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The MHC Complex

Friday, February 15, 2008
10:00 AM

- Diversity
 - Not as diverse as TCR or antibodies
 - Purpose is to increase range of peptides that can be presented to T cells
 - Diversity w/in population has major medical implications (organ transplantation)
 - Basis of Diversity
 - Genes are stable and not rearranged
 - Polygeny - each individual has multiple genes that encode for class I heavy and class II α and β chains
 - Polymorphism - for each MHC gene there are many different variants w/in population
- MHC Genes
 - On human chromosome 6
 - MHC locus is so called b/c genetic polymorphisms encoded in this region identified as principal cause of graft rejection btwn individuals
 - Aka HLA complex
 - Polygeny
 - Six MHC class I heavy chain genes - HLA-A through G
 - A,B,C involved in presentation of antigens - many alleles
 - E and G expression may prevent attack by NK cells which recognize and kill class I negative targets
 - F fxn unknown
 - Remember $\beta 2$ is invariant
 - Class II - DM, DO, DP, DQ, DR
 - DP, Q, R involved in antigen presentation
 - Number of DRB genes is variable (can have two)
 - HLA-DR is most variable along w/ HLA-A,B,C
 - Haplotypes
 - Particular combination of alleles
 - HLA expressed co-dominantly so heterozygotes express two haplotypes
 - Can express as few as 3 class I and 3 class II molecules or as many as 6 and 8, respectively
 - Homozygote: HLA-A, B, C, DP, DQ, DR X 1 = 3 class I, 3 class II
 - Heterozygote: HLA-A, B, C, DP, DQ, DR (2) X 2 = 6 class I, 8 class II
 - Sequence Differences
 - Concentrated in the regions involved in binding peptide and TCR
 - Affect nature of peptides that can be bound by MHC molecules and interaction of MHC-peptide w/ TCR
 - MHC Restriction
 - T cells from one individual recognize peptide together w/ MHC molecules from same individual but not MHC from another
 - Ability to recognize in context of self MHC is known as MHC restriction and is imprinted upon T cells during development
- MHC Diversity and Peptide-binding
 - Different MHC molecules bind different sets of peptides
 - For each molecule there is an identifiable peptide-binding motif
 - Conserved residues w/in a motif are called anchor residues
 - Polygenic nature of MHC and co-dominant expression of genes permits a larger set of peptides and the activation of more effective immune response
 - Polymorphism is driven by intense selective pressure to be able to bind peptides from wide variety of pathogens

- Generation of new MHC alleles
 - During meiosis, interallelic conversion (crossing-over)
 - Resort different alleles into new haplotypes
 - Gene conversion btwn different genes on same chromosome
 - Combination of alleles is referred to as HLA type
 - T cells from individual of one haplotype can recognize and respond to MHC molecules of another haplotype --> allogenic differences
 - Basis for transplantation rejection
 - Some T cells may cross-react w/ complexes of donor MHC-donor peptide --> mimics self MHC/foreign peptide complex
 - May affect 1-10% of T cell clones
 - Alloreactivity places constraint upon polygeny at the MHC locus
- HLA region
 - Btwn DP and DQ, proteins for processing and presentation encoded (TAP, tapasin, proteasome)
 - Interferons up-regulate expression of these genes and MHC genes
 - Constitutive and induced expression of MHC class II is coordinated by CIITA
 - Deficiency causes BLS of class II/CD4 T cells
 - Class III region
 - Located btwn class II and I
 - Encodes other immune related genes, incl. complement proteins, TNF, LTB, LTA