Antigen Recognition and Receptor Diversity

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Topic Outline

• Antibody-antigen reactions
  – Linear vs. conformational determinants
  – Cross-reaction
• TcR recognition of peptide-MHC complexes, restriction by CD4 and CD8
• Recombinational mechanisms of receptor diversity
• Ig isotype switching and isotype functions

Antigen-Antibody Reactions: Terms to know.

• Size of Epitope/antigenic determinant
• specific, noncovalent, reversible binding
• affinity vs. avidity
• valency, crosslinking, agglutination, precipitation
• multideterminant antigens,
• heterogeneous antibody responses
• cross reactions
Antibodies can bind continuous (linear) structures or discontinuous portions of a folded macromolecule (conformational determinants).

Protein denaturation can destroy conformational determinants.

**LINEAR EPITOPE**

**DISCONTINUOUS EPITOPE**

**CROSS-REACTIVITY** = antibody binding of two structurally similar but different antigenic determinants

**Antigen 1**

**Antigen 2**

Antibody to antigen 1

**CROSS-REACTIVITY** = Antibody binding to a determinant shared on 2 different immunogens

**Immunogen 1**

**Immunogen 2**

**CROSS-REACTIVITY** = Antibody binding to a determinant shared on 2 different immunogens
T Cell Receptor for Antigen

• The receptor for antigen on T cells (TcR) is similar to Fab fragments of immunoglobulin.
• TcR is composed of 2 different disulfide linked polypeptides:
  – α:β TcR or γ:δ TcR
• TcR recognizes antigen as a complex of a foreign peptide bound to an MHC molecule on antigen presenting cells.

T Cell Receptor for Antigen

• Whereas the B cell receptor (antibody) for antigen can recognize native undigested antigens of any chemical form (proteins, polysaccharides, lipids, etc.), the TcR recognizes only processed (digested) proteins as peptide-MHC complexes on the surface of antigen presenting cells.

Peptides from digested foreign proteins are bound by MHC I or MHC II proteins on antigen-presenting cells for recognition by T cells.
T Cell Receptor for Antigen

- T cells express a co-receptor (CD4 or CD8) which binds to the MHC portion of the composite MHC:peptide ligand.
- Regulatory CD4-T helper cells recognize peptides complexed with Class II MHC on specialized antigen presenting cells.
- Cytotoxic CD8-T cells recognize peptides complexed with Class I MHC on any nucleated cell.
CD4 and CD8 proteins act as co-receptors to restrict T cell interactions with MHI or MHCII and are used to identify functional T-helper (CD4+) vs. cytotoxic T cells (CD8+).

Antigen Receptor Synthesis & Diversity

- The expression of B and T lymphocyte antigen receptors is initiated by somatic recombination of gene segments that code for the variable regions of the receptors, and diversity is generated during this process.

Recombination of V gene segments to generate intact V regions.
Germline organization of immunoglobulin H and L chain gene loci. V + J or V+D+J gene segments are recombined to generate intact V_L or V_H domains.

Antigen Receptor Synthesis & Diversity

- Diversity of antigen receptors is produced by:
  - Combinatorial diversity: use of different combinations of V, D, and J gene segments in different clones of lymphocytes. Different combinations of H and L chains in intact Ig.
  - Junctional diversity: changes in nucleotide sequences introduced at the junctions of V, D, and J gene segments
  - Somatic mutation of V genes in antigen-activated B cells
Recombinational signal sequences (RSS) flanking the V region gene segments are brought together to allow recombination to take place. Juxtaposition of RSSs results in the looping out of the intervening DNA. The joining of V and J segments creates a functional V-region exon.

Functional TcR α- and β-chain genes are generated by somatic recombination in the same way that complete Ig genes are created.

Isotype switching occurs by recombination between switch signal sequences upstream of each C-region gene. Intervening DNA is deleted.
Transmembrane and secreted forms of Ig are derived from the same H chain sequence by alternative RNA processing.

### Chemical and functional properties of Ig classes.

<table>
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<tr>
<th>Immunoglobulin</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgM</th>
<th>IgA1</th>
<th>IgA2</th>
<th>IgD</th>
<th>IgE</th>
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<td>Heavy chain</td>
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<tr>
<td>Molecular weight (kDa)</td>
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<td>146</td>
<td>146</td>
<td>970</td>
<td>160</td>
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<tr>
<td>Serum level (mean adult mg/mL)</td>
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<td>3</td>
<td>1</td>
<td>0.5</td>
<td>1.5</td>
<td>3.5</td>
<td>6.5</td>
<td>0.03</td>
<td>5 x 10⁻⁶</td>
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<td>Half-life in serum (days)</td>
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<td>50</td>
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<td>10</td>
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<td>Classical pathway of complement activation</td>
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<td>Alternative pathway of complement activation</td>
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<td>Precipitin transfer</td>
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<td>Binding to macrophage and phagocytic Fc receptors</td>
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<td>High-affinity binding to intact cells and antibodies</td>
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<td>Reactivity with anti-immunoglobulin P Ab &amp; Fe Ab</td>
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Figure 3 (part 1) [Immunology 16, p. 17] (Garfield Science 2000)