Lecture 4: Structure of MHC and Immunogens and Antigens

Chapter 3, Chapter 8 pp 151-154.

Structure of MHC class I:

- Larger chain: $\alpha 1\alpha 2$ $\alpha 3$ domain.
- $\alpha 3$ domain is an immunoglobulin fold and is the attachment point to the membrane.
- $\alpha 1$-$\alpha 2$ domain forms an 8-stranded β-sheet that serves as a platform for peptide binding.
- Edges of the peptide binding site are defined by long α-helices, one from $\alpha 1$ and one from $\alpha 2$
- $\alpha 3$ is paired with β_2 microglobulin, which also has a typical Ig fold.
- β_2 microglobulin is essential for stability and peptide binding.
- CD8 on T_C cells binds to the $\alpha 3$ domain.

Peptide binding to Class I:

- Peptide configuration: extended chain
- Length Restriction: 8 optimal. MHC interacts with amino and carboxy terminus.
- Peptides of length 9-10 can bind, but do so by bulging at the center.
- Peptide-MHC interaction: This is largely through the mainchain atoms of the peptide, this results in binding that is generally, but not completely, insensitive to the peptide sequence.
- A few residues in the peptide, called anchor residues, bind to specific pockets on the MHC I, resulting in some specificity of interactions with MHC.
- Many different peptides can bind to a single MHC, some peptides can bind to more than one MHC.

Structure of Class II MHC:

- Almost identically sized α and β chains.
- Each chain is divided into two segments, e.g. $\alpha 1\alpha 2$, $\beta 1\beta 2$
- $\alpha 2$ and $\beta 2$ are immunoglobulin domains that pair with each other.
- $\alpha 2$ and $\beta 2$ are the point of membrane attachment.
- $\alpha 1$ and $\beta 1$ form the peptide binding domain, conformation quite similar to Class I MHC, **except,** the ends are open allowing the binding of longer peptides.
- CD4 on T_H cells binds to $\beta 2$ domain.

Antigen Presentation of Peptides in Class I and Class II MHC.

Class I MHC: Endogenous Foreign Peptide (Figure 8.6 in Benjamini et al)

1. Non-self proteins are produced during viral replication, intra-cellular bacterial growth, tumor cell growth.
2. Proteins are digested by the proteasome, peptides are passed into the endoplasmic reticulum (ER) via transporter (TAP-1, TAP-2).
3. Associate with Class I MHC in ER.
4. Pass through the Golgi to the surface for presentation of T_C (CD8) cells.
5. T_C cells become cytotoxic killer cells after recognition of MHC-peptide complex by the T-cell receptor (TCR) and CD8

Class II MHC: Exogenous Foreign Peptide (Figure 8.4 in Benjamini et al)

1. Exogenous antigen ingested by either phagocytosis (macrophage) or receptor mediated endocytosis (e.g. membrane bound immunoglobulins on the surface of B-cells).
2. Foreign material processed in endosomes, proteases produce short peptides.
3. Fusion of vesicles from Golgi (Containing Class II MHC) with endosomes permits peptides to bind MHC.
4. Vesicles fuse with cell membrane, exposing Class II-peptide complex.
5. T-cell receptors (TCR) and CD4 on the surface of T_H cells recognize Class II-peptide complex.
6. Activation of T_H cell result in the production of cytokines that activate **both** B-cells and T_C cells.

The Nature of Antigens and Immunogens:

- Membrane bound (and soluble) antibodies produced by B-cells are capable of recognizing a broad array of antigens. This includes, in the order of frequency of observation:
    1. Proteins
    2. Carbohydrates
    3. Haptens
    4. Lipids
    5. Nucleic acids

Thus, technically, all of the above are antigens. However, not all of these are immunogenic or capable of generating a cell mediated immune response. In general the antigen must be coupled to a protein (or peptide) such that stimulation of T_H cells can occur via interaction between the TCR and peptides presented on the class II MHC molecules that are on the surface of a B-cell.

- Immunoglobulins that bind to proteins are capable of recognizing both continuous (i.e. primary structure of a protein) as well as discontinuous epitopes. A discontinuous epitope is a surface area of the protein antigen that is composed of different segments of the primary structure. The bulk of naturally occurring epitopes are of the discontinuous type.
- Although it is possible to generate antibodies against peptides (this is done routinely and is how antibodies to epitope tags on proteins are generated), the binding affinity of antibodies towards peptides is usually considerably lower than towards folded proteins.

Experimental determination of Epitopes and Immunogens:

- As a result of the fact that antibodies recognize discontinuous epitopes, the only sure-fire way of determining the B-cell epitope on a protein is to determine the structure of the antibody-protein complex.
- In contrast, it is quite easy to determine which parts of a foreign protein are responsible for the cellular response (i.e. MHC mediated) because MHCs only bind short linear peptides. One can simply chop a protein up into peptides 7-9 long and then see which ones bind to the MHC.

Self Study:

Can you describe the immune response to:

i. A bacterial infection in your arm,
ii. A bacterial infection from your intestinal tract,
iii. A viral infection,
iv. A cancerous cell in your body.

What is the process of generating immunity? When are B-cells involved? When might B-cells not be involved? Which MHC type is most likely to be involved?