Chapter 7: The Development of T Lymphocytes

The development of T cells in the thymus

- Immature cells are called thymocytes
- The thymus is a primary organ (production of lymphocytes, not its application - activation - during infection)
- Epithelial cells of the thymus form a network surrounding developing thymocytes (thymic stroma)
The proportion of thymus that produces T cells decreases with age

The development of T cells in the thymus

- T cells develop in the thymus (progenitor cells that enter the thymus are not committed to the T-cell lineage)
- Thymocytes do not express CD4 or CD8 (and are called DN (Double Negative))
- Thymocytes commit to the T-cell lineage before rearranging their T-cell receptor genes

DiGeorge’s syndrome results in SCID
Thymectomy in adults does not have a gross impact

Commitment to the T cell lineage involves changes in gene expression and in cell surface markers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Uncommitted progenitor cell</th>
<th>Double-negative thymocytes committed to the T-cell lineage</th>
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<tbody>
<tr>
<td>CD4</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD8</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD25</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IL-7R</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>TCR</td>
<td>antigen receptor</td>
<td>germline</td>
</tr>
</tbody>
</table>

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T-cell development is driven by the receptor Notch 1

Gene rearrangement in double-negative thymocytes leads to assembly of either a $\gamma\delta$ receptor or a pre-T-cell receptor

The two lineages of T cells arise from a common thymocyte progenitor

Thymocytes can make 4 attempts to rearrange a Tcr$\beta$-chain gene (88% success rate)
Comparison of the Pre-T-cell receptor and T-cell receptor

After formation of pre-T cell receptor, RAG genes are temporarily inactivated and pre T cell is induced to proliferate which creates a clone of cells all expressing the same chain.

Rearrangement of the α-chain gene occurs only in pre-T cells

The α-chain locus can sustain many attempts at a functional rearrangement:

- First unproductive rearrangement
- Second unproductive rearrangement
- Third rearrangement is productive
- Transcription of functional α-chain mRNA
- Synthesis of T-cell receptor α-chain

Rearrangement of an α-chain gene always eliminates the linked δ-chain locus

Thymal development of double positive T cells in a nutshell
T cells that recognize self-MHC molecules are positively selected in the thymus

Receptor editing to match MHC

- If first gene rearrangement of Tcr α-chain is productive, subsequent positive selection (MHC) will shut off RAG gene transcription.
- Continuing α-chain gene rearrangement increases the chance for positive selection.
- No allelic exclusion at the α-chain locus, a small proportion of T cells (1 to 2%) has two receptors, of which only one is functional.

Positive selection determines expression of either the CD4 or the CD8 co-receptor

T cells specific for self antigens are removed in the thymus by negative selection

No MHC class I or II expression is called Bare Lymphocyte syndrome.
Positive and negative selection of the T-cell repertoire

• Tissue-specific proteins are expressed in the thymus and participate in negative selection (AIRE=autoimmune regulator).
  Aire deficient patients suffer from autoimmune polyglandular syndrome type I which is a broad spectrum autoimmune disease.

• Negative selection by thymus produces central tolerance.

It takes two to Tango

Positive and negative selection of the T-cell repertoire

• Regulatory CD4 T cells (T_{reg}) comprise a distinct lineage of self reactive T cells.
  -express CD25 (cell surface) and FoxP3 encoded on the x chromosome (transcriptional repressor protein).
  - FoxP3 deficiency results in polyendocrinopathy, enteropathy, X-linked syndrome (IPEX).

• T cells undergo further differentiation in secondary lymphoid tissues after encounter with antigen.
  • The T cell rich areas of secondary lymphoid tissues provide specialized sites where naive T cells are activated by their specific antigens.