IMMUNOLOGY SHEET

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LECTURE: MAJOR HISTOCOMpatibility COMPLEX
The Major Histocompatibility Complex (MHC)

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

• 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.

So B cells can recognize antigens by receptor on their surface or by the antibodies they secrete.

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.

Remember that T cells don't secrete antibodies like B cells and they bind to antigens by receptors on their surface.

**T cells receptor (on T cell surface only) can recognize linear peptide antigen presented by MHC on cell surface but B cell receptor on B cells or secreted antibodies can recognize linear & not linear antigens, peptide & non peptide antigens, bound to cell surface or soluble and without MHC**
• T cells are of main 3 types:
  - Helper T cells (CD4+)
  - Cytotoxic (cytolytic) T cells (CD8+)
  - Regulatory T cells... inhibit 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) (dendritic cells, macrophage, and B lymphocyte)...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 (MHC class II)
the APC cells mentioned above produce this type but MHC I produced by all nucleated cells in the body and platelets

Extracellular microbe → phagocytosis by APC→peptide antigen with MHC II then TCR on T helper cells bind to it and CD4 will bind to part of MHC II

• 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

Cytotoxic T cells bind to antigens of intracellular peptides (without the use of APC cells) but T helper cells bind to extracellular peptides presented by APC

...MHC is used here (MHC class I)

And as we said all nucleated cells and platelets can produce MHC I

The binding process is the same mechanism as T helper

TCR on T cells bind to MHC I and the peptide & CD8 bind to part of the MHC I

• 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)

HLA : Human leukocyte antigen

مثلاً، إنما كشفناه عن طريق antibodies خارجية الأختصاص لانه اكتشفنا عن طريق HLA : Human leukocyte antigen

• Encoding genes are clustered on chromosome 6...highly polymorphic (thousands of alleles)... (and that’s why it’s hard to find organs compatible with the patients in transplantation) and even in our bodies we don't have only 1 type of MHC
• 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? **Because it's specificity is low ( not like TCR )**

**Class I MHC**

• Expressed on: -all nucleated cells
  - platelets

• Heterodimer: polymorphic alpha (heavy) chain + non-polymorphic protein called beta2-microglobulin (**comes from another gene and not from the complex gene of MHC**)...non-covalent bond between the 2 chains

The **diversity of MHC I is controlled by alpha chain . beta 2-microglobulin is the same in all humans**

• Alpha chain: encoded by 3 genes: HLA-A, HLA-B and HLA-C

• Alpha chain has: extracellular region with 3 domains (**α1, α2**, and **α3**)

  **α1, α2 domains** form cleft (groove) that binds peptides (look at the pic in the next page) and this is the part that is different (polymorphic) in populations and to some extent in individuals
different amino acid sequence between different alleles

  **α3** is non-polymorphic and is the same in population (there may be some differences but not like in **α1, α2**)
Here as we can see is the structure of MHC I with the $\alpha_1$, $\alpha_2$ domains creating a groove to bind the peptide to make peptide-MHC I complex.

TCR receptor on the cytotoxic T cells will bind to this complex and the nearby CD8 will bind to $\alpha_3$ domain.

- They display peptides that are localized in the cytoplasm and usually produced in the cell (not from extracellular microbe as we said before).
- The peptides in this case are recognized by cytotoxic T cells (= CD8+ lymphocytes).
- Proteins that are produced in the cell will be degraded in proteasome transferred into ER where they bind newly-synthesized MHC I.
- 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).
Proteins produced from malignant/viral infected cells → degraded to peptides → bind to MHC I → associate with β2-microglobulin → go to cell membrane → cytotoxic T cell bind to it to kill the infected cell

- 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
- 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
- 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)
- 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
• **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

Here we have the same mechanism with a little difference

Extracellular microbe / soluble protein $\rightarrow$ phagocytosis and degraded into peptides $\rightarrow$ bind to MHC II (there is no β2-macroglobulin) $\rightarrow$ go to the cell surface $\rightarrow$ T helper cells bind to and produce cytokines.

TCR bind to peptide-MHC II complex ($\alpha_1$, $\beta_1$) and CD4 bind to $\beta_2$.

• Expressed on cells that: -present ingested antigens
  
  and  
  -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

The presentation is simple, but we can evaluate them between MHC I & MHC II. Between each species and their differences, characteristics may be transplanted. In the process of transplantation, there is a requirement for compatibility between the donor and the recipient. Unless there is compatibility of the immune system, we will recognize it as a foreign body. Macrophages and other microorganisms will destroy it.