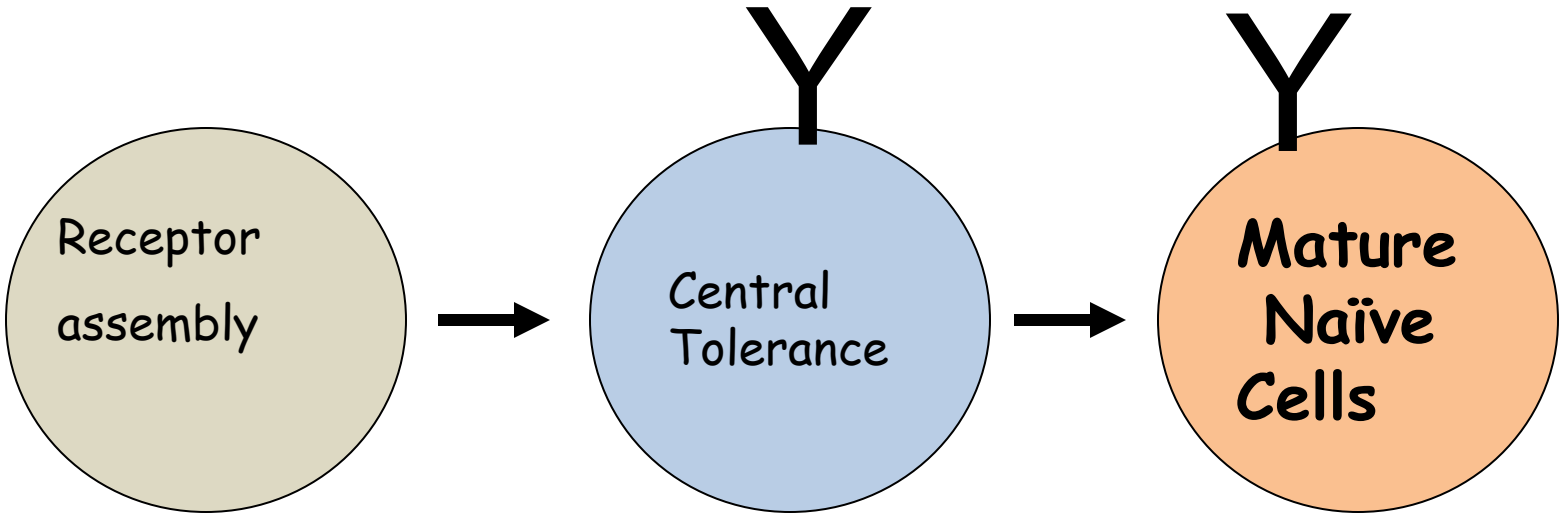
T cell Regulation and Tolerance
FOCIS 2023

1. Central Tolerance
2. Receptor Editing in B cells
3. Clonal Deletion in the cortex and medulla
4. Natural and Peripheral Regulatory T cells
5. What Regulatory T cells Do
6. Inhibitory Receptors
7. Autoimmunity
8. “QUIETLY INTO THE NIGHT”

CENTRAL LYMPHOID ORGANS

PERIPHERY

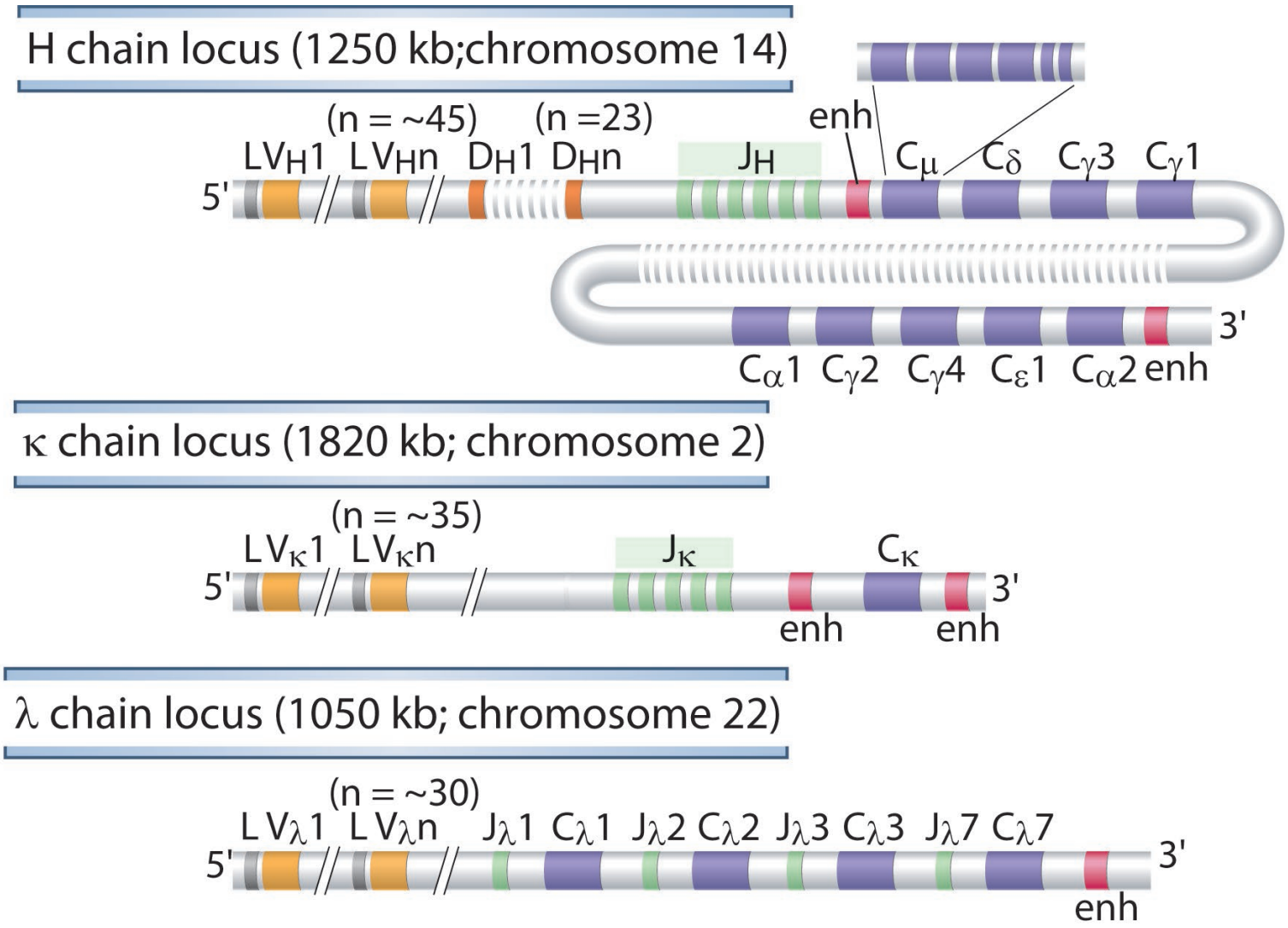


EDIT OR ELIMINATE SELF-REACTIVE CELLS

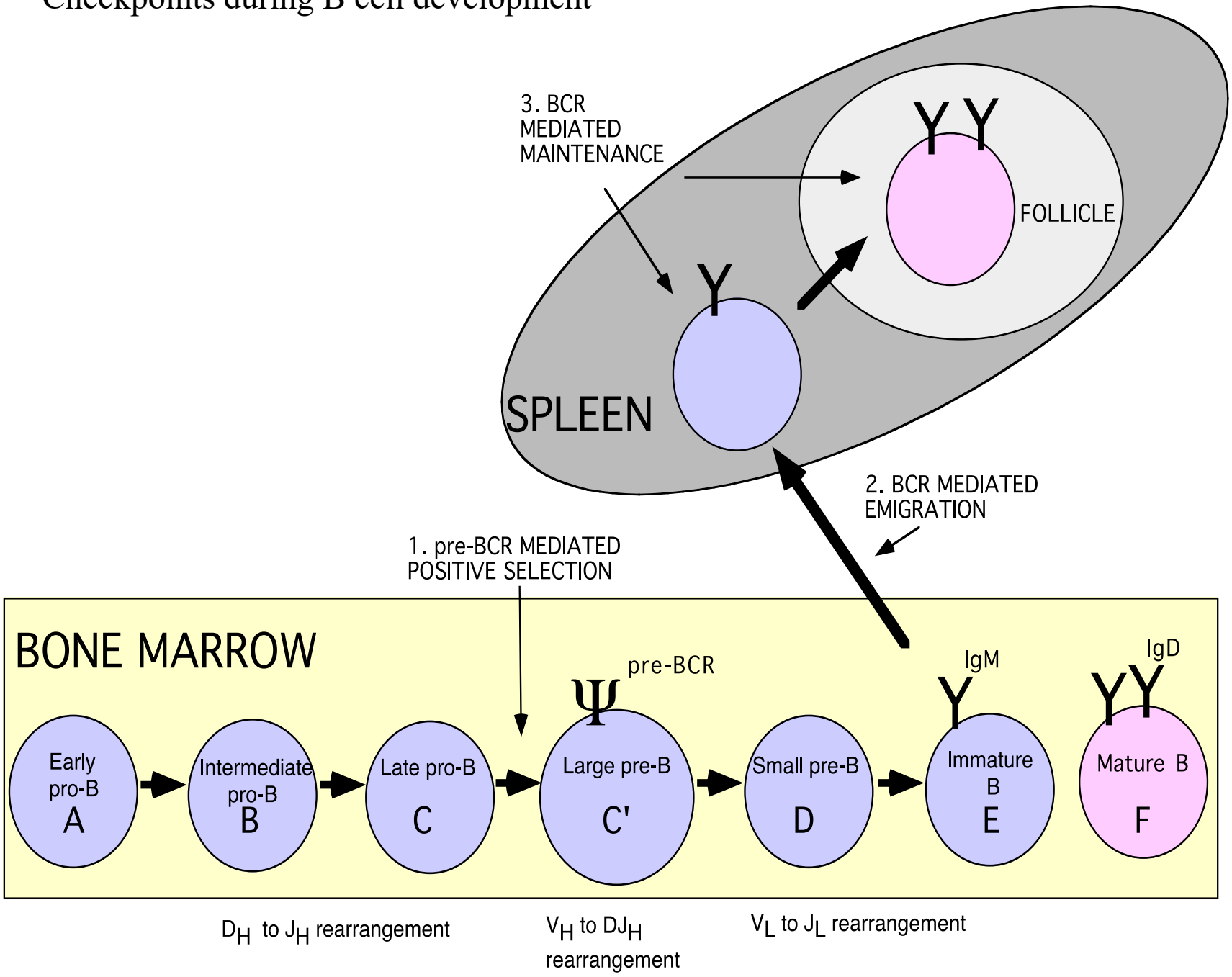
GOD

Self Non-Self Recognition

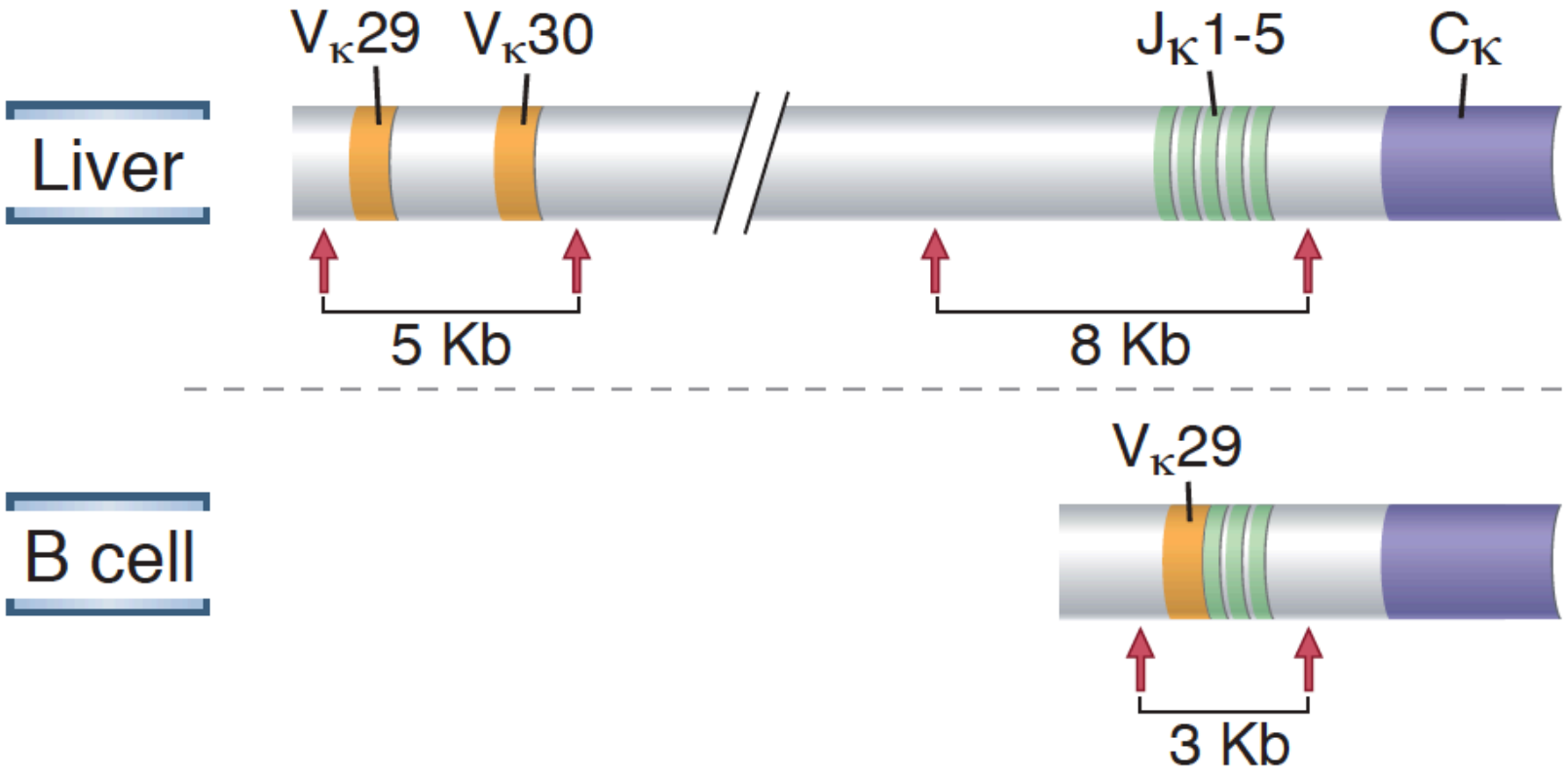
Germline Organization of Human Ig Loci

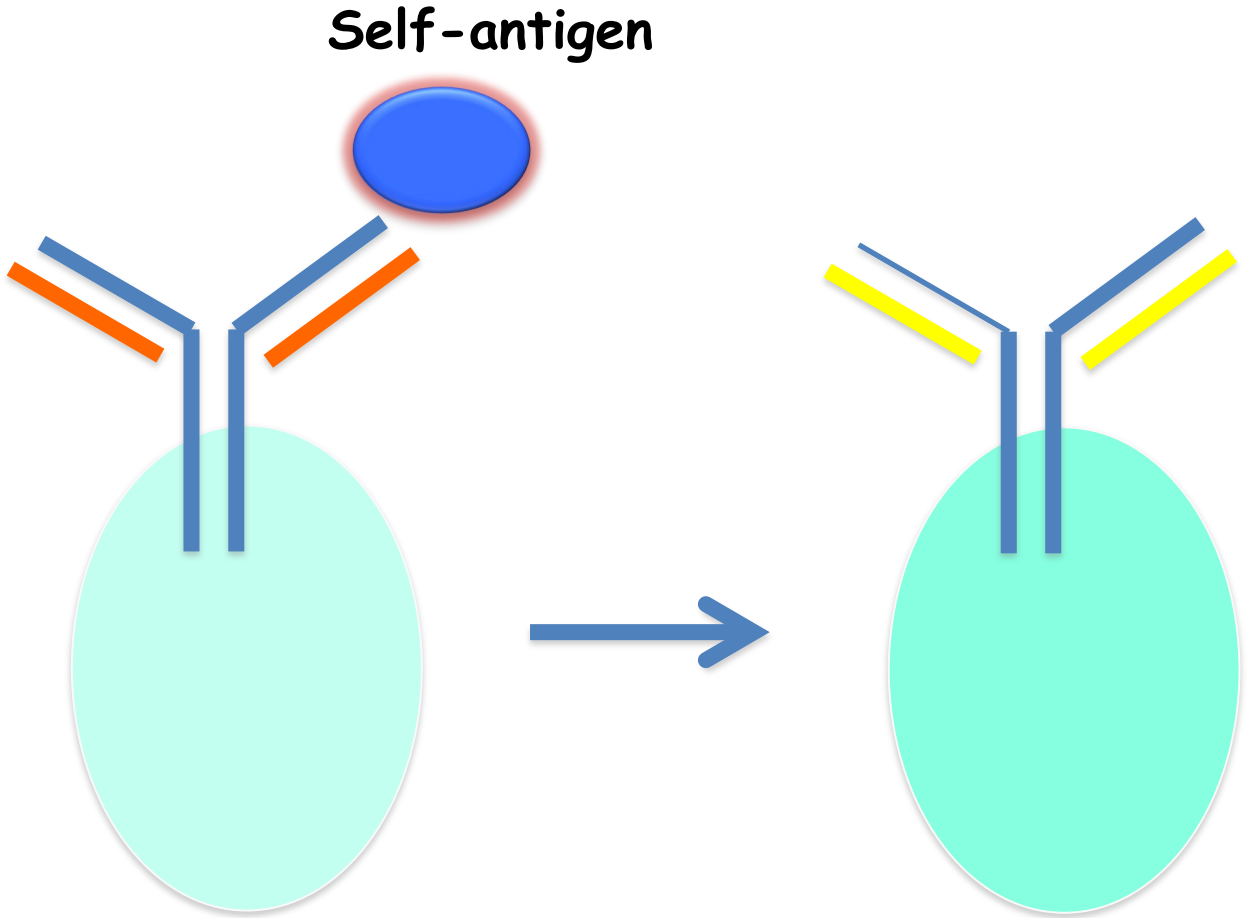


Checkpoints during B cell development



Distant segments are recombined during receptor assembly



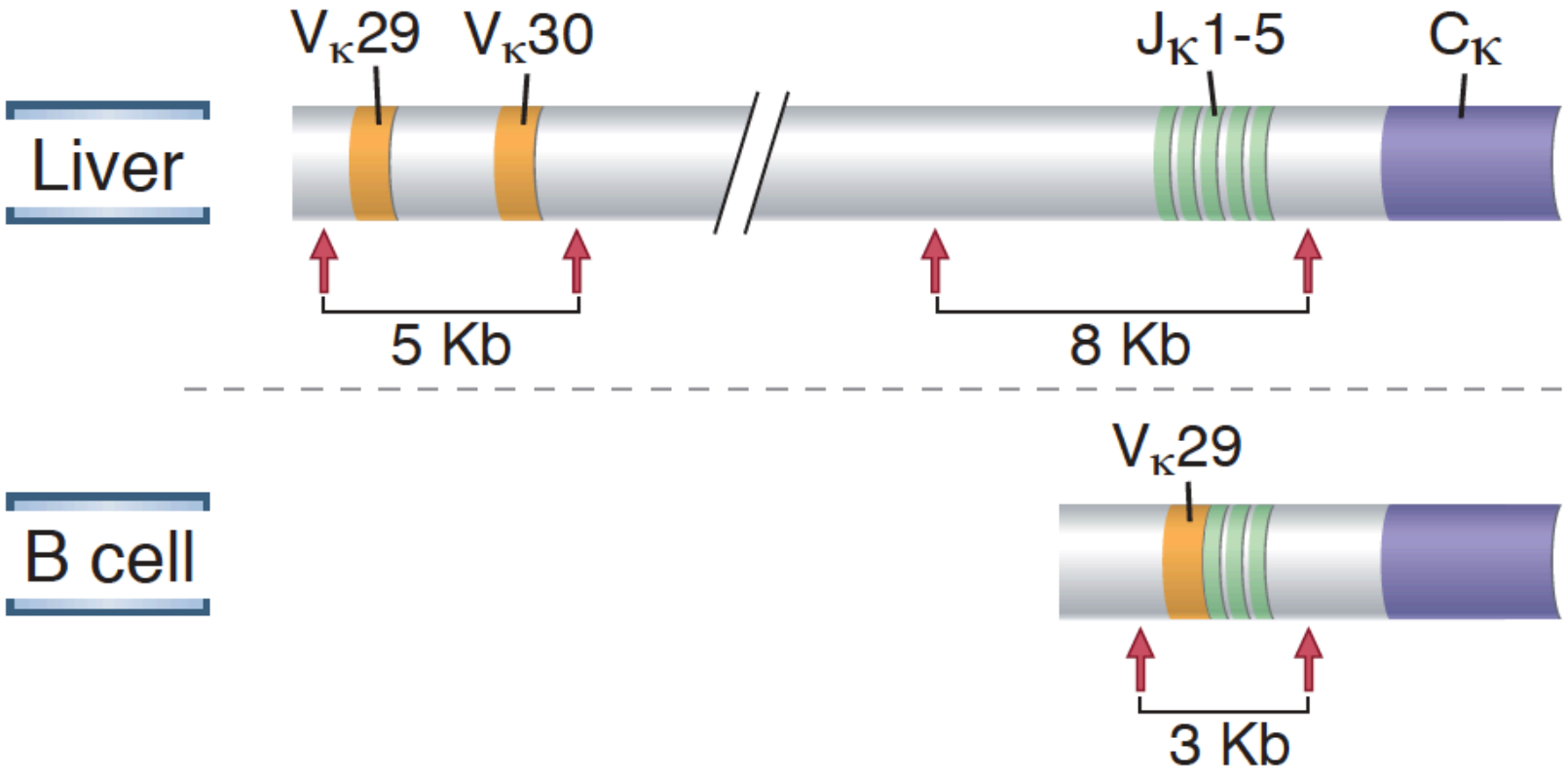


Self-reactive B cell

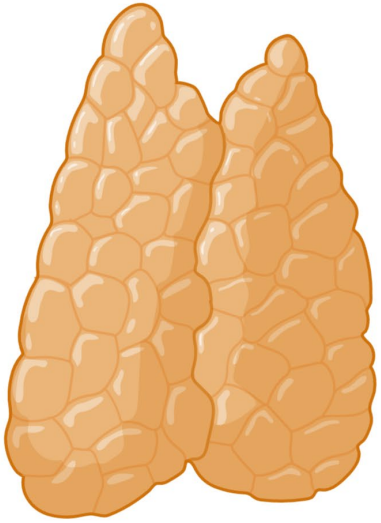
Edited B cell

Receptor editing occurs in the bone marrow

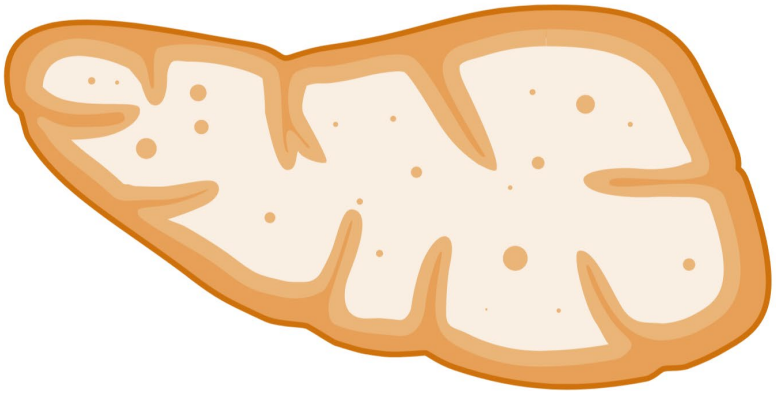
ONE STEP L-CHAIN REARRANGEMENT DRIVES RECEPTOR EDITING



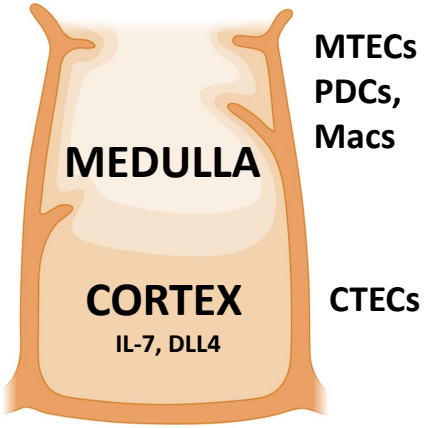
THYMUS



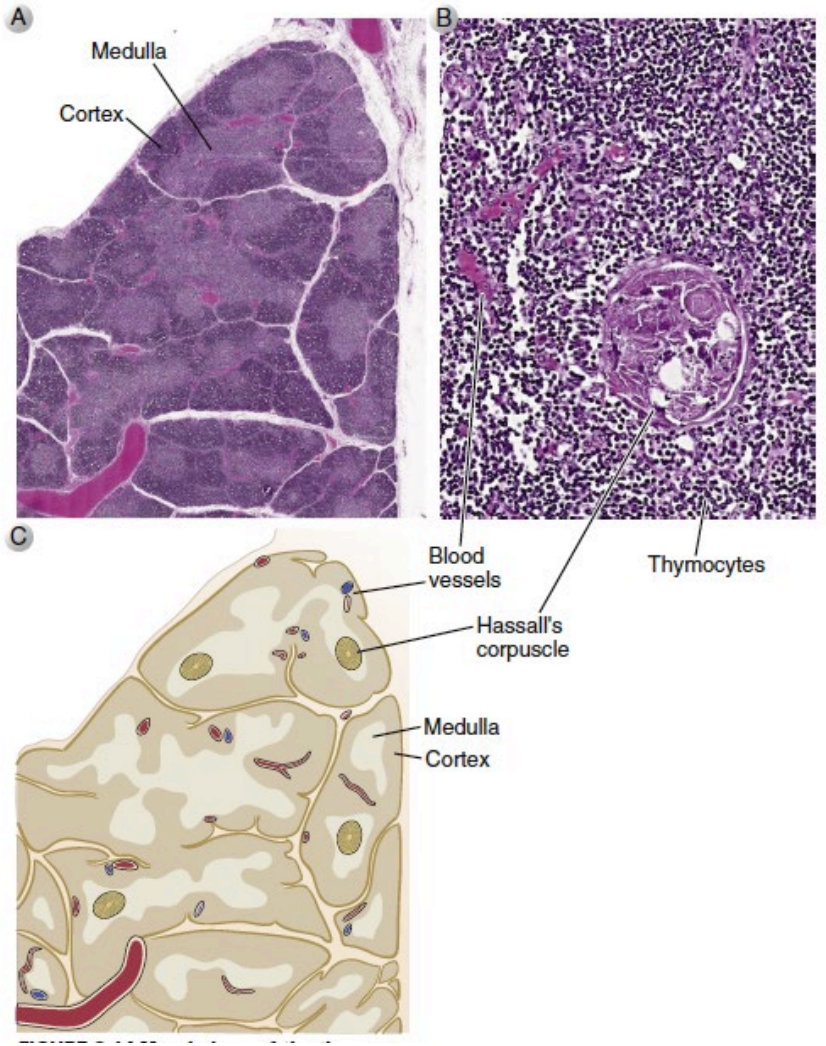
FoXN1 required for medullary and cortical thymic epithelial development



CROSS-SECTIONAL VIEW



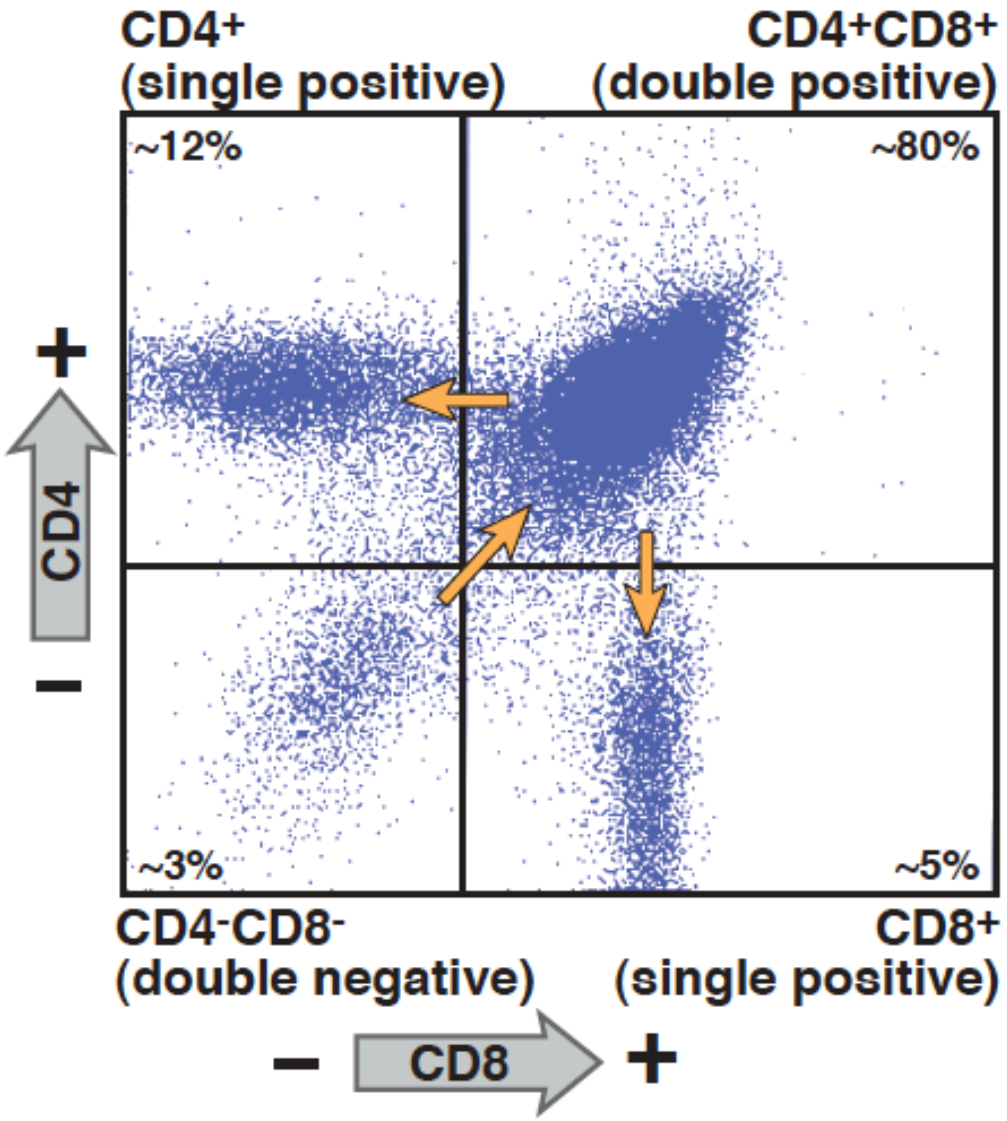
MORPHOLOGY OF THE THYMUS



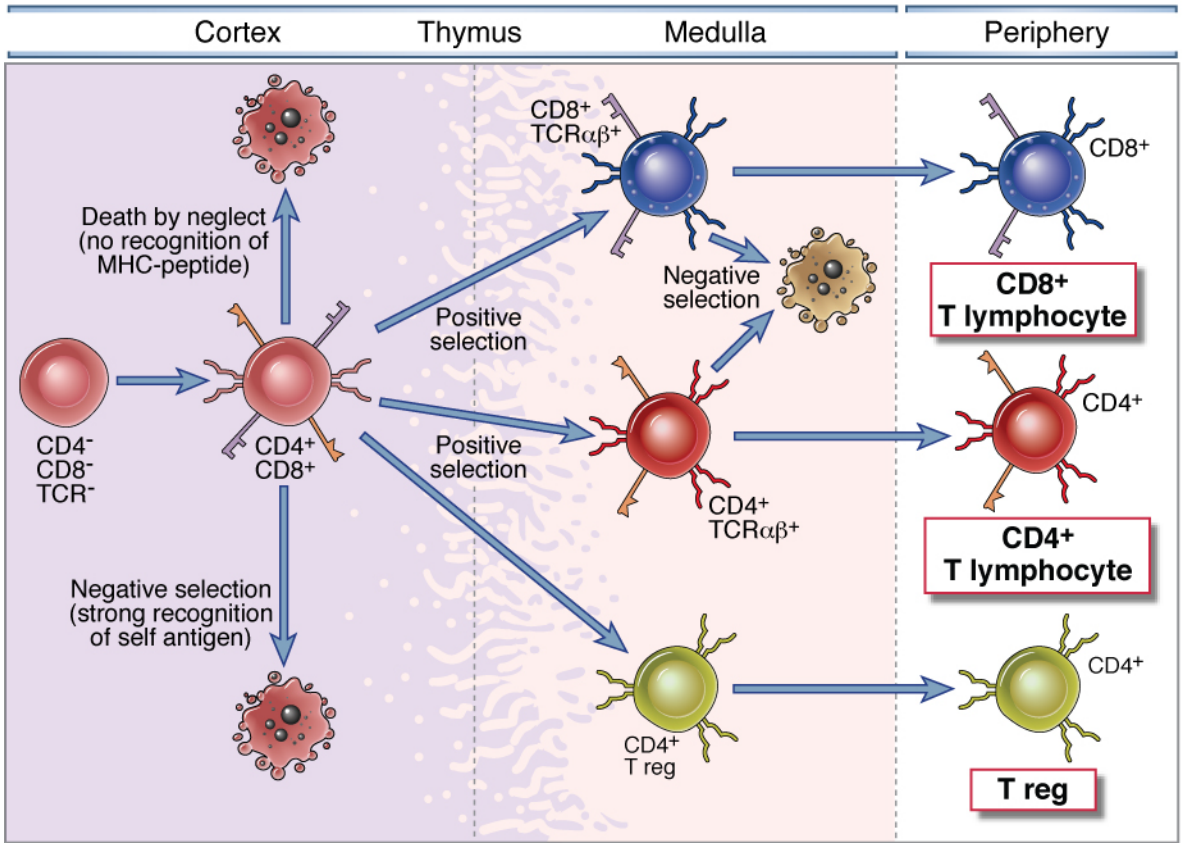
DiGeorge syndrome
22q11.2 heterozygous deletion;
Tbx1 gene a major gene'

Cleft palate, heart anomalies
Typical facial dysmorphia

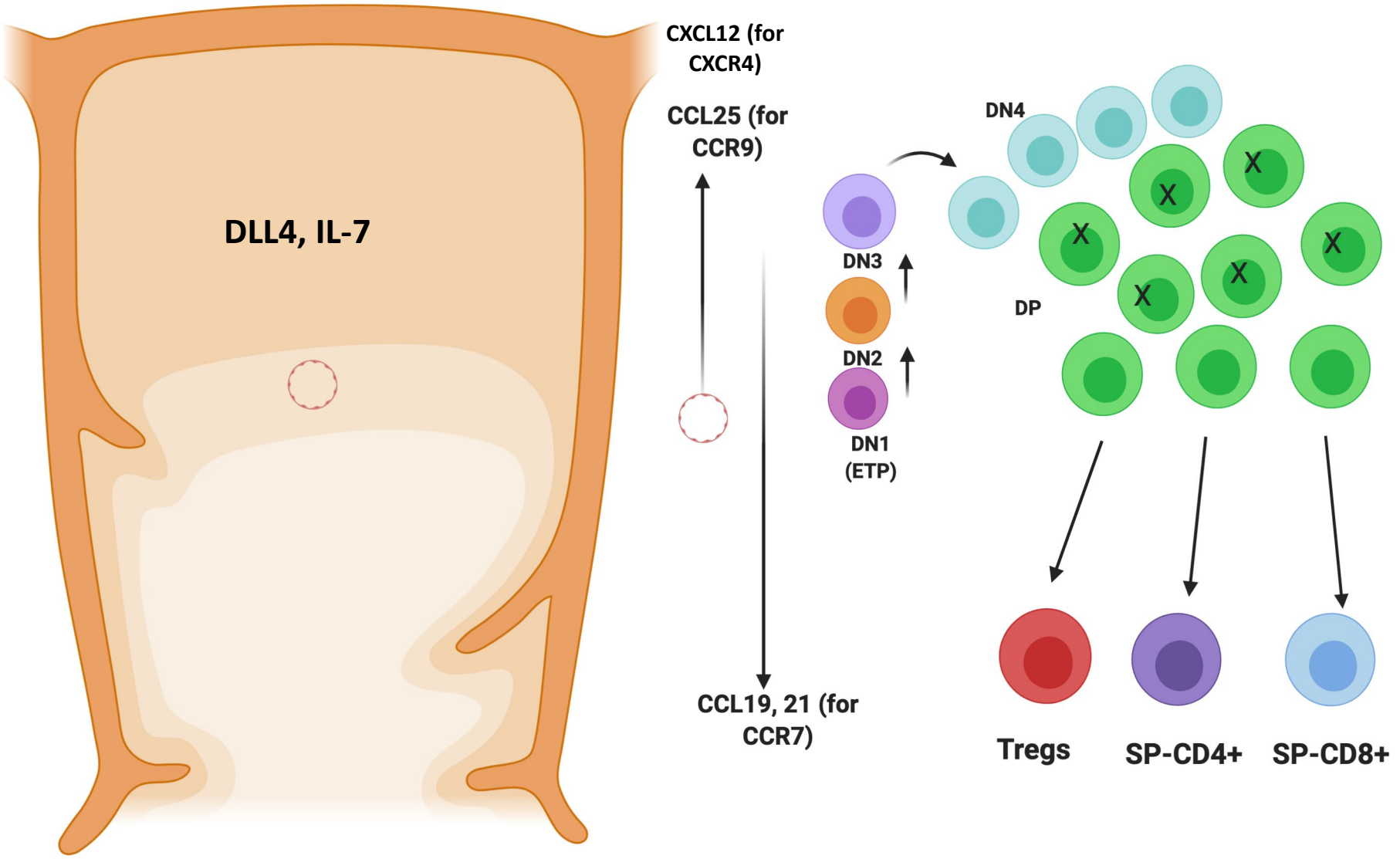
An overview of T cell development



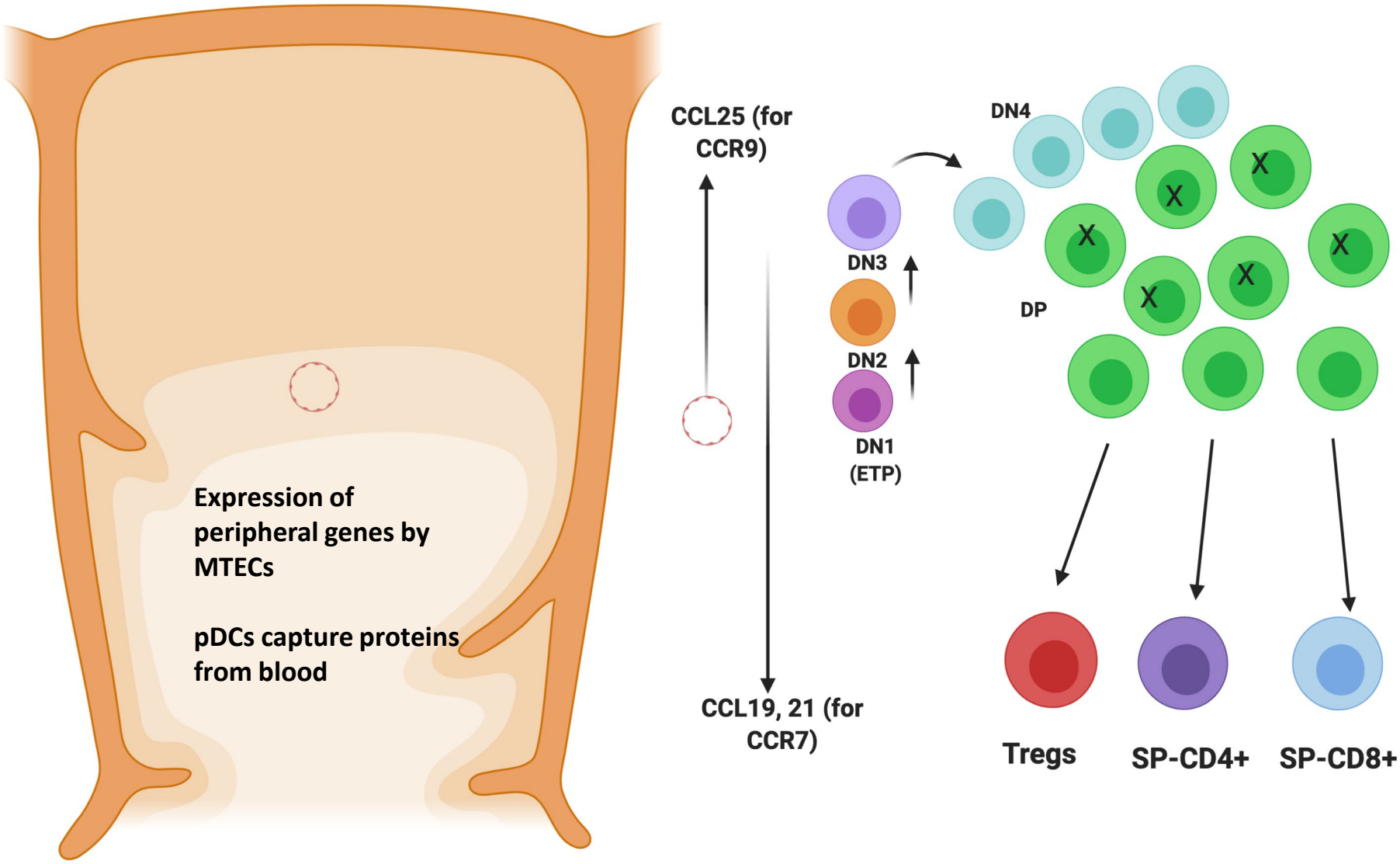
Thymic T cell development



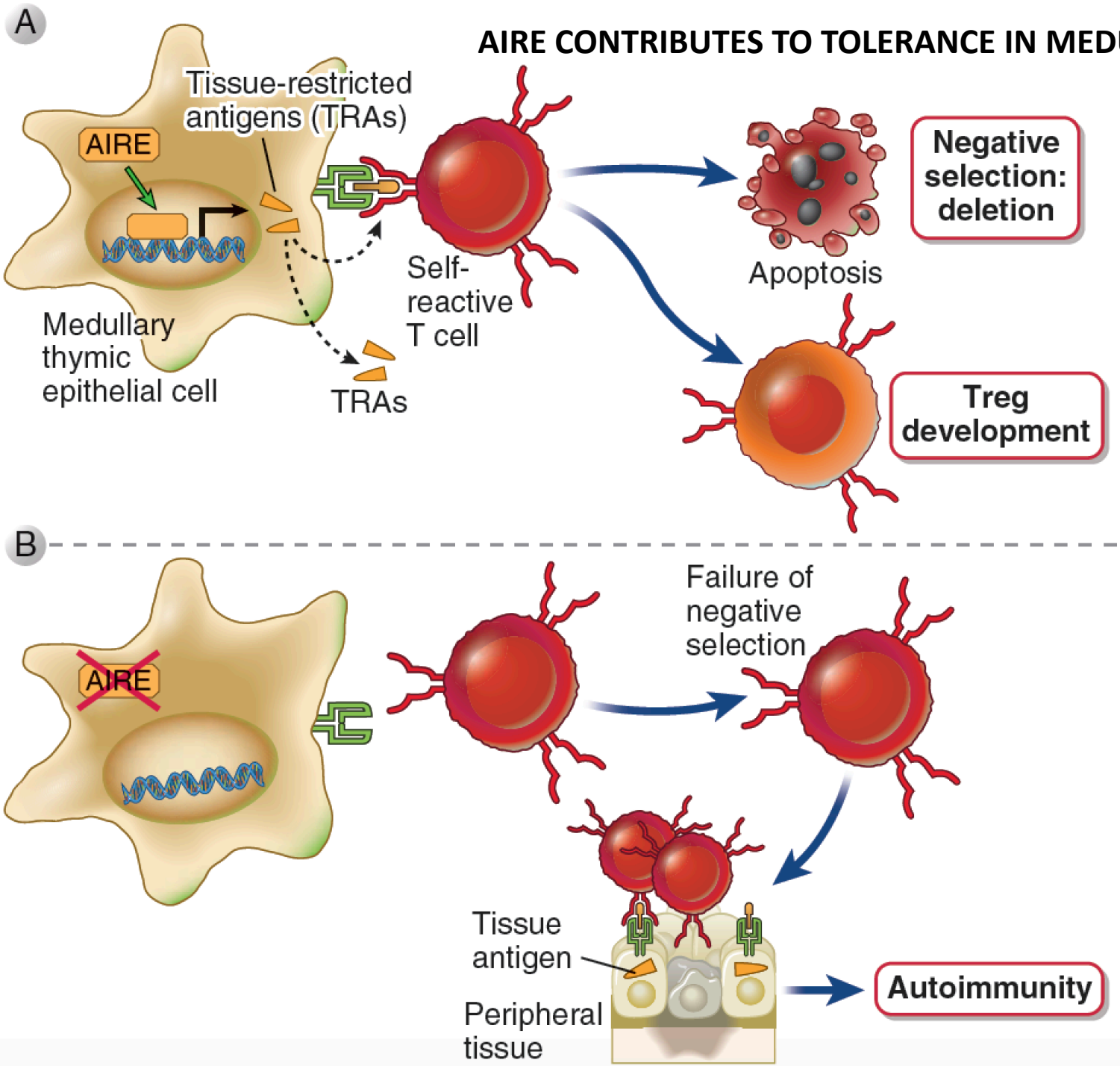
PROGRESSIVE MIGRATION AND POSITIVE SELECTION



NEGATIVE SELECTION OF SINGLE POSITIVE CELLS IN MEDULLA



AIRE CONTRIBUTES TO TOLERANCE IN MEDULLA

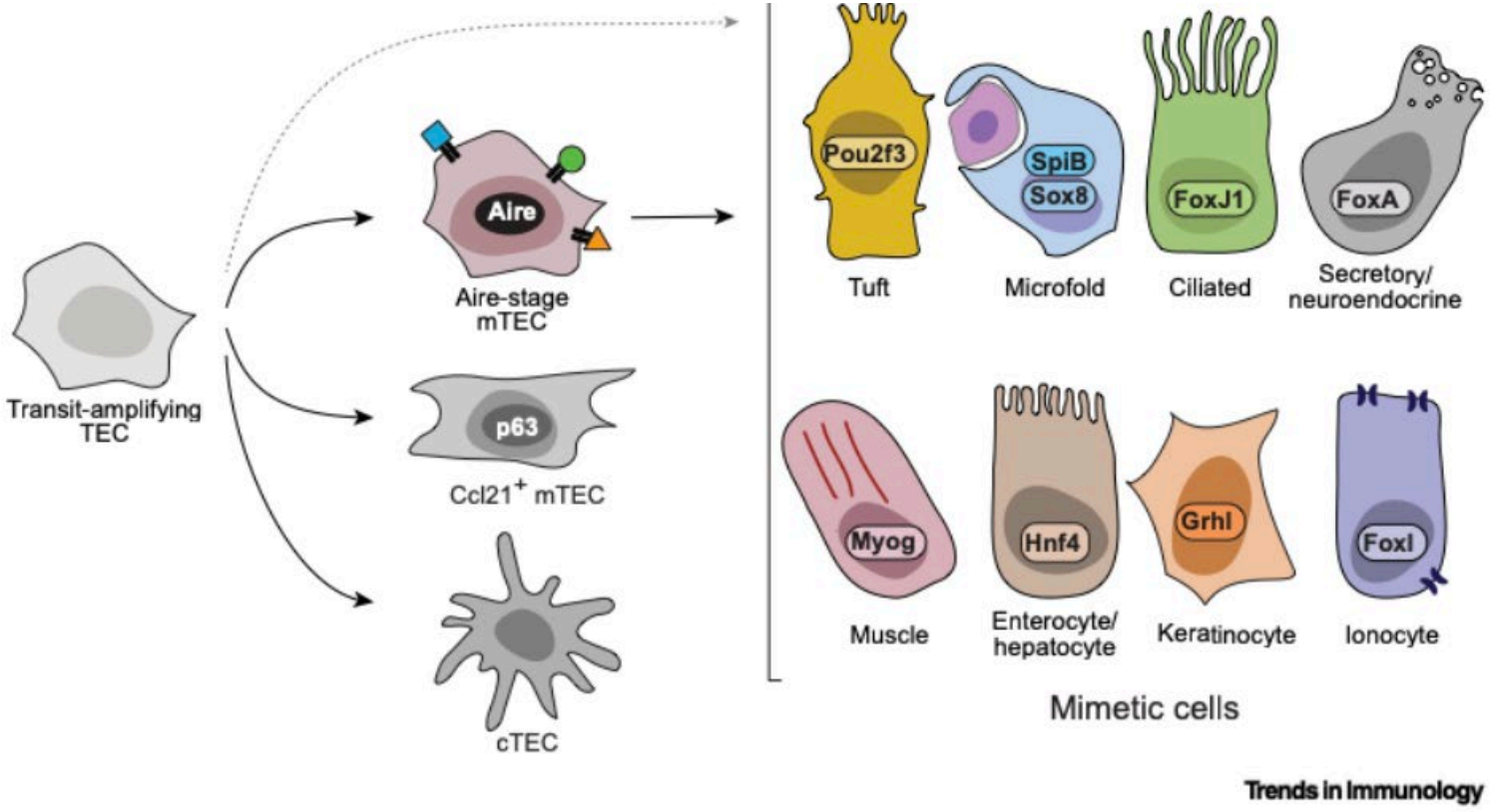


Trends in
Immunology

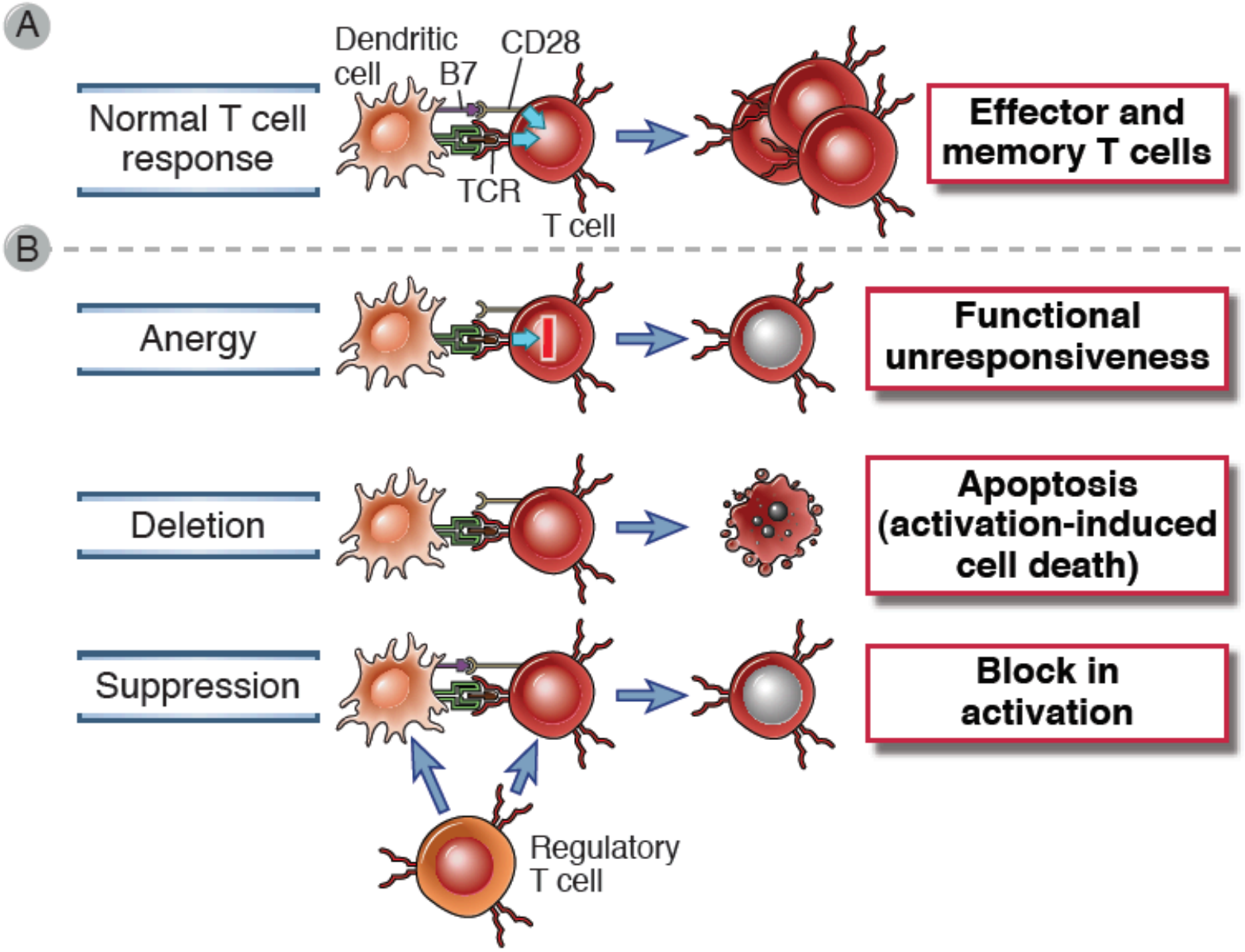
Opinion

Thymic mimetic cells: tolerogenic masqueraders

Daniel A. Michelson[1] and Diane Mathis [1,*]

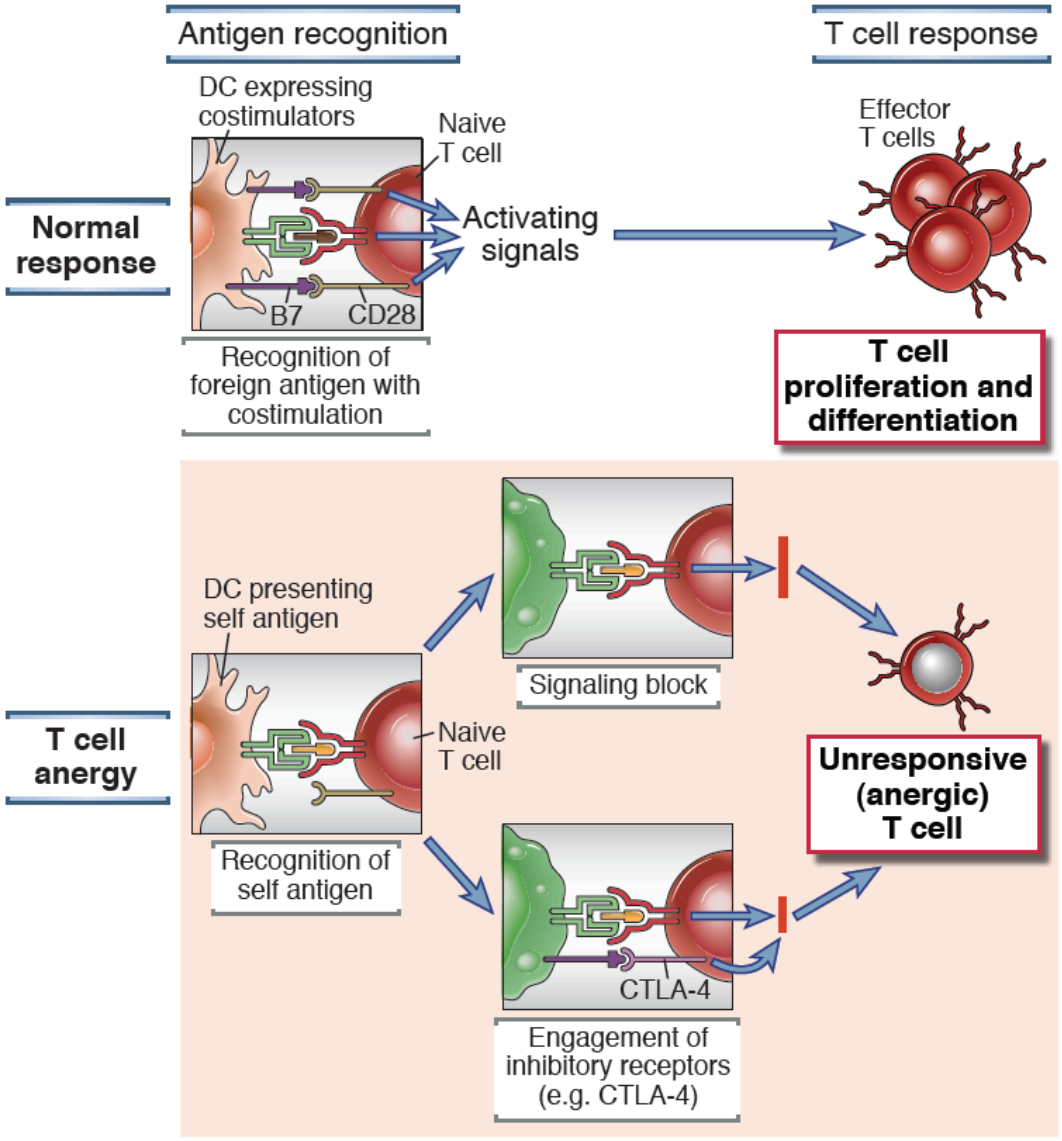


Mechanisms of peripheral T cell tolerance



????

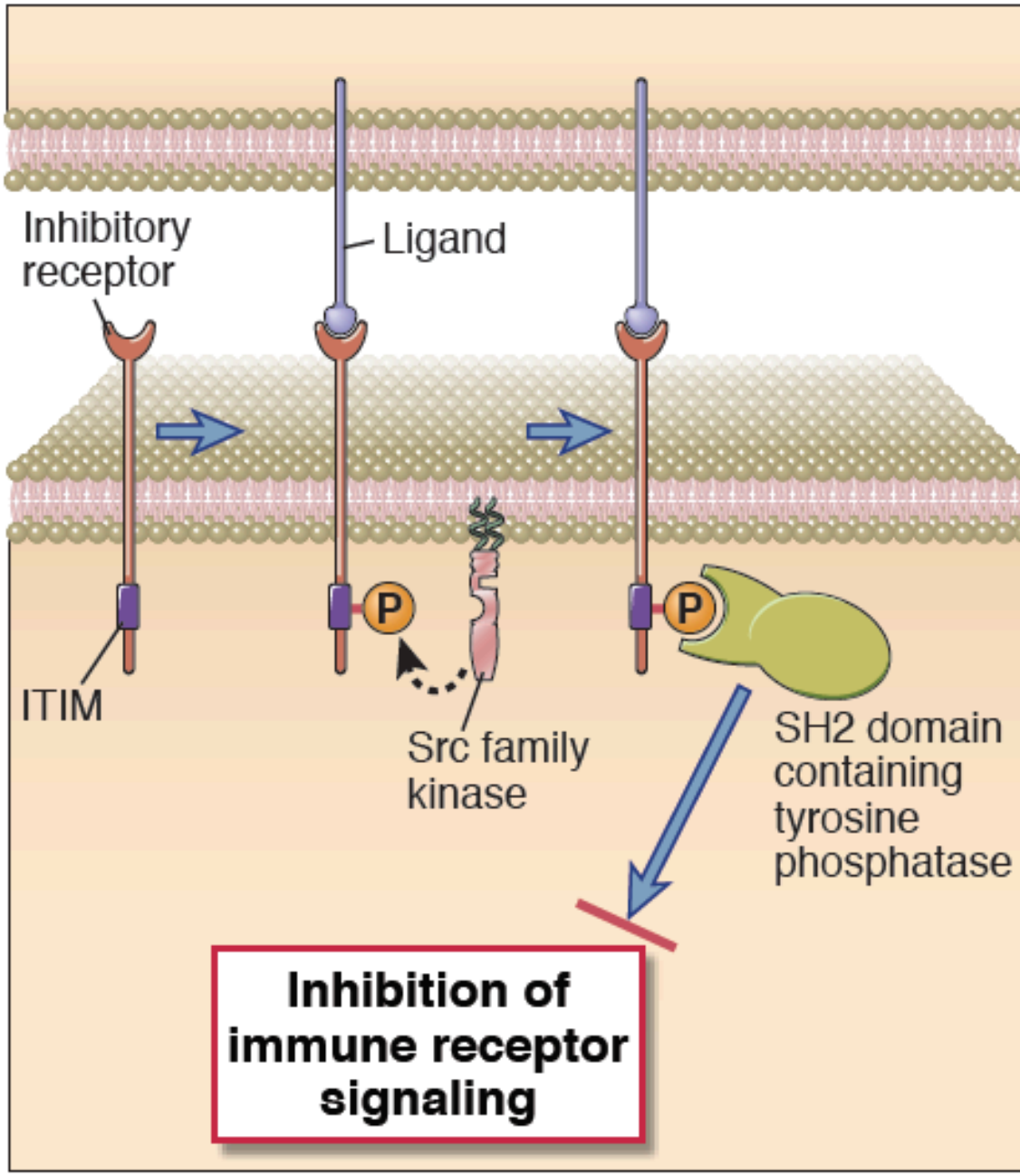
T cell anergy- no Signal Two and role for CTLA-4



Inhibitory Receptors Dampen Immune Responses

They help mediate:
1. Peripheral Tolerance
2. Lymphocyte Exhaustion
3. Activation Induced Cell Death

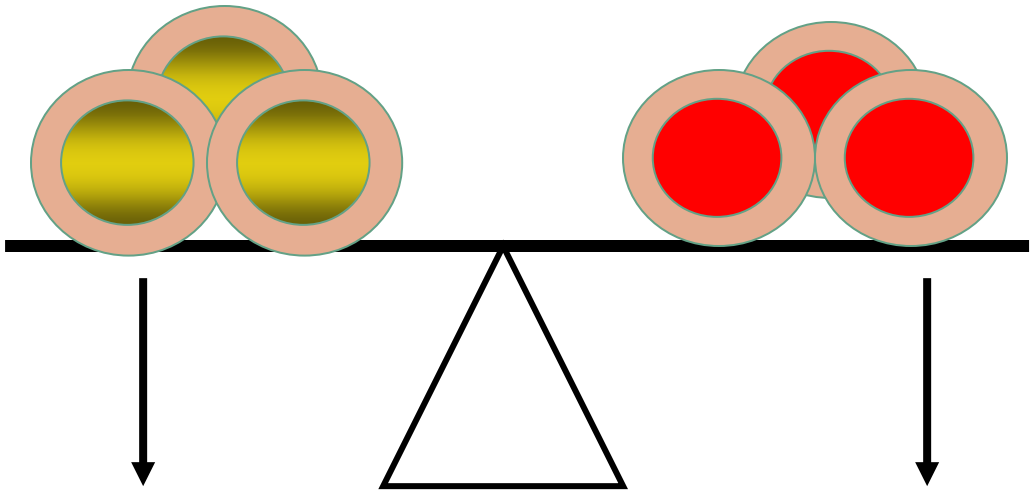
CTLA-4, PD-1, TIM-3 etc



Balancing lymphocyte activation and control

Activation
Effector T cells

Inhibition
Regulatory T cells, Anergy, AICD,
Exhausted T cells



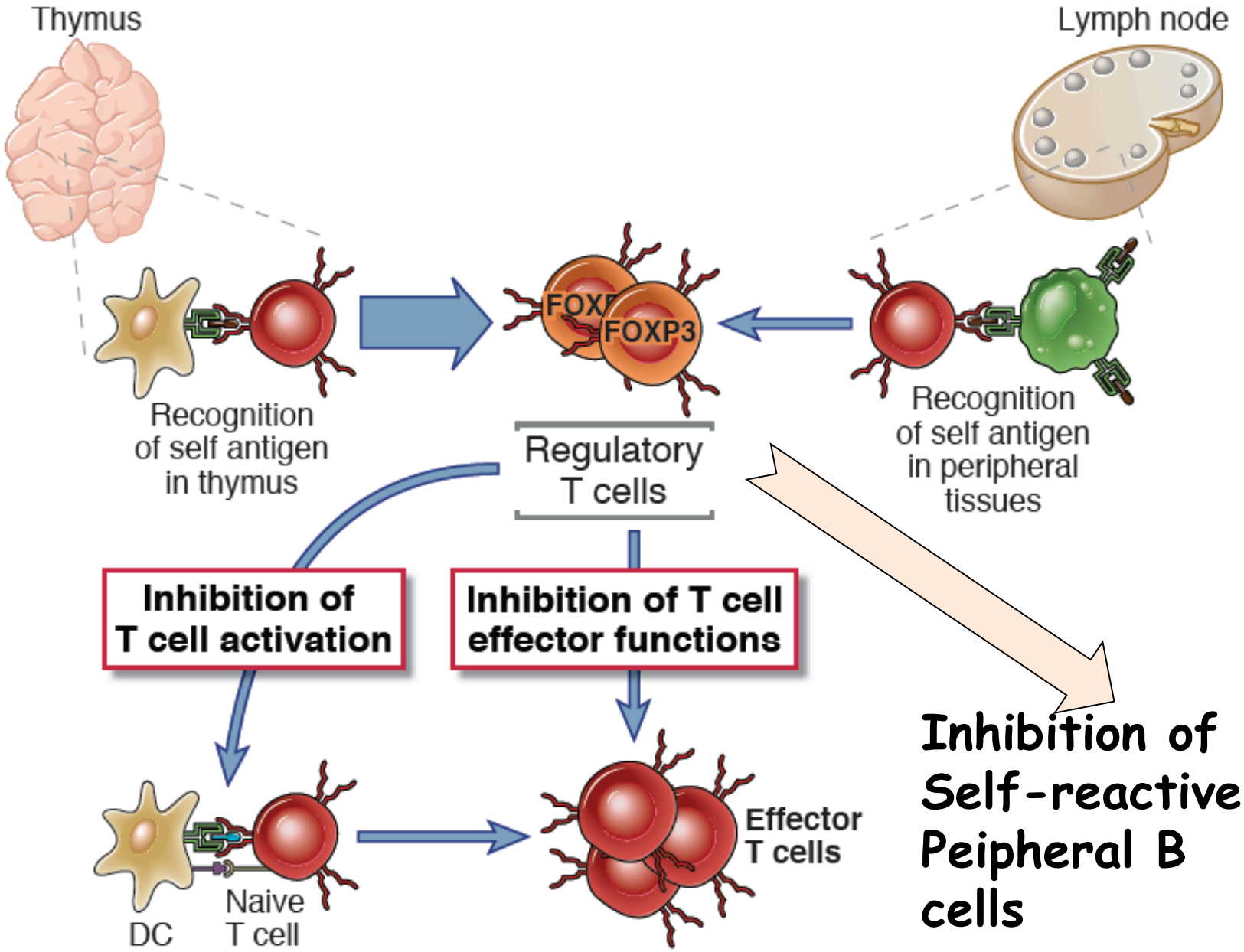
Normal: reactions against pathogens
Pathologic: inflammatory disease, e.g. caused by reactions against self or pathogens

No response to self
Controlled response to pathogens

Properties of regulatory T cells

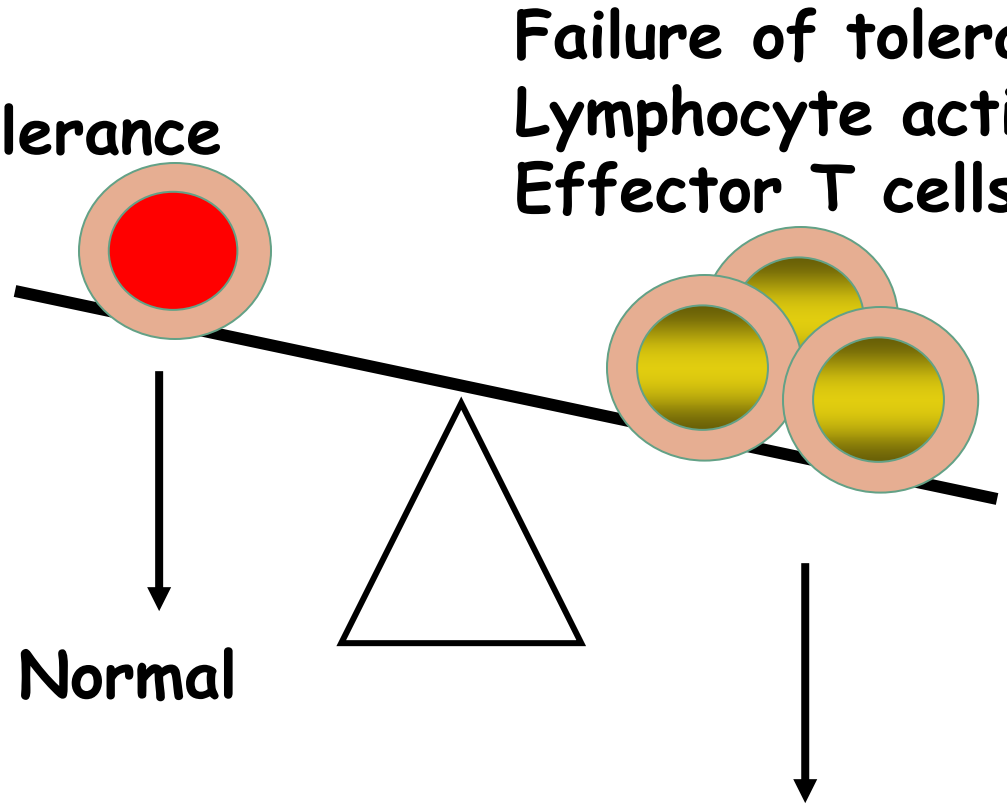
- **Phenotype:** CD4+, high IL-2 receptor (CD25), low IL-7 receptor, Foxp3 transcription factor; other markers
- **Significance:** Foxp3 mutations --> autoimmune disease (IPEX); many autoimmune diseases may be associated with defects in or resistance to Tregs
- **Mechanisms of action:** multiple
  - secretion of immune-suppressive cytokines (TGFβ, IL-10; IL-35?)
  - inhibition of APC function (role of CTLA-4?)

Regulatory T cells

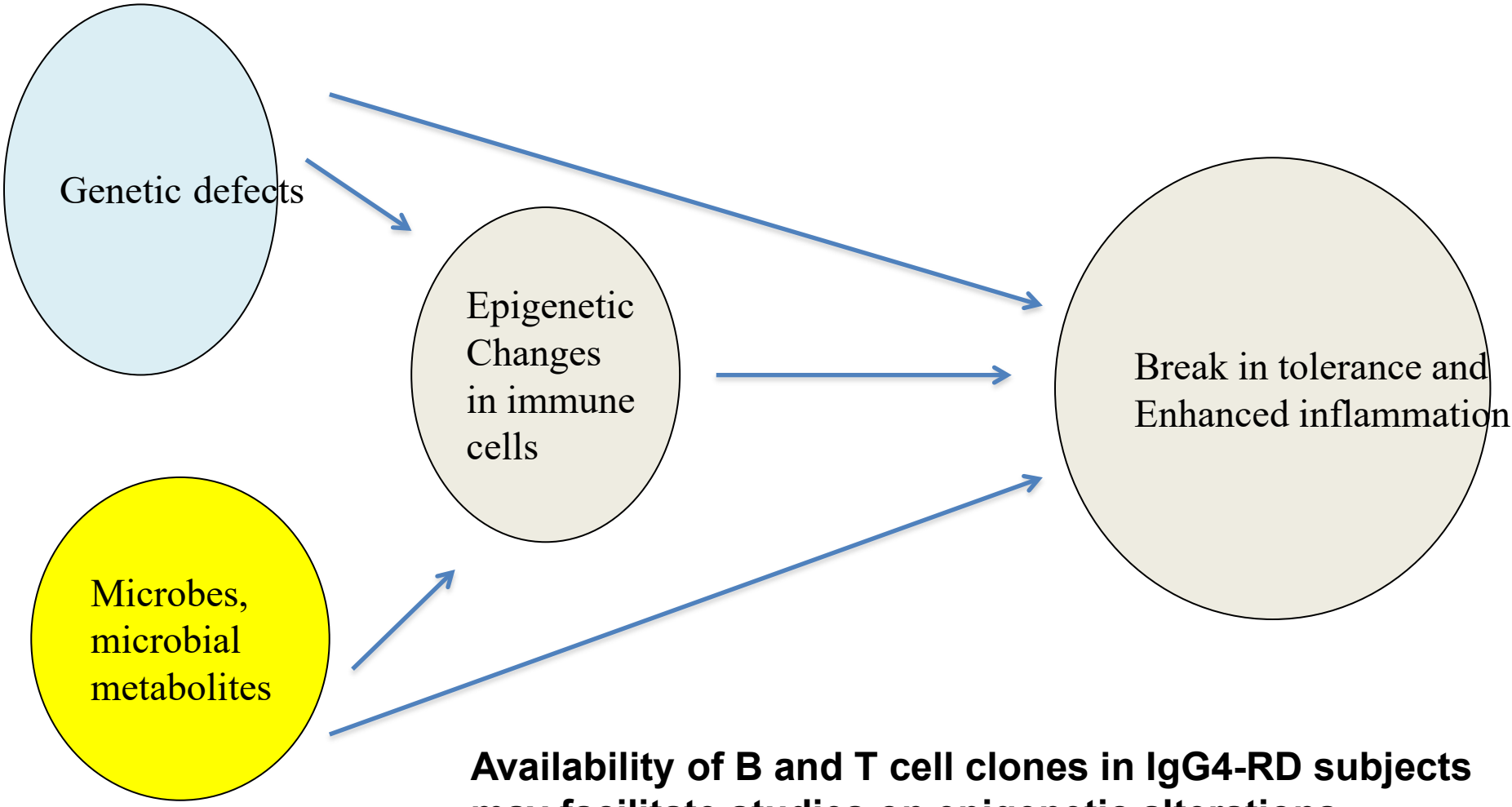


Inhibition of Self-reactive Peipheral B cells

Autoimmune diseases: failure of control

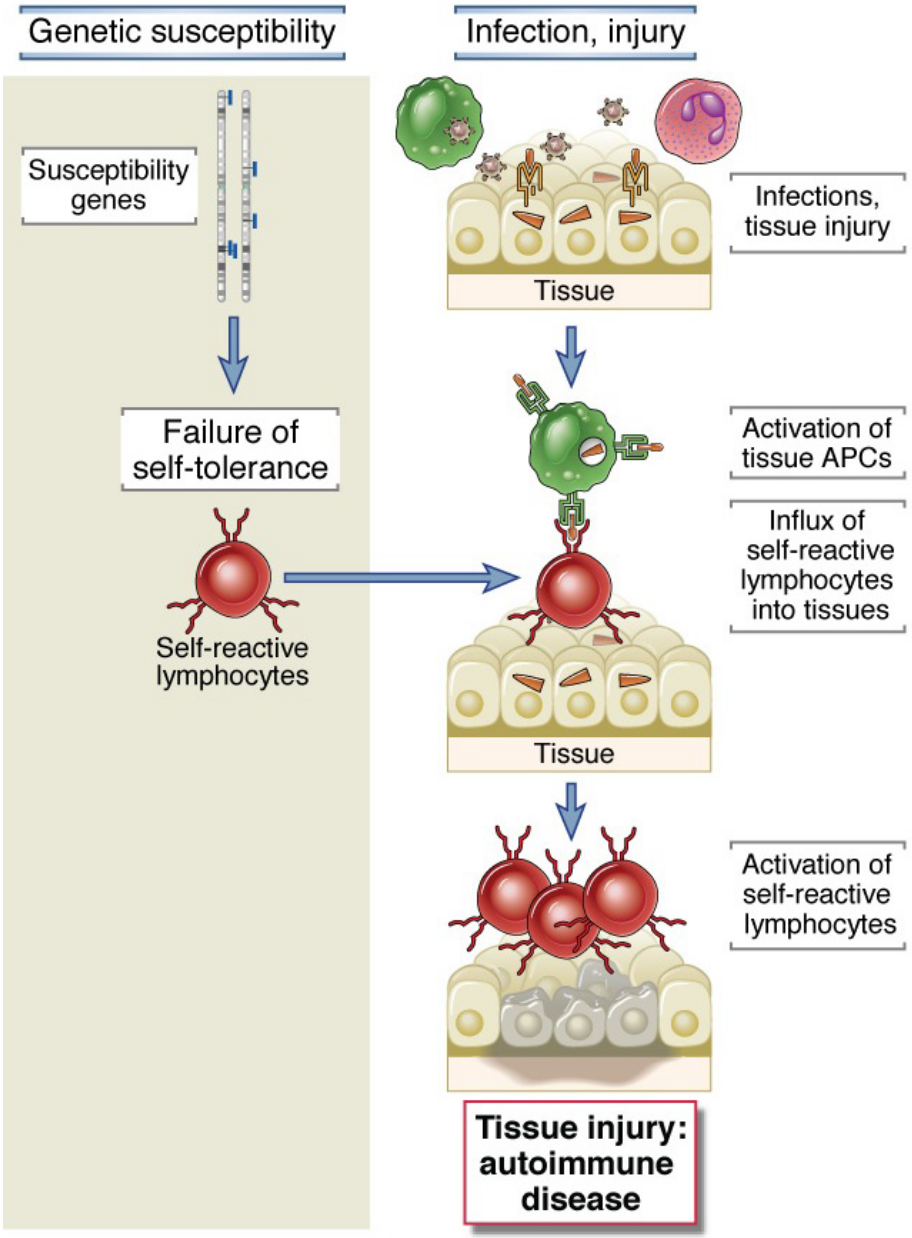


Pathogenesis of autoimmunity



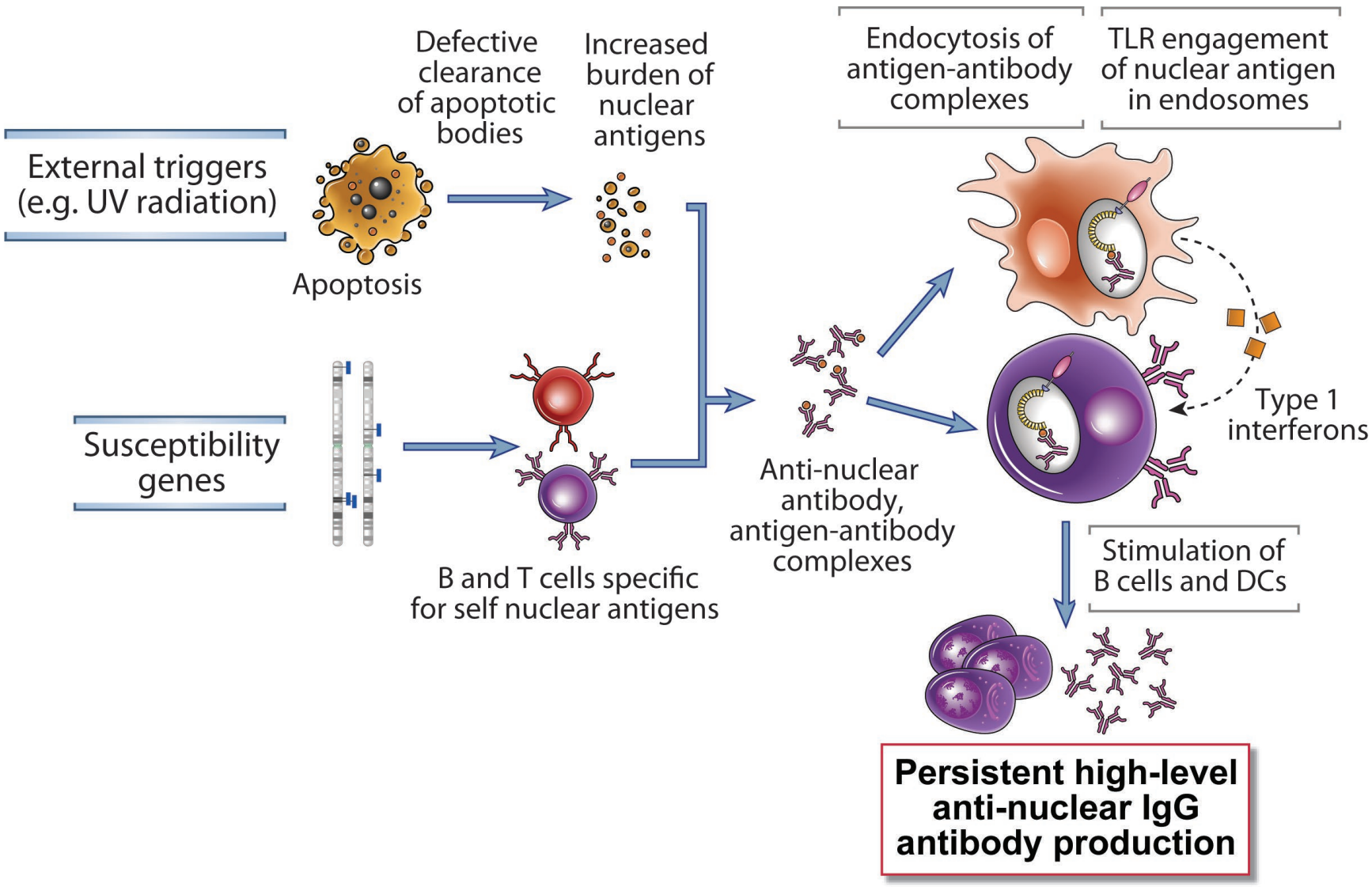
Availability of B and T cell clones in IgG4-RD subjects may facilitate studies on epigenetic alterations

Pathogenesis of organ-specific autoimmunity



Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 7th edition, 2011* © Elsevier

Model for the Pathogenesis of SLE



QUIETLY INTO THE NIGHT……