



Transplantation

Lecture 2

Prof. Zahid Shakoor

Explanation & Extra Notes

Major Histocompatibility Complex & Transplantation

Introduction

- **MHC:** 'major histocompatibility complex', they were discovered with tissue transplant
- **HLA:** 'human leukocyte antigens', encoded by HLA genes
- Transplantation depends upon the donor's and recipient's HLA gene combinations.
- These proteins are *allo-antigens**
- HLA gene proteins are found in the MHC located on the short arm of chromosome 6

You can use '**MHC**' & '**HLA**' interchangeably, they are the same.

Allo-antigen: an antigen present in different individuals of the same species. (important in transplant)

MHC Classes

MCH I

Three genes codes

HLA-A

HLA-B

HLA-C

MHC Class I molecules are found on the surface of virtually all **nucleated cells**.

Associates with **T-cytotoxic cells (CD8)**.

MCH II

HLA-D is divided into 3 subgroups

DP

DQ

DR

MHC Class II molecules are present on the surface of antigen presenting cells.

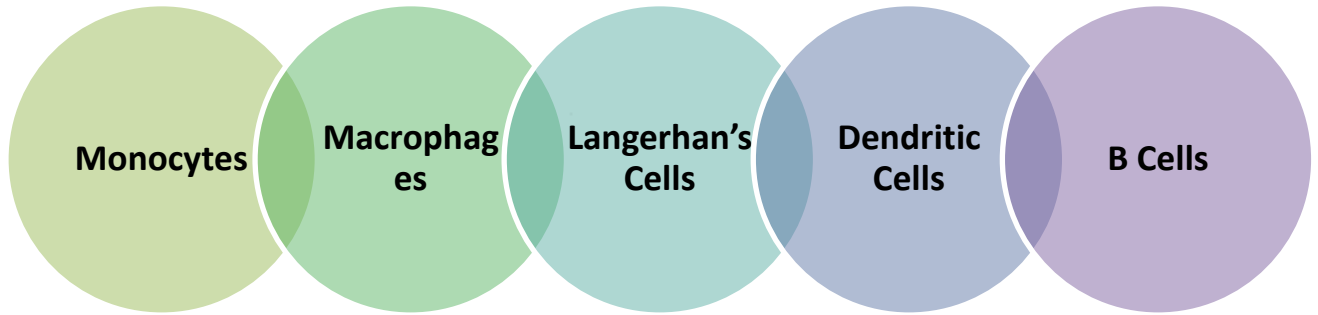
Associates with **T-helper cells (CD4)**.

MHC Classes

- Each group of MHC consists of several *glycoproteins*.
- Each individual has two “*haplotypes*” i.e. two sets of these genes: one paternal and one maternal.
- These genes are very diverse “*polymorphic*”.
- Each individual has a different combination (identity set), except for identical twins.

Note: The numbers of molecules in each HLA group are just to show the diversity.

Antigen Presenting Cells



Biologic Importance of MHC

Antigen Recognition (MHC Restriction)

- **T cytotoxic (CD8)** cells kill virus infected cells in association with **class I MHC** proteins.
- **Helper T (CD4)** cells recognize antigen in association with **class II MHC** proteins.

Transplantation

- Success of organ transplant is determined by compatibility of the MHC genes.

Minor HLA Genes

- Weak immune response
- Play role in *chronic rejection* of a graft
- No laboratory tests to detect it
- Class III MHC locus – between MHC I & II
- Encode for TNF, lymphotoxin, C2 & C4

Transplantation

Types of Grafts:

Auto-	Synergic	Allo-	Xeno-	Artificial
Self	Twin	Same Species (person to person)	Different Species (animal to person)	Man-made
Skin, bone marrow		Heart, lung, kidney, liver		Joints, valves

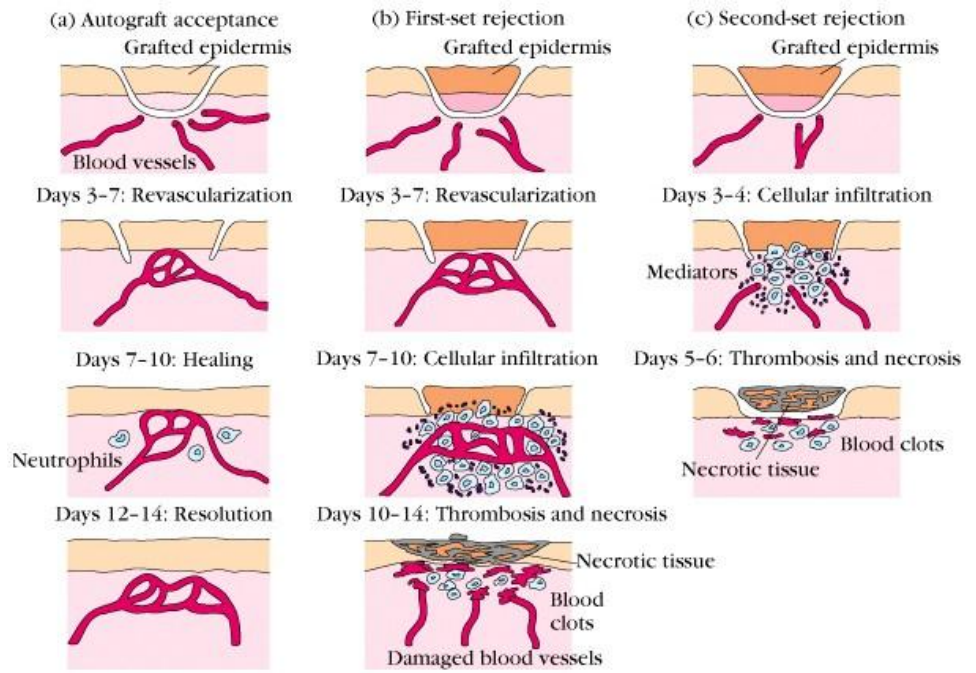
The Immune Response

- The immune response is a major barrier to transplantation.

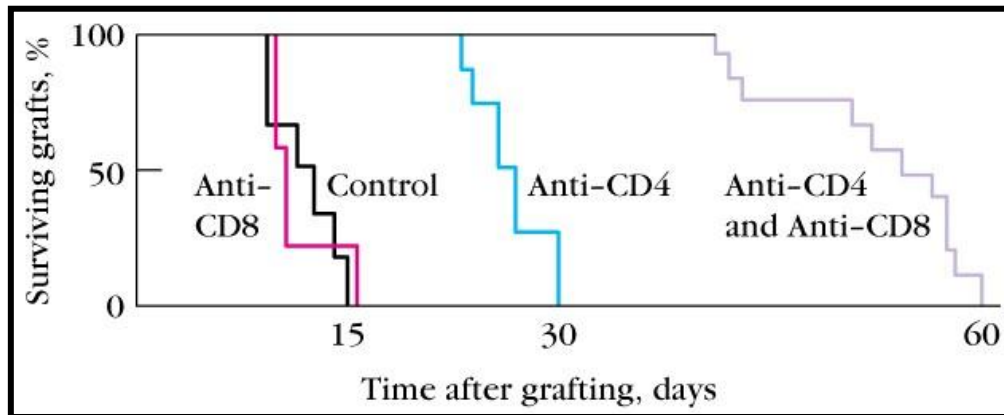
Classic adaptive/acquired immune response:

- **T cells** (main)
 - Memory
 - Specificity
- **B cells** (sometimes)
- If a graft is rejected the first time, it is rejected even faster the second time due to *memory cells*.
- Nude mouse with no T-cells accepts allo-grafts, but a mouse with no B-cells and present T-cells with reject the graft.
- Depleting one or both T-cells (CD4/CD8) will increase chances of graft survival.

Graft rejection and memory cells response

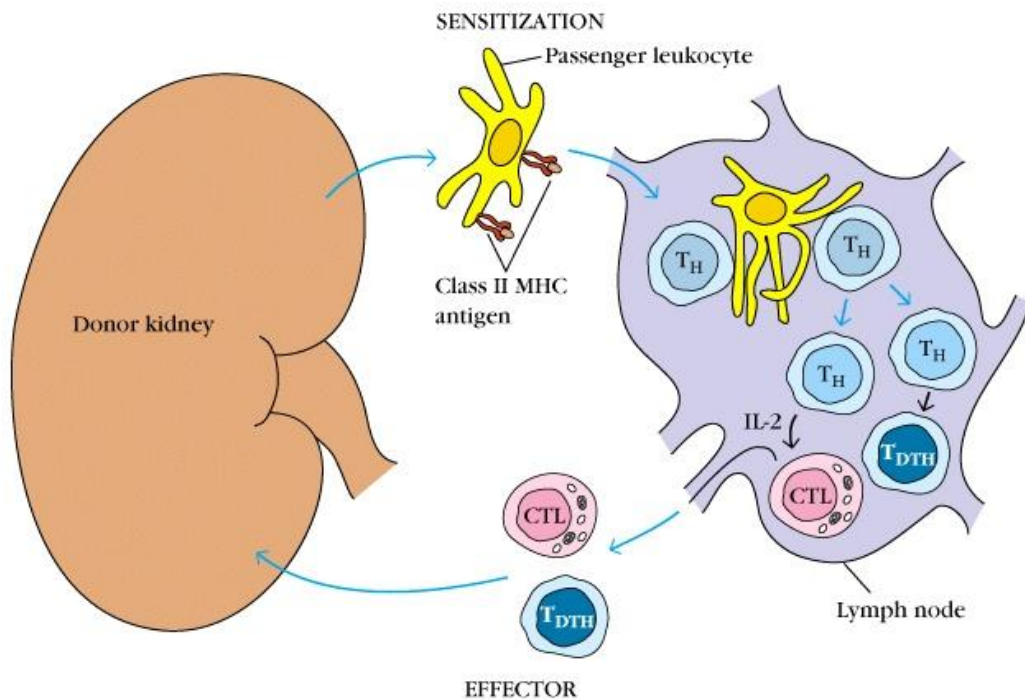


Knocking down CD4 is more effective than CD8, both is most effective



Nude mouse (with no T-cells) accept the rabbit skin graft

Mechanisms Involved In Graft Rejection



Sensitization phase: Portions of the graft's HLA complex (MHC) are processed and presented as 'antigen', recognition of antigen by T-cells triggers lymphocyte proliferation.

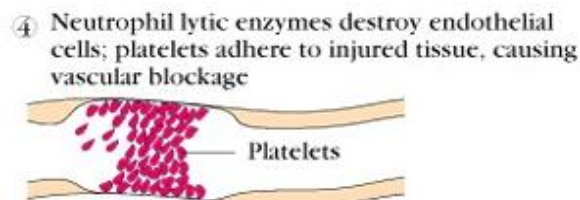
Effector phase: The host immune system attacks the graft, destroying it through antibodies and cytotoxins.

Clinical Manifestations of Graft Rejection

Hyper-acute Rejection	Acute Rejection	Chronic Rejection
Very quick Minutes-hours	10 days (cell mediated)	Months-years (both cell mediated & humoral)

Chronic Rejection

- This occurs *months to years* after engraftment
- Main pathologic finding in chronic rejection is **atherosclerosis of the vascular endothelium**
- Main cause of chronic rejection is *not known*
 - Minor histocompatibility antigen miss match
 - Side effects of immunosuppressive drugs



Graft vs. Host Reaction (GVH)

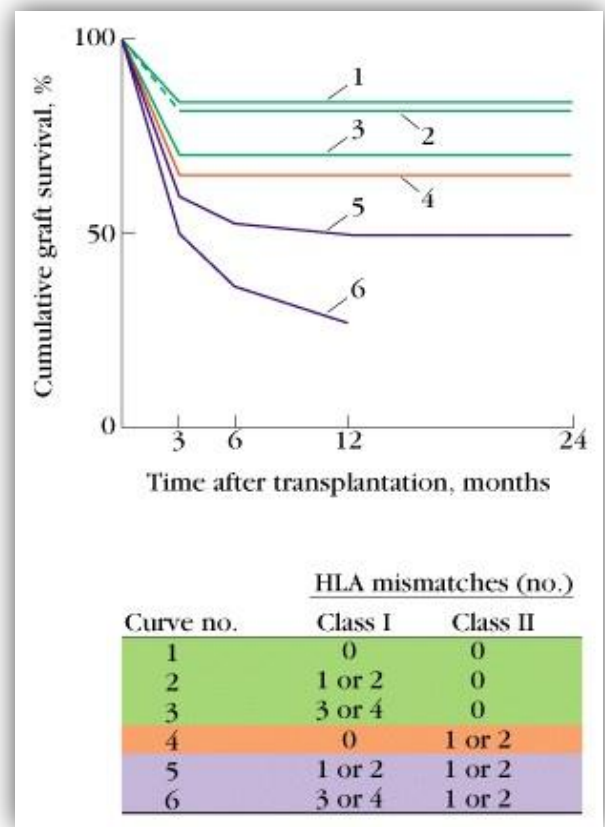
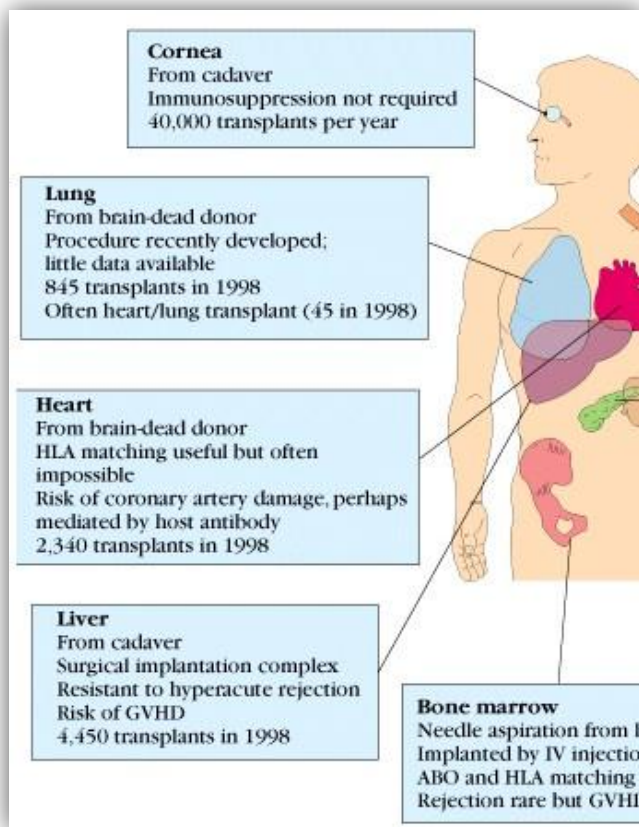
- Occurs in about two thirds of *bone marrow transplants*
- Occurs because grafted immunocompetent T cells proliferate in the irradiated* immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction
- Donor's *T-cytotoxic cells* play a major role in destroying the recipient's cells
- **Symptoms are:** maculopapular rash, **jaundice**, hepatosplenomegaly and diarrhea
- GVH reactions usually end in *infections and death*

Irradiated: a process in which the patient is exposed to radiation, to suppress immunity.

HLA Typing in the Laboratory

- Prior to transplantation laboratory test commonly called as *HLA typing* or tissue typing to determine the closest MHC match between the donor and recipient is performed.
- **Methods:**
 - **DNA sequencing by Polymerase Chain Reaction (PCR)** (most common)
 - Serologic Assays
 - **Mixed Lymphocyte Reaction (MLR)** (best but least used, due to equipment)
 - Cross matching – (D) lys +(R) serum + complement

Tissue Matching



The only graft that does not need tissue matching: **'cornea'**

Effect of HLA class I & II matching on survival of grafts **(II is more important)**

Immunosuppression Therapy

General Therapy

- **Mitotic inhibitor:** azathioprine (pre & post)
- **Corticosteroids**
- **Cyclosporine***
- **Total lymphoid irradiation***

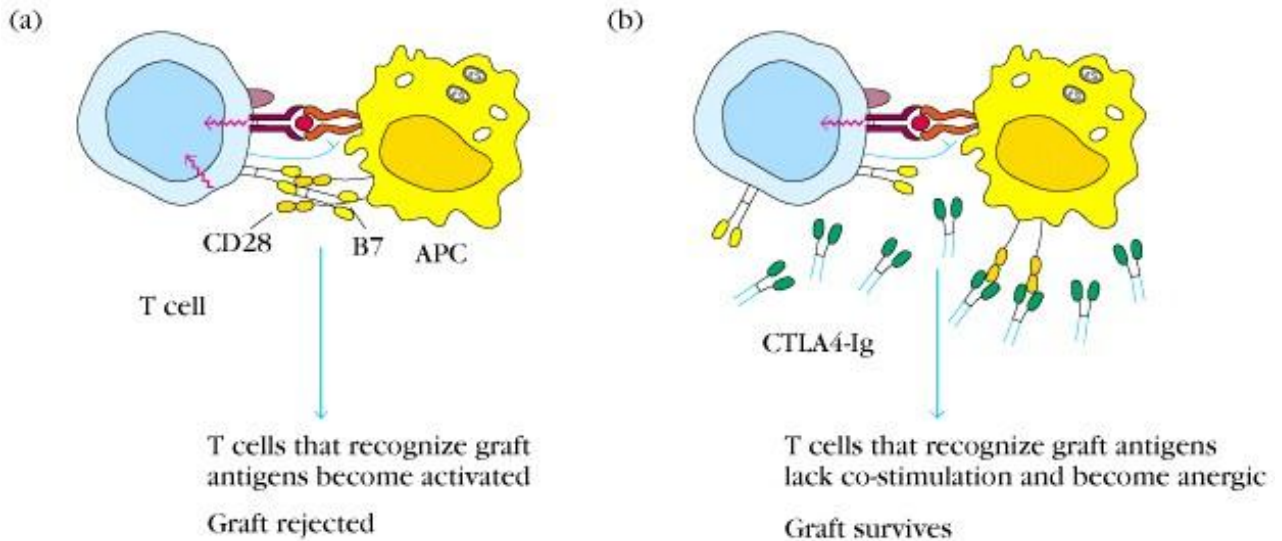
Specific Therapy

- **MABs*** to T cell components or cytokines
- **Agents that blocking co-stimulatory signal**

Cyclosporine: it reduces the activity of the immune system by interfering with the activity and growth of T cells.

Total irradiation: total immunosuppression by radiation.

MABs: 'Monoclonal antibody therapy' Monoclonal antibodies are designed to recognize and attach to specific proteins on the surface of cells.



Agents blocking the co-stimulating signal cause the T-cell to become anergic (inactive)

Downsides of Therapy

- Must be maintained for life
- Toxicity
- Susceptibility to infections
- Susceptibility to tumors

MCQs

1. Which one of the following classes of MHC is found on the surface of B cells:

- A) I
- B) II
- C) III
- D) All the above

2. A patient developed atherosclerosis after getting kidney transplantation. Which type of rejection is this?

- A) Hyper-acute
- B) Acute
- C) Chronic
- D) None of the above

3. Location of MHC is on:

- A) Long arm of chromosome 9
- B) Short arm of chromosome 9
- C) Long arm of chromosome 6
- D) Short arm of chromosome 6

4. Graft versus host reaction occurs most commonly in

- A) Bone marrow transplant
- B) Skin grafting
- C) Kidney transplant
- D) Heart transplant

5. What is the most common HLA typing in laboratories?

- A) Mixed Lymphocyte Reaction
- B) Cross matching
- C) Immunofluorescence
- D) DNA sequencing