



Lecture 38...

BT 304

07Nov 2023



Transplantation and Rejection

- **Studying the immunology of transplantation and rejection is important because:**
 - ✓ Its impact on understanding of immunological practice
 - ✓ Its applications in the development of clinical transplantation

IT has led to:

- ❖ Discovery of MHC molecules
- ❖ Better understanding of T cell physiology and function
- ❖ Development and use of immunomodulatory drugs

Applications

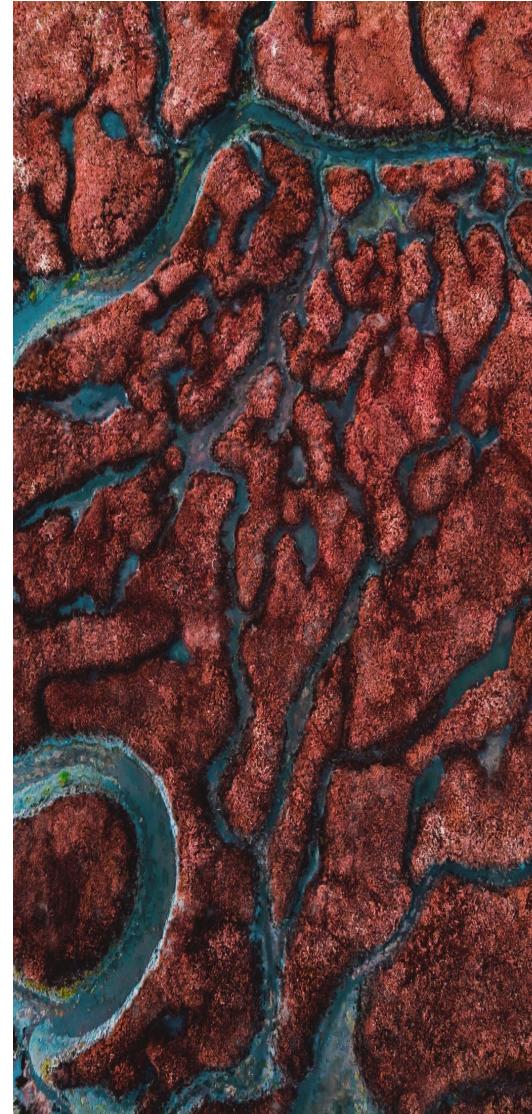
| Organ transplanted | Example of disease |
|---------------------------|----------------------------|
| Kidney | End stage renal failure |
| Heart | Terminal cardiac failure |
| Liver | Cirrhosis, Cancer |
| Cornea | Dystrophy |
| Pancreas or Islets | Diabetes |
| Bone marrow | Immunodeficiency, Leukemia |
| Small bowel | Cancer |
| Skin | Burns |

Barriers to transplantation:

Genetic differences between the donor and recipient:

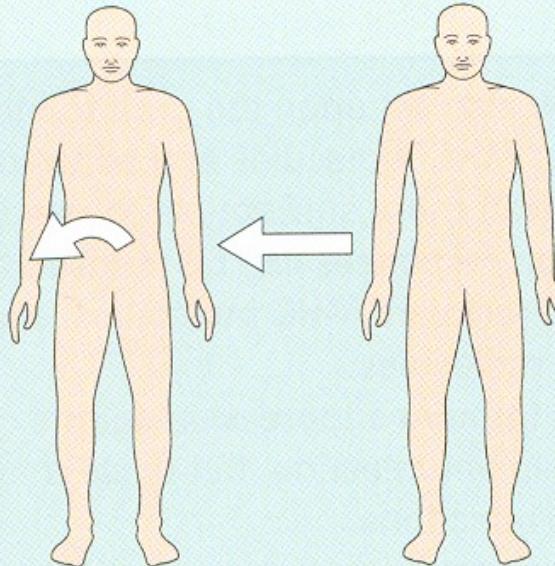
Graft can be classified into:

- **Autografts:** From one part of the body to another
- **Isografts:** Between isogenic individuals
- **Allografts:** Between genetically different individuals from the same species (Most common)
- **Xenografts:** Between members of different species (rapidly rejected by IgM or cell mediated rejection)



autograft

from one part
of the body
to another
e.g. trunk
to arm

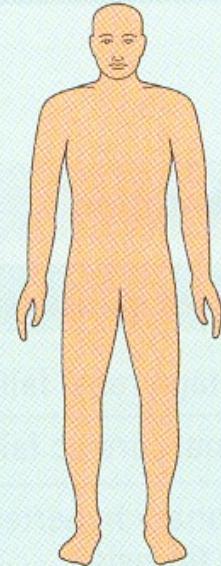


isograft

between
genetically
identical
individuals
e.g.
monozygot
twins, or
within an
inbred stra

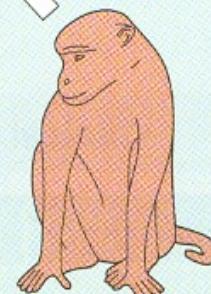
allograft

between
different
members
of the same
species
e.g. Mr Smith
to Mr Jones



xenograft

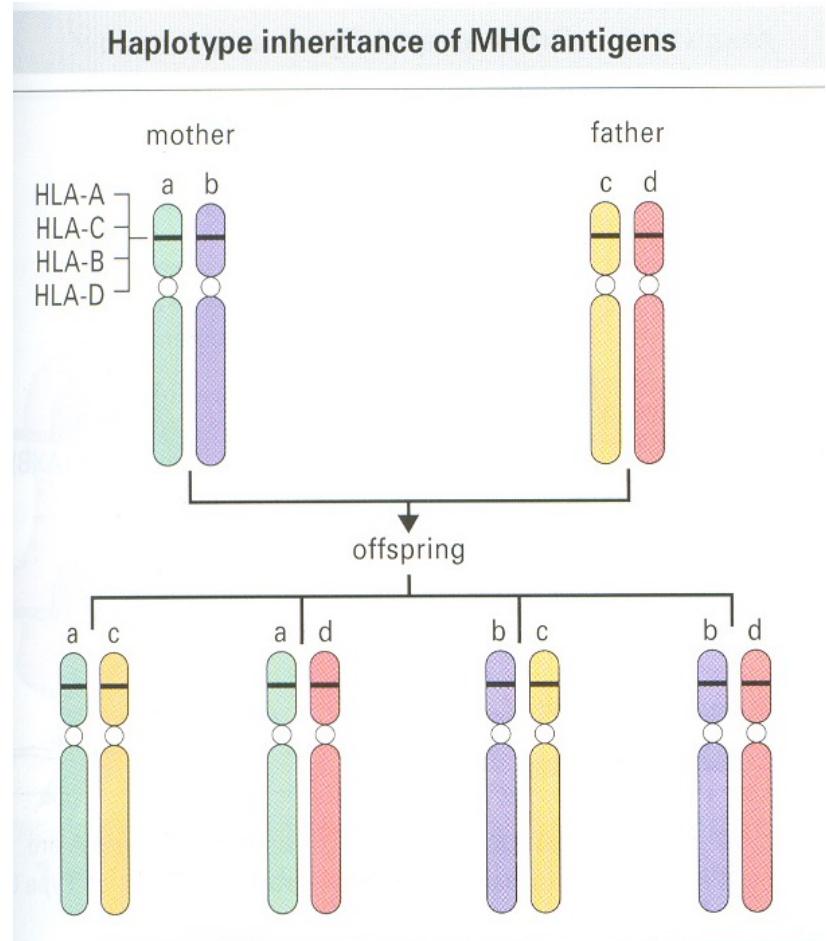
between
members o
different
species
e.g. monke
to man

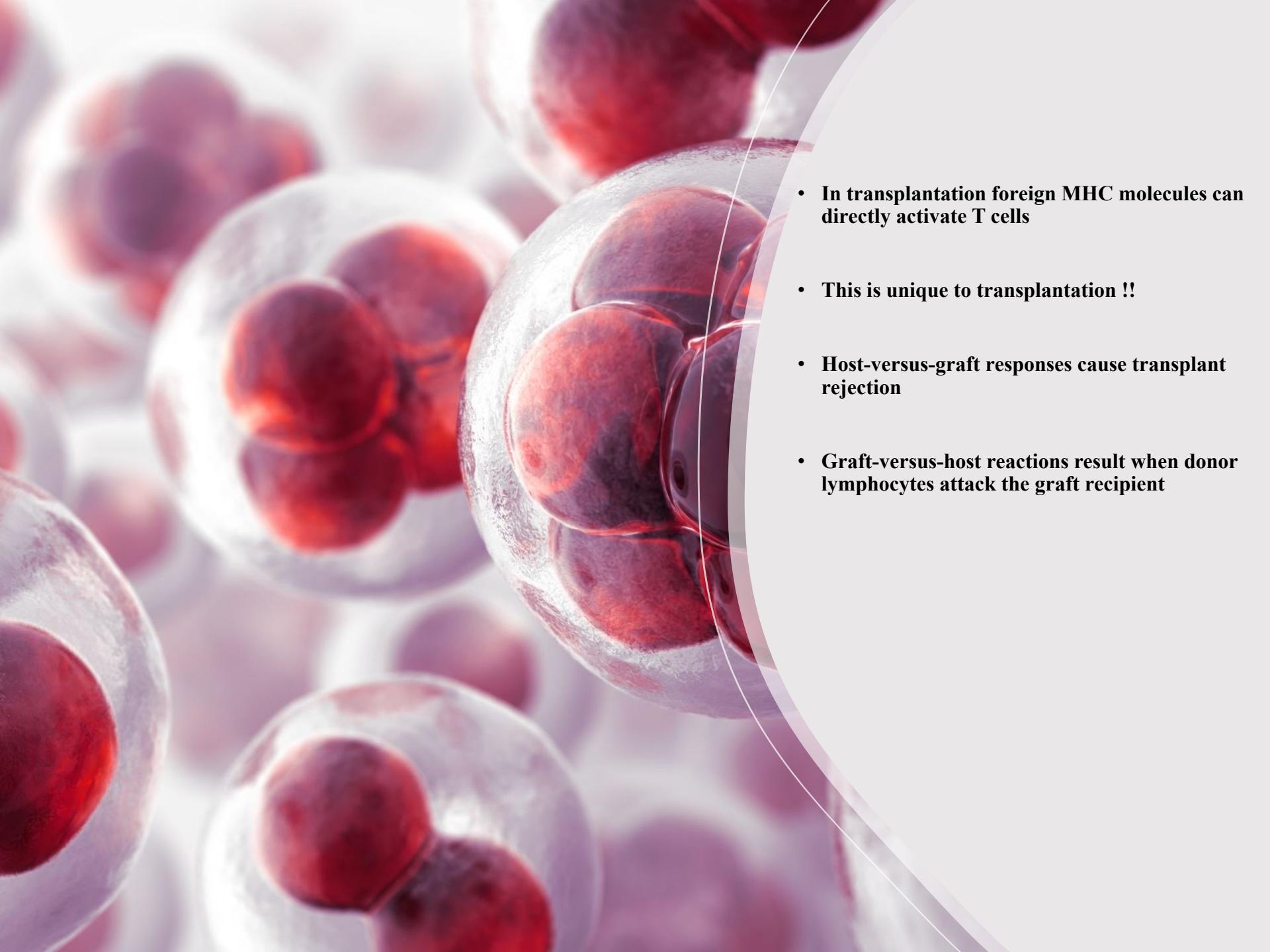


Histocompatibility antigens

- Genes that are responsible for rejection
- There are more than 30 gene loci
- Reject at different rate
- In human known as human leucocyte antigens (**HLA**)
- Cellular constituents are called minor histocompatibility antigens
- These induce rejection at a slower rate
- Combination of several minor antigens induce strong rejection

- MHC haplotypes are inherited from both parents and are co dominantly expressed
- MHC are expressed in transplanted tissues and are induced by cytokines (INF γ and TNF)



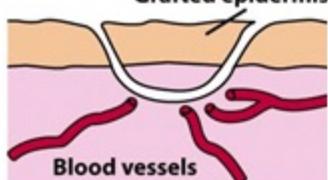
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- In transplantation foreign MHC molecules can directly activate T cells
 - This is unique to transplantation !!
 - Host-versus-graft responses cause transplant rejection
 - Graft-versus-host reactions result when donor lymphocytes attack the graft recipient



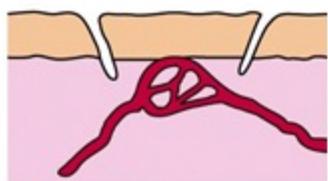
The role of lymphocyte in rejection

- In experimental animals:
 - Removal of thymus leads to inability to reject transplant
 - Irradiation to remove existing T cells leads to inability to reject transplant
 - Ability to restore rejection can be achieved by injecting T cells from animal of the same strain
- This gives strong evidence that T cells are crucial in the rejection process.
- Ab cause graft damage and macrophages are involved in inflammation

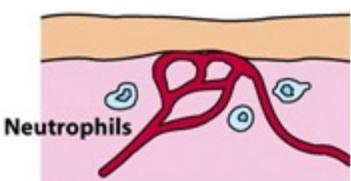
(a) Autograft acceptance



Days 3–7: Revascularization



Days 7–10: Healing



Days 12–14: Resolution

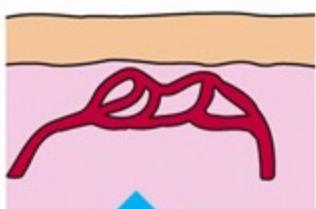
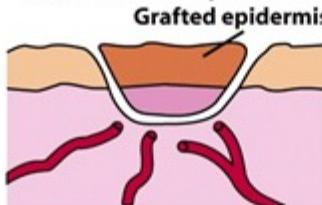


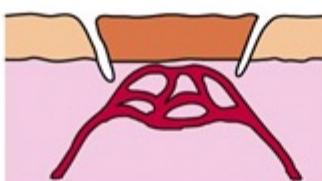
Figure 17-1
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Skin graft acceptance

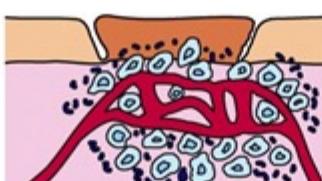
(b) First-set rejection



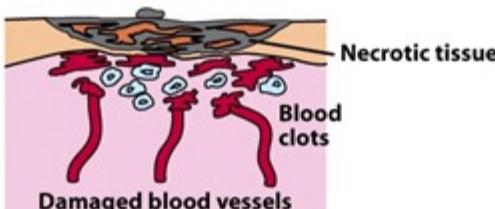
Days 3–7: Revascularization



Days 7–10: Cellular infiltration

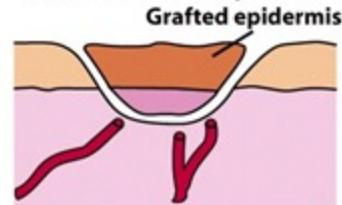


Days 10–14: Thrombosis and necrosis

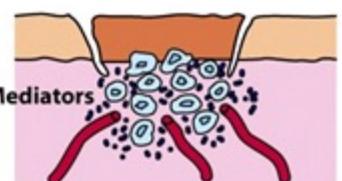


1st set rejection, necrosis results

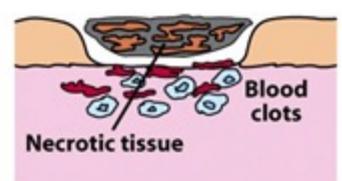
(c) Second-set rejection



Days 3–4: Cellular infiltration



Days 5–6: Thrombosis and necrosis



2nd set rejection
(same transplant is attempted for 2nd time). quicker

T cells play key role in allograft rejection •
Both CD4+ and CD8+ populations present •

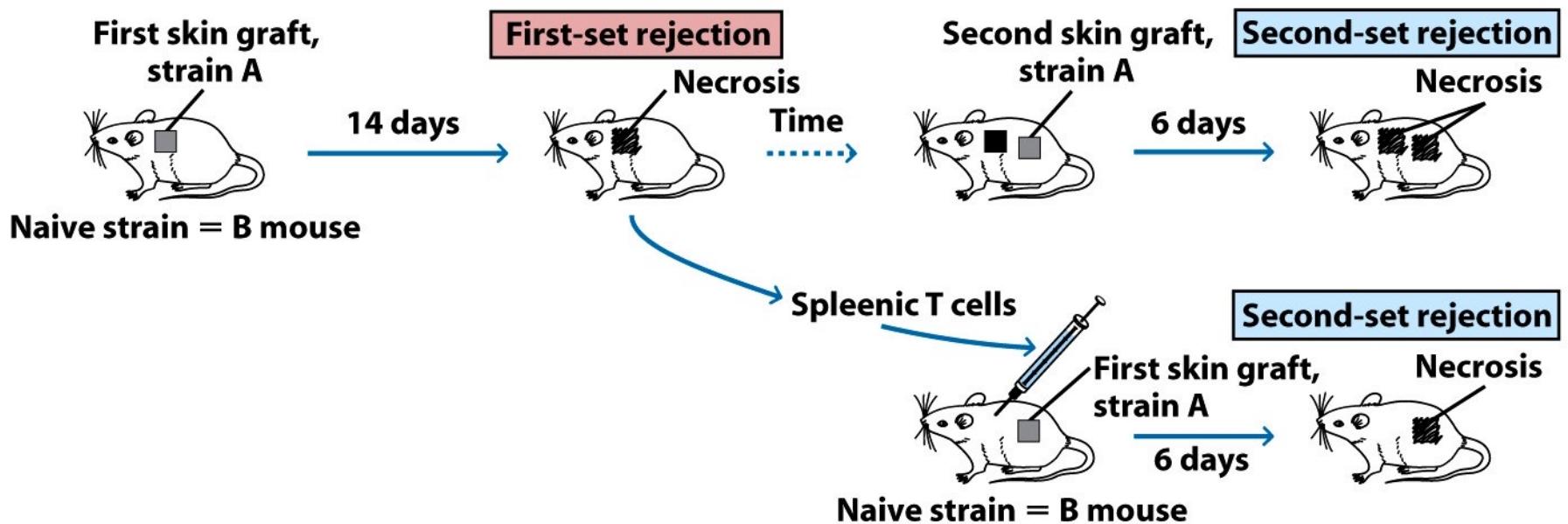
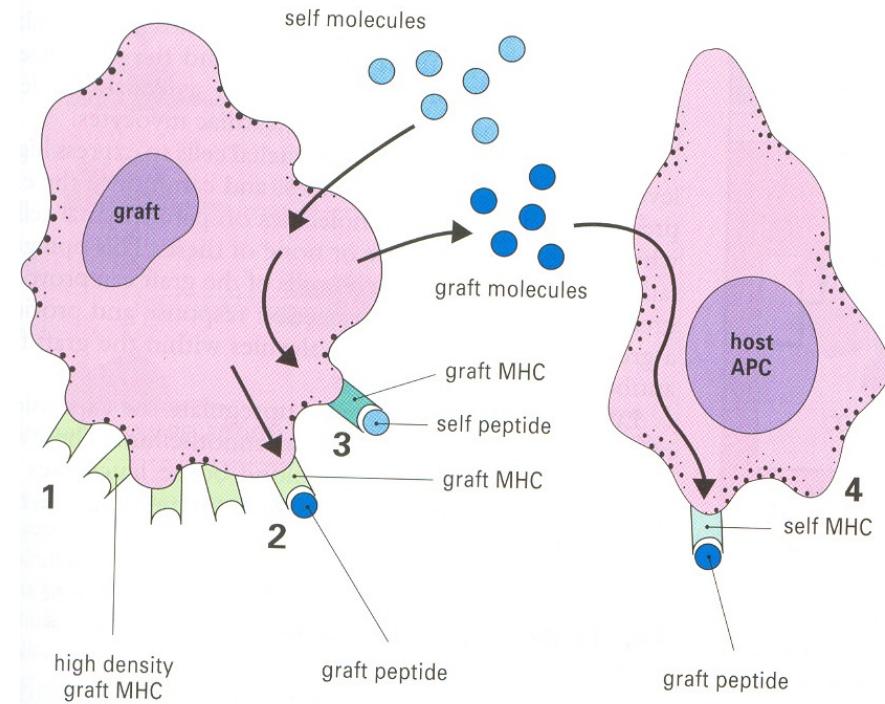


Figure 17-2
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Presentation of Graft antigen

- 1- High density of graft MHC molecules react weakly with TCR and generate signal for T cell activation
- 2- Graft MHC molecules can present the graft's own peptides including peptides from both major /minor MHC molecules
- 3- Graft MHC can present processed antigen of host molecules causing lack of host tolerance
- 4- Host antigen presenting cells can uptake different graft molecules and process and present these antigens



| <i>Type of rejection</i> | <i>Time taken</i> | <i>cause</i> |
|--------------------------|-------------------|-------------------------------|
| Hyperacute | Min-hours | Anti-donor Ab and complement |
| Acute | Days- weeks | Primary activation of T cells |
| Chronic | Months-Years | Unclear |

Rate of rejection: The rate of rejection depends on the type underlying effector mechanisms:

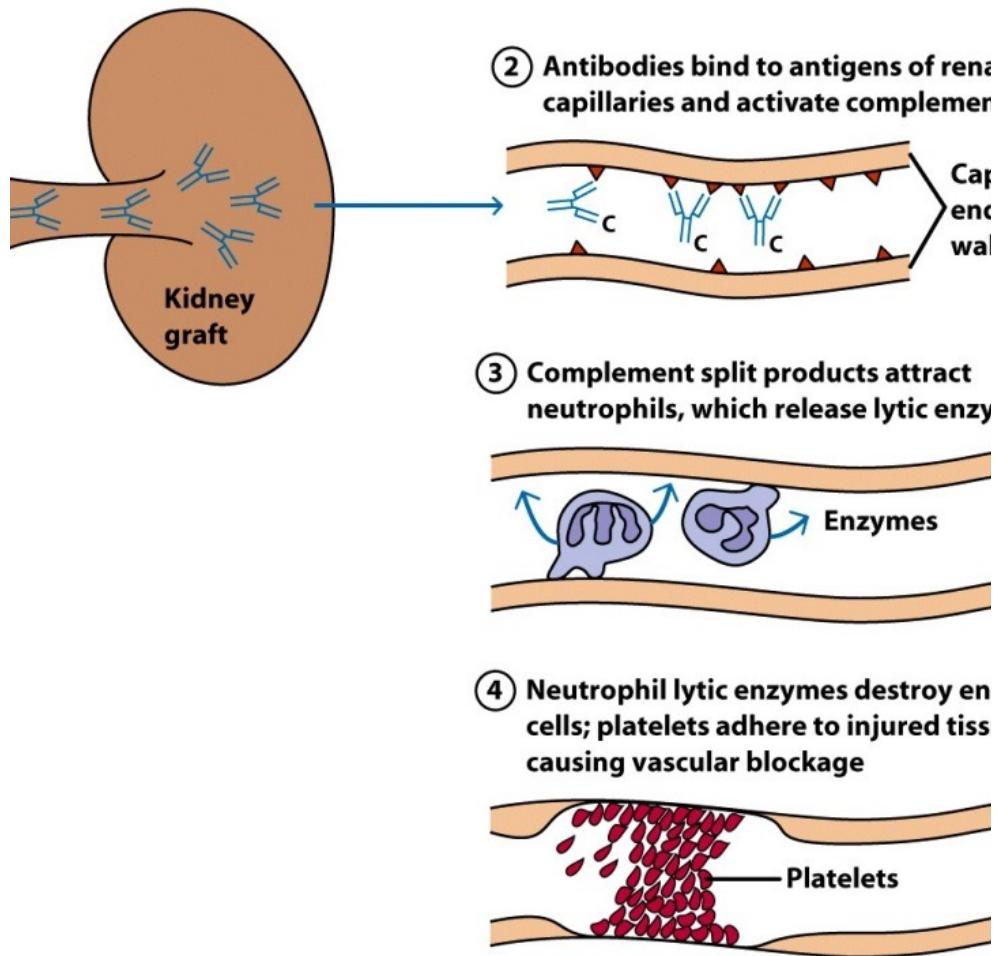
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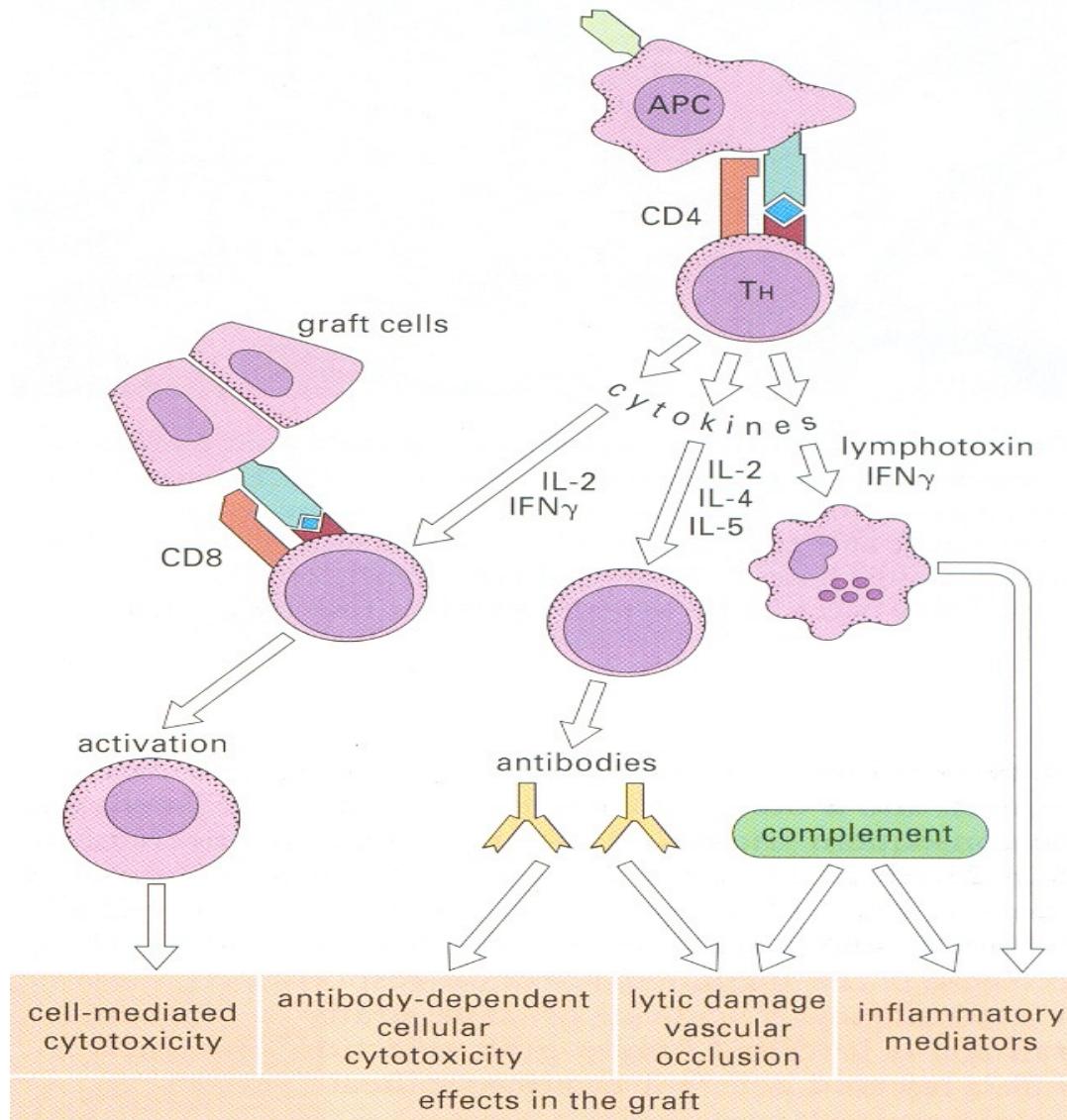
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Clinical Manifestations of Graft Rejection

- Hyperacute
 - Pre-existing recipient antibodies
 - Graft never become vascularized



Immunological components of rejection



PREVINTION OF REJECTION

- Non specific immunosupression can reduce rejection reaction;
 - Large dose of X-rays
 - Steroid : have anti-inflammatory activity and suppress macrophages
 - Cyclosporin: suppress lymphokines production
 - Azatioprine :blocks Tc proliferation



Laboratory testing for Histocompatibility:

- 1-Tissue typing by using flow cytometry or FACS (Fluorescence activated cell sorter) to identify human leukocyte antigens (HLA)

- 2- Serological tissue typing

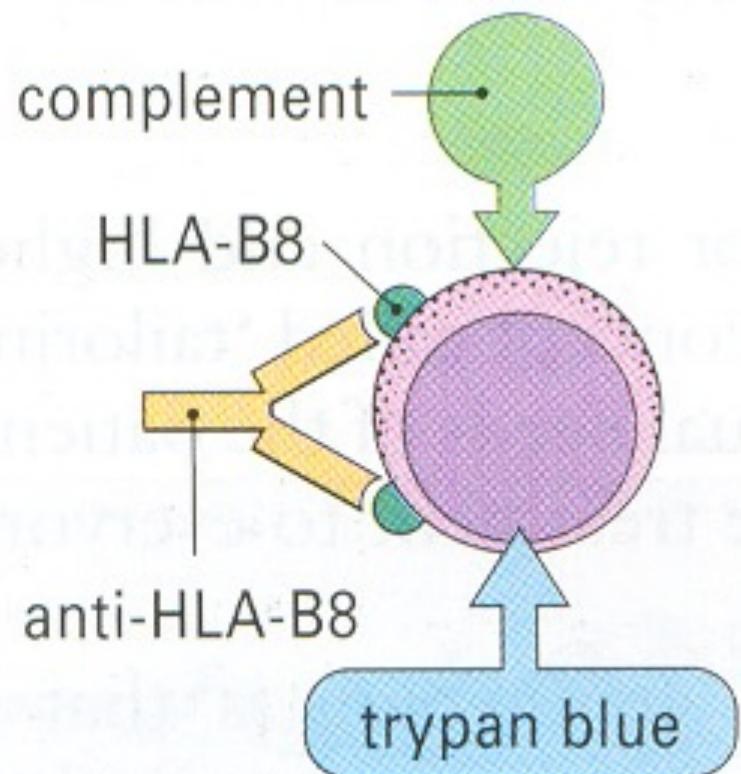
- 3-Tissue typing-mixed lymphocyte reaction



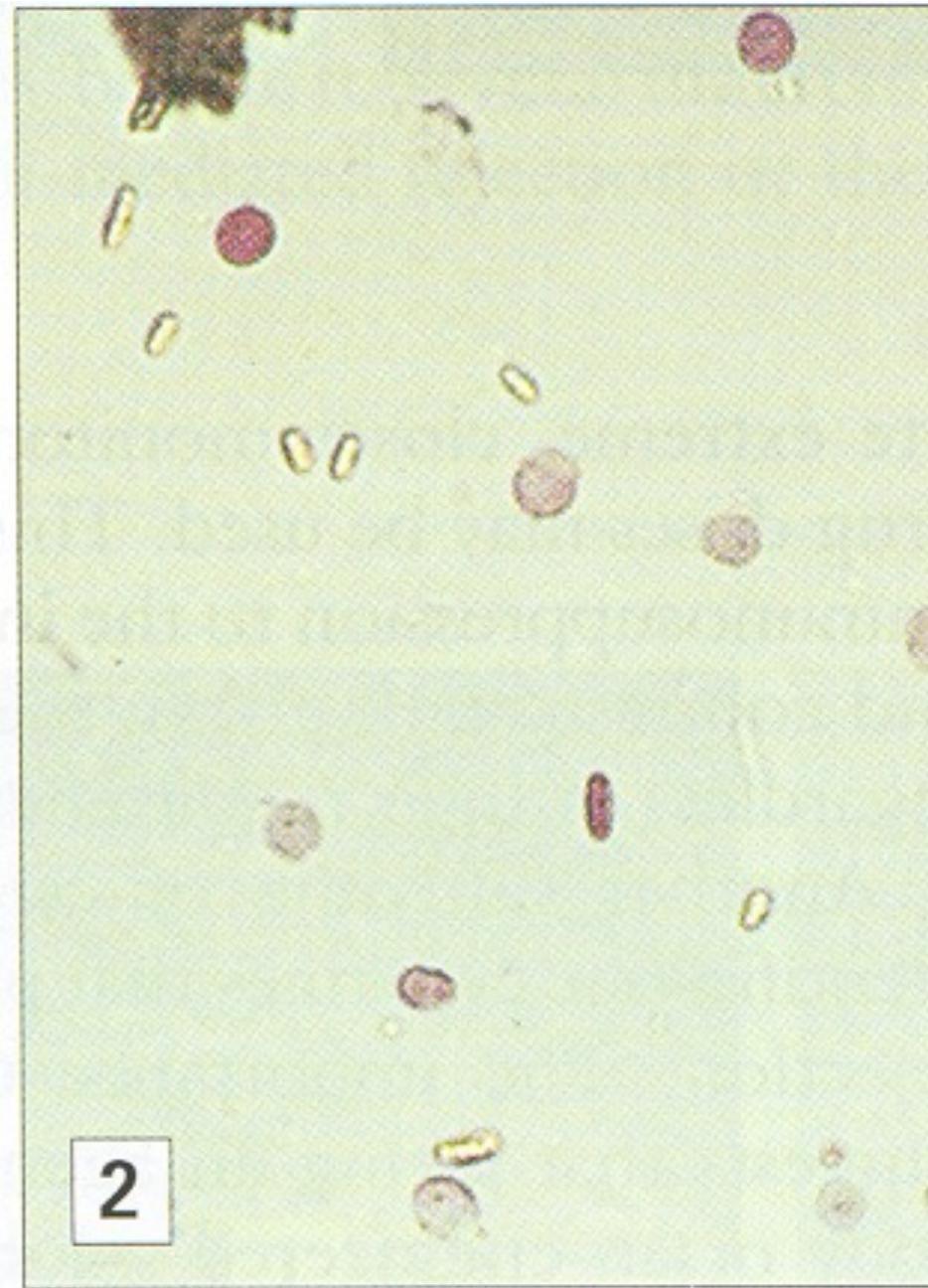
Serologic tissue typing:

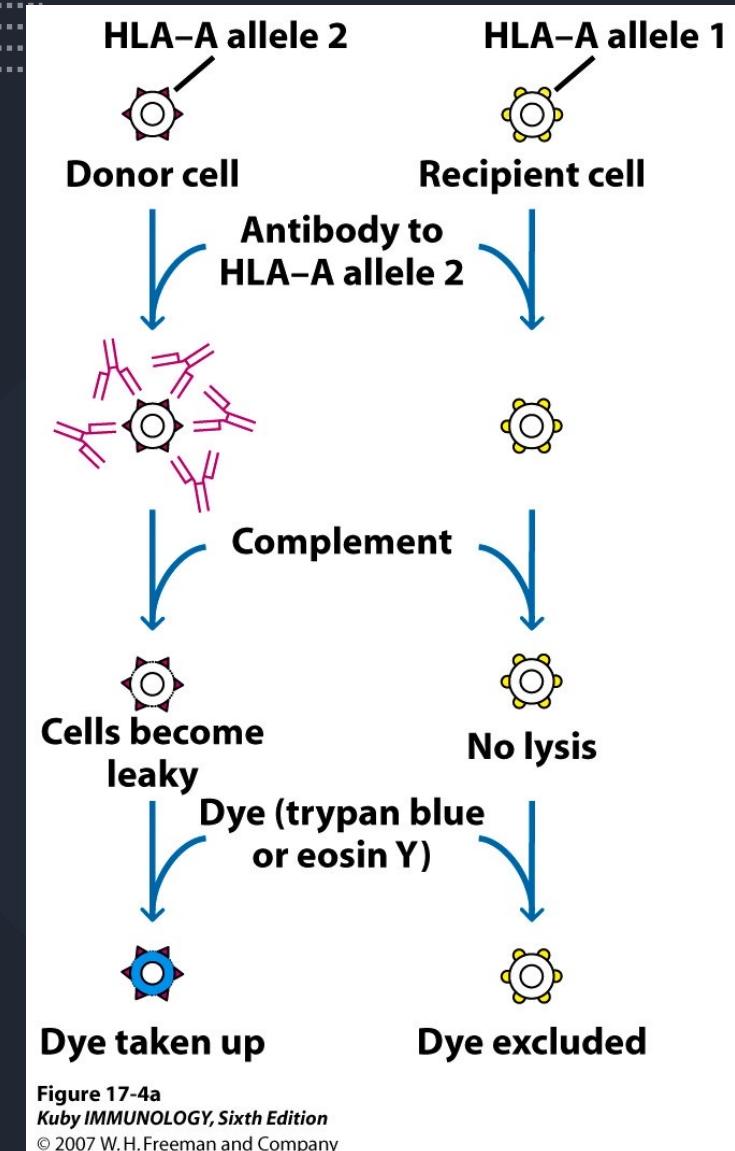
Principle:

- Performed by adding typing antisera of defined specificity (e.g. anti-HLA-BB)
- Complement and trypan blue stain are added to the test
- The trypan stain will stain dead cells with blue color
- This indicates that the tested cells carry the antigen



1





| Antibody to different HLA-A antigens | | | | | | | | | |
|--------------------------------------|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Recipient | ● | ○ | ○ | ○ | ○ | ○ | ● | ○ | ○ |
| Donor 1 | ● | ○ | ○ | ○ | ○ | ○ | ● | ○ | ○ |
| Donor 2 | ○ | ● | ● | ○ | ○ | ○ | ○ | ○ | ○ |

Figure 17-4b
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- Microcytotoxicity assay for MHC haplotypes
- If antigen is present on cell, complement will lyse it, and it will uptake dye (blue)
- Donor 1 has antigens in common with recipient

A close-up, high-magnification microscopic image showing several red blood cells. The cells are spherical with a distinct biconcave discoid shape. They appear translucent with a bright red color, allowing some internal structure to be seen. The background is white, and other cells are visible in soft focus.

Tissue typing-mixed lymphocyte reaction (MLR)

Principle:

- The cells being tested are incubated with “typing cells” of known specificity
- The tested cells will recognize the typing cells as foreign cells and proliferate
- If the tested cells are carrying the same specificity as the typing cells they will not proliferate
- or The lymphocytes of two individual are mixed and One donor serves as responder and other as stimulator
- In one way MLR: stimulator Lymphocytes are treated to render them non-proliferative so that measurement of responding cells is not obscured.