MHC GENES, POLYMORPHISM AND IMMUNE RESPONSES

- Human MHC genes are generally given the prefix HLA (human leukocyte antigen). To distinguish from RBC antigens that determine the classical ABO blood groups for transfusion compatibility.

One mechanism of MHC diversity is due to **gene families**:
- Each individual has three genes encoding class I α chains that present Ag to CD8 T cells: HLA-A, HLA-B, HLA-C. (Fig. 5.24) Sometimes called class I isotypes. Other class I-related proteins associate with β2-mic. but have other functions (i.e. HLA-E).
- Each human has three pairs of genes encoding class II α and β chains that present Ag to CD4 T cells: HLA-DP, HLA-DR, HLA-DQ (Fig. 5.24) Sometimes called class II isotypes. Other class II-related proteins do not bind peptides but regulate class II presentation (i.e. HLA-DM, DO)
- Thus, each person has three genes for class I MHC and three pairs of genes (α and β) for class II MHC.

**Definition:** **Genetic polymorphism:** variation at a single genetic locus and its product within a species; the individual variant gene is called **allele**.

The other mechanism of MHC diversity is due to genetic polymorphism:
- There are multiple alleles for each MHC gene in the population (Fig. 5.25)
- Therefore, different alleles have different sets, capable of binding different population of antigenic peptides.
- Each individual usually is heterozygous for most MHC isotypes because father and mother contribute different alleles
- Therefore, most individuals express 6 different class I and 6 different class II.
- The full array of alleles for the MHC molecules on chromosome 6 in an individual is called the **haplotype** (e.g. HLA-A2, B27, C16, DRα1, etc.)

**Peptide binding cleft** (Fig. 5.15)
- Note that the main structural aspects of each MHC are similar, they just bind different peptides because the polymorphisms are primarily in the peptide-binding contact residues and TCR contact residues. (Fig. 5.29)

**TCR/MHC-peptide interaction** (Fig. 5.22)
- Involves CDR loops of TCRα and β binding to the composite surface of MHC+peptide.

- A given MHC molecule can bind with high affinity a wide variety of peptides with some common sequence features: **anchor residues** are identical or similar among set of peptides that bind with high affinity (Fig. 5.30).
**MHC restriction** means that a given T cell receptor is specific not only for a given peptide, but for a unique combination of peptide plus a particular MHC molecule. (Fig. 5.31)

The advantage of MHC gene families and polymorphism (Fig. 5.32)

- Each pathogen expresses many proteins with different possible peptides presented
- Multiple MHC isotypes and polymorphism allow an individual to present a larger pool of foreign peptides to T cells, thus increasing the chances of an effective adaptive immune response
- Heterozygosity at HLA alleles prolongs time to progression in HIV (Fig. 5.35)
- Having multiple combinations of alleles in the species population ensures that at least some individuals will survive an epidemic
- Certain alleles more prevalent in geographic areas where specific pathogens have long been present (e.g. malaria)

**MHC genetic organization**

- MHC genes are linked in a large cluster of genes ~200 (human chr. 6) (Fig. 5.26)

- Genes for many other proteins involved in antigen peptide processing are in MHC class II locus. e.g. TAP1 and 2, tapasin, LMP2 and 7 proteasome subunits. (Fig. 5.28)
- When LMP2 and 7 are expressed, they change the proteasome specificity to generate peptides that are better fit for MHC class I binding

- "Class III MHC" locus: some genes important for immune response including complement proteins and cytokines. Usually not polymorphic.

- Transcription of many of these genes is coordinated: **interferons** can increase transcription of many MHC genes via common transcriptional activators.
  - Expression of class I genes, β2-microglobulin, as well as proteosome and TAP subunits, is upregulated by interferon α and β, factors induced by viral infection
  - Class II genes are turned on by interferon-γ, made by T helper cells in response to bacterial infection

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B CELL DEVELOPMENT

Life of a B cell (Fig. 6.1)
B cell precursors rearrange VDJ in the bone marrow.
Immature B cells that are self-reactive are eliminated.
Mature B cells circulate from blood to secondary lymphoid tissues (Fig. 6.2) where they survey for foreign antigens.
Activated B cells give rise to plasma cells and memory B cells.

B cell development occurs in several stages: brief overview (Fig. 6.4)
1) Stem cell (common lymphoid progenitor)

2) Pro-B cell stage: two stages - early and late pro-B cell stages
   Heavy chain rearrangement occurs in the pro-B cell stage.
   Early pro-B cell: D and J recombination
   Late pro-B cell: V and DJ recombination
   Complete µ chain is produced by the end of the pro-B cell stage.

3) Pre-B cell stage: two stages - large pre-B cell and small pre-B cell
   Large pre-B cells express pre-B cell receptor
   composed of µ heavy chain plus surrogate light chain. (Fig. 6.7)
   B cells proliferate between the large and small pre-B cell stages - they rest after proliferation and become small pre-B cells.
   Light chain rearrangement occurs during the small pre-B cell stage.

4) Immature B cell: IgM is expressed on the surface.
   Immature B cells (with surface IgM) are subject to selection for self-tolerance; B cells with the IgM that's reactive to self epitopes are eliminated/inactivated during this stage.

5) Mature B cells: B cells that have undergone selection now express IgM and IgD on the surface by alternative splicing. They are also called naïve B cells until they encounter antigens.
Bone marrow provides the environment for B cell maturation. (Fig. 6.5)

- **Bone marrow stromal cells** provide the necessary factors and ligands to B cells for development.
- Stem cells isolated from the bone marrow fail to develop into B cells in vitro unless bone marrow stromal cells are also present.

1) Cell-to-cell contact: Bone marrow stromal cells express adhesion molecules to which B cells bind. **Adhesion molecules** are receptors expressed on the cell surface that allow cell-to-cell adhesion. Many cell types need to be in contact with others in order to survive. Adhesion molecules and their ligands often signal (usually for cell survival), so the B cells may receive signals through adhesion molecules expressed on the stromal cells.

2) Secreted factors: Bone marrow stromal cells also secrete several factors that guide B cells through different stages of development: **SCF** (stem cell factor, recognized by very early B cells), **IL-7** (recognized by late pro-B and pre-B cells), and chemokines (small cytokines involved in migration and activation of immune cells).