Chapter 5:
Antigen Recognition by T Lymphocytes

Recap of chapter 3

- What’s the difference between the innate and adaptive immune system?
- In which way are the epitopes of B and T cells different?
- What does this imply for their role in the immune response?

Antigen recognition by B cells

And by T cells...
Antibodies and T-cell receptors have a similar structure.

The T-cell receptor resembles a membrane-associated Fab fragment of immunoglobin.

T-cell receptor diversity is generated by gene rearrangement.

Gene rearrangement similar for generation of T cell receptors and immunoglobulins.

Main difference:
T cell receptor C region simpler: only one Cα gene
Rearrangement of immunoglobulin genes occurs in the bone marrow, rearrangement of T cell receptor genes in the thymus.

Germline organization of TCR α and β

Rearrangement of the segments necessary to produce a functional receptor.

α-chain consists of V and J, β of V, D, and J.

Immunoglobulin heavy- and light-chain loci

Rearrangement similar for generation of T cell receptors and immunoglobulins.
The **RAG genes** were key elements in the origin of adaptive immunity

RAG genes lack introns and resemble the *transposase* gene of transposons. Important for function: Recombination process results in an excision circle rather than a linear (and potentially harmful) element.

How do RAG genes work?
Repeat sequences

![Diagram of RAG genes and their functions](image)

Evolution of RAG reflects the evolution of adaptive immunity

V(D)J recombination arose abruptly during early vertebrate evolution

How do RAGs work?

![Diagram of RAGs and their roles](image)
The magnitude of potential B and T cell receptor diversity

<table>
<thead>
<tr>
<th>Element</th>
<th>Immunoglobin</th>
<th>(\alpha/\beta) T-cell receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable segments (V)</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>Diversity segments (D)</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>D segments read in three frames</td>
<td>rarely</td>
<td>often</td>
</tr>
<tr>
<td>Joining segments (J)</td>
<td>6</td>
<td>50% of joints</td>
</tr>
<tr>
<td>Joints with N- and P-nucleotides</td>
<td>2</td>
<td>50% of joints</td>
</tr>
<tr>
<td>Number of V gene pairs</td>
<td>(1.9 \times 10^4)</td>
<td>(5.8 \times 10^4)</td>
</tr>
<tr>
<td>Junctional diversity</td>
<td>(-3 \times 10^7)</td>
<td>(-2 \times 10^{11})</td>
</tr>
<tr>
<td>Total diversity</td>
<td>(-5 \times 10^{13})</td>
<td>(-10^{18})</td>
</tr>
</tbody>
</table>

Somatic recombination results in combinatorial & junctional diversity
CDR3β analysis of specific T-cells against different viruses

<table>
<thead>
<tr>
<th>Vβ</th>
<th>CDR3 (AA)</th>
<th>Jβ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2</td>
<td>CASSVLSSPTYYEQYF</td>
<td>2.7</td>
</tr>
<tr>
<td>3.1</td>
<td>CASSQTTSVNTEAFF</td>
<td>1.1</td>
</tr>
<tr>
<td>27</td>
<td>CASSSSLNTEAFF</td>
<td>1.1</td>
</tr>
<tr>
<td>11.2</td>
<td>CASSHYINQEFF</td>
<td>2.1</td>
</tr>
<tr>
<td>7.9</td>
<td>CASSLPRGRDNIEQFF</td>
<td>2.1</td>
</tr>
<tr>
<td>11.2</td>
<td>CASSLGTGHIEQFF</td>
<td>2.1</td>
</tr>
<tr>
<td>5.6</td>
<td>CASSSNRDNTYF</td>
<td>1.3</td>
</tr>
<tr>
<td>7.9</td>
<td>CASSSLGVNNEQFF</td>
<td>2.1</td>
</tr>
<tr>
<td>7.9</td>
<td>CASSSTGPNSQPF</td>
<td>1.6</td>
</tr>
<tr>
<td>29.1</td>
<td>CSVSAEEEOTQYF</td>
<td>2.3</td>
</tr>
<tr>
<td>4.2</td>
<td>CASSQVGTSQGEYQYF</td>
<td>2.7</td>
</tr>
<tr>
<td>12.3</td>
<td>CASSMVAGEYEQYF</td>
<td>2.1</td>
</tr>
<tr>
<td>7.2</td>
<td>CASSLVIEQETQYF</td>
<td>2.5</td>
</tr>
<tr>
<td>7.9</td>
<td>CASSPSKGDNEQFF</td>
<td>2.1</td>
</tr>
<tr>
<td>7.2</td>
<td>CASSPSKGDNEQFF</td>
<td>2.1</td>
</tr>
</tbody>
</table>

What do you think happens to an individual who lacks RAG?

A defect in V(D)J recombination results in severe immunodeficiency

SCID = Severe combined immunodeficiency syndrome

- absence of adaptive immunity
- May be caused by mutations in at least 13 different genes, e.g. the RAG genes.
- fatal in the first 2 years of life because of opportunistic infections
- Therapy only possible if diagnosis is made at birth or shortly thereafter.
- Therapy in the form of bone marrow stem-cell transplantation
The composition of the T cell receptor complex

Expression of the T cell receptor on the cell surface requires association with additional proteins.

A distinct population of T cells expresses a second class of T-cell receptor with γ and δ chains.

T cells either express αβ receptors or γδ receptors! Never both!

MHC class I presents peptide antigens to CD8 T cells
MHC class II presents peptide antigens to CD4 T cells

MHC = major histocompatibility complex
The two classes of MHC molecules have very similar structures!

MHC molecules bind a variety of peptides!

Processing of antigens which bind to MHC class I or II occurs in different cellular compartments!

Processing of antigens which bind to MHC class I or II occurs in different cellular compartments!
In infected tissue, cells switch to immunoproteasome for protein degradation.

Prefential cleavage after hydrophobic or basic residues produces peptides that fit the C-terminal binding motif of TAP and many HLA allotypes.

Klein et al. (2009), Nat Rev Immunol 9(12):833-44

In the ER, peptides may be further trimmed from the N-terminal end by an amino peptidase

The MHC class II antigen processing pathway

MHC class II molecules are prevented from binding peptides in the endoplasmic reticulum by the invariant chain

CLIP = class II-associated invariant-chain peptide
The major histocompatibility complex

- Cluster of closely linked genes on chromosome 6
- Numerous genetic variants of MHC class I and II present in the human population
  => diversity due to multigene families and genetic polymorphism

The human MHC: human leukocyte antigen (HLA) complex

Most of the genes in the HLA class II region are involved in the processing and presentation of antigens to T cells
Diversity of HLA class I molecules in human population is caused by polymorphism.

Diversity of HLA class II molecules in human population is caused by copy number variation and polymorphism.

Genetic mechanisms that generate new MHC polymorphisms:

**Interallelic conversion**

- **Gene conversion**
MHC polymorphism affects the binding and presentation of peptide antigens to T cells

A great variety of binding motifs...

Seemingly small differences may have a big impact on the peptide binding motif!

A*6801 and A*6802 have very different peptide binding motifs.
T cell recognition of antigens is MHC restricted.

MHC restriction

<table>
<thead>
<tr>
<th>T cell</th>
<th>T cell</th>
<th>T cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR</td>
<td>TCR</td>
<td>TCR</td>
</tr>
<tr>
<td>HLA-A</td>
<td>HLA-B</td>
<td>HLA-A</td>
</tr>
<tr>
<td>*0201</td>
<td>*3201</td>
<td>*0201</td>
</tr>
<tr>
<td>antigen-presenting cell</td>
<td>antigen-presenting cell</td>
<td>antigen-presenting cell</td>
</tr>
<tr>
<td>Recognition</td>
<td>No recognition</td>
<td>No recognition</td>
</tr>
</tbody>
</table>

But: Some T cells are alloreactive => problem for organ and bone marrow transplantations!

Nobel Prize Medicine 1996

Peptide determines TCR diversity

MHC molecules are expressed in a codominant fashion.

Which consequences does that have for an individual?

Koning et al JI 2013
Heterozygous individuals are able to present a more diverse set of peptides to their T cells

Heterozygote advantage in peptide selection

Haplotype 1

Haplotype 2

Haplotype 3

Haplotype 4

Haplotype 1 + 2

Haplotype 3 + 4

Carrington et al. Science 1999;283:1748-1752

Exposure to pathogens shapes MHC gene frequencies

Population emerges from a period of few source resources, poor nutrition and increasing poor health

Population is reduced in size by 50%

Population expands in size

Population is reduced in size by 75%

Successive epidemics of infectious disease, e.g., smallpox, diphtheria, cholera, and influenza. Only heterozygotes survive. Strong balancing selection is imposed.

A period of peace, plenty, social harmony and effective medicine ensues. Weak selection.

Epidemic of a newly emergent infectious disease, e.g., HIV/AIDS. Only individuals with blue MHC survive. Strong directional selection is imposed.

Despite strong selection, all four MHC haplotypes are present in the surviving population.

=> Balancing selection maintains diversity of HLA allotypes in populations

Worldwide HLA class I diversity

Global HLA class I diversity

=> Balancing selection maintains diversity of HLA allotypes in populations

Goulder & Watkins (2008) Nat Rev Imm. 8:619-630
Best determinant of HIV-1 disease progression: HLA molecules

- HIV-1 viral load roughly predicts speed of disease progression
- Specific HLA class I molecules have been associated with either slow or fast progression to AIDS


Another important role of MHC class I molecules?

Best determinant of HIV-1 disease progression: HLA-B

- >300 significant SNPs within the MHC region
- Specific amino acids in the HLA-B binding groove best determinants of HIV-1 control.
- Independent HLA-C effect

The international HIV-1 Controllers Study Science Express, 2010

A variety of inhibitory and activating receptors allows NK cells to identify infected cells.