Mechanisms of Central Tolerance

During thymic development, T cells interact with stromal cells presenting self-MHC molecules. If T cells strongly bind to self-antigens, they are eliminated (negative selection). If they weakly bind, they survive (positive selection). This process is largely chance-based, with some self-reactive T cells escaping into the periphery due to the stochastic nature of selection.

Peripheral Tolerance and Control of Escaping T Cells

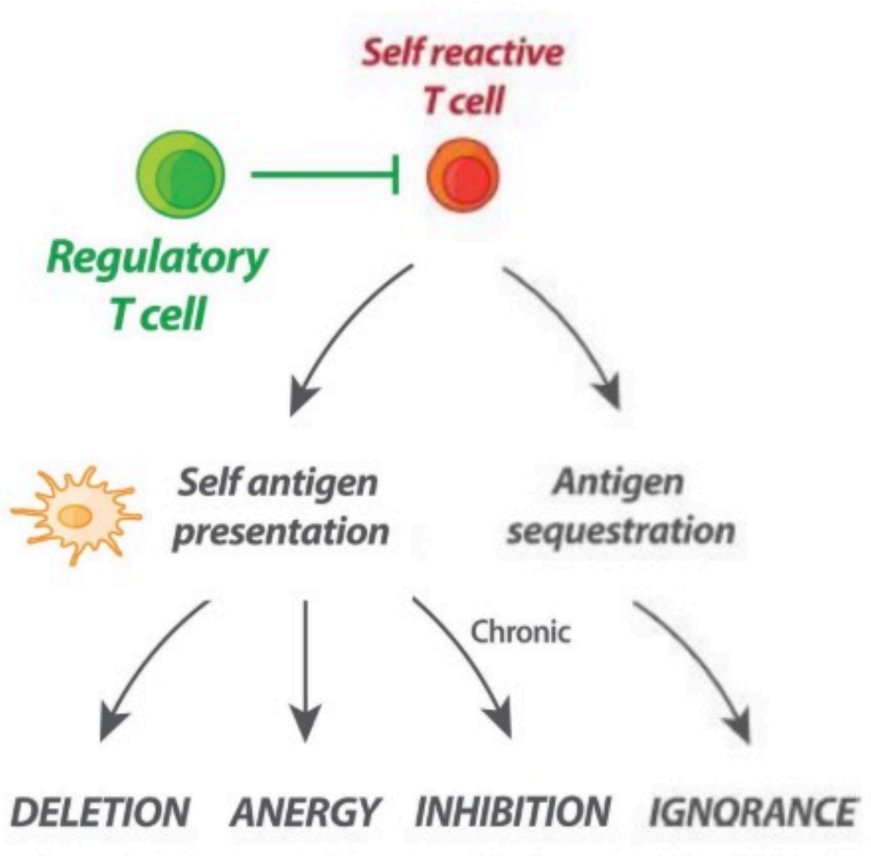
Once in the periphery, several mechanisms prevent self-reactive T cells from causing damage:

- **Regulatory T cells (Tregs):** Secrete inhibitory cytokines and directly suppress autoreactive T cells.
- **Intrinsic properties:** T cells can become anergic, or express inhibitory receptors that dampen their activity.
- **Antigen presentation:** The nature and level of antigen expression influence T cell activation. High expression in certain areas can lead to tolerance, while low or absent expression may allow escape.

Factors Influencing T Cell Activation

The activation of T cells depends on several factors:

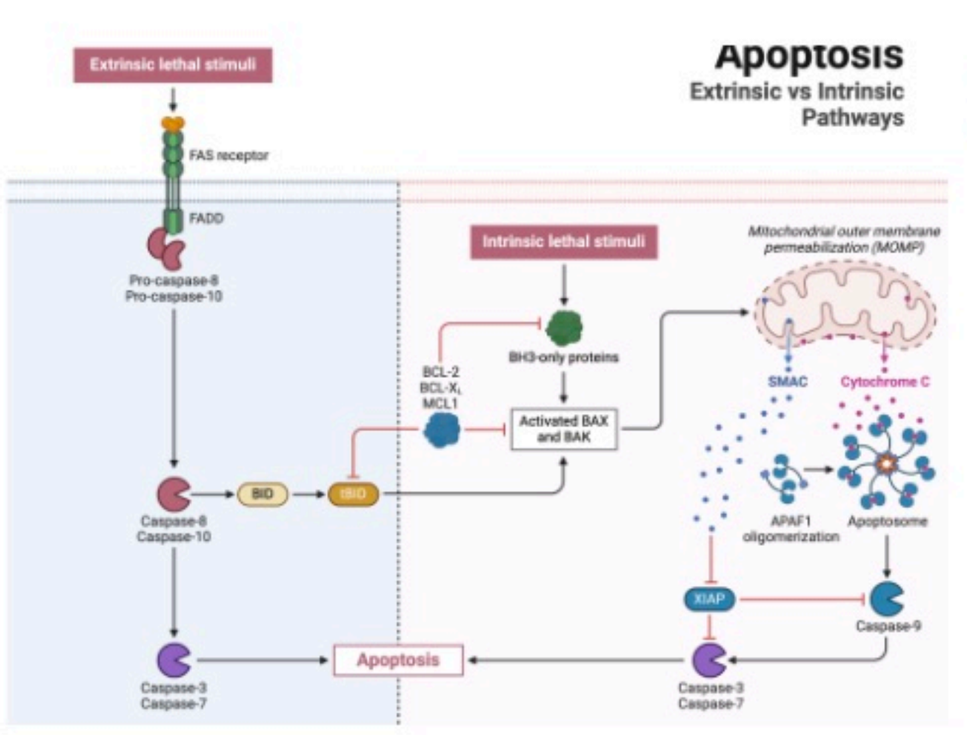
- **Antigen distribution:** Highly expressed antigens in specific tissues can promote tolerance or activation depending on context.
- **Antigen-presenting cells (APCs):** Their activation status affects whether they present self-antigens in a tolerogenic or stimulatory manner.
- **Self-reactive T cells:** When these encounter self-antigens, mechanisms like antigen sequestration help prevent unwanted immune responses, maintaining self-tolerance.

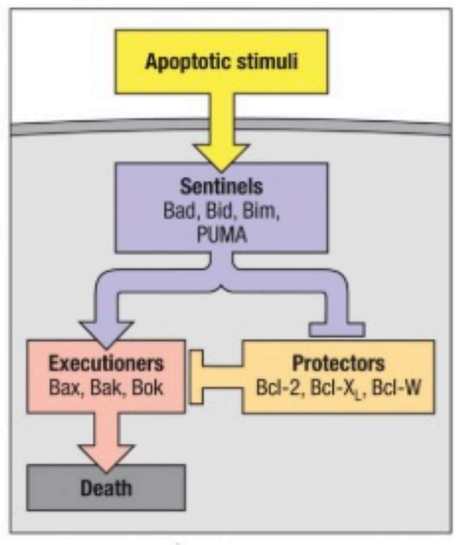


Cell Deletion via Apoptosis

Cell deletion is a crucial process in immune regulation, primarily involving the removal of cells once they are no longer needed. This can occur at the end of an immune response or to prevent unintended effects from active cells. The main mechanism for deleting T cells in the periphery is through apoptosis, a form of controlled cell death that does not provoke inflammation. Unlike pyroptosis, which causes inflammation, apoptosis ensures a silent removal of cells.

Apoptosis in immune cells mainly involves the mitochondrial pathway, which can be activated via two routes: extrinsic and intrinsic pathways. Both pathways ultimately activate caspases, a family of proteases that execute cell death by disrupting mitochondrial integrity and releasing apoptotic factors like cytochrome C. This cascade leads to the systematic dismantling of the cell.





Intrinsic Pathway of Apoptosis

The intrinsic pathway is triggered internally within the cell, often due to a lack of survival signals such as IL-2 and IL-7. When these cytokines are absent, pro-survival proteins like BCL2 and BCL-XL are downregulated or inhibited, allowing pro-apoptotic factors such as Bim and p53 to activate. These sentinels will trigger the “executioners” and inhibit pro-survival proteins. These factors promote mitochondrial outer membrane permeabilization, releasing cytochrome C and activating caspases.

Key regulators include:

- **Pro-survival proteins (Protectors):** BCL2, BCL-XL (which inhibit apoptosis)
- **Pro-apoptotic factors (Sentinels):** Sentinels that promote cell death when upregulated

The pathway is influenced by cytokine signaling, especially the absence of IL-2 and IL-7, which normally support T cell survival. When these signals are missing, the balance shifts toward apoptosis.