The Major Histocompatibility Complex (MHC)

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An introduction to adaptive immune system before we discuss MHC...B cells

• The main cells of adaptive immune system are:
  - B cells
  - T cells

• B cells: Recognize antigens that are either on cell surface or are circulating alone (soluble) and bind to them by their receptors...

• B cells are able to secrete their receptors (circulating antibodies) that are soluble and able to bind the antigens when the antigens are alone or when they are on cell surface
An introduction to adaptive immune system before we discuss MHC...T cells in general

• T cells: Recognize peptide antigens only when they are bound to MHC on the cell surface

• T cells are of main 3 types:
  - Helper T cells
  - Cytotoxic (cytolytic) T cells
  - Regulatory T cells... and control the immune response
An introduction to adaptive immune system before we discuss MHC...T helper cells

• T helper cells bind to antigens on the surface of antigen presenting cells (APC)...the antigen is of internalized extracellular microbe (e.g., bacteria), processed and presented on the surface of the APC to the helper T cell

...MHC is used here

• T helper cell secretes cytokines which do the following:
  - Activation of macrophages
  - Activation of inflammation
  - Activation of proliferation and differentiation of: -T cells
    - B cells
Antigen presenting cells

• They present antigens mainly for T cells. However, there are also APCs for B cells (follicular dendritic cells).

• Dendritic cells in epithelia and connective tissues ingest the microbe and present its peptides attached to the MHC on the surface. After that they travel to the draining lymph node and spleen where there is large chance to meet T lymphocytes with receptors specific for this peptide.

• Macrophages also present peptides for T cells

• So: APCs may be dendritic cells, monocytes/macrophages, B cells or follicular dendritic cells (for B cells in lymph node germinal center)
An introduction to adaptive immune system before we discuss MHC...Cytotoxic T cells (CTL)

• CTLs bind the peptides that were produced in the cytoplasm and displayed on the surface of the cell that is infected by virus (cytoplasmic microbe) or the malignant cell

...MHC is used here

• **So**: Both T helper and cytotoxic T cells recognize only peptide antigens when these antigens are attached to MHC molecules on cell surface
The Major Histocompatibility Complex (MHC)

• First discovered as mediators of organ transplant rejection...named so because of their role in determining tissue compatibility between individuals
• First detected on WBCs by antibodies...so called: human leukocyte antigens (HLA)
• Encoding genes are clustered on chromosome 6...highly polymorphic (thousands of alleles)...see next slide
• 2 major classes: I and II
Genetic polymorphism of MHC

• MHC is polygenic and polymorphic

• MHC genes are extensively polymorphic with multiple forms (alleles) of each gene
  ...this feature is at the level of population not the individual (every cell in each individual expresses the same set of MHC molecules)

How can the individual recognize the large number of microbial peptides by the limited MHC types expressed by his cells?
Class I MHC

- Expressed on: - all nucleated cells
  - platelets
- Heterodimer: polymorphic alpha (heavy) chain + non-polymorphic protein called beta2-microglobulin...non-covalent bond between the 2 chains
- Alpha chain: encoded by 3 genes: HLA-A, HLA-B and HLA-C
- Alpha chain has: extracellular region → 3 domains ($\alpha_1$, $\alpha_2$, and $\alpha_3$) form cleft (groove) that binds peptide
different amino acid sequence between different alleles
Class III molecules  Cytokines  Class I MHC molecules

Peptide-binding cleft

Peptide

β1

β2 microglobulin

HOOC

NH₂

NH₂

α1 domain

α2 domain

α3 domain

α chain

β2m

Peptide

Crystal structures are courtesy Dr. P. Bjorkman, California Institute of Technology, Pasadena, Calif. [modified]
Class I MHC, cont’d

• They display peptides that are localized in the cytoplasm and usually produced in the cell

• The peptides in this case are recognized by cytotoxic T cells (= CD8+ lymphocytes)

• Proteins that are produced in the cell degraded in proteasome transferred into ER where they bind newly-synthesized MHC I
Class I MHC, cont’d

• The molecule now associates with beta2-microglobulin then be transported to the cell membrane

• Alpha3 domain of class I MHC molecule is non-polymorphic and it has a binding site for CD8...so the cell that will recognize the peptide-MHC I complex is the CD8+ cytotoxic T lymphocyte (CTL)

• So: TCR (T cell receptor) recognizes peptide-MHC I complex, and the CD8 molecule on this T cell (acts as a co-receptor) binds to the class I heavy chain
Class I MHC, cont’d

• Because CD8+ T cells recognize peptides only when complexed with MHC I, they are called: class I MHC-restricted

*CTLs attack virally-infected and malignant cells, and because virus can infect any nucleated cell, and cancer can arise from any nucleated cell:

→ MHC class I is present in all nucleated cells to help CTLs in viral infections and cancers
Class II MHC

- Encoded in the region HLA-D
  
  ...3 sub-regions: HLA-DP, HLA-DQ, and HLA-DR

- Each molecule is a heterodimer of alpha and beta chains that are both polymorphic
Class II MHC

• Extracellular portion of alpha: 2 domains: alpha1 and alpha2

• Extracellular portion of beta: 2 domains: beta1 and beta2

• A cleft is formed by alpha1 and beta1...polymorphism mainly here (site of peptide recognition)
Class II MHC

- The peptides here are derived from internalized extracellular microbes or soluble proteins

...by proteolytic digestion in endosomes or lysosomes...then attached to MHC II and transported in vesicles to the cell membrane
Class II MHC

- Beta2 domain of MHC II has binding site for CD4 on CD4+ T cells (T helper cells)...so MHC II-peptide complex is recognized by CD4+ T helper cells

...CD4 acts as co-receptor

- CD4+ T cells are class II MHC-restricted
Class II MHC molecules

Peptide-binding cleft

Peptide

α1

β1

β2

α2

β2 n

H₂N

NH₂

(S-S)

(S-S)

HCOOH

COOH

Crystal structures are courtesy Dr. P. Bjorkman, California Institute of Technology, Pasadena, Calif.
Class II MHC

- Expressed on cells that:
  - present ingested antigens
  - respond to T cell help

...so we talk about:
- macrophages
- dendritic cells
- B cells
Other molecules encoded in MHC locus

• Cytokines: TNF and lymphotoxin

• Some complement components (MHC class III)

• Others
Thank You