Immunopathology lecture 1 Dr. Alia Essam Mahmood Alubadi

- **Normal Immune Response**: The immune system can react to a wide variety of microbes while remaining unresponsive to the individual's own antigens (self antigens).

- **Lymphocyte Maturation**: Lymphocytes capable of recognizing self antigens are generated during normal maturation, yet mechanisms exist to prevent their activation against these antigens.

- **Antigen-Presenting Cells (APCs)**: APCs present both foreign and self proteins to T cells, meaning self antigens are regularly encountered by the immune system.

- **Mechanisms of Self-Discrimination**: The immune system has mechanisms that discriminate between self and non-self (typically microbial) antigens to prevent immune responses against the body's own cells.

- **Autoimmunity**: If self-tolerance mechanisms fail, the immune system may attack the body's own cells, leading to autoimmune diseases.

- **Interaction with Commensals and Pregnancy**: The immune system coexists with commensal microbes and accepts a fetus, which expresses paternal antigens, through similar tolerance mechanisms.

Immunologic tolerance:

1. **Definition of Immunologic Tolerance**: Immunologic tolerance is the lack of response to antigens induced by lymphocyte exposure to these antigens.
2. **Outcomes of Antigen Encounter**:
    - Lymphocytes may be activated, leading to an immune response (immunogenic).
    - Lymphocytes may be inactivated or killed, resulting in tolerance (tolerogenic).
    - Lymphocytes may not react at all, termed immunologic ignorance.
3. **Antigen Characteristics**:
    - Microbes are typically immunogenic.
    - Self antigens are generally tolerogenic.
4. **Activation vs. Tolerance**: The outcome of lymphocyte activation or tolerance is influenced by the nature of the antigen and additional signals present during antigen presentation. The same antigen can induce either response depending on how it is administered.
5. **Significance of Immunologic Tolerance**:

    - Self-tolerance failure is a primary cause of autoimmune diseases.
    - Inducing tolerance in specific lymphocytes may help prevent unwanted immune reactions, aiding in the treatment of allergies, autoimmune diseases, and organ transplant rejection.
    - Tolerance strategies could also benefit gene therapy and stem cell transplantation.
6. **Types of Tolerance**:
    - **Central Tolerance**: Induced in generative (central) lymphoid organs (bone marrow and thymus) when developing lymphocytes encounter self antigens.
    - **Peripheral Tolerance**: Induced when mature lymphocytes encounter self antigens in peripheral lymphoid organs or tissues.
7. **Mechanisms of Tolerance**: Understanding the mechanisms of immunologic tolerance is crucial, especially in T cells (particularly CD4+ helper T lymphocytes), as their tolerance is vital for preventing both cell-mediated and humoral immune responses against self proteins.
8. **Consequences of Tolerance Failure**: The failure of tolerance in CD4+ T cells can lead to autoimmunity, characterized by T cell-mediated attacks on tissue self antigens or the production of autoantibodies against self proteins.

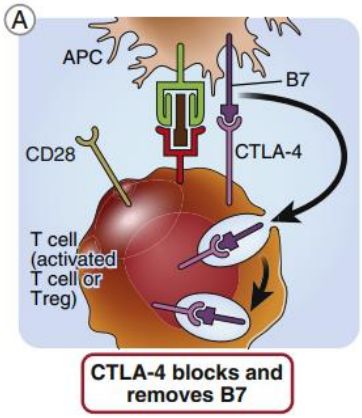
- **Central Tolerance**: The primary mechanisms for central tolerance in T cells include:
    - Death of immature T cells.
    - Generation of CD4+ regulatory T cells.
- **Outcome of Self Antigen Recognition**: It is not fully understood what determines whether a thymic CD4+ T cell that recognizes a self antigen will undergo apoptosis or develop into a regulatory T cell.
- **Negative Selection**: Immature T cells can interact strongly with antigens present at high concentrations in the thymus, especially if they have high-affinity receptors. Common antigens that induce negative selection include abundant proteins found throughout the body.
- **Tissue-Restricted Antigens**: Many self proteins that are normally found only in specific peripheral tissues are also expressed in some thymic epithelial cells. This expression is mediated by a protein called AIRE (autoimmune regulator).
- **AIRE and Autoimmunity**: Mutations in the AIRE gene lead to autoimmune polyendocrine syndrome, where certain tissue antigens are not expressed in the thymus. As a result, T cells specific to these antigens are not eliminated and can mature into functional T cells that attack peripheral tissues.
- **Targeting of Endocrine Organs**: It is unclear why endocrine organs are frequent targets of autoimmune attacks in this syndrome.

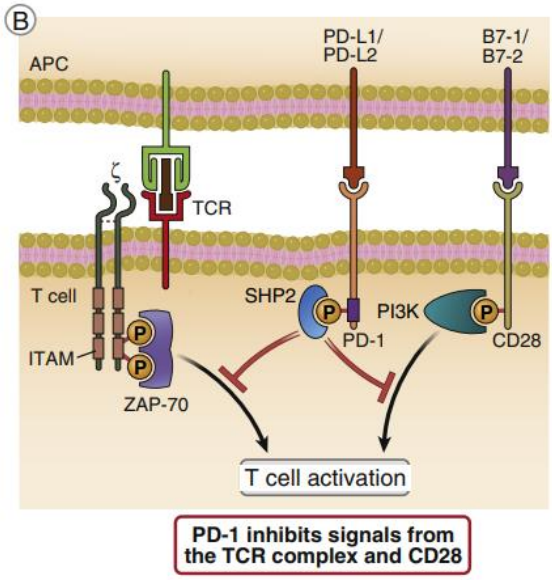
- **Imperfect Central Tolerance**: Central tolerance is not foolproof; some self-reactive lymphocytes can mature and persist in healthy individuals.
- **Peripheral Mechanisms**: To prevent activation of these self-reactive lymphocytes, additional peripheral tolerance mechanisms may be involved.
- **Definition of Peripheral Tolerance**: Peripheral tolerance occurs when mature T cells recognize self-antigens in peripheral tissues, leading to:
    - Functional inactivation (anergy) or death of T cells.
    - Suppression of self-reactive lymphocytes by regulatory T cells.
- **Importance of Peripheral Tolerance**: This mechanism is crucial for preventing T cell responses to self antigens not present in the thymus and serves as a backup for incomplete central tolerance.
- **Anergic Response**: T cell recognition of antigens without sufficient costimulation can result in anergy or death, or make T cells more susceptible to suppression by regulatory T cells.
- **Signal Requirements for T Cell Activation**: Naive T lymphocytes require two signals for activation:
    - **Signal 1**: Recognition of the antigen.
    - **Signal 2**: Provided by costimulatory molecules expressed on antigen-presenting cells (APCs).
- **Role of Dendritic Cells**: In normal, uninfected tissues, dendritic cells are often in a resting (immature) state, expressing minimal costimulatory signals (e.g., B7 proteins). They process and display self antigens but do not provide strong costimulation.
- **Costimulation as a Determinant**: The presence or absence of costimulation is a critical factor in determining whether T cells are activated or undergo tolerance.
- **Anergy**: Anergy refers to a state of long-lived functional unresponsiveness in T cells that occurs when they recognize self antigens.
- **Costimulation and Anergy**: Self antigens are typically displayed with low levels of costimulation. Anergy is induced when T cells recognize these antigens without adequate costimulatory signals.
- **Survival of Anergic Cells**: Anergic T cells survive but are unable to respond to the corresponding antigen.
- **Mechanisms of Anergy Induction**:
    - **Abnormal Signaling**: Recognition of antigens without costimulation can lead to the T cell receptor (TCR) complex losing its ability to transmit activating signals. This may involve the activation of enzymes (ubiquitin ligases) that modify signaling proteins for degradation.
    - **Inhibitory Receptor Engagement**: Anergic T cells may preferentially utilize inhibitory receptors from the CD28 family, such as CTLA-4 (CD152) and PD-1 (CD279), which inhibit responses to subsequent antigen

recognition. Anergic T cells often express higher levels of these inhibitory receptors.

The regulation of T cell responses by inhibitory receptors:

1. **Balance of Receptors**: Immune responses are influenced by the balance between activating receptors (like the TCR complex and CD28) and inhibitory receptors (coinhibitors) such as CTLA-4 and PD-1.
2. **CTLA-4**:
    - **Expression**: Transiently expressed on activated CD4+ T cells and constitutively on regulatory T cells.
    - **Function**: Suppresses T cell activation by blocking and removing B7 molecules from the surface of antigen-presenting cells (APCs), thereby reducing costimulation via CD28.
    - **Affinity**: CTLA-4 has a higher affinity for B7 than CD28, effectively preventing CD28 engagement, especially when B7 levels are low.
3. **PD-1**:
    - **Expression**: Found on CD8+ and CD4+ T cells after antigen stimulation.
    - **Mechanism**: Its cytoplasmic tail contains inhibitory signaling motifs that, when phosphorylated upon ligand binding (PD-L1 or PD-L2), inhibit kinase-dependent activating signals from CD28 and the TCR complex.
    - **Role in Chronic Activation**: PD-1 expression increases with chronic T cell activation, making this pathway particularly active in chronic infections, tumors, and self-antigens.
4. **Checkpoint Blockade Therapy**:
    - Blocking inhibitory receptors like CTLA-4 and PD-1 with antibodies enhances anti-tumor immune responses and can lead to tumor regression.
    - This therapy is referred to as "checkpoint blockade," as it removes the inhibitory "brakes" on immune responses.
5. **Autoimmunity and Checkpoint Blockade**: Patients receiving checkpoint blockade therapy may develop autoimmune reactions, highlighting the role of inhibitory receptors in maintaining self-tolerance.
6. **CTLA4 Mutations**: Rare mutations in the CTLA4 gene can lead to multiorgan inflammation and a defect in antibody production.
7. **Other Inhibitory Receptors**: Additional inhibitory receptors are being tested for their potential in checkpoint blockade therapy, though their roles in maintaining tolerance to self antigens are not well understood.





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	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

Fig. 9.5 Mechanisms of action and properties of cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). A, CTLA-4 is a competitive inhibitor of the B7-CD28 interaction. B, PD-1 activates a phosphatase that inhibits signals from the TCR complex and CD28. C, Some of the major differences between these checkpoint molecules are summarized. *APC*, Antigen-presenting cells; *TCR*, T cell receptor.

Immune suppression by regulatory T cells:

1. **Development of Regulatory T Cells**: Regulatory T cells (Tregs) develop in the thymus or peripheral tissues upon recognition of self antigens, suppressing potentially harmful lymphocytes specific to these antigens.
2. **Characteristics of Regulatory T Cells**:
    - Most are CD4+ and express high levels of CD25, the α chain of the interleukin-2 (IL-2) receptor.

    - They express the transcription factor FoxP3, which is essential for their development and function.
    - Mutations in the FoxP3 gene lead to systemic autoimmune diseases, exemplified by IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome).
3. **Role of IL-2**: The survival and function of Tregs depend on IL-2, a cytokine produced by activated T cells. Deletion of IL-2 or its receptor genes leads to severe autoimmune diseases, demonstrating IL-2's dual role in promoting T cell proliferation and maintaining Treg function.
4. **TGF-β in Treg Generation**: Transforming growth factor β (TGF-β) is involved in generating Tregs, potentially by stimulating FoxP3 expression. The specific source of TGF-β for Treg induction remains undefined.
5. **Mechanisms of Immune Suppression**:
    - Some Tregs produce inhibitory cytokines (e.g., IL-10, TGF-β) that inhibit the activation of lymphocytes, dendritic cells, and macrophages.
    - Tregs express CTLA-4, which blocks or removes B7 molecules from APCs, preventing costimulation and T cell activation.
    - Tregs can consume IL-2, reducing its availability for responding T cells.
6. **Clinical Implications**: There is significant interest in regulatory T cells due to the hypothesis that some autoimmune diseases may stem from defective Treg function or resistance of pathogenic T cells to regulation. Tregs are being explored in cellular therapies for graft-versus-host disease, graft rejection, and autoimmune disorders.

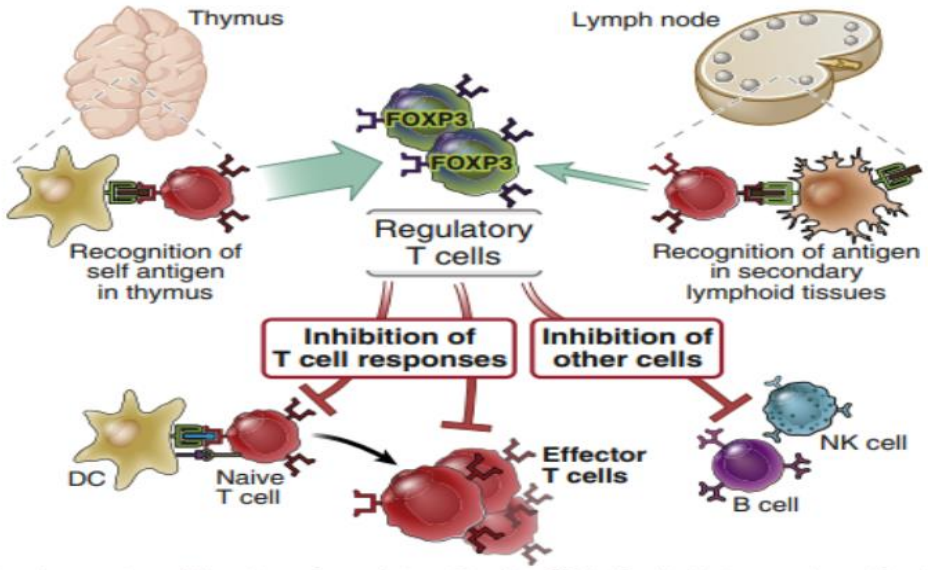


Fig. 9.6 Development and function of regulatory T cells. CD4+ T cells that recognize self antigens may differentiate into regulatory cells in the thymus or peripheral tissues, in a process that is dependent on the transcription factor FoxP3. (The *larger arrow* from the thymus, compared with the one from peripheral tissues, indicates that most of these cells probably arise in the thymus.) These regulatory cells inhibit the activation of naive T cells and their differentiation into effector T cells by contact-dependent mechanisms or by secreting cytokines that inhibit T cell responses. The generation and maintenance of regulatory T cells also require interleukin-2 (not shown). *DC*, Dendritic cell; *NK*, natural killer.

The deletion (apoptosis) of mature lymphocytes:

1. **Apoptosis Triggered by Self Antigens**: Recognition of self antigens can initiate apoptosis in self-reactive lymphocytes, leading to their elimination (deletion).
2. **Mechanisms of Apoptosis in T Lymphocytes**:
    - **Proapoptotic Protein Production**: Antigen recognition induces the production of proapoptotic proteins, causing mitochondrial proteins (e.g., cytochrome c) to leak, activating caspases that induce apoptosis. This process is counteracted by antiapoptotic proteins induced by costimulation, which are absent during self antigen recognition.
    - **Death Receptor Signaling**: Recognition of self antigens may lead to the coexpression of death receptors (e.g., Fas/CD95) and their ligands (e.g., Fas ligand/FasL), activating caspases and triggering apoptosis.
3. **Genetic Evidence for Apoptosis in Self-Tolerance**:
    - Mice lacking the mitochondrial apoptosis pathway fail to delete self-reactive T cells, both in the thymus and peripheral tissues.
    - Mutations in the fas and fasl genes, as well as in caspase-8 or -10, lead to autoimmune diseases characterized by lymphocyte accumulation (collectively known as autoimmune lymphoproliferative syndrome, ALPS).
4. **Differences Between Self and Microbial Antigens**:

- **Location and Deletion**: Self antigens are present in the thymus, promoting deletion and regulatory T cell generation, while microbial antigens are typically excluded from the thymus.
- **APC Activation**: Self antigens are displayed by resting APCs without innate immune activation, favoring T cell anergy or apoptosis. In contrast, microbial antigens elicit innate immune responses, promoting T cell activation.
- **Longevity of Antigen Presence**: Self antigens persist throughout life, leading to prolonged TCR engagement and further promoting anergy, apoptosis, and regulatory T cell development.

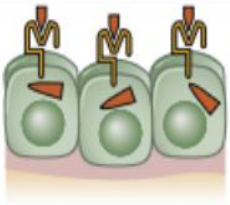
Feature of antigen	Tolerogenic self antigens	Immunogenic foreign antigens
	 Tissue	 Microbe
Location of antigens	Presence in generative organs (some self antigens) induces negative selection and other mechanisms of central tolerance	Presence in blood and peripheral tissues (most microbial antigens) permits 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

Fig. 9.8 Features of protein antigens that influence the choice between T cell tolerance and activation. This figure summarizes some of the characteristics of self and foreign (e.g., microbial) protein) antigens that determine why the self antigens induce tolerance and microbial antigens stimulate T cell–mediated immune responses. *TCR*, T cell receptor; *Treg*, T regulatory cells.

B lymphocyte tolerance:

- **T-Independent Antigens**: Self polysaccharides, lipids, and nucleic acids are T-independent antigens that do not interact with T cells and must induce tolerance in B lymphocytes to prevent autoantibody production.
- **Self Proteins and Tolerance**: Self proteins typically do not trigger autoantibody responses due to tolerance mechanisms in both helper T cells and B cells.
- **Autoimmune Diseases**: Conditions like systemic lupus erythematosus (SLE) may arise from defects in tolerance mechanisms affecting both B lymphocytes and helper T cells, leading to autoantibody production.

A- Central B cell tolerance:

1. **Mechanisms of Central B Cell Tolerance**: Immature B lymphocytes in the bone marrow interact with self antigens, leading to either:
    - **Receptor Editing**:
        - Immature B cells that recognize self antigens may reexpress RAG genes, allowing for light-chain gene recombination.
        - This process produces a new Ig light chain that can associate with the existing heavy chain, potentially resulting in a new antigen receptor that does not recognize the self antigen.
        - It is estimated that 25% to 50% of mature B cells may undergo receptor editing during maturation.
2. **Deletion**:
    - If receptor editing fails, immature B cells that strongly recognize self antigens receive death signals and undergo apoptosis, similar to negative selection in T lymphocytes.
    - This elimination targets B cells with high-affinity receptors for abundant self antigens, whether membrane-bound or soluble.
3. **Anergy**:
    - Some self antigens, particularly soluble proteins, may be recognized with low avidity.
    - B cells specific for these antigens survive but have reduced antigen receptor expression and become functionally unresponsive (anergic).

B- Peripheral B cell tolerance:

1. **Response to Self Antigens**: Mature B lymphocytes that encounter self antigens in peripheral lymphoid tissues become incapable of responding to those antigens.
2. **Hypothesis of Anergy**:
    - If B cells recognize a protein antigen without receiving helper T cell support (due to T cell elimination or tolerance), they become anergic, which involves a block in signaling from the antigen receptor.
    - Anergic B cells may exit lymphoid follicles and are often excluded from these areas, leading to their potential death due to lack of survival signals.
3. **Additional Mechanisms of Tolerance**: B cells recognizing self antigens in the periphery may also:
    - Undergo apoptosis.
    - Have inhibitory receptors engaged, preventing their activation.

4. **Role of Regulatory T Cells**: Regulatory T cells may also play a role in promoting B cell tolerance.

tolerance to commensal microbes and fetal antigens:

Tolerance to Commensal Microbes

1. **Microbiome Composition**: The human microbiome consists of approximately 101410^{14}1014 bacteria and viruses, outnumbering human nucleated cells, indicating a symbiotic relationship where microbes play essential roles in digestion, absorption, and preventing harmful organism overgrowth.
2. **Immune Response to Commensals**: Mature lymphocytes can recognize commensal microbes but do not mount an immune response against them, preventing harmful inflammation.
3. **Mechanisms of Tolerance**:
    - High levels of IL-10–producing regulatory T cells in the gut.
    - Unique properties of intestinal dendritic cells that can inhibit activation through certain Toll-like receptors.
    - Physical separation of commensal bacteria from the intestinal immune system by epithelial barriers.
4. **Skin Tolerance**: Mechanisms maintaining tolerance to commensal bacteria in the skin are less well defined.

Tolerance to Fetal Antigens

1. **Placental Evolution**: Eutherian mammals have evolved placentation, allowing fetal development before birth, which introduces paternal antigens that must be tolerated by the mother's immune system.
2. **Regulatory T Cells**: Peripheral FoxP3+ regulatory T cells specific for paternal antigens are generated, correlating with the evolution of placentation and the ability to maintain stable peripheral regulatory T cells.
3. **Recurrent Pregnancy Loss**: It is unclear if women experiencing recurrent pregnancy losses have defects in generating or maintaining regulatory T cells.
4. **Additional Mechanisms of Fetal Tolerance**:
    - Exclusion of inflammatory cells from the pregnant uterus.
    - Poor antigen presentation in the placenta.
    - Inhibition of harmful Th1 immune responses in the healthy pregnant uterus.