

It seems like a lot of this lecture overlaps with other lectures that we have had. It also took the lecturer a long time to get to the point of the lecture and when he finally did, he didn't go into that much detail.

I. The concept of "immunologic self" arose when people started to look at skin grafts

- A. The first interest arose in relation to transplanting animal tumors
- B. Had a renewed interest in Britain because of burn victims from the war
- C. Compatibility is genetically determined but extremely polymorphic
 - 1. The MHC are a set of genes working together that regulate this system
- D. The differences between MHCs in individuals are central to "immunologic self"

II. T-Cells and the adaptive immunity are responsible for rejection of grafts

- A. T-cells recognize a complex ligand
 - 1. MHC on the cell surface bound to the peptide that that T-cell is specific for
 - a. Specificity is determined by certain peptide amino acids that bind the MHC and separate amino acids that bind the TCR
- B. T-cells are the heart of adaptive immunity and regulate the B-cells

III. Clonal selection is key to regulating the adaptive immunity

- A. Use clonal selection to identify the appropriate clones for the repertoire
- B. A large number of clones are needed to recognize a diverse array of antigens
- C. All clonal selection is done with the MHC bound to self-peptides in the thymus
 - 1. Self-peptides function as surrogates for later non-self peptides
 - 2. Could lead to problems with autoimmunity
 - 3. Thus, our uniqueness is actually determined by the combination of self-peptide and self-MHC
- D. Selection of thymocytes expressing TCR has multiple stages
 - 1. T-cells with no affinity for self-MHC complex undergo apoptosis
 - 2. T-cells with "appropriate" affinity are positively selected to survive
 - 3. T-cells with "high" affinity are negatively selected to undergo apoptosis
- E. Definition of "Immunologic self"
 - A. The recognition specificity of an individual's T cell repertoire for peptides presented by MHC
 - B. Also the set of self-peptides and self-MHC molecules that generated the repertoire

IV. Immune response to antigens

- A. Recapitulates the selection pathways but uses non-self instead of self
 - 1. The foreign peptide is a mimic/partial mimic of the self-peptide
- B. Our recognition of antigens differs from each other because of MHC polymorphisms
 - 1. Need 250K-1 Million individuals to find someone with the same HLA alleles as you
 - 2. Provides a selective advantage to the species as a whole
 - a. Any attempts to evade a single individual's immune system may not provide any advantage in a 2nd individual who recognizes different peptides.

V. 2 Different threats that the immune system must recognize

- A. Virus infecting a cell and commandeering the cell machinery to replicate
 - 1. Immune system is forced to kill this cell
- B. Bacteria/other pathogen that is extracellular and engulfed by a phagocyte
 - 2. These cells must be helped to eliminate the ingested pathogen rather than be killed.

VI. Immune system makes the distinction by putting the peptides on different forms of the MHC molecule

- A. Virally infected cell

1. Antigenic peptide is synthesized within the cell and degraded in the cytosol
2. It is bound to MHC class I on the surface of the cell and recognized by CD8 T-cell
3. Cell is killed

B. Extracellular pathogen

1. Peptide is degraded in endocytic vesicles
2. Presented on the cell surface in the context of Class II MHC and presented to CD4 T-cells
3. T-cell helps the antigen presenting cell eliminate the pathogen.

VII. MHC Class I and Class II differences

A. MHC is 4 million base pairs on the short arm of chromosome 6 near the telomere.

1. Class I locus has HLA-A, HLA-B, HLA-C
2. Class II locus has HLA DR, HLA DQ, and HLA DP

B. Class I structure (Slides 13-17)

- A. Symmetrical molecule that has the peptide bound like a hot dog in a bun for TCR recognition
- B. In a space filling model from the side you see a transmembrane portion, an intracellular portion, and 3 extracellular domains with the peptide sitting in them.
- C. Also binds β 2 microglobulin for stability
- D. 2 peptide binding domains are part of same heavy chain with a 3rd domain that holds the peptide binding domain up
- E. Peptide must be held on tightly so that exchange of peptides between cells does not occur.
 1. This would lead to killing of non-infected cells
 2. The Class I molecule without a peptide is unstable and degraded.

C. Class II structure (Slides 15-18)

- A. Homologous to Class I but not identical
- B. 2 chain molecule, linked with disulfide bonds
 1. Similar conformation but biochemically different from class I
 2. Both chains are encoded by the MHC locus

VIII. 2 levels of diversity in the MHC locus

A. Within the individual you have different loci within the MHC (ex- HLA A,B,C)

1. This is due to gene duplication allowing for mutations in one locus with no affect of function
2. Allows different antigen specificity within the individual
3. Are expressed as a dominant genetic traits (I'm assuming he means like blood group antigens, co-dominant)

B. Allelic diversity between individuals

1. Have hundreds of alleles for these loci
2. This constitutes the basis for immunologic self

C. Why only 3 loci (A,B,C and DR,DQ, DP)? Why not 10?

1. Each time you duplicate, you magnify self and the thymus must remove more T-cells
 - a. T-cell population is too low
2. If less than 3, you're MHC repertoire is much too low for the number of antigens
3. 3 is the magic number in all species

IX. Peptide binding

A. N-term and C-term are always oriented in the same direction. This is critical for T-cell recognition.

1. Amino acids within the peptide binding pocket determine the specificity

B. Class I

1. Binds peptides of length 9 amino acids usually, sometimes 8 (don't worry about it binding to 10)
2. 2nd amino acid is anchored to the Class I molecule and the C-term side chain as well (amino acid 9)

C. Class II

1. Peptide length varies from 12-24 amino acids.
 - a. Endosomally digested peptides are not degraded precisely
 - b. Class I is a much more precise mechanism
2. The peptide is usually tethered in the center, not the ends (amino acids 4&6)

D. For both Class I and II you get no peptide exchange on cellular surfaces

X. Class I loading

A. Chaperone proteins are very important

1. Calnexin stabilizes MHC class I in ER until $\beta 2$ microglobulin binds
2. Calreticulin and esp57 bind to the fully assembled Class I molecule and bind to tapasin, which is next to the TAP transporter

B. The proteasome degrades peptides in the cytosol

1. These are passed through the TAP transporter, into the ER.
2. Peptide is loaded co-synthetically onto the class I molecule, the chaperones disassociate
3. A vesicle pinches off and goes to the Golgi and cell surface

C. TAP proteins

1. Have ATP binding cassettes thus you burn energy to load peptides
2. Have a hole in the top through which the peptide is sent into the ER

D. Proteasome

1. Garbage disposal unit that degrades ubiquitin bound proteins that are linearized and send through the proteasome's catalytic domains.
2. Has 2 β rings which has 7 subunits
 - a. $\beta 1$, $\beta 2$, $\beta 5$ have catalytic activity.
3. IFN- γ is very important cytokine that changes antigen processing and presentation
 - a. Upregulates MHC class I, class II and TAP gene products
 - b. Replaces the 3 catalytic subunits with LMP1, LMP7 and MECL1
 1. These have specificity to make peptides which are more likely to bind MCH class I
4. Proteasome knockout mice have T-cell repertoires that are much less effective
5. Leucine amino peptidase (LAP also induced by IFN- γ) nibbles peptide until it is 8-9 amino acids

E. DRIPS- Defective ribosomal products

1. Only 1 in 10,000 proteins made in the cytosol ends up on the cell surface
2. These defective ribosomal products make up the majority of proteins which end up in the ER attached to class I molecules
3. Cell makes a bet that the viral proteins that are made are not made as efficiently as normal proteins
 - a. incorrectly made proteins are the first to be degraded by the proteasome

XI. Class II loading

A. Critical molecule is invariant chain (Ii)

1. Class II MHC is made within the ER and complexes with Ii
2. This plugs the peptide binding site so that no other ER peptide enters the cleft
3. Recognition sequence on Ii targets the newly formed molecule to be sent to the endosome

B. In the proteolytic environment of the endosome

1. Parts of Ii are cleave away so that on the Class II invariant peptide (CLIP) is left in the binding cleft
2. HLA-DM acts as a catalyst to release CLIP from the binding site
3. HLA-DM remains associated so that the peptide with highest affinity actually remains bound to Class II