Ontogenesis of T lymphocytes

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Early Thymocyte Development

- Lymphoid precursors migrate into thymus from bone marrow
- Directed to thymus via chemokine receptors
- T-cell precursors first travel to outer cortex, proliferate, pass through thymic medulla, then exit at cortico-medullary junction
- In thymus, they proliferate, differentiate & undergo selection processes that result in development of mature T cells
- Thymic microenvironment provides membrane-bound & soluble signals that regulate T-cell maturation
- Stages of maturation defined by changes in their cell surface phenotype

- **Double-negative** (DN) cells lack detectable CD4 &CD8
- 4 subsets, based on presence or absence of other cell surface molecules

	Genotype	Location	Description
DN1	c-kit $(CD117)^{++}$, $CD44^{+}$, $CD25^{-}$	BM to thymus	Migration to thymus
DN2	c-kit^{++}, $CD44^{+}$, $CD25^{+}$	Subcapsular cortex	TCR γ, δ & β chain rearrangement T-cell lineage commitment
DN3	c-kit^{+}, $CD44^{-}$, $CD25^{-}$	Subscapular cortex	Expression of pre-TCR; β-selection
DN4	c-$kit^{low/-}$, $CD44^{+}$, $CD25^{-}$	Subcapsular cortex to cortex	Proliferation Allelic exclusion of β-chain locus α-chain locus rearrangement begins Becomes DP thymocyte

c-kit – receptor for stem cell growth factor
CD44 – adhesion molecule
CD25 – α-chain of IL-2 receptor

Early Thymocyte Development

- 2 broad categories of T-cells
  - Those that express TCR α & β receptor chains – TCRαβ cells
    - Dominant cells in adaptive immune response in secondary lymphoid organs
  - Those that express TCR γ & δ receptor chains - TCRγδ cells
    - Important role in protecting mucosal tissues from outside infection
- Choice to become a γδ or αβ cell is dictated by when and how fast the genes that code for each of the receptor chains successfully rearrange

Early Thymocyte Development – β-Selection

- Expression of **pre-Tα chain** – surrogate for the real TCRα chain that has not yet rearranged
- Pre-Tα chain complexes with the rearranged & translated β-chain & CD3 complex proteins to form the **pre-TCR**

Early Thymocyte Development – β-Selection

- The pre-TCR initiates a signal transduction pathway that leads to:
  - Maturation to the DN4 stage
  - Rapid proliferation in subcapsular cortex
  - Suppression of further rearrangement of TCRβ-chain genes, resulting in allelic exclusion of the β-chain locus
  - Development to the CD4+CD8+ **double-positive** (DP) stage
  - Cessation of proliferation
  - Initiation of TCRα-chain rearrangement

Early Thymocyte Development – β-Selection

- Clones of cells with the same TCRβ-chain rearrangement can rearrange a different α-chain gene
- Resulting in a diverse population of cells (TCR diversity)
- Most T-cells fully rearrange & express a TCRβ-chain from only one of their two TCR alleles (**allelic exclusion**) – inhibition of further rearrangement of the other TCRβ allele
- Once a young DP thymocytes successfully rearranges & expresses a TCRα-chain, this will associate with the already produced TCRβ-chain, taking the place of the surrogate α-chain

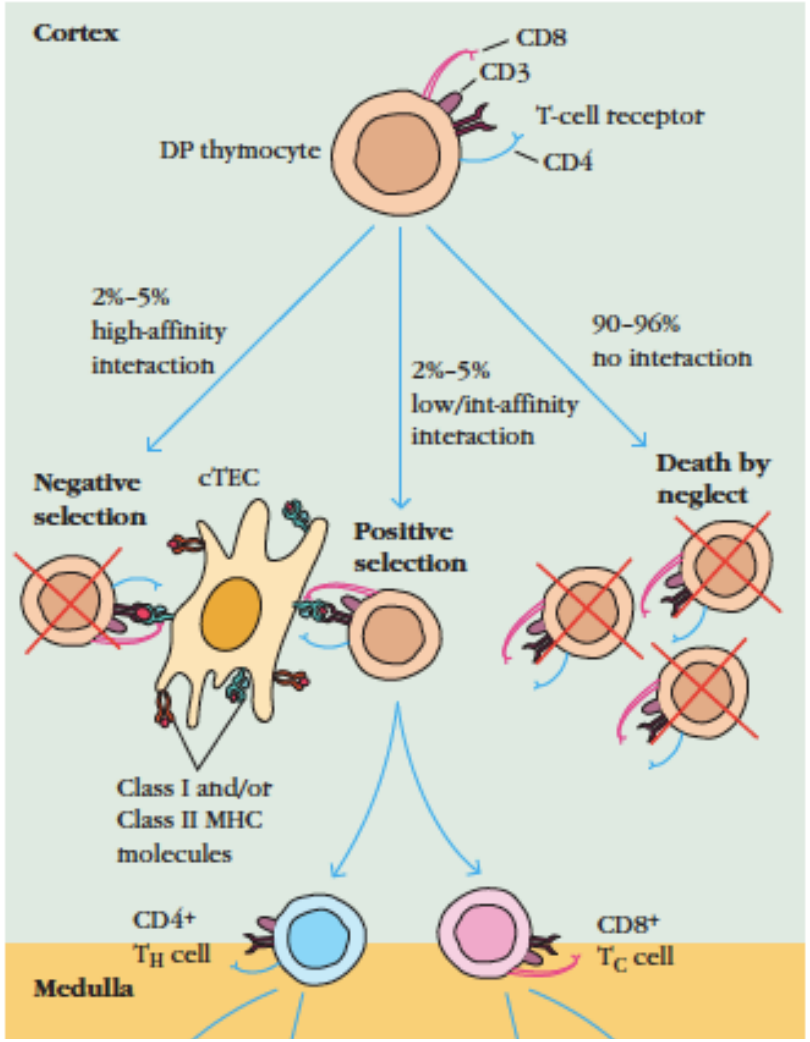
Positive and Negative Selection

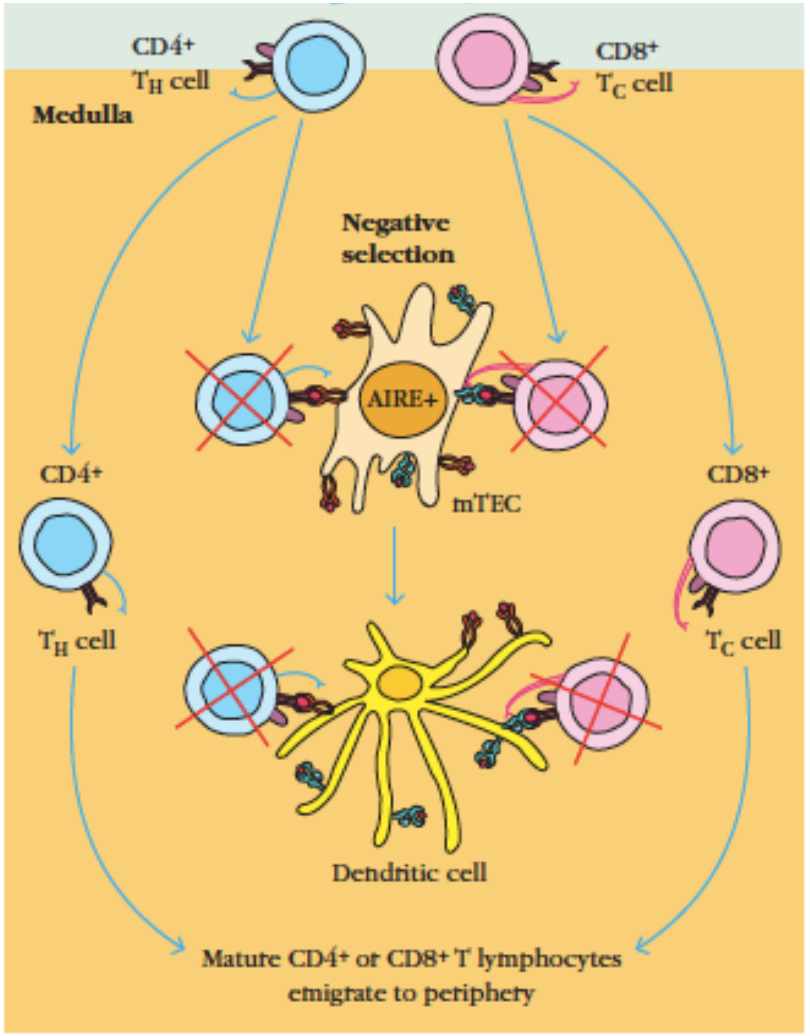
- DP thymocytes expressing a fully mature surface TCRαβ/CD3 complex undergo thymic selection
- Based on affinity of TCR for the MHC/peptides they encounter in the thymic cortex
- Positive selection – selects for thymocytes whose receptors can bind self-MHC from thymic epithelial cells, resulting in **MHC restriction**
- Negative selection – selects against thymocytes bearing high-affinity receptors for self-MHC/peptide complexes; results in **self-tolerance**

Positive and Negative Selection

- T-cells that do not meet the selection criteria (~98%) die by apoptosis
  - Thymocytes that do not bind MHC undergo **death by neglect**
  - Autoreactive thymocytes with high-affinity receptors for self-MHC/self-peptide complexes undergo **clonal deletion**
- Negative selection ensures self-tolerance

Positive and Negative Selection





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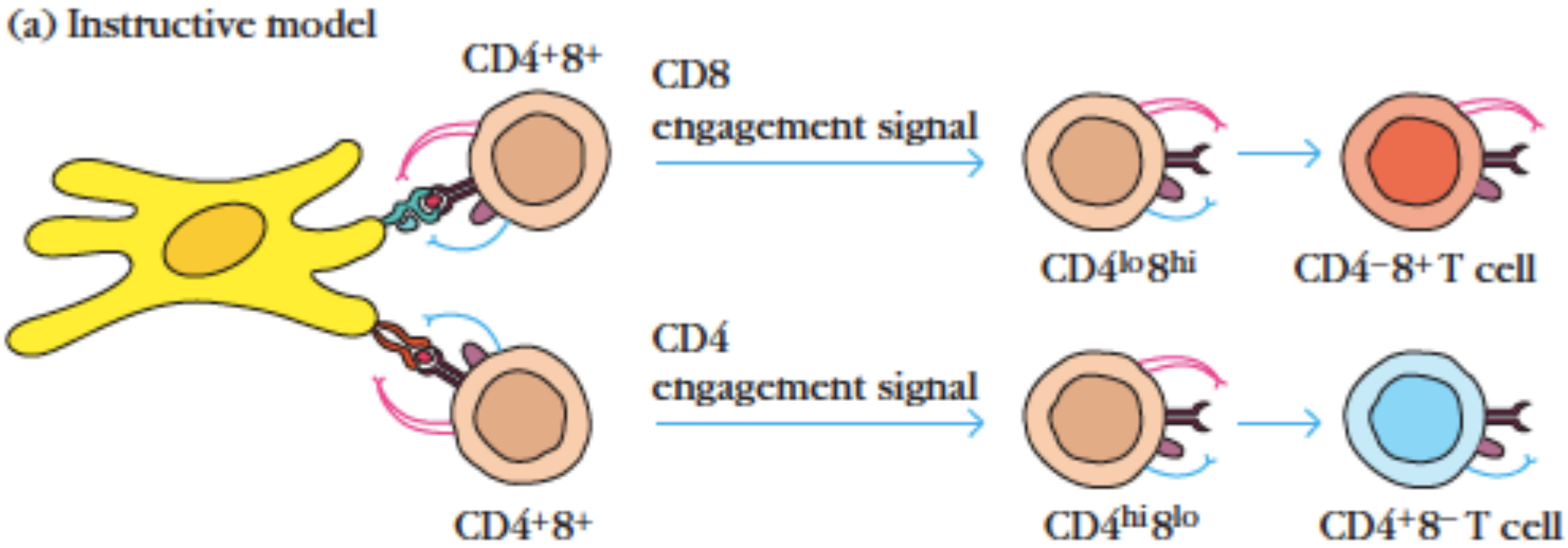
Lineage Commitment

- Changes in gene expression that result in
  - Silencing of one co-receptor gene (CD4 or CD8)
  - Expression of genes associated with a specific lineage function
- Affinity for MHC class I vs MHC II preference dictates the $CD8^+$ vs $CD4^+$ fate of developing thymocytes
- Several proposed models of lineage commitment



Interaction of a co-receptor with the MHC molecule for which it is specific results in down-regulation of the other co-receptor

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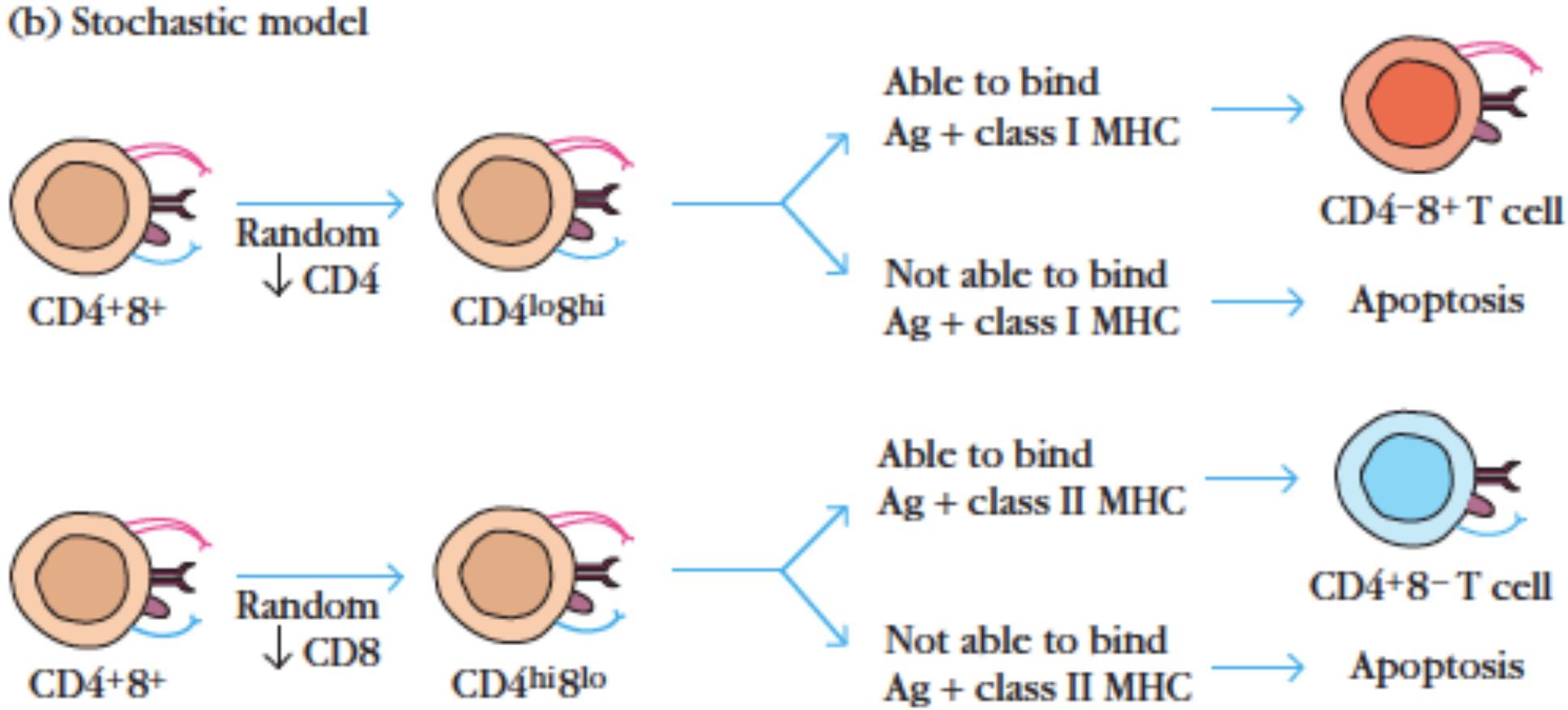

Down-regulation of CD4 or CD8 is a random process

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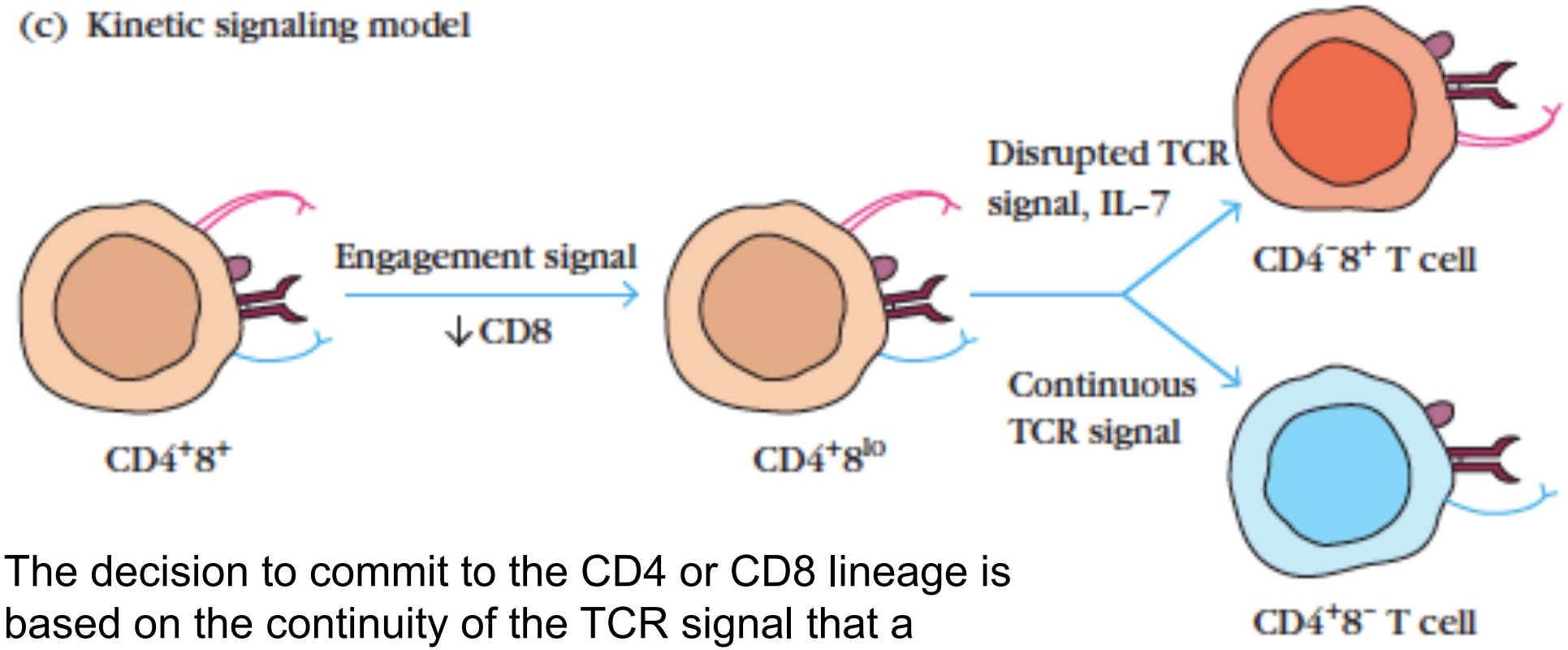

- The decision to commit to the CD4 or CD8 lineage is based on the continuity of the TCR signal that a thymocyte receives.
- Positive selection results in down-regulation of CD8 on all thymocytes. This does not alter the intensity of a TCR/CD4/MHC II signal; cells receiving this signal continue to the CD4 SP lineage.
- However, the TCR/CD8/MHC I signal is interrupted, sending that cell towards CD8 lineage

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Lineage Commitment

- Small populations of DP thymocytes can also commit to other T-cell types
  - NK T-cells
  - Regulatory T-cells (T_{REG})
  - Intraepithelial lymphocyte lineages (IEL)

Exit from Thymus and Final Maturation

- After successful selection & lineage commitment, the thymocytes enter a quiescent stage & leave the thymus