LECTURE: 17

Title MAJOR HISTOCOMPATIBILITY MOLEUCLES (MHCs)

LEARNING OBJECTIVES:

The student should be able to:

- **Describe the organization & structure of MHC Genes & Products (MHC class I, II, & III molecules).**
- **Describe the role of the MHC in controlling the T-Cell response.**
- **Explain the MHC restriction.**
- **Explain the activation of $CD8^+$ cytotoxic T cells, & what determines whether an antigen elicits a class I or class II restricted response.**
- **Enumerate some common associated diseases with MHC types.**
- **Enumerate some common tests for MHC antigens (Serological detection of transplantation antigens, and detection of transplantation antigens by mixed leukocyte).**

LECTURE REFRENCE:

1. TEXTBOOK: NATIONAL MEDICAL SERIES FOR INDEPENDENT STUDY. RICHARD M. HYDE. 3RD EDITION. Chapter 2. pg 23-30.

2. TEXTBOOK: JONATHAN M. AUSTYN AND KATHRYN J. WOOD Principles of Cellular and Molecular Immunology. Chapter 2. pg 63-84.

3. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. pg 58, 216, 489.

4. TEXTBOOK: LAUREN SOMPAYRAC. HOW THE IMMUNE SYSTEM WORKS. PP 13.

MAJOR HISTOCOMPATIBILITY MOLECULES (MHCs)

■ INTRODUCTIO

Transplantation is important for many reasons, both in terms of its impact on our understanding of immunological processes as well as its application in the development of clinical transplantation. Studying of transplantation indicates the central role of the T lymphocytes in the transplantation and rejection, also the physiology of T cells, self tolerance and autoimmunity, and of the thymus in T-cell education is derived from the studies of transplantation. Rejection phenomenon has led to the development of immunomodulatory drugs and search for ways to induce tolerance of the grafted tissues. These approaches also have a more general application in the treatment of many immune disorders, such as immune-mediated tissue-damage in hypersensitivity and autoimmunity.

UNLESS THE DONOR AND RECIPIENT ARE GENETICALLY IDENTICAL, THE GRAFT ANTIGEN WILL ELICIT AN IMMUNOLOGICAL REJECTION RESPONSE

Transplantation can stimulate humoral and cellular immunity, specific and non-specific (all the various active mechanisms of the immune system). The reason for all of these activations is the recognition of recipient's T cells of foreign peptide antigens associated with the foreign MHC molecules on grafted cells. The peptide antigens in this context are the normal constituents of donor cells, but they may also come from viruses within the cells, or from other microbes.

■ GENETIC DISPARITY BETWEEN DONOR AND RECIPIENT FORM THE TRASPLANTATION BARRIER.

Grafts can be classified as:

1. **Autograts** are grafts removed from and placed in the same individual.
2. **Isografts** or **(syngeneic grafts)** involve the transfer of normal tissue between genetically identical (syngeneic) individuals; that is, between identical twins or animals of the same inbred line.
3. **Allografts**, or **(homografts)**, involve the transfer of normal tissue between allogeneic individuals; that is, between genetically different individuals of the same species. For example; from Mustafa Linjawi to Hasan Abdul-Allah.
4. **Xenografts or (heterografts)** also called **xenogenic** grafts, involve the transfer of tissue between animals of two different species.

OUTCOME

1. **Generally, autografts and isografts survive** for an indefinite period of time.

2. **Allografts and xenografts** result in an **immune rejection** phenomenon of a lesser or greater degree, which may or may not be prevented or aborted by the use of immunosuppressive agents.

■ HISTOCOMPATIBILITY ANTIGENS

In human the highly polymorphic cell surface structures involved in rejection is called in human "**Human leukocyte antigens** (**HLA**) **system"**, but in mice the **MHC** is called, (**H-2**). Three classes of molecules (I, II, and III) have been identified as encoded within the murine and human MHCs. Class I, and II molecules represent distinct structural entities; all class I, and II gene products have similar overall structure. In contrast, class III region contains a rather **diverse** collection of over 20 genes, including some that encode complement system molecules (C4, C2, factor B), and some that involve in the processing of antigen. **There are no established functional or structural similarities between class III gene products and the class I or class II molecules. Therefore, only those loci involved in triggering T lymphocytes-the class I and II genes and their gene products (Figure-1).**

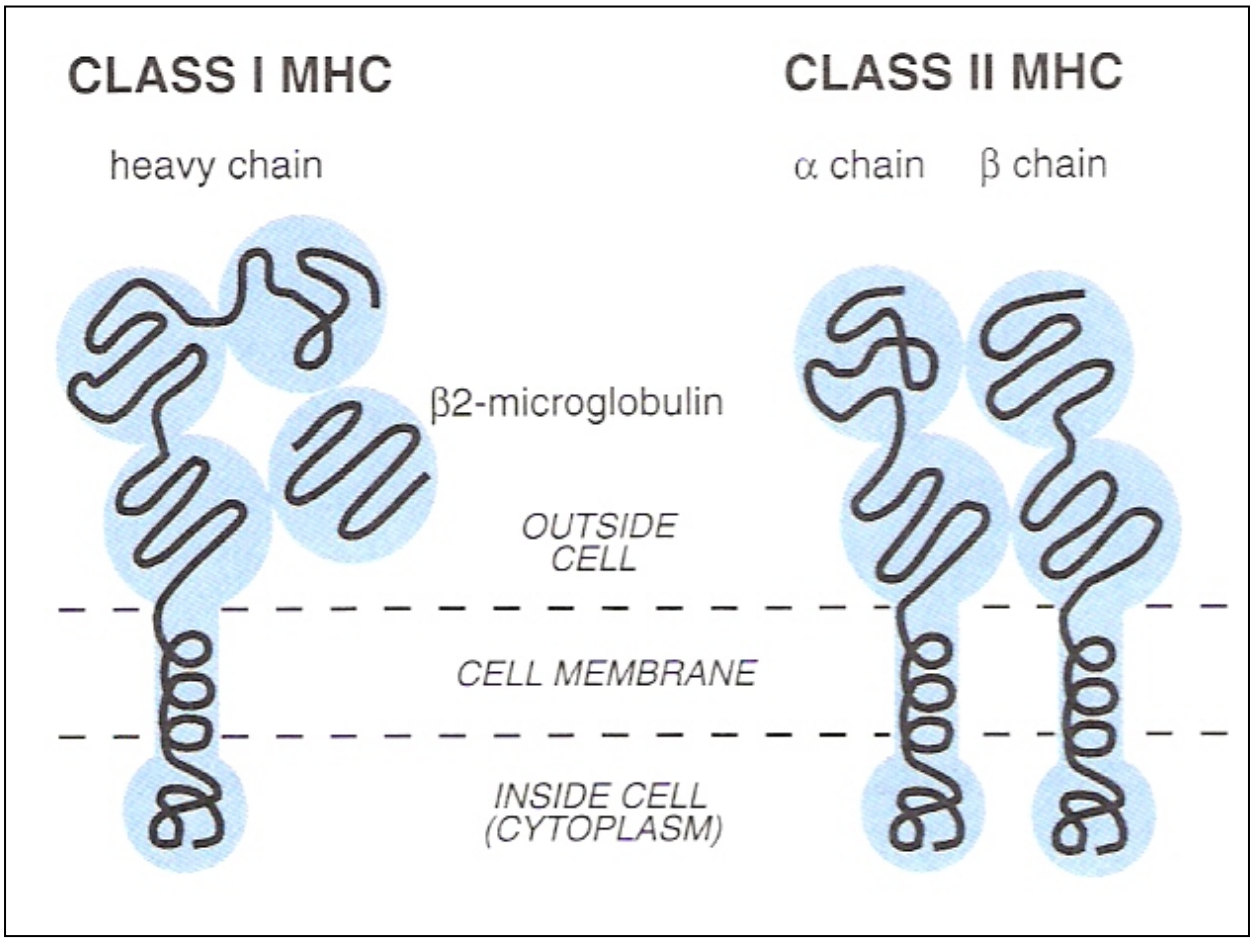

Figure-1 Class-I and II of the MHC molecules

Histocompatibility antigens are the targets for rejection

The antigens are responsible for rejection of genetically different tissues is known as histocompatibility (e.g., tissue compatibility) antigens, and the genes coding for these antigens are referred to as histocompatibility genes on chromosome 6. **They are more than 30 histocompatibility gene loci (Figure-2, and 3),** and they cause rejection at **different rates.** Of these, alloantigens encoded by the genes of the MHC induce particularly: **MAJOR HISTOCOMPATIBLILITY ANTIGENS**, these are the molecules which present antigens in a form recognizable by T- cells (**strong reactions**), all vertebrate species have an MHC. The products of the allelic variants of the other histocompatibility genes **individually cause weaker rejection responses** and are consequently known as **MINOR HISTOCOMPATIBILITY.**

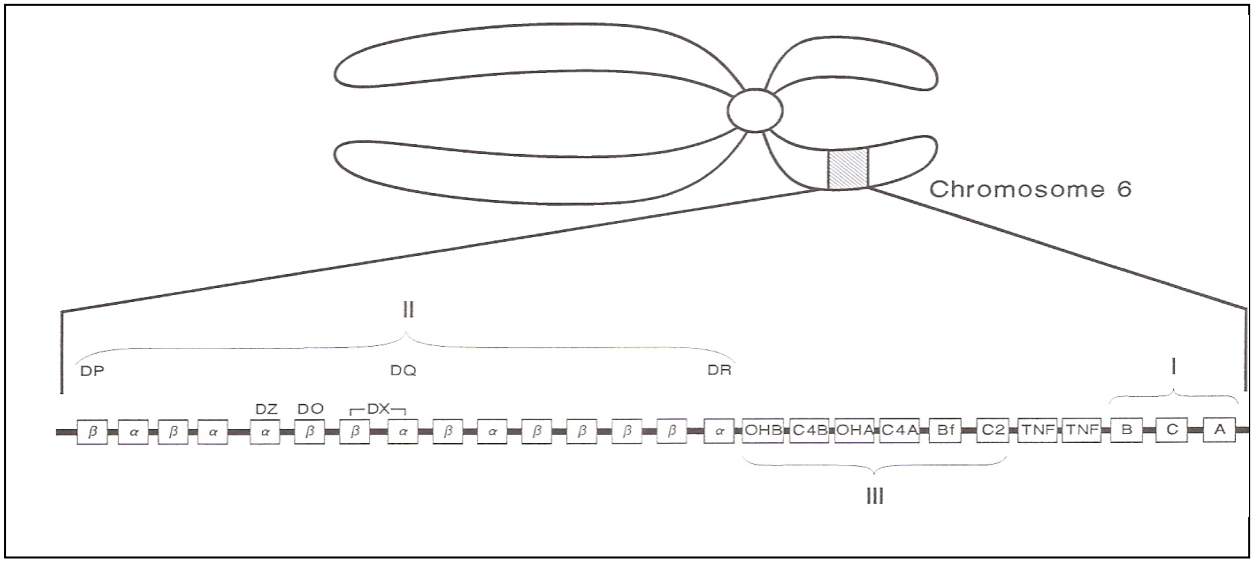

Figure-2 HLA is an abbreviation for human leukocyte antigen. The HLA locus in humans is found on the short arm of chromosome 6. The class I region consists of HLA-A, HLA-B, and HLA-C loci and the class II region consists of the D region which is subdivided into HLA-DR, HLA-DQ and HLA-DR subregions.

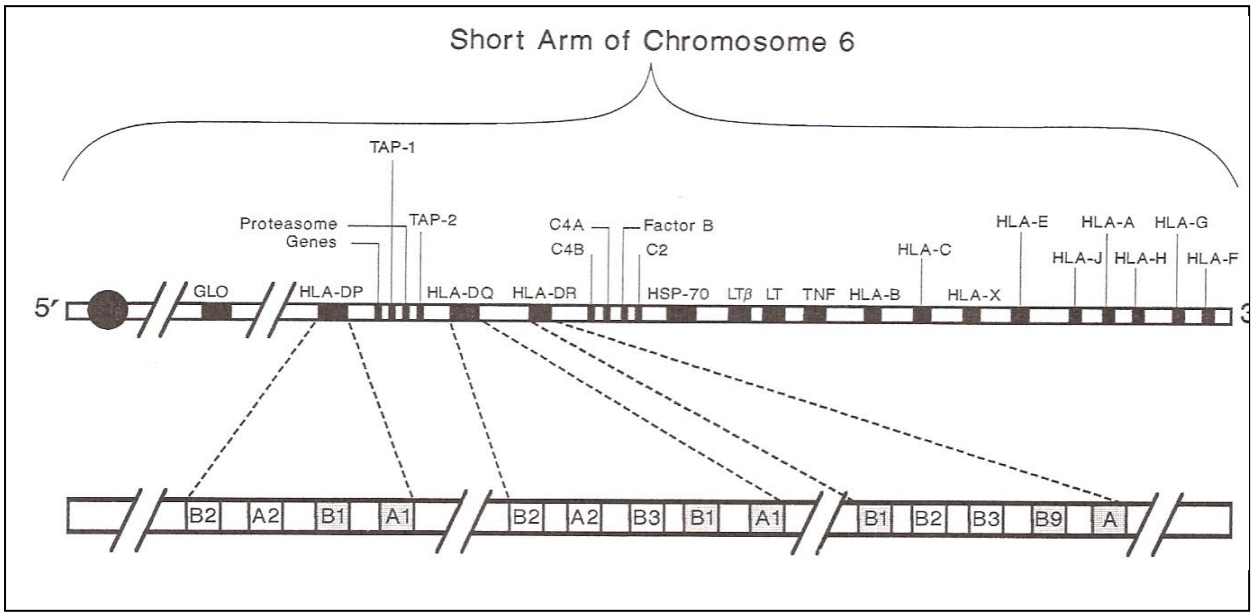

Figure-3 MHC genes (major histocompatibility complex genes) encode the major histocompatibility antigens that are expressed on cell membrane. MHC genes in the mouse are located at the H-2 locus on chromosome 17 whereas the MHC genes in man are located at the HLA locus on the short arm of chromosome 6.

MHC haplotype are inherited from both parents and are co-dominantly expressed.

Each individual has two "half-sets" (haplotypes) of genes, one haplotype inherited from each parent. Both of these haplotypes are expressed equally so that each cell in the offspring has both maternal and paternal MHC molecules on its surface. MHC molecules are expressed on transplanted tissues and induced by cytokines.

MHC molecules are not equally distributed on all cells of the body. **Class I molecules** are normally expressed on most nucleated cells (and on erythrocytes and platelets in some species). **Class II molecules** are **restricted** to antigen-presenting cells (APCs, e.g., dendritic cells and activated macrophages), B cells and in some species, activated T cells and vascular endothelial cells.

The expression of MHC on cells is controlled by cytokines: Interferon-gamma and tumour necrosis factor (TNF) these are powerful inducers of MHC expression on many cell types which would otherwise express MHC molecules only weakly.

■ THE LOWS OF TRANSPLANTATION

The transplant situation is unique in that foreign MHC molecules can directly activate T cells. Conventional T cell responses against foreign proteins require that such antigens are processed into peptides and presented on the surface of the recipient's APCs in association with MHC molecules.

Host-versus-graft responses cause transplant rejection

The principle of host-versus-graft reactions is whether, the graft carries any antigens that are not present in the recipient. For example;

1. **Isografts**, which are identical at the MHC locus, accept grafts from each other.
2. Animals that differ at the MHC locus **reject** grafts from each other
3. The ability to accept a graft is dependent on the recipient **sharing all the donor's histocompatibility genes: this is illustrated by the difference between grafting from parental to offspring.**
4. Animals that differ at the loci other than the MHC **reject** the grafts from each other, **but** much more slowly.

Graft-versus-host reactions result when donor lymphocytes attack the graft recipient.

Special situation occurs in bone marrow transplantation, in which graft-versus-host disease **[(GVHD) is major complication of bone marrow transplantation]** is induced by immunologically competent T cells being transplanted into allogeneic recipient which are unable to reject them. This inability may be due to the genetic differences between the donor and recipient, or because of a lack of immunocompetence (through immaturity or immunsuppression) of the recipient. In this situation, the immunocompetent T cells transplanted with the bone marrow can attack the recipient.

■ THE ROLE OF T-LYMPHOCYTES IN REJECTION

T cells are pivotal in graft rejection

To prove this:

1. Adult thymectomy (AT), [to stop the production of T cells].
2. Irradiation (x) [to remove existing mature T cells] and,
3. Bone marrow transplantation (to restore haematopoiesis) produces 'Atx.BM recipient's which have no T cells and cannot reject grafts.

The ability to reject grafts is restored by the injection of T cells from a normal animal of the same strain. **Thus T cell is necessary for rejection, but this does not imply that antibodies, B cells, or other cells play no part. Indeed, antibodies cause graft damage and macrophages may be involved in inflammatory reactions in grafted tissues.**

Rejection responses have a molecular basis in the TCR-MHC interaction

Via their T-cell receptors (TCRs), the T cells involved in rejection recognize donor-derived peptide in association with the MHC antigens expressed on the graft. As it was explained, the T cells recognize peptide antigens when they are associated with MHC molecules, and this MHC restriction is imposed by positive selection in the thymus. The negative selection (deletion of self –reactive clones) occurs when the T cells meet dendritic cells in corticomedullary junction.

Different MHC molecules have similar structures but different peptide-binding grooves

The structures of different MHC molecules are almost identical, with the overall shape consisting of two alpha helices lying on a beta-plated sheet. The part of the MHC molecules that is important in T-cell recognition is the **outer surface** of the **alpha helices**, which is highly **conserved** between different MHC molecules. For T cell recognition the principal difference between MHC molecules is in the **shape** and **charge** of the peptide-binding groove (**Figures 4,5, and 6**).

Figure-4 Fitting of the protein's fragments into the groove

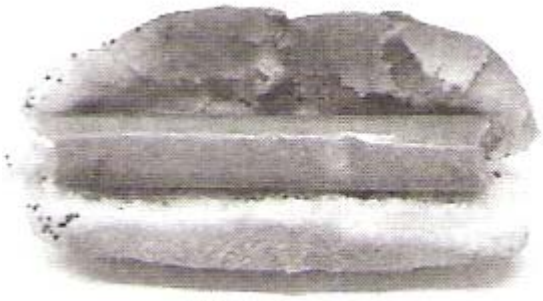

Figure-5 Class I because the peptide tits nicely into the groove.

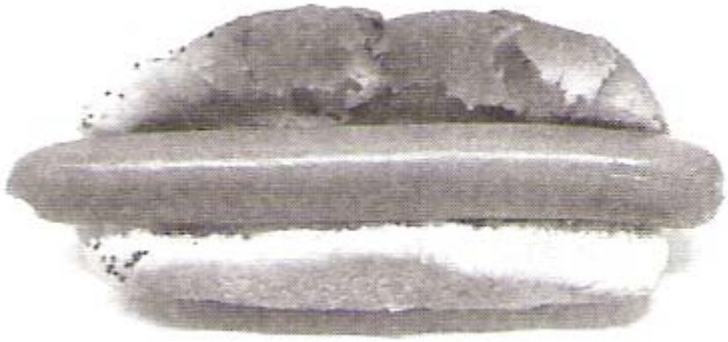

Figure-6 Class II antigenic peptide overflows the groove

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