

COMPLEMENT

1. **Definition:** Complement is a set of 20 serum proteins and several membrane-associated proteins (receptors) that interact as a primary recognition and defense effector arm of the immune system.

2. Classical Complement Cascade

- a) Antibody bound to Ag will link to C1q.
- b) Changes in C1q bring about the sequential activation of C1r and C1s.
- c) The complex of C1q, C1r and C1s (C1) binds C4 and splits it into a C4a fragment and C4b. This reaction is controlled by C1-INH.
- d) The C4b complex binds C2 and splits it into C2a and C2b.
- e) C4b2b is a C3 convertase which splits C3 into C3a and C3b.
- f) C4b2b3b is a C5-splitting enzyme releasing C5a.
- g) Sequential attachment of C6 and C7 to C5b forms a complex which binds C8 and then C9.
- h) The complex polymerizes to an annular membrane attack complex which inserts itself into the wall of the antigen forming a transmembrane channel.

3. Alternative Complement Cascade

- a) This pathway is activated when C3b released by the spontaneous and natural breakdown of C3 binds to a foreign microorganism.
- b) Bound C3b attracts Factor B, Factor D and Factor P to form a complex C3bBbP which is a C3 and C5 convertase.
- c) There will now be sequential attachment of the late acting complement components forming the membrane attack complex.
- d) Two further proteins, Factor H and Factor I, regulate the alternative complement system.

COMPLEMENT (Continued)

4. <u>Functions</u>	<u>Mediated By:</u>
a) Opsonization	C3b
b) Chemotaxis and Activation of PMN	C3a, C5a
c) Degranulation of Mast Cells & Basophils	C3a, C5a
d) Cell Lysis	C5b-C9
e) Viral Neutralization	C3b, C5b-C9
f) Clearance of Immune-Complexes	C3b, CR1 (on red cells)

5. <u>Complement Deficiencies</u>	<u>Mediated By:</u>
a) C1q, C1r, C2, C4	SLE
b) C3	Recurrent infection
c) C5	Recurrent infection
d) C6, C7, C8	Neisserial infection
e) C9	No disease
f) C1 INH	HANE
g) Factor I	Recurrent infection
h) Factor D	Recurrent infection
i) Factor H	Recurrent infection

Most C2 deficient patients are normal.

6. Hereditary Angioneurotic Edema (HANE)

- a) 85% of cases lack C1-INH.
- b) 15% have an abnormal variant of C1-INH.
- c) Attacks of angioedema in skin and mucosa.
- d) Abdominal pain, skin swellings, laryngeal obstruction.
- e) C2 and C4 levels are decreased.

MAJOR HISTOCOMPATIBILITY COMPLEX

TERMINOLOGY: The following definitions are offered as an aid:

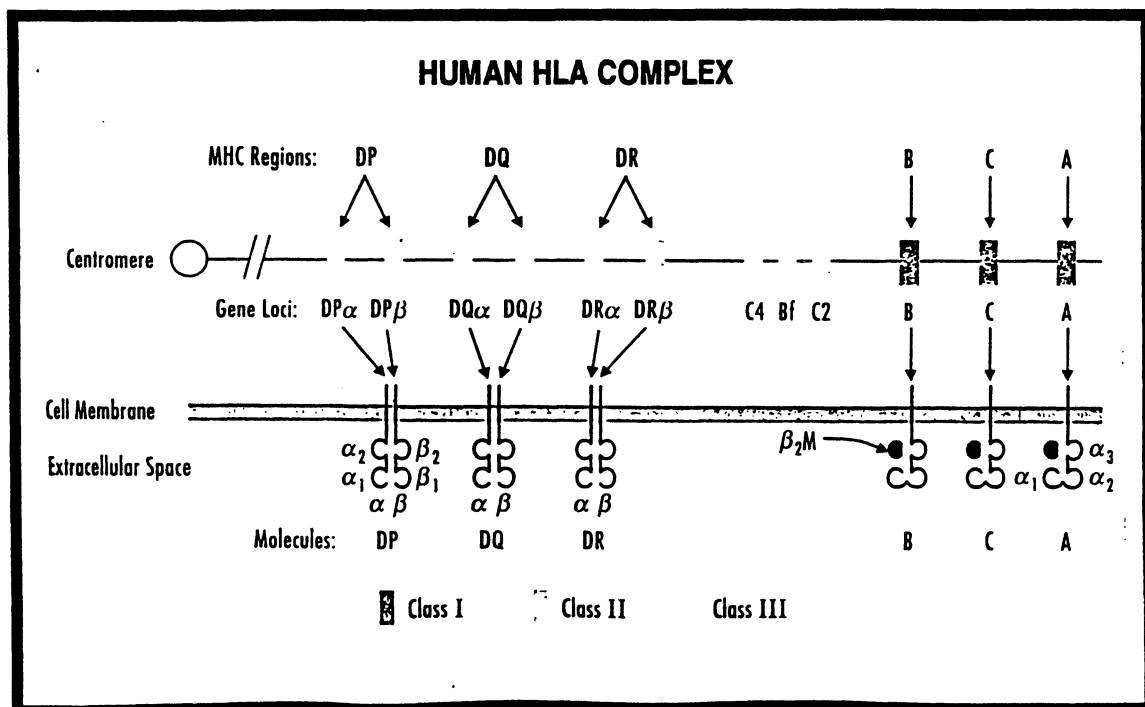
Genes are units of DNA that code for the amino acid sequence of a polypeptide chain. Genes can exist in two or more alternative forms known as **alleles**.

Alleles are located on chromosomes at sites called loci. In the case of histocompatibility antigens, as many as 150 different alleles can be coded for at one locus, but in any individual animal a single locus can contain only one gene. Because chromosomes are paired, one being inherited from each parent, alleles are also inherited in pairs. Since there may be three or more class I loci and no more than two alleles inherited at each locus in any individual animal, the number of possible allelic combinations is very large.

A **gene complex** is a cluster of related genes, occupying a restricted area of a chromosome.

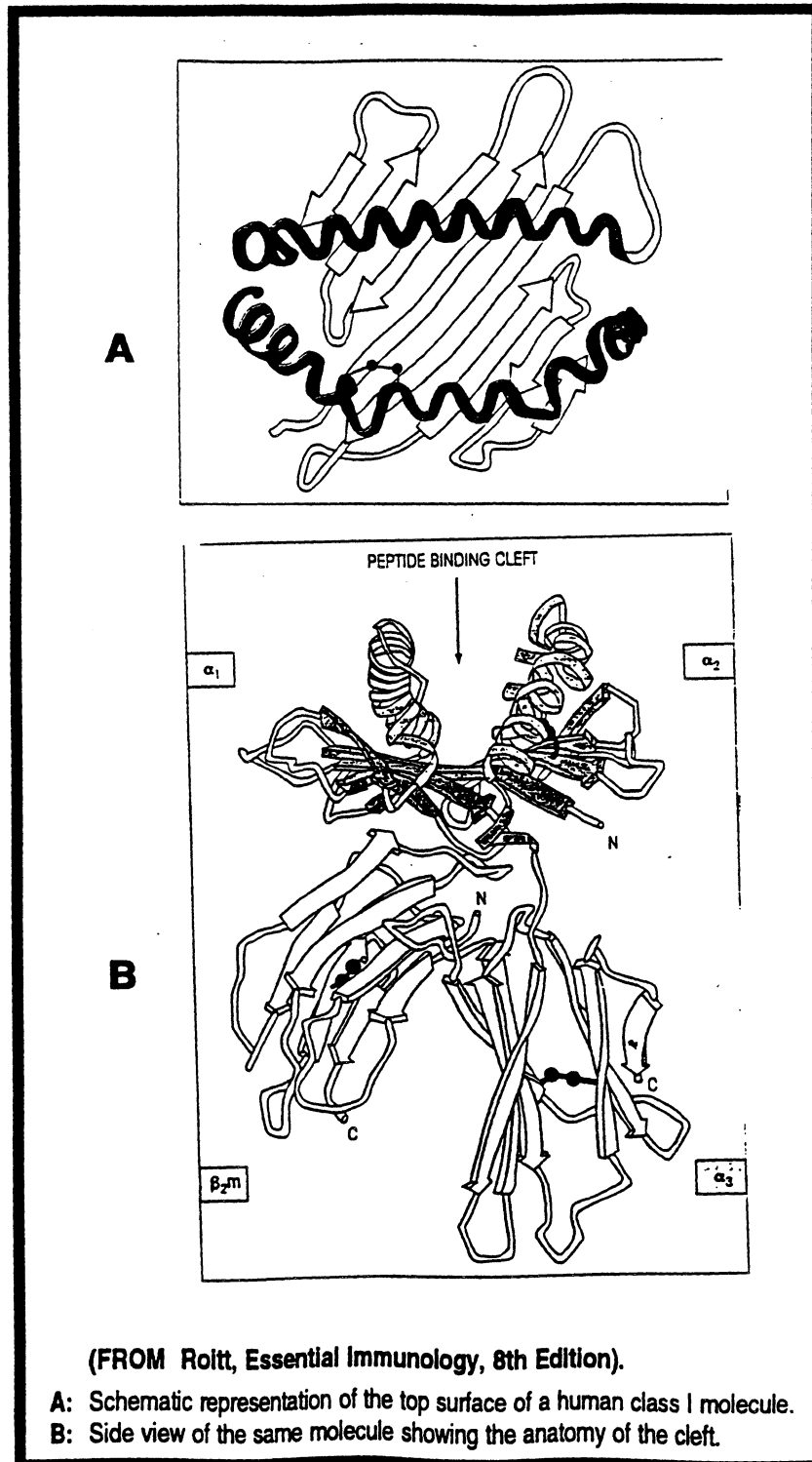
The term **haplotype** is used to describe the complete set of alleles at all loci within a gene complex on a single chromosome.

1. Structure of MHC Gene Complex:



MAJOR HISTOCOMPATIBILITY COMPLEX (Continued)

2. Structure of MHC Molecules



MAJOR HISTOCOMPATIBILITY COMPLEX (Continued)

3. Function of MHC Molecules

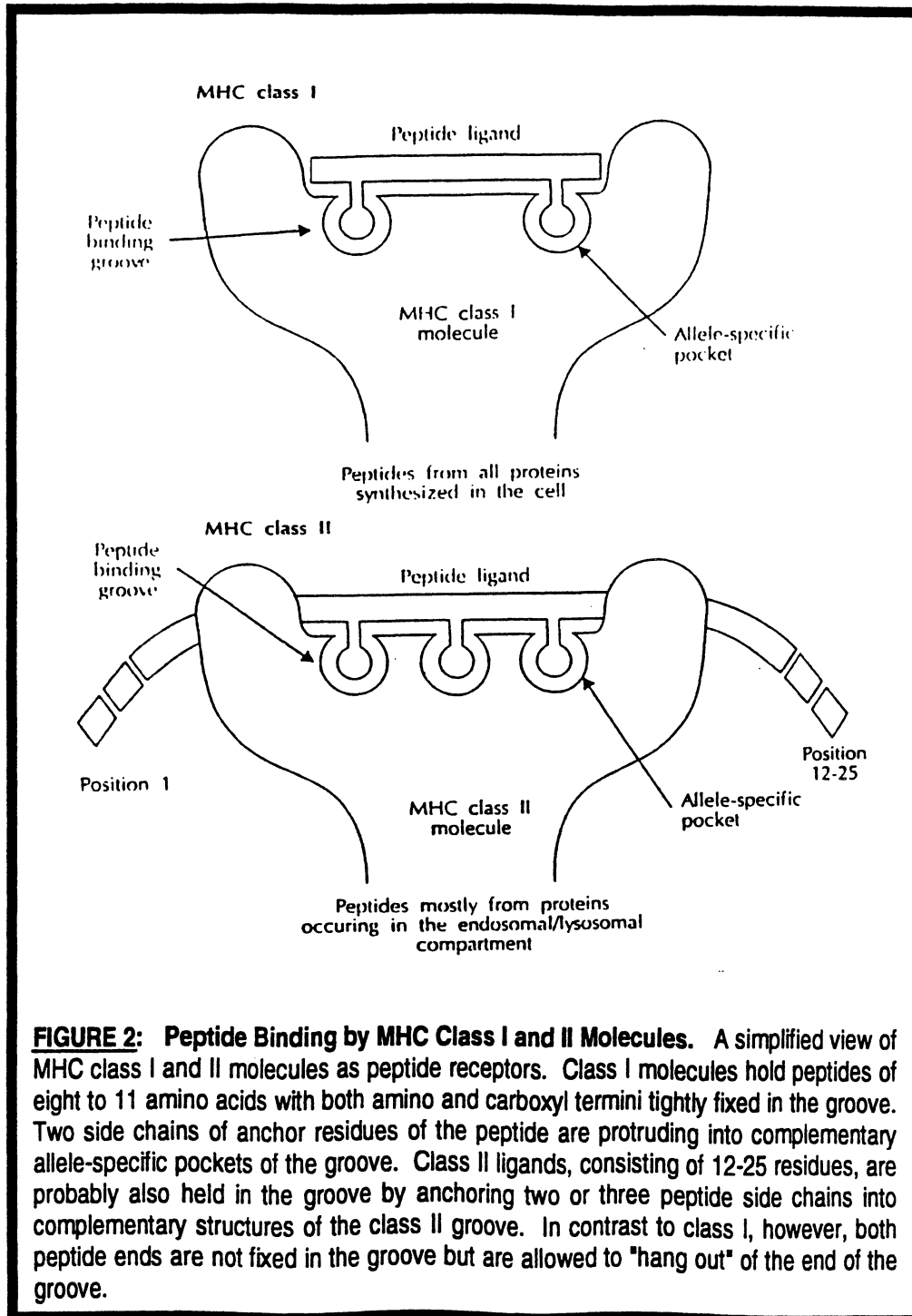


FIGURE 2: Peptide Binding by MHC Class I and II Molecules. A simplified view of MHC class I and II molecules as peptide receptors. Class I molecules hold peptides of eight to 11 amino acids with both amino and carboxyl termini tightly fixed in the groove. Two side chains of anchor residues of the peptide are protruding into complementary allele-specific pockets of the groove. Class II ligands, consisting of 12-25 residues, are probably also held in the groove by anchoring two or three peptide side chains into complementary structures of the class II groove. In contrast to class I, however, both peptide ends are not fixed in the groove but are allowed to "hang out" of the end of the groove.

THE IMMUNE RESPONSE

1. Lymphocyte Surface Markers

T-Cells

CD3:	Transducing element of the T-cell receptor
CD4 (T Helper):	Receptor for MHC Class II; Receptor for HIV
CD8 (T-Cytotoxic):	Receptor for MHC Class I
CD28:	Receptor for B7 costimulator

B-Cells

CD19:	Pan B-cell marker
CD40:	Receptor for CD40 ligand costimulator
κ or λ :	Part of the Ig molecule

2. Activation of the Immune Response

- Antigen is taken up by antigen presenting cells (APC's) including B-cells, macrophages and dendritic cells.
- Intracellular antigen is processed by the APC (i.e., degraded to peptides).
- The peptide is transported inside the groove of an MHC molecule to the surface of the APC for presentation to T-cells.
- The T-cell receptor recognizes the foreign peptide inside the MHC molecule. CD4 cells recognize the outside of class II MHC, CD8 cells recognize class I MHC.
- Interaction of T cell receptor and APC depends upon complementary molecules on the surfaces of these cells:

<u>APC</u>	<u>T-CELL</u>
MHC II	CD4
MHC I	CD8
LFA-3	CD2
B7	CD28

THE IMMUNE RESPONSE (Continued)

- f) The T-cells are activated by two signals:
 - MHC-peptide and the T-cell receptor
 - B7 and CD28
- g) The CD3 molecule attached to the T-cell receptor is crucial for activation of the T-cell.

3. T-Cell Effector Functions

- a) Expression of cytokines and cytokine receptors.
- b) Activated T-cells proliferate in response to cytokines, forming a clone of sensitized T-cells.
- c) Two subsets of CD4 cells based on cytokine production:
 - TH1 cells produce IFN γ and IL-2 which activate macrophages and cause delayed hypersensitivity.
 - TH2 cells produce IL-3, IL-4, IL-5, and IL-6 and act as helper cells for B-cells.
- d) T-cells release chemokines which attract macrophages and other phagocytic cells to the site.
- e) IFN γ activates macrophages to kill intracellular organisms, and to upregulate MHC molecules.
- f) Cytotoxic CD8⁺ cells are generated against cells (e.g., virally infected) which present peptide inside MHC class I.
- g) Antigen presenting cells secrete cytokines such as IL-1 and tumor necrosis factor (TNF) which have the following effects:
 - fever
 - anorexia
 - depression
 - production of acute phase reactants from the liver (e.g., C-reactive protein)

THE IMMUNE RESPONSE (Continued)

- h) Proliferation of B-cells response and production of IgM is mediated by cytokines.
- i) CD40L on T-cells interacts with CD40 on B-cell to produce the switch from IgM to IgG, IgA or IgE production.

