Tolerance and Autoimmunity

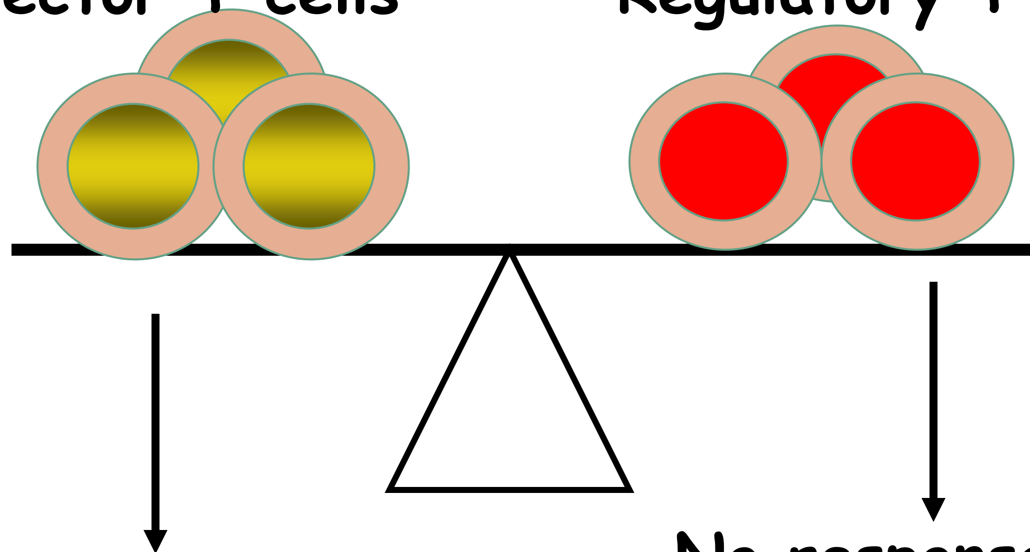
Objectives

- Define and discuss the general characteristics of tolerance
- Define the main factors that influence the development of tolerance
- Identify the main mechanisms of tolerance induction in B and T cells
- Identify the mechanisms involved in the development of autoimmunity
- Approach to treatment of autoimmune diseases

Balancing lymphocyte activation and control

Activation
Effector T cells

Tolerance
Regulatory T cells



Normal: reactions against pathogens

No response to self
Controlled response to pathogens

Inflammatory disease, e.g. reactions against self

The importance of immune regulation

- To avoid excessive lymphocyte activation and tissue damage during normal protective responses against infections
- To prevent inappropriate reactions against self antigens (“self-tolerance”)
- Failure of control mechanisms is the underlying cause of immune-mediated inflammatory diseases (autoimmune diseases)

General principles of controlling immune responses

- Responses against pathogens decline as the infection is eliminated
  - Apoptosis of lymphocytes that lose their survival signals (antigen, etc)
  - Memory cells are the survivors

- Active control mechanisms may function to limit responses to persistent antigens (self antigens, possibly tumors and some chronic infections)
  - Often grouped under "tolerance"

- **Immunological tolerance**: specific unresponsiveness to an antigen that is induced by exposure of lymphocytes to that antigen (tolerogen vs immunogen)
- **Autoimmunity**: immune response against self (auto-) antigen, by implication pathologic
  - Disorders are often classified under "immune-mediated inflammatory diseases"

Tolerogen versus Immunogen

- Tolerogen: antigen that induce tolerance
- Immunogen: antigen that induce immune response
- The same chemical compound can be an immunogen or tolerogen depending on how it is presented to the immune system
- Factors promoting tolerance rather than stimulation of immune system include:

1. High dose of antigen
2. Persistence of antigen in host
3. Intravenous or oral introduction
4. Absence of adjuvants
5. Low level of co-stimulation

Central tolerance	Peripheral tolerance
• This occurs during the development of immune cells in primary lymphoid organs • Immature lymphocytes are tested for their ability to recognize "self":If they strongly recognize self-antigens → ✓ They are eliminated (Deletion,negative selection) ✓ Some T cells may change their specificity (called "receptor editing") ✓ Some CD4 T cells may differentiate into regulatory (suppressive) T lymphocytes. • So the purpose of central tolerance is to eliminate self-reactive cells early, before enter circulation.	• This occurs after lymphocytes leave primary organs, in peripheral tissues. • Central tolerance is not perfect, so some self-reactive cells escape → peripheral tolerance controls them through: ✓ Anergy: Cells become inactive when they recognize antigen without proper co-stimulation. ✓ Suppression: Controlled by regulatory T cells (Tregs) that suppress immune responses. ✓ Deletion (apoptosis): Self-reactive cells are eliminated after activation. • So the purpose of peripheral tolerance is to control escaped self-reactive cells.

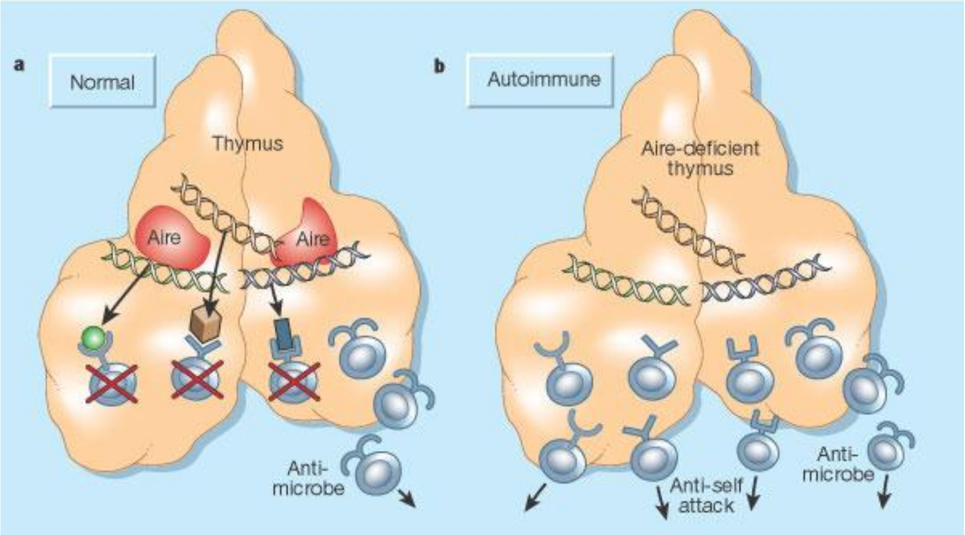
Thymic ("natural") regulatory T cells (Treg)

- are a subset of $CD4^+$ T cells that develop in the thymus and are specialized to maintain self-tolerance—preventing the immune system from attacking the body's own tissues.

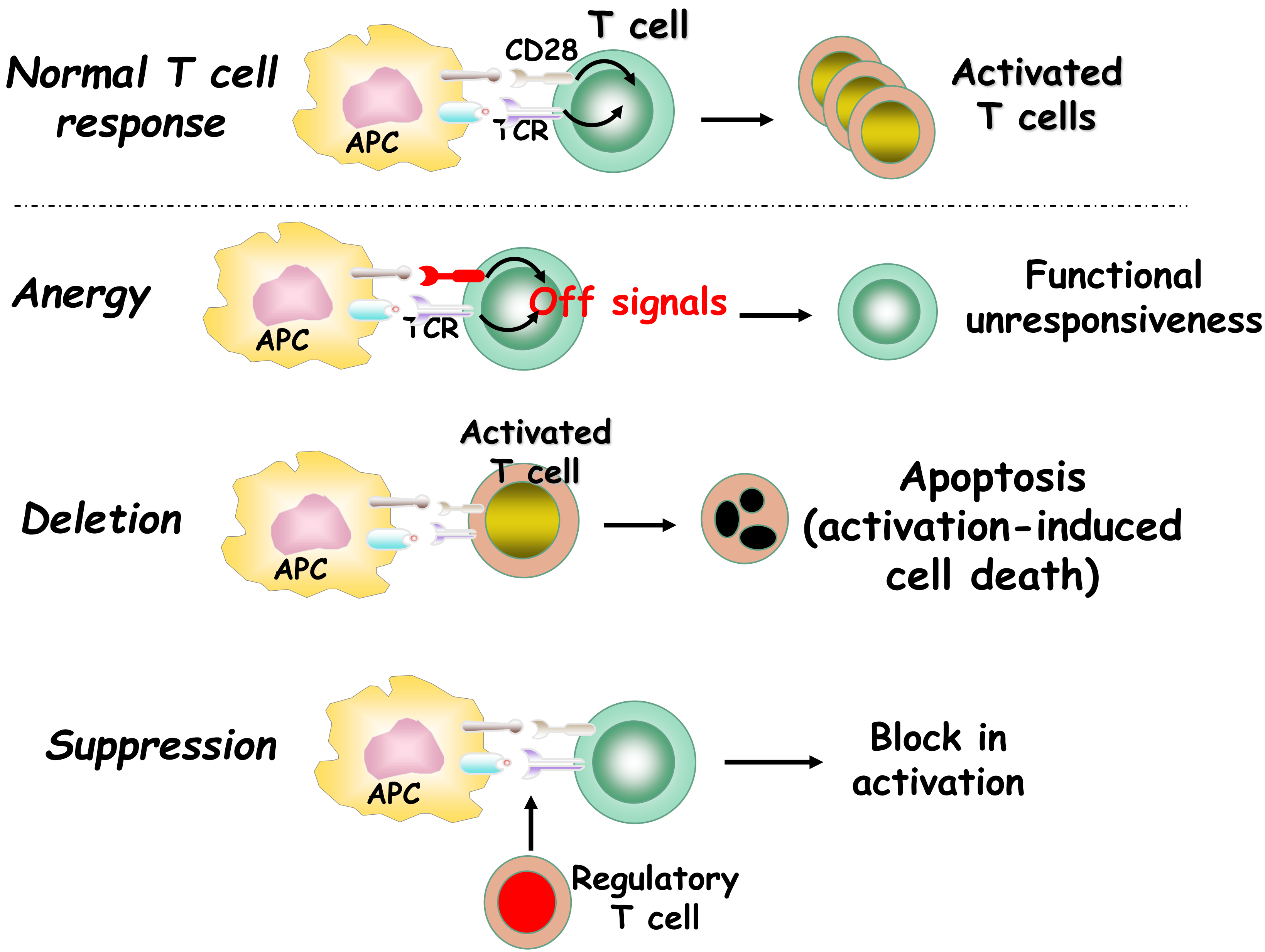
- Development requires recognition of self-antigen during T cell maturation

- Reside in peripheral tissues to prevent harmful reactions against self

Autoimmune Regulator (AIRE)



Peripheral tolerance



1. T cell anergy

In Peripheral tolerance how does T cell anergy happen?

- For a T cell to become fully activated, it needs two signals:

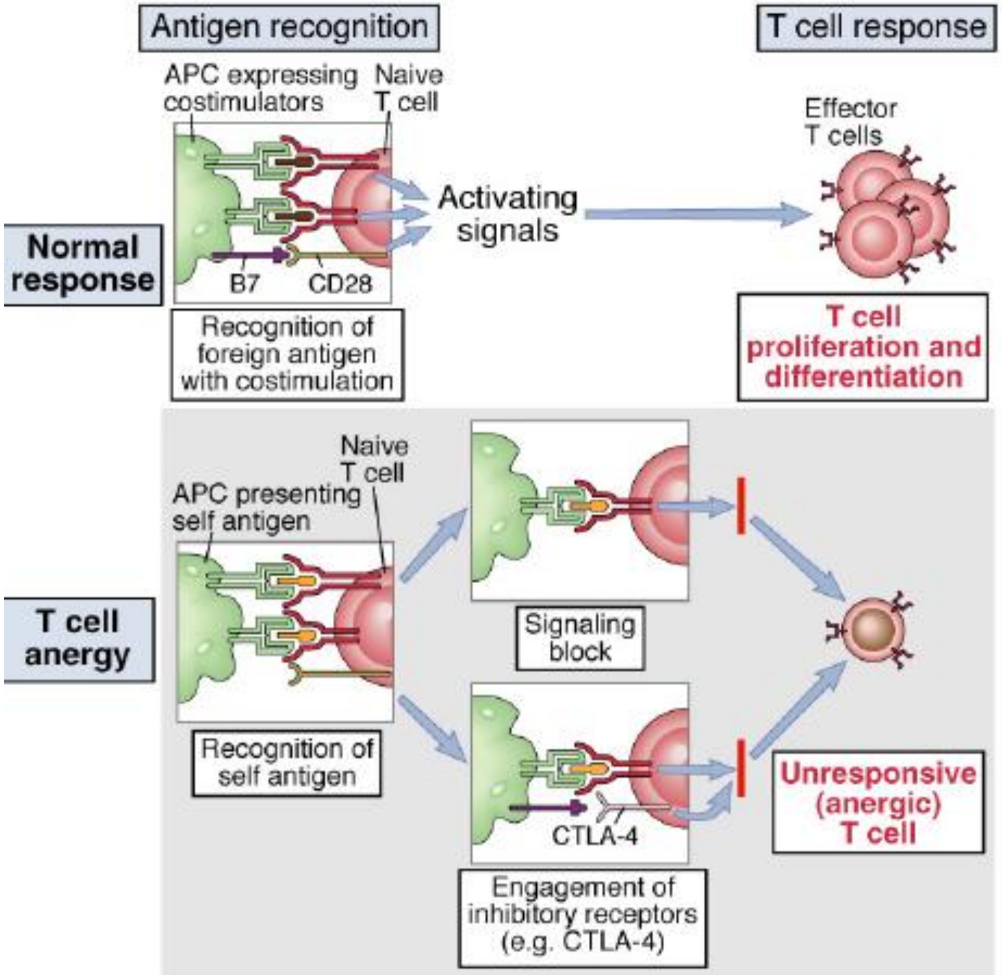
1. **Signal 1:**
Recognition of antigen presented on MHC by an antigen-presenting cell (APC)
2. **Signal 2** (co-stimulation):
Interaction between CD28 (on T cell) and B7 (on APC)

- If **Signal 1** occurs WITHOUT **Signal 2**:

➡️ The T cell does not activate
➡️ Instead, it becomes anergic (inactive).

- CTLA-4 acts as a "brake" on T cell activation, ensuring that:

✓ Self-reactive T cells become anergic instead of activated
✓ Immune responses do not become excessive.



- After a T cell is activated (or partially stimulated), it begins to express CTLA-4 on its surface.

- CTLA-4 competes with CD28 for binding to B7 (CD80/CD86) on antigen-presenting cells (APCs)

✓ CD28 + B7 → activation (stimulatory signal)
✓ CTLA-4 + B7 → inhibition (turns off the signal)
👉 Important: CTLA-4 binds B7 with much higher affinity than CD28

So its role in cell energy as following:

1. Blocks co-stimulation

✓ Prevents CD28 from binding B7
✓ So the T cell receives Signal 1 without Signal 2 ➡️ Leads directly to anergy

2. Sends inhibitory signals inside the T cell

✓ Reduces IL-2 production
✓ Inhibits proliferation
✓ Dampens TCR signaling pathways ➡️ Reinforces the unresponsive state

3. Removes B7 from APCs (advanced mechanism)

CTLA-4 can physically capture and remove B7 molecules from APCs ➡️ Makes APCs less able to activate other T cells

- **What characterizes anergic T cells?**

✓ Do not proliferate
✓ Do not produce IL-2
✓ Cannot respond effectively even if stimulated again later
✓ Remain alive but “switched off”

Why is anergy important?

It is a key mechanism of peripheral tolerance:

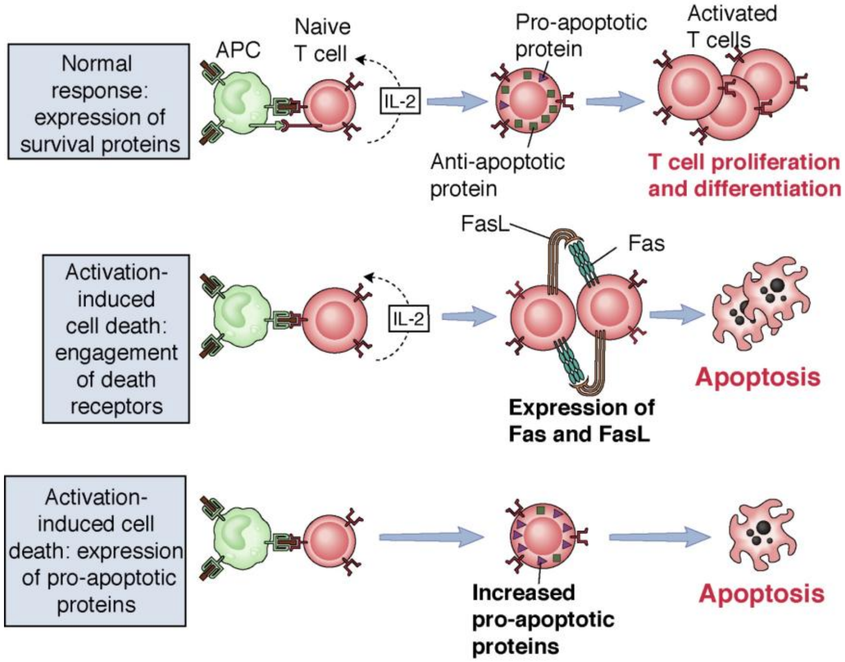
•Prevents T cells from attacking self-antigens

◆ Clinical relevance

•Failure of anergy → can lead to autoimmune diseases
•Some tumors exploit anergy → they present antigen without co-stimulation, helping them evade the immune system.

2. Apoptosis "Activation-induced cell death (AICD)"

When does AICD happen?
•After a T cell has been activated and expanded, then encounters the same antigen repeatedly (especially self-antigens or chronic infections)
👉 Instead of continuing to respond, the T cell is programmed to die.



- **<u>Main mechanism</u> (Fas–FasL pathway)**

✓ **Fas (CD95) → death receptor on T cells**
✓ **Fas Ligand (FasL) → expressed on activated T cells**

📌 What happens?

✓ **Activated T cell expresses Fas and FasL**
✓ **FasL binds to Fas (on the same cell or nearby T cells)**
✓ **This triggers an intracellular cascade: Activation of caspases (especially caspase-8)**
✓ **Leads to programmed cell death (apoptosis)**

- **What does apoptosis look like?**

- Cell shrinks
- DNA fragments
- Membrane blebbing
- No inflammation (clean removal by phagocytes)

- **Why is AICD important?**

1. Maintains peripheral tolerance

- Eliminates self-reactive T cells that escaped central tolerance

2. Controls immune responses

- After infection is cleared → removes excess T cells

➡️ Prevents lymphocyte overexpansion

Pro-apoptotic proteins

Most of them belong to the Bcl-2 family, which controls the intrinsic (mitochondrial) pathway of apoptosis.

1. Effector proteins: Bax and Bak

📌 **Function:**

- Create pores in the mitochondrial membrane
- Cause release of cytochrome c
- This activates caspases → apoptosis

2. BH3-only proteins (initiators/sensors) like Bim

📌 **Function:**

- Sense cellular stress (DNA damage, cytokine withdrawal, repeated stimulation)
- Activate Bax/Bak
- Inhibit anti-apoptotic proteins (like Bcl-2)

🔹 **How they work (intrinsic pathway summary)**

1. Cell stress or repeated activation occurs
2. BH3-only proteins are activated
3. They activate Bax/Bak
4. Mitochondria release cytochrome c
5. Formation of apoptosome
6. Activation of caspase-9 → caspase-3
7. Cell undergoes apoptosis.

In T cells:

- Repeated stimulation → ↑ Bim (very important in lymphocytes)
- Leads to activation of Bax/Bak
- Promotes apoptosis alongside the Fas–FasL pathway

👉 **So AICD involves:**

- Extrinsic pathway (Fas–FasL)
- Intrinsic pathway (Bcl-2 family proteins like Bim)

🔹 **Balance is key**

Apoptosis depends on the balance between:

- 🔺 Pro-apoptotic proteins (Bax, Bak, Bim…)
- 🔻 Anti-apoptotic proteins (Bcl-2, Bcl-xL)

👉 If pro-apoptotic dominate → cell dies

👉 If anti-apoptotic dominate → cell survives

🔹 **Clinical relevance**

- ↑ Pro-apoptotic activity → excessive cell death (degeneration, immune deficiency)
- ↓ Pro-apoptotic activity → survival of abnormal cells (e.g., cancer, autoimmunity)

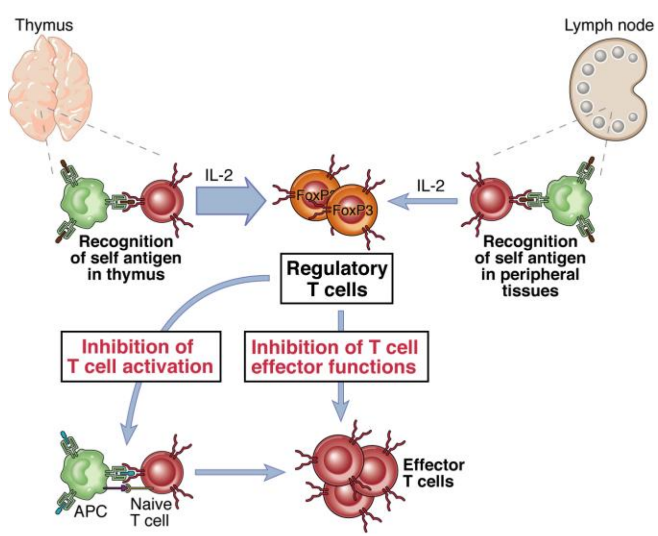
3. Regulatory T cells

❖ T regulatory cells are:
- •A specialized subset of $CD4^+$ T cells
- •Characterized by:
  - CD25 (IL-2 receptor α chain)
  - FOXP3 (master transcription factor)

👉 Without FOXP3, Tregs don't develop properly → severe autoimmunity.

❖ Tregs function in peripheral tissues:
- •Lymph nodes
- •Spleen
- •Sites of inflammation

👉 They control T cells that escaped central tolerance

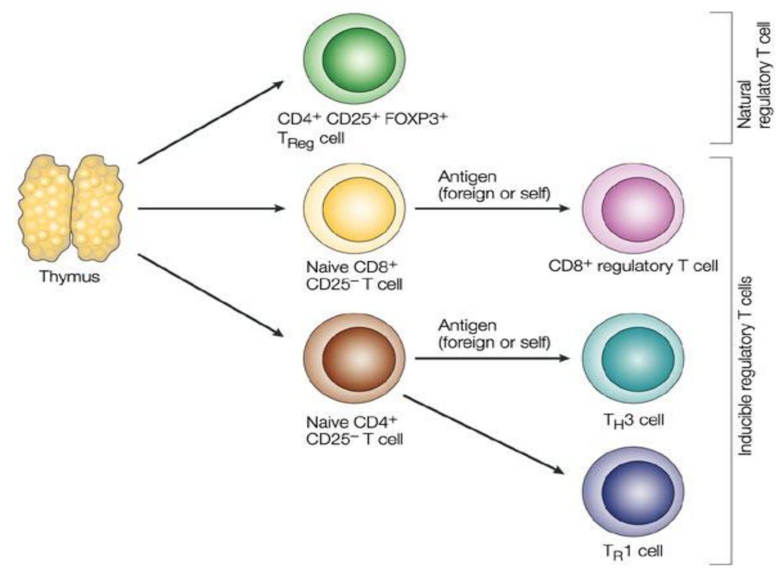


Regulatory T cell subsets

•Natural regulatory T cells express the cell-surface marker CD25 and the transcriptional repressor FOXP3 (forkhead box P3).

•Regulatory T cells include distinct subtypes of $CD4^+$ T cell:

1. T regulatory 1 (T_R1) cells, which secrete high levels of IL-10, or low levels of TGF-β
2. T helper 3 (T_H3) cells, which secrete high levels of TGF-β
3. $CD8^+$ T cells a subtype of these cells can secrete IL-10 and have been called $CD8^+$ regulatory T cells.



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Main roles in peripheral tolerance

1. Suppress activation of other T cells
- Inhibit proliferation and activation of effector T cells
- Prevent responses to self-antigens

2. Secretion of inhibitory cytokines:
- IL-10 → reduces immune activation
- TGF-β → suppresses T cell proliferation and differentiation

👉 Creates an anti-inflammatory environment

3. Inhibition of co-stimulation (via CTLA-4)
- Tregs express CTLA-4
- Bind to B7 on APCs → block CD28 signaling

➡️ Leads to:
- Reduced T cell activation
- Induction of anergy

4. Consumption of IL-2
- Tregs express high levels of CD25
- "Soak up" IL-2

➡️ Effector T cells are deprived of IL-2 → reduced survival and proliferation

5. Direct killing (in some cases)
- Can induce apoptosis of target T cells (via granzyme/perforin, less common but possible).

Properties of peripheral regulatory T cells

- Phenotype: CD4, high IL-2 receptor (CD25), low IL-7 receptor
- Develop from mature CD4 T cells that are exposed to persistent antigen in the periphery
- May be generated in all immune responses, to limit collateral damage
- Mechanisms of action:
  - secretion of immune-suppressive cytokines (TGFβ, IL-10, IL-35)
  - inactivation of dendritic cells or responding lymphocytes
- Some autoimmune diseases are associated with defective generation or function of Tregs or resistance of effector cells to suppression by Tregs

Signals for the generation and maintenance of regulatory T cells

- Tregs are generated either in the thymus (tTregs) or in the periphery (pTregs), but the key signals overlap.

- **Signals for Treg generation:**

✓ TCR signals: Antigen recognition via TCR–MHC.

✓ TGF-β (especially for peripheral Tregs), induces FOXP3 and converts naïve $CD4^{+}$ T cells → induced Tregs (pTregs).

- Cytokine signal: IL-2 (originally identified as T cell growth factor; major function is to control immune responses by maintaining functional Treg; works via Stat5). Most important cytokine for:FOXP3 expression and Treg survival and expansion

- Low levels of Co-stimulation (CD28–B7): Promotes survival, expansion, and induction of FOXP3.
- Transcription factor Foxp3
  - Many activated T cells (not only Treg) may transiently express Foxp3.

- **Signals for Treg Maintenance**

1. IL-2 (most important survival signal)
2. FOXP3 expression
3. TCR stimulation
4. CTLA-4 and inhibitory signaling

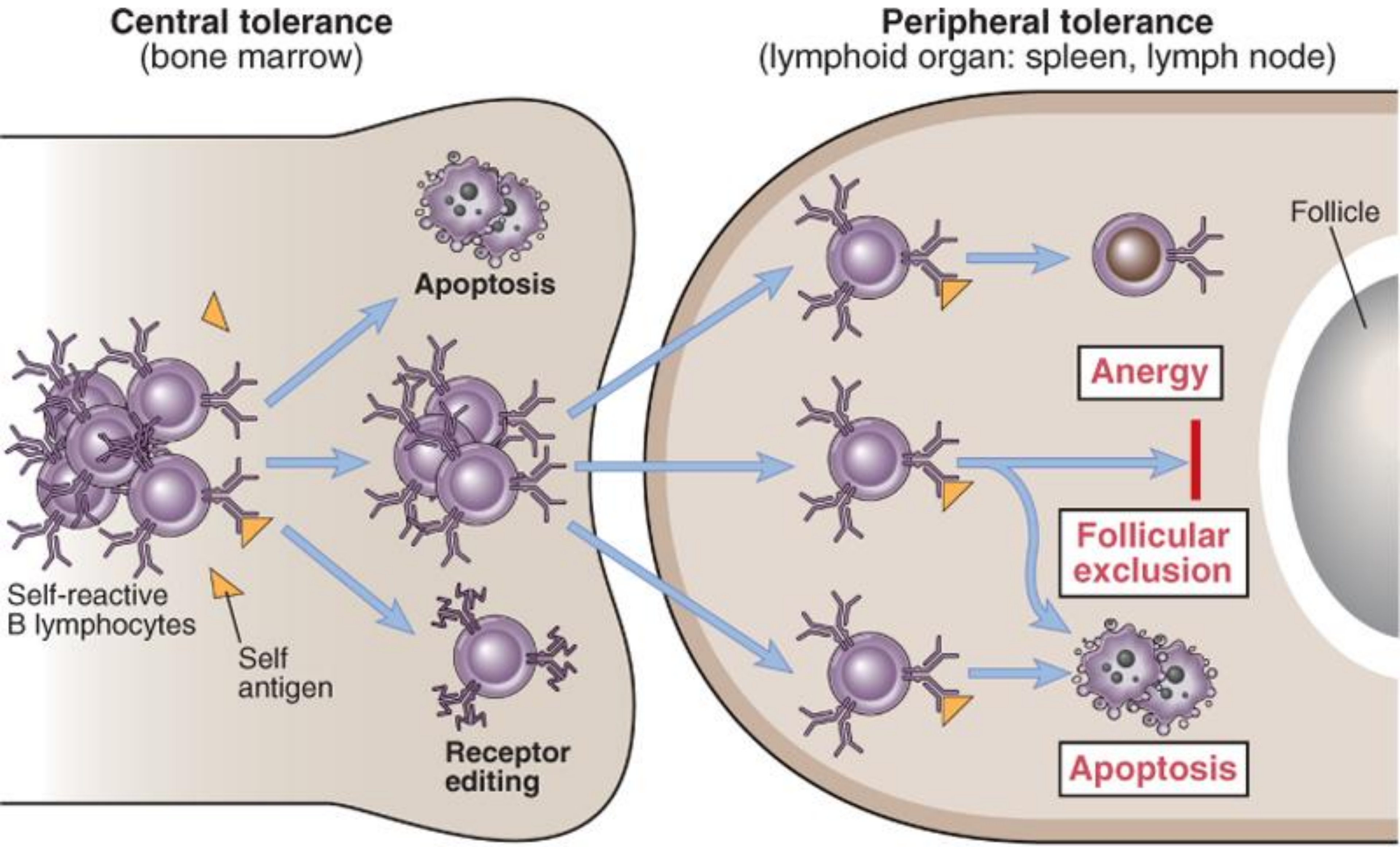
👉 **To GENERATE Tregs:**

•TCR + CD28 + IL-2 (± TGF-β)

👉 **To MAINTAIN Tregs:**

•IL-2 + FOXP3 + continuous TCR signals

Central and peripheral Tolerance in B cells



Central and peripheral tolerance