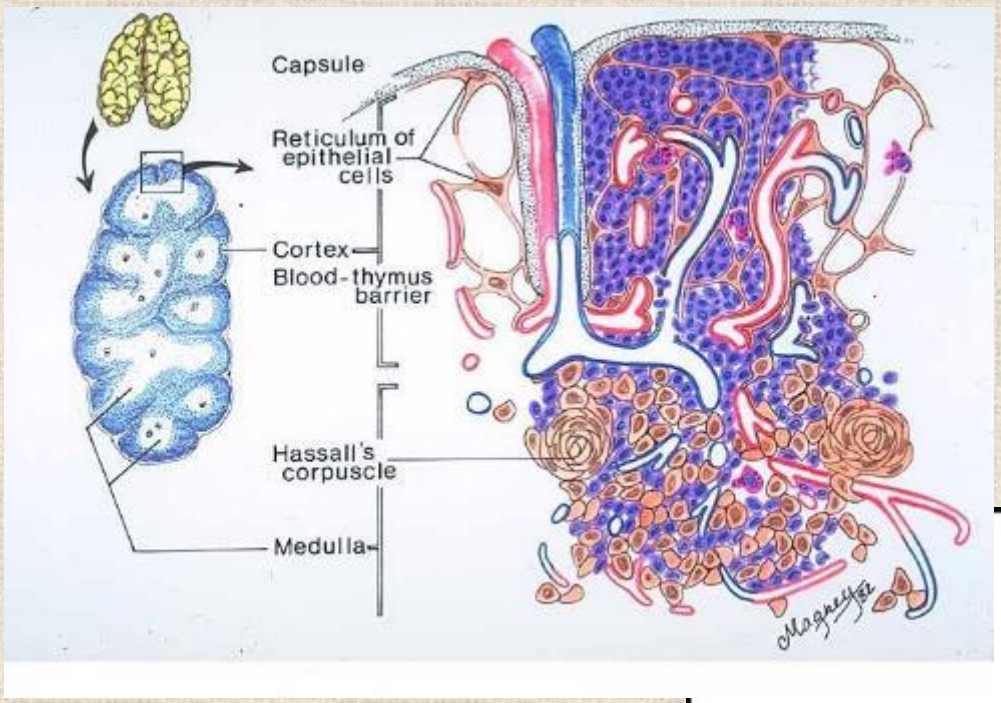
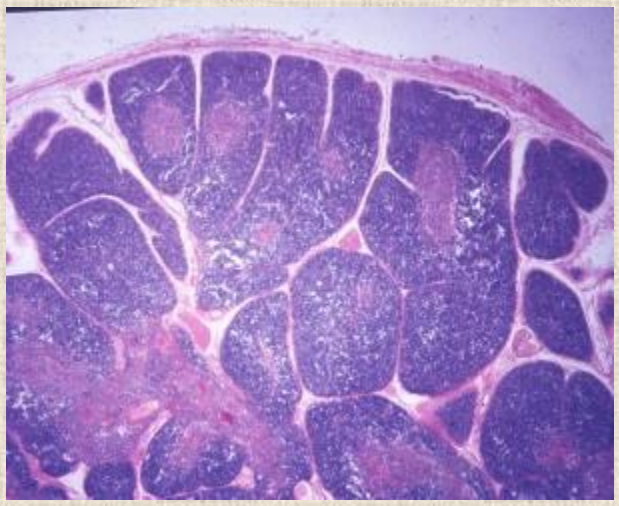
Basic Immunology

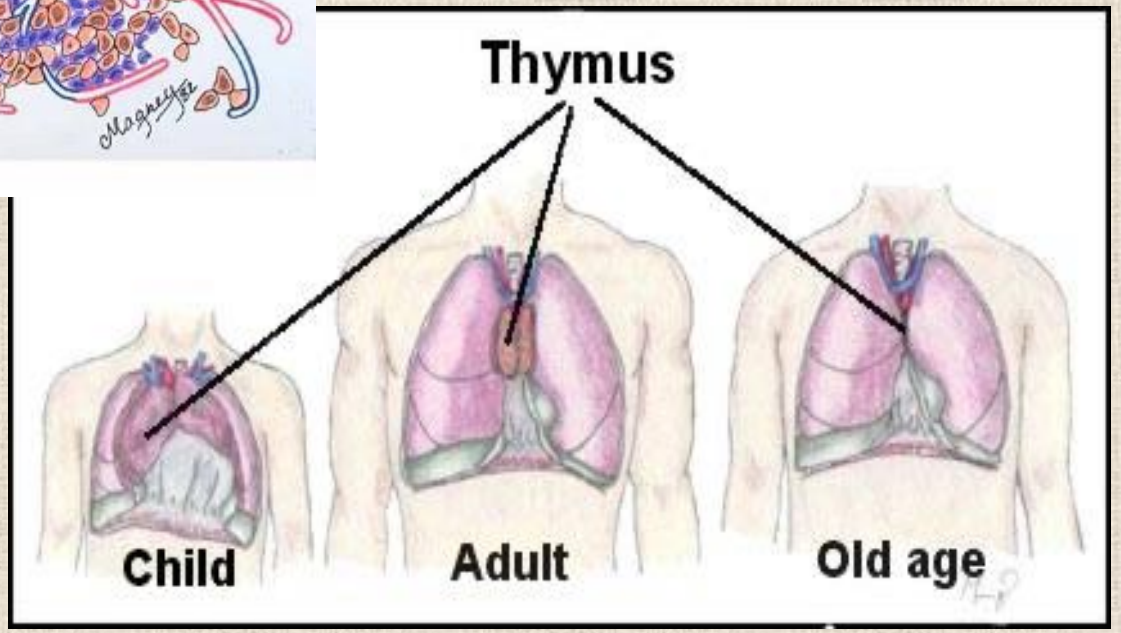
T-cell development in the thymus. Stages of maturation and the role of environmental factors

Timea Berki MD, PhD

Structure of the thymus

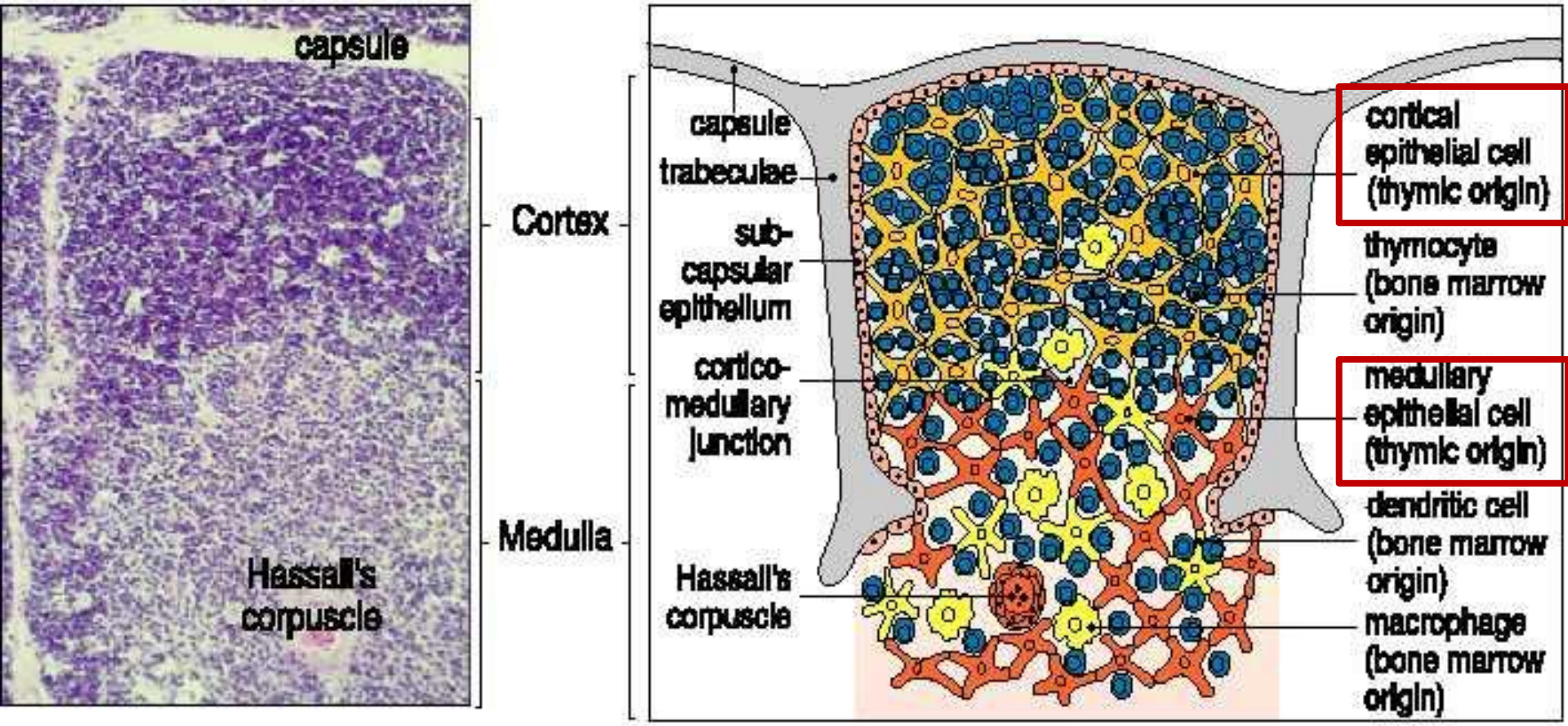






Structure of the thymus

Figure 5.3

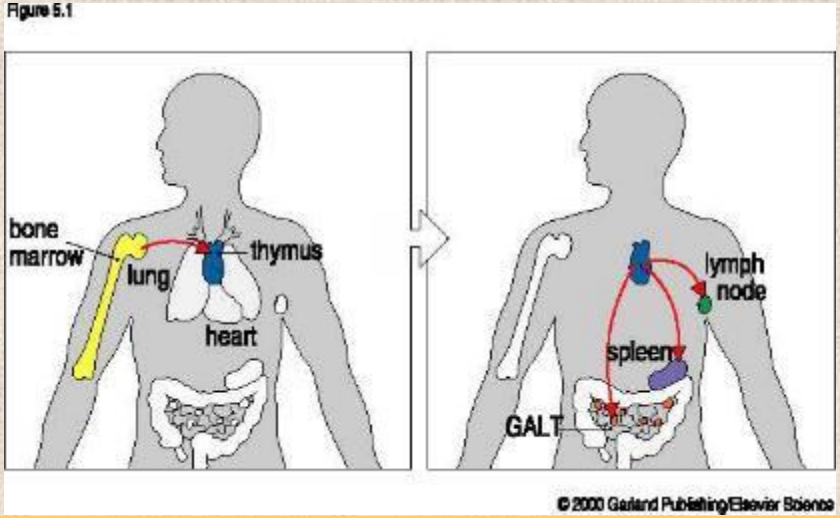


The thymic stoma creates the microenvironment that is essential for T-cell development

T-cell source: thymus and beyond.

- **Thymus: prime T-cell source**
- **Absence of thymus – *nude* mouse (FoXN1)**
  Ectodermal (skin) and endodermal developmental abnormalities. Profoundly reduced T-cell pool.
- **DiGeorge's syndrome**: Complex cardiac, facial, endocrine and immune defects

- **Extrathymic T-cell source**: intestinal „cryptopatch" (in LP 1000-5000 c-*kit*$^+$, CD44$^+$, IL7R$^+$, CD25$^-$ phenotype cells), maturation in MLN and PPs (based on RAG-expression).
- Second thymus



T cell repertoire

Total repertoire:
TCR α, β: 10^{15}
TCR γ, δ: 10^{16}

T cell precursors are produced in the **bone marrow** from the common haemopoietic stem cell
They migrate through the blood circulation to the thymus

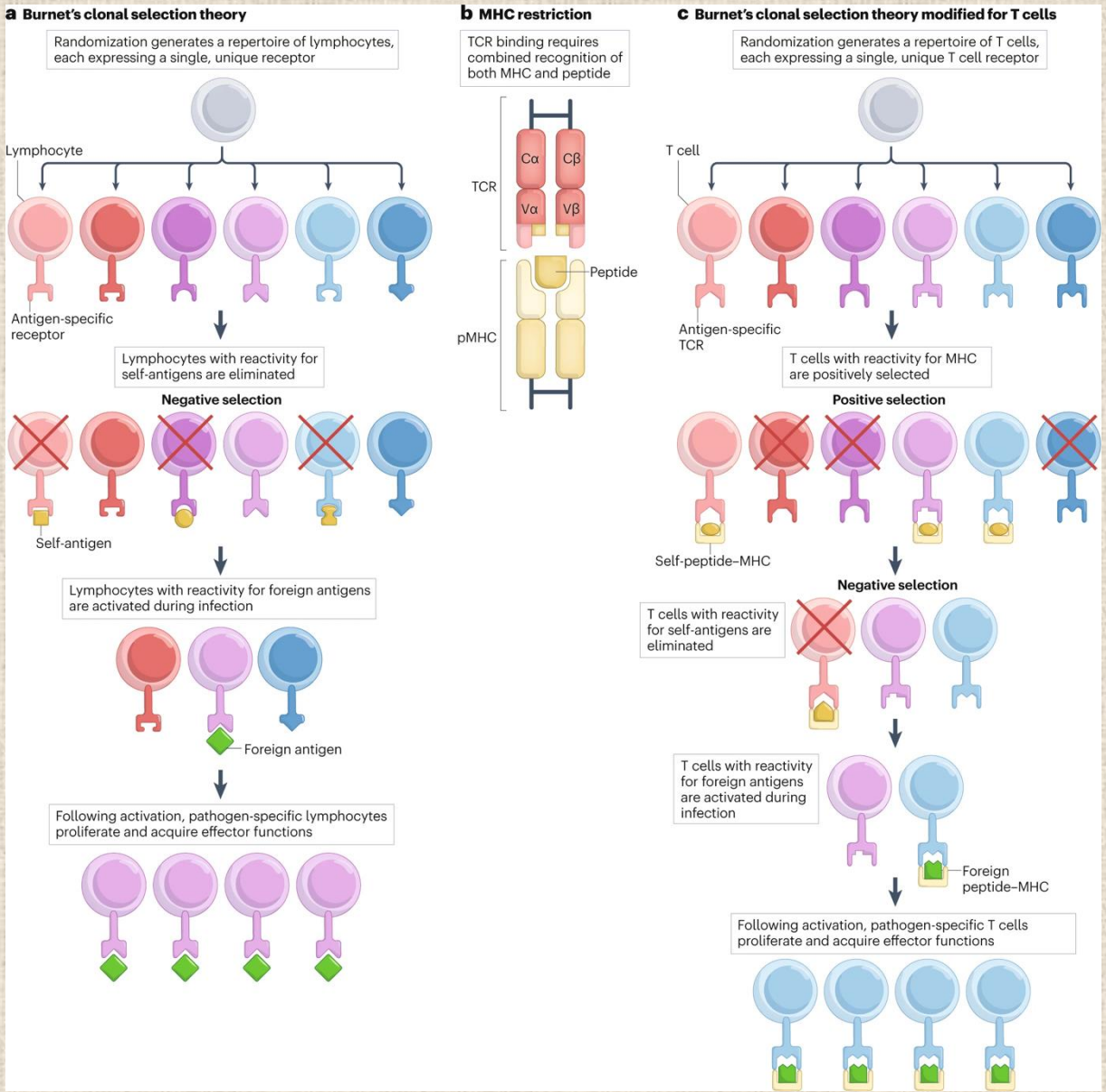
In the thymus: T cell maturation, educational steps
„double recognition" (MHC and peptide)

Periphery: mature, TCR expressing, CD4 or CD8 positive T cells

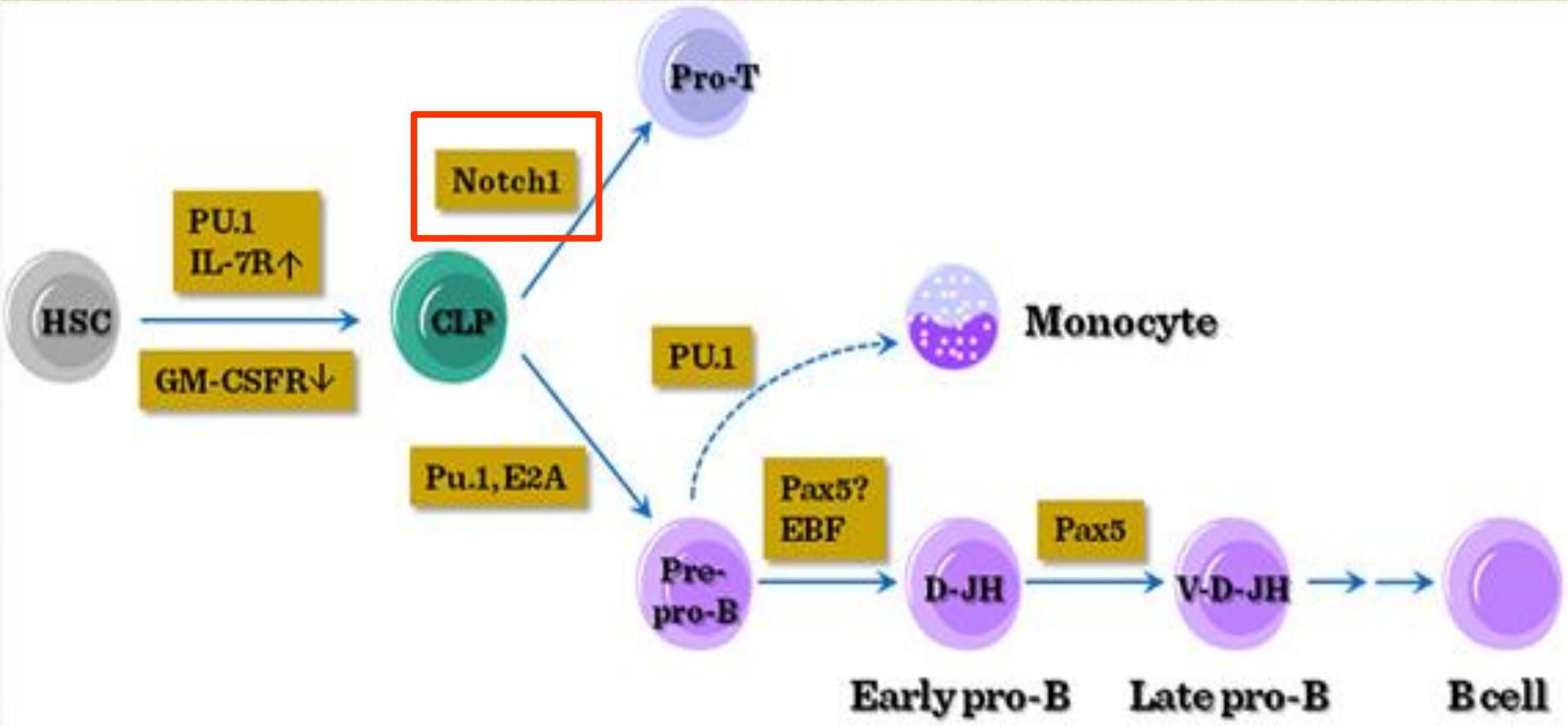
→ **Self-MHC restricted**

Self-tolerant T cells

The ‘clonal selection theory’ first proposed by Frank Macfarlane Burnet in 1956 predicts that each lymphocyte expresses a single, unique, antigen-specific receptor.

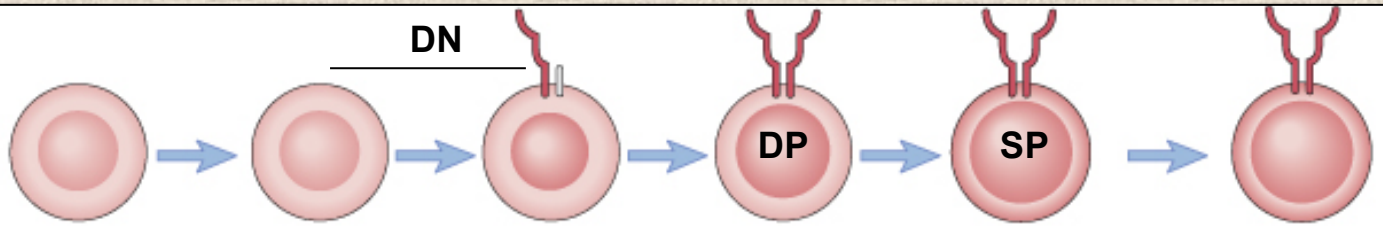


NOTCH1 is required for the commitment of multipotent hematopoietic progenitors to the T-cell lineage



NOTCH1 support cell growth, proliferation and survival at multiple stages of thymocyte developmentis involved in the progression through the early DN1, DN2 and DN3 stages of thymocyte development and in the regulation of TCRB rearrangement

In: Transdifferentiation and regenerative medicine (Dr. Péter Balogh, Dr. Péter Engelmann (2011); University of Pécs)



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
RAG expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^+$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection	Negative selection	Activation (proliferation and differentiation)

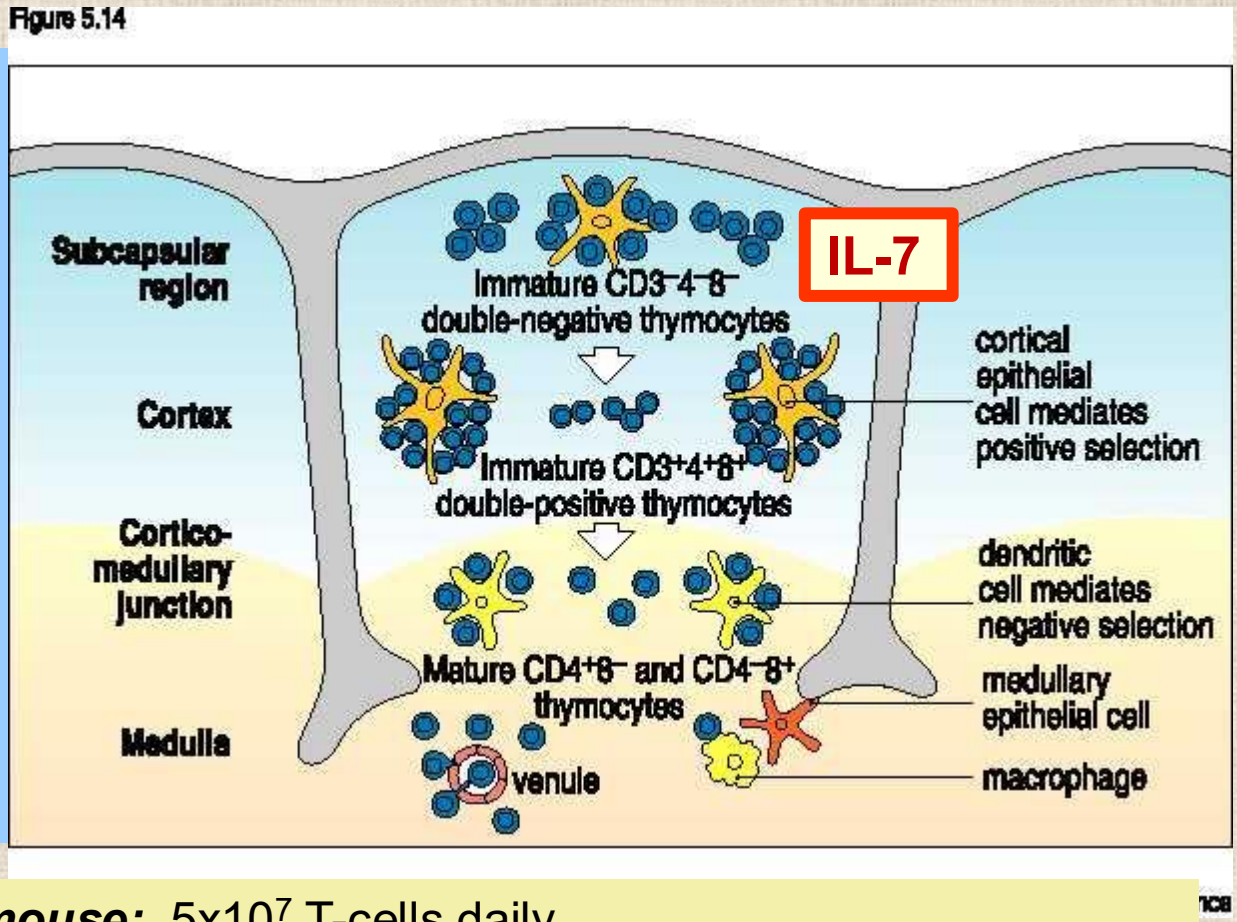
T-cell development in the thymus

Thymocytes:

DN: 2-5 %

DP: 70-80%

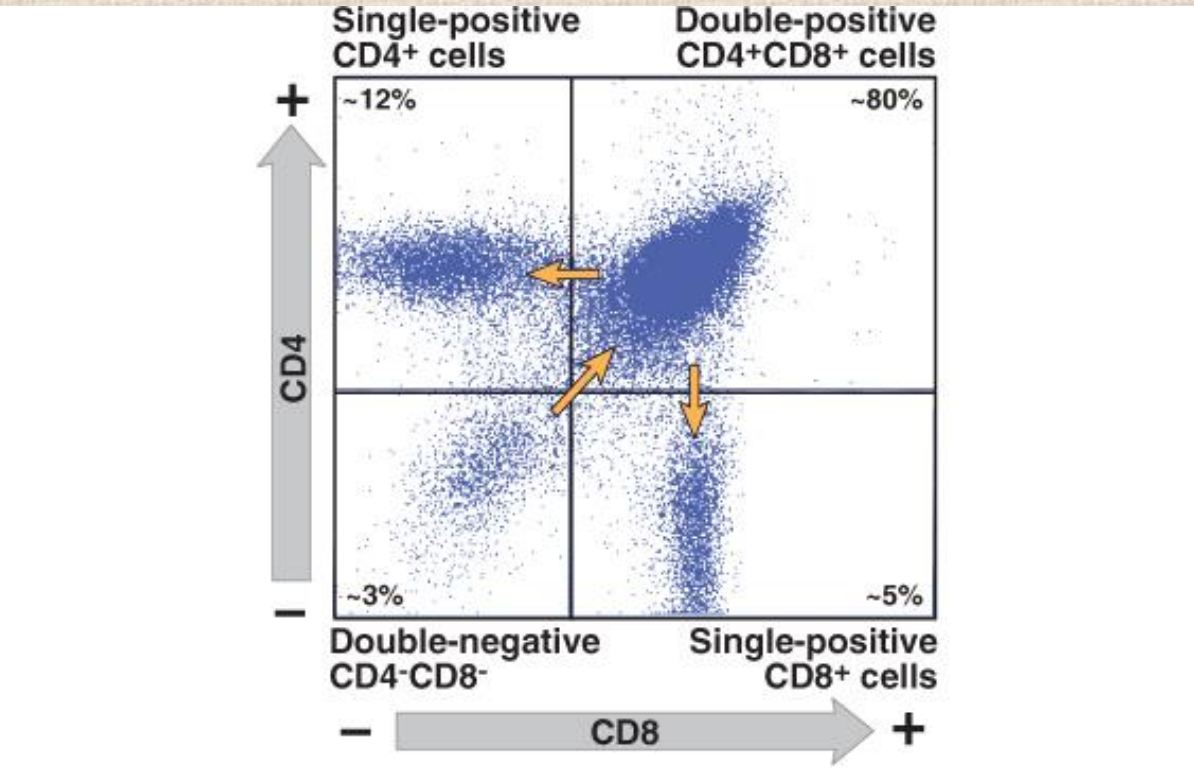
CD4 SP: 10-15%
CD8 SP: 5-8%



Young mouse: 5x10^7 T-cells daily
During selection 98 % of thymocytes die by apoptosis

Daily 1-2 x 10^6 mature T-cell migrate to the periphery

Thymocyte populations based on their cell surface markers



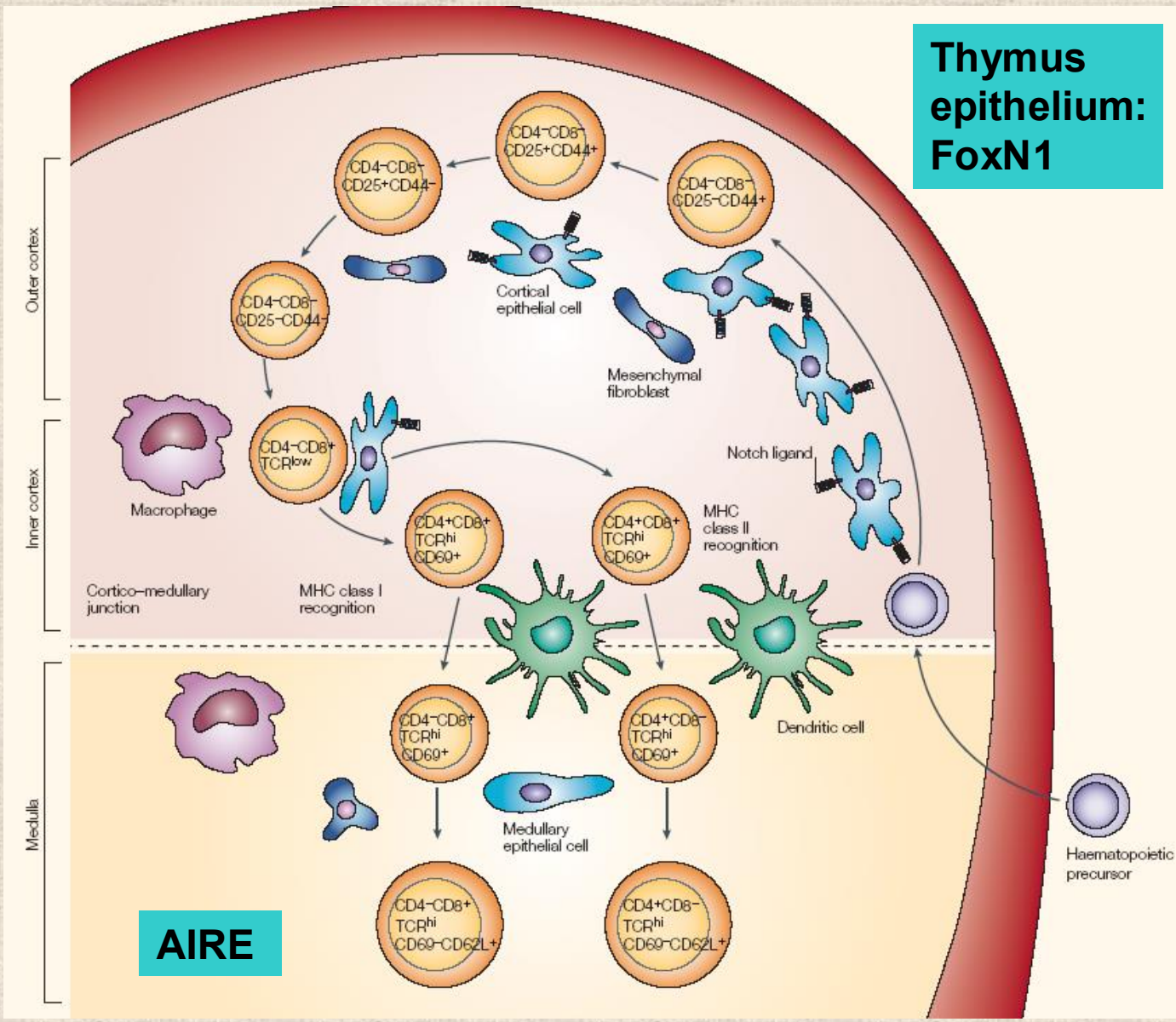
Thymic Microenvironment and T-cell Development

1. **Migration**:
   Chemokines

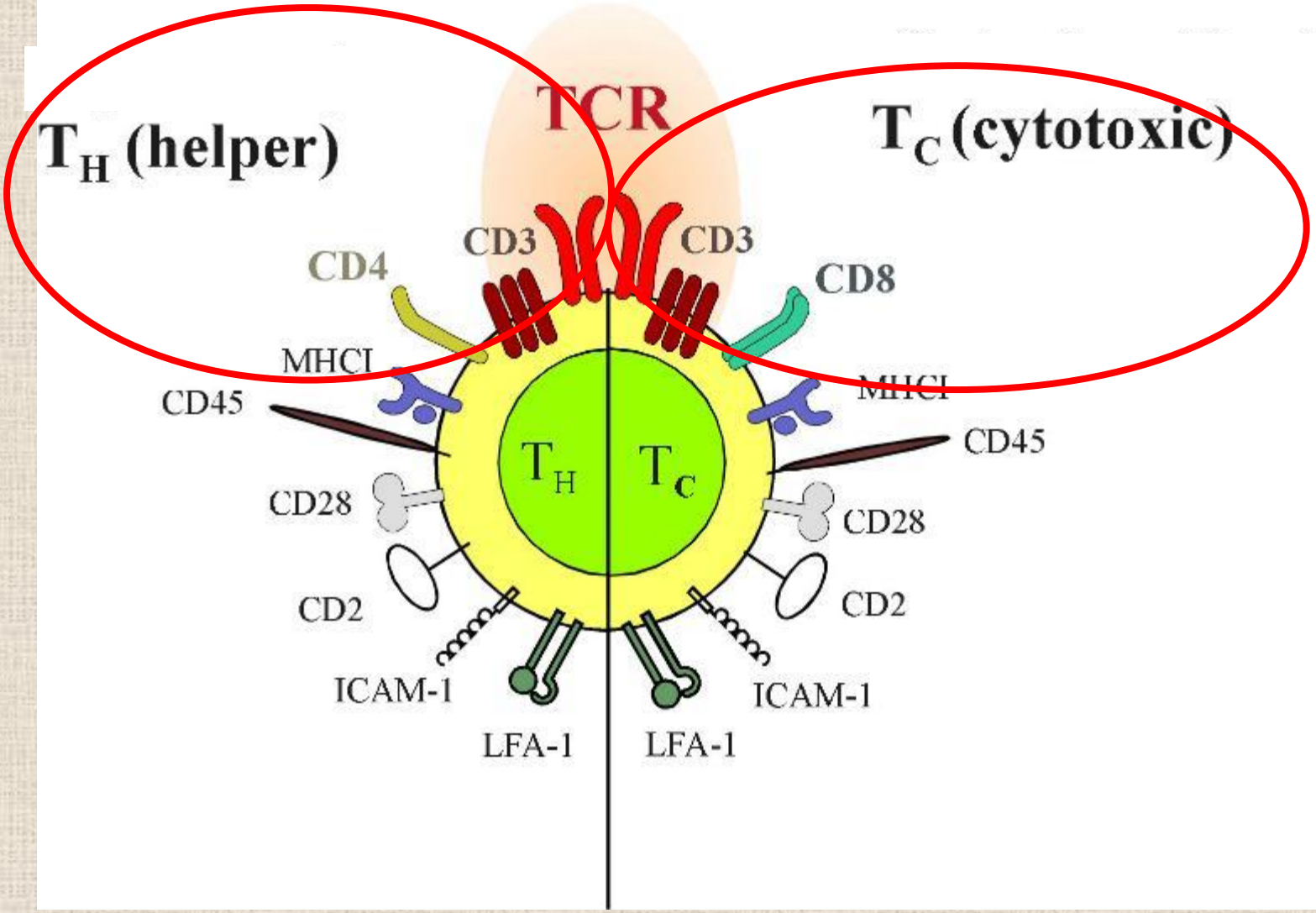
2. **Proliferation**
   IL-7

3. **Differentiation**
   - TcR-rearragement
   - Phenotypes

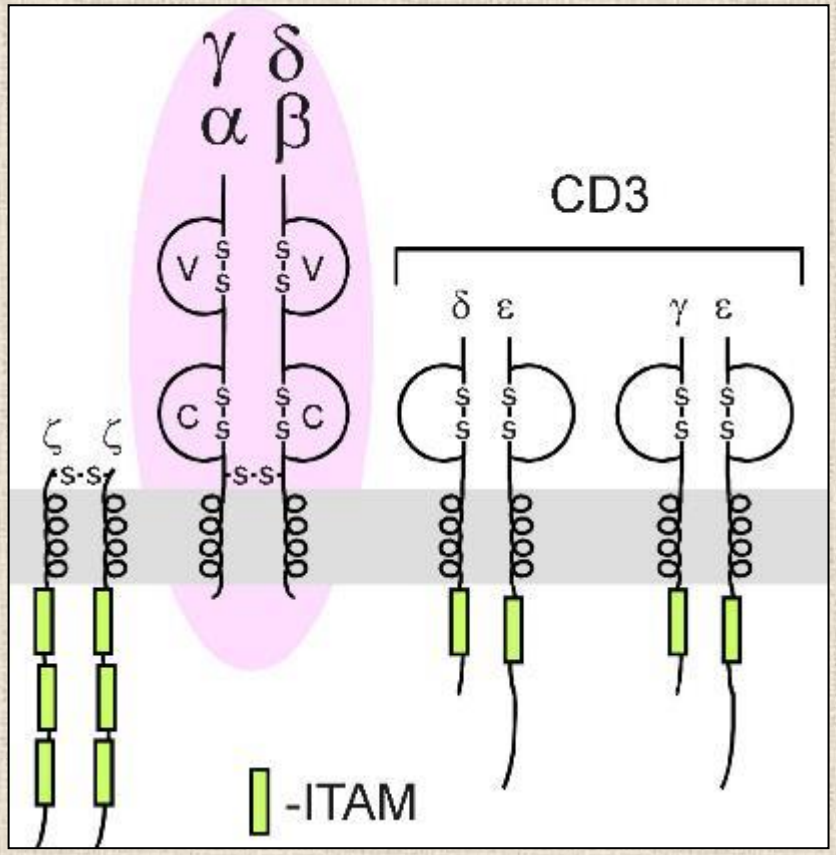
4. **Selection**
   Apoptosis



αβT lymphocytes



T cell receptor complex on mature T cells



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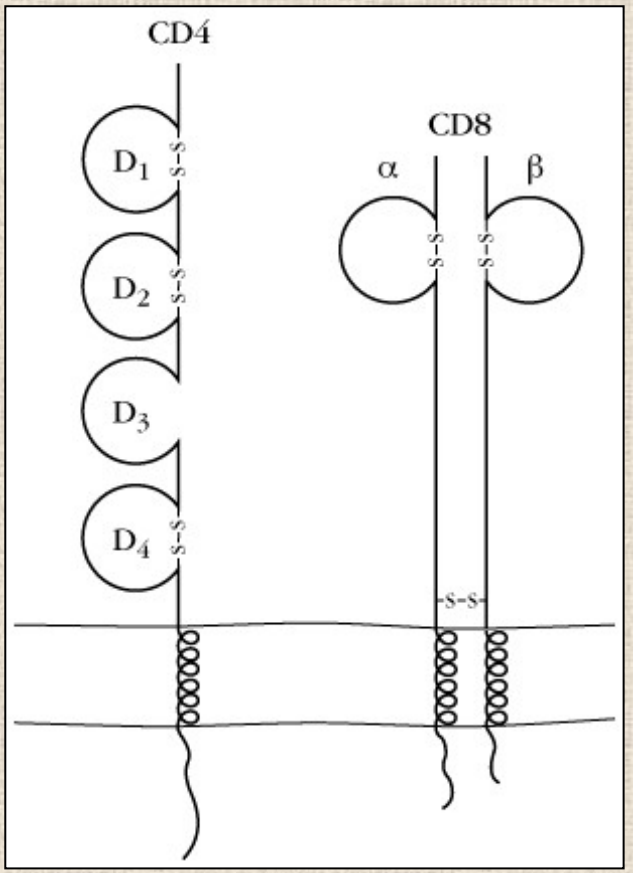
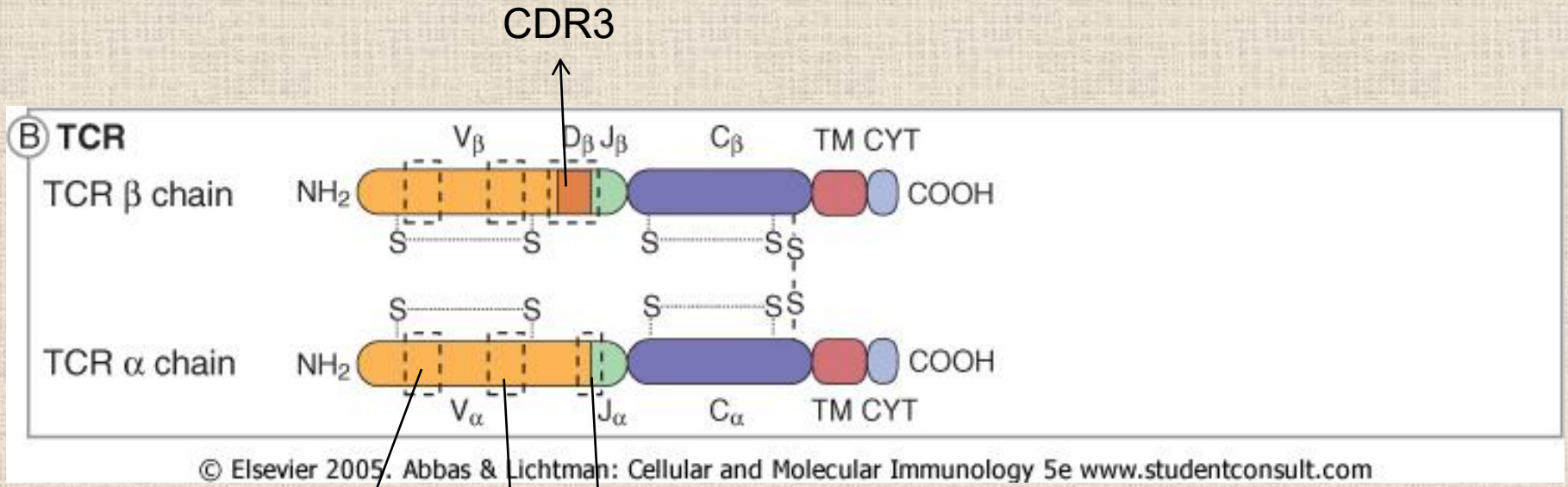


αβ TcR – SP(CD4+ or CD8+)

γδ TcR – DN (CD4-CD8-)

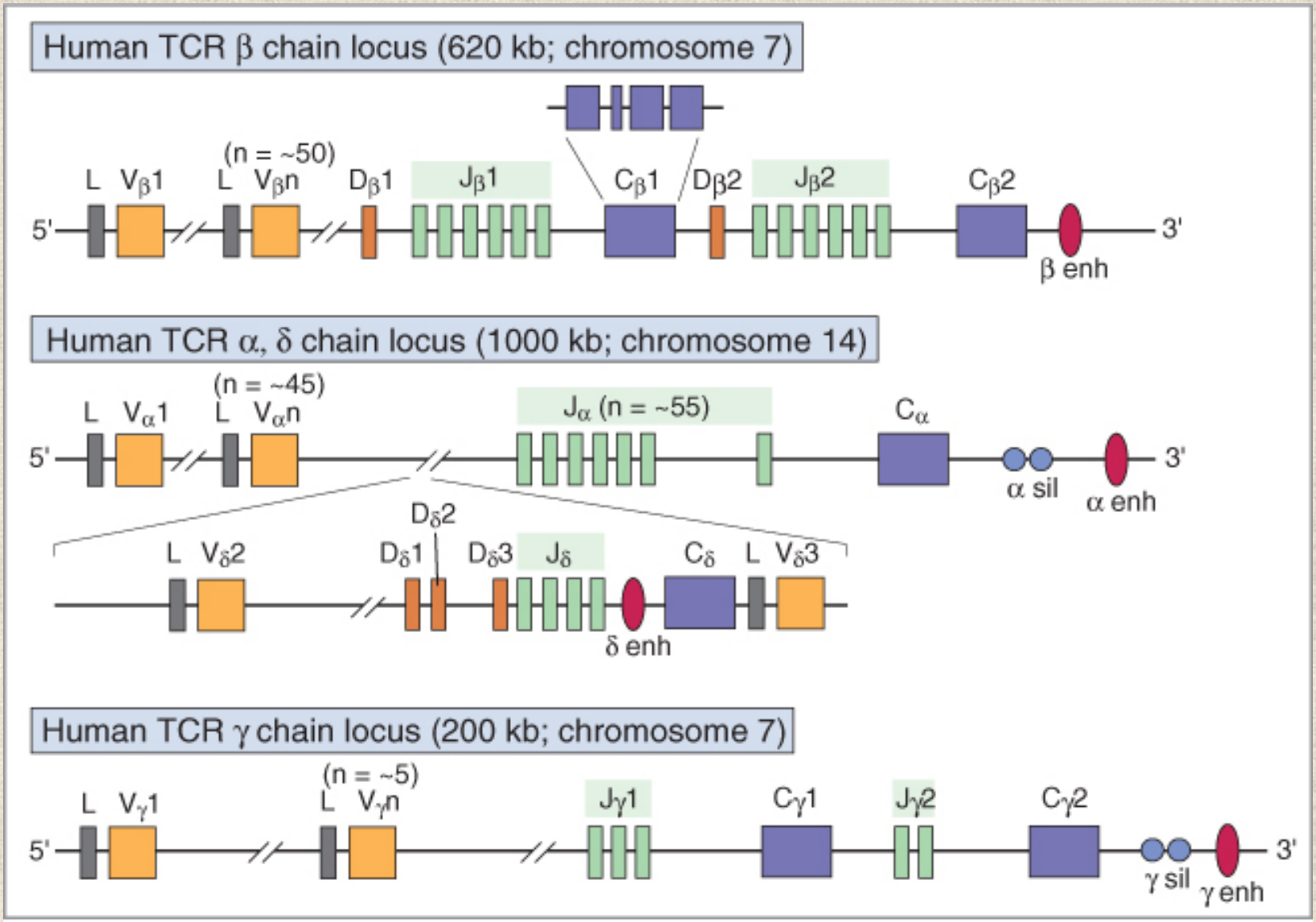
TCR protein chains and their CDR regions

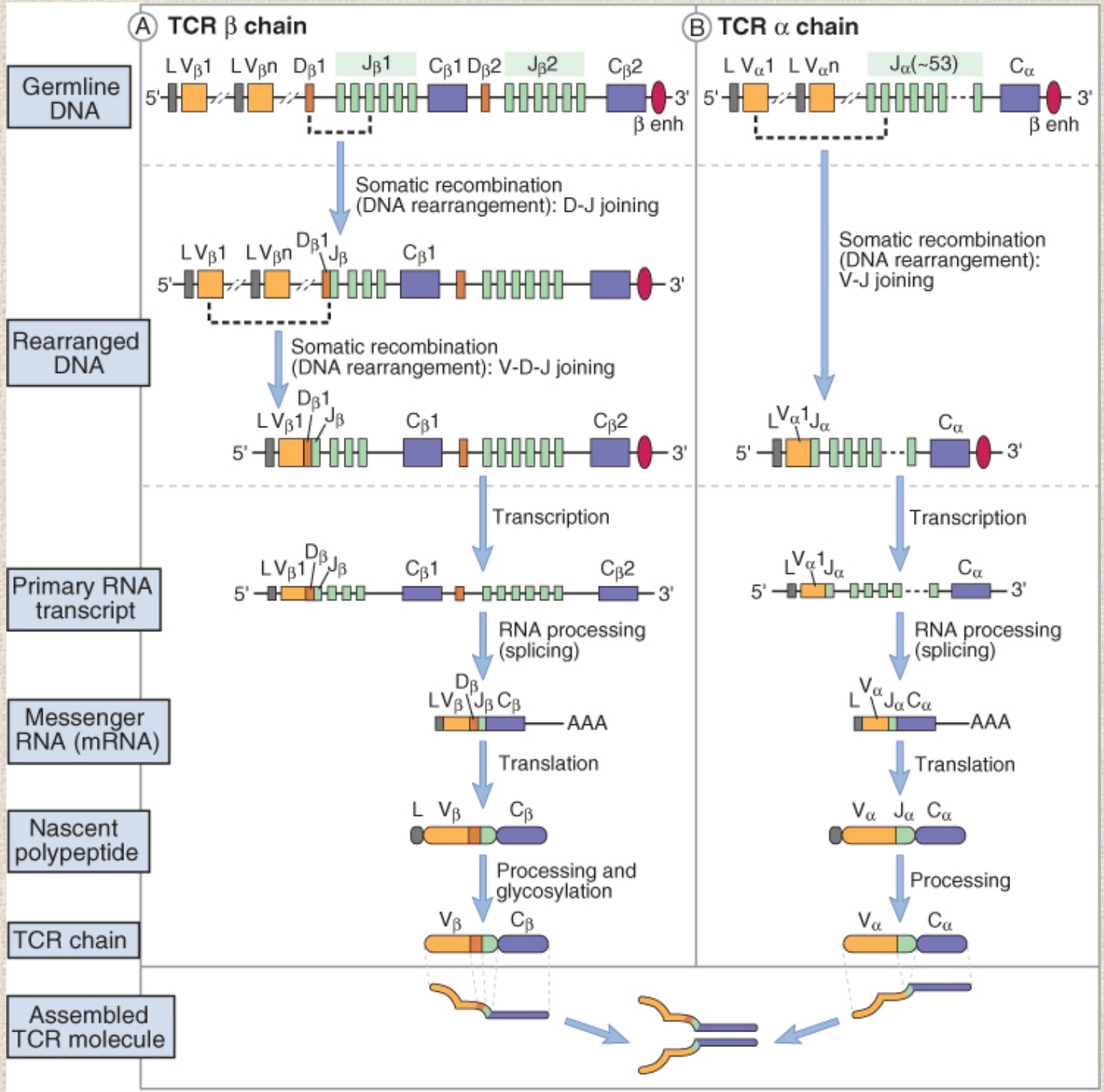


TcRα
TcRγ ⟶ V-J rekombináció

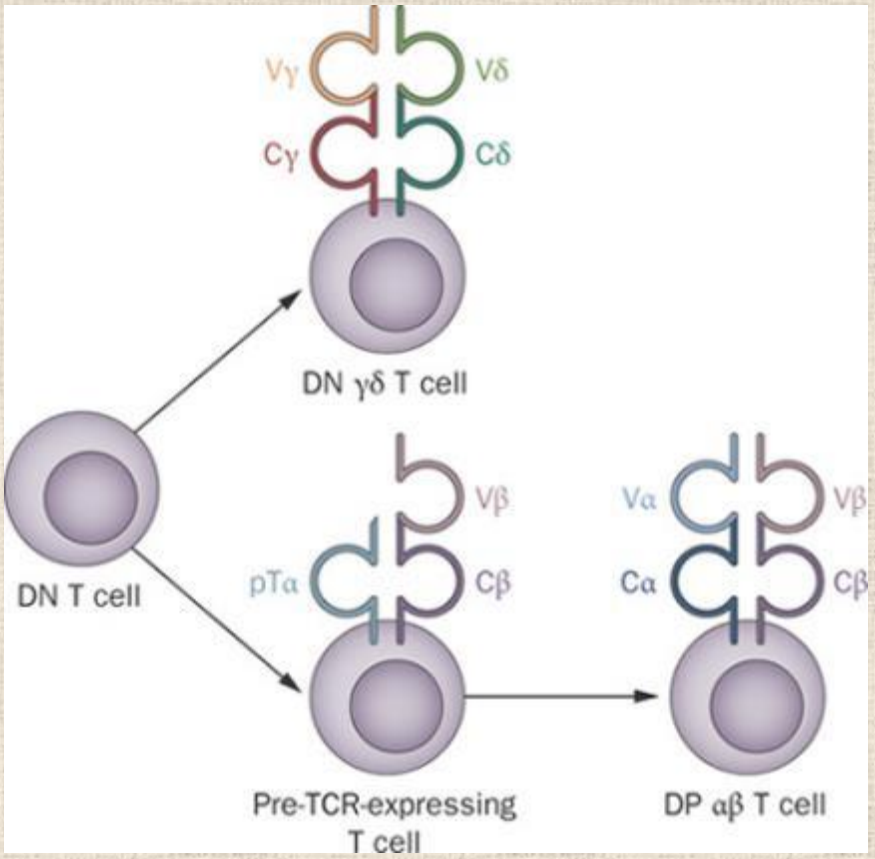
TcRβ
TcRδ ⟶ V-D-J rekombináció

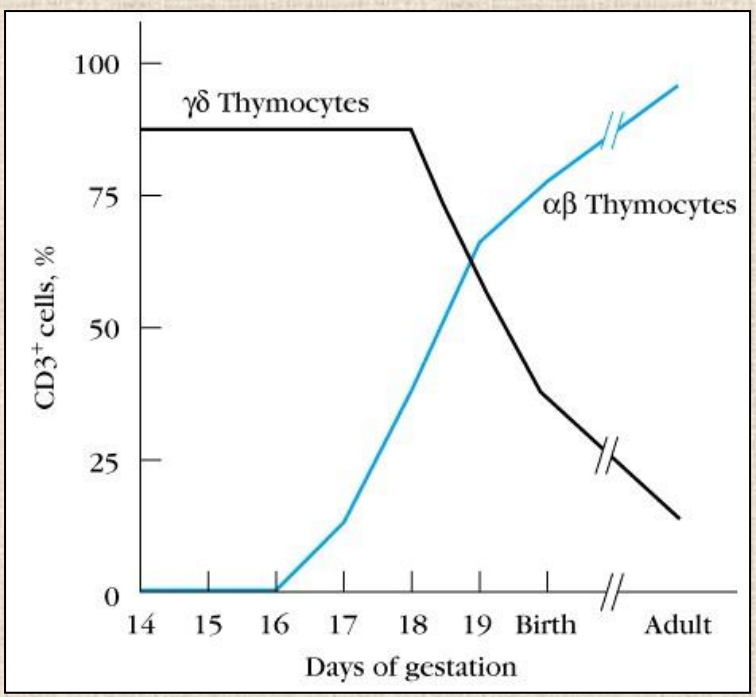
TCR β, α, δ γ loci





γδ -and αβT cell maturation





Tripodo, C. *et al.* (2009) Gamma-delta T-cell lymphomas
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2009.169

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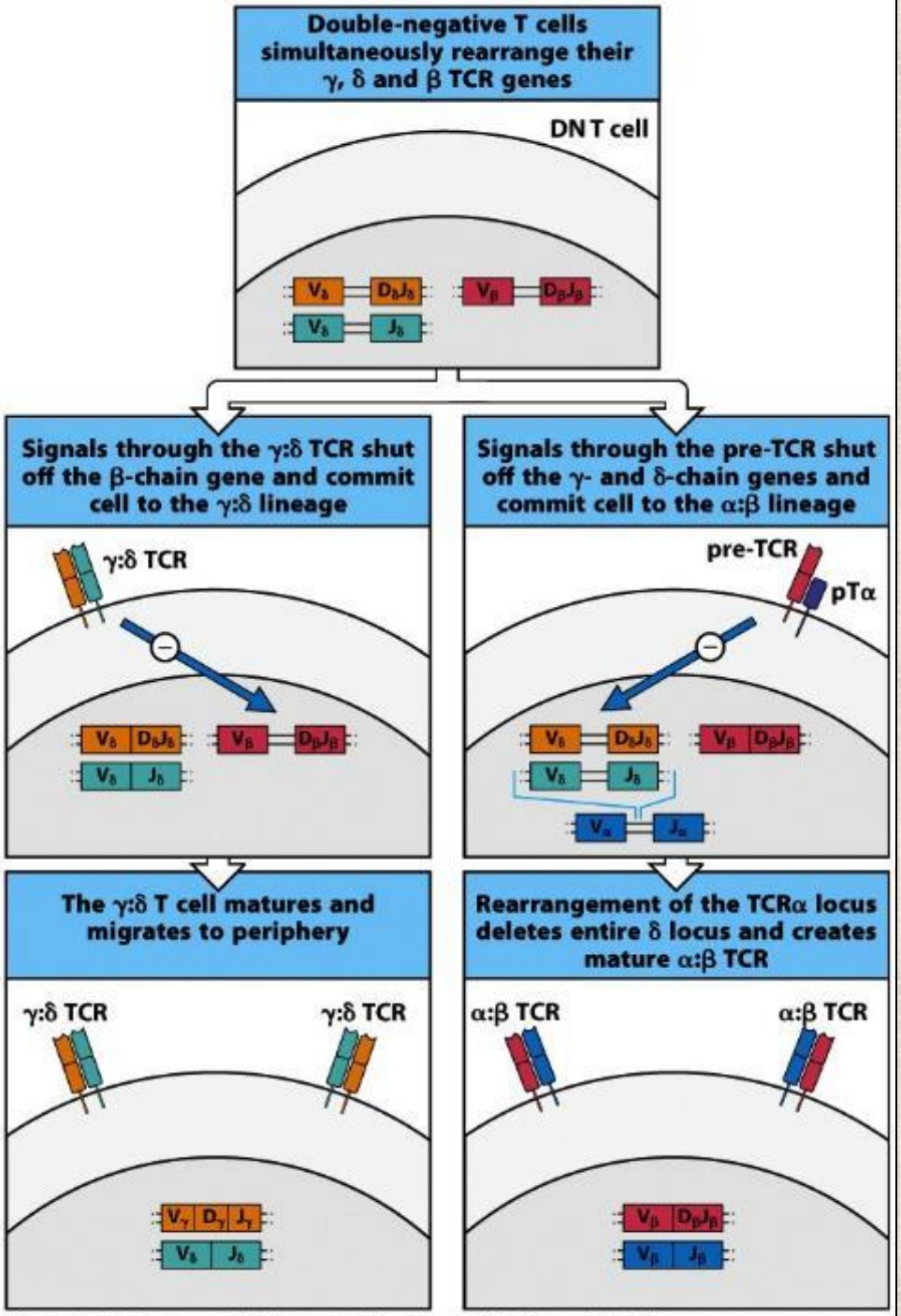
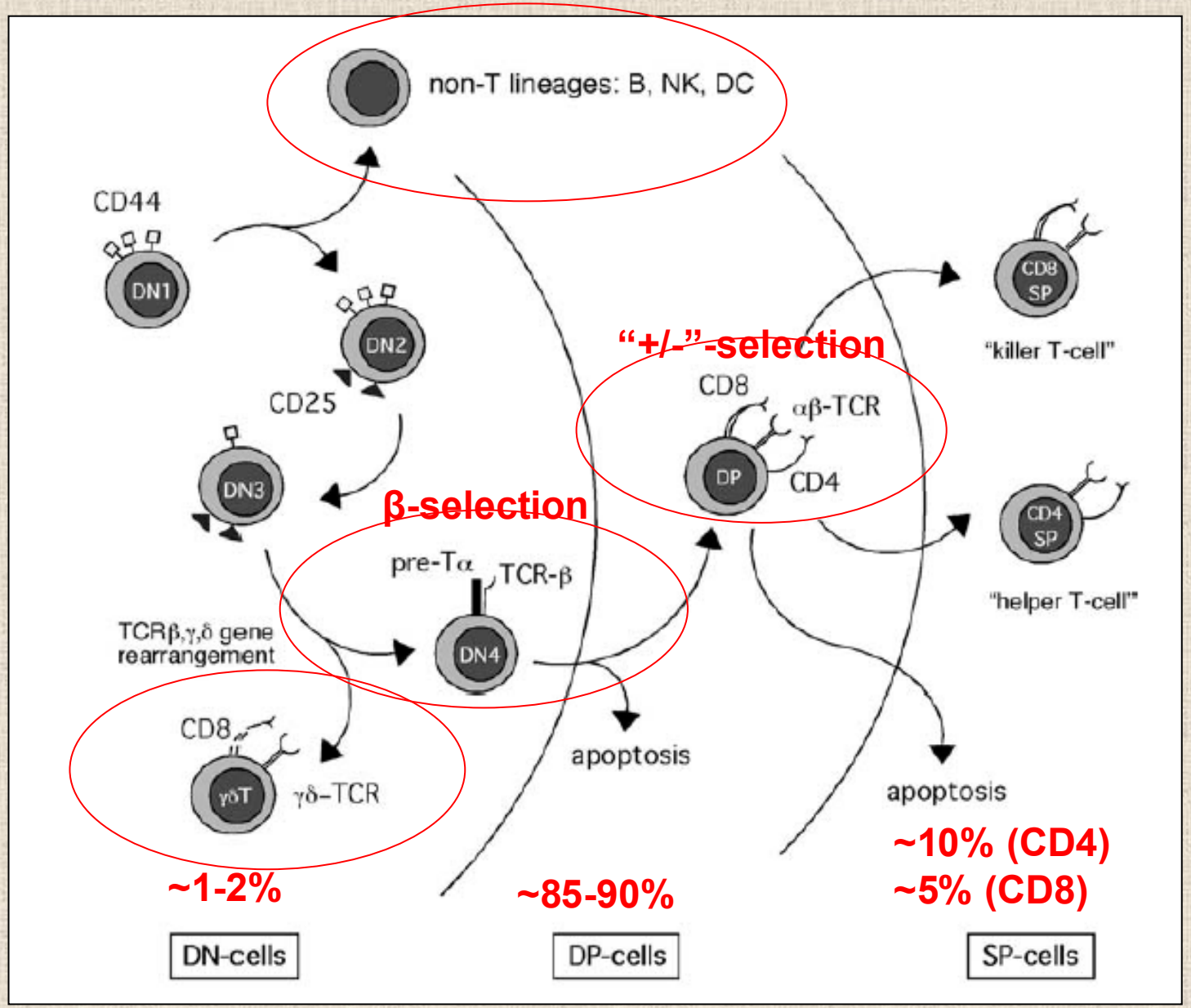
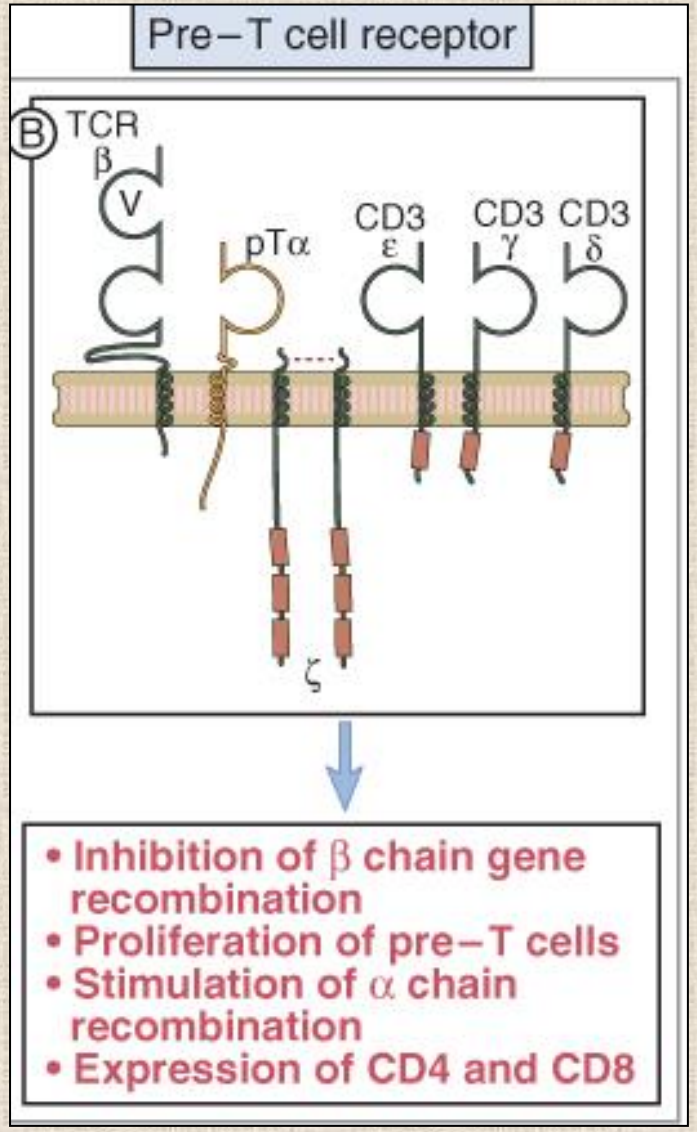


Figure 7-22 Immunobiology, 7ed. (© Garland Science 2008)

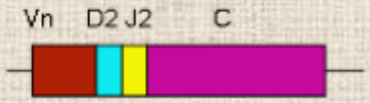
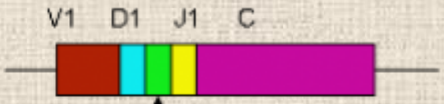
Decision-making during the development of T cells



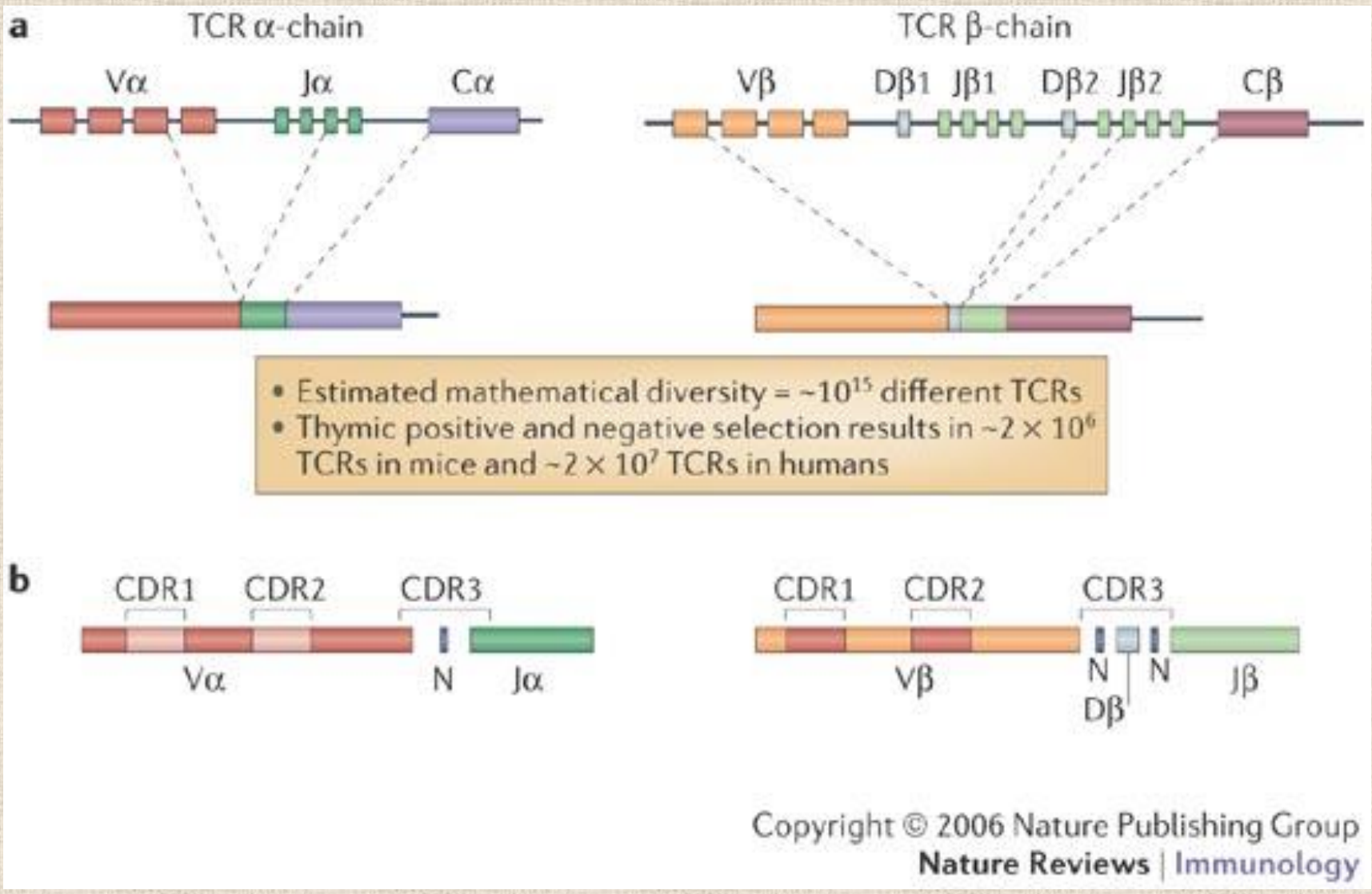
Structure and role of preTCR



V-D-J combinatorial and junctional diversity of TCR

	α	β
Number of V Gene Segments	45	50
Number of diversity (D) gene segments	0	2
Number of joining (J) gene segments	~50	12
Combinational Diversity Number of Possible V-(D)-J Combinations	 TCR: ~3 x 10^6	
Junctional Diversity Total potential repertoire with junctional diversity	 Addition of Nucleotides TCR: ~10^{16}	

TCR diversity



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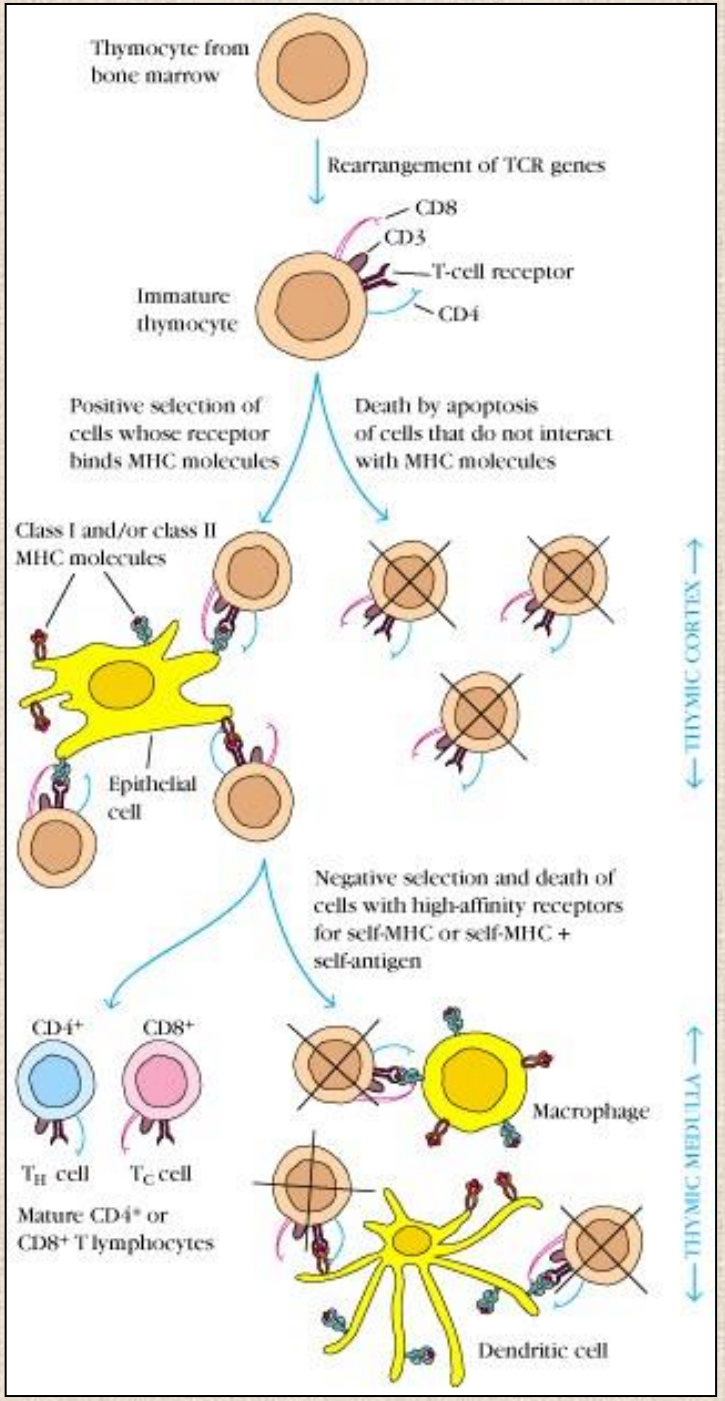


Positive selection:

Epithelial cell - thymocyte interaction in the thymus cortex

Survival of DP cells whose TcR is appropriate for self MHC recognition

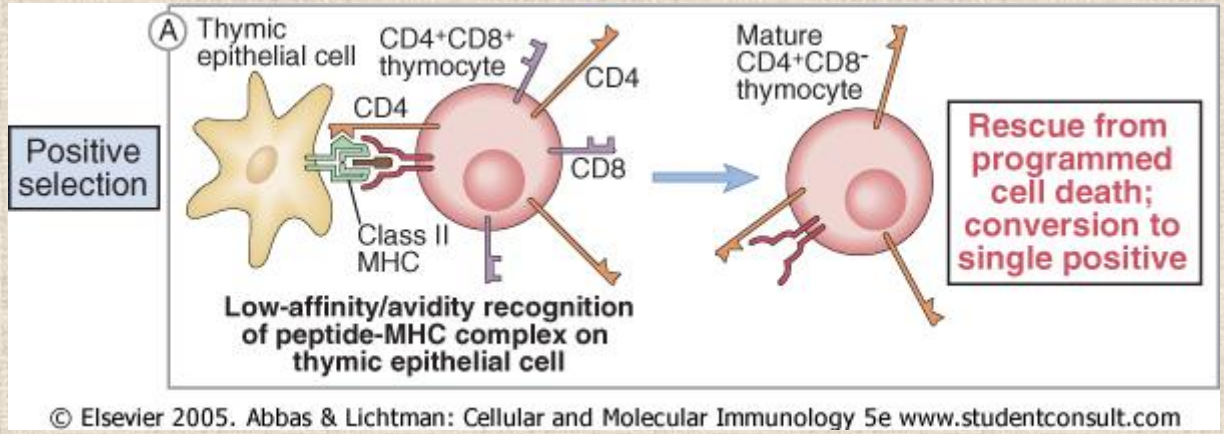
Negative selection:

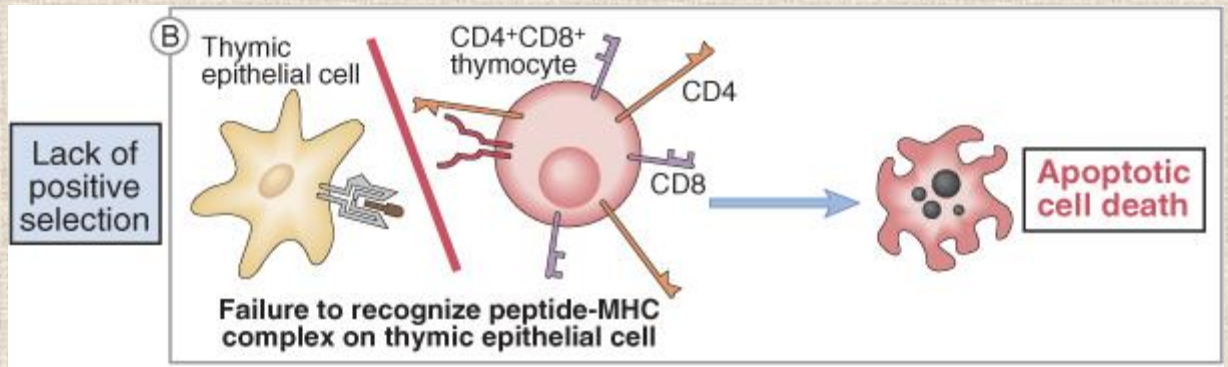
APC (macropahge or DC) – thymocyte Interaction in thymus medulla

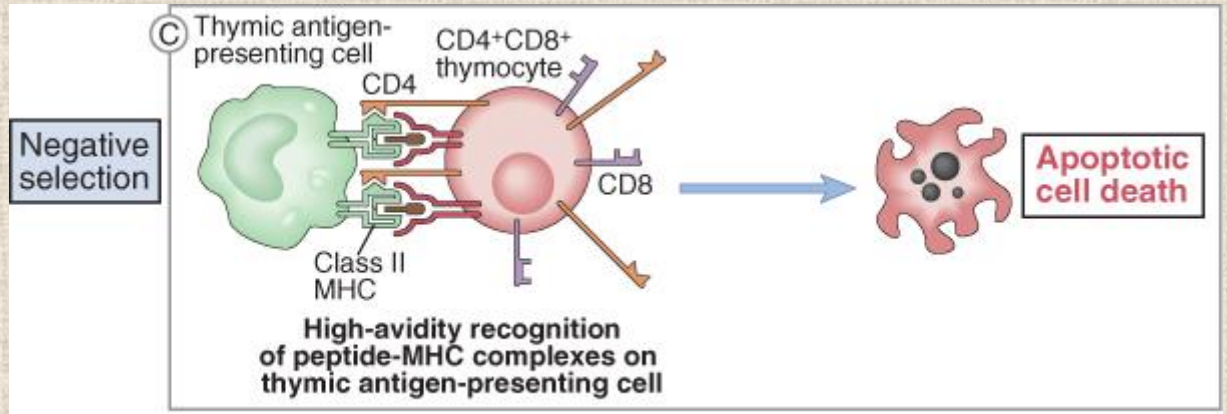
Death of DP cells with high affinity TcR for self MHC + self peptide recognition

Differentiation into SP stage

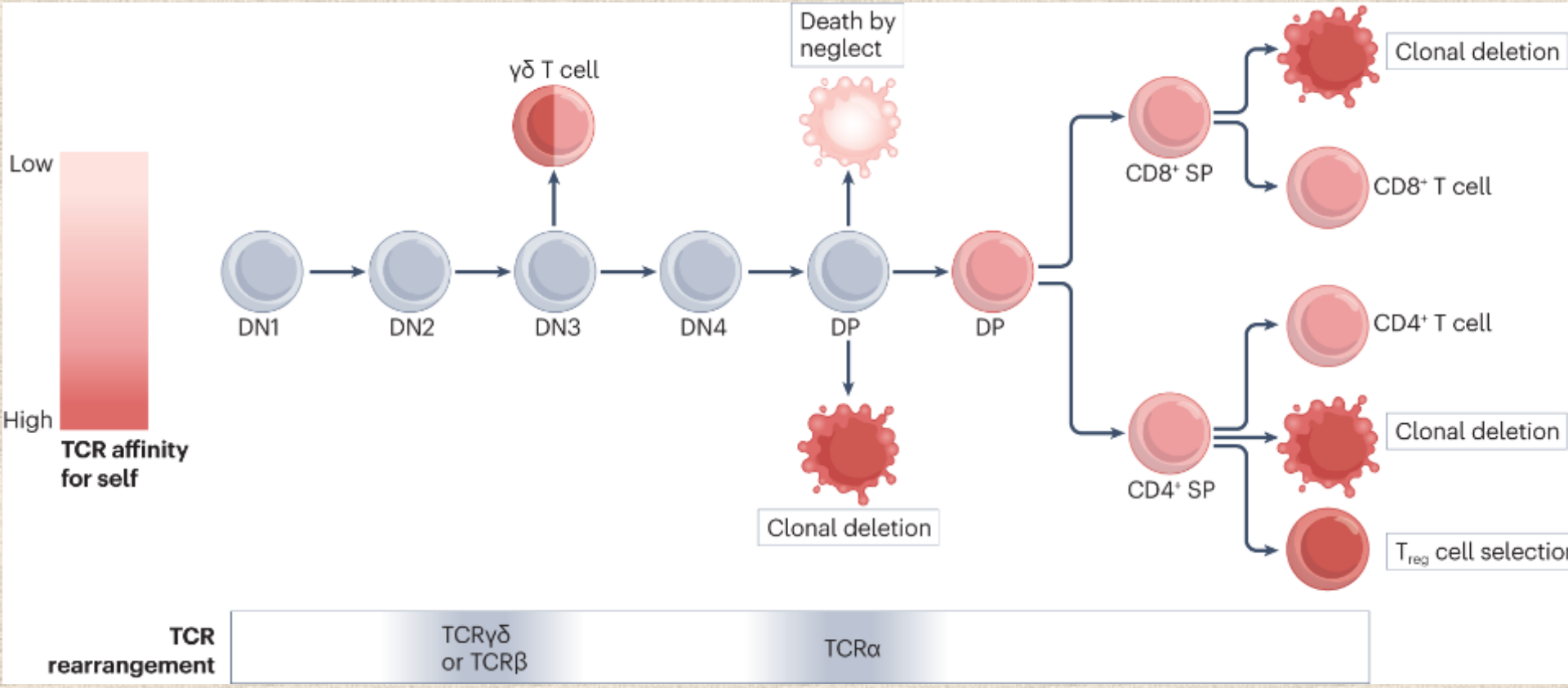
AIRE



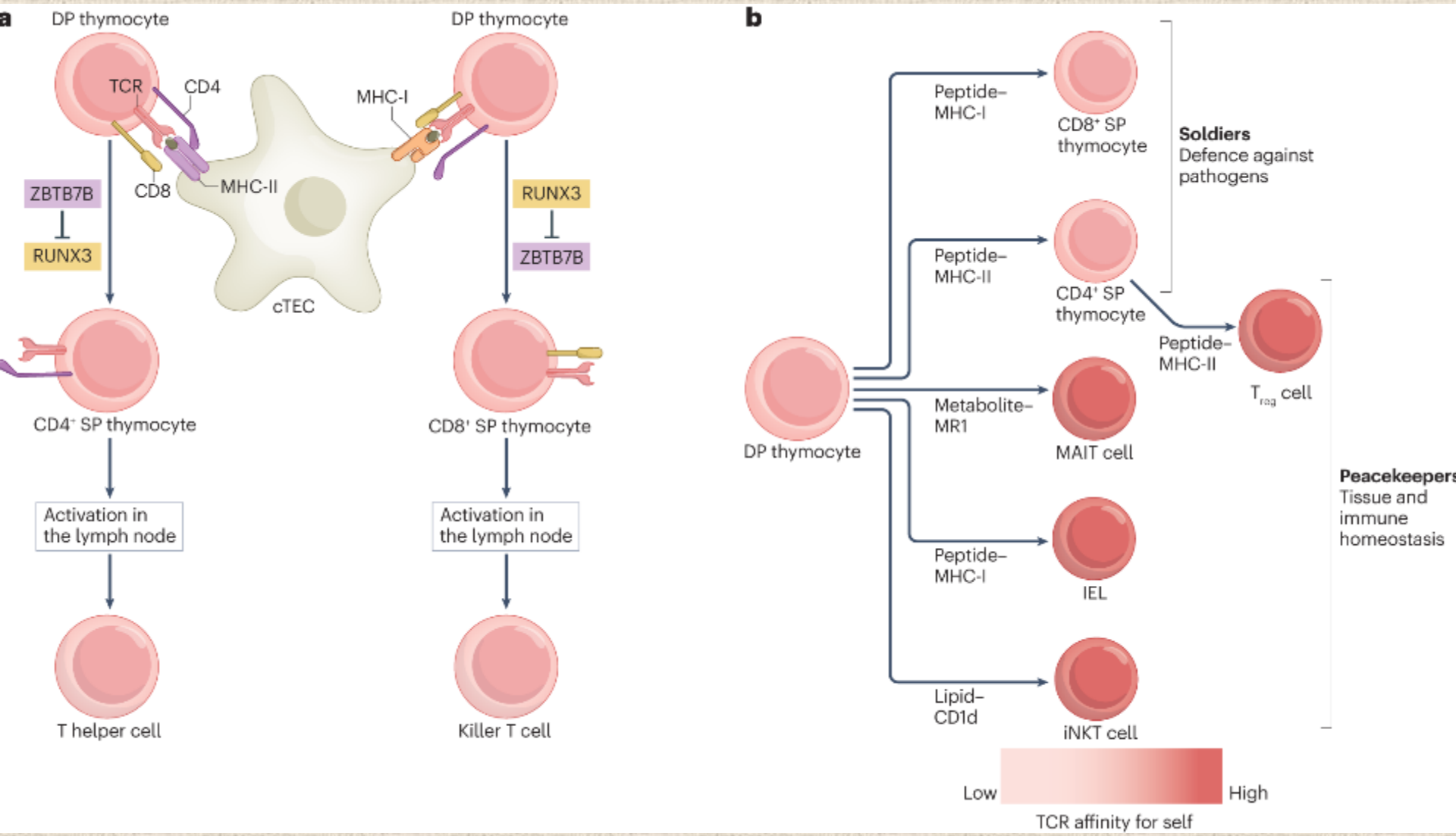




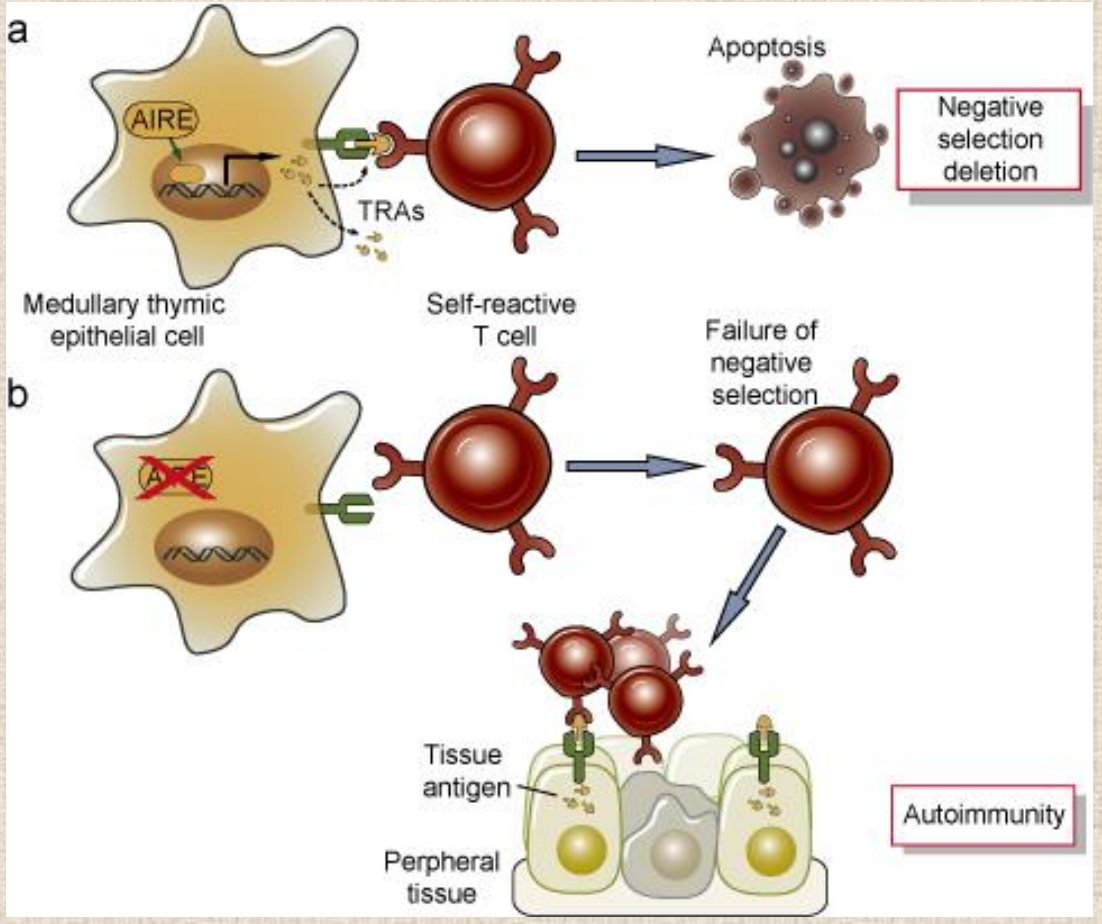
The thymus selects for self-reactive T cells



MHC recognition determines T cell lineage and function.



Role of mTEC in negative selection

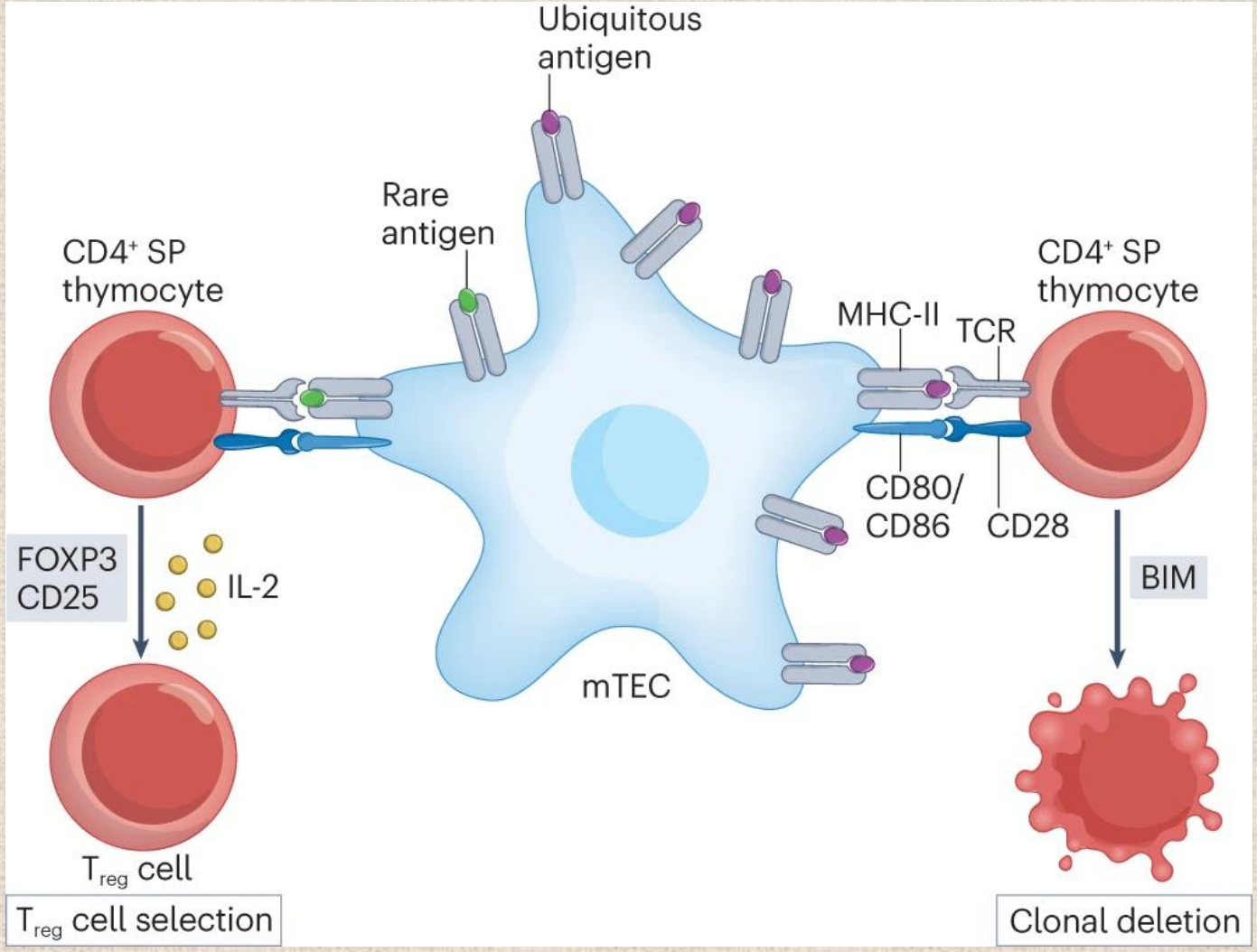


mTEC = medullary thymic epithelial cell
AIRE = autoimmune regulator transcription factor
TRA = tissue related antigens

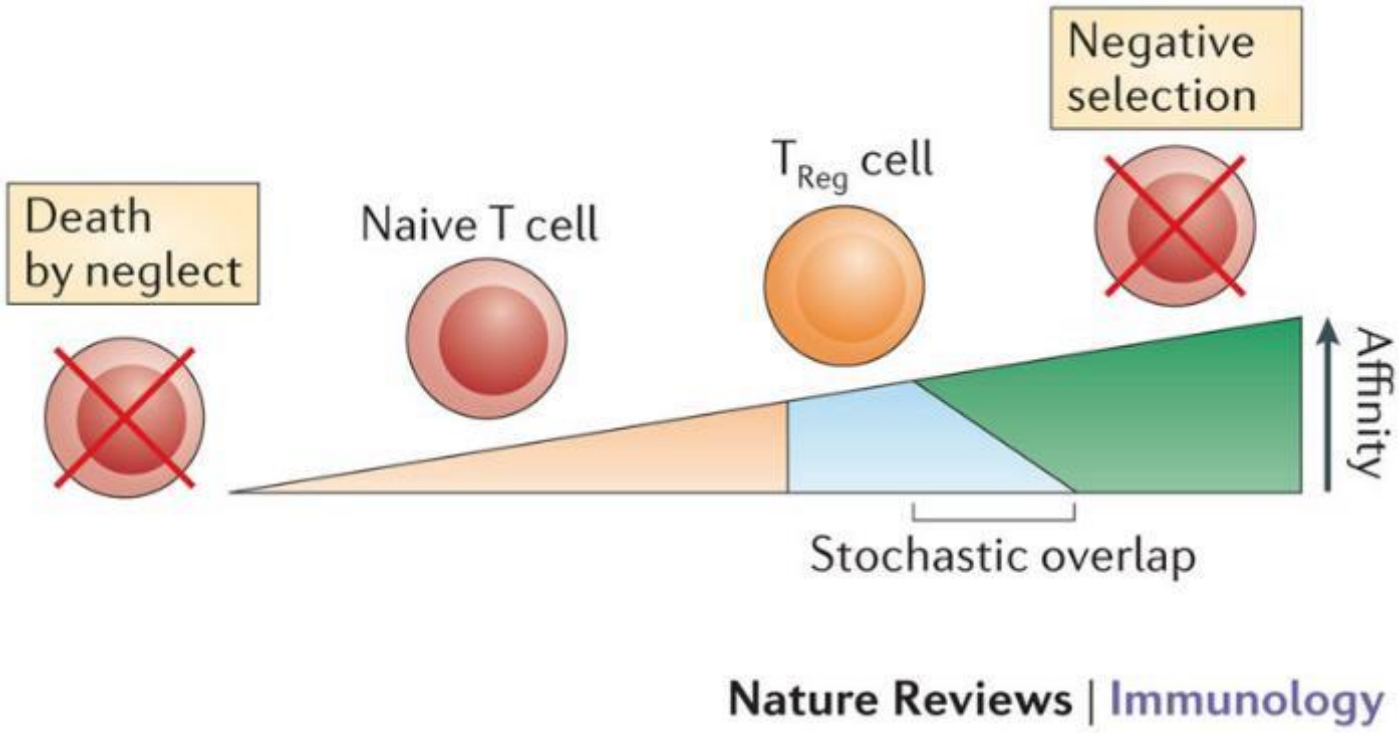
AIRE: autoimmune regulator

- AIRE is a transcription factor expressed in the medulla (inner part) of the thymus and controls a mechanism that prevents the immune system from attacking the body.
- In the thymus, the AIRE causes transcription of a wide selection of organ-specific genes. These self antigen reactive T cells that bind strongly to self-antigen are eliminated in the thymus in the negative selection.
- The AIRE gene is mutated in the rare autoimmune syndrome Autoimmune Polyendocrinopathy Syndrome type 1 (APS-1), also known as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED). Disruption of *AIRE* results in the development of a range of autoimmune diseases,

Clonal deletion and regulatory T cell selection are the major thymic tolerance mechanisms.



Affinity model of T cell selection

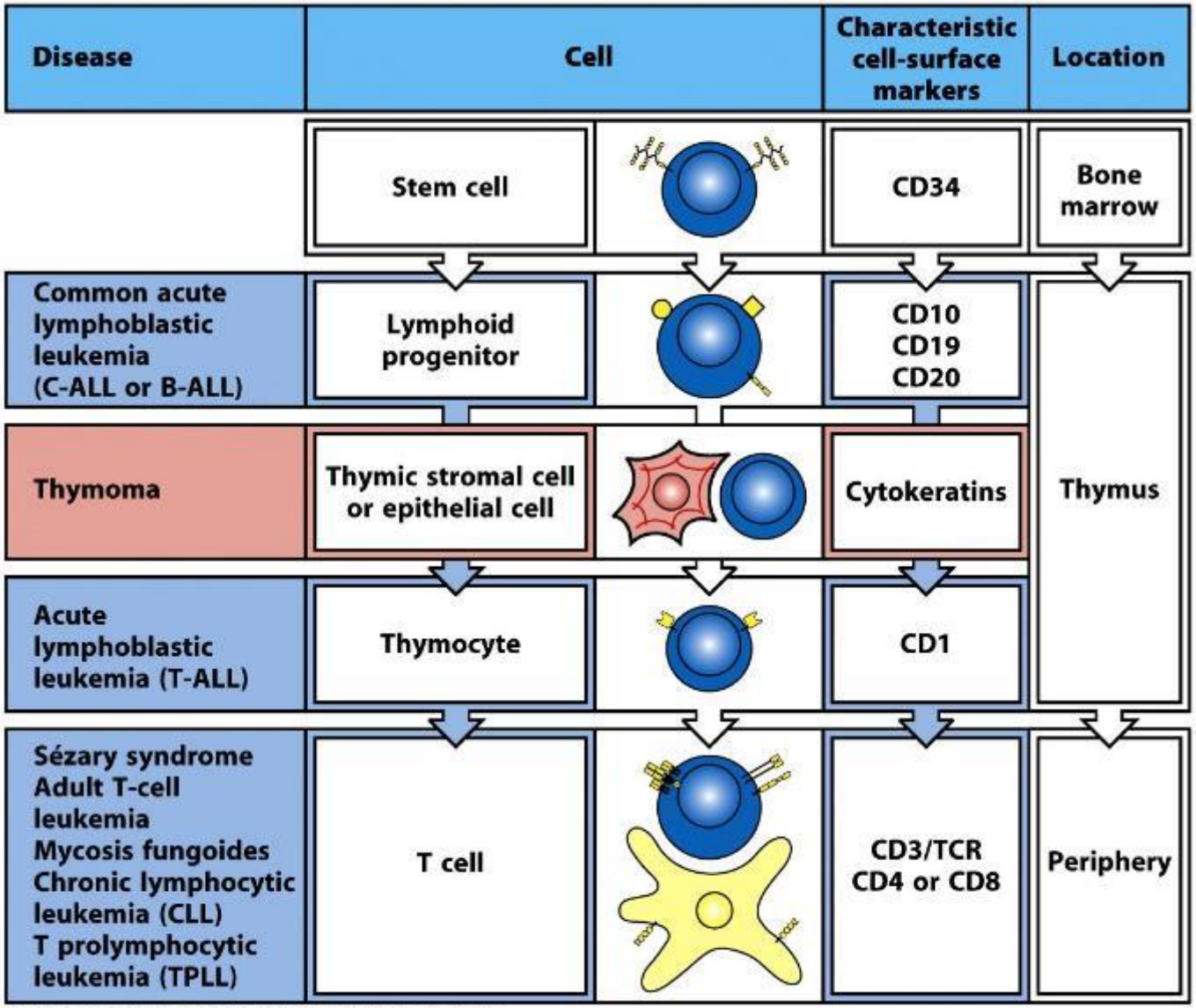


The affinity model of thymocyte selection centres on the strength of the interaction of the T cell receptor (TCR) with self-peptide–MHC complexes as a crucial determinant of cell fate. Weak interactions are required to protect thymocytes from death by neglect and to promote the positive selection of naive T cells. Strong interactions cause negative selection by apoptosis

Phases of T-cell maturation in the thymus.

1. Initiation of either TCR β or γ/δ chain gene rearrangement.
2. Formation of pTα/TCRβ/CD3 (pTCR), allelic exclusion, IL-7-dependent proliferation - *β-selection.*
3. Initiation of TCRα gene rearrangement.
4. Completion of TCR α/β gene rearrangement, co-expression of CD4/CD8 molecules.
5. Recognition of MHC/peptide complexes displayed by thymic cortical epithelium – *positive selection*.
6. Binding to MHC/peptide complex displayed by thymic APC/medullary epithelial cells – *negative selection.*
7. Influence of stronger/more persistent signal: commitment towards CD4 or Treg (CD4/CD25+) subset.

Malignant haematopoietic diseases originated from immature cells of lymphoid cell lineage



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