

Transplantation

Immunology Unit
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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
- To be familiar with types of immune responses mediating transplant rejections 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 (macrophages, B cells, dendritic cells and Langerhans 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	I			II			III	
Region	A	B	C	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				

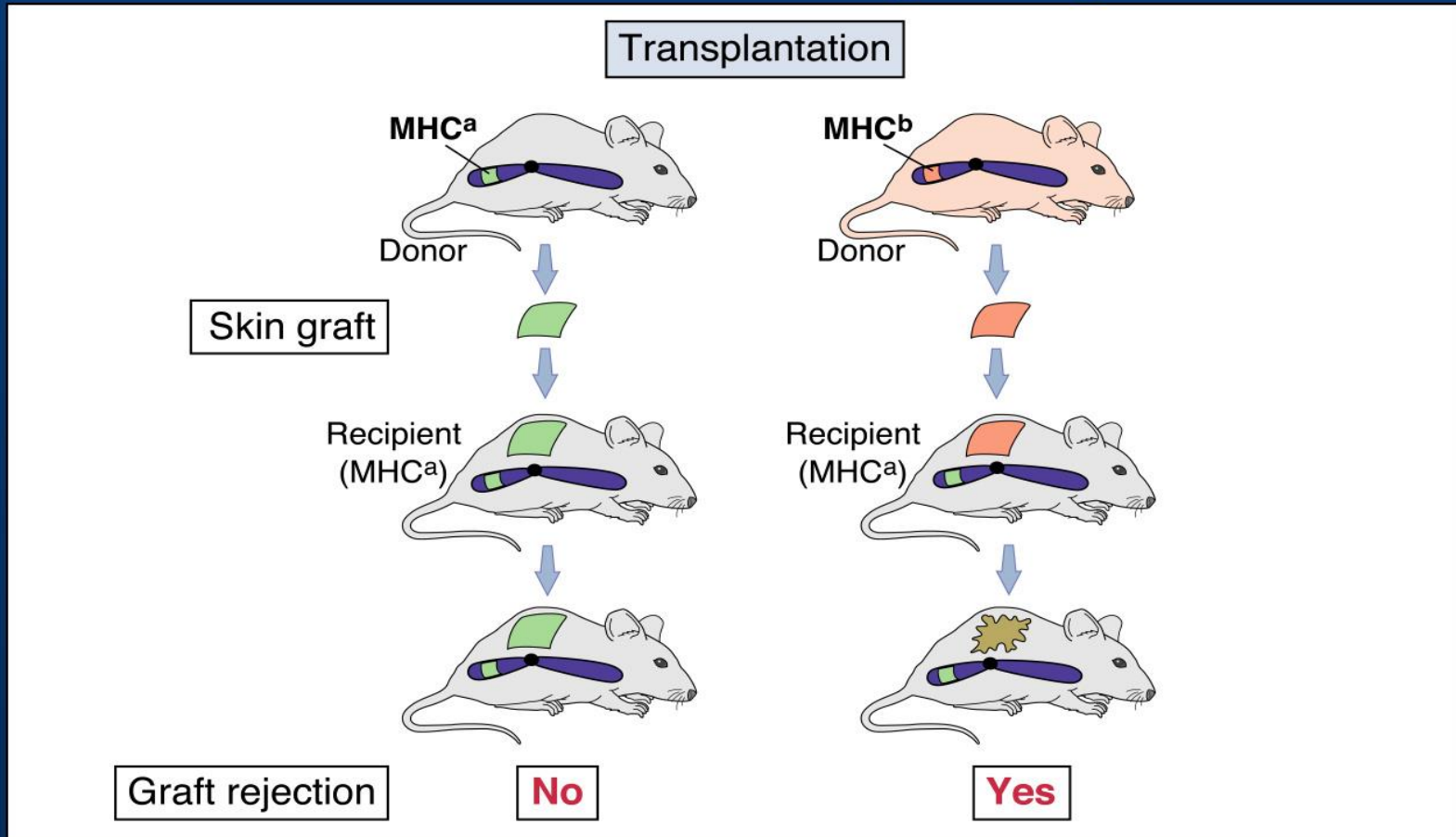
Minor HLA genes and Transplantation

- Minor HLA genes – unknown
 - They mount a **weak immune response**
 - Play role in **chronic rejection** of a graft
 - There are **no laboratory tests** to detect minor antigens

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

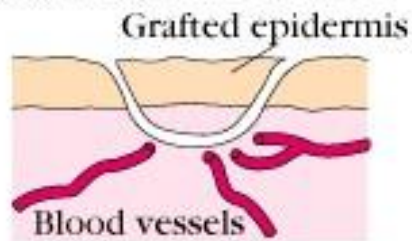
- Types of transplants:
 - **Allogeneic grafts**
 - Donor and recipient are same species, but genetically unrelated
 - Common heart, lung, kidney, liver graft
 - **Xenogeneic grafts**
 - Donor and recipient are different species
 - **Artificial grafts**

Transplantation (Rejection)

- Major Barrier to transplantation is the immune response
 - 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

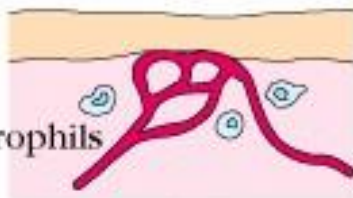
(a) Autograft acceptance



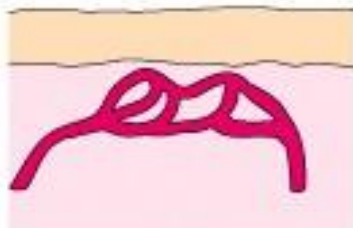
Days 3-7: Revascularization



Days 7-10: Healing



Days 12-14: Resolution



(b) First-set rejection



Days 3-7: Revascularization



Days 7-10: Cellular infiltration



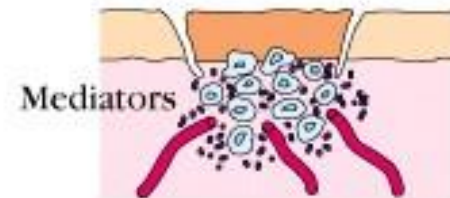
Days 10-14: Thrombosis and necrosis



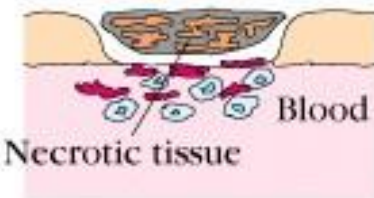
(c) Second-set rejection



Days 3-4: Cellular infiltration



Days 5-6: Thrombosis and necrosis

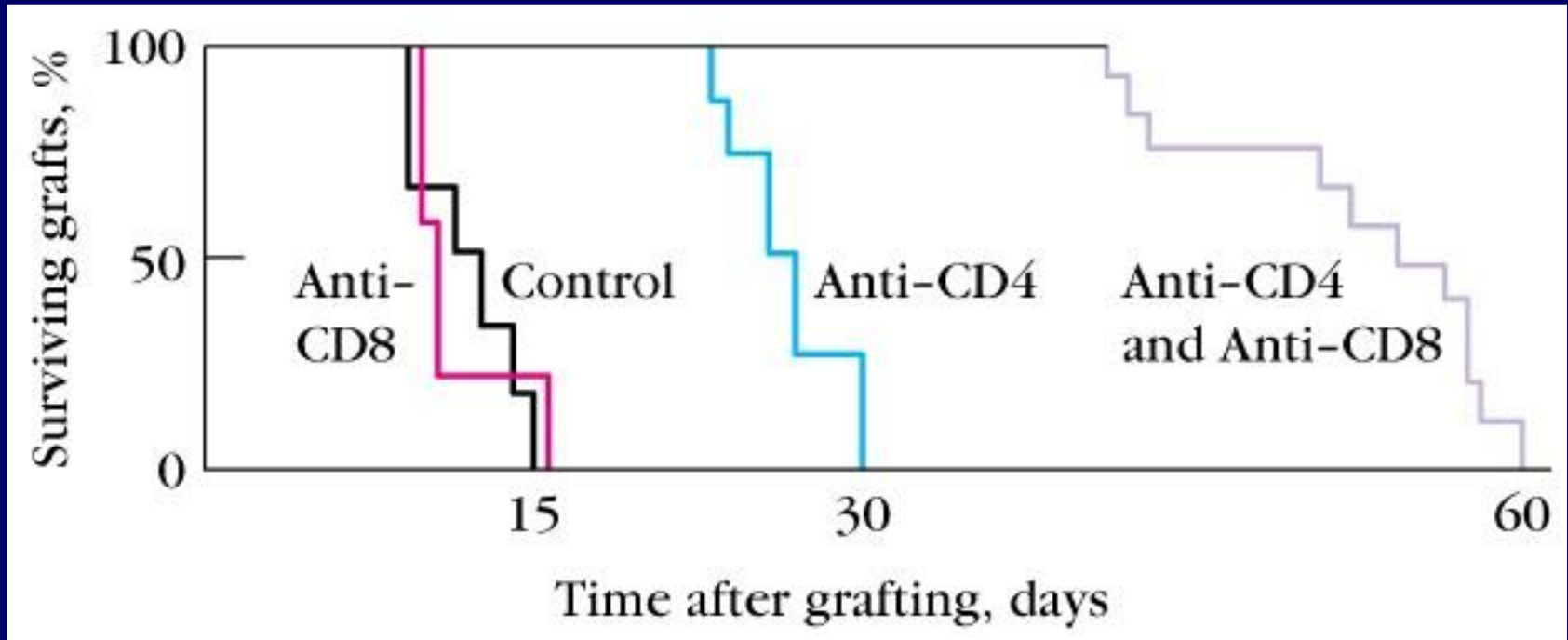


Necrotic tissue

Blood clots

Damaged blood vessels

Role of CD4⁺ versus CD8 T⁺ cells



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

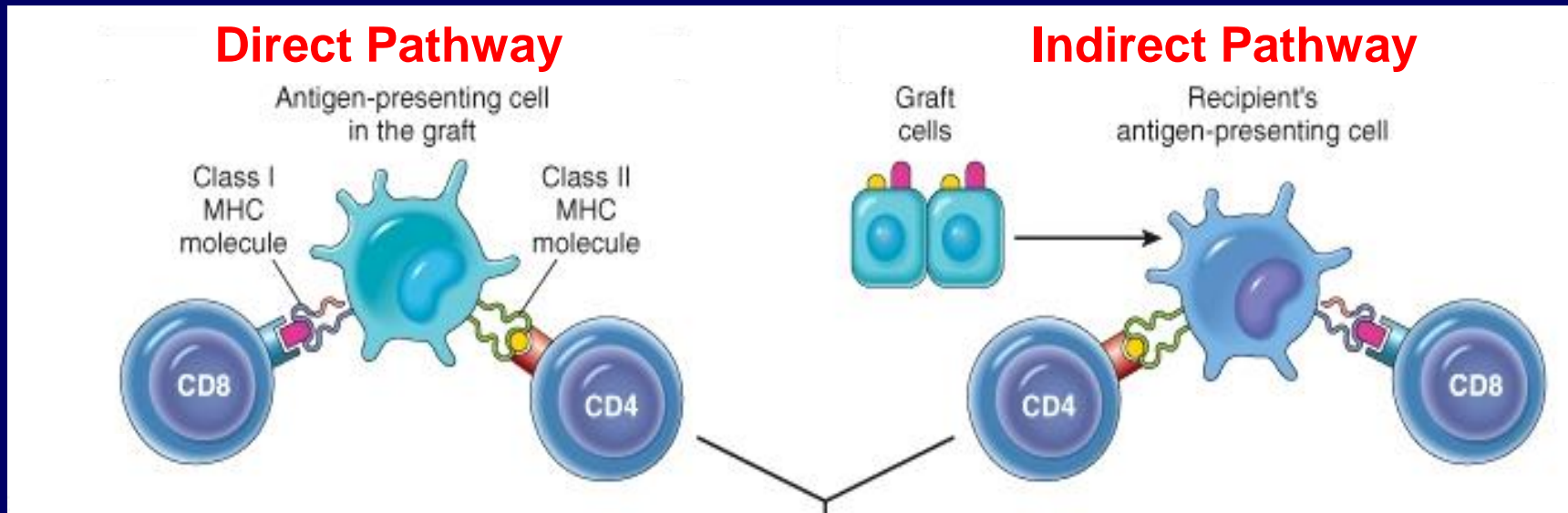
Transplantation

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

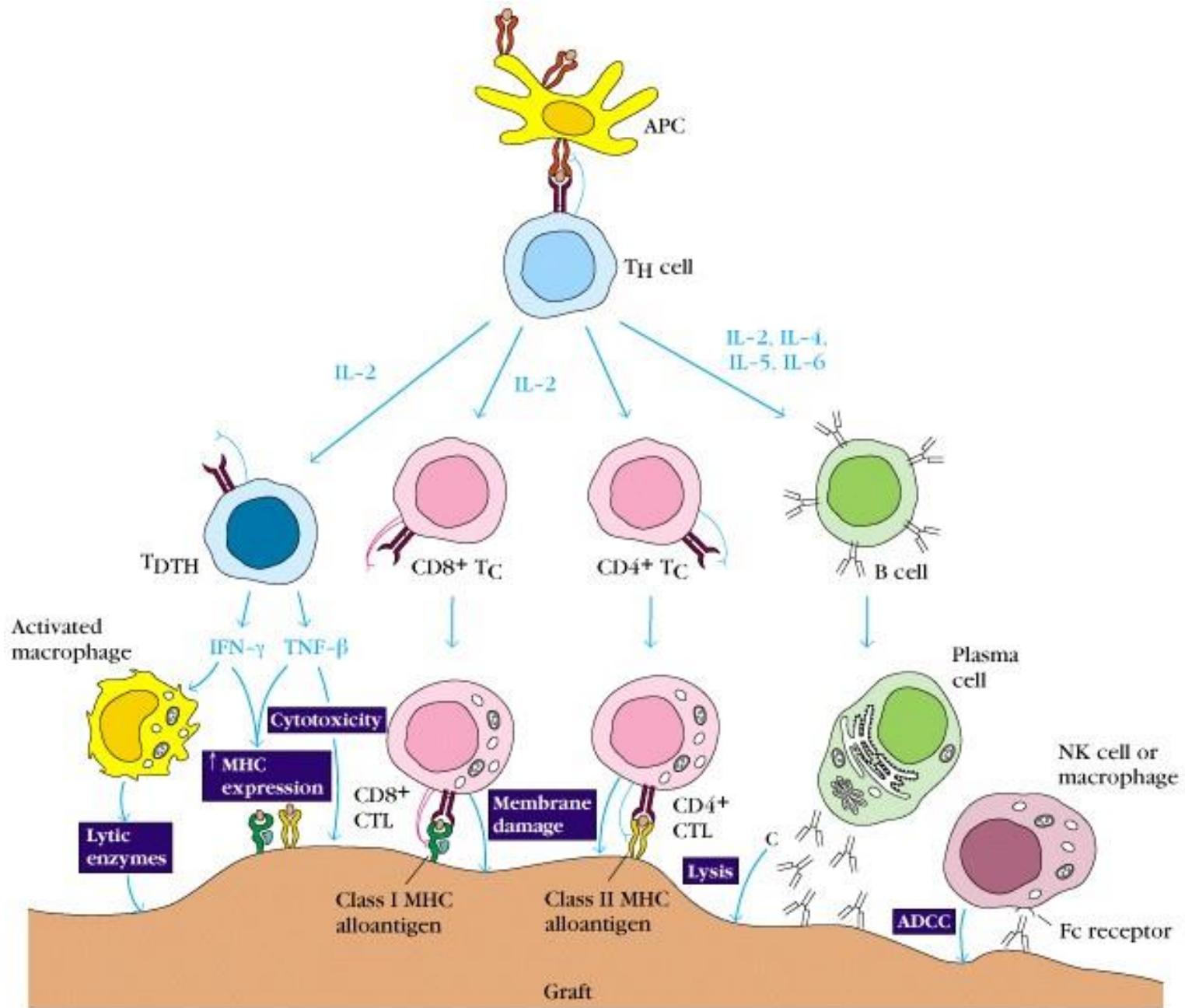


Nude mouse has a transplant of rabbit skin

Mechanisms involved in Graft Rejection

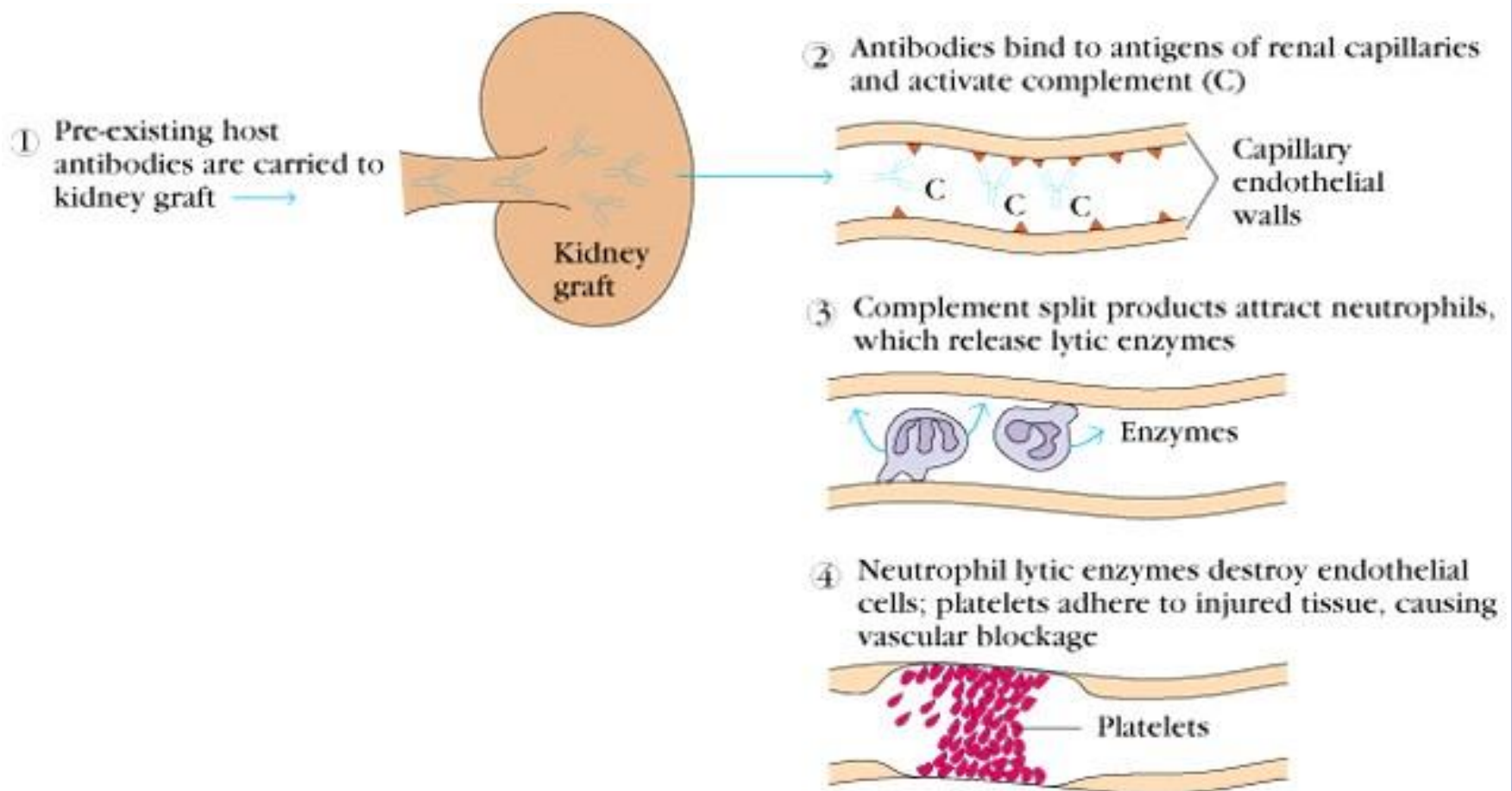


Rejection Response



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

Graft-versus-Host (GVH) Reaction

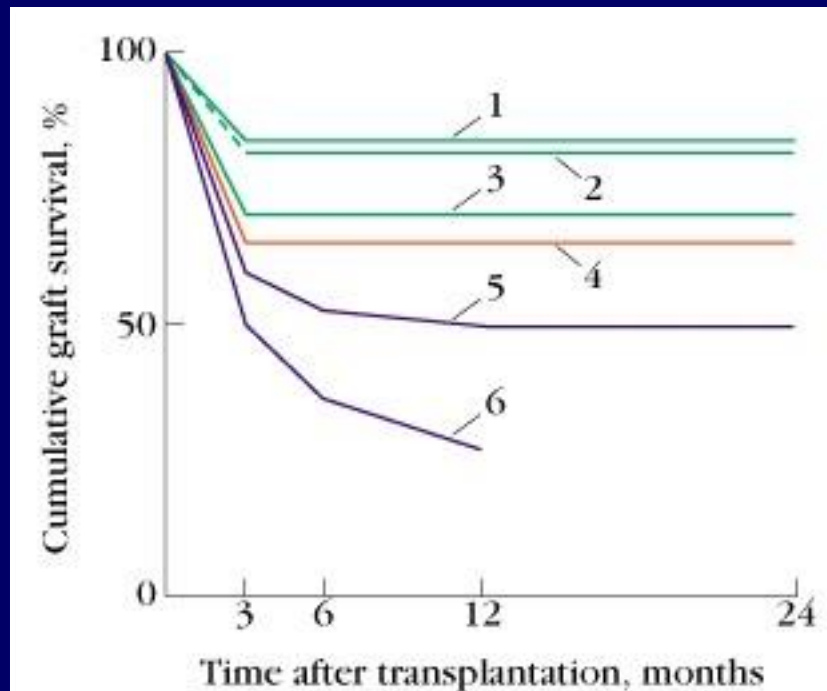
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's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



Curve no.	HLA mismatches (no.)	
	Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2

Tissue Matching

Cornea

From cadaver
Immunosuppression not required
40,000 transplants per year

Skin

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

Lung

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

Blood

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

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

Pancreas

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

Liver

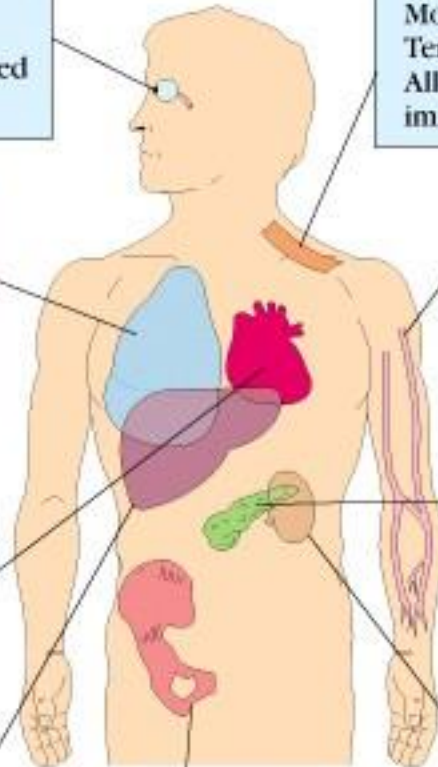
From cadaver
Surgical implantation complex
Resistant to hyperacute rejection
Risk of GVHD
4,450 transplants in 1998

Kidney

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

Bone marrow

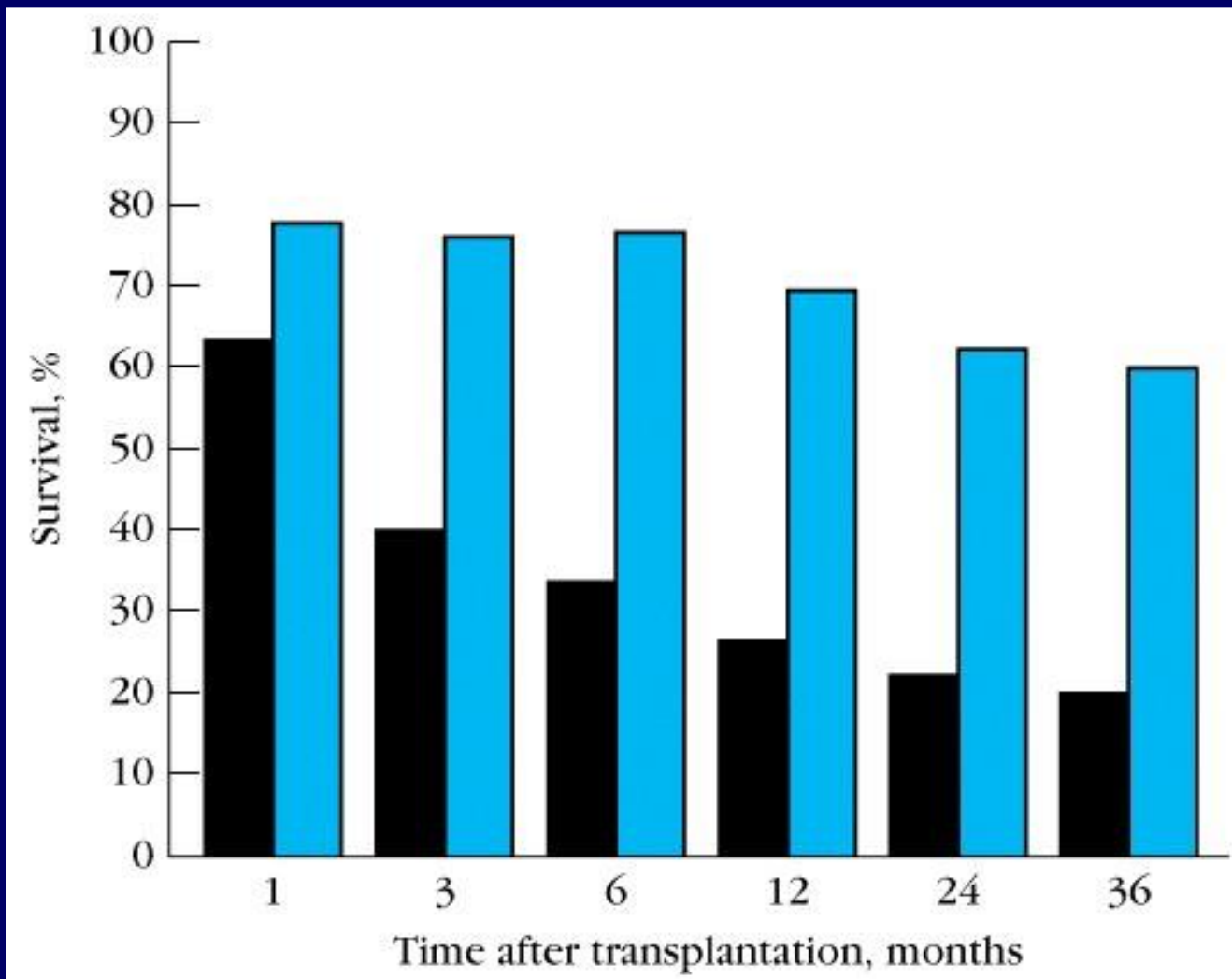
Needle aspiration from living donor
Implanted by IV injection
ABO and HLA matching required
Rejection rare but GVHD a risk



General Immunosuppression Therapy

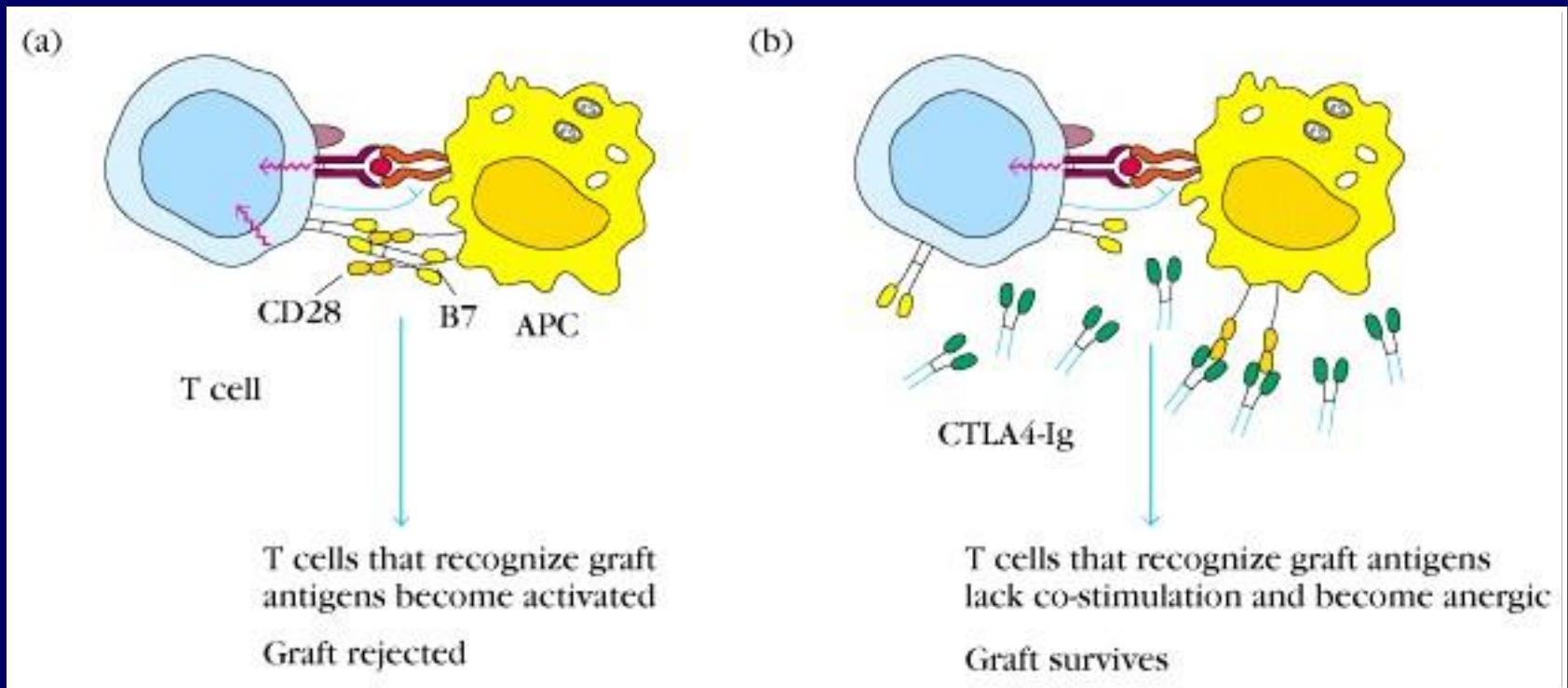
- 1) Mitotic inhibitor: azathioprine (pre & post)
- 2) Corticosteroids
- 3) Cyclosporin
- 4) Total lymphoid irradiation

Immunosuppressive Therapy



Specific Immuno-suppression therapy

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



Immuno-suppressive Therapy

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

Take home message

- 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-suppressive therapy is usually required after transplantation