The Role of the MHC in the Immune Response

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Lecture Objectives:

• Understand genetic organization of the major histocompatibility complex.

• Present an overview of differential processing of antigens in the MHC class I and class II pathways.

• Discuss MHC restriction as related to presentation of antigens.

• (Present an overview of disease association with MHC type.)
In 1980 the Nobel Prize was awarded to Baruj Benacerraf, Jean Dausset and George D. Snell, for their work involving the major histocompatibility complex and rejection of skin grafts using inbred strains of lab mice.

They discovered that genetically determined cell-surface structures regulate immunologic reactions. It has since been determined that the function of the MHC is the presentation of antigen fragments (epitopes) to T cells.
The Major Histocompatibility Complex (MHC) is a locus on a chromosome comprised of multiple genes encoding histocompatibility antigens.

- The Histocompatibility antigens are cell surface glycoproteins which play critical roles in interactions among immune system cells.
- MHC genes are very polymorphic.
Recognition of Antigen by T cells

Recognition of antigen by the TCR requires the presence of a set of MHC molecules on the surface of antigen-presenting cells (APCs).

- T cells recognize antigen only when antigen is associated with a MHC molecule.
- T cells cannot recognize free antigen like B cells can.
  - B cells recognize the three-dimensional shapes (antigen conformation) and/or linear peptides
  - T cell receptors recognize linear primary amino acid sequences.
MHC Molecule Organization

3 Classes of MHC Encoded Molecules

• **Class I** participates in antigen presentation to CD8+ lymphocytes (CTL).
  – all nucleated cells express Class I MHC

• **Class II** molecules participate in antigen presentation by professional antigen presenting cells to CD4+ lymphocytes (T helper).
  – macrophages, dendritic cells and B cells

• **Class III** MHC molecules include complement proteins, tumor necrosis factor, and lymphotoxin.
Human HLA Gene Complex

- **HLA**=Human Leukocyte Antigen.
- The Class I region consists of HLA-A, HLA-B, and HLA-C loci.
- The Class II region consists of the D region which is subdivided into HLA-DP, HLA-DQ, and HLA-DR subregions.
- Class III molecules are encoded by genes located between those that encode class I and class II molecules.
In man, the MHC locus is designated as HLA (Human Leukocyte Antigen).

The HLA locus in humans is found on the short arm of chromosome 6.
The Class I region consists of HLA-A, HLA-B, and HLA-C loci.

Transmembrane, associated with $\beta_2$-microglobulin ($\beta_2$M).
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2 transmembrane polypeptide chains (α and β).
Class III molecules are encoded by genes located between those that encode class I and class II molecules.

Complement components C2, C4, factor B, and TNF-(α and β).
MHC Genetic Polymorphism

- All MHC molecules show a high level of **allotypic polymorphism**, i.e. certain regions of the molecules differ from one person to another.
  - 3 Class I molecules (A, B and C).
  - 3 Class II molecules (DR, DP and DQ).

- MHC class I and class II molecules that are not possessed by an individual are seen as foreign antigens.

- **High polymorphism allows recognition of foreign antigens and ability to distinguish “self” from “non-self”**. The prevalence of different HLA types vary widely in different populations.
The Class I locus contains three smaller loci of Genes for three distinct Class I Genes, named A, B and C.

All code for Class I molecules, but each is distinct in its structure and binding capacity. Every human possesses at least one version of A, B and C Class I molecules.

Since an individual gains one strand of DNA from each parent, most people have two distinct variants of A, two of B and two of C, for a total of six distinct MHC I Genes.

The Class I Gene codes only for the alpha protein of the Class I molecule. The beta-2 Microglobulin Gene is constant and is located elsewhere in the Genome.
MHC Polymorphism

A similar situation exists for MHC II, where the locus is split into three smaller loci named DP, DQ and DR.

Most people have two variants of each, for a total of six MHC II Genes. Each Gene codes for a variant of both the alpha and beta protein.

Since it is possible for an alpha unit from one Gene to associate with a beta of another, there is a combination of twelve different MHC II molecules.

<table>
<thead>
<tr>
<th>DP</th>
<th>DQ</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. alpha m beta m</td>
<td>1. alpha m beta m</td>
<td>1. alpha m beta m</td>
</tr>
<tr>
<td>2. alpha d beta d</td>
<td>2. alpha d beta d</td>
<td>2. alpha d beta d</td>
</tr>
<tr>
<td>3. alpha m beta d</td>
<td>3. alpha m beta d</td>
<td>3. alpha m beta d</td>
</tr>
<tr>
<td>4. alpha d beta m</td>
<td>4. alpha d beta m</td>
<td>4. alpha d beta m</td>
</tr>
</tbody>
</table>

m = mom; d = dad
MHC and Antigen Presentation
MHC and Antigen Presentation

• Antigen is recognized by T cells in conjunction with MHC molecules.

• CD8+ T Cell recognize Ag-MHC Class I.

• CD4+ T Cell recognize Ag-MHC Class II.

More on presentation later..... Let's first look at structure/function relationship
Structure of the MHC Class I Molecule

- 45 kDa molecule.
- 3 extracellular domains (α1, α2, α3).
- Non-covalent association with β2M (member of Ig superfamily).
Class I/β₂M - Peptide Interactions

- Peptide-binding groove
- Peptide (8-9 amino acid residues)
- T cell receptor
- MHC class I molecule
MHC/Pepptide/TCR Complex......
MHC Class I
Molecule Structure
Structure of the MHC Class II Molecule

- 2 transmembrane polypeptide chains (α and β, 30-34 and 26-29 kDa).
- Peptide-binding site is shared by the two domains furthest from the cell membrane.
Class II - Peptide Interactions

T cell receptor

Peptide (12–17 amino-acid residues)

MHC class II molecule

Peptide-binding groove

\( \beta_1 \)

\( \alpha_1 \)
Structure of the MHC Class II Molecule

• Base is made of β-pleated sheet, as in an immunoglobulin domain.
• The sides of the groove that holds the peptide are α-helices.

Image of peptide groove
MHC and Antigen Presentation

- Different antigen degradation and processing pathways produce MHC-peptide complexes.

- “Endogenous” peptides associate with Class I molecules.
  - All nucleated cells are able to present with Class I.

- “Exogenous” peptides associate with Class II molecules.
  - Only specialized APCs may present with Class II, such as macrophages, B cells and dendritic cells, and thymic epithelial cells.
Differential Ag Processing and Intracellular Trafficking of MHC

- Class I and Class II molecules are synthesized in RER.
- They differ as to how, and when, they interact with peptide antigenic fragments.
  - Class I -> **Endogenous Processing**
  - Class II -> **Exogenous Processing**
Endogenous Ag Processing

- Class I MHC molecules interact with peptides degraded by proteasomes, part of a large cytoplasmic proteolytic complex called the low-molecular-mass polypeptide.
- Degraded peptides are carried into the rough endoplasmic reticulum by the transporter of antigenic peptides (TAP).
- Upon peptide binding, the interaction between a class I MHC chain and β2-microglobulin is stabilized.
- Complex is routed through the Golgi to the plasma membrane.
Exogenous Ag Processing

- The presence of the invariant chain (Ii) prevents peptide binding to class II MHC molecules within the endoplasmic reticulum and facilitates their routing to endosomal compartment.
- Late in the exogenous processing pathway, endosomes containing class II MHC molecules and the invariant chain fuse with lysosomes.
- Enzymes within the lysosomes degrade the invariant chain, enabling the class II MHC molecules to bind peptides.
TABLE 8.2. Comparison of the Properties and Functions of MHC Class I and Class II Molecules

<table>
<thead>
<tr>
<th>Structure</th>
<th>MHC class I</th>
<th>MHC class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domains</td>
<td>α chain + β2m</td>
<td>α and β</td>
</tr>
<tr>
<td></td>
<td>α₁, α₂ and α₃ + β2m</td>
<td>α₁ + α₂ and β₁ + β₂</td>
</tr>
<tr>
<td>Constitutive cellular expression</td>
<td>Nearly all nucleated cells</td>
<td>Antigen presenting cells (B cells, dendritic cells, thymic epithelial cells)</td>
</tr>
<tr>
<td>Peptide binding groove</td>
<td>Closed, binds 8–9 amino acid peptides formed by α₁ and α₂ domains</td>
<td>Open, binds 12–20 amino acid peptides formed by α₁ and β₁ domains</td>
</tr>
<tr>
<td>Peptides derived from</td>
<td>Endogenous antigens, catabolized in the cytoplasm</td>
<td>Exogenous antigens, catabolized in acid compartments</td>
</tr>
<tr>
<td>Peptide presented to</td>
<td>CD₈⁺ T cells</td>
<td>CD₄⁺ T cells</td>
</tr>
</tbody>
</table>

Coico, Table 9.1
Role of MHC in Thymic Education

Simply Put: Involved in Education of Self
Role of MHC in Activation of T Cells

The binding between the TCR and the MHC antigen peptide complex is highly specific and acts as the first signal to induce T cell activation.

- Activated T cells proliferate and secrete lymphokines and/or lytic substances.
- The affinity of the TCR for the MHC/antigen complex is too low to activate the T cell; numerous accessory molecules increase avidity between the T cell and APC.
The interaction between T lymphocytes and the APC is mediated by adhesion molecules and cytokines.

- Adhesion molecules synergize transient binding between lymphocytes and APCs
  - allows T-cells to sample large numbers of MHC molecules on the APC.

- T-cell recognizes its peptide ligand bound to MHC
  - signals sent intracellular -> production of cytokines.
  - cytokines elicited during infection can upregulate both Class I and Class II molecules.
  - infectious agents and tumors can down regulate expression, to escape detection.
Critical Molecules in Antigen Presentation

Activation depends on multiple signals than simply MHC/TCR.

- MHC+Ag. CD4 or CD8, stabilization of MHC/TCR interaction.
  - CD28, co-stimulatory molecule that bind B7-1 (CD80) or B7-2 (CD86).
  - Costimulatory pairs and adhesion pairs.
    - ICAM-1 (CD54) with LFA-1 (CD11a) (migration)
    - LFA-3 (CD58) with CD2 (adhesion)
B cells as Presenters

T-dependent B cell activation:

- B cells can specifically take up exogenous antigen via binding through their surface Ig.

- Proteins are internalized, broken down to peptides.

- Peptides are presented on the B cell surface held in the peptide binding grooves of MHC class II molecules.
- CD4 + T Helper cells (1) assist phagocytes to kill intracellular pathogens, and (2) aid antigen-stimulated B cells to proliferate and differentiate toward antibody producing cells. CD4 binds to invariant portion of MHC II β chain to stabilize process.

- CD8+ CTLs kill target cells. CD8 binds to invariant portion of MHC I to stabilize process.
A few more points to consider....
Association of Disease with MHC Haplotype

Particular MHC alleles are associated with better protection against infectious disease.

- Because MHC molecules differ in their ability to accommodate different peptides, some individuals may lack the ability to present microbial epitopes.

- Individuals differ slightly in proteosome and protein processing.

- There may simply be no T cells capable of recognizing a particular MHC/antigen combination ("hole in the T cell repertoire").

- An infectious agent possesses antigens that resemble MHC molecules (molecular mimicry), allowing escape of immune detection because it is seen as "self".
MHC Molecules Differ in Their Ability to Accommodate Different Peptides

Protein antigen → Processed peptides

- Protein antigen:
  - 1
  - 13
  - 122, 110, 35, 48

- Processed peptides:
  - 1 - 13
  - 35 - 48
  - 110 - 122

- HLA-DR4
  - 35 - 48

- HLA-DP2
  - 110 - 122
## Autoimmune Disease and HLA Association

<table>
<thead>
<tr>
<th>Class I MHC Associations</th>
<th></th>
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<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td>HLA-B27</td>
</tr>
<tr>
<td>Grave’s Disease</td>
<td>HLA-B8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class II MHC Associations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>HLA-DR4</td>
</tr>
<tr>
<td>Sjogren’s Syndrome</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Systemic Lupus Erythematous</td>
<td>HLA-DR3, DR2</td>
</tr>
<tr>
<td>Type I Diabetes</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>HLA-DR2</td>
</tr>
</tbody>
</table>

(More on this in lecture on Autoimmunity)
Q: How does deficiency in MHC class II selectively affect CD4 T cell function, and what are the implications towards immune responses to infective agents?
CD1 is a Surface glycoprotein which can present lipids/glycolipids to T cells.

- Non-MHC encoded/Non-polymorphic
- Expressed in association with β2-microglobulin
- Binds hydrophobic region of lipid, exposing polar region for T cell interaction

- Can present to αβ or γδ T cells, and NKT cells.
Presentation is EVERYTHING!!!!
FIGURE 8.3. Different depictions of MHC class I molecule. (A) Cartoon of an MHC class I molecule associated at the cell surface with $\beta_2$m. (B) Side view of MHC class I molecule with $\beta$2m, showing peptide-binding groove. (C) Top view of peptide-binding groove, showing bound peptide. (D) Diagram of interaction of T-cell receptor with MHC class I molecule and peptide bound in peptide-binding groove. (Parts B and C adapted from Bjorkman et al., 1987, with permission; part D adapted from Rammensee et al., 1993.)
FIGURE 8.7. Processing of endogenous antigen in MHC class I pathway.
FIGURE 8.4. Different depictions of MHC class II molecule. (A) Cartoon of MHC class II molecule at cell surface. (B) Side view of MHC class II molecule showing peptide-binding groove. (Adapted from Stern and Wiley, 1994, with permission.) (C) Top view of peptide-binding groove. (Adapted from Stern et al., 1994, with permission.) (D) Diagram of interaction of T-cell receptor with MHC class II molecule and peptide bound in peptide-binding groove. (From Rammensee et al., 1993.)
FIGURE 8.5. Processing of exogenous antigen in MHC class II pathway, (li = invariant chain; CLIP = fragment of li bound to MHC class II groove.)