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 T cell receptor

- 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

αβ T cells       γδ T cells

- % CD3+          90-99%     1-10%
- TCR V gene      Large      Small
- CD4/CD8
  CD4            60%        <1% **
  CD8            30%        30%
  CD4-CD8-       <1%        60% **
- MHC restriction Yes        No **
- Ligands        Peptide+ MHC Phospholipid antigen, intact antigen

Organization and rearrangement of TCR genes

Table 9.2 TCR Multigene families in humans

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>NO. OF GENE SEGMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>α Chain</td>
<td>14</td>
<td>50 30 70 1</td>
</tr>
<tr>
<td>δ Chain†</td>
<td>14</td>
<td>3 3 3 1</td>
</tr>
<tr>
<td>β Chain†</td>
<td>7</td>
<td>57 2 13 2</td>
</tr>
<tr>
<td>γ Chain‡</td>
<td>7</td>
<td>14 5 2</td>
</tr>
</tbody>
</table>

†The α-chain gene segments are located between the Vα and Jα segments.
‡There are two repeats, each containing 1 Dα, 6 or 7 Iα, and 1 Cα.
§There are two repeats, each containing 2 or 3 Jγ, and 1 Cγ.

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 - V-J rearrangement only
- β and δ chains - DJ and then V-D-J 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. N-nucleotide addition
6. N-nucleotide addition

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)

(b) Alternative joining of D gene segments

Antibody

1.6 x 10^{11} VS 3 x 10^7

Note: Increased diversity in TCR!
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)
- N-nucleotide addition to both chains

Properties of Ig and TCR Genes

<table>
<thead>
<tr>
<th></th>
<th>Ig</th>
<th>TCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many VDJs, few Cs</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>VDJ rearrangement</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>V-regions form antigen recognition site</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Somatic hypermutation</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Properties of Ig and TCR Proteins

<table>
<thead>
<tr>
<th></th>
<th>Ig</th>
<th>TCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmembrane forms</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Secreted forms</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Isotypes with different functions</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Valency</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The TCR complex includes CD3 - 3 heterodimers: γ, δ, 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
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

<table>
<thead>
<tr>
<th>Affinity Constant (µM)</th>
<th>T-cell receptors</th>
<th>Adhesion Molecules</th>
<th>Growth Factor Receptors</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weak</td>
<td>Strong binding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RECAP:
- The BCR consists of IgM or IgD plus 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 αβ chains or the γδ chains plus CD3. The αβ or γδ chains bind the antigen while CD3 is involved in activation of the T cell.

Accessory Molecules Involved in Cell-Cell Interactions

Interactions of Th Cell and APC

Interactions of Tc and Target Cell

T-cell Accessory molecules
- CD4 and CD8 are co-receptors because they recognize the peptide-MHC complex
- CD8 recognizes the α3 MHC-I domain; while CD4 interacts with α2 MHC-II domain
- Both CD4 and CD8 act in signal transduction
- OTHER
Accessory Molecules Involved in Cell-Cell Interactions

**Cell Adhesion:**

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

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

**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:
  - **T cell**
  - **Ligand on 2nd cell**
  - CD28: B7-1 (CD80), B7-2 (CD86)
  - CTLA-4: B7-1 (CD80), B7-2 (CD86)
  - CD45R: CD22
  - CD4/CD8: MHC-I/II

**Alloreactive T cells**

- Allogeneic – genetically different individual of the same species (humans!!)
- MHC molecules are alloantigens: CD4 T cells are alloreactive to MHC-II alloantigens and CD8 T cells are alloreactive to MHC-I alloantigens
- Direct and Indirect recognition of alloantigens: a) nonself MHC molecule on foreign cell recognized in its native form; b) peptides from allogeneic MHC after processing are presented by self-MHC molecules

**Table 9-6**

<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>CD80 (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>?</td>
<td>+</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>CD8</td>
<td>CD32</td>
<td>+</td>
</tr>
</tbody>
</table>

The End