Chapter 9

T cell Receptor

Self-MHC restriction of the T cell receptor (TCR)

- **Self restriction**: T cell can only be activated by a unique peptide associated with self-MHC.
- Two models:
  - A) **Dual receptor model**: two receptors, one for the antigen and one for the MHC molecule
  - B) **Altered self model**: One receptor that recognizes both antigen and MHC molecule

The αβ TCR is similar in size and structure to an antibody Fab fragment

- Two chains - α and β
- Two domains per chain
  - constant (C) domain
  - variable (V) domain
- Chains held together by disulfide bonds
- Small cytoplasmic tails on each chain
- Some T cells express a TCR made of two alternate chains - γ and δ
- The γδ TCR is structurally similar to the αβ TCR.
- 0.5-15% of peripheral blood T cells use the γδ TCR. A higher proportion of T cells in the skin and intestinal epithelium use the γδ TCR.
- γδ T cells seem to be biased toward recognition of specific microbial antigens.
- γδ T cells are thought to represent a different lineage of T cells with specialized functions.

Table 9.1 Comparison of TCR

<table>
<thead>
<tr>
<th></th>
<th>αβ T cells</th>
<th>γδ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CD3*</td>
<td>90-99%</td>
<td>1-10%</td>
</tr>
<tr>
<td>TCR V gene</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>in germline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4/CD8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>60%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CD8</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>&lt;1%</td>
<td>60%</td>
</tr>
<tr>
<td>MHC restriction</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
| Ligands              | Peptide+ MHC | Phospholipid antigen | Intact protein

The TCR complex includes CD3 - 3 heterodimers: γε, εδ and ζζ
- 1) TCR is not expressed without CD3. It is required to bring TCR to surface
- 2) All chains of CD3 possess ITAM motifs. (Immunoreceptor tyrosine-based activation motif) → Signal Transduction

RECAP:
-The BCR consists of IgM or IgD plus two Ig-α/Ig-β heterodimers. The Ig binds the antigen while the Ig-α/Ig-β heterodimers are involved in activation of the B cell.

- The TCR consists of either the α/β chains or the γ/δ chains plus CD3. The αβ or γδ chains bind the antigen while CD3 is involved in activation of the T cell.

The signaling components possess ITAM motifs.

So, Which one is the “light” chain? Which one is the “heavy” chain?
Rearrangement of TCR genes

- TCR Genes also composed of V, D, J and C gene segments
- Genes are located in different chromosomes
- The β and δ chains contain D segments (like Ig Heavy chains!) while the α and γ chains do not.
- α and γ chains - VJ rearrangement only
- β and δ chains - DJ and then V-DJ rearrangement
- Segments of the δ chain are embedded within the segments encoding the α chain
- When the α chain rearranges, δ segments are deleted
- T cells express only αβ or γδ TCR
- Rearrangement involves RAG-1 and RAG-2 and TdT
- Rearrangement is governed by the one turn-two turn rule
**Generation of antibody diversity**
1. Multiple germline V, D and J gene segments
2. Combinatorial V-J and V-D-J joining
3. Somatic hypermutation
4. Junctional flexibility
5. P-nucleotide addition
6. N-nucleotide addition
7. Combinatorial association of heavy and light chains

**Generation of TCR diversity**
- Combinatorial V-J and V-D-J joining
- Combination of two chains to make the antigen-binding site

**MAJOR DIFFERENCES BETWEEN TCR AND Ig GENES**
- Somatic hyper-mutation (affinity maturation)
  - During an antibody response, mutations accumulate at a rapid rate in the VDJ gene segments encoding the BCR.
  - Thus, as an immune response proceeds, the affinity of the antibody produced (i.e. its ability to bind to the antigen) increases.
- Alternative joining of D segments (β, δ)

**Generation of TCR diversity**
- Varying number of D segments in the delta (and beta) chain, why?
  - (arrangement of RSS sequences differs from that in Ig loci to allow this)
  - Alternative joining of D gene segments

**Generation of TCR diversity**
- N-region nucleotide addition
  - Occurs in all chains
  - Addition of 16 nucleotides (5464 permutations)

**Note:** Increased diversity in TCR!
WHY ACCESSORY MOLECULES?

1) Due to low affinity of TCR with peptide MHC complex
2) Provide:
   - Adhesion, Activation and Co-stimulation
   - Some show increased expression in response to cytokines

Accessory Molecules Involved in Cell-Cell Interactions

- Interactions of Th Cell and APC
  - CD4+ T cell
  - LFA-2
  - LFA-3
  - LFA-2
  - TCR
  - CD8

- Interactions of Tc Cell and Target Cell
  - CD8+ T cell
  - LFA-1
  - TCR
  - LFA-2 (CD2)
  - ICAM-1
  - Class I MHC
  - LFA-3

Peptide

Class II MHC

Figure 5.24
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**T-cell Accessory molecules**

- CD4 and CD8 are co-receptors because they recognize the peptide-MHC complex
- CD8 recognizes the $\alpha_3$ MHC-I domain; while CD4 interacts with $\alpha_2$ MHC-II domain
- Both CD4 and CD8 act in signal transduction
- **OTHER**

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**Accessory Molecules Involved in Cell-Cell Interactions**

**Cell Adhesion:**

<table>
<thead>
<tr>
<th>T Cell</th>
<th>Ligand on APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFA-2(CD2)</td>
<td>LFA-3</td>
</tr>
<tr>
<td>LFA-1</td>
<td>ICAM-1, ICAM-2</td>
</tr>
</tbody>
</table>

LFA = Leukocyte Function-associated Antigen
ICAM = InterCellular Adhesion Molecule

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**Costimulatory Molecules**

- Molecules on T cell and 2nd cell that engage to deliver 2nd signal required for activation of T cell
- Most important co-stimulatory molecules:

<table>
<thead>
<tr>
<th>T cell</th>
<th>Ligand on 2nd cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD28</td>
<td>B7-1 (CD80), B7-2 (CD86)</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>B7-1 (CD80), B7-2 (CD86)</td>
</tr>
<tr>
<td>CD45R</td>
<td>CD22</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>MHC-I/II</td>
</tr>
</tbody>
</table>

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**TABLE 9-4** Selected T cell accessory molecules

<table>
<thead>
<tr>
<th>T cell</th>
<th>APC</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Class II MHC</td>
<td>+</td>
</tr>
<tr>
<td>CD8</td>
<td>Class I MHC</td>
<td>+</td>
</tr>
<tr>
<td>CD2 (LFA-2)</td>
<td>CD10 (LFA-3)</td>
<td>+</td>
</tr>
<tr>
<td>LFA-1 (CD11a/CD18)</td>
<td>ICAM-1 (CD54)</td>
<td>+</td>
</tr>
<tr>
<td>CD28</td>
<td>B7</td>
<td>+</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>B7</td>
<td>+</td>
</tr>
<tr>
<td>CD45R</td>
<td>CD22</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>CD72</td>
<td>+</td>
</tr>
</tbody>
</table>