Immunological Tolerance and Autoimmunity

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IMMUNOLOGICAL TOLERANCE

- **Immunological tolerance is a lack of response to antigens that is induced by exposure of lymphocytes to these antigens.**
- Antigens that elicit such a response are said to be **immunogenic.**
- The lymphocytes may be functionally inactivated or killed, resulting in tolerance; antigens that induce tolerance are said to be **tolerogenic.**
- In some situations, the antigen-specific lymphocytes may not react in any way; this phenomenon has been called **immunological ignorance**, implying that the lymphocytes simply ignore the presence of the antigen.

Importance of of immunological tolerance

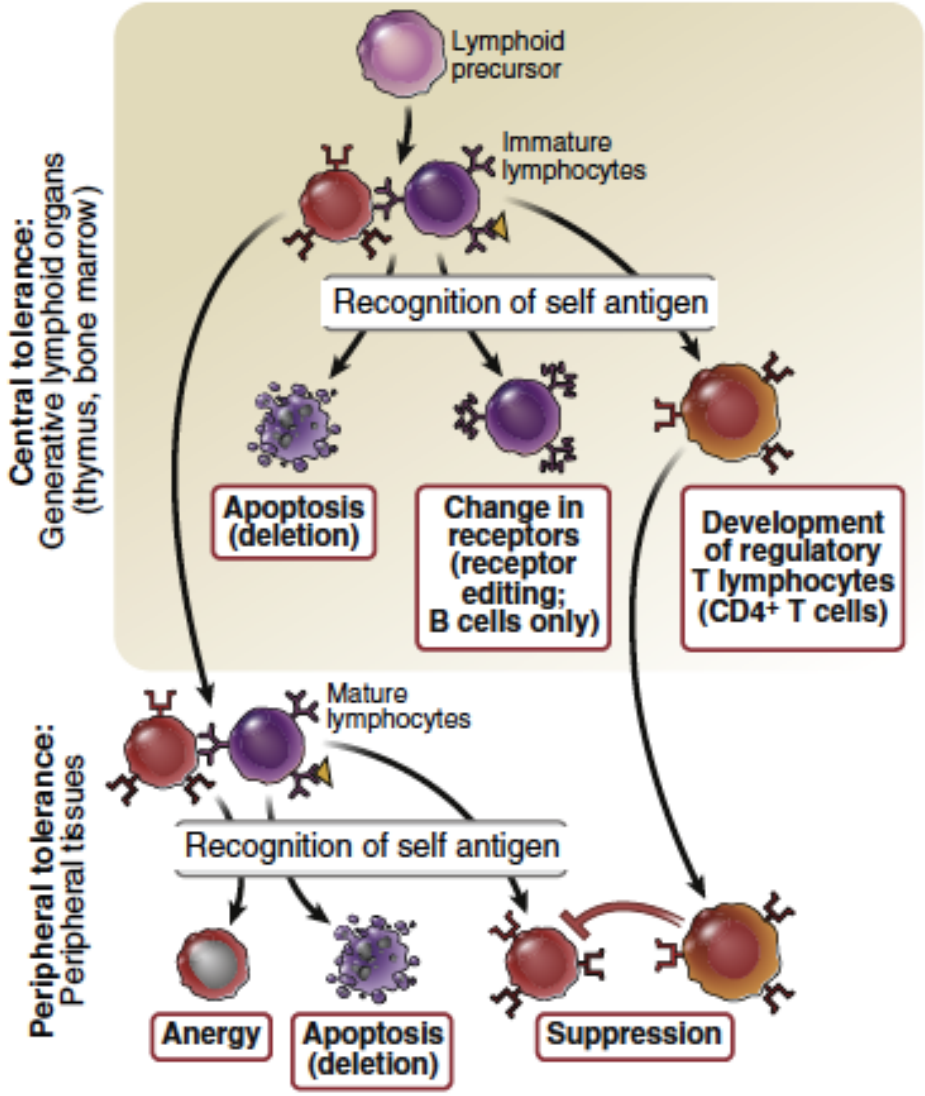
- First, self antigens normally induce tolerance, and failure of self-tolerance is the underlying cause of autoimmune diseases.
- Second, if we learn how to induce tolerance in lymphocytes specific for a particular antigen, we may be able to use this knowledge to prevent or control unwanted immune reactions.
- Strategies for inducing tolerance are being tested to treat allergic and autoimmune diseases and to prevent the rejection of organ transplants.
- The same strategies may be valuable in gene therapy to prevent immune responses against the products of newly expressed genes or vectors and even for stem cell transplantation if the stem cell donor is genetically different from the recipient.

Tolerance Types

- Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative **(central) lymphoid organs, a process called central tolerance,**

- Or when mature lymphocytes encounter self antigens in **peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance .**

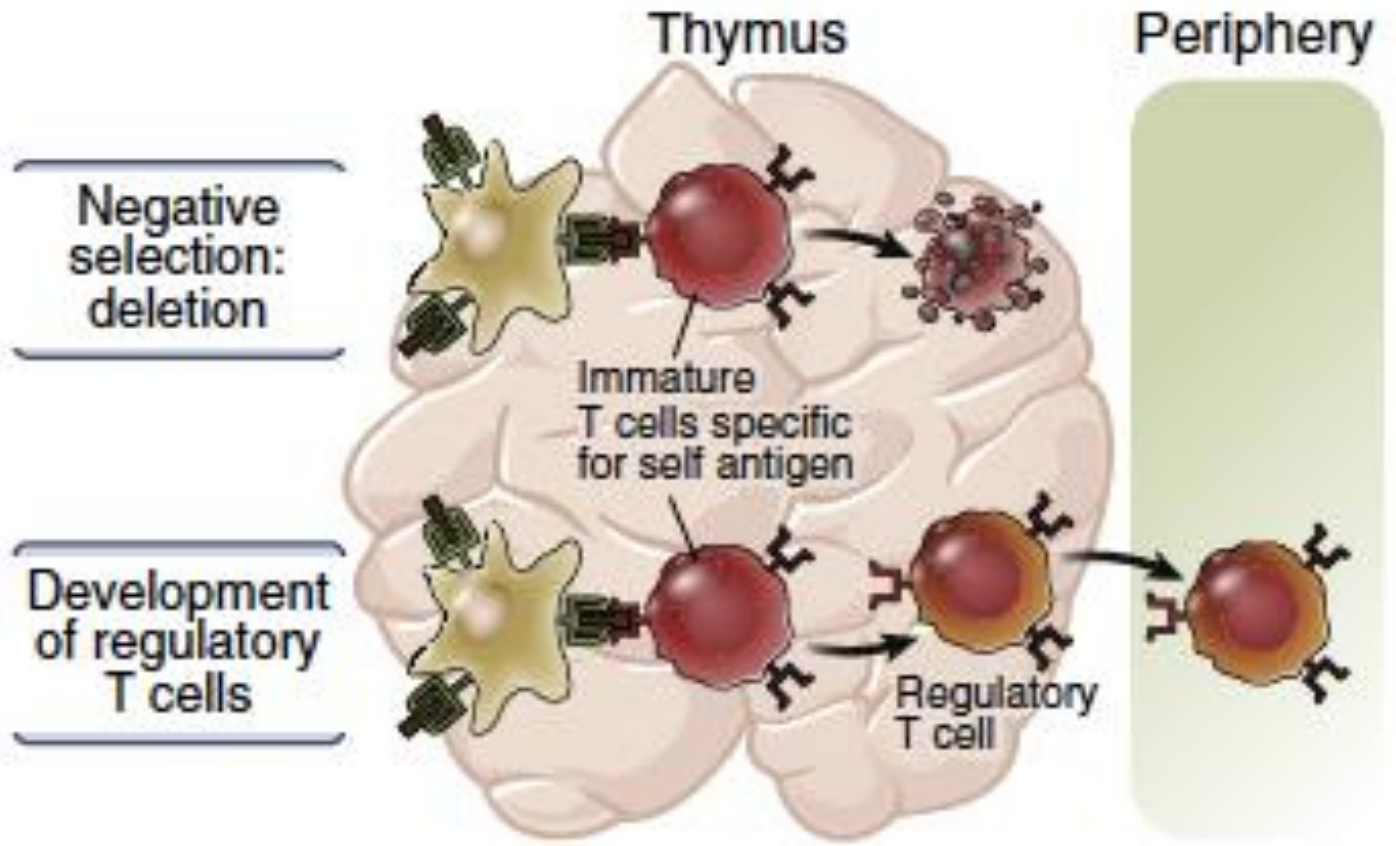
Central and peripheral tolerance to self antigens.



CENTRAL T LYMPHOCYTE TOLERANCE

- **The principal mechanisms of central tolerance in T cells are death of immature T cells (negative selection) and the generation of CD4+ regulatory T cells .**
- Immature lymphocytes may interact strongly with an antigen if the antigen is present at high concentrations in the thymus and if the lymphocytes express receptors that recognize the antigen with high affinity. Antigens that induce negative selection may include proteins that are abundant throughout the body, such as plasma proteins and common cellular proteins.
- A protein called **AIRE** (autoimmune regulator) is responsible for the thymic expression of peripheral tissue antigens.

Central T cell tolerance

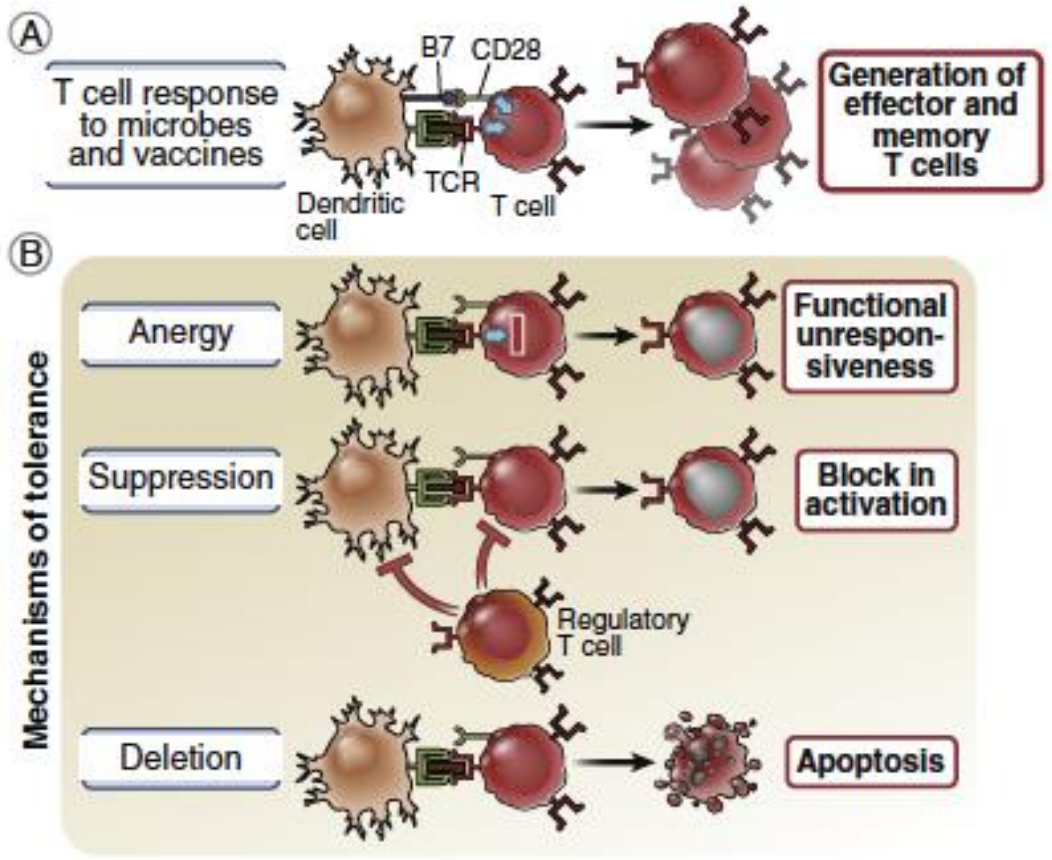


PERIPHERAL T LYMPHOCYTE TOLERANCE

- **Peripheral tolerance is induced when mature T cells recognize self antigens in peripheral tissues, leading to functional inactivation (anergy) or death, or when the self-reactive lymphocytes are suppressed by regulatory T cells .**

- **Antigen recognition without adequate co-stimulation results in T cell anergy or death, or makes T cells sensitive to suppression by regulatory T cells .**

Peripheral T cell tolerance

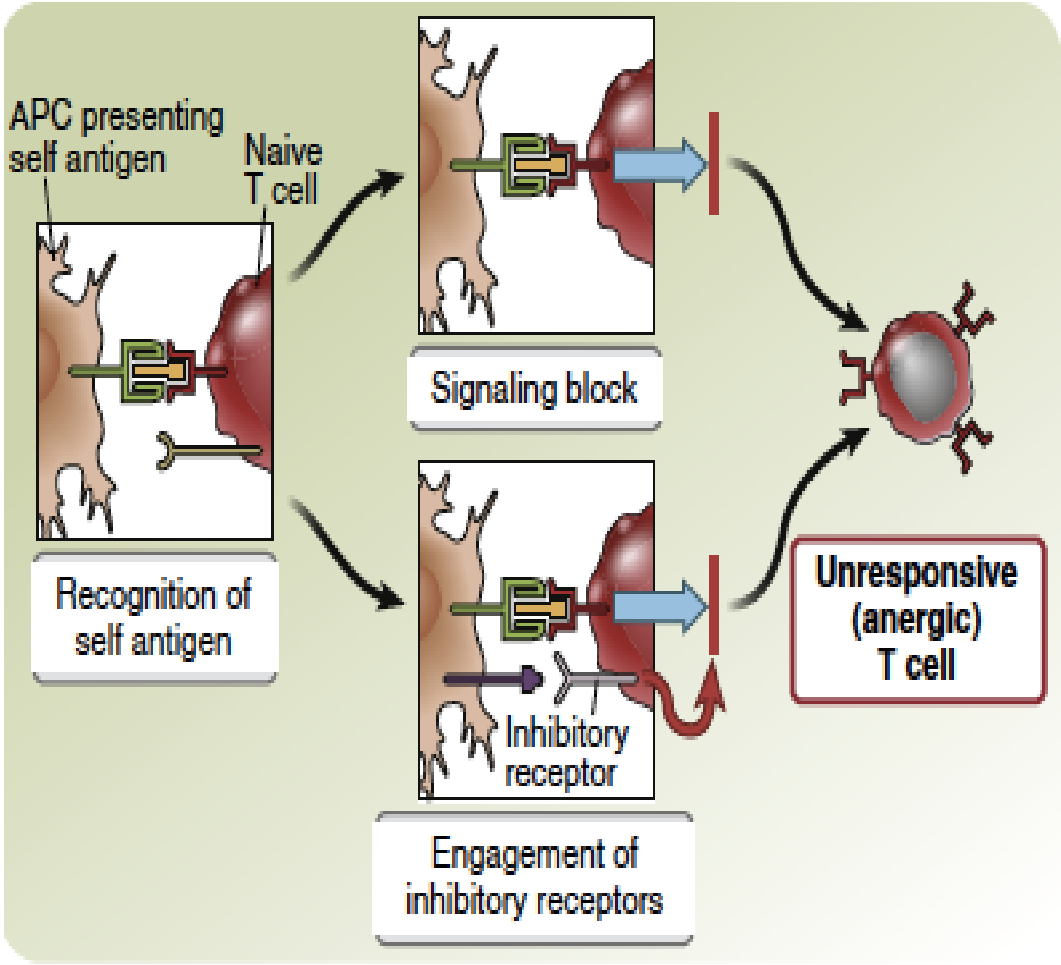


Anergy

- **Anergy in T cells refers to long-lived functional unresponsiveness that is induced when these cells recognize self antigens**

- When T cells recognize antigens without costimulation, the TCR complex may lose its ability to transmit activating signals. In some cases, this is related to the activation of enzymes (ubiquitin ligases) that modify signaling proteins and target them for intracellular destruction by proteases.

- On recognition of self antigens, T cells also may preferentially engage one of the inhibitory receptors of the CD28 family, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4, or CD152) or programmed death protein 1 (PD-1) .



Regulation of T Cell Responses by Inhibitory Receptors

- CTLA-4 is expressed transiently on activated CD4+ T cells and constitutively on regulatory T cells. It functions to terminate activation of responding T cells and also mediates the suppressive function of regulatory T cells. CTLA-4 works by blocking and removing B7 molecules from the surface of APCs, thus reducing costimulation and preventing the activation of T cells.

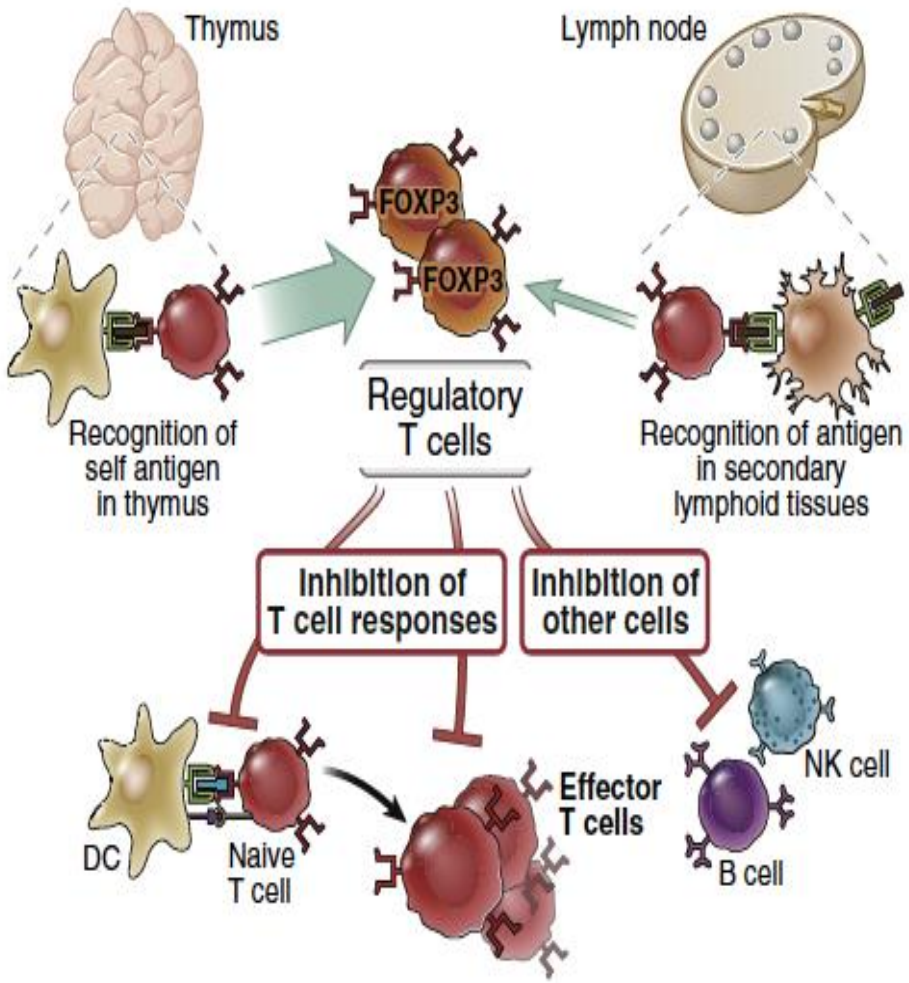
- PD-1 is expressed on CD4+ and CD8+ T cells after antigen stimulation. It has an immunoreceptor tyrosine-based inhibitory motif (ITIM) typical of receptors that deliver inhibitory signals. PD-1 terminates responses of T cells to self antigens and also to chronic infections, notably virus infections.

Immune Suppression by Regulatory T Cells

- **Regulatory T cells develop in the thymus or peripheral tissues on recognition of self antigens and suppress the activation of potentially harmful lymphocytes specific for these self antigens .**

- **Most regulatory T cells are CD4+ and express high levels of CD25, also express a transcription factor called FoxP3**

- **The survival and function of regulatory T cells are dependent on the cytokine IL-2.**



Regulatory T cells may suppress immune responses by several mechanisms.

- Some regulatory cells produce cytokines (e.g., IL-10, TGF-β) that inhibit the activation of lymphocytes, dendritic cells, and macrophages.

- Regulatory cells express CTLA-4, which, may block or remove B7 molecules made by APCs and make these APCs incapable of providing costimulation via CD28 and activating T cells.

- Regulatory T cells, by virtue of the high level of expression of the IL-2 receptor, may bind and consume this essential T cell growth factor, thus reducing its availability for responding T cells.

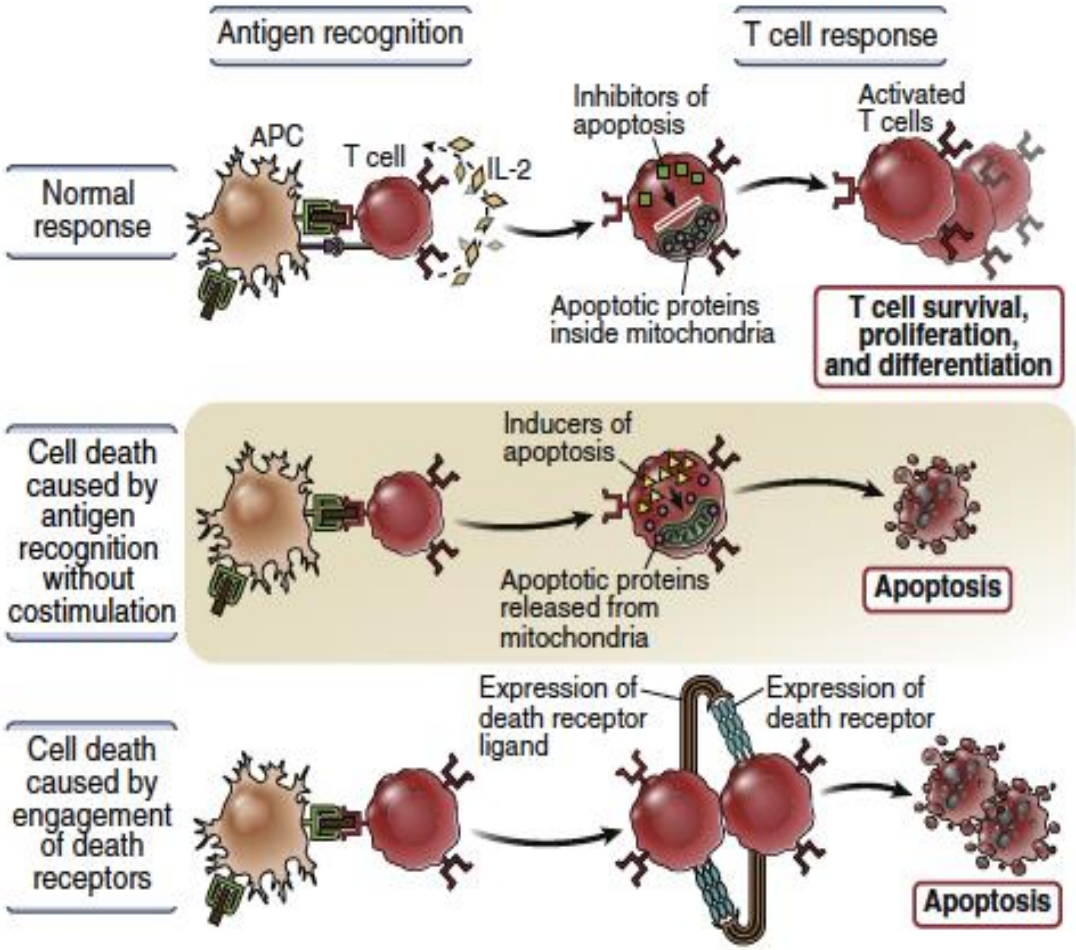
Deletion: Apoptosis of Mature Lymphocytes

- **Recognition of self antigens may trigger pathways of apoptosis that result in elimination (deletion) of the self-reactive lymphocytes .**

- Antigen recognition induces the production of pro-apoptotic proteins in T cells that induce cell death by causing mitochondrial proteins to leak out and activate caspases, cytosolic enzymes that induce apoptosis.

- Recognition of self antigens may lead to the coexpression of death receptors and their ligands. This ligand-receptor interaction generates signals through the death receptor that culminate in the activation of caspases and apoptosis (Fas-FasL).

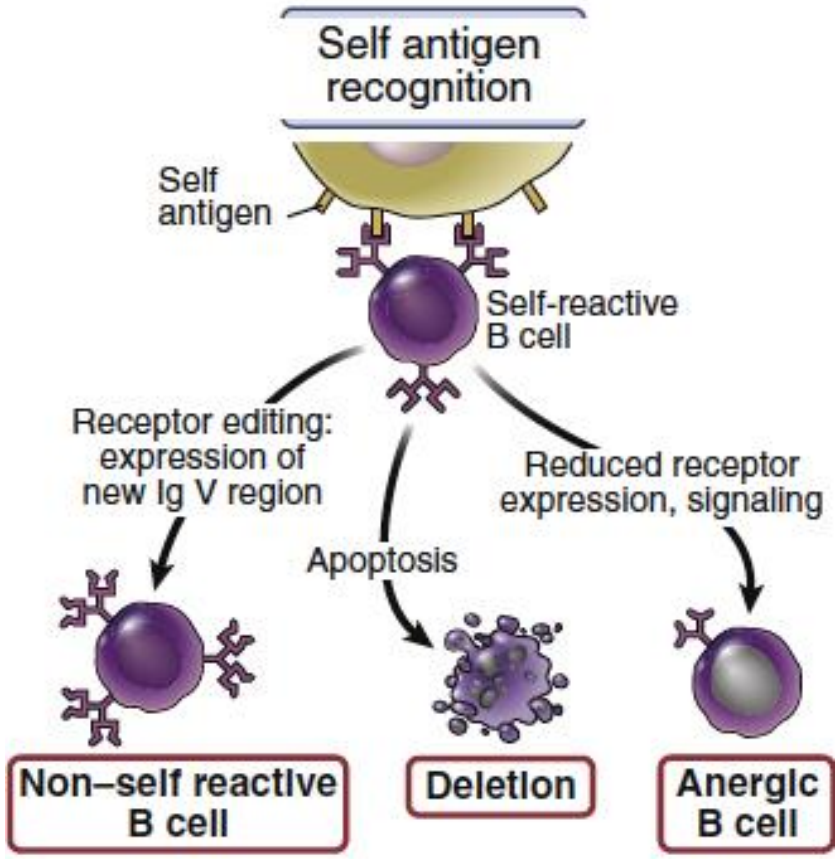
Mechanisms of apoptosis of T lymphocytes.



B LYMPHOCYTE TOLERANCE

- **When immature B lymphocytes interact strongly with self antigens in the bone marrow, the B cells either change their receptor specificity (receptor editing) or are killed (deletion) .**
- *Receptor editing.* Some immature B cells that recognize self antigens in the bone marrow may reexpress RAG genes, resume immunoglobulin (Ig) light-chain gene recombination, and express a new Ig light chain. This new light chain associates with the previously expressed Ig heavy chain to produce a new antigen receptor that may no longer be specific for the self antigen.
- *Deletion.* If editing fails, immature B cells that strongly recognize self antigens receive death signals and die by apoptosis. This process of deletion is similar to negative selection of immature T lymphocytes. As in the T cell compartment, negative selection of B cells eliminates lymphocytes with high-affinity receptors for abundant, and usually widely expressed, cell membrane or soluble self antigens
- *Anergy.* Some self antigens, such as soluble proteins, may be recognized in the bone marrow with low avidity. B cells specific for these antigens survive, but antigen receptor expression is reduced, and the cells become functionally unresponsive (anergic).

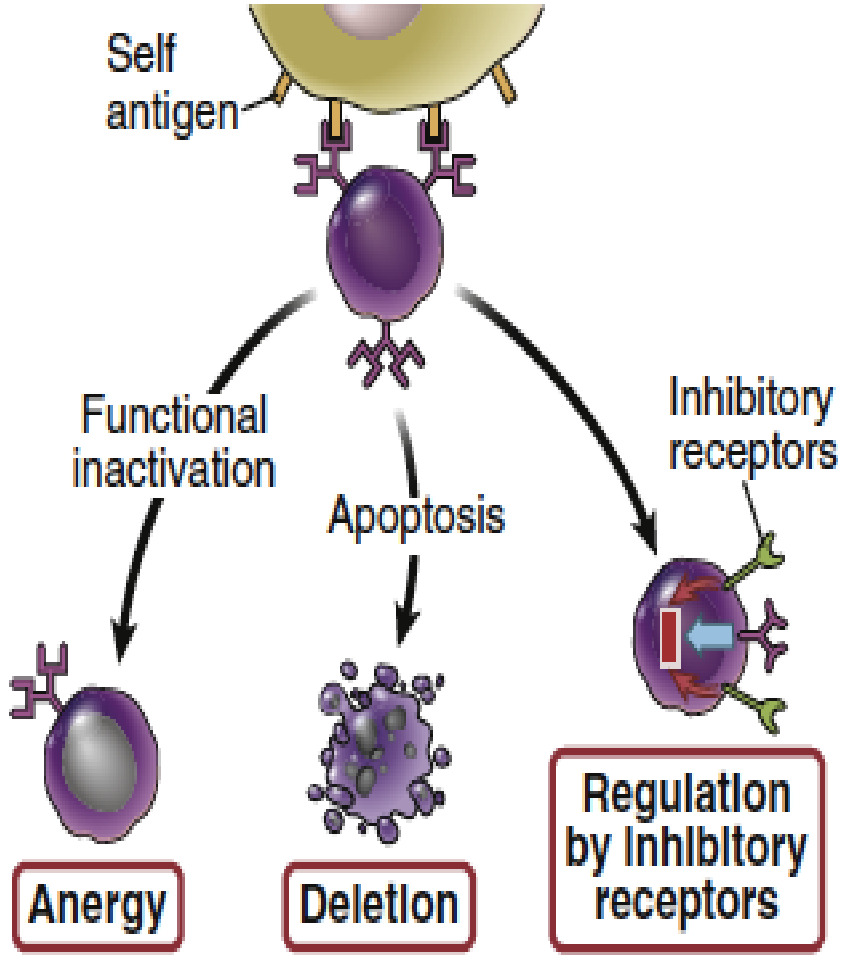
Central tolerance in immature B lymphocytes



Peripheral B Cell Tolerance

- **Mature B lymphocytes that encounter self antigens in peripheral lymphoid tissues become incapable of responding to that antigen**.

- B cells express high **levels of Fas and are killed by FasL-expressing T cells.**



TOLERANCE TO COMMENSAL MICROBES AND FETAL ANTIGENS

- **Commensal Microbes** reside in the intestinal and respiratory tracts and on the skin, where they serve many essential functions. Mature lymphocytes in these tissues are capable of recognizing the organisms but do not react against them, so the microbes are not eliminated, and harmful inflammation is not triggered .

- Paternal antigens expressed in the **fetus**, which are foreign to the mother, have to be tolerated by the immune system of the pregnant mother.

AUTOIMMUNITY

- **Autoimmunity** is defined as **an immune response against self** (autologous) antigens.
- It is an important cause of disease, estimated to affect 2% to 5% of the population in developed countries, and the prevalence of several autoimmune diseases is increasing.
- Different autoimmune diseases may be organ-specific, affecting only one or a few organs, or systemic, with widespread tissue injury and clinical manifestations.
- Tissue injury in autoimmune diseases may be caused by antibodies against self antigens or by T cells reactive with self antigens .
- A cautionary note is that in many cases, diseases associated with uncontrolled immune responses are called autoimmune without formal evidence that the responses are directed against self antigens.

Pathogenesis

- **The principal factors in the development of autoimmunity are the inheritance of susceptibility genes and environmental triggers, such as infections .**
- **Inherited risk for most autoimmune diseases is attributable to multiple gene loci, of which the largest contribution is made by MHC genes.**

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

- **Polymorphisms in non-HLA genes are associated with various autoimmune diseases and may contribute to failure of self-tolerance or abnormal activation of lymphocytes**

A

Genes that may contribute to genetically complex autoimmune diseases

Gene(s)	Disease association	Mechanism
PTPN22	RA, several others	Abnormal tyrosine phosphatase regulation of T cell selection and activation?
NOD2	Crohn's disease	Defective resistance or abnormal responses to intestinal microbes?
IL23R	IBD, PS, AS	Component of IL-23 receptor; role in generation and maintenance of Th17 cells
CTLA4	T1D, RA	Impaired inhibitory checkpoint and regulatory T cell function
CD25 (IL-2Rα)	MS, type 1 diabetes, others	Abnormalities in effector and/or regulatory T cells?
C2, C4 (Complement proteins)	SLE	Defects in clearance of immune complexes or in B cell tolerance?
FCGRIIB (FCγRIIB)	SLE	Defective feedback inhibition of B cells

Roles of non-MHC genes in autoimmunity

B

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

Role of Infections and Other Environmental Influences

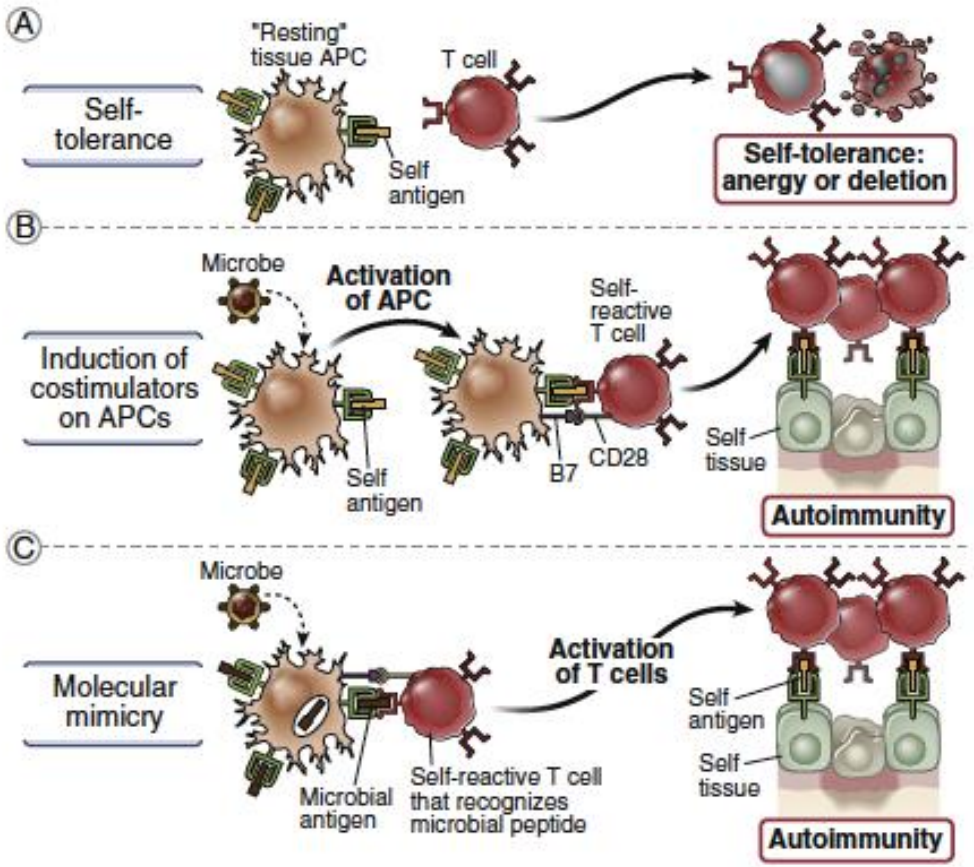
- **Infections may activate self-reactive lymphocytes, thereby triggering the development of autoimmune diseases.** Clinicians have recognized for many years that the clinical manifestations of autoimmunity sometimes are preceded by infectious prodromes. This association between infections and autoimmune tissue injury has been formally established in animal models.

Role of Infections

- An infection of a tissue may induce a local innate immune response, which may lead to increased production of co-stimulators and cytokines by tissue APCs. These activated tissue APCs may be able to stimulate self-reactive T cells that encounter self antigens in the tissue. In other words, infection may break T cell tolerance and promote the activation of self-reactive lymphocytes.

- Some infectious microbes may produce peptide antigens that are similar to, and cross-react with, self antigens. Immune responses to these microbial peptides may result in an immune attack against self antigens. Such cross-reactions between microbial and self antigens are termed **molecular mimicry.**

Mechanisms by which microbes may promote autoimmunity.



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