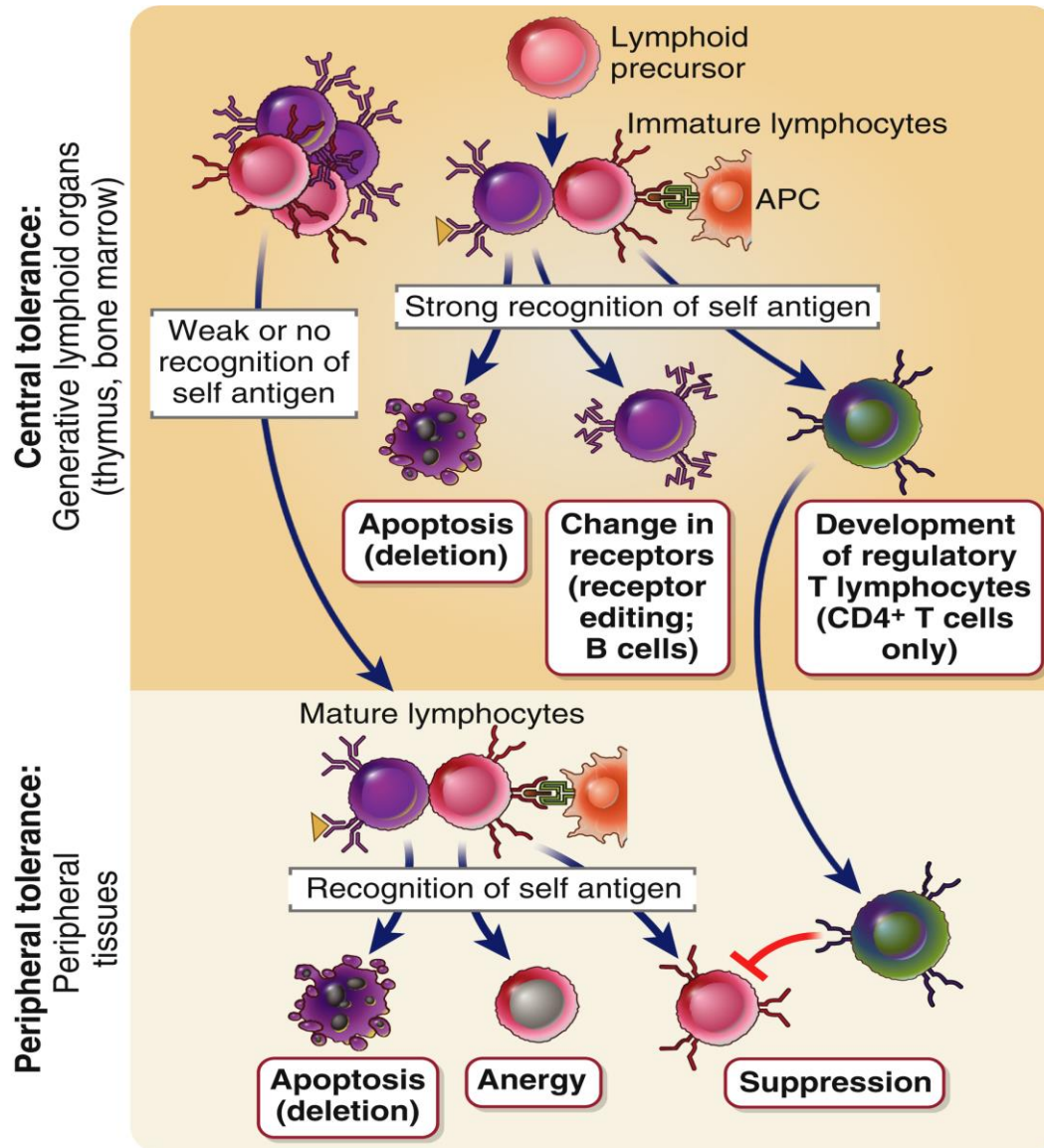
The outcome depends on:

- the nature of lymphocytes
- the nature of the antigen
- the way of presentation

Why is it important to understand the mechanisms of immunologic tolerance?

- to understand the pathogenesis of autoimmune diseases
- to learn how to control unwanted immune reactions, such as allergic and autoimmune diseases, or to prevent transplant rejection

Immunologic tolerance to self-antigens is induced when...



Immature lymphocyte meets antigen in central lymphoid organ
CENTRAL TOLERANCE

Mature lymphocyte meets antigen in peripheral lymphoid organ
PERIPHERAL TOLERANCE

The central role in tolerance mechanisms, as well as in the development of autoimmune diseases, belongs to **CD4+ T** lymphocytes

Nota bene:

- CD4+ T lymphocytes control the immune response to almost all protein antigens. There are irreplaceable **inductors** and cellular and humoral response to protein antigens. Also, there is an entire subpopulation of regulatory T lymphocytes that actively suppress immune responses and maintain autotolerance.
- If Th lymphocytes cannot respond to the self protein antigens, this may be enough to prevent both **cellular** and **humoral** immune response to those antigens. **The failure of tolerance of these lymphocytes will cause the autoimmunity of both cellular and humoral type.**

Central tolerance of T lymphocytes

The negative selection is important for tolerance in both CD8+ and CD4+ lymphocyte populations.

Normally, only self-peptides are displayed in the thymus.

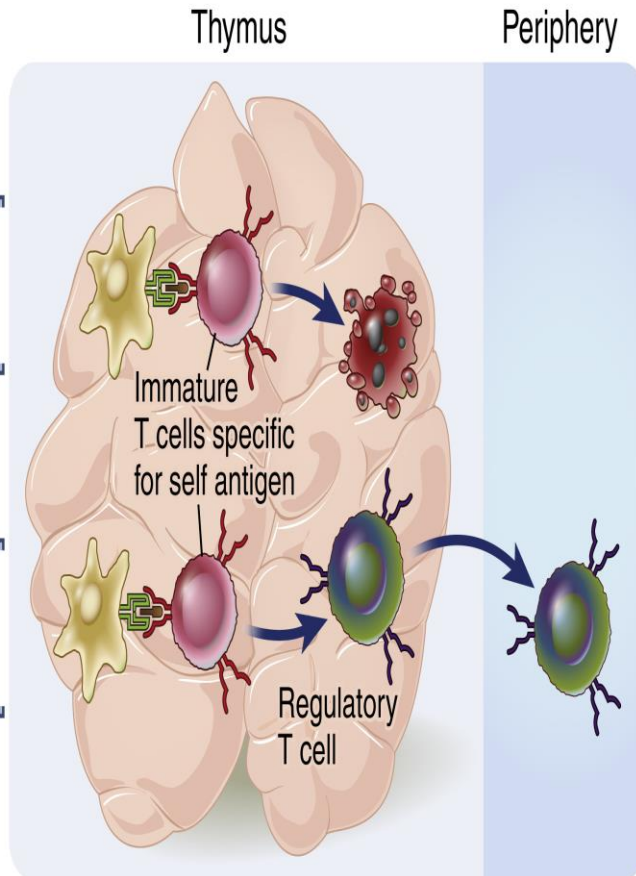
AIRE (**autoimmune regulator**) is responsible for the expression of many of self proteins in the thymus.

Mutations in the *AIRE* gene are the cause of an autoimmune disease called autoimmune polyendocrine syndrome type 1 (APS1).

Rare systemic autoimmune disease:

- hypoparathyroidism
- candidiasis
- adrenal insufficiency
- insulinitis

It is inherited recessively



Peripheral tolerance of T lymphocytes

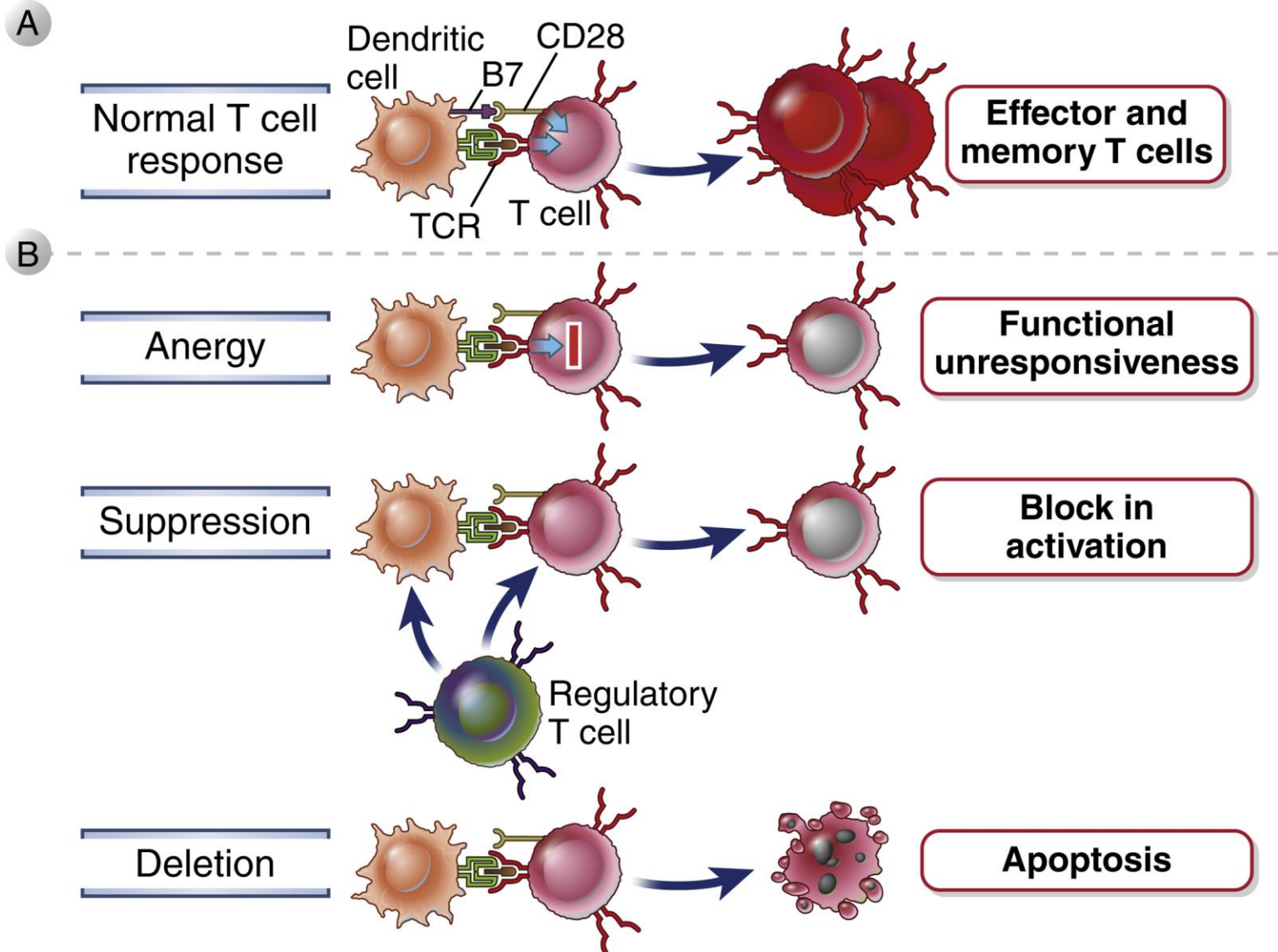
It occurs when mature T lymphocytes (which have escaped negative selection in the thymus) recognize self antigens in peripheral tissues.

Peripheral tolerance also refers to CD4+ and CD8+ T lymphocytes.

This is achieved in several ways:

- ✓ those T lymphocytes become functionally inactive (**anergy**)
- ✓ or die (**deletion**)
- ✓ regulatory cells suppress autoreactive lymphocytes (**suppression**)

Peripheral tolerance of T lymphocytes



Peripheral tolerance of T lymphocytes is important in the response to:

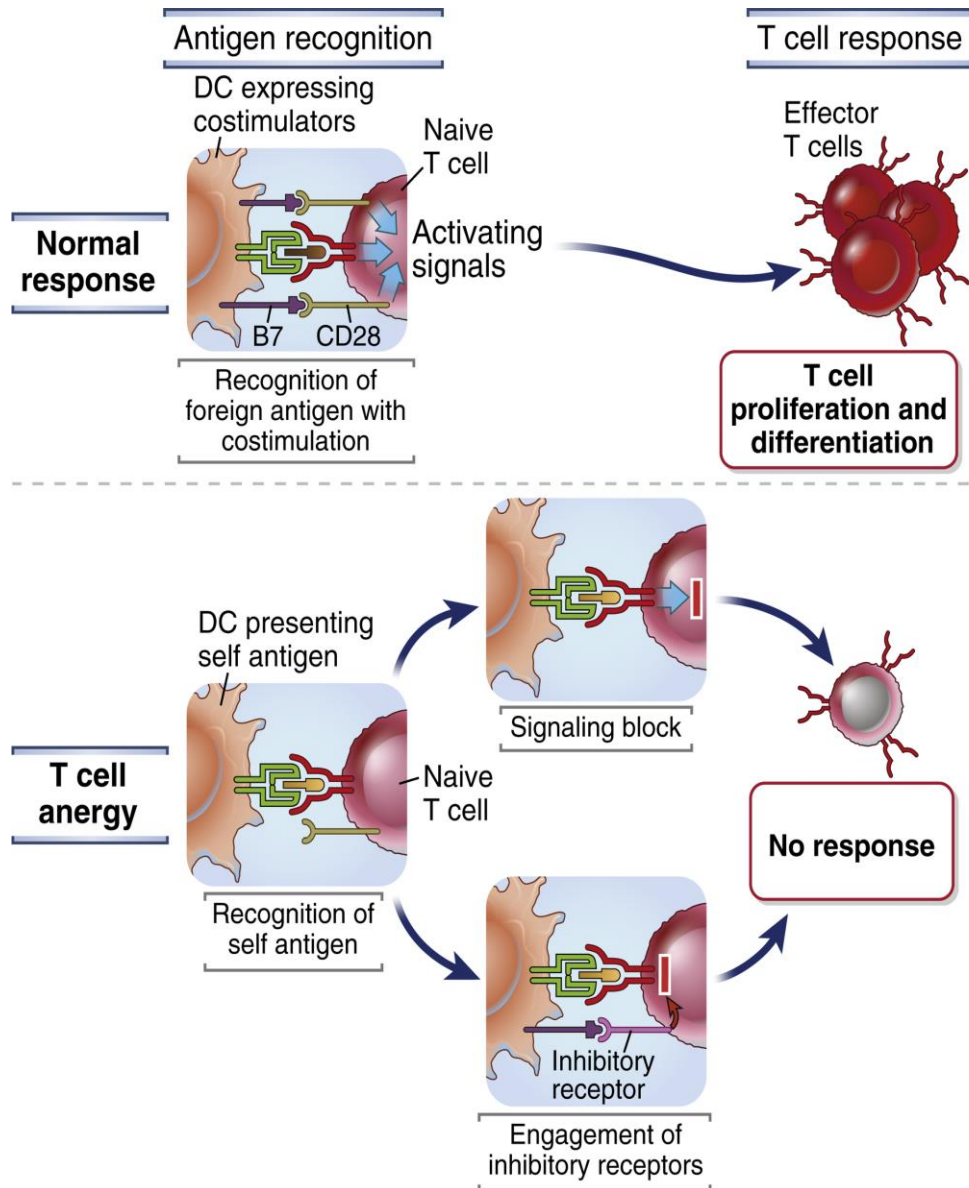
- those antigens that are present in the periphery and are not available for presentation in the thymus
- those antigens for which central tolerance is incomplete

Anergy ...

... is one of the ways of peripheral tolerance of T lymphocytes

... is the functional inactivation of T lymphocytes that occurs if these cells recognize a peptide in the context of MHC molecules and there is no costimulation (second signal)

Energy



APCs present in tissues and peripheral lymphoid organs are in a resting state, when they express little or no costimulatory molecules.

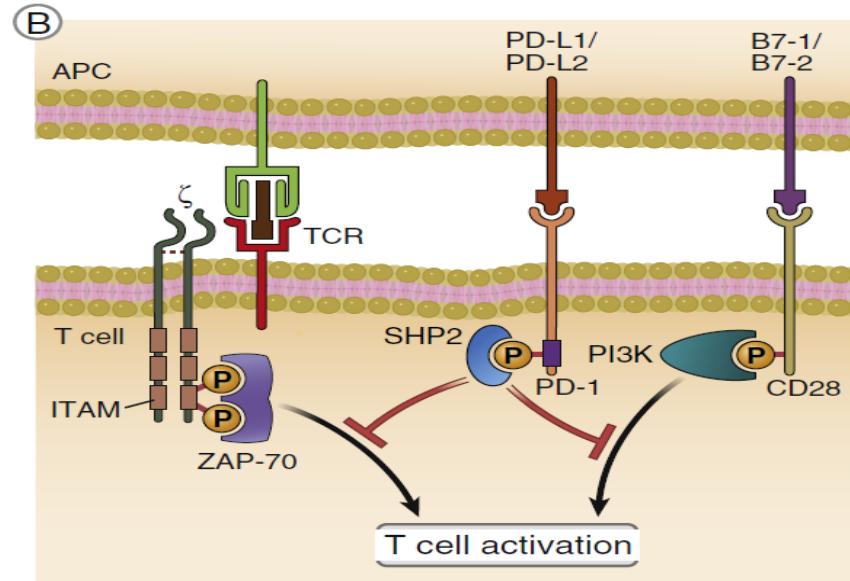
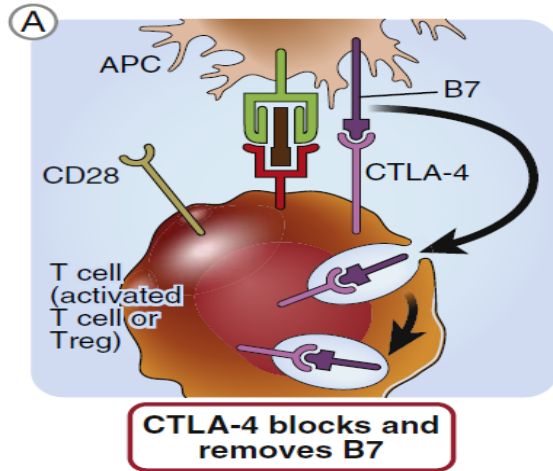
In such a state, they display self peptides.

Prolonged signal 1 without costimulation (signal 2) introduces the cell into anergy:

- Blockade TCR signaling
- Activation of ubiquitin ligases
- Engagement of inhibitory receptors CTLA4 or PD-1 on T lymphocytes (disorder of the gene for CTLA4 is associated with some autoimmune diseases in humans)

CTLA4 binds B7 costimulators with a much higher affinity than CD28.

Mechanisms of action and properties of CTLA4 and PD-1



(C)

	CTLA-4	PD-1
Major site of action	Secondary lymphoid organs	Peripheral tissues
Stage of immune response that is inhibited	Induction (priming)	Effector phase
Cell type that is inhibited	CD4 ⁺ same as or more than CD8 ⁺	CD8 ⁺ > CD4 ⁺
Cellular expression	Tregs, activated T cells	Mainly activated T cells
Main signals inhibited	Competitive inhibitor of CD28 costimulation by binding to B7 with high affinity and removing B7 from APCs	Signaling inhibitor of CD28 and TCR: inhibits kinase-depending signals by activating phosphatase
Role in Treg-mediated suppression of immune responses	Yes	No

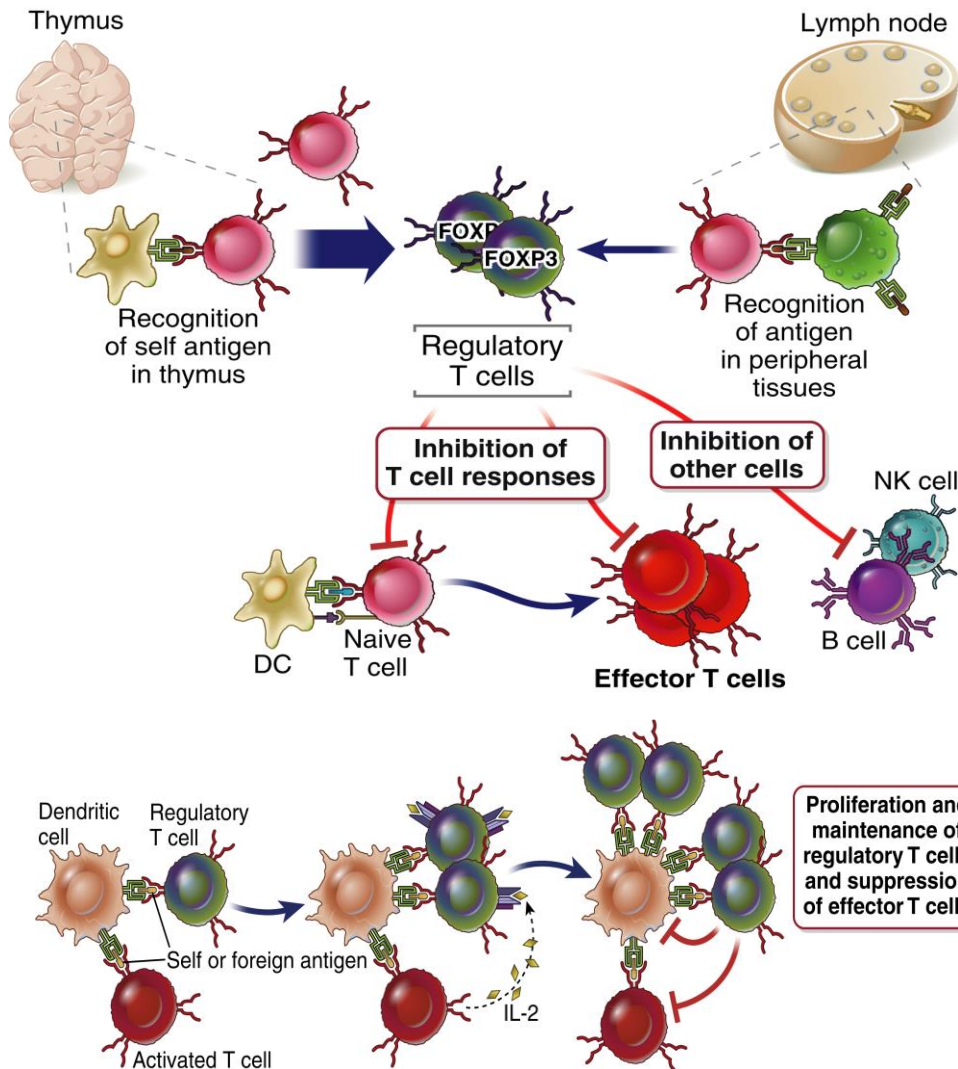
Suppression...

... occurs when, after encountering an antigen, some autoreactive T lymphocytes become regulatory.

Regulatory lymphocytes (mostly CD4+) recognize self antigens and prevent or suppress the activity of other potentially autoreactive T lymphocytes of the same clone.

Regulatory lymphocytes can arise centrally (in the thymus - nTregs), but also peripherally (iTregs).

Suppression



Regulatory cells:

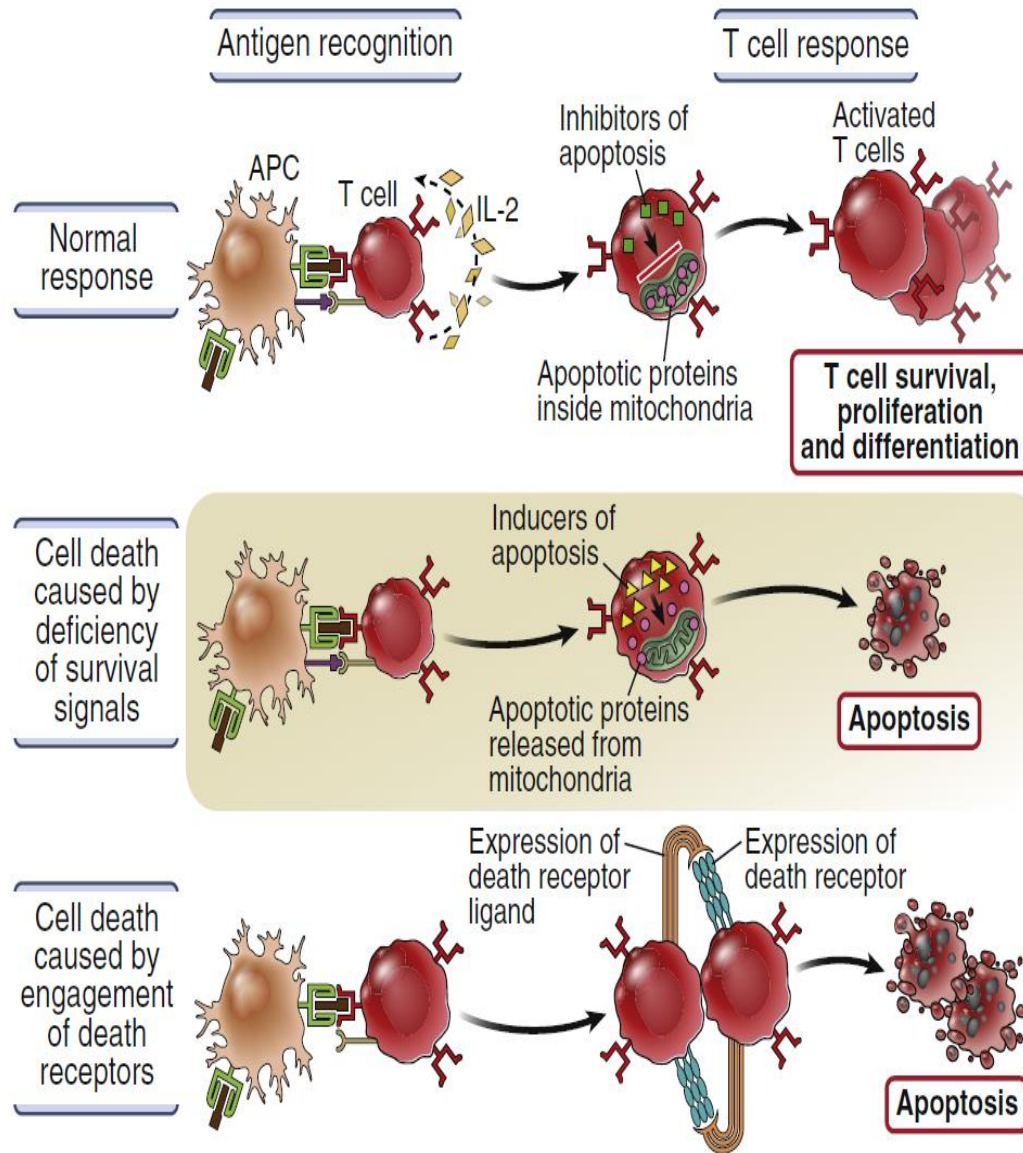
- are mostly **CD4+CD25+** (α chain of the receptor for IL-2)
- the generation, maintenance, and function of these cells depends on the transcription factor **FoxP3**
- **FoxP3 gene mutation** is the cause of a systemic autoimmune disease that affects many organs
- the survival and function of these lymphocytes depends on **IL-2**
- these cells prevent the activation of lymphocytes and macrophages - by cell contact and cytokines (TGF- β , IL-10)

Deletion...

... is apoptotic death of T lymphocytes induced by activation

... occurs as a result of repeated activation of mature T lymphocytes by self antigens

Deletion



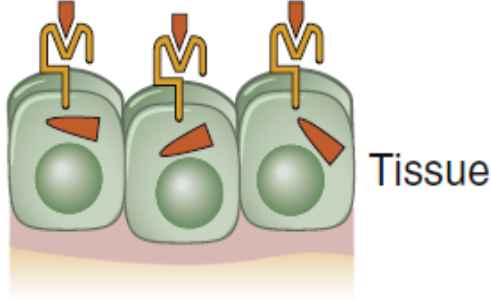

In response to microorganisms **proapoptotic** proteins are opposed **antiapoptotic** proteins induced by costimulators and growth factors.

Antigen recognition induces the production of proapoptotic proteins - the mitochondrial pathway of caspase activation. No costimulation - no antiapoptotic proteins either.

Repeated stimulation of T lymphocytes causes simultaneous expression of death receptors and their ligands (death receptor pathway). Fas(CD95) –FasL

Mutation in the *Fas* gene - **Autoimmune lymphoproliferative syndrome (ALPS)** (primarily, autoreactive B lymphocytes accumulate)

Why do self antigens cause tolerance and foreign ones cause activation?

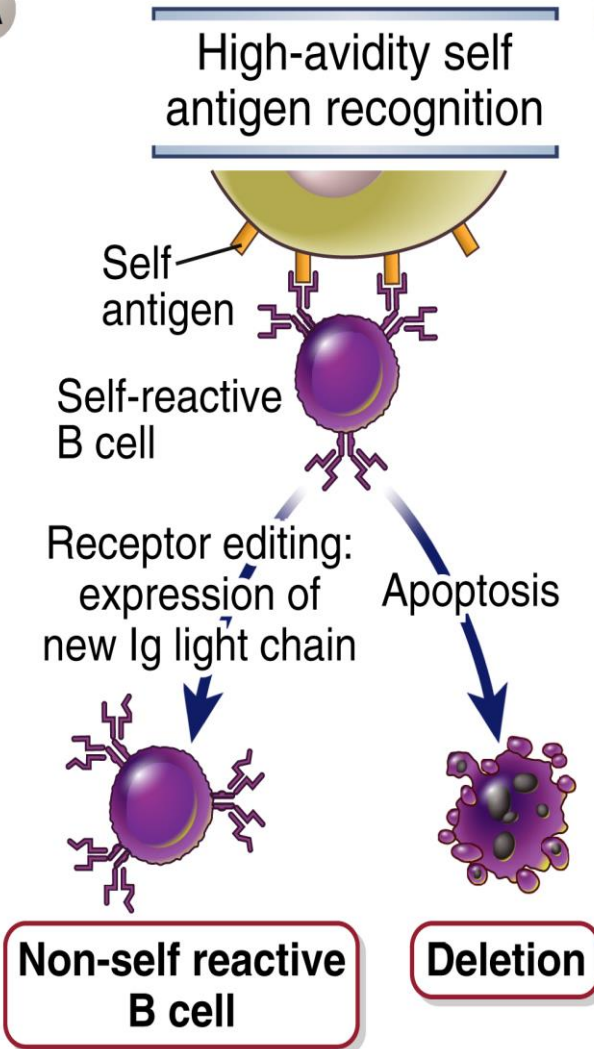
Feature of antigen	Tolerogenic self antigens	Immunogenic foreign antigens
		
Location of antigens	Presence in generative organs (some self antigens) induces negative selection and other mechanisms of central tolerance	Presence in blood and peripheral tissues (most microbial antigens) permits concentration in peripheral lymphoid organs
Accompanying costimulation	Deficiency of costimulators may lead to T cell anergy or apoptosis, development of Treg, or sensitivity to suppression by Treg	Expression of costimulators, typically seen with microbes, promotes lymphocyte survival and activation
Duration of antigen exposure	Long-lived persistence (throughout life); prolonged TCR engagement may induce anergy and apoptosis	Short exposure to microbial antigen reflects effective immune response

Immunologic tolerance of B lymphocytes

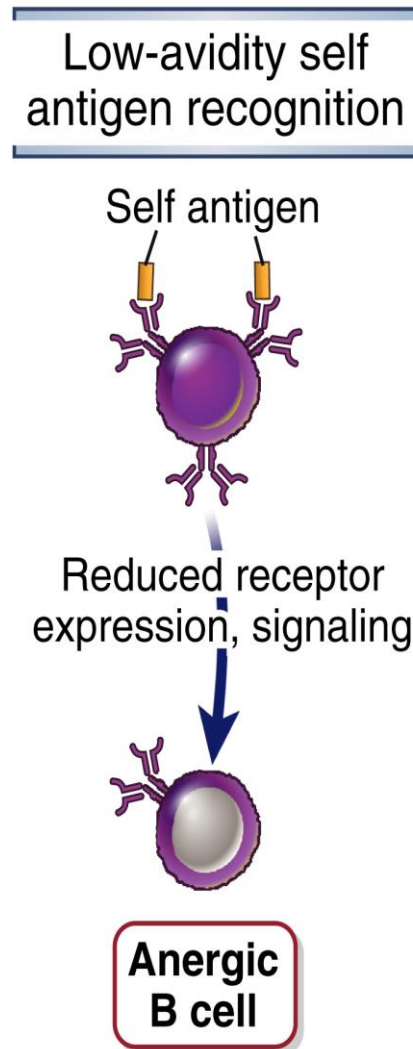
- Self polysaccharides, lipids and nucleic acids are T-independent antigens.
- Mostly these antigens induce tolerance of B lymphocytes.
- However, the tolerance of B lymphocytes to protein antigens is also important.

Central tolerance of B lymphocytes

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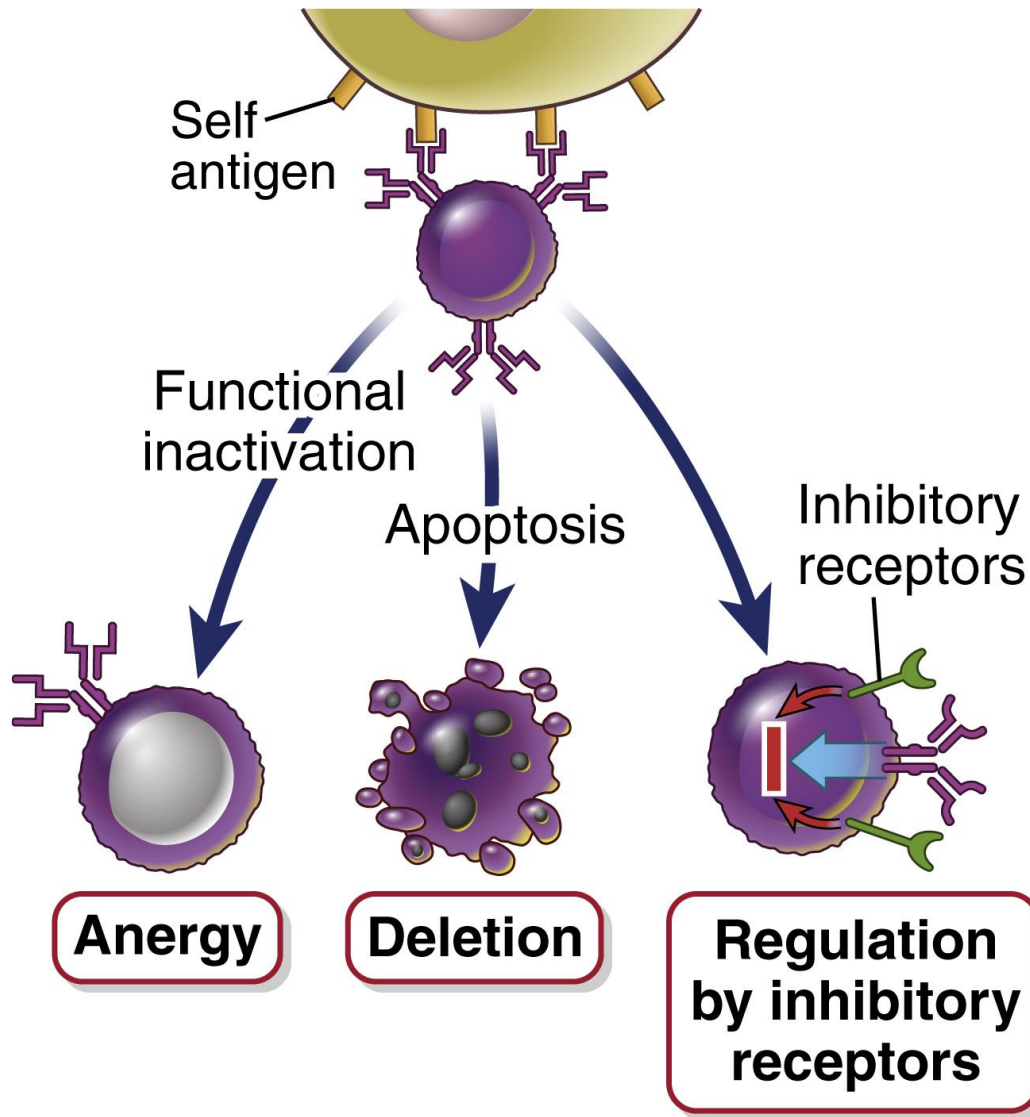
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Immature B lymphocytes, which express a high-affinity receptor for self-antigens, undergo:

- new round of VDJ recombination for light chains - **receptor editing** (receptor rearrangement)
- **apoptosis** (negative selection)
- **anergy**

Peripheral tolerance of B lymphocytes



When mature B lymphocytes encounter self antigens in peripheral tissues **become anergic** or **die by apoptosis**. In some situations, recognition of self antigens may trigger **inhibitory receptors that prevent B cell activation**.

Diseases associated with the production of autoantibodies such as: **Systemic lupus erythematosus (SLE)** are caused by breaking the tolerance at the level of both B and CD4⁺ T lymphocytes

Immunologic tolerance to commensal microorganisms and fetal antigens

Tolerance to commensal microorganisms in the intestines and skin:

- Regulatory T lymphocytes, IL-10
- dendritic cells

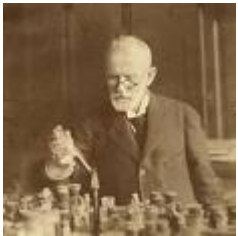
Tolerance to fetal antigens:

- peripheral Foxp3⁺ regulatory T lymphocytes, ...

Autoimmunity: principles and pathogenesis

Autoimmunity occurs due to the interruption (cancellation) of tolerance to one's own, therefore:

Autoimmunity implies an immune response to self (autologous) antigens



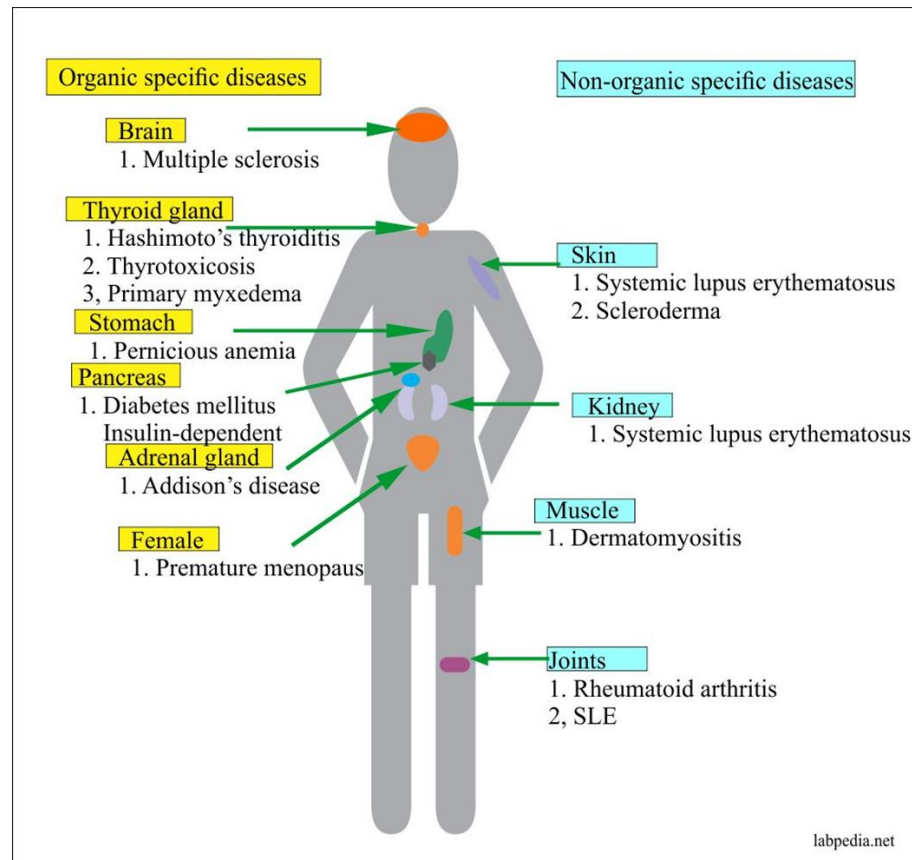
Horror autotoxicus = the horror of self-toxicity

2-5% of all people suffer from autoimmune diseases

- For now, the etiology (cause) of any autoimmune disease is unknown.
- These diseases are heterogeneous and multifactorial.
- Autoantigens are often unknown.
- Diseases often appear much later than the immune reaction has started.

General characteristics of autoimmune diseases

Depending on the distribution of autoantigens, autoimmune diseases can be **systemic** or **organ specific**.



General characteristics of autoimmune diseases

Various effector mechanisms are responsible for tissue damage in autoimmune diseases:

- **circulating autoantibodies**
- **immune complexes**
- **autoreactive T lymphocytes**

The clinical and pathological characteristics of autoimmune diseases are determined by the nature of the dominant autoimmune response.

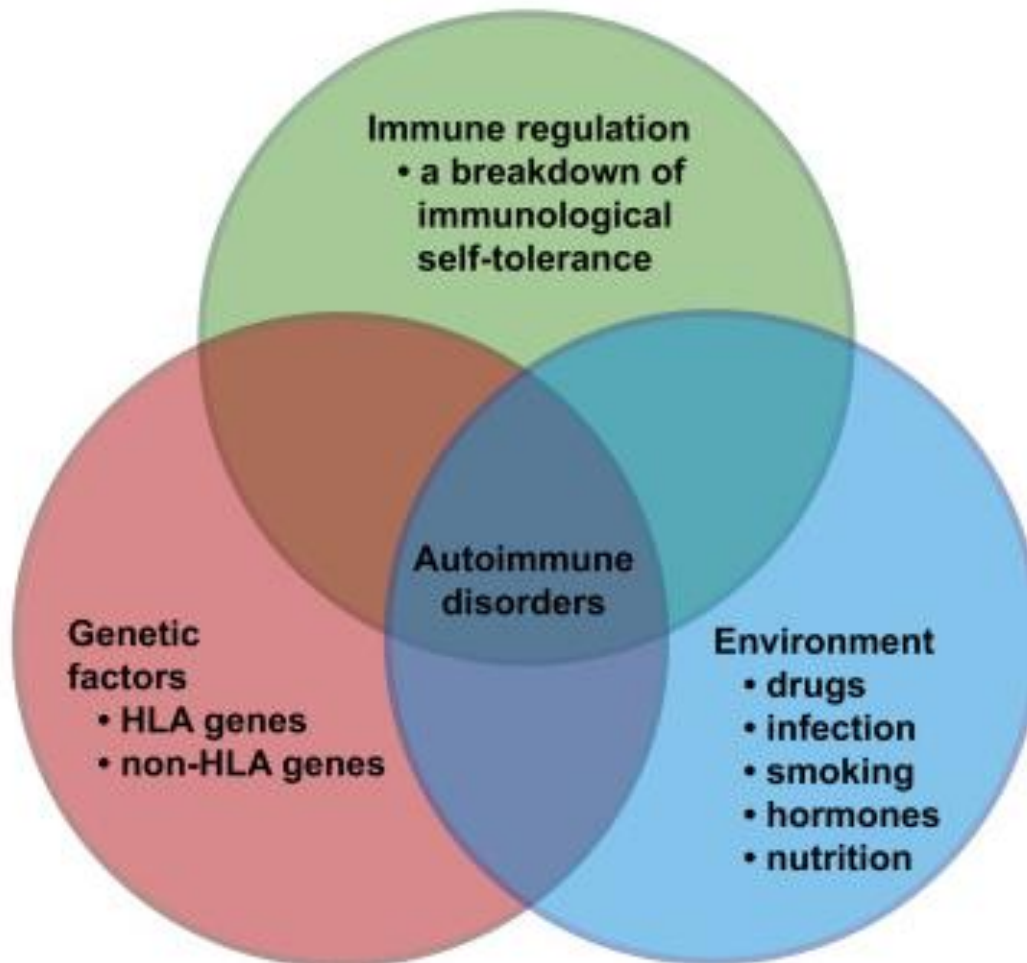
General characteristics of autoimmune diseases

Autoimmune diseases are chronic and progressive.

Autoantigens that trigger an immune reaction are persistent, and when the immune response begins, the mechanisms that amplify it are activated.

The resulting tissue damage induces the release and change of other potential autoantigens, activation of autoreactive lymphocytes specific for these antigens, and exacerbation of the disease. This phenomenon is called **epitope spreading**, and it contributes to the progression of an autoimmune process once started.

Factors involved in the development of autoimmune diseases



Disorders of immunoregulation in the development of autoimmune diseases

Disruption of self-tolerance:

- Defects in deletion (negative selection) of T or B lymphocytes, or rearrangement of B lymphocyte receptors, during their maturation in the central lymphoid organs
- Defects in the number or function of regulatory T lymphocytes
- Defective apoptosis of mature autoreactive lymphocytes
- Inadequate function of inhibitory receptors

Disorders of immunoregulation in the development of autoimmune diseases

Disorders in the presentation of self antigens:

- Increased expression and persistence of autoantigens that are normally removed from the body
- Structural changes in autoantigens resulting from enzymatic modifications that occur because of cellular stress or injury

If such changes affect the expression of antigenic epitopes that are not present normally, the immune system may not be tolerant to these "neoantigens", resulting in the development of an autoimmune response.

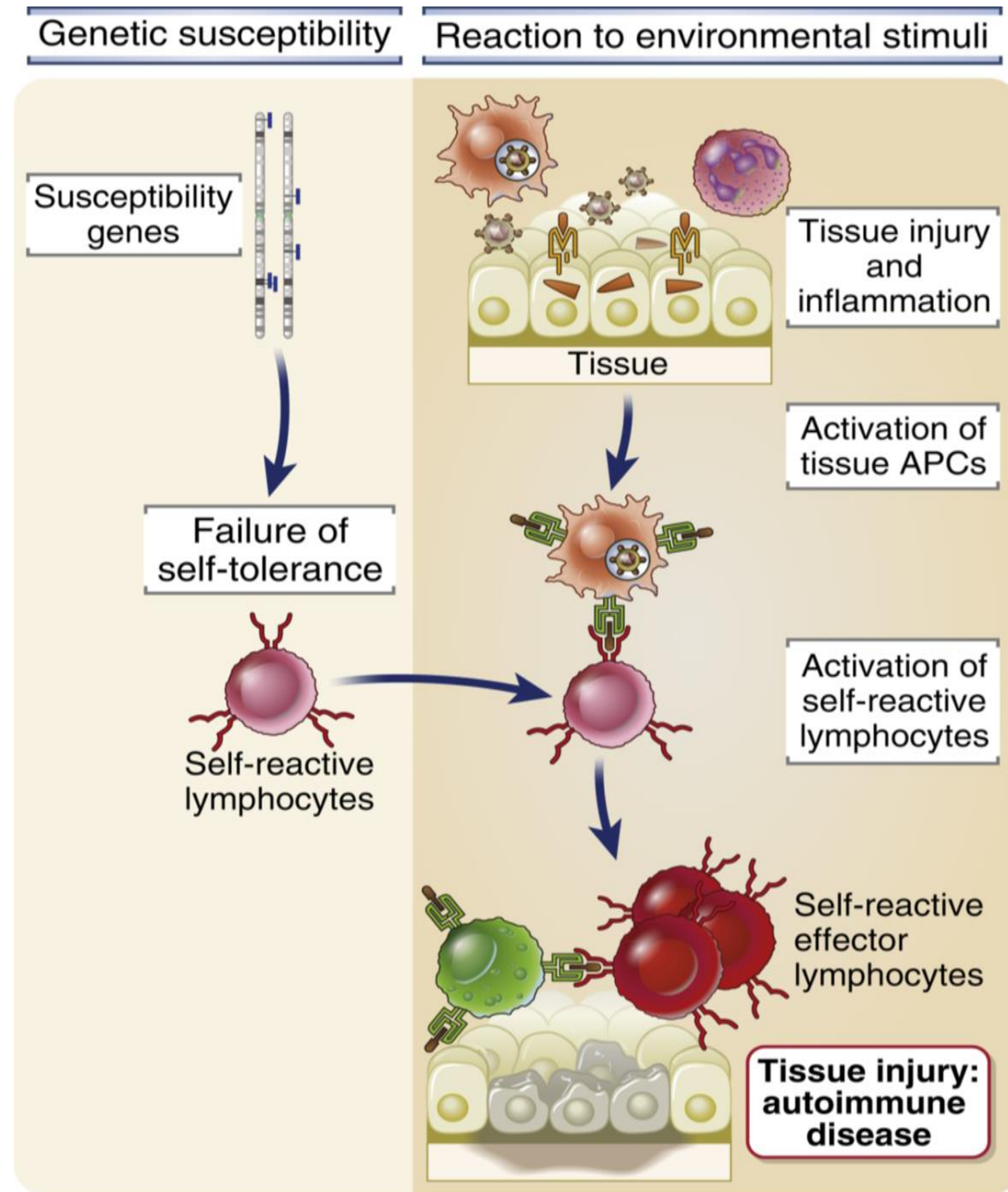
Disorders of immunoregulation in the development of autoimmune diseases

Inflammation and activation of the innate immune response:

- Infection or cell injury activates the innate immune response and local inflammation
- This may contribute to the development of autoimmune disease, mainly by activating antigen-presenting cells that exceed regulatory mechanisms and result in excessive activation of T lymphocytes

The occurrence of autoimmune diseases mainly depends on two groups of factors:

- predisposing genes that favor the interruption of self-tolerance
- infections that can activate autoreactive lymphocytes



Genetic factors in autoimmunity...

Among the many genes that predispose to the onset of autoimmune diseases, the most important are genes that encode **MHC molecules**.

Many autoimmune diseases are associated with certain MHC alleles.

The incidence of certain diseases is higher in the group of people who inherited a certain allele (or alleles) than in the general population - **relative risk**. That is a number that shows how many times a certain disease is more present in a group of carriers of a gene than in the general population.

Association of MHC alleles with autoimmune diseases

Disease	MHC allele	Relative risk
Ankylosing spondylitis	HLA-B27	90
Rheumatoid arthritis	HLA-DRB1*01/*04/*10	4-12
Type 1 diabetes mellitus	HLA-DRB1*0301/0401	35
Pemphigus vulgaris	HLA-DR4	14

Possible explanations:

- That MHC allele does not display self antigens in the thymus – there is no negative selection.
- That allele does not stimulate regulatory cells.
- That MHC allele is responsible for antigenic mimicry.
- That MHC allele is inherited in conjunction with the responsible gene ...

The role of some genes outside the MHC complex in autoimmunity

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Genes that may contribute to genetically complex autoimmune diseases

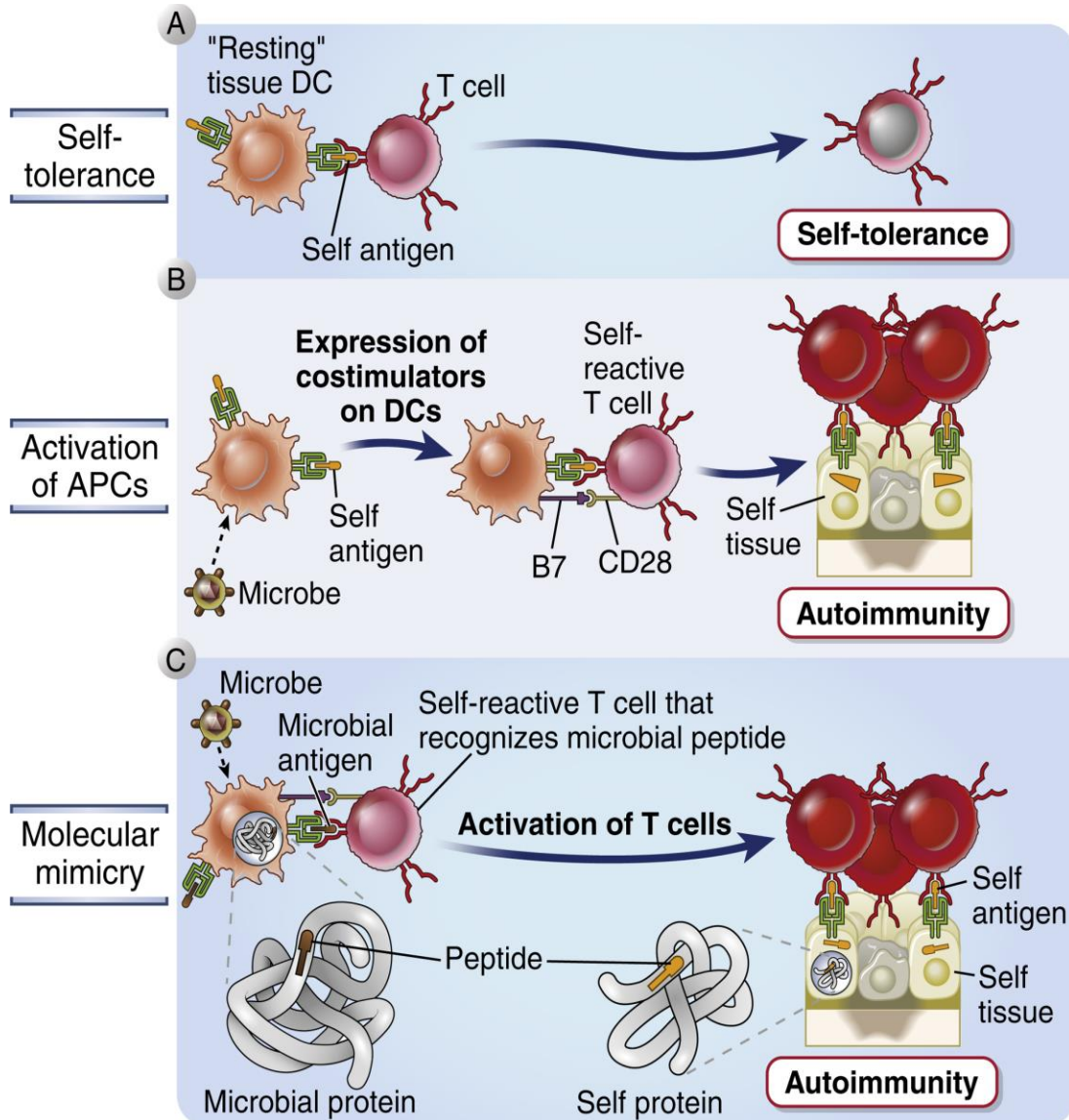
Gene(s)	Disease association	Mechanism
<i>PTPN22</i>	RA, several others	Abnormal tyrosine phosphatase regulation of T cell selection and activation?
<i>NOD2</i>	Crohn disease	Defective resistance or abnormal responses to intestinal microbes?
<i>IL23R</i>	IBD, PS, AS	Component of IL-23 receptor; role in generation and maintenance of Th17 cells
<i>CTLA4</i>	T1D, RA	Inhibitory receptor of T cells, effector molecule of regulatory T cells
<i>CD25</i> (IL-2R α)	MS, type 1 diabetes, others	Abnormalities in effector and/or regulatory T cells?
<i>C2, C4</i> (Complement proteins)	SLE	Defects in clearance of immune complexes or in B cell tolerance?
<i>FCGR1IB</i> (FC γ RIIb)	SLE	Defective feedback inhibition of B cells

B

Single-gene defects that cause autoimmunity (Mendelian diseases)

Gene(s)	Disease association	Mechanism
<i>AIRE</i>	Autoimmune polyendocrine syndrome (APS-1)	Reduced expression of peripheral tissue antigens in the thymus, leading to defective elimination of self-reactive T cells
<i>CTLA4</i>	Autosomal dominant immune dysregulation syndrome	Impaired regulatory T cell function leading to loss of B and T cell homeostasis
<i>FOXP3</i>	Immune dysregulation, X-linked polyendocrinopathy and enteropathy (IPEX)	Deficiency of regulatory T cells
<i>FAS</i>	Autoimmune lymphoproliferative syndrome (ALPS)	Defective apoptosis of self-reactive T and B cells in the periphery

Infection and autoimmunity



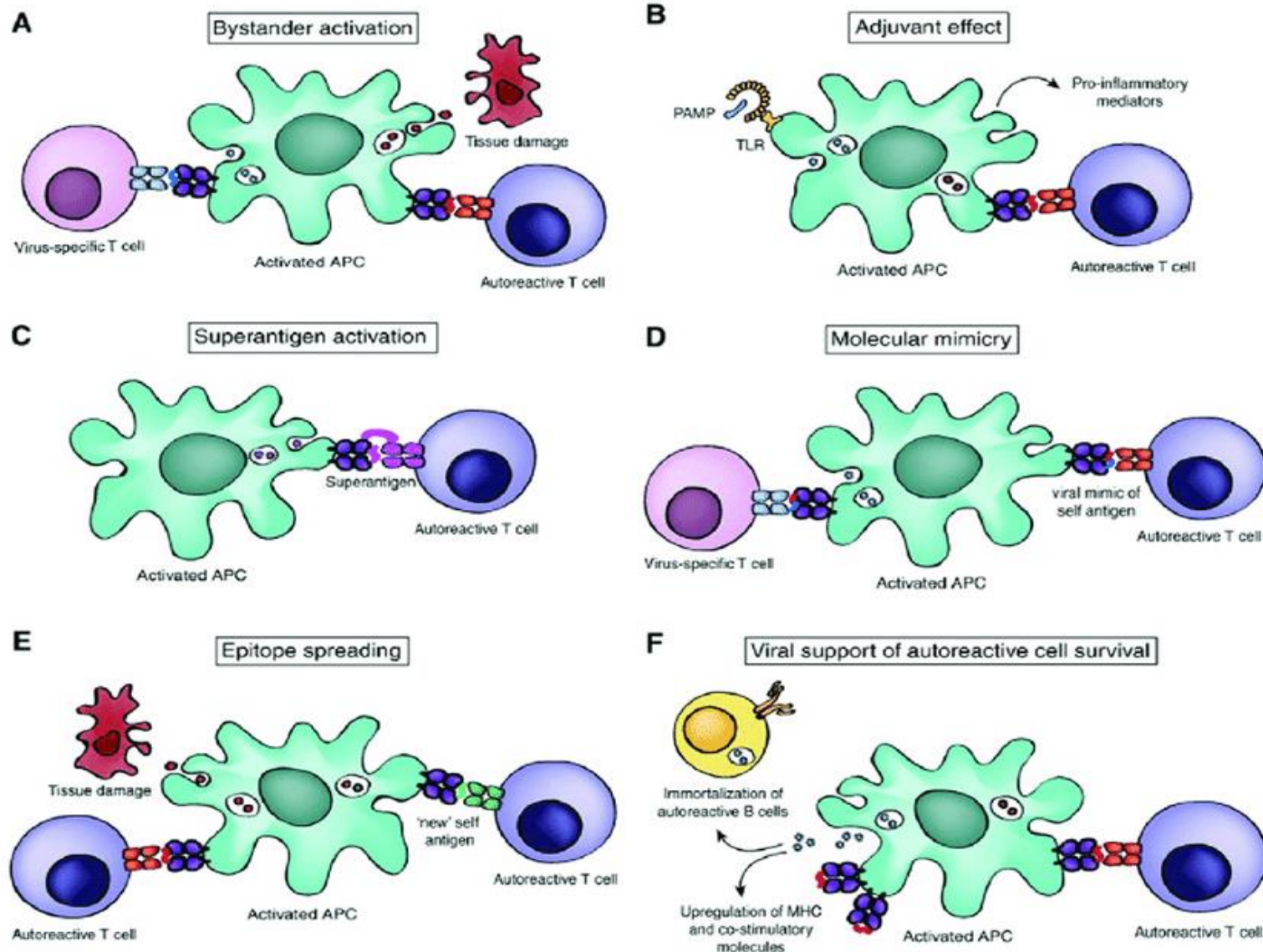
Infection can activate autoreactive clones of lymphocytes in different ways:

- interrupting anergy on self antigens by the induction of the expression of costimulators
- molecular mimicry
- release of "invisible" antigens
- by changing the chemical structure of self antigens
- engagement TLRs on autoreactive B lymphocytes

Инфекција и аутоимуност - механизми

134

K. Kakalacheva et al. / Biochimica et Biophysica Acta 1812 (2011) 132–140



Literature:

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