Transplantation

Renal block

second lecture

Brought to you by:

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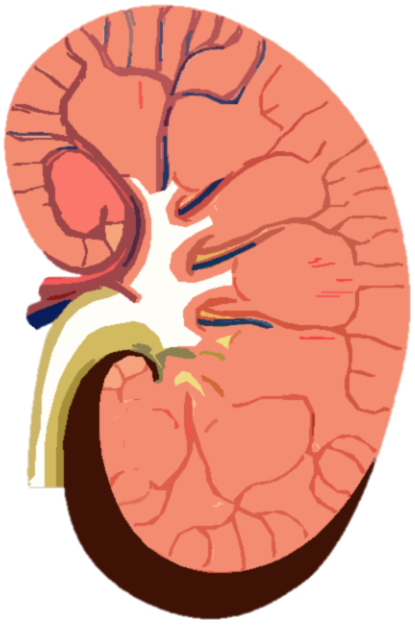


Objectives:

- To understand the diversity among human leukocyte antigens (HLA) or major histo-compatibility 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

Black : Slides

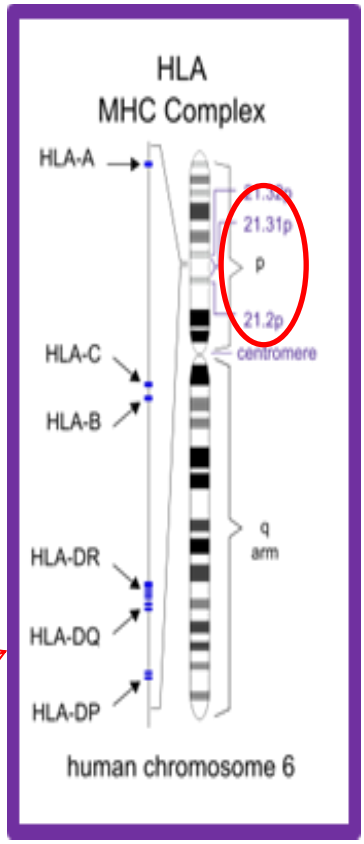
Purple: Extra notes for further understanding

Orange: Notes said by the doctor

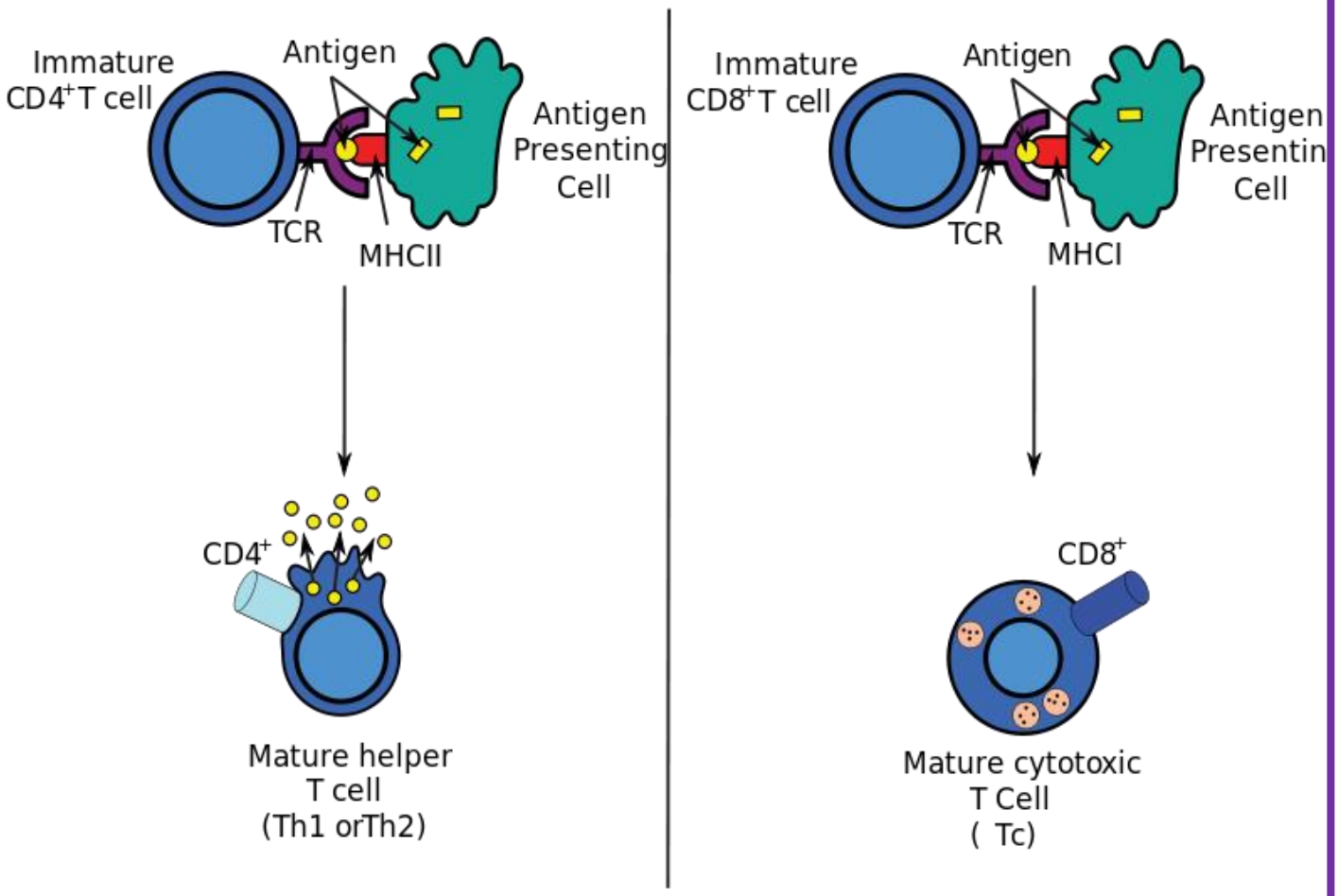
Red : important

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 .
- Human Leukocyte antigen system = Major histocompatibility Complex in humans. Cause Major Histocompatibility complex genes found in different species like mammals for example.
- These proteins are allo-antigens(Allo-antigens are antigens from members of the same species.)
- Genes for HLA proteins are clustered in the MHC complex located on the short arm (p arm)of chromosome 6
- MHCs or HLAs are different between one person and another, so in transplantation they will act as a foreign antigen in the recipient body, and an immune response will be directed against those bodies this is known as **rejection**. Unless the HLAs collection is a bit similar like in siblings or exactly the same like in identical twins.



For Further understanding:



- MHC Class 1: are glycoproteins that will appear on both antigen presenting cells and nucleated cells for example, RBCs are not nucleated so there is no MHC.
- Antigens: two types: endogenous (viruses) and exogenous (Bacteria).
- Antigen (virus) + MHCI= activates CTLS (CD8 cytotoxic cells) that will kill the infected cell.
- MHC Class 2: are glycoproteins only found on the surface of APCs (macrophages, B cells, dendritic cells and Langerhans cells).
- Antigen (bacteria) + MHC II = activates T-helper cells (CD4) that will pick up the presented antigen and get rid of it.
- So Antigen presenting cells present both MHCI and MHCII.

MHC Class I and II Proteins

Class II

A Type of glycoproteins

found on the surface of antigen presenting cells(an antigen presenting cell also has a nucleus so normally it carries MHC I AND II)

Helper T cell recognize antigen in association with class II MHC proteins

Genes : HLA-D
- DP
- DQ
- DR

Class I

A Type of glycoproteins

on surface of virtually all the nucleated cells

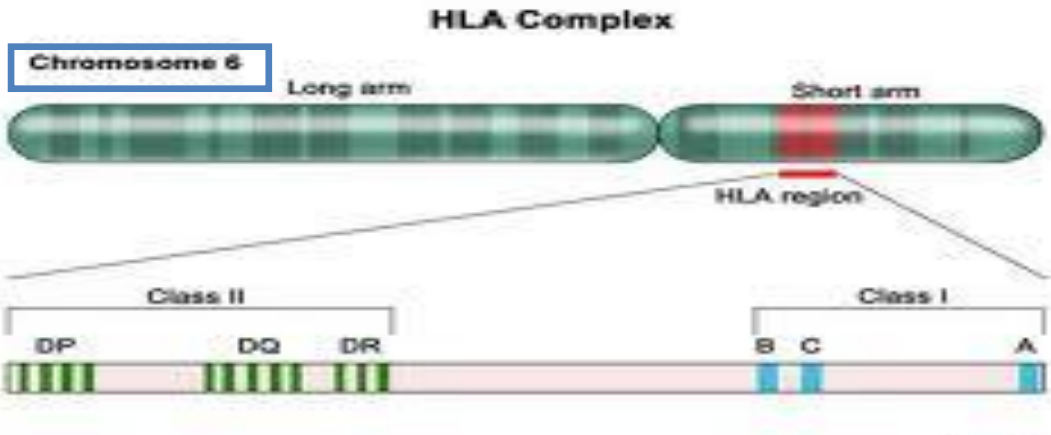
Cytotoxic T cell kills virus infected cells in association with class I MHC proteins

Genes : HLA-A, HLA-B and HLA-C

Notes:

- MHC main function is presentation of antigens.
- This will take a part in Cell mediated immunity.
- Remember that immunity is divided into:
  - Innate immunity.
  - Adaptive immunity (Which is further divided into humoral and cell mediated).
- HLA system is used for paternity test.
- Example, Father: HLA-A1, HLA-B5,HLA-C4
- Mother: HLA-A4, HlA-B8,HLA-C2
- Son:HLA-A1,HLA-B8,HLA-C4 (the son will have a collection from both).

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

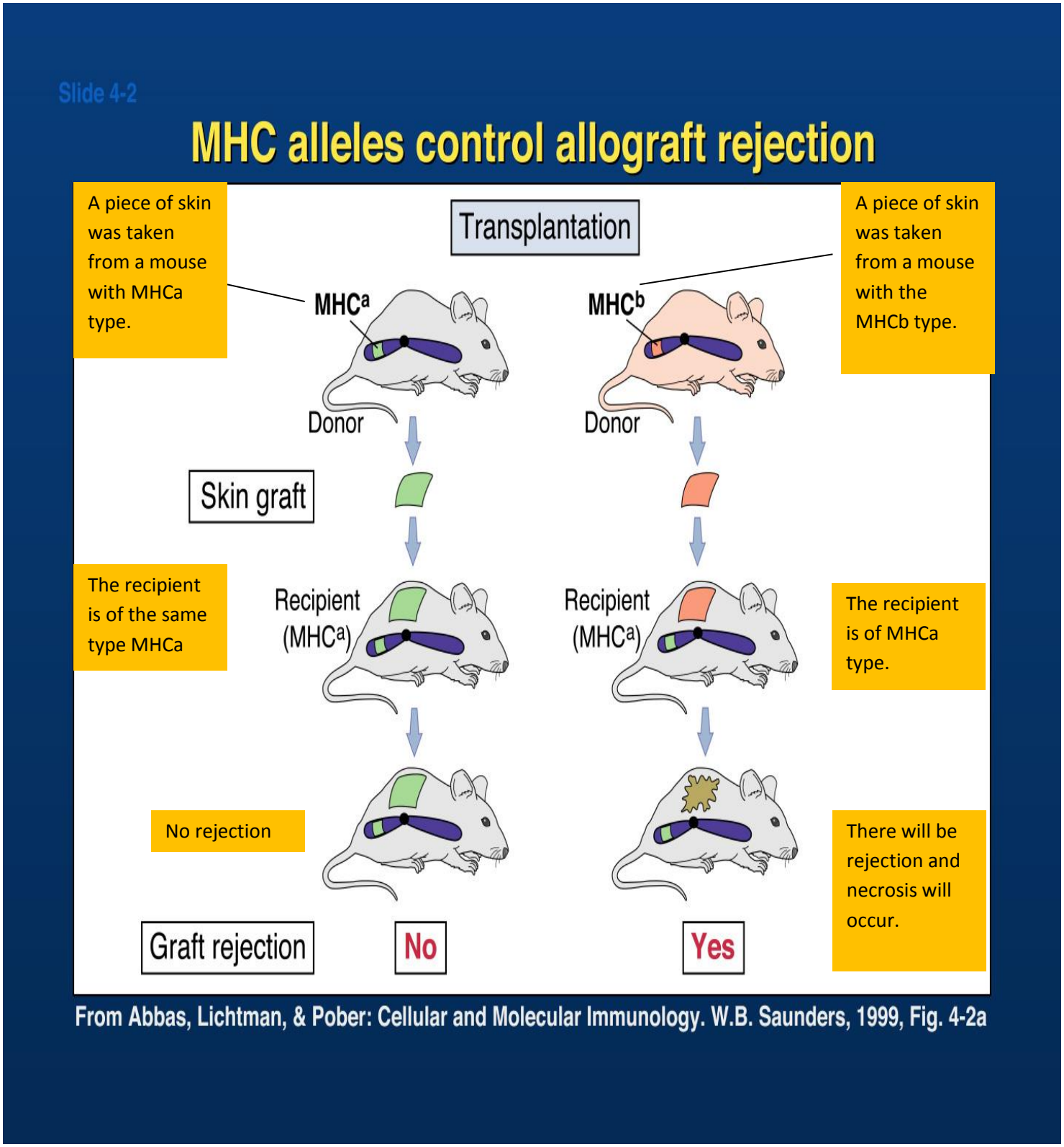


II			MHC class	I		
DP	DQ	DR	Region	B	C	A
DP	DQ	DR	Gene product	HLA-B	HLA-C	HLA-A
More than 300 HLA-D			Polymorphism	88	29	47

- MHC class III is for complementary system (C4,C2,BF) and their genes products are C proteins and TNF-alpha, beta.
- MHC class III has nothing to do with encoding HLA molecules it is just called MHC because it is between class I and II on the chromosome.
- You can call HLA molecules MHC as well but technically it is MHC region on chromosome 6 encoding HLA molecules.
- Minor HLA genes (unknown):

1. They mount a weak immune response.
2. Play role in chronic rejection of a graft.
3. There are no laboratory tests to detect minor antigens.

Transplantation antigens



Transplantation

Types of transplants	Autografts, Autologous grafts	Syngeneic grafts or (isograft)	Allogeneic grafts	Xenogeneic grafts	Artificial grafts
	Donor and recipient are same individual	Donor and recipient are genetically identical	Donor and recipient are same species, but genetically unrelated	Donor and recipient are different species	For example: prosthetic valves and artificial knees
	Common in skin grafting; bone marrow and hair	Animal models; and identical twins	Common heart, lung, kidney, liver graft		

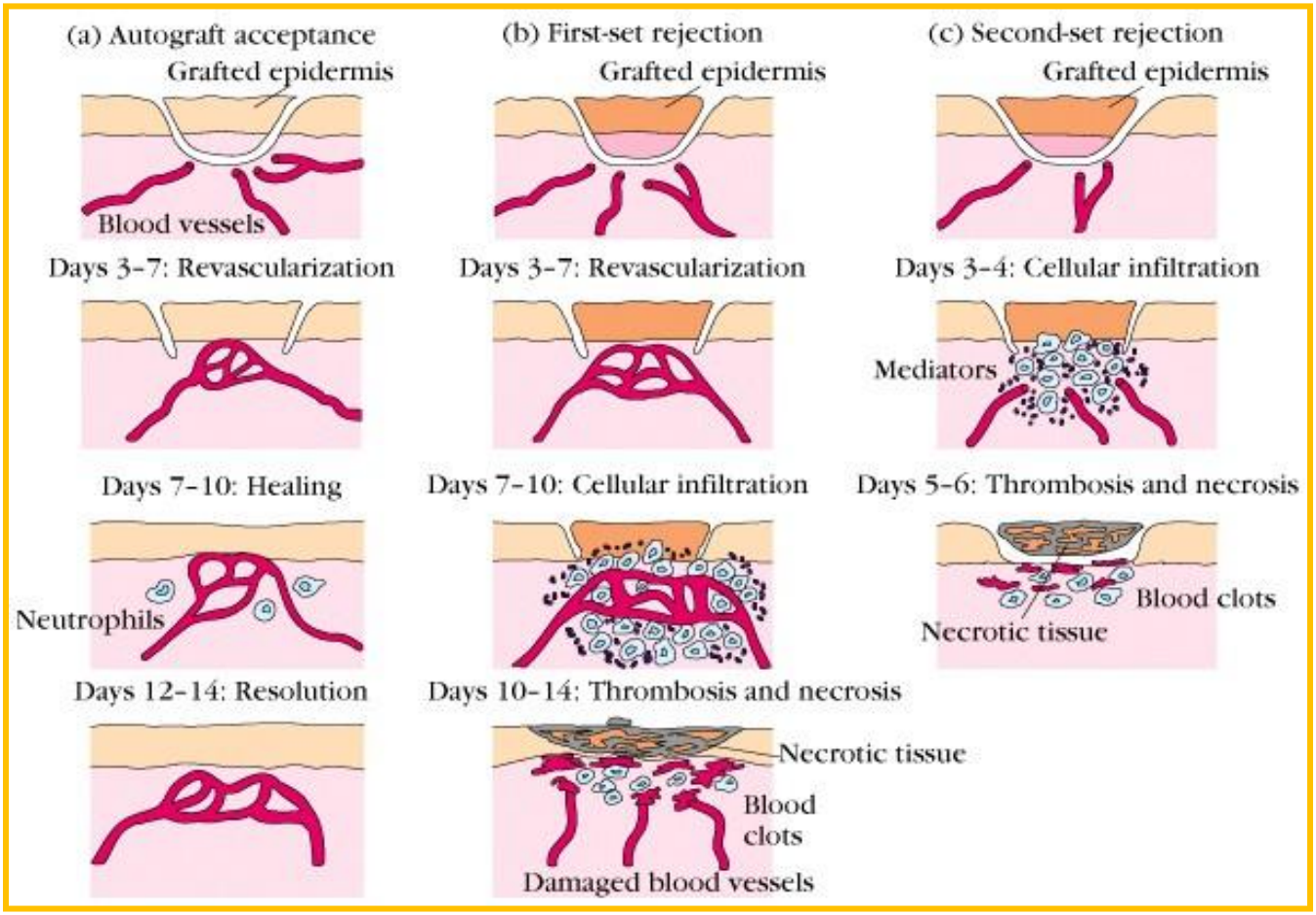
Rejection

- Major Barrier to transplantation is the immune response
  - T cells play primary role (cell mediated immunity a type of adaptive immunity)
  - B cells can/do play a role (Humoral immunity (antibodies) a type of adaptive immunity)
  - Classic adaptive/acquired immune response include:
    - Memory (the reason for the 2nd set rejection)
    - Specificity

Acceptance: similar HLA

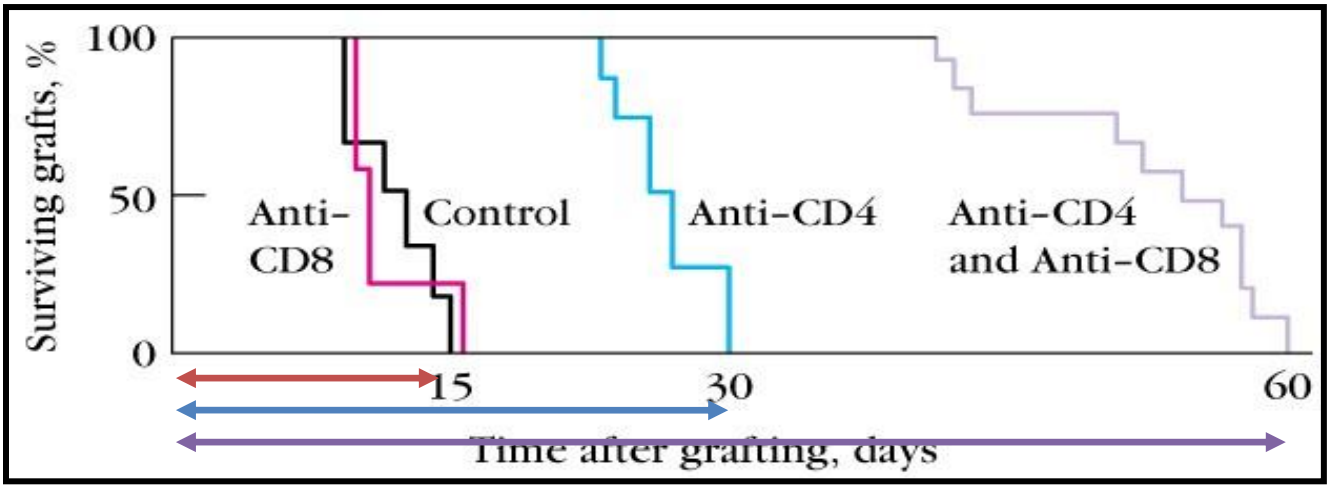
1st set rejection: different HLA

2nd set rejection: it's faster (acute) because of memory cells.



2nd set rejection happens: if the1st set rejection happened &then the same graft is introduced again to the same recipient. Necrosis will happen even faster than the first time. It's known as developing immunity against the graft due to presence of memory cells.

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



Removing CD8 from the recipient mouse made the graft survive for 15 days .

Removing CD4 from the recipient mouse made the graft survive for 30 days . This shows how T cells play an important role in transplant rejection in general, but the most important cells are CD4 cells in rejecting the transplant because they lead to activation of other immune cells, so by inhibiting CD4 cells the graft will survive more.

Removing both CD8 and CD4 will make the graft survive for 60 days.

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

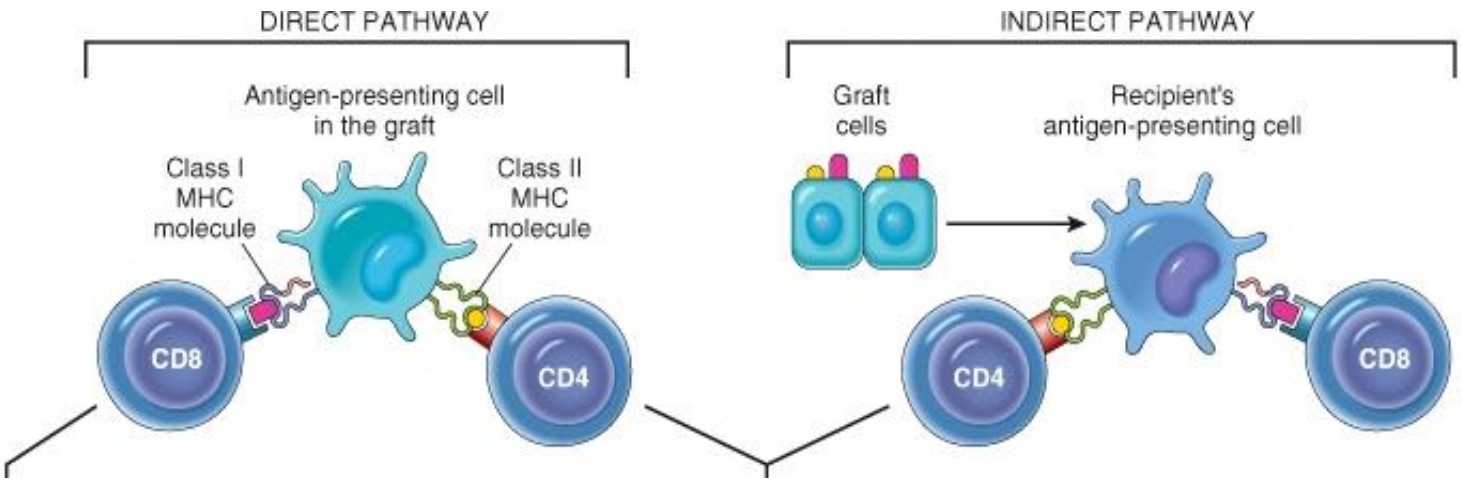
Transplantation

- T cells play a primary role in 1st and 2nd set rejection
- Nude mice accept allografts (no T cells due to genetic modification resulting in absent thymus).
- Remember that the thymus is responsible for producing mature T lymphocytes coming from the bone marrow.
- B cell deficient mice reject allografts.

Nude mouse with a transplanted rabbit skin

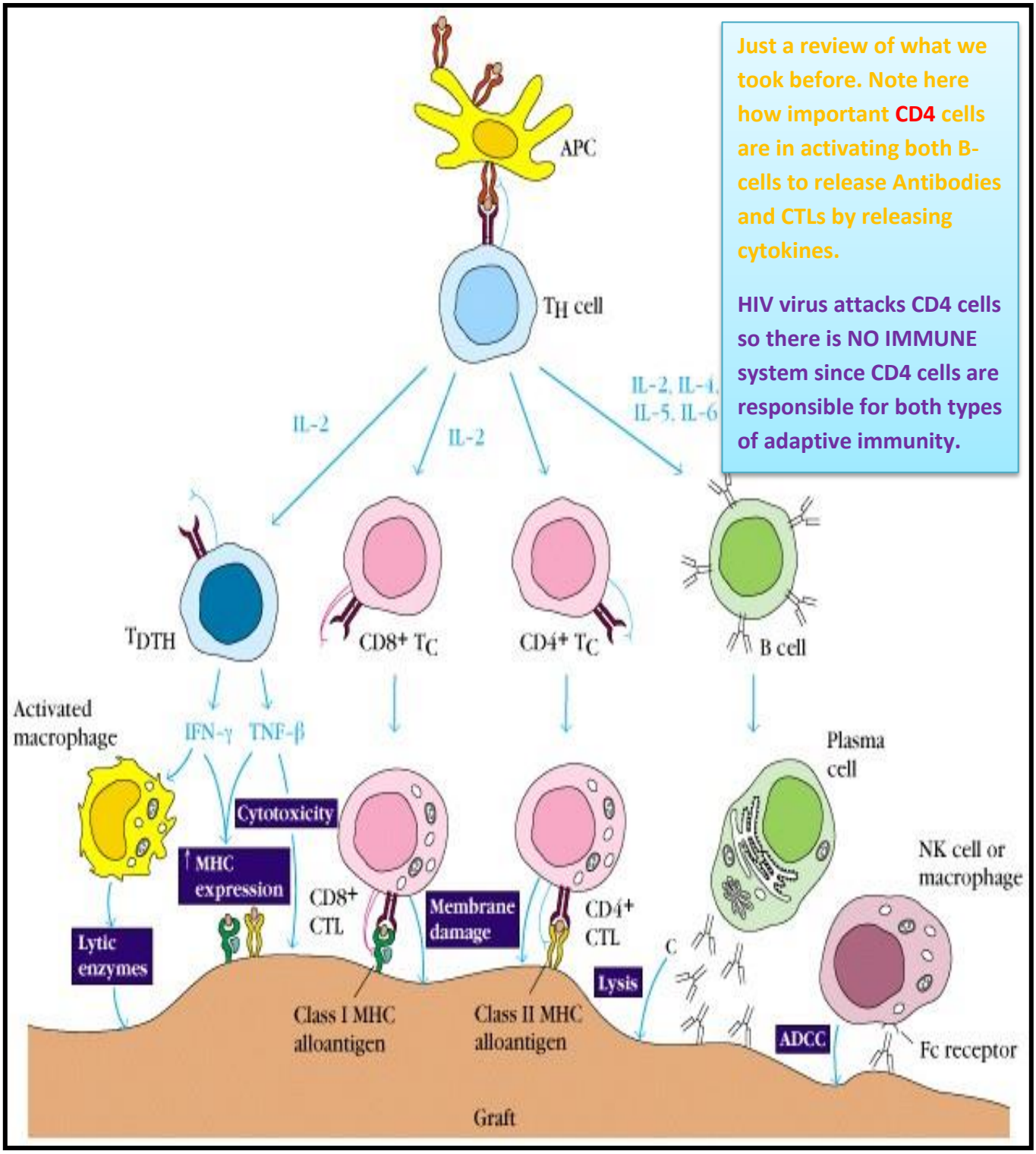
- If someone does not carry T cells there is no fear of rejection like in the absent thymus on the other hand if he has B cells deficiency he might reject the graft due to the presence of T cells.
- This shows that T cells play a primary role in transplant rejection as we said before.

Mechanisms involved in Graft Rejection



- Both pathways are activated.
- Direct pathway: APCs here will engulf the antigen (the graft with different or mismatched MHC) then CTLs will come and destroy it directly.
- Indirect pathway: Macrophages which is also an APC will take the antigen make some modification then it will present it to CD8 and CD4 by MHCI and MHCII and they will release cytokines to destroy it.
- Note that the indirect pathway is more effective and stronger.

Rejection Response

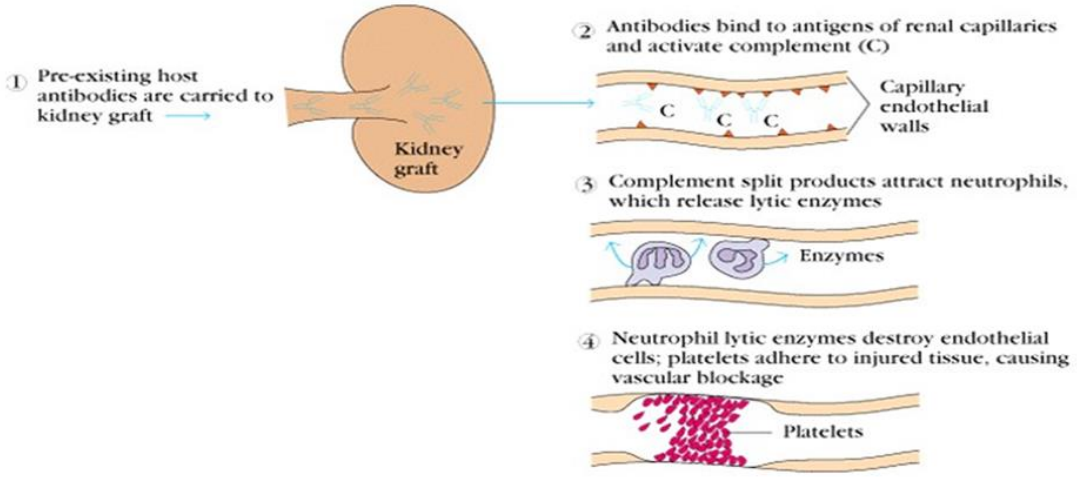


Just a review of what we took before. Note here how important **CD4** cells are in activating both B-cells to release Antibodies and CTLs by releasing cytokines.

HIV virus attacks CD4 cells so there is NO IMMUNE system since CD4 cells are responsible for both types of adaptive immunity.

Clinical manifestations of graft rejection

Hyper acute rejection	• **Sudden onset, from minutes to hours (very quick).** • **Can occur in front of the surgeon. (Maroon in color= fine, Pale= Rejection).** • **Due to presence of Natural occurring antibodies.**
acute rejection	• **Rejection can occur in about 10 days** • **(cell mediated)**
Chronic rejection	• **Months to years after engraftment** • ***Main pathologic finding is atherosclerosis of the vascular endothelium*** • **Main cause of chronic rejection is not known** **-Minor histo-compatibility antigen miss match.** Go back to page 5 • **Both types of immunity are involved.**



Graft-versus-Host (GVH) Reaction

Bone marrow transplantation:

1. **Bone marrow is the site of formation for WBCs.**
2. **Immunocompremised patients (e.g. leukemia) need bone marrow transplantation to restore their immunity.**
3. **Of course, Donor must be immunocompetent**
4. **Before the transplantation, the patient is exposed to heavy radiation to kill every single immune cell in his body**
5. **This will prevent rejection**

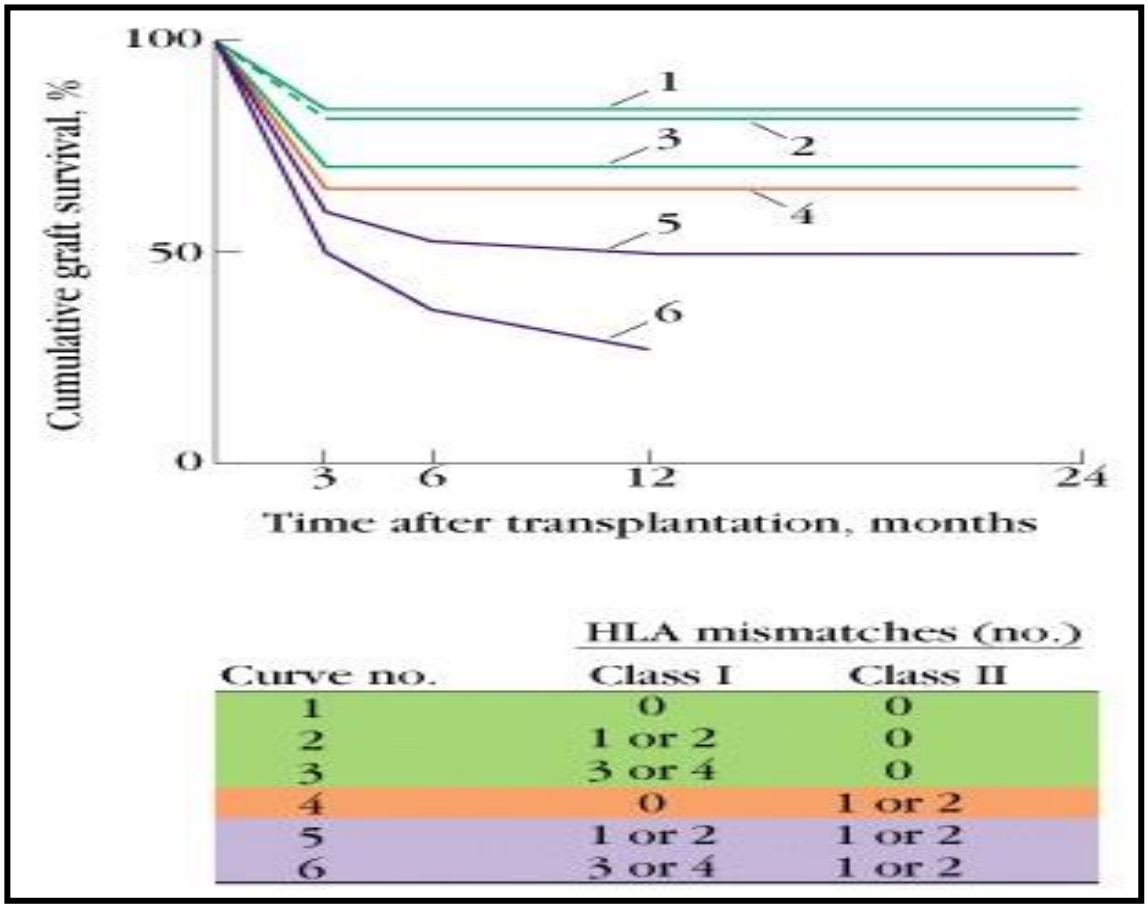
- **Occurs in about two thirds of bone marrow transplants**
- **Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in sever organ dysfunction**
- **Donor's Tc cells play a major role in destroying the recipient's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

HLA Typing In the Laboratory

Laboratory Test MUST be done prior to the transplantation it's called ''HLA typing'' or ''Tissue Typing'' to determine the closest MHC match between the donor and recipient. (There is no 100% match except between identical twins; 50%-60% match is enough)

Methods:

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



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

1 : No mismatches in either Class I nor Class II -----> Great survival rate .

2 : 1 or 2 molecules are mismatched in class I but no mismatch at class II

gives a good survival rate also.

3: 3 or 4 molecules are mismatched in class I but no mismatch at class II

This will still give an acceptable result.

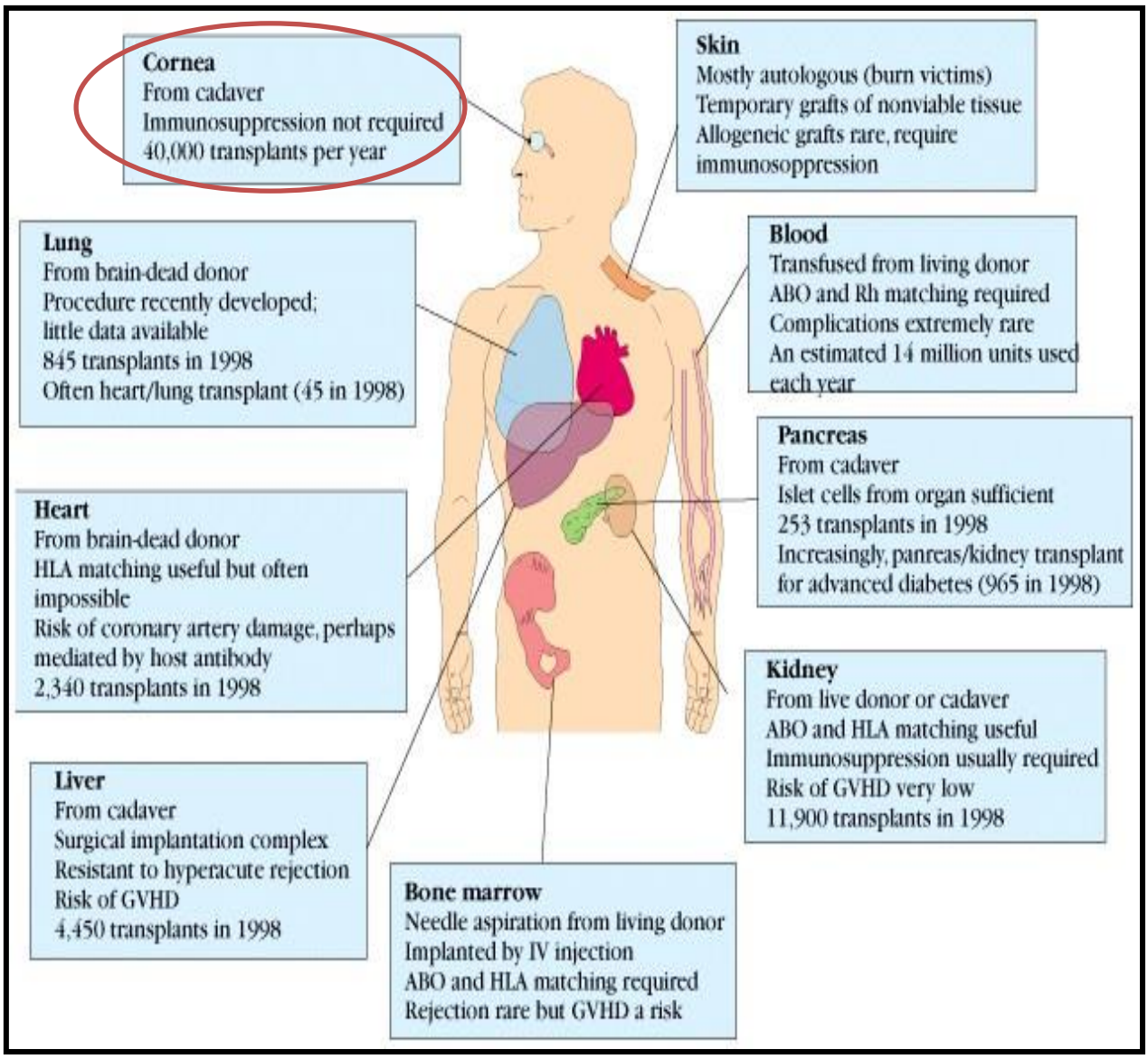
4: No mismatch at class I but 1 or 2 mismatches at class II ---> Less survival

5: 1 or 2 mismatches in both classes ---> even lesser survival rate

6: 3 or 4 mismatches in class I and 1 or 2 mismatches in class II --->

Much lesser survival rate.

Absolute requirement is matching of class II between donor and recipient, if there was no matching in class II don't transplant.



- Mismatches in cornea are not important because there is no blood supply (avascular) = no contact with immune system= No need for immunosuppression therapy.
- In liver, lung and heart transplantation we need immunosuppression.

General Immunosuppression Therapy

Every recipient must be treated with immunosuppression therapy:

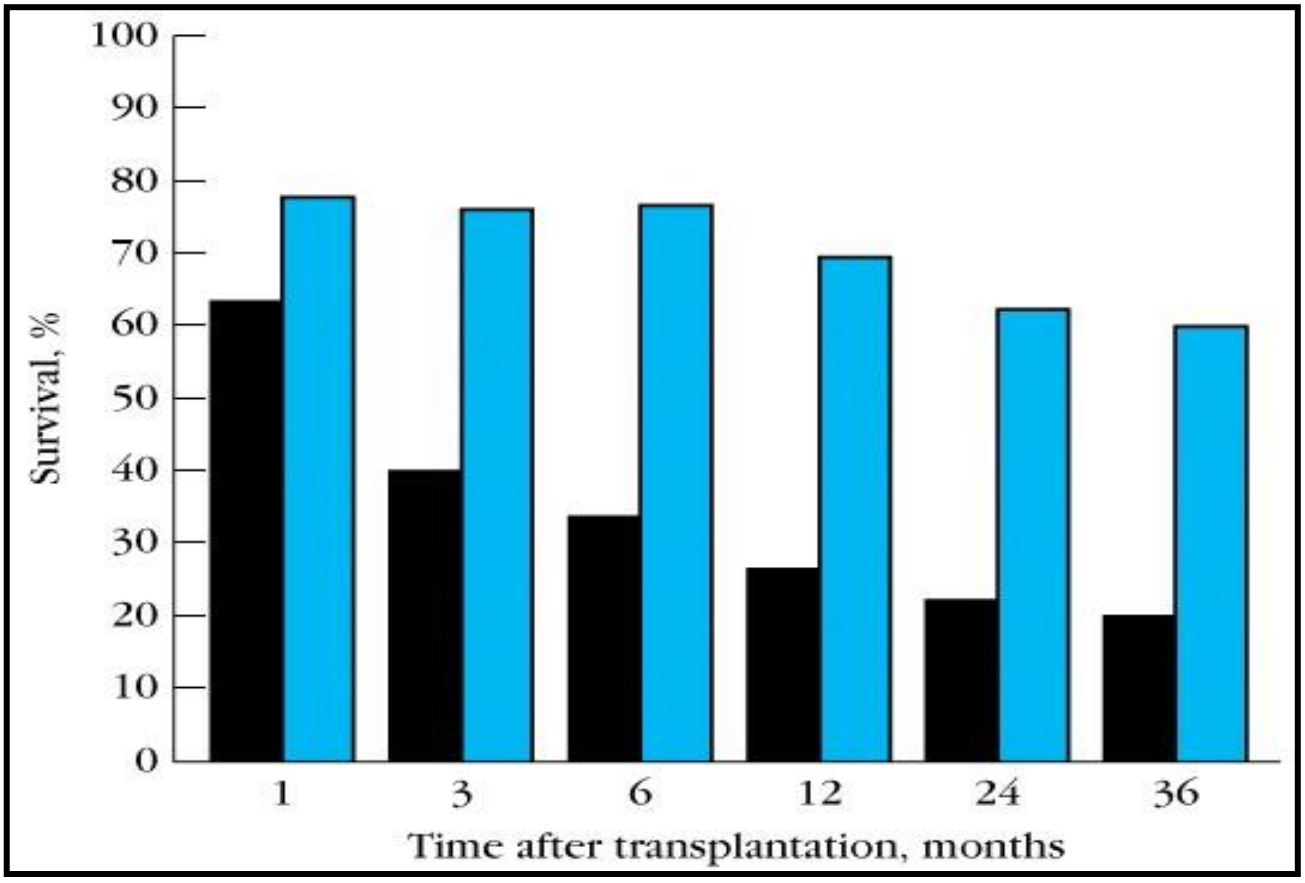
1. Mitotic inhibitor: azathioprine
2. (pre & post)
3. Corticosteroids
4. Cyclosporine
5. Total lymphoid irradiation

Downsides of immunosuppressive therapy:

1. -Must be maintained for life
2. –Toxicity
3. –Susceptibility to infections & tumors

In the picture below we can see that the survival rates increases with immunosuppressive therapy.

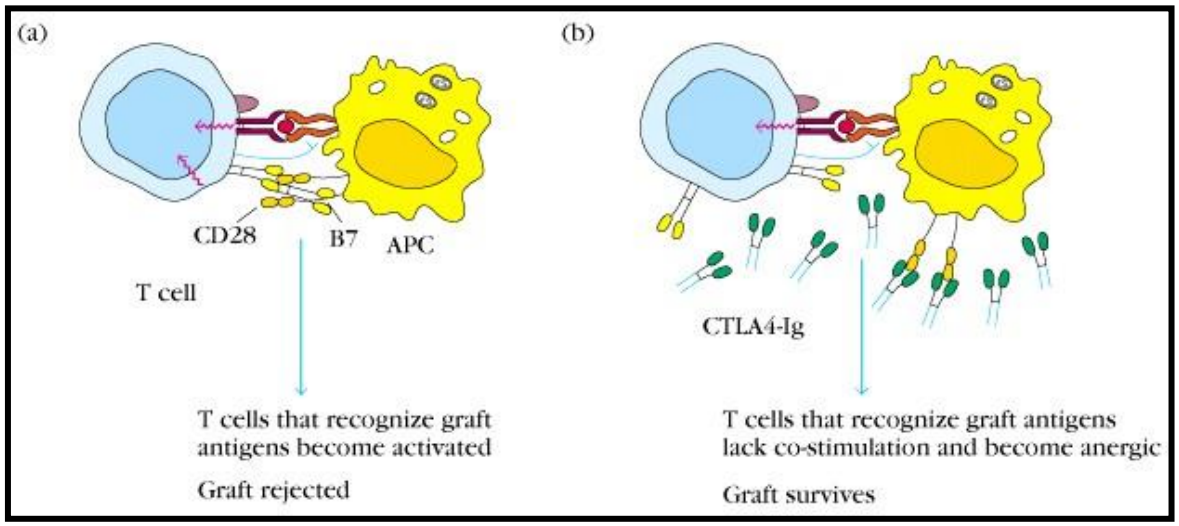
Black: without therapy Blue: with therapy



Specific Immuno-suppression therapy

a) Monoclonal antibodies against T cell components or cytokines

b) Agents blocking co-stimulatory signal



If you remember in foundation block, T-cells becomes anergic (not active) if the co-stimulatory signal is not there, this is one of the methods that is used with the immunosuppressive therapy.

- 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

- MCQs:

Q1: Which one of the followings is found on the surface of Antigen presenting cells?

a) MHC class I
b) MHC class II
c) Both a and b
d) None

Q2: What are the gens that encode for MHC I?

A. HLA-A

B. HLA-B

C. HLA-C

D. All of the above

Q3: Which one of the following is an important sign of GVH reaction in bone marrow transplantation?

a) Maculopapular rash
b) Vomiting
c) Systemic pain
d) Fever

Q4: Donor and recipient are same individual what type of transplantation is it?

A.Autografts

B.Syngeneic grafts

C. Allogeneic grafts

D. Artificial grafts

Q5: Main cause of chronic rejection?

A. Minor histo-compatibility antigen miss match
B. Class I MHC proteins
C. Class II MHC

Answers:

1-C

2-D

3-A

4-A

5-A