Lectures 5. and 6. Antigen presentation and MHC: Structure and genetics

Learning objectives:

1. Understand how T cells recognize antigen and that the diversity of the peptides to be recognized requires an enormous repertoire of different T cell clones, distinguished by receptors of different specificity that react with MHC and peptide. The T cell receptor (TCR) binds to both the peptide and the MHC molecule.
2. Understand that in order to prevent microbial pathogens mutating around a static antigen presenting MHC, the evolutionary strategy is to evolve many alternative MHC molecules that bind different peptides. Some of this diversity comes from duplicating MHC loci within the MHC accounting for its organization, and some comes from alleles at each locus. The MHC contains by far the greatest number of alleles in the genome, understand why this is so. Be able to explain frequency dependent selection and heterozygote advantage, and why further duplication of MHC loci is not likely to be beneficial.
3. Appreciate that T cell clones specific for pathogen peptides must be developed before the individual encounters the pathogen and that the solution to this problem is the use of self-peptides as surrogates.
4. Consider that as a consequence of these first three points that a clonal selection process is required to select a different T cell repertoire appropriate for each individual's combination of MHC genes and self peptides, immunologic self. Appreciate that the consequences of this are autoimmunity and graft rejection.
5. Understand the significance of the statement "Immunologic self is the nearly unique set of self-peptides and self-MHC molecules that generates, and in turn is recognized, by the individual's unique adaptive immune system T cell repertoire".
6. Understand the two types of challenges pathogens present to the adaptive immune system, how the T cells are specialized to kill or to help, how each type of pathogen peptide is routed to either class I or class II to elicit respectively killing or help, the different molecular mechanisms used to accomplish pathogen peptide recognition and pathogen elimination in different immune responses.
7. Appreciate the structure of class I and II MHC molecules, how they are genetically encoded, how they are expressed, the differences in peptide binding to class I and class II molecules, and how their polymorphisms enables them to bind different peptides.
8. Learn the overall organization of the MHC and important genes in class I, class II and class III regions. Understand the nomenclature used to describe MHC genes.
9. Understand the implications of the codominant expression of MHC genes and the genetic relationship between parents and their children and between siblings. Appreciate how this influences the selection of a graft donor or the inheritance of an autoimmune disease.
10. Understand how different MHC alleles confer different functional properties on the adaptive immune system by specifying molecules that have different peptide binding abilities.
11. Appreciate the processes involved in how cytoplasmic or ingested peptides get loaded onto the proper kind of MHC molecule during immunosurveillance.

12. Review how it is that 6 different kinds of class I molecules are expressed on the surface of virtually every nucleated cell, and how each of these has its own separate T cell repertoire. Review how an “professional” antigen presenting cell (DC, macrophage, B cell) that expresses class IIMHC molecules is associated with additional T cell repertoires. Appreciate how HLA-DR differs from HLA-DQ in this respect (This will be important to understanding who can develop celiac disease).
13. Be able to explain how the T cell responses differ in two unrelated individuals with different MHC genes that are responding to the same viral infection.