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

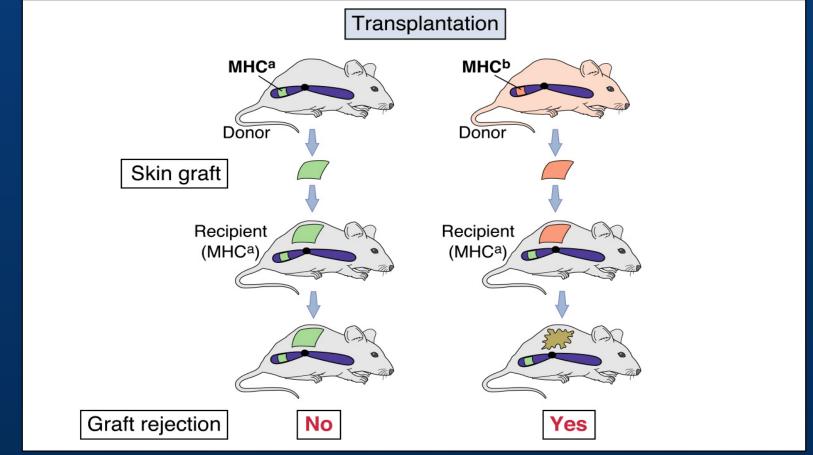
Each individual has two "*haplotypes*" i.e, two sets of these genes one paternal and one maternal

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	TNF- α TNF- 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

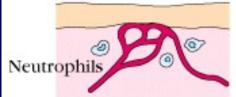
1st set versus 2nd set reactions

(a) Autograft acceptance Grafted epidermis Blood vessels

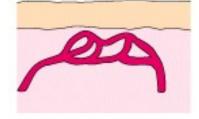
Days 3-7: Revascularization



Days 7-10: Healing



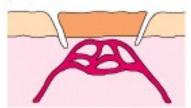
Days 12-14: Resolution



(b) First-set rejection Grafted epidermis



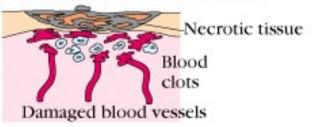
Days 3-7: Revascularization



Days 7-10: Cellular infiltration



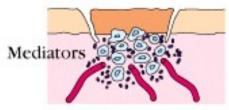
Days 10-14: Thrombosis and necrosis



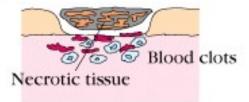
(c) Second-set rejection Grafted epidermis



Days 3-4: Cellular infiltration



Days 5-6: Thrombosis and necrosis



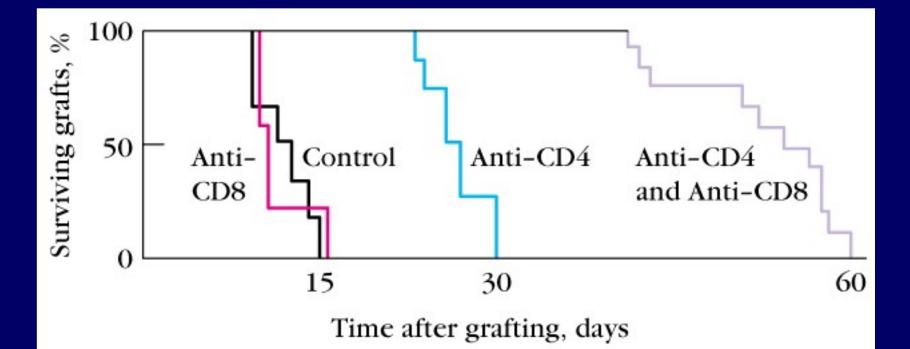
Transplantation

- <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



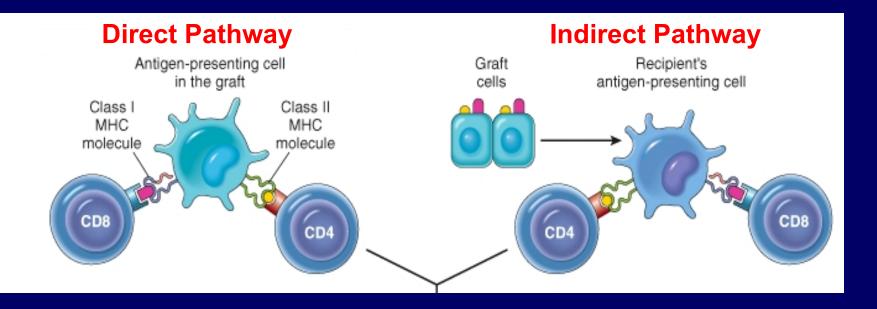
Nude mouse has a transplant of rabbit skin

Role of CD4⁺ versus CD8 T⁺ cells

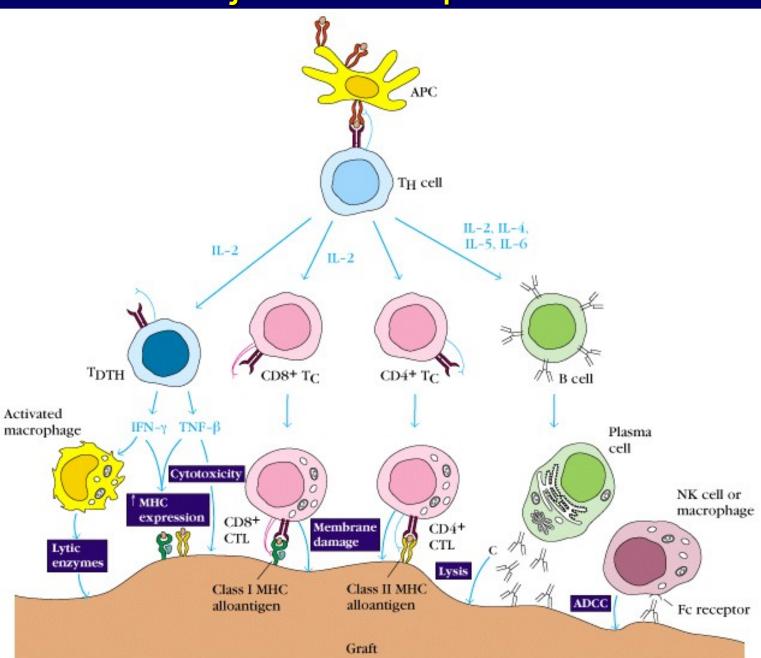


Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells

Mechanisms involved in Graft Rejection

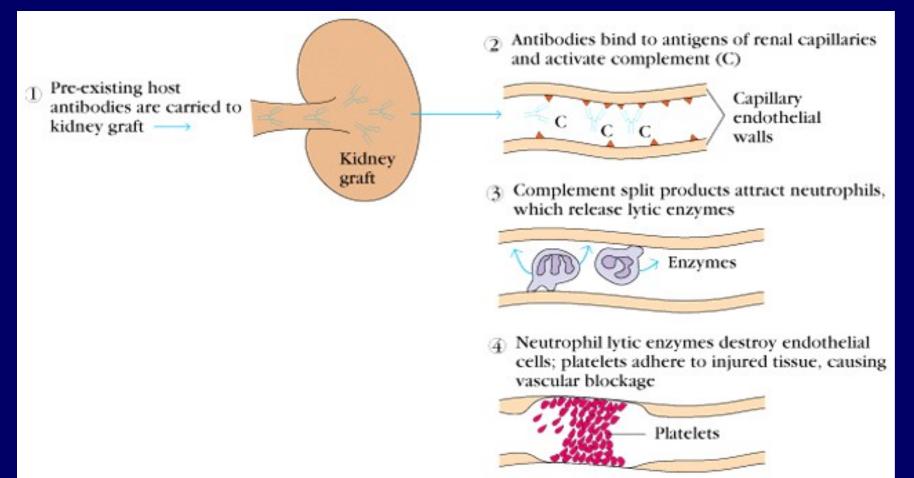


Rejection Response



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

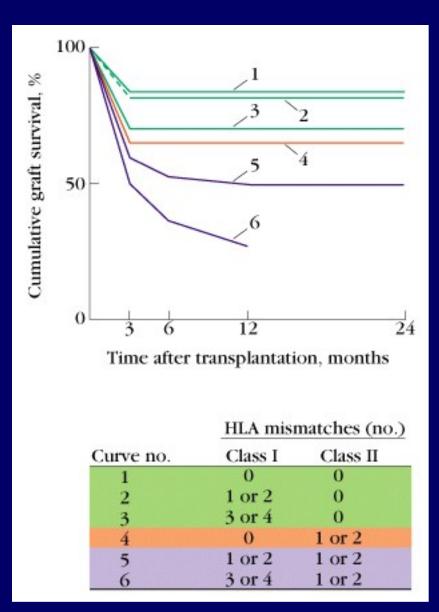
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in sever organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's 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

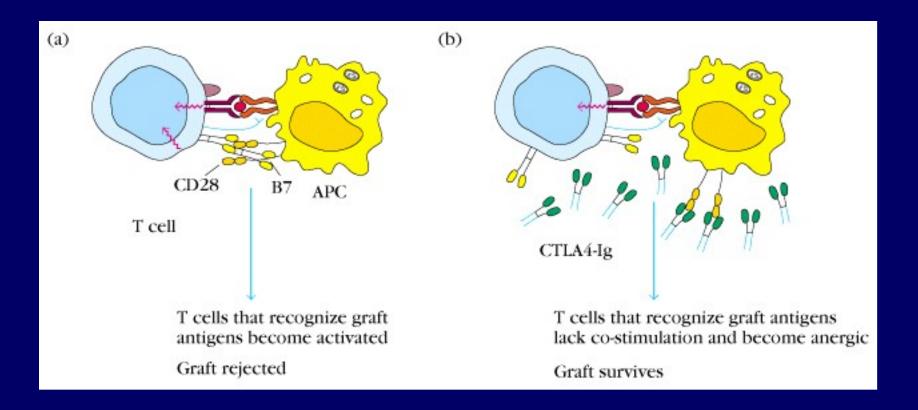
From live donor or cadaver ABO and HLA matching useful Immunosuppression usually required Risk of GVHD very low 11,900 transplants in 1998

General Immunosuppression Therapy

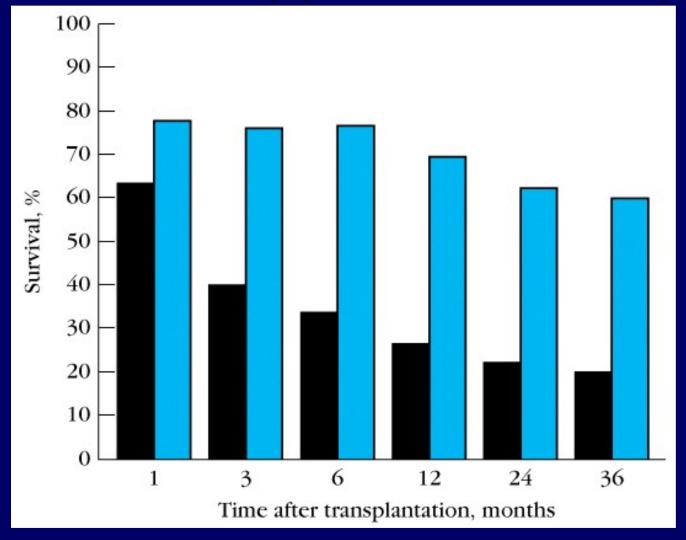
- 1) Mitotic inhibitor: azathioprine (pre & post)
- 2) Corticosteroids
- 3) Cyclosporin
- 4) Total lymphoid irradiation

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