# Transplantation

Immunology Unit College of Medicine King Saud University

## Objectives

- To understand the diversity among human leukocyte antigens (HLA) or major histocompatibility complex (MHC)
- To know the role of HLA antigens in transplant rejection and graft versus host disease
- To be familiar with types of immune responses mediating transplant rejections and graft versus host disease and importance of tissue matching
- To understand the principles of management after transplantation

### Major Histocompatibility Complex and Transplantation

- Major histocompatibility complex (MHC) proteins were discovered for the first time with the advent of tissue transplantation
- The success of tissue and organ transplantation depends upon the donor's and recipient's "human leukocyte antigens" (HLA) encoded by HLA genes
- These proteins are allo-antigens

## MHC Class I and II Proteins

- MHC Class I are glycoproteins found on surface of virtually all the nucleated cells
  - Cytotoxic T cell kills virus infected cells in association with class I MHC proteins
- MHC Class II glycoproteins are normally found on the surface of antigen presenting cells (marophages, B cells, and dendritic cells)
  - Helper T cell recognize antigen in association with class II MHC proteins

## Major Histocompatibility Complex and Transplantation

- Genes for HLA proteins are clustered in the MHC complex located on the short arm of chromosome 6
- Three genes HLA-A, HLA-B and HLA-C code for Class I MHC proteins
- HLA-D loci encode for Class II MHC proteins ie, DP, DQ and DR

### Major Histocompatibility Complex and Transplantation

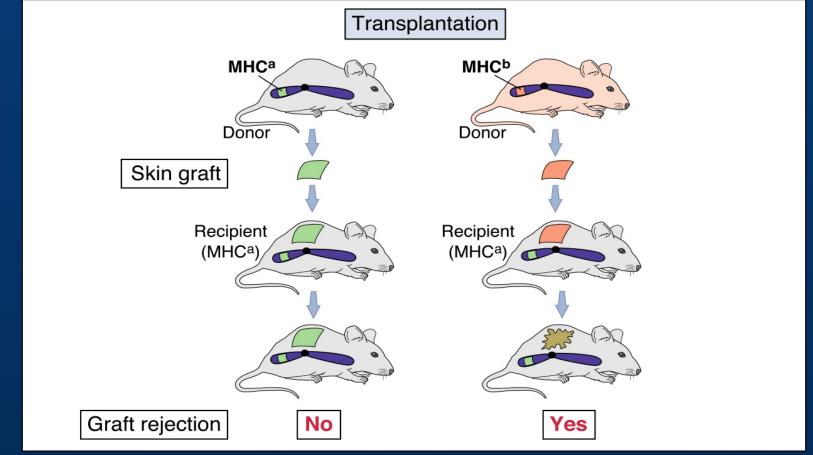
Each individual has two "*haplotypes*" i.e, two sets of these genes one paternal and one maternal

MHC class	Ι			II			III	
Region	Α	В	С	DP	DQ	DR	C4, C2, BF	
Gene products	HLA-A	HLA-B	HLA-C	DP	DQ	DR	C' proteins	<b>TNF-</b> α <b>TNF-</b> β
Polymorphisms	47	88	29	More than 300 HLA-D				

### **Transplantation antigens**

Slide 4-2

#### MHC alleles control allograft rejection



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 4-2a

## **Transplantation**

- Types of transplants:
  - Autografts, Autologous grafts
    - Donor and recipient are same individual
    - Common in skin grafting; bone marrow
  - Syngeneic grafts or (isograft)
    - Donor and recipient are genetically identical
    - Animal models; identical twins

## Transplantation

- <u>Types of transplants:</u>
  - Allogeneic grafts
    - Donor and recipient are same species, but genetically unrelated
    - Common heart, lung, kidney, liver graft
  - Xenogeneic grafts
    - Donor and recipient are different species
  - Artificial grafts

Transplantation (Rejection)

- <u>Major Barrier to transplantation is the</u> <u>immune response</u>
  - T cells play primary role
  - B cells can/do play a role
  - Classic adaptive/acquired immune response
    - Memory
    - Specificity

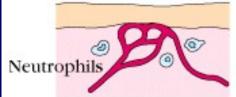
## 1<sup>st</sup> set versus 2<sup>nd</sup> set reactions

(a) Autograft acceptance Grafted epidermis Blood vessels

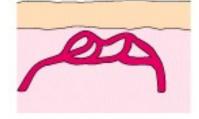
Days 3-7: Revascularization



Days 7-10: Healing



Days 12-14: Resolution



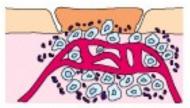
(b) First-set rejection Grafted epidermis



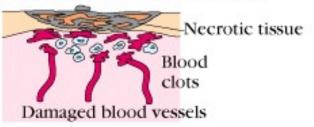
Days 3-7: Revascularization



Days 7-10: Cellular infiltration



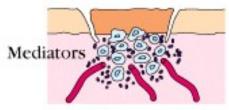
Days 10-14: Thrombosis and necrosis



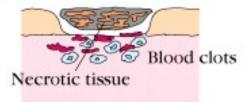
(c) Second-set rejection Grafted epidermis



Days 3-4: Cellular infiltration



Days 5-6: Thrombosis and necrosis



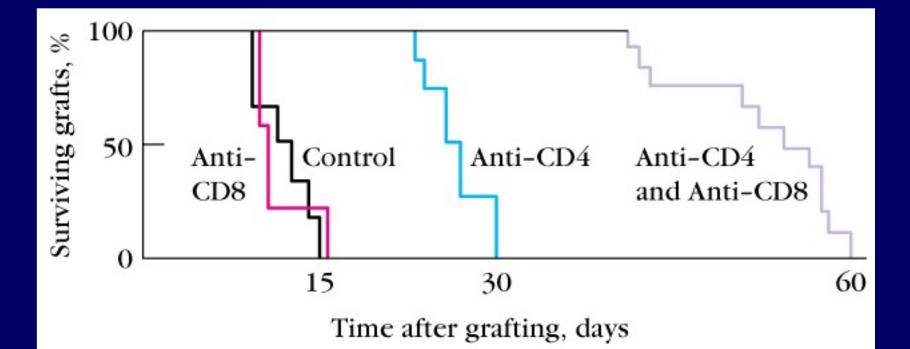
## Transplantation

- <u>T cells play primary role in 1st and 2nd set rejection</u> reactions
  - Nude mice accept allografts (no T cells due to genetic modification resulting in absent thymus)
  - B cell deficient mice reject allografts



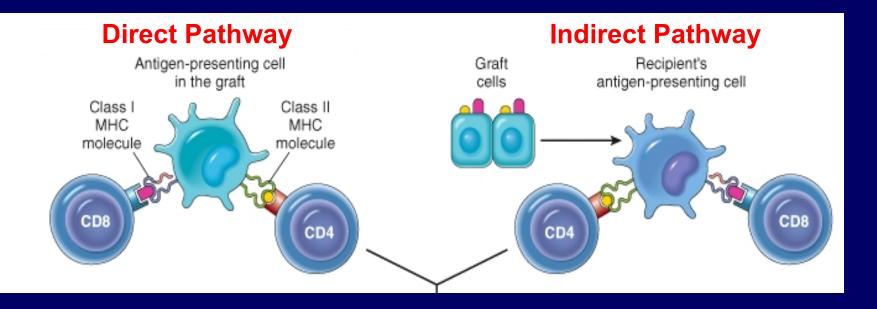
#### Nude mouse has a transplant of rabbit skin

## Role of CD4<sup>+</sup> versus CD8 T<sup>+</sup> cells

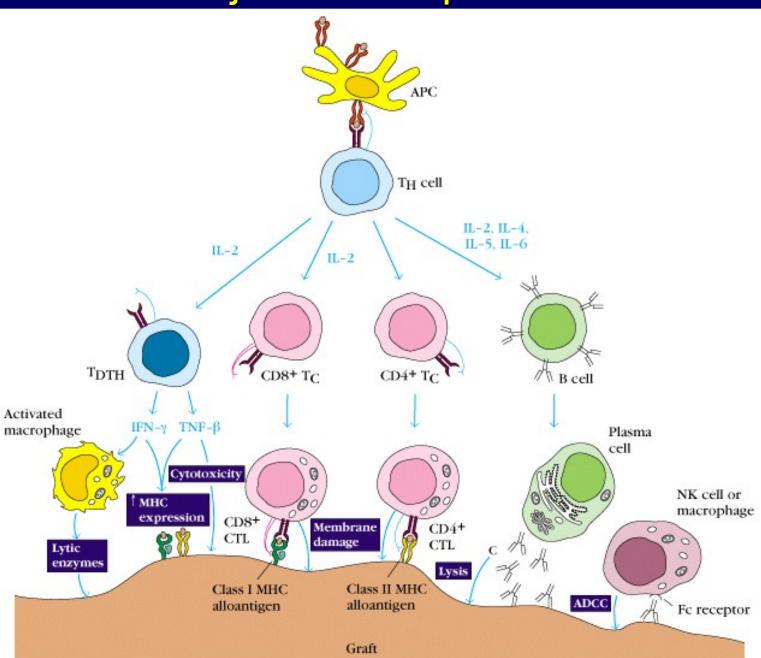


Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells

### Mechanisms involved in Graft Rejection

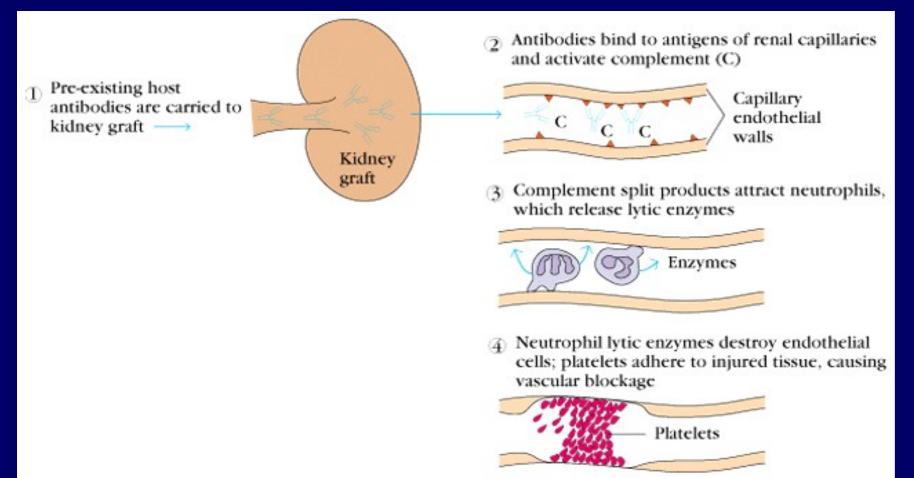


### **Rejection Response**



### **Clinical manifestations of graft rejection**

- I. Hyperacute rejection: very quick
- II. Acute rejection: about 10 days (cell mediated)
- III. Chronic rejection: months-years (both)



## **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 histo-compatibility antigen miss match

### Minor antigens and Transplantation

Minor antigens – unknown

– They mount a weak immune response

- Play role in chronic rejection of a graft

 There are no laboratory tests to detect minor antigens

## Graft-versus-Host (GVH) Reaction

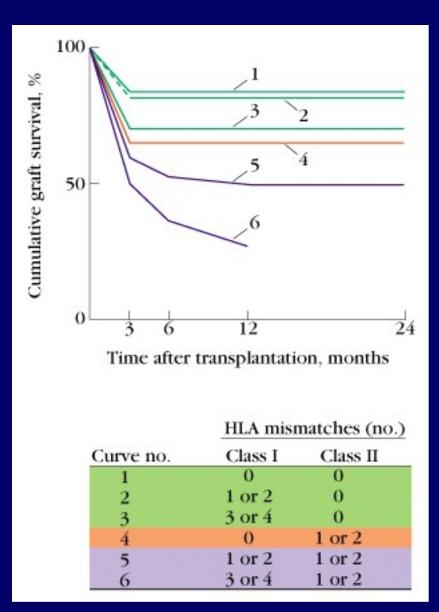
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in sever organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's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

## **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)
  - Serologic Assays
  - Mixed Lymphocyte Reaction (MLR)
  - Crossmatching (Donor) lymphocytes +(Recipient) serum + complement.

### **Tissue Matching**

#### Effect of HLA class I & II matching on survival of kidney grafts



## **Tissue Matching**

#### Cornea

From cadaver Immunosuppression not required 40,000 transplants per year

#### Lung

From brain-dead donor Procedure recently developed; little data available 845 transplants in 1998 Often heart/lung transplant (45 in 1998)

#### Heart

From brain-dead donor HLA matching useful but often impossible Risk of coronary artery damage, perhaps mediated by host antibody 2,340 transplants in 1998

#### Liver

From cadaver Surgical implantation complex Resistant to hyperacute rejection Risk of GVHD 4,450 transplants in 1998

#### Bone marrow Needle aspiration

Needle aspiration from living donor Implanted by IV injection ABO and HLA matching required Rejection rare but GVHD a risk

#### Skin

Mostly autologous (burn victims) Temporary grafts of nonviable tissue Allogeneic grafts rare, require immunosoppression

#### Blood

Transfused from living donor ABO and Rh matching required Complications extremely rare An estimated 14 million units used each year

#### Pancreas

From cadaver Islet cells from organ sufficient 253 transplants in 1998 Increasingly, panreas/kidney transplant for advanced diabetes (965 in 1998)

#### Kidney

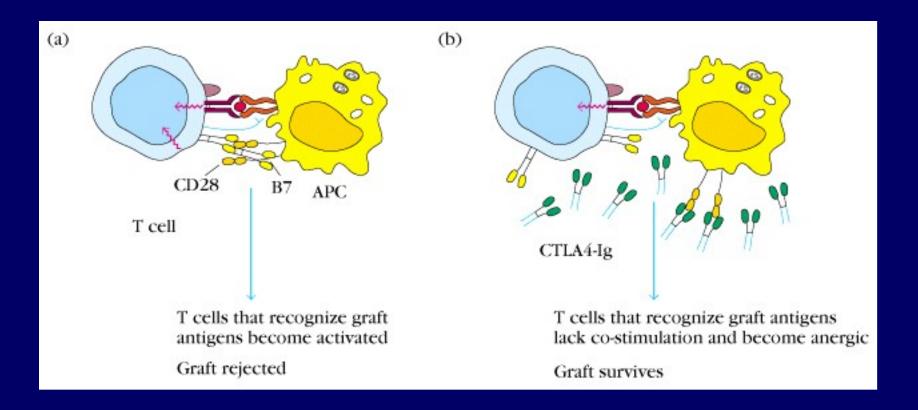
From live donor or cadaver ABO and HLA matching useful Immunosuppression usually required Risk of GVHD very low 11,900 transplants in 1998

### **General Immunosuppression Therapy**

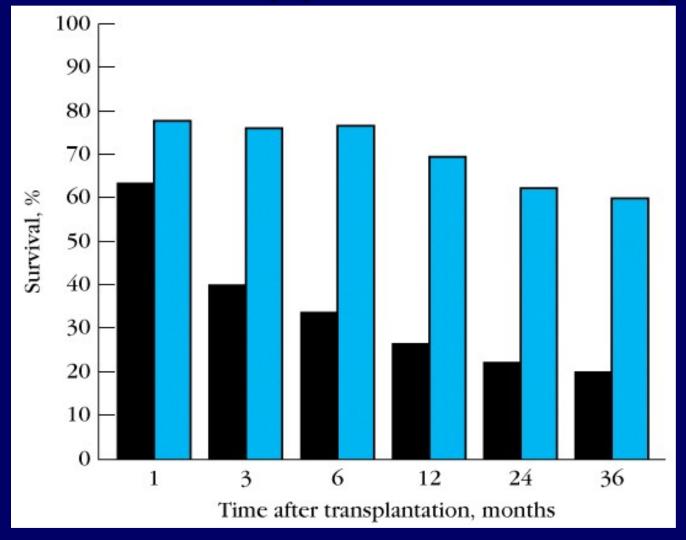
- 1) Mitotic inhibitor: azathioprine (pre & post)
- 2) Corticosteroids
- 3) Cyclosporin
- 4) Total lymphoid irradiation

## Specific Immuno-suppression therapy

- a) Monoclonal antibodies against T cell components or cytokines
- b) Agents blocking co-stimulatory signal



## Immunosuppresive Therapy



## Immuno-suppresive Therapy

### <u>Downsides</u>

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

## Take home messages

- HLA or MHC molecule miss-match can stimulate humoral and cell mediated immunity which is the main cause of rejection of transplants
- Cell mediated immune responses play a major role in transplant rejection
- Tissue matching particularly for HLA-D antigens is important for successful transplantation
- Immuno-suppresive therapy is usually required after transplantation

Thank you