Immunology Team

Transplantation

Lecture 2

Renal Block

→ Note or explanation

Red → Important point

Abdullah Almazyad

Ibrahim Alsaleem

Abdulrahman Alshaya

Afnan AlRashoud

Hadeel Helmi

Rand Alhaweal

Jumanah Mirah

Jaazeel Mulla

Major Histocompatibility Complex and Transplantation

Tissue antigen

- **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 " HLA " .**

Remember :

Cytotoxic T cell → CD8 → MHC class I

Helper T cell → CD4 → MHC class II

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, 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.**

All MHC classes are found on Chromosome 6 , and part of Chro.6 is HLA antigen

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

MHC class	I			II			III **MHC class III is not related to the HLA molecules → is in charge of complement, TNF**	
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 "Number of antigems"	47	88	29	More than 300 HLA-D				

Because of these polymorphisms ,we can see in one individual the HLA-A,B,C different from other individual .

*the person will have 2 HLA-A form 47 different HLA-A

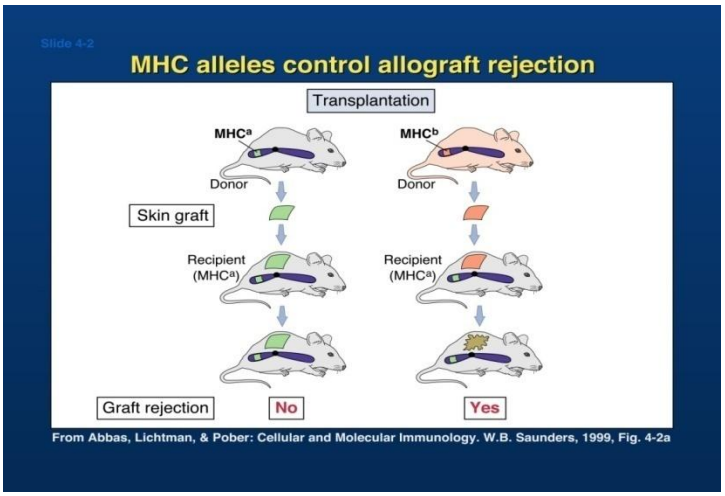
Minor HLA genes and Transplantation

- **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

*When the MHC is the same from Donor and recipient the graft will not be rejected .

*But if it's different it will be rejected .



Transplantation

- **Types of transplants:**
  - **Autografts, Autologous grafts**
    - **Donor and recipient are same individual**
    - **Common in skin grafting; bone marrow.**

in cases of burns where over 40-50% of the skin is lost (grafting is a necessity since with burns the patient losses plasma and proteins) → if the burns are on the patients arms (for example), they take some of his skin from another place on his body (for example, from legs) and they put the skin on his arms

  - **Syngeneic grafts or (isograft)**
    - **Donor and recipient are genetically identical**
    - **Animal models; identical twins**

In case of identical twins , it will be 100% MHC matching ,because they are from same placenta.

  - **Allogeneic grafts " commonest type of transplantation "**
    - **Donor and recipient are same species, but genetically unrelated**
    - **Common heart, lung, kidney, liver graft.**
  - **Xenogeneic grafts**
    - **Donor and recipient are different species.**

"xeno" meaning animal source

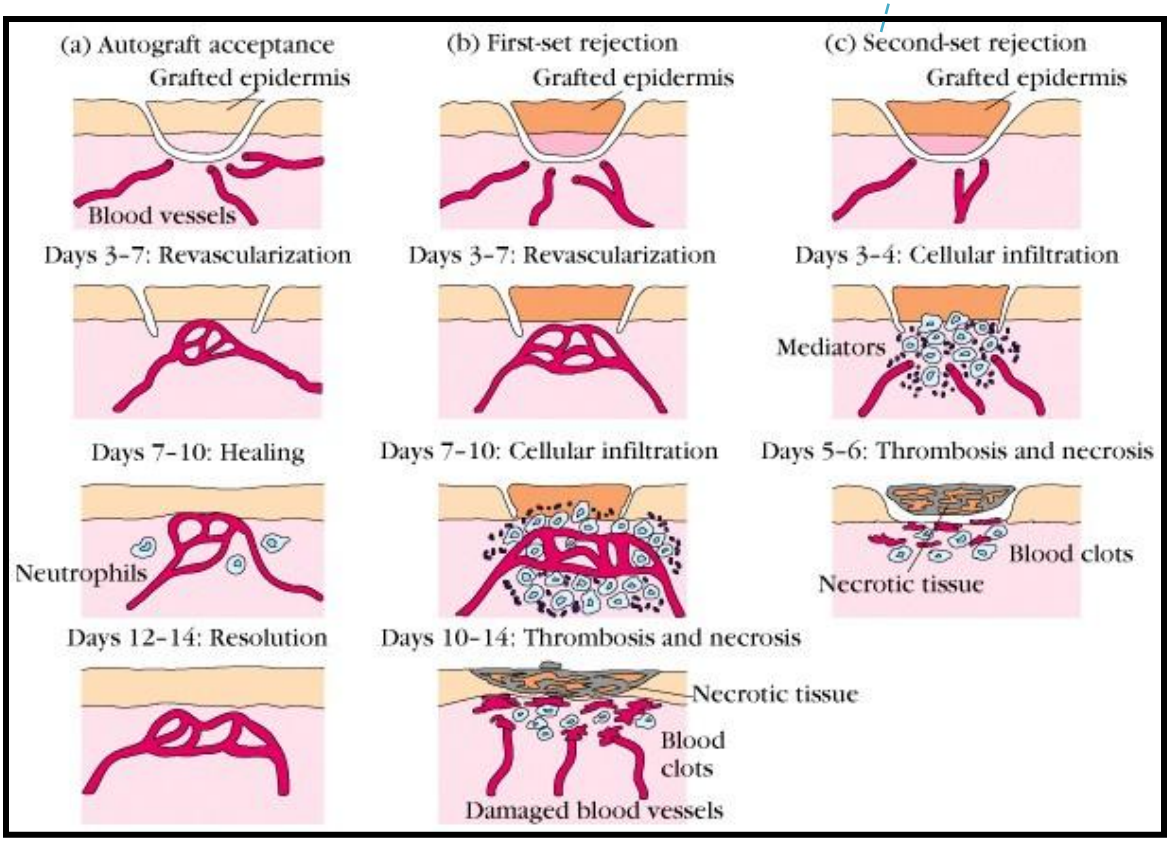
- **Artificial grafts**

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**

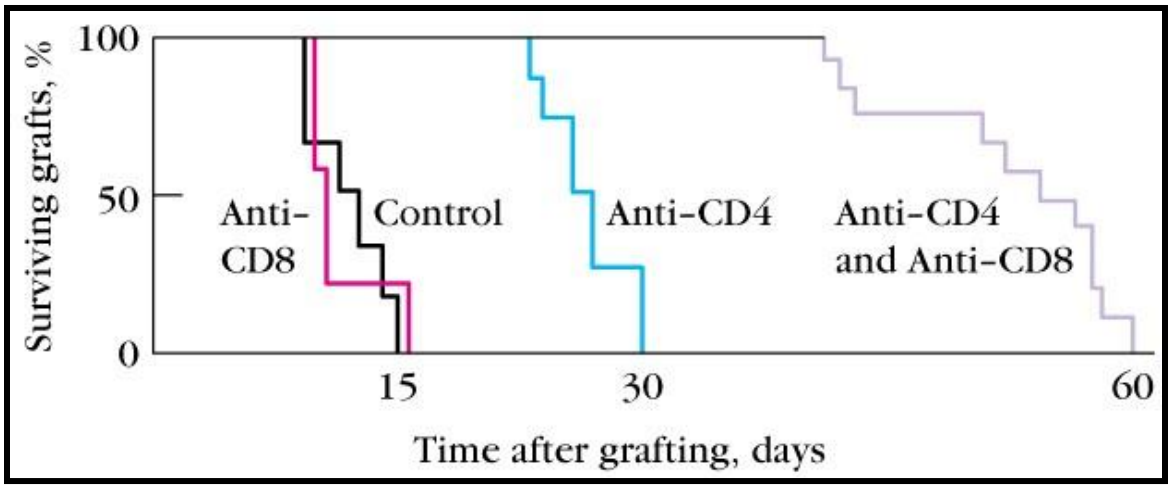
1st set versus 2nd set reactions

Occurs after 2nd transplant as a result of the MEMORY CELLS



The reason why 1st set reaction takes longer than 2nd set reaction, is that the body(cells) are building antibodies during 1st set rejection against the donor's antigens , while in the 2nd set rejection, the body already has those antibodies " memory ".

Role of $CD4^+$ versus $CD8\ T^+$ cell



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

Explanation :

If we inhibit the CD4 the tissue will survive longer than inhibiting of CD8 , but if we inhibit both of them the tissue will survive much longer .

*so, CD4 is more important then CD8

Transplantation

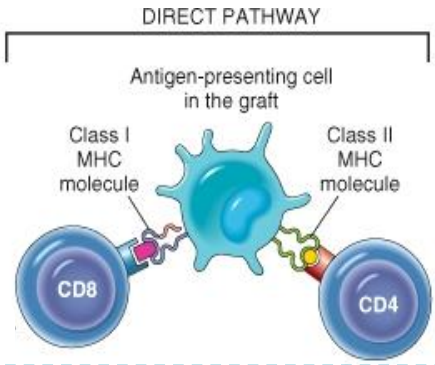
- **<u>T cells play primary role in 1st and 2nd set rejection reactions</u>**
  - **Nude mice accept allografts (no T cells due to genetic modification resulting in absent thymus)**
  - **B cell deficient mice reject allografts**

nude mice prepared in the lab by genetic mutation to have NO THYMUS ➔ NO T CELL PRODUCTION → **accepted skin graft from a rabbit with NO REACTION**

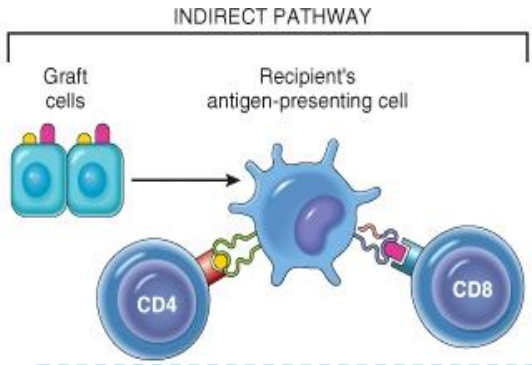
* with no B cell formation, the mice still reject the graft

Nude mouse has a transplant of rabbit skin

Mechanisms involved in Graft Rejection

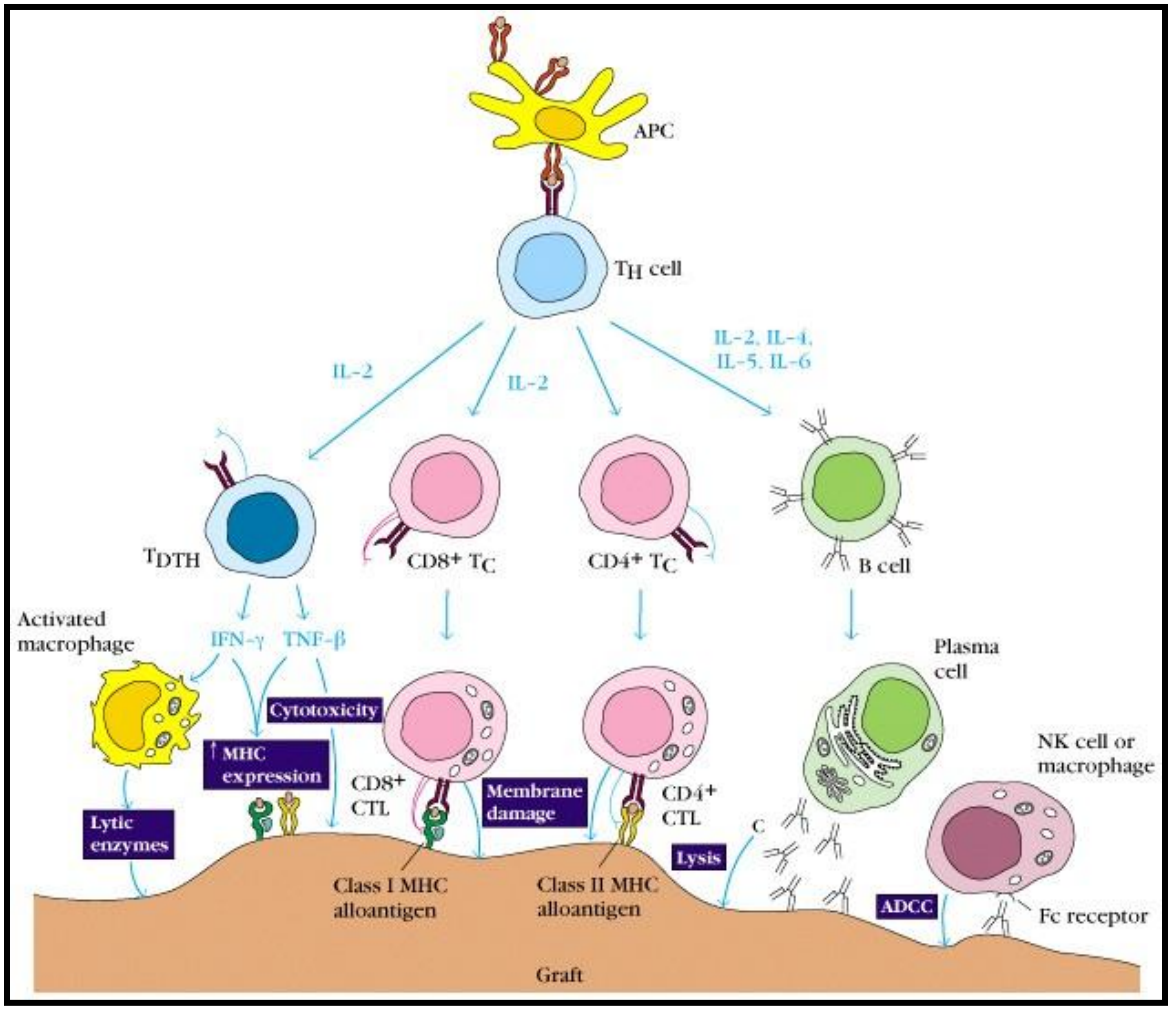


The CD4 or 8 is directly attack the graft and it will be rejected .



The graft cell is taken first by antigen presenting cell then the CD4 or 8 will attack the graft and rejected .

Rejection Response



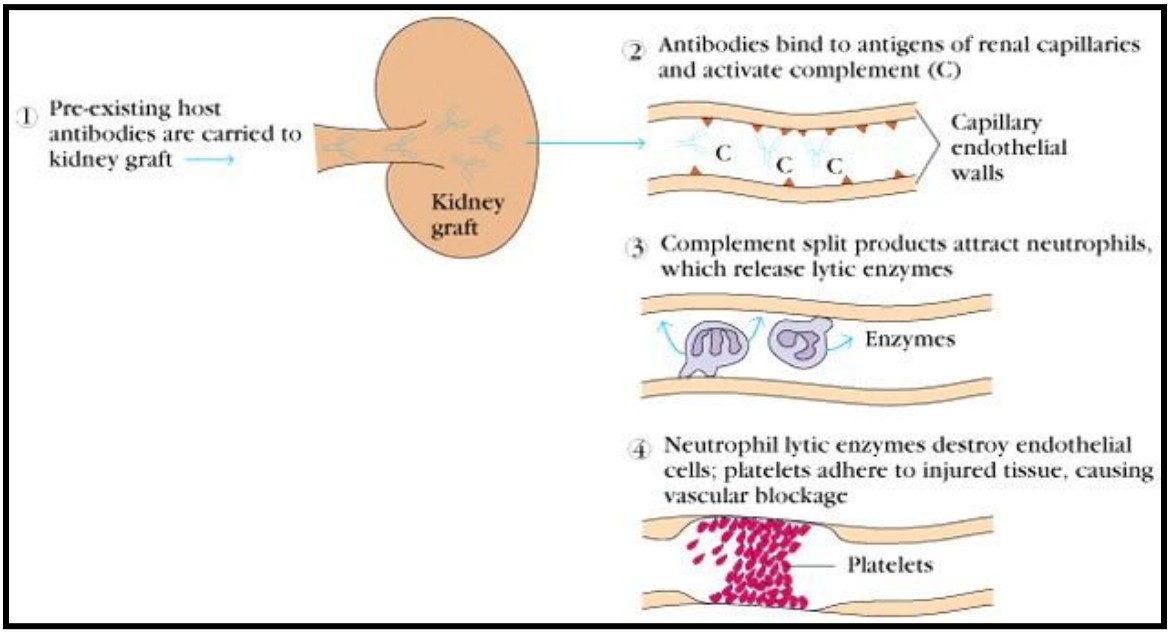
Clinical manifestations of graft rejection

I. **Hyperacute rejection: very quick**

Happens within minutes on the operation, because the recipient already had Ab (naturally occurring and because of blood transfusion before the operation) against those Ag.

II. **Acute rejection: about 10 days (cell mediated)** — Mediated by Tcell

III. **Chronic rejection: months-years (both)** — Mediated by Antibody & Tcell



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 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 (important)**
  - **DNA sequencing by Polymerase Chain Reaction (PCR)**
  - **Serologic Assays**
  - **Mixed Lymphocyte Reaction (MLR)**
  - **Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.**

mixing the lymphocytes of both donor and recipient → 3-4 days → if there is multiplication of cells ➔ no transplantation

Tissue Matching

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

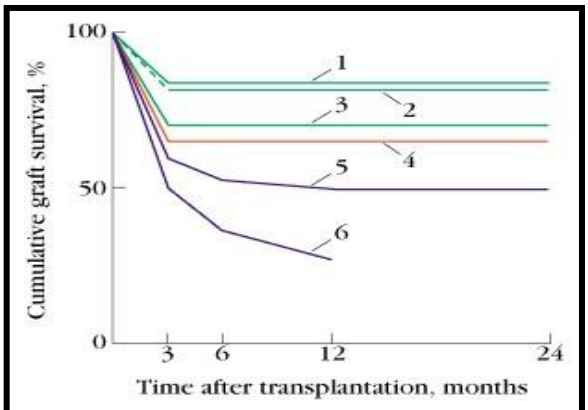
If there is mismatching in :

*Class I & II → the survival will be very low >

*Class I only → the survival not affected very much.

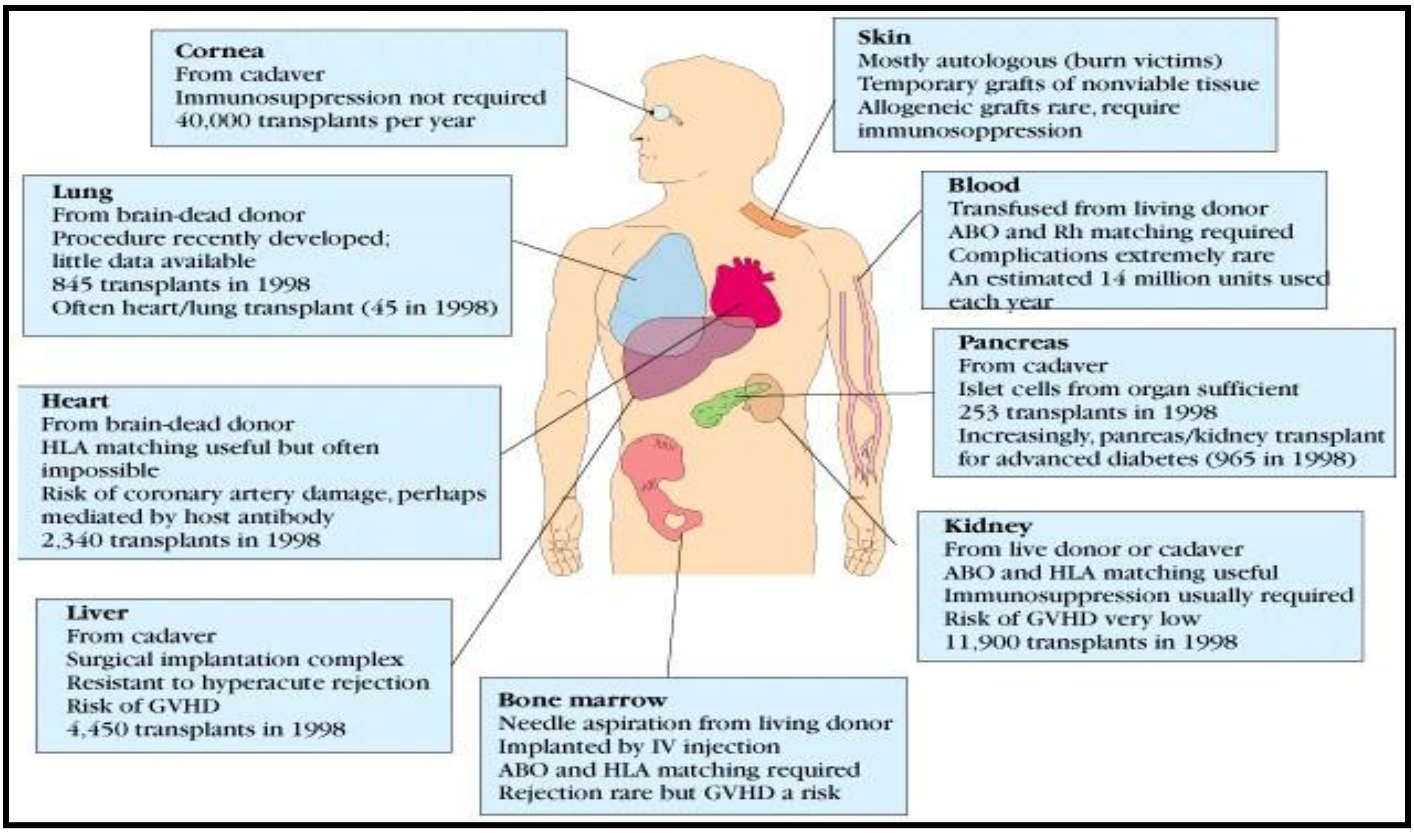
*Class II only → the survival will be about 50%.

0" meaning NO mismatch! Exactly similar



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

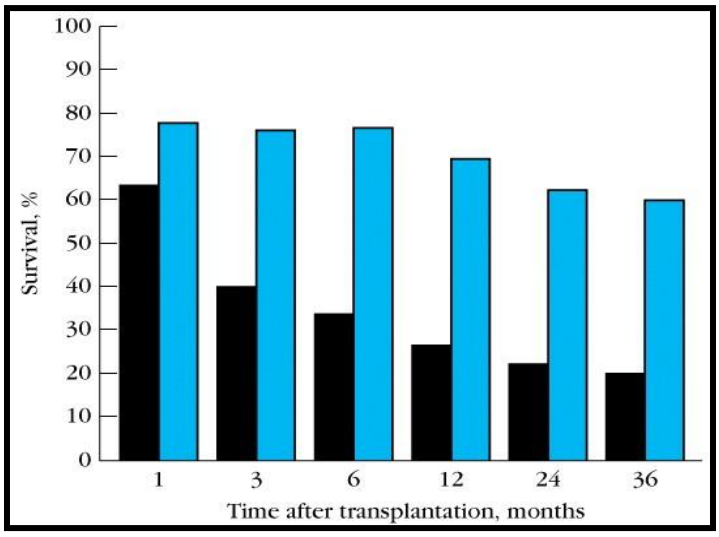
Tissue Matching



Cornea : we don't give immunosuppressant because it's avascular → no rejection will occur.

General Immunosuppression Therapy

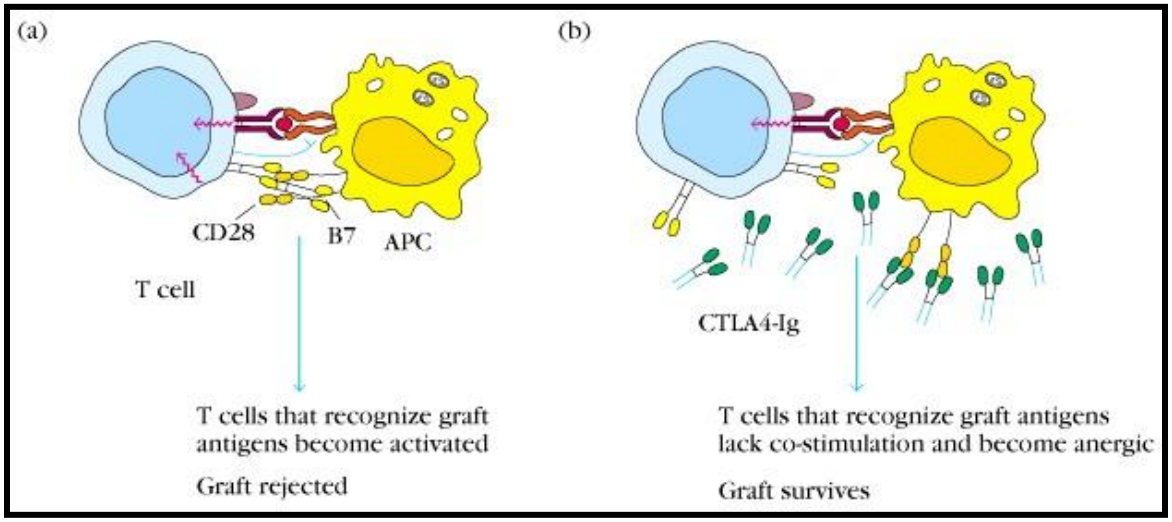
1) **Mitotic inhibitor: azathioprine (pre & post).**
2) **Corticosteroids.**
3) **Cyclosporin.**
4) **Total lymphoid irradiation.**



Specific Immuno-suppression therapy

a) **Monoclonal antibodies against T cell components or cytokines**

b) **Agents blocking co-stimulatory signal "B7 , CD28 "**



Immuno-suppresive Therapy

- **<u>Downsides</u>**
  - **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-suppresive therapy is usually required after transplantation.**