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

  Receptor for B cells, T cells→ specific and very diversity,
  So these receptor will bind with huge number of antigens

• 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

Can’t bind to antigen that are on cell surface or on circulating alone so its need to MHC on the cell surface. MHC helps in binding, its important in recognition between T cell and antigen.

• 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 CD4+
  - Cytotoxic (cytolytic) T cells CD8+
  - Regulatory T cells... and control the immune response

Reduce the number of leukocyte.
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 polymorphic with multiple forms (alleles) of each gene
  - T cells and B cells differ in their expression of MHC genes, with different alleles expressed in T cells and B cells.
- 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 beta 2-macroglobulin...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 (α1, α2, and α3) form cleft (groove) that binds peptide
- For intracellular cells (virus) and cancer cells so cytotoxic T cell

Have gene that will produce MHC1

Because every cell can expose to virus or convert to cancer cells

MHC2, population

Variable (polymorphic), bind to peptide

Bind to CD8 of cytotoxic lymphocyte

different amino acid sequence between different alleles
Class I MHC, cont’d

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

  Peptide of cancer or virus,, so cytotoxic T cells will recognize it.

• 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-macroglobulin 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

They are manufactured by macrophages, dendritic cells, and B lymphocytes, as we talked previously.

- 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)

Variable,, that make simple differences in our body ..and large differences in population (between persons)

Bind to peptides,, antigen T helper
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...

In T helper cells there is a receptor (co-receptor) >> CD4>>bind to beta 2 of MHC

...CD4 acts as co-receptor

• CD4+ T cells are class II MHC-restricted
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