TOLERANCE

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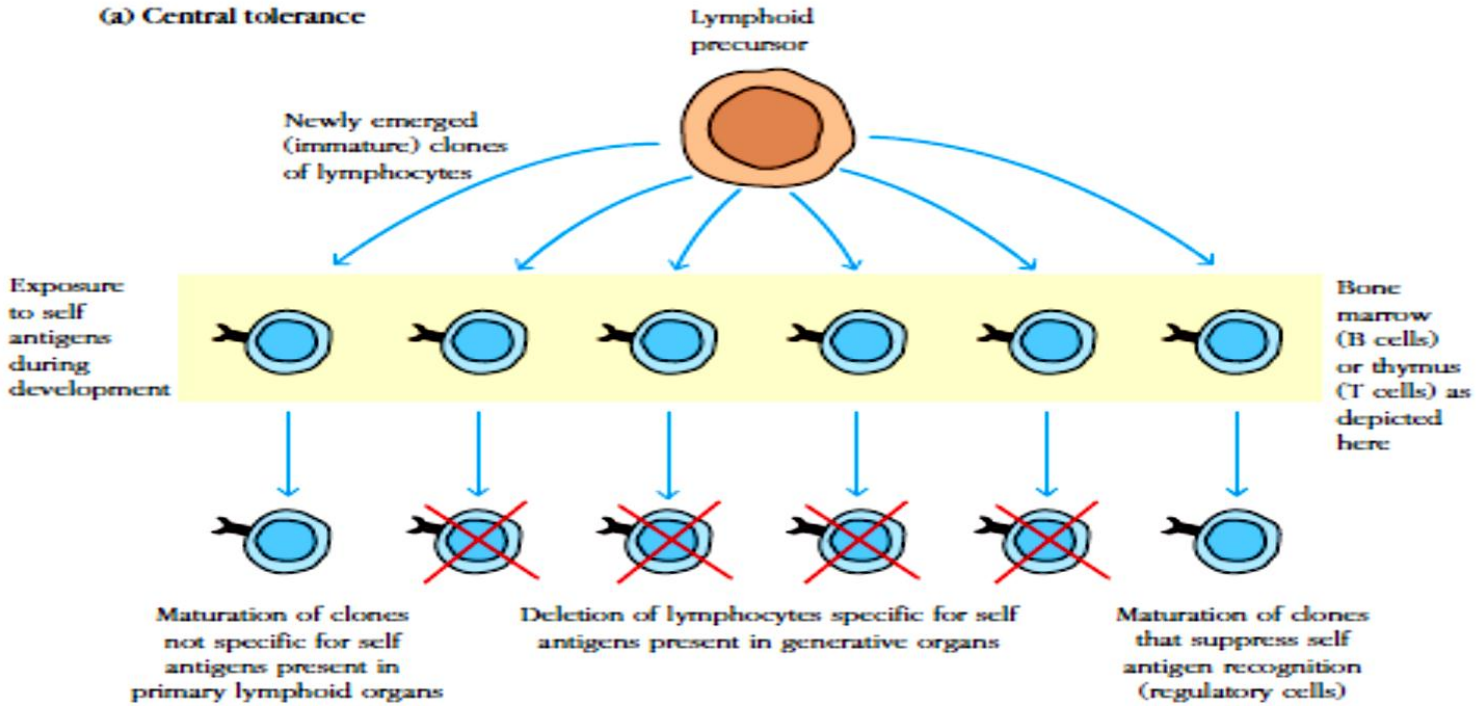
- The term *tolerance* applies to the many layers of protection imposed by the immune system to prevent the reaction of its cells and antibodies against host components.
- this was thought to be mediated by the elimination of cells that can react against self-antigens, yielding a state of unresponsiveness to self.

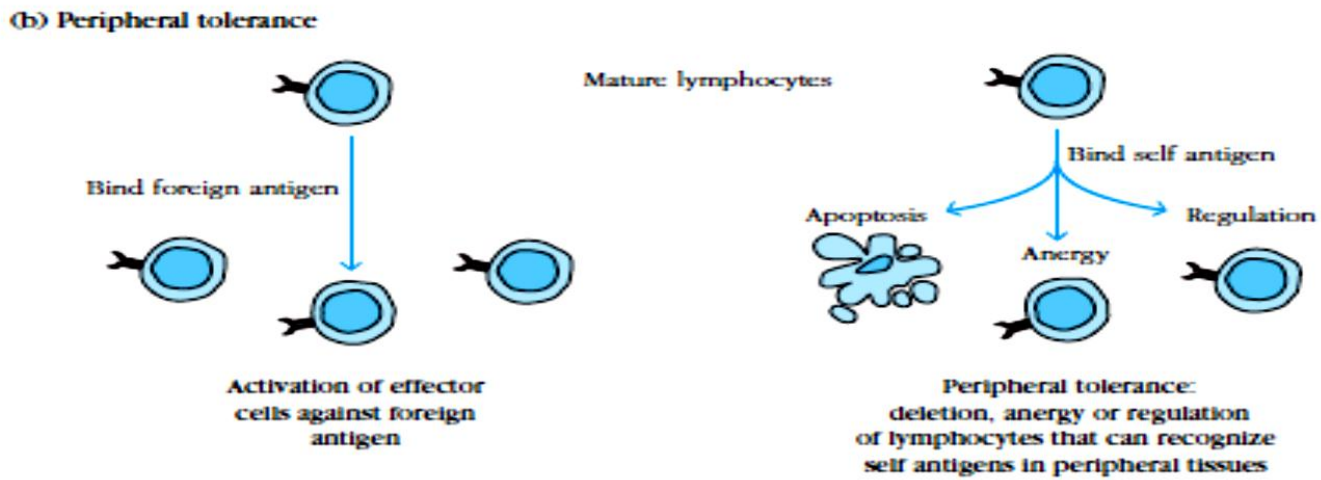
Central tolerance

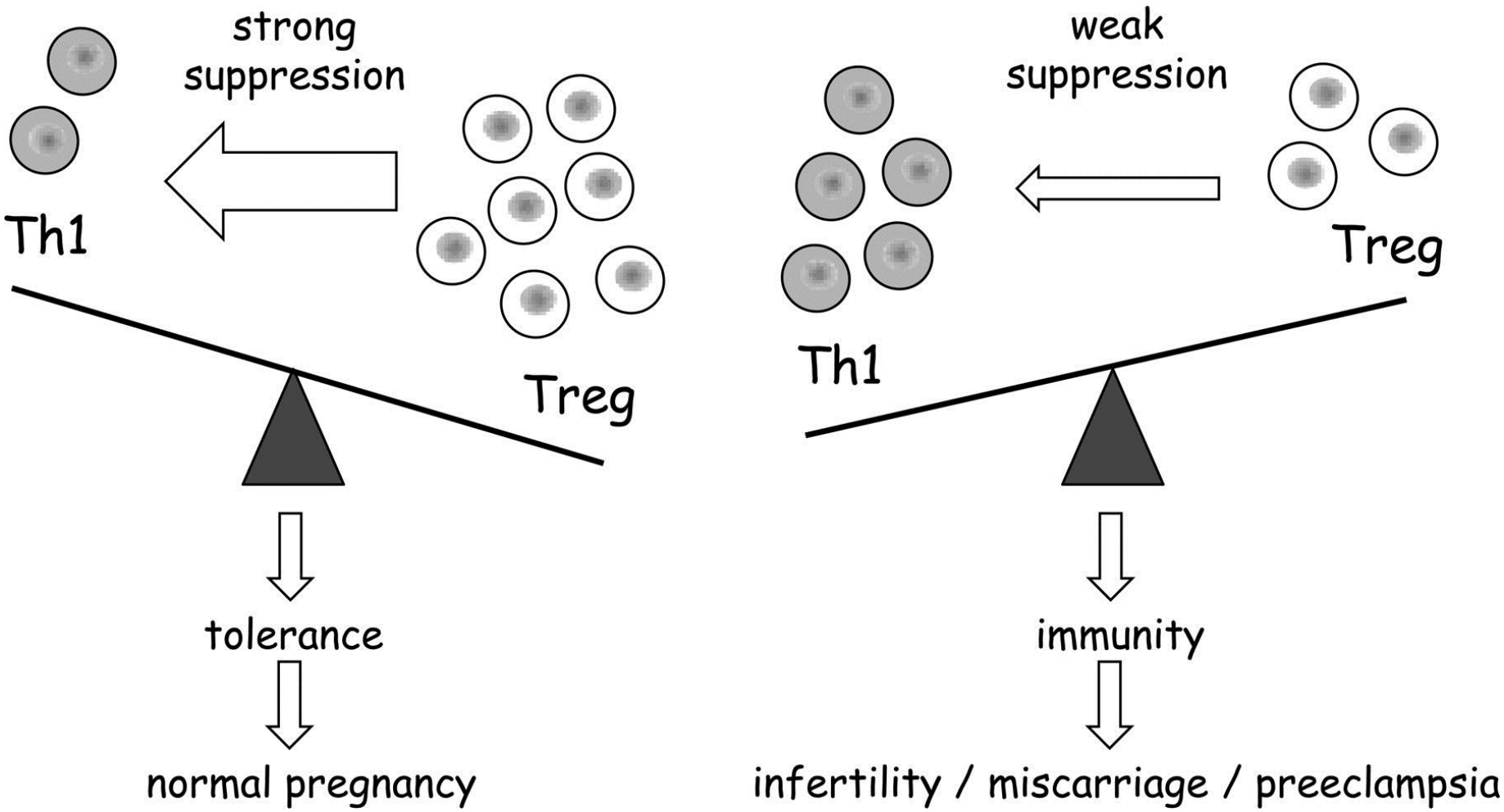
- deletes T- or B-cell clones before the cells are allowed to mature if they possess receptors that recognize self antigens with high affinity. Central tolerance occurs in the primary lymphoid organs: the bone marrow for B cells and the thymus for T cells.

Peripheral tolerance

- which renders some self-reactive lymphocytes in secondary lymphoid tissues inactive and generates others that actively inhibit immune responses against self.
- The possibility of damage from self-reactive lymphocytes is further limited by the life span of activated lymphocytes, which is regulated by programs that induce cell death (apoptosis) following receipt of specific signals.


(a) Central tolerance
Lymphoid precursor
Newly emerged (immature) clones of lymphocytes
Exposure to self antigens during development
Bone marrow (B cells) or thymus (T cells) as depicted here
Maturation of clones not specific for self antigens present in primary lymphoid organs
Deletion of lymphocytes specific for self antigens present in generative organs
Maturation of clones that suppress self antigen recognition (regulatory cells)


(b) Peripheral tolerance
Bind foreign antigen
Activation of effector cells against foreign antigen
Mature lymphocytes
Bind self antigen
Apoptosis
Anergy
Regulation
Peripheral tolerance: deletion, anergy or regulation of lymphocytes that can recognize self antigens in peripheral tissues


strong
suppression
Th1
Treg
tolerance
normal pregnancy
weak
suppression
Treg
Th1
immunity
infertility / miscarriage / preeclampsia

Tolerogens

- Antigens that induce tolerance are called **tolerogens** rather than *immunogens*.
- Here, context is important; the same chemical compound can be both an immunogen and a tolerogen, depending on how and where it is presented to the immune system.
- For instance, an antigen presented to T cells without appropriate costimulation results in a form of tolerance known as **anergy** (unresponsiveness to antigenic stimulus), whereas the same antigen presented with costimulatory molecules can become a potent immunogen.

- When some antigens are introduced orally, tolerance can be the result, whereas the same antigen given as an intradermal or subcutaneous injection can be immunogenic. In other instances, mucosally administered antigens provide protective immunity, such as in the case of Sabin’s oral polio vaccine.

- factors that promote tolerance rather than stimulation of the immune system by a given antigen include the following:

- High doses of antigen
- Long-term persistence of antigen in the host
- Intravenous or oral introduction
- Absence of adjuvants (compounds that enhance the immune response to antigen)
- Low levels of costimulation
- Presentation of antigen by immature or unactivated antigen-presenting cells (APCs)