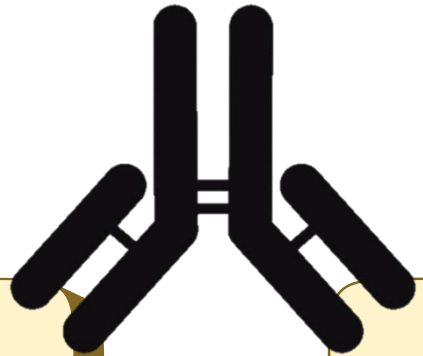
بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

IMMUNOLOGY

FINAL | Lecture 2

Immunologic Tolerance & Autoimmunity



Written by: Saleh Al-Naji
Almothana Khalil

Reviewed by: Mohammad Mahasneh

Immunological Tolerance and Autoimmunity

By: Nader Alaridah, MD, PhD

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.
- Immunological tolerance means antigen-specific unresponsiveness, in which the immune response to certain antigens does not occur, although the immune system is otherwise functioning normally.
- Antigens encountered during fetal development are recognized as **self** by the developing immune system, leading to **immunological tolerance rather than an immune response**.

Immunological Tolerance

- Immunological tolerance and autoimmunity refer to **self-non-self discrimination**. During **lymphocyte development**, lymphocytes undergo a process that enables them to discriminate between **self antigens** and **non-self antigens**, non-self antigens include those derived from **microbes**, as well as **tumor cells**.

Immunologic Ignorance

- Immunologic ignorance is a **mechanism of immunological tolerance** in which lymphocytes **do not respond to certain antigens** because they are present in **very low amounts** or are located in **immune-privileged sites**, such as the **eyes, brain, and testes,** protected by barriers like the blood-brain barrier. **Release of sequestered self antigens** from these sites can expose them to **self-reactive lymphocytes**, leading to **autoimmune disease**.
- An **increase in antigen amount**, **release of antigens from immune-privileged sites** after **tissue trauma**, or **breakdown of blood-tissue barriers** allowing **sequestered antigens** to reach **regional lymph nodes** may lead to **autoimmune disease**.
  The **bone marrow and thymus** are **sterile organs** and **normally lack microbial antigens**.

Importance 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.

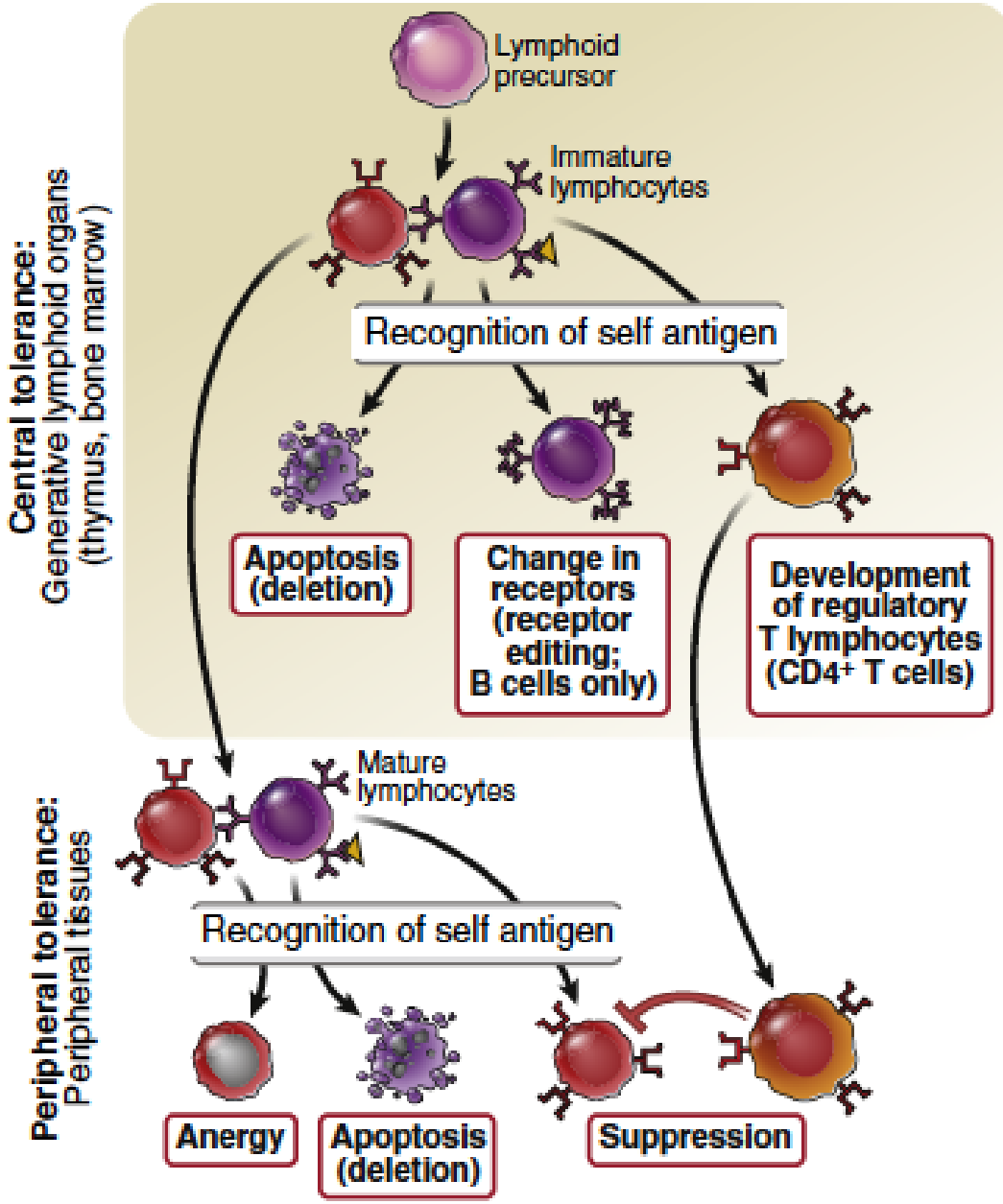
Tolerance Types

- 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,** which involves **immature B lymphocytes in the bone marrow** and **immature T lymphocytes in the thymus**.

- Or when mature lymphocytes encounter self antigens in **peripheral (secondary) lymphoid organs or peripheral tissues,** such as the **spleen and lymph nodes**, and involves **mature B and T lymphocytes, this is called peripheral tolerance.**

Central and peripheral tolerance to self antigens.

Explained in next slides



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.

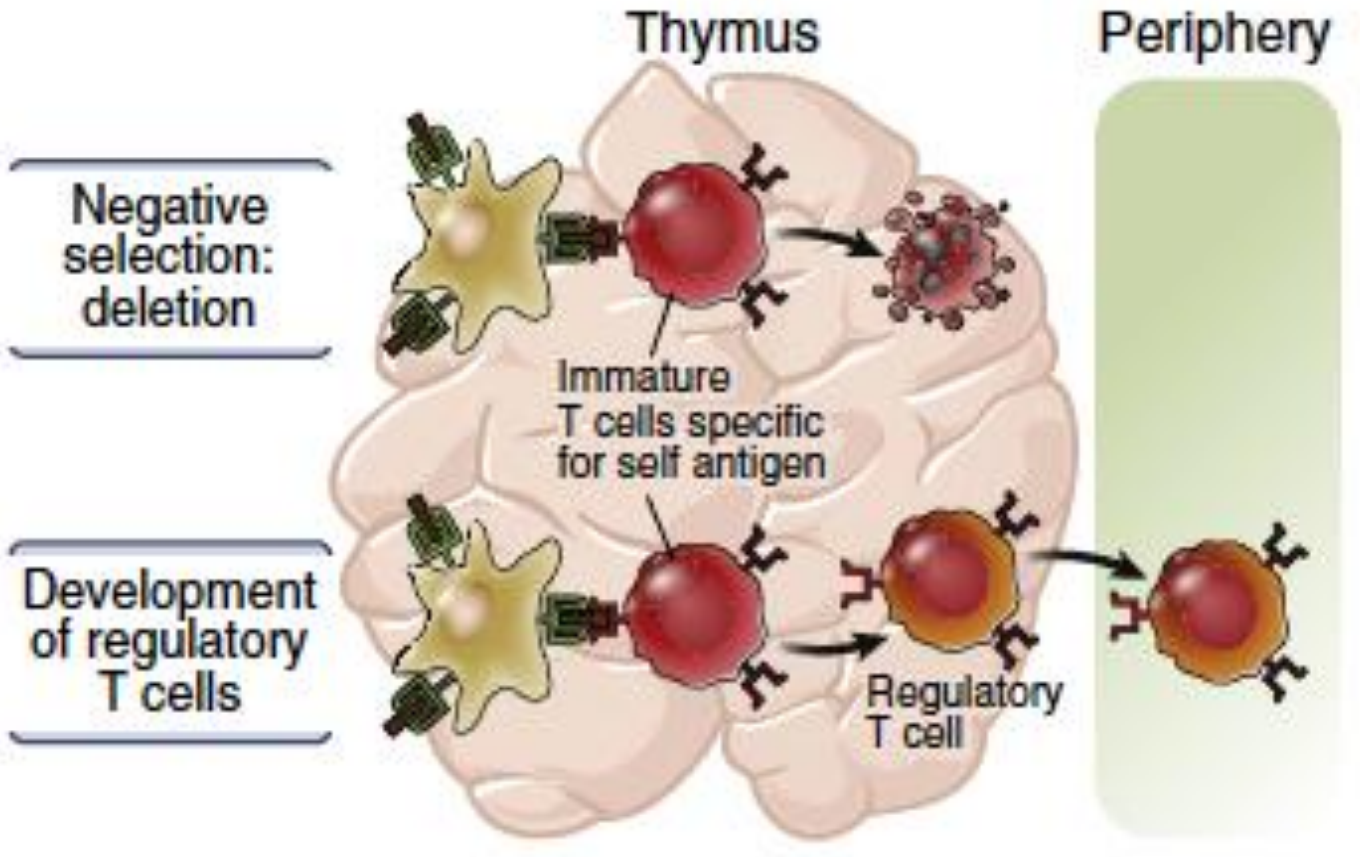
Central Tolerance – Negative selection

- **Common lymphoid progenitors** committed to the T-cell lineage through **Notch signaling** leave the **bone marrow** and migrate to the **thymic cortex**, where they initially exist as **double-negative T lymphocytes** lacking **CD4 and CD8**. In the thymus, **pro-T lymphocytes** differentiate into **pre-T lymphocytes** and then into **immature T lymphocytes** expressing the **αβ T-cell receptor**. Developing T cells that bind **self-peptide-MHC complexes with high affinity** undergo **apoptosis (negative selection)**, ensuring **self-tolerance**, while appropriately selected cells survive maturation. At this developmental stage, the goal is **selection**, not pathogen defense. Later in the **periphery**, **strong TCR binding to non-self peptide MHC complexes** is required to initiate **T-cell activation, proliferation, and differentiation**.
- During T-cell development, thymocytes progress from double-negative ($CD4^-$ $CD8^-$) to double-positive ($CD4^+$ $CD8^+$) stages, where they undergo positive and negative selection. During positive selection, double-positive T lymphocytes differentiate into single-positive $CD4^+$ or $CD8^+$ T cells, while cells that bind self-peptide MHC complexes with high affinity undergo **negative selection (apoptosis).**

Central Tolerance – Receptor Editing

- Receptor editing is a process that occurs in **approximately 20–25% of immature IgM-expressing B lymphocytes** and **does not occur in T lymphocytes**. It involves **reactivation of the RAG1 and RAG2 enzymes**, leading to **rearrangement of the light-chain variable region** to **alter or refine B-cell receptor specificity**. This process reduces **self-reactivity**, allowing B lymphocytes to **avoid strong binding to self antigens** and thereby **escape apoptosis**.
- **Antibody-mediated autoimmune diseases** result from **failure of B-lymphocyte tolerance**, leading to the production of **autoantibodies**.

Central T Cell Tolerance



Central Tolerance - Development of Regulatory T-lymphocytes

- Not all self-reactive lymphocytes that bind self antigens with high affinity and avidity undergo apoptosis. Some **T lymphocytes** instead differentiate into **regulatory T cells (Tregs)** through **upregulation of transcription factors such as FOXP3**, express **CD25** (the **α chain of interleukin-2**) on their surface, and **secrete interleukin-10**.
- **$CD4^+$ T lymphocytes** orchestrate much of the immune response, including the **regulation of B lymphocytes**; therefore, **failure of T-lymphocyte tolerance** can lead to **failure of B-lymphocyte tolerance**.
- Cells with **intermediate-to-high affinity for self-peptide–MHC complexes**, below the threshold for **negative selection**, may be **diverted into the regulatory T-cell lineage (Tregs)** rather than undergoing apoptosis.

AIRE protein

- Not all self antigens are naturally expressed in the thymus; therefore, the **autoimmune regulator (AIRE)** protein plays a critical role in central tolerance. AIRE **induces medullary thymic epithelial cells (mTECs)** to express and present **tissue-restricted self antigens** from **peripheral organs**, such as **insulin from the pancreas** and **myelin from the brain**, as well as **intracellular antigens**, to developing T lymphocytes. AIRE expression also occurs outside the thymus in peripheral lymphoid tissues. **Mutations in the AIRE gene** cause **Autoimmune Polyendocrine Syndrome type 1 (APS-1)**. In summary, central T-cell tolerance in the thymus is achieved through negative selection and generation of regulatory T cells.

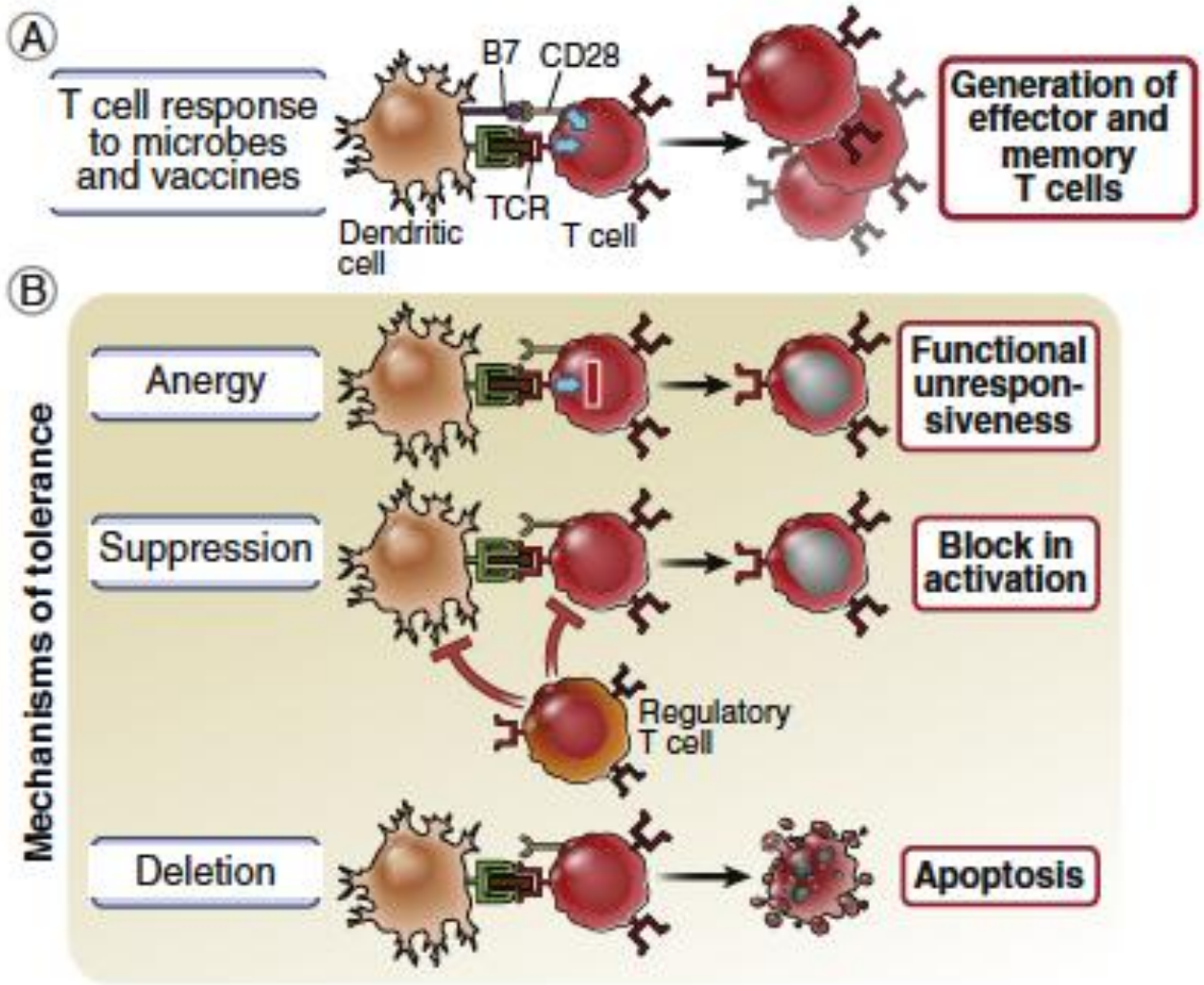
Peripheral T Lymphocyte Tolerance

- **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

Explained in next slides



Activation of Adaptive Immunity

- Before discussing peripheral tolerance, it is important to understand normal peripheral adaptive immune activation. **The adaptive immune system requires three signals for T-cell activation:**

1. **Antigen recognition**, achieved by binding of the **T-cell receptor (TCR)** on T lymphocytes to **peptide–MHC complexes** on an **antigen-presenting cell**, such as a **dendritic cell**.
2. **Co-stimulatory signals**, provided by interaction of **CD28 on T cells** with **B7 molecules (CD80 or B7-1/CD86 or B7-2)** on antigen-presenting cells. Expression of these co-stimulatory molecules is **upregulated following innate immune activation** through recognition of **PAMPs and DAMPs** by **pattern recognition receptors (PRRs)**.
3. **Polarizing signals**, delivered by **cytokines in the local microenvironment**, such as **interleukin-2**, which promote **T-cell proliferation, survival, and differentiation** into **effector T lymphocytes**.

Peripheral Tolerance

Peripheral tolerance maintains **self-tolerance in mature lymphocytes** through **three main mechanisms**:

1. Anergy

Anergy is a state of **long-lived functional unresponsiveness** in which viable B or T lymphocytes fail to respond to self antigens. It occurs when the **first signal is present**, meaning the **T-cell receptor binds peptide-MHC on an antigen-presenting cell**, but the **co-stimulatory signals B7-1 (CD80) and B7-2 (CD86) are absent**. The absence of co-stimulatory signaling results in **signal blockade**, leading to activation of **ubiquitin ligases** that promote **proteolytic degradation of key signal-transduction molecules**. As a result, **TCR signaling becomes ineffective**, since the **TCR itself has no intrinsic effector function and depends on intact signal-transducing pathways**.

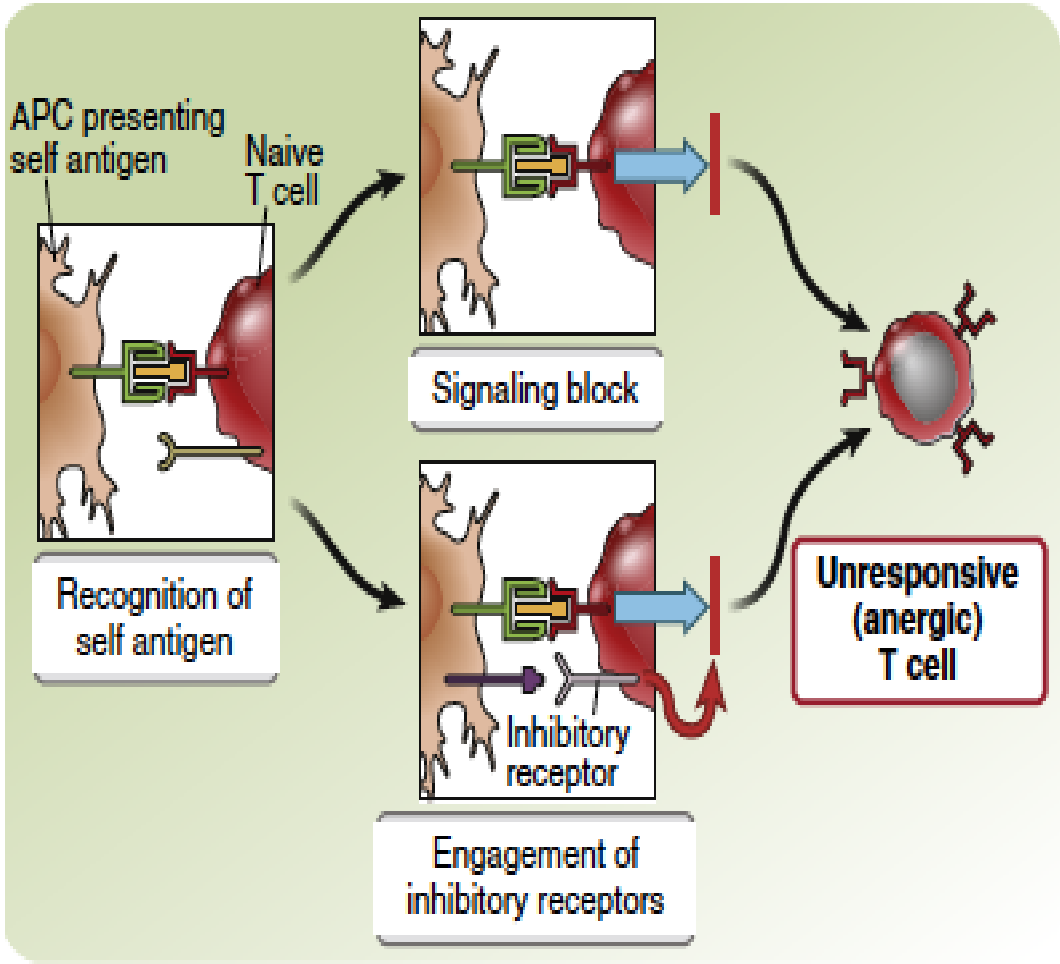
Under certain conditions, such as exposure of sequestered self antigens following trauma to immune-privileged sites, this unresponsive state may convert to responsiveness, potentially leading to autoimmunity.

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.

CD28 family

- The **CD28 family** contains both **activating** and **inhibitory receptors** that regulate T-cell responses. The **activating members** of the CD28 family include **CD28** and **ICOS**, whereas the **inhibitory members** include **CTLA-4 (CD152)**, **PD-1**, and **BTLA**. These inhibitory receptors are also known as **immune checkpoints**, because **blocking them enhances T-lymphocyte activation**, which is why they are widely used in **cancer therapy** using **monoclonal antibody drugs (ending with -mab)**.
- Both **agonists and antagonists** exist for these checkpoint molecules. **Abatacept**, a CTLA-4-Ig fusion protein, acts as a **functional agonist (the doctor said it's an antagonist) of CTLA-4 inhibitory signaling** by binding **B7 (CD80/CD86)** on antigen-presenting cells, thereby **blocking CD28-mediated co-stimulation**; it is used in the treatment of **rheumatoid arthritis**. In contrast, **PD-1 antagonists** are commonly used in **cancer immunotherapy**, while **agonistic signaling through PD-1** contributes to immune inhibition.
- Patients treated with **checkpoint inhibitors** are **more prone to autoimmune diseases** due to excessive immune activation. **PD-1** delivers inhibitory signals through its **immunoreceptor tyrosine-based inhibitory motif (ITIM)**, which functions to **terminate T-cell responses**.

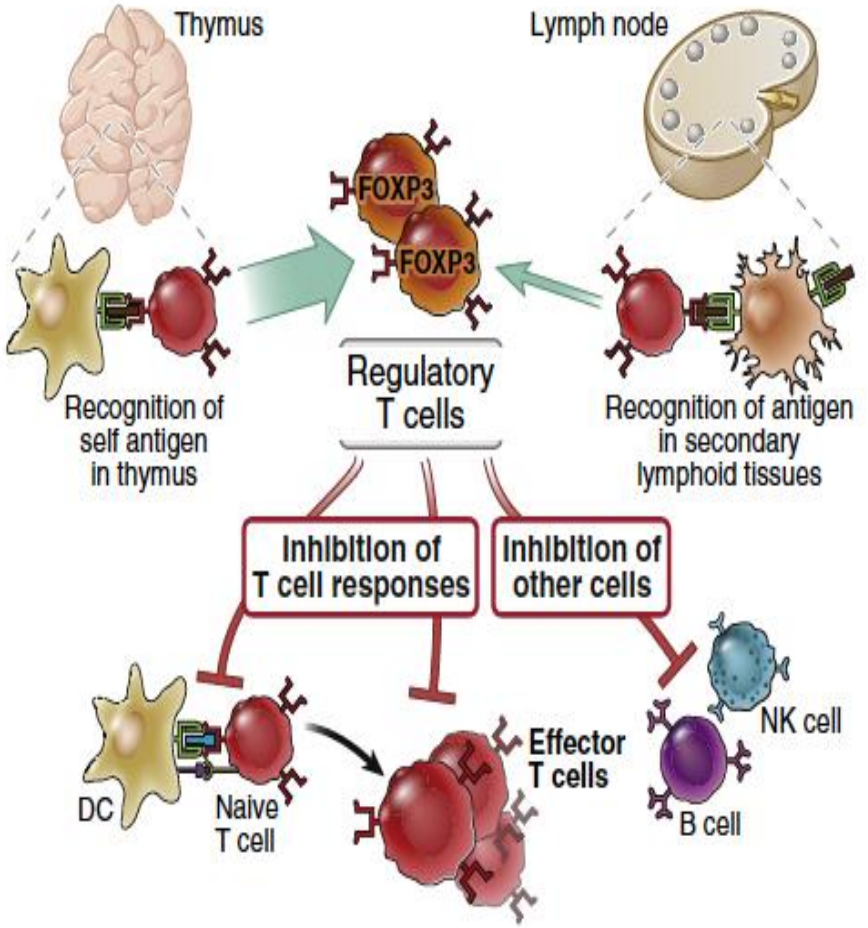
BTLA: B and T Lymphocyte Attenuator

B7 expression level determines activation versus inhibition

- The **B7 molecule is expressed on the antigen-presenting cell**, but it preferentially binds to **inhibitory receptors on the T lymphocyte** rather than to the activating receptor. The main **inhibitory receptors** involved are **CTLA-4 (CD152)**, **PD-1 (programmed death protein-1)**, and **BTLA (B and T lymphocyte attenuator)**. Although the **activating receptor CD28** is present on the T cell, **B7 is not engaged with CD28** under these conditions.
- The **determinant factor** for whether **inhibitory or activating signaling occurs** is the **amount of B7 expressed on the antigen-presenting cell**. Under **normal, non-inflammatory conditions**, B7 expression is relatively **low**, and B7 preferentially binds to **inhibitory receptors**, particularly **CTLA-4 and PD-1**, due to their **higher affinity and avidity**, resulting in **suppression of T-cell activation**. In contrast, during **infection or activation of the innate immune system**, **B7 expression is markedly upregulated**, allowing sufficient B7 molecules to engage **CD28**, thereby shifting the balance toward **activating signals and T-cell activation**.

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.



Note how the green arrow on the left is wider than on the right, indicating more Treg from central pathways.

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.

Peripheral tolerance

2. Suppression by regulatory T lymphocytes (Tregs)

Not all **regulatory T lymphocytes** develop centrally in the thymus; some are **generated peripherally**. These **Tregs suppress immune responses** by inhibiting the **activation, proliferation, and function of B and T lymphocytes** through **multiple suppressive mechanisms**, thereby maintaining peripheral tolerance.

Deletion: Apoptosis of Mature Lymphocytes

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

- **Intrinsic pathway:**

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.

- **Extrinsic pathway:**

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).

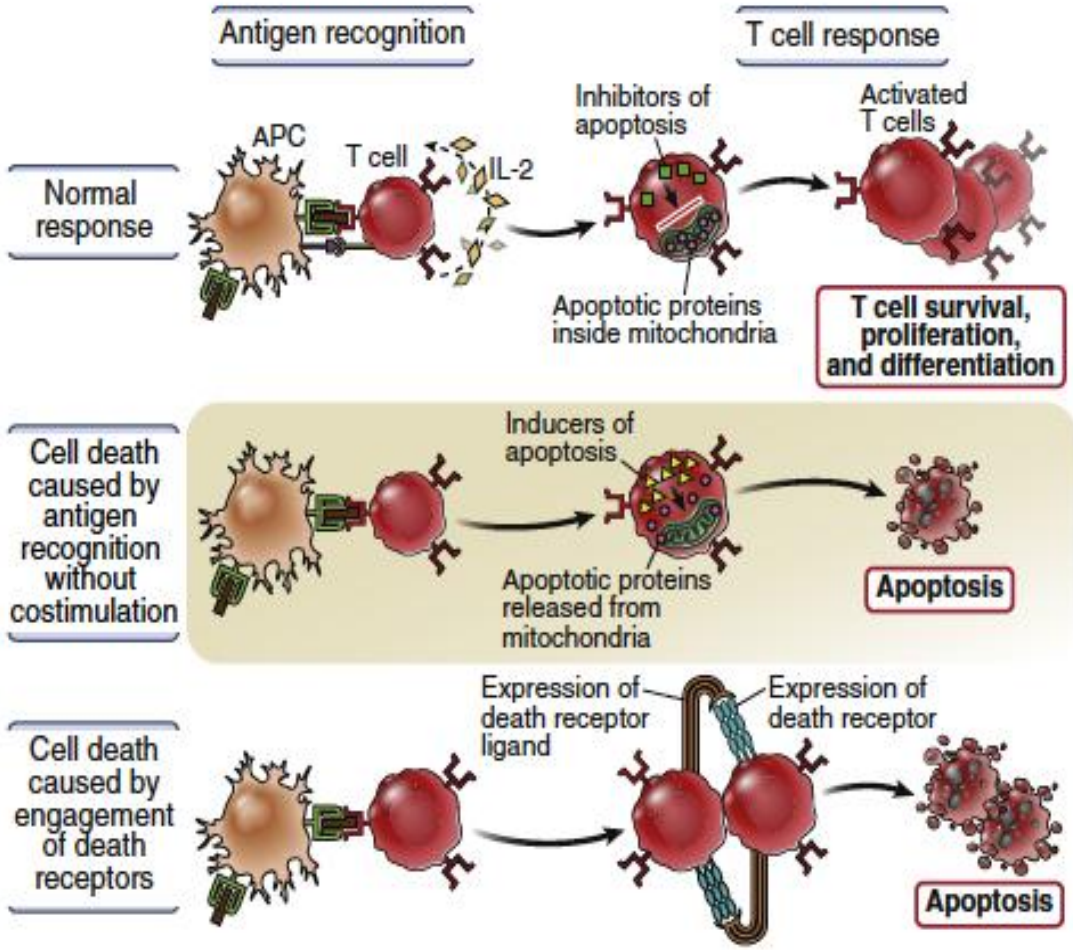
- Apoptosis occurs when the **balance of proapoptotic vs antiapoptotic signals** favors apoptosis.

Peripheral tolerance

3. Deletion (apoptosis)

- Some mature self-reactive lymphocytes undergo **apoptosis** in the periphery. When the **first signal is present without adequate co-stimulation**, survival signals are insufficient, leading to **upregulation of pro-apoptotic molecules**. Apoptosis may occur through the **intrinsic (mitochondrial, caspase-dependent) pathway** or the **extrinsic pathway**, mediated by **death receptors such as Fas (CD95) and Fas ligand**.

Mechanisms of Apoptosis of T lymphocytes.



All 3 signals present → antiapoptotic dominate → survival, proliferation, differentiation.

Only the 1st signal is present, (no costimulation) → leakage of apoptotic proteins from mitochondria → apoptosis *by way of* ***intrinsic*** *pathway*.

Only the 1st signal is present (no costimulation) → increased expression of Fas and Fas-L on T cells → apoptosis *by way of* ***extrinsic*** *pathway*.

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.
- Variable (V) domain on light chain is edited.
- If editing fails (still of strong affinity to self antigen), the cell dies.

B Lymphocyte Tolerance

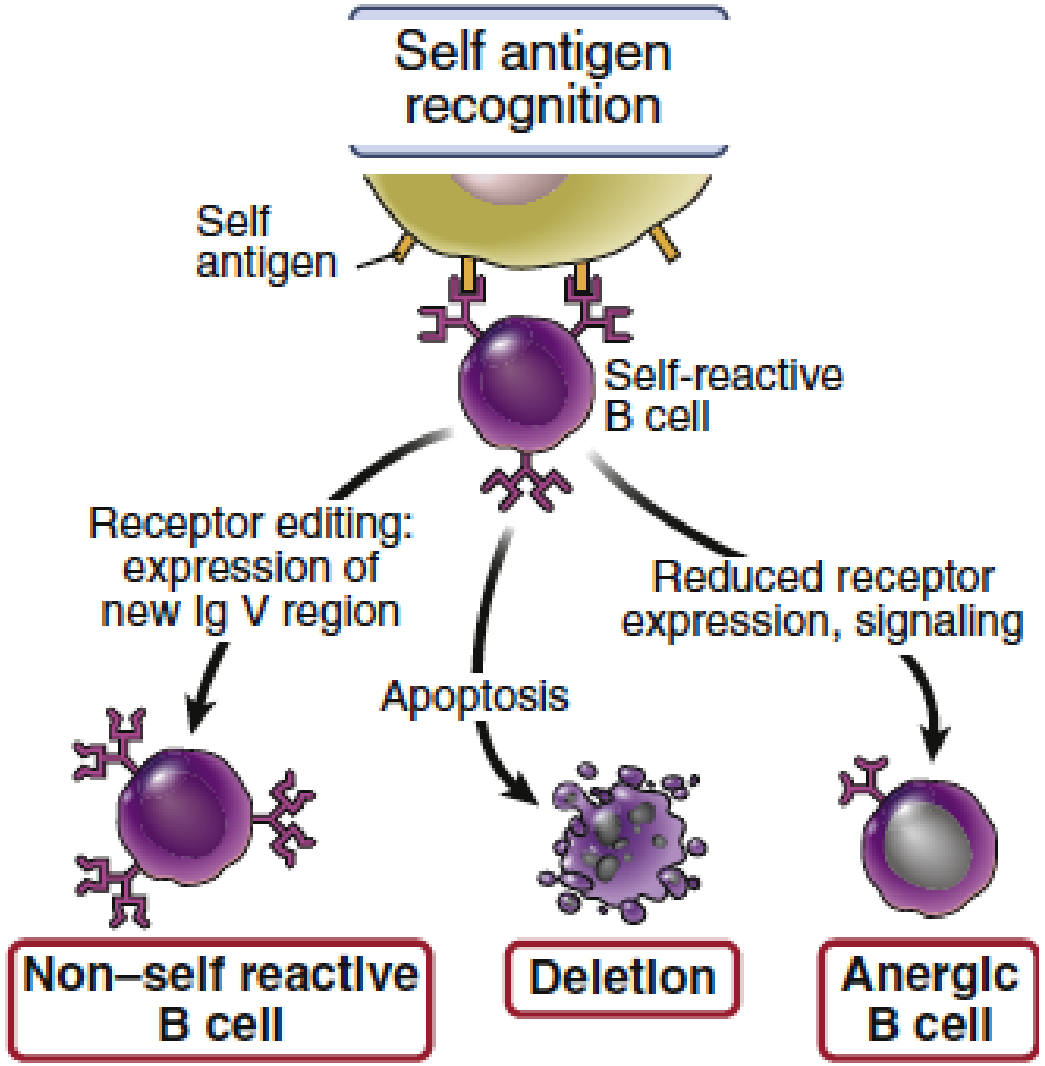
- *Deletion*. If editing fails, immature B cells that strongly recognize self antigens receive death signals and die by apoptosis. This process of deletion is similar to negative selection of immature T lymphocytes. As in the T cell compartment, negative selection of B cells eliminates lymphocytes with 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).
- Anergy can be due to lack of stimulation from helper T cells *or* due to inhibitory signals as discussed in T cell tolerance.

Central Tolerance in Immature B lymphocytes

This diagram illustrates events that occur **after B cells have passed positive selection**.
In **self-reactive B cells that fail negative selection**, three possible fates are shown:

1. Receptor editing, approximately 25-50% of circulating B cells have gone through this process.
2. Apoptosis.
3. Anergy, due to lack of stimulation of T cell signals or direct inhibitory signals.

- B cell responses are either T cell-dependent or T cell-independent. T-cell dependent B-cell responses are the ones prone to anergy by lack of T-cell stimulation.



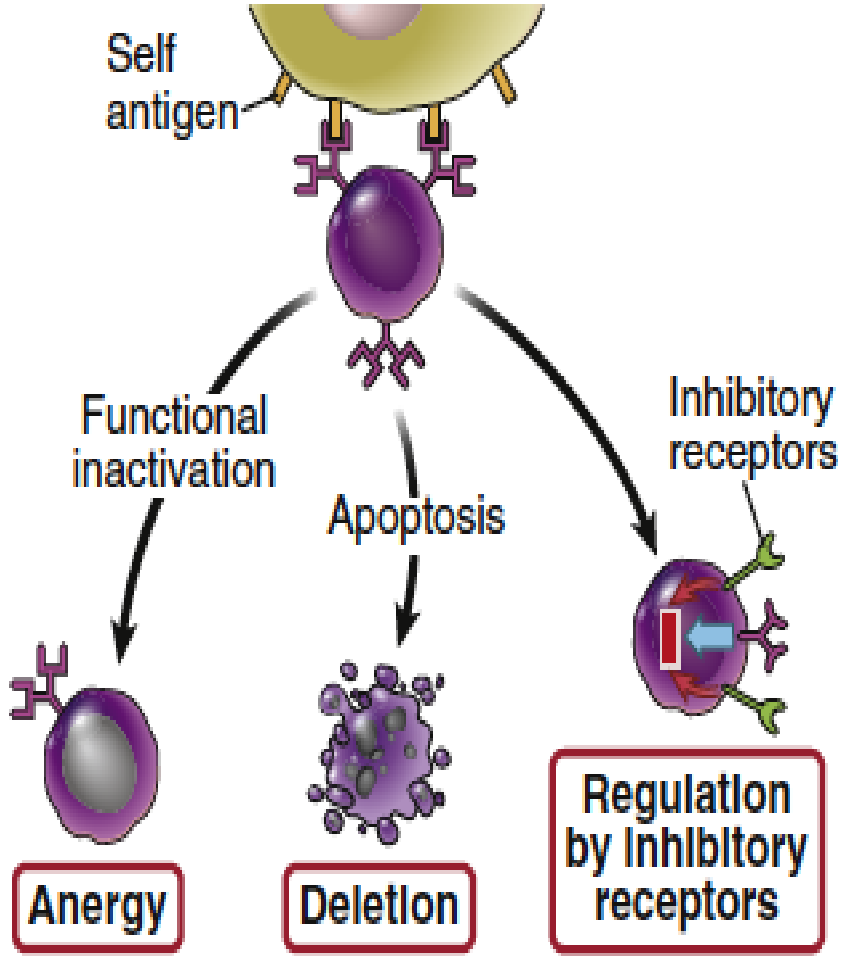
Peripheral B Cell Tolerance

- 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.

- Generally, B-cell tolerance is not very well-understood and also not strong to the extent T cell tolerance is. This explains why most autoimmune diseases are antibody-mediated.

Peripherally, there are also 3 fates:



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.

Theories behind the tolerance to commensal microbes include:

- Presence of intestinal epithelial barrier.
- An **abundance of regulatory T cells (Tregs)** in the intestinal mucosa, which actively suppress immune activation.
- A local microenvironment rich in **inhibitory cytokines**, especially **TGF-β and IL-10**, which dampen inflammatory immune responses.

Tolerance To Commensal Microbes And Fetal Antigens

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

Theories behind this type of tolerance include:

- An **abundance of regulatory T cells (Tregs)**, which suppress maternal immune responses.
- **Exclusion or limited access of inflammatory immune cells** within the **pregnant uterus**, reducing immune activation against fetal antigens.
- **Predominant activation of PRRs that promote tolerogenic signaling**, rather than PRRs that induce strong **co-stimulatory molecule expression**, thereby limiting adaptive immune activation.

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.

Autoimmunity Inducers

Factors that contribute to the pathogenesis of autoimmune diseases include:

- Genetic predisposition.
- Failure of central or peripheral tolerance mechanisms.
- Environmental factors.
- Certain drugs.
- Molecular mimicry, seen in rheumatic fever.
- **Hormonal and sex-related factors**, with a **female predominance** in many autoimmune diseases (approximate **F:M ratio ~1.7:1**).
- Pregnancy, which can *exacerbate systemic lupus erythematosus.*

Note that developing countries in general have less autoimmune disease burden explained by the “hygiene theory”, where individuals are exposed to many antigens earlier in life, inducing tolerance.

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.

Take a look on the table and appreciate the **association** between the specific MHC genotypes and the relative risk of the mentioned 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

Pathogenesis

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

Abbreviations in the table:

- **PTPN22**: Protein Tyrosine Phosphatase Non-receptor Type 22.
- **RA**: Rheumatoid Arthritis.
- **IBD**: Inflammatory Bowel Disease.
- **PS**: Psoriasis.
- **AS**: Ankylosing Spondylitis.
- **T1D**: Type-1 Diabetes.
- **MS**: Multiple Sclerosis.
- **SLE**: Systemic Lupus Erythematosus.

The doctor read the examples.

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
Autosomal Recessive	*AIRE*	Autoimmune polyendocrine syndrome (APS-1)	Reduced expression of peripheral tissue antigens in the thymus, leading to defective elimination of self-reactive T cells
Autosomal Dominant	*CTLA4*	Autosomal dominant immune dysregulation syndrome	Impaired inhibitory checkpoint and regulatory T cell function leading to loss of B and T cell homeostasis
X-linked Recessive	*FOXP3*	Immune dysregulation, X-linked polyendocrinopathy and enteropathy (IPEX)	Deficiency of regulatory T cells
Autosomal Dominant	*FAS*	Autoimmune lymphoproliferative syndrome (ALPS)	Defective apoptosis of self-reactive T and B cells in the periphery

Role of Infections and Other Environmental Influences

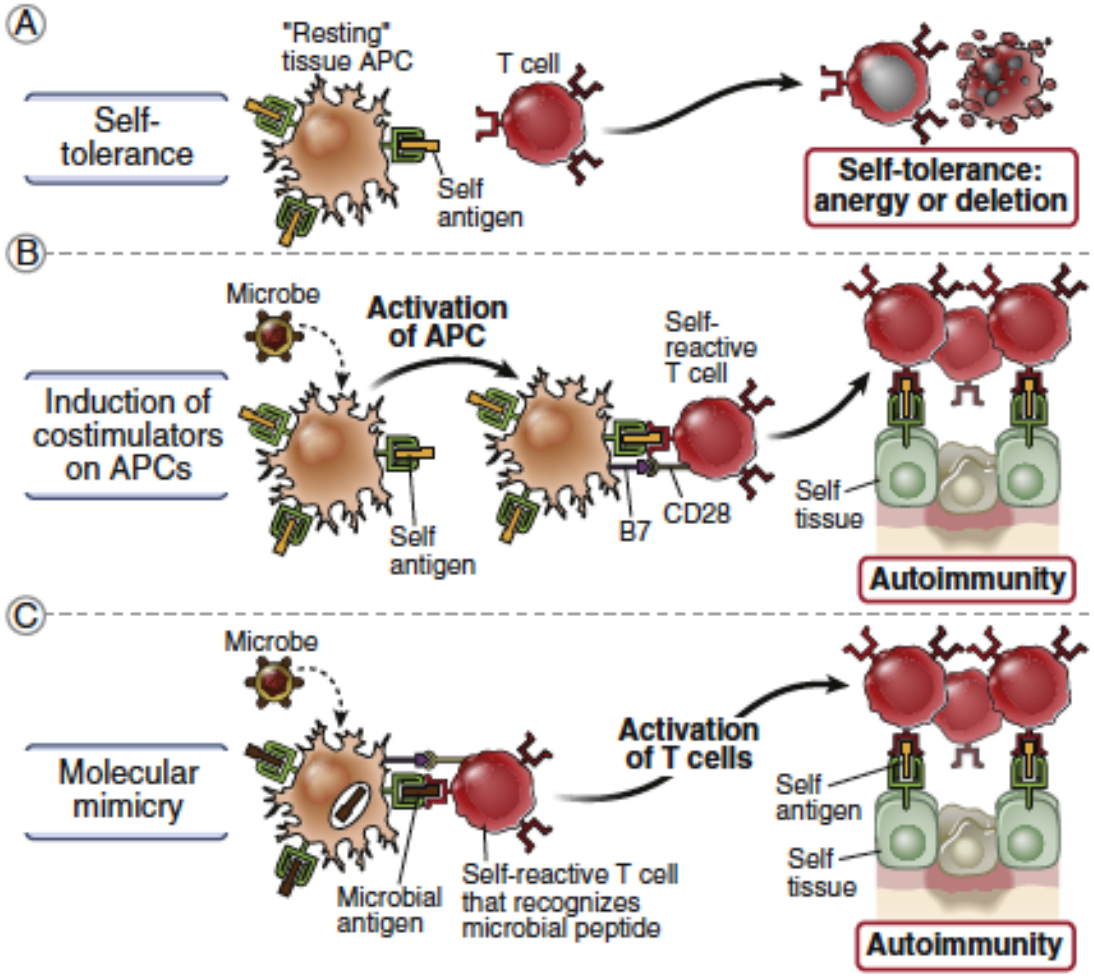
- Procainamide (class Ia antiarrhythmic agent) induces SLE.
- Intake of heavy metals also induces autoimmunity.
- **Infections may activate self-reactive lymphocytes, thereby triggering the development of autoimmune diseases.** Clinicians have recognized for many years that the clinical manifestations 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.**

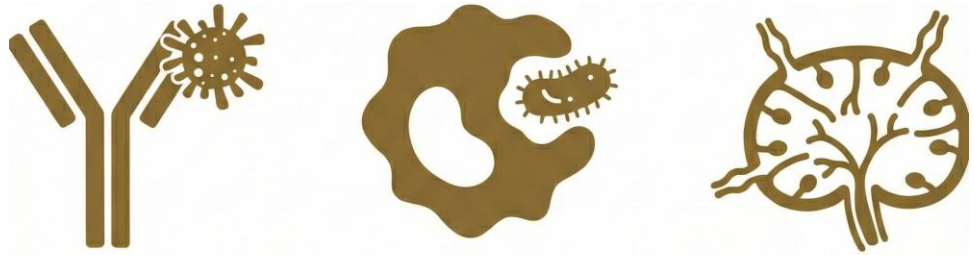
Mechanisms by Which Microbes May Promote Autoimmunity.



No costimulatory molecules → **Tolerance**.

Induction of signal 2 by the microbe → activation of self-reactive cells → **Autoimmunity**.

Recognition of mimicry-inducing microbial antigen by self-reactive cells → activation and clonal expansion → targeting host antigens (such as cardiac myosin) → **Autoimmunity**.



IMMUNOLOGY QUIZ

LECTURE 2

External Resources

رسالة من الفريق العلمي

References as cited:

1. **“Other resources were considered… Then Dr. Nader spoke.”**
   - ***Mahasneh***

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			