E-content for

B.sc. Part-III Zoology Honours Paper VII: Group B- Immunology

Major Histocompatibility Complex

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MHC

- Major Histocompatibility Complex
 - Cluster of genes found in all mammals
 - Its products play role in discriminating self/non-self
 Participant in both humoral and cell-mediated immunity
- MHC Act As Antigen Presenting Structures
- In Human MHC Is Found On Chromosome 6
 Referred to as HLA complex
- In Mice MHC Is Found On Chromosome 17

Referred to as H-2 complex

MHC

- Genes Of MHC Organized In 3 Classes
 Class I MHC genes
 - Glycoproteins expressed on all nucleated cells
 - Major function to present processed Ags to $T_{\rm C}$
 - Class II MHC genes
 - Glycoproteins expressed on $M\Phi$, B-cells, DCs
 - Major function to present processed Ags to $T_{\rm H}$
 - Class III MHC genes
 - Products that include secreted proteins that have immune functions. Ex. Complement system, inflammatory molecules

MHC Genes Are Polymorphic

- MHC Products Are Highly Polymorphic
 - Vary considerably from person to person
- However, Crossover Rate Is Low
 - 0.5% crossover rate
 - Inherited as 2 sets (one from father, one from mother)
 - Haplotype refers to set from mother or father
- MHC Alleles Are Co-dominantly Expressed
 Both mother and father alleles are expressed
- Inbred Mice Haplotypes Are Designated With Italic Superscript
 - Ex. H-2^b
 - Designation refers to entire set of H-2 alleles

Class I MHC Molecule

- Comprised of 2 molecules
 - $-\alpha$ chain (45 kDa), transmembrane
 - $-\beta_2$ -microglobulin (12 kDa)
 - Non-covalently associated with each oth
- Association Of α Chain and β_2 Is Required For Surface Expression
- α Chain Made Up Of 3 Domains ($\alpha 1$, $\alpha 2$ and $\alpha 3$)
- β_2 -microglobulin Similar To $\alpha 3$
- α1 And α2 Form Peptide Binding Cleft
 - Fits peptide of about 8-10 a/a long
- α3 Highly Conserved Among MHC I Molecules
 - Interacts with CD8 (T_C) molecule



Class II MHC Molecule

- Comprised of α and β chains
 - α chain and β chain associate non-covalently
- α and β chains Made Up Of Domains
 - $-\alpha 1$ and $\alpha 2$ (α chain)
 - $-\beta 1$ and $\beta 2$ (β chain)
- αland βl Form Antigen Binding Cleft
- α and β Heterodimer Has Been Shown To Dimerize
- CD4 Molecule Binds $\alpha 2/\beta 2$ domains

Class I MHC Peptides

- Peptides Presented Thru MHC I Are Endogenous Proteins
- As Few As 100 Peptide/MHC Complex Can Activate T_C
- Peptide Features
 - size 8-10 a/a, preferably 9
- Peptides Bind MHC Due To Presence Of Specific a/a Found At The Ends Of Peptide.



Class II MHC Peptides

- Peptides Presented Thru MHC II Are Exogenous
 Processed thru endocytic pathway
- Peptides Are Presented To $T_{\rm H}$
- Peptides Are 13-18 a/a Long
- Binding Is Due To Central 13 a/a
- Longer Peptides Can Still Bind MHC II
 Like A long hot dog
- MHC I Peptides Fit Exactly, Not The Case With MHC II Peptides

MHC Expression

- Expression Is Regulated By Many Cytokines
 IFNα, IFNβ, IFNγ and TNF Increase MHC expression
- Transcription Factors That Increase MHC gene Expression
 - CIITA (Transactivator), RFX (Transactivator)
- Some Viruses Decrease MHC Expression
 CMV, HBV, Ad12
- Reduction Of MHC May Allow For Immune System
 Evasion

Antigen Processing & Presentation

- Formation of peptide-MHC complexes require that a protein antigen be degraded into peptides & displayed within the cleft of the MHC molecule on the cell membrane. The sequence of the above events is called *antigen processing*.
- The display of the transported peptide-MHC molecules on the cell membrane is called *antigen presentation*.
- Class I MHC molecules bind peptides derived from endogenous antigens processed in the cytoplasm.
- Class II MHC molecules bind peptides derived from exogenous antigens that are internalized by phagocytosis or endocytosis & processed within the endocytic pathway.

Antigen Presenting Cells

- □ Cells expressing class I or II MHC molecules can present peptides to T cells.
- By convention, cell that display peptides associated with class I MHC molecules to CD8⁺ T cells are referred to as *target cells*.
- □ Those cells that display peptides associated with MHC class II molecules to T_H cells are called antigen presenting cells.

TABLE 8-3	Antigen-presenting cells		
Professional antigen- presenting cells presenting cells			
Dendritic cells (several types	; Fibrob)	lasts (skin)	Thymic epithelial cells
Macrophages	Glial co	ells (brain)	Thyroid epithelial cells
B cells	Pancre cells	atic beta	Vascular endothelial cells

Antigen Processing

- Extracellular (exogenous) antigens are eliminated by secreted antibody whereas intracellular (endogenous) antigens are eliminated by CTLs.
- There are 2 different antigen-presenting pathway to mediate responses.
 - Cytosolic pathway (endogenous pathway)
 - Endocytic pathway (exogenous pathway)

Endogenous Pathway

- Endogenous antigens are degraded into peptides that can be presented in class I MHC molecules to T_C cells involving similar mechanisms as of intracellular proteins.
- Ubiquitin \rightarrow Ubiquitin-protein conj \rightarrow Proteosome
- Subunits of large cytoplasmic proteolytic complex are called low-molecular mass polypeptides (LMP).

Cytosolic (endogenous) Pathway





Endocytic (exogenous)Pathway

- APCs can internalize antigen by phagocytosis &/or endocytosis.
- Macrophages do both; B cells use receptor-mediated endocytosis.
- After antigen is internalized, it is degraded into peptides.
- Internalized antigen takes 1-3 hours to traverse the endocytic pathway & appear on cell membrane in the form of peptide-class II MHC complexes.
- Internalized antigen moves from early to late endosomes & finally to lysosomes where they are hydrolyzed into oligopeptides of about 13-18 residues that bind to class II MHCs.



Exogenous Pathway



CYTOSOLIC PATHWAY



