Renal Block

Immunology

Lecture 2

Immunology of Transplantation.

In this document you will find some main points gathered from the 2nd lecture..This document is NOT a replacement for the lecture..If you need additional information go back to the lecture or use a book as a reference so you understand everything correctly.

Hopefully all the information is correct and Hope you find them Useful.

Good Luck to everyone.

430 Immunology Team

Abdelelah AlFreem AlEnazi **Hadeel F. AlSajjan**

Immunology

Some main points you can go through and revise from:

Major Histocompatability Complex (MHC) and Transplantation.

- Major histocompatability 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(Glycoprotiens present on the surfaces of cells)

*located in the short arm of chromosome 6 (Part of MHC region)

MHC: divided into 3 classes..

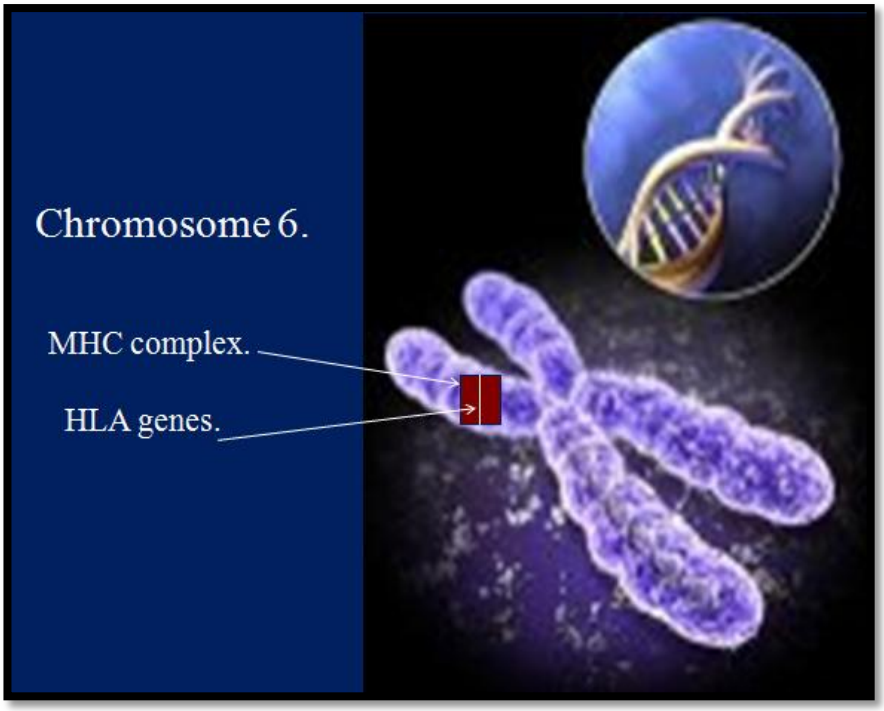
*MHC class 1 → code the molecules:

HLA-A, HLA-B, HLA-C. → *Present in almost all nucleated cells

*MHC class11→ code the molecules:

HLA-DR, HLA-DQ, HLA-DP. → *Present only on Immune cells

Examples of immune cells:
APC(Antigen Presenting Cells) B- cells, Activated, T-cells, Macrophages, Dendritic cells, Thymic epith.cells.



* To clarify *

Basically we have 3 MHC classes..

*HLA-A, HLA-B & HLA-C → Located on almost all nucleated cells → Correspond to MHC 1

*HLA-D →Located on Immune cells only → Corresponds to MHC 2

*HLA-D is divided into 3 allo-sites → HLA-DR, HLA-DQ, HLA-DP.

Other MHC genes :

*Minor HLA genes – unknown.

There are no laboratory tests to detect minor antigens.

- They mount a weak immune response.
- Play role in chronic rejection of a graft

*MHC Class III locus → Located between MHC I & II. →encode for TNF, lymphotoxin, C2 and C4. *TNF is the most important.

Inheritance of HLA genes:

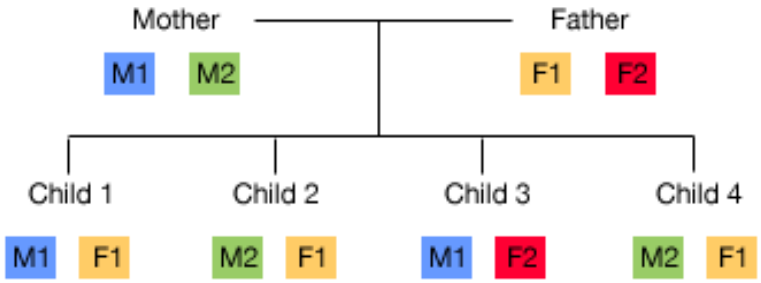
- Each individual has two "haplotypes" i.e., two sets of these genes one paternal and one maternal.
- These genes are very diverse "polymorphic".
    - HLA-A. many alleles.(e.g. HLA-A1,HLA-A9 etc.)
    - HLA-B. many alleles.
    - HLA-C. many alleles.
    - HLA-D many alleles.

To clarify

*Each of us inherit one haplotype from our mothers & one haplotype from our fathers → Therefore we end up with two sets of genes "2 haplotypes"

*Each HLA has many divisions → therefore they are "Polymorphic"

One example of the inheritance of HLA haplotypes



NOTE: In this illustration Child 2 and Child 4 have matching HLA genes and antigens. Child 2 and Child 1 have one set that matches, and Child 2 and Child 3 do not have any matching HLA haplotypes.

A mother inherits two haplotypes from her parents and a father inherits two haplotypes from his parents. Each passes on one of their two haplotypes to each child with a total of four combinations of haplotypes possible. Full siblings have approximately a 1 in 4 (25%) chance of being HLA identical. Identical twins will have matching haplotypes. There is sometimes crossover between the HLA genes thus changing the haplotypes but this event is rare.

MHC Class I, II & III Genes

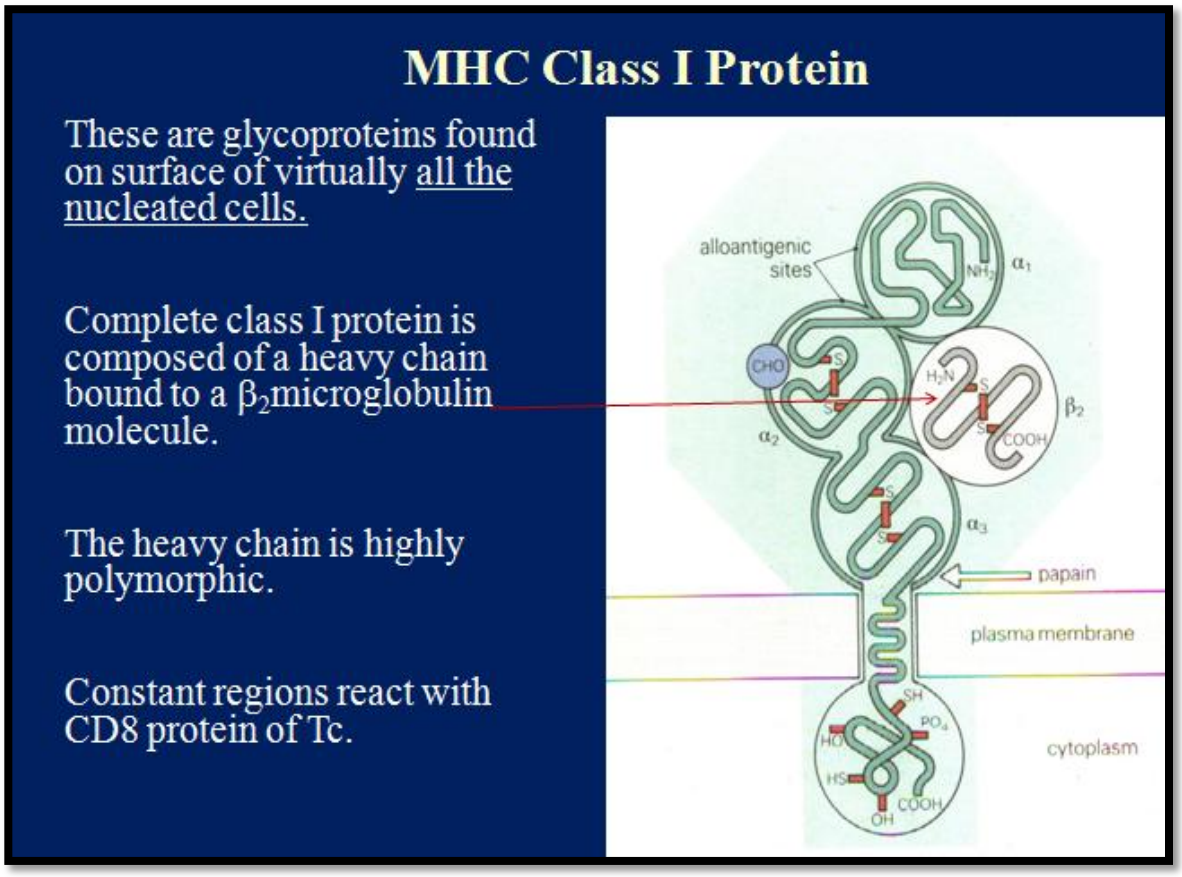
Mouse H-2 complex

Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L

Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

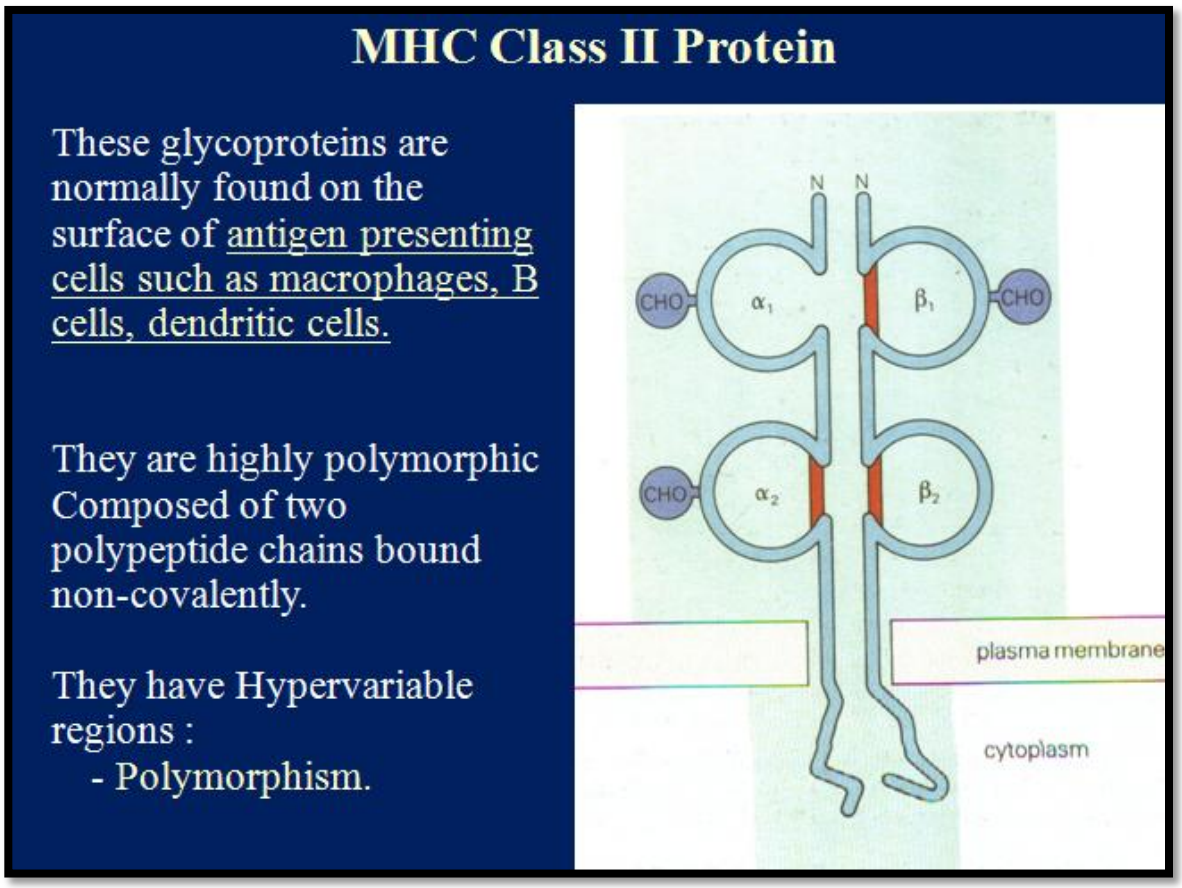
MHC Class 1 Protien



An addition to the information on the picture above:

- Found on almost all nucleated cells.
- 3 Alpha complexes & 1 Beta complex.
- Its tail attaches to the cells surface.
- Interact with CD8 (Cytotoxic) T-Cells (Therefore they play major roles in immune complexes & not only transplantations)

MHC Class 2 Proteins



An addition to the information on the picture above:

- Found only on immune cells such as:
  - Macrophages, B cells, Dendritic cells.
- 2 Alpha complexes (Alpha 1 & Alpha 2) & 2 Beta complexes (Beta 1 & Beta 2)
- Interact with CD4 (Helper) cells (Therefore they play an important role in immune responses)

To help you remember

The Rule of 8:

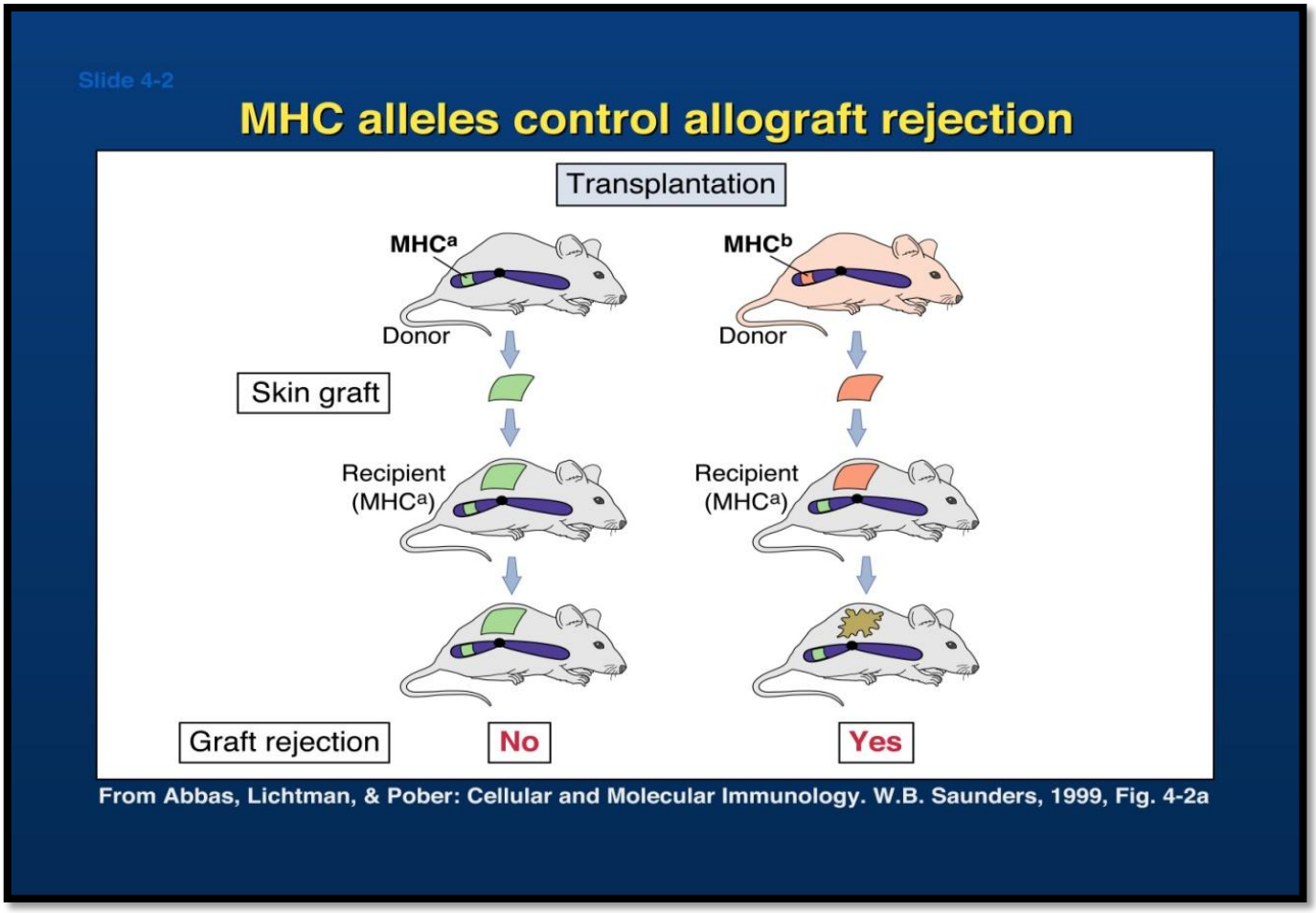
MHC 2 → CD4 (2 x 4= 8)

MHC1 → CD8 (1 x 8 = 8)

Biologic Importance of MHC.

- Cytotoxic T-cells kill virus infected cells in association with class I MHC proteins.
- Helper T- cell recognize antigen in association with class II MHC proteins.
- This is called MHC restriction.
- Success of organ transplant is determined by compatibility of the MHC genes.

Transplantation antigens



Types of grafts :

1. Autografts, Autologous grafts.
    a. Donor and recipient are same individual.
    b. Common in skin grafting; bone marrow.

2. Syngeneic grafts or (isograft).
    a. Donor and recipient are genetically identical.
    b. Animal models; identical twins.

3. Allogeneic grafts.
    a. Donor and recipient are same species, but genetically unrelated.
    b. Common type e.g. heart, lung, kidney, liver graft

4. Xenogeneic grafts
    a. Donor and recipient are different species.

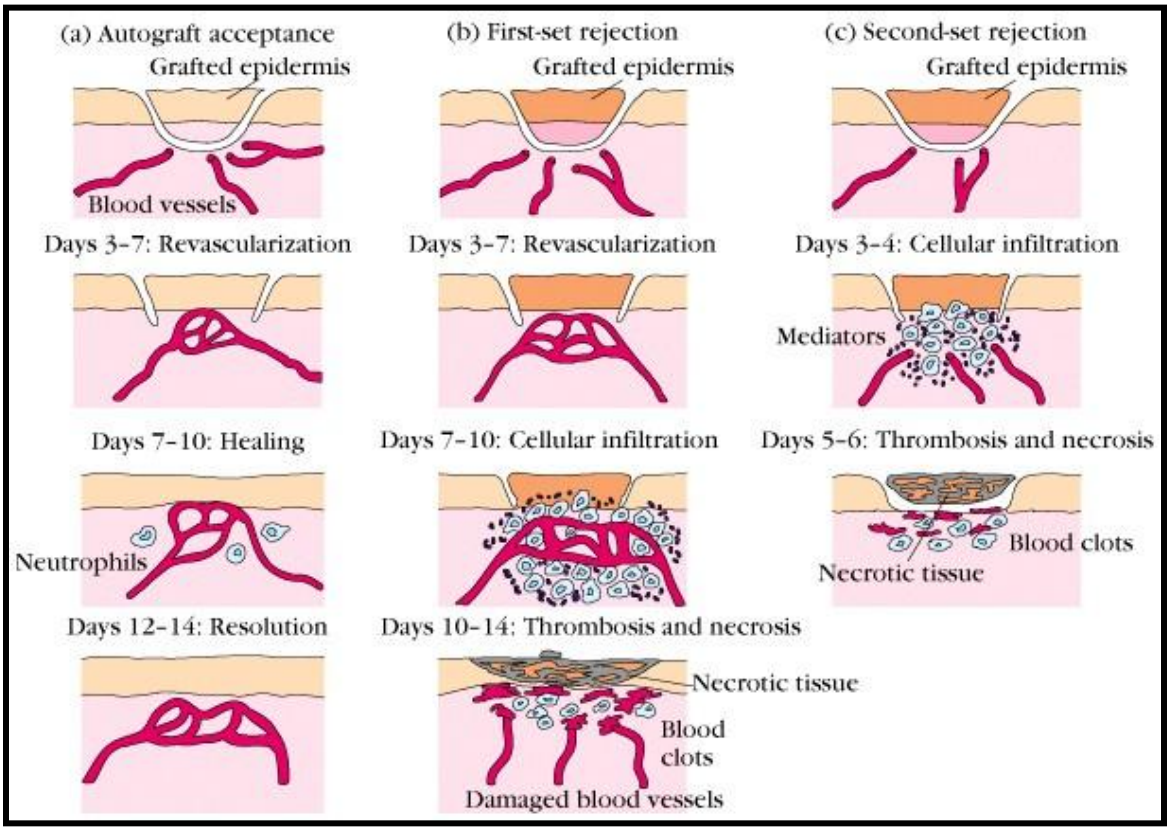
5. Artificial grafts.

Transplantation:

- 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

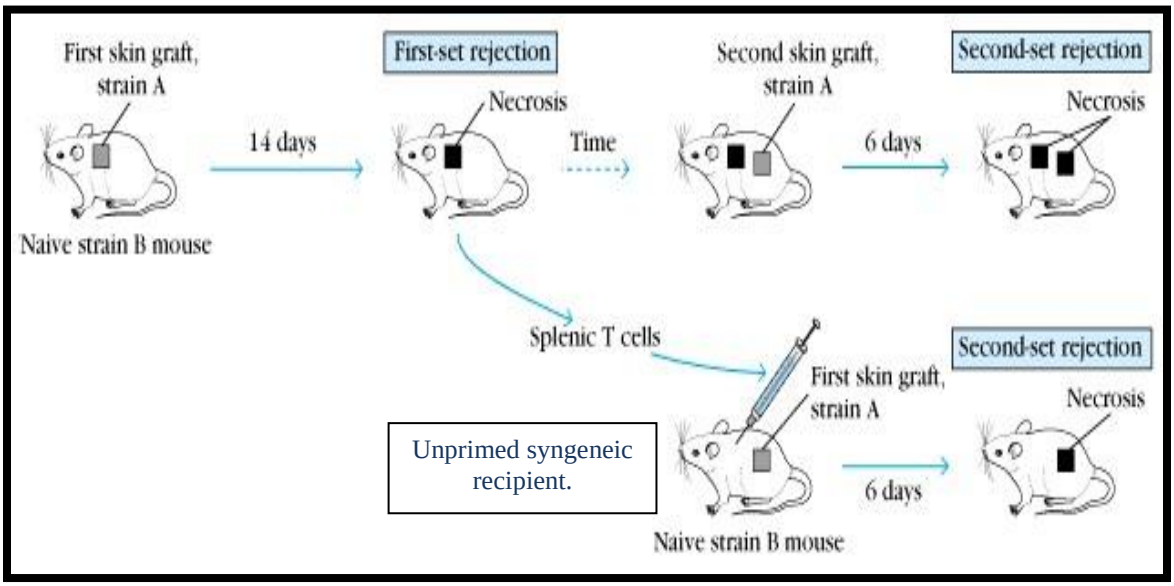
*In transplantation T-Cells are more important than B-Cells

1st set versus 2nd set reactions

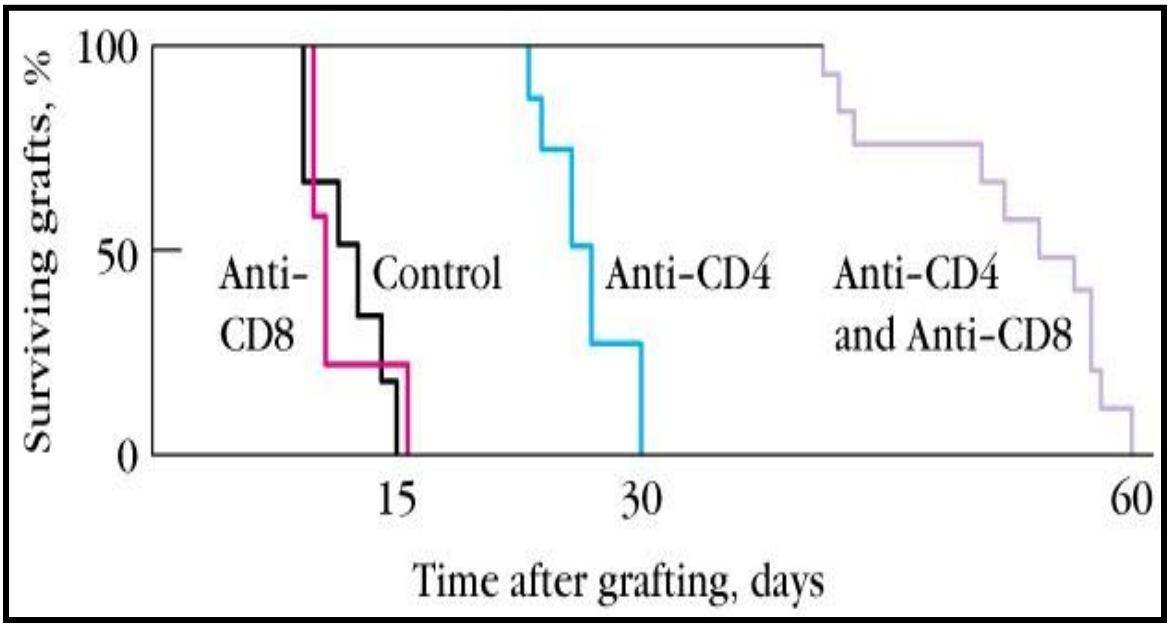


*1st set reactions take a longer time to occur.
*2nd set reactions happen faster than 1st set reactions due to the formation of memory cells during 1st set reactions

Role of cell- mediated responses



Role of CD4+ versus CD8 T+ cells



Injecting recip. mice with mab to deplete one or both types of T cell

*CD4 cells are more important than CD8 Cells (Because CD4 cells initiate responses while CD8 cells carry them on)

Transplantation.

T cells play primary role in 1st and 2nd set rejection reactions

- Nude mice accept allograft.
- B cell deficient mice reject allograft.

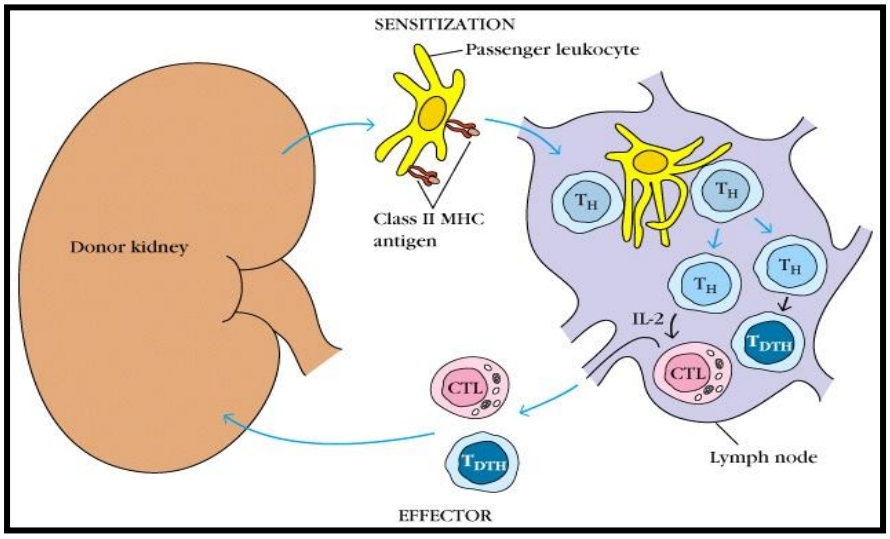
- Nude mouse has a transplant of rabbit skin.
- Nude mice have no thymus and therefore no T cells.

To clarify

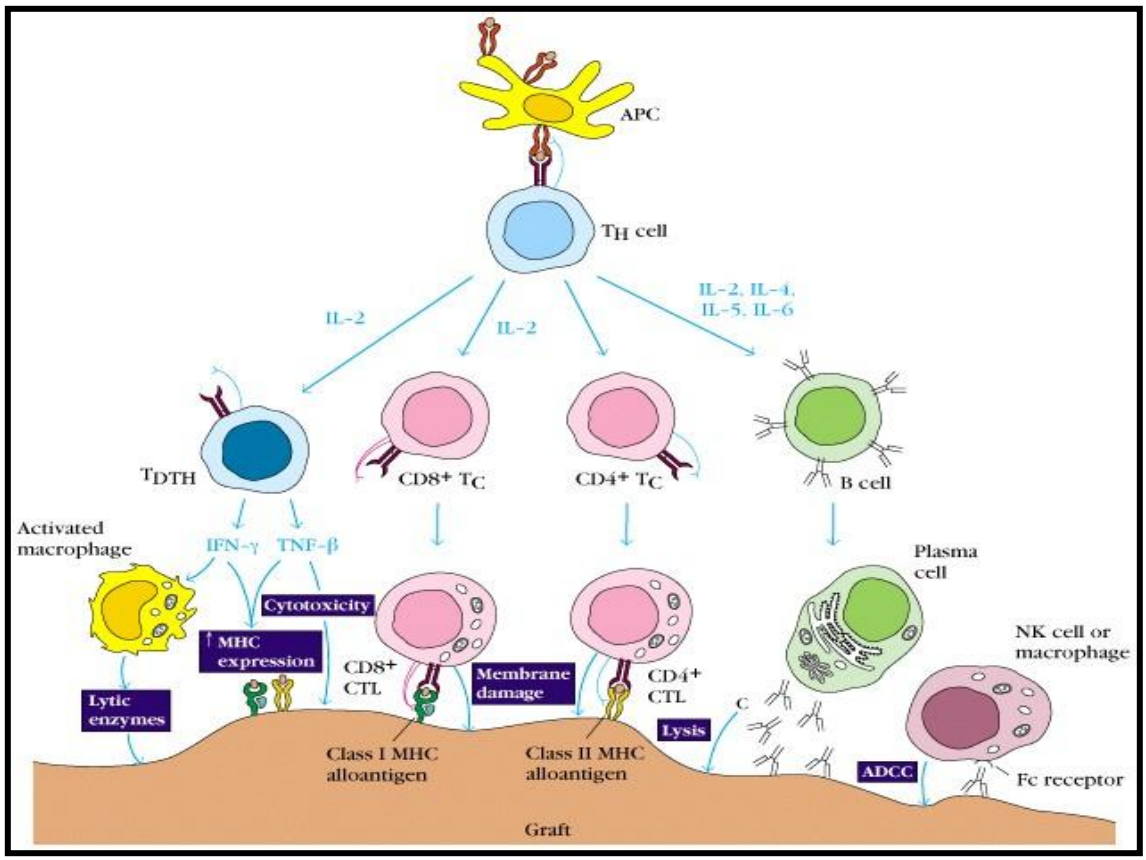
Nude mice have no Thymus → Therefore they do not produce T-Cells → that's why they accept rabbit skin grafts

Mechanisms involved in Graft Rejection:

Sensitization stage - Effector stage



Mechanisms of rejection



Types of rejection reactions.

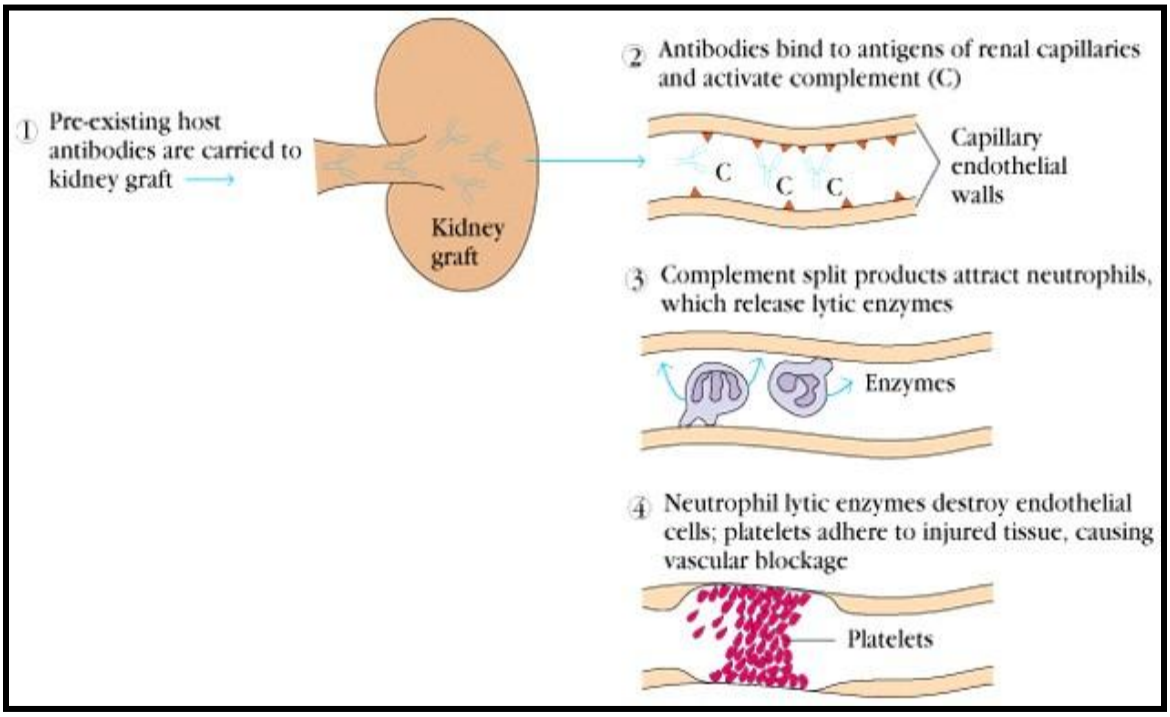
1. Hyperacute rejection:
    - antibody-mediated ,very quick (1-2 days).

2. Acute rejection:
    - T-cell & antibody- mediated (about 10-14 days).

3. Chronic rejection:
    - T-cell mediated (months-years).

Clinical manifestations of graft rejection.

Hyperacute rejection: very quick.



Chronic Rejection.

- This occurs months to years after engraftment.
- Main pathologic finding in chronic rejection is arteriosclerosis of the vascular endothelium.
- Main cause of chronic rejection is not known.
    - Minor histocompatability antigen miss -match.
    - Side effects of immunosuppressive drugs.

Graft-versus-Host (GVH) Reaction.

- Occurs in about two thirds of bone marrow transplants.
- Occurs because grafted immunocopmpetent 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

- Maculopapular rash .
- Jaundice .
- Hepatosplenomegally.
- Diarrhea.

GVH reactions usually end in infections and death.

HLA Typing in the Laboratory.

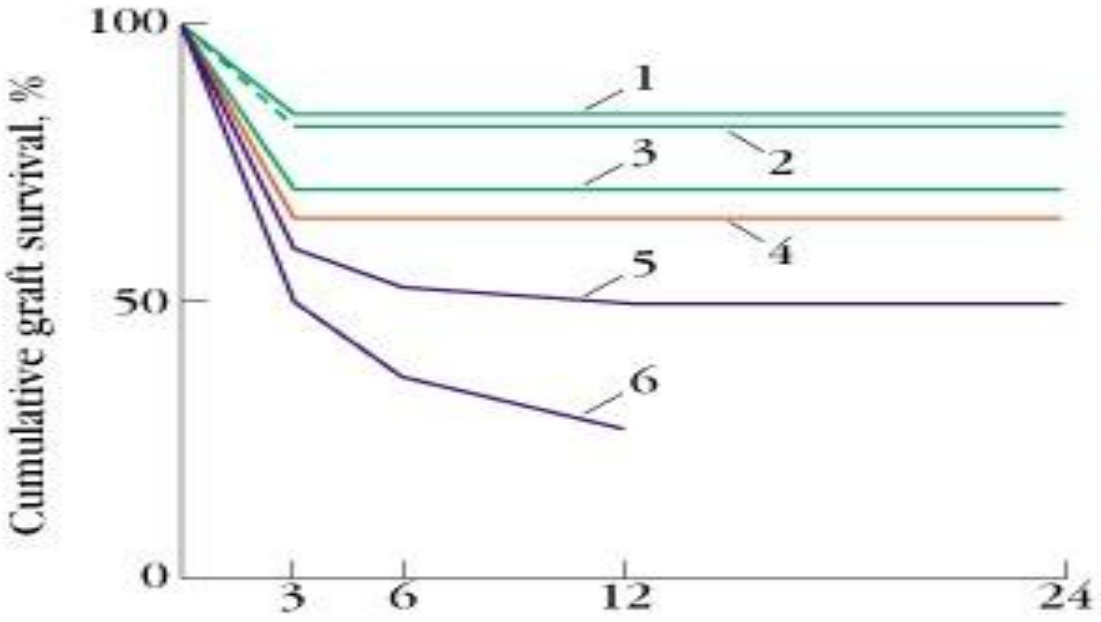
- Prior to transplantation laboratory tests commonly called :HLA typing or tissue typing are performed.
  → (to determine the closest MHC match between the donor and recipient).

Methods :

- DNA sequencing by Polymerase Chain Reaction (PCR).
- Serologic Assays.
- Mixed Lymphocyte Reaction (MLR).
- Cross matching – (D) lys +(R) serum + complement.

Tissue Matching

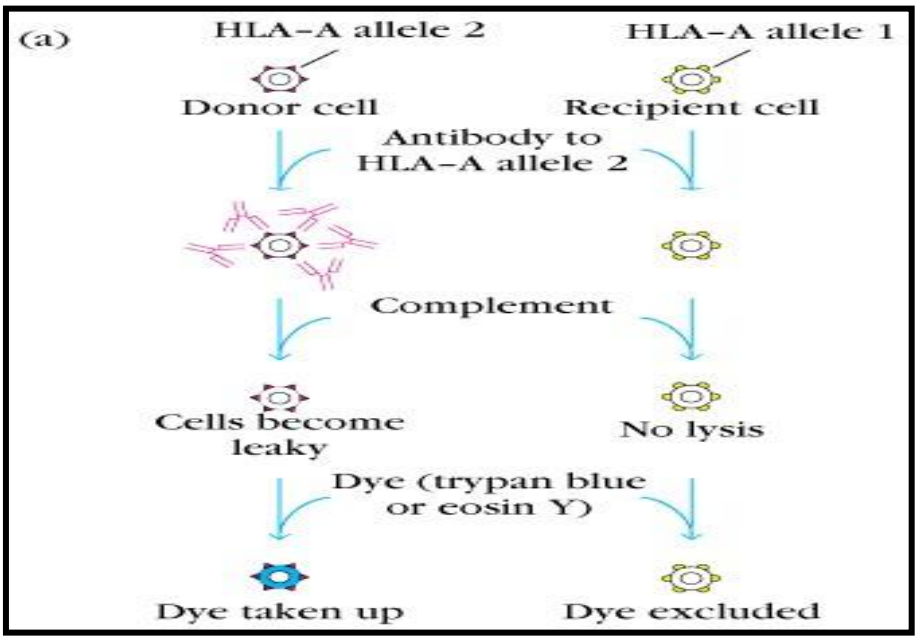
Effect of HLA class I & II matching on survival of kidney grafts



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

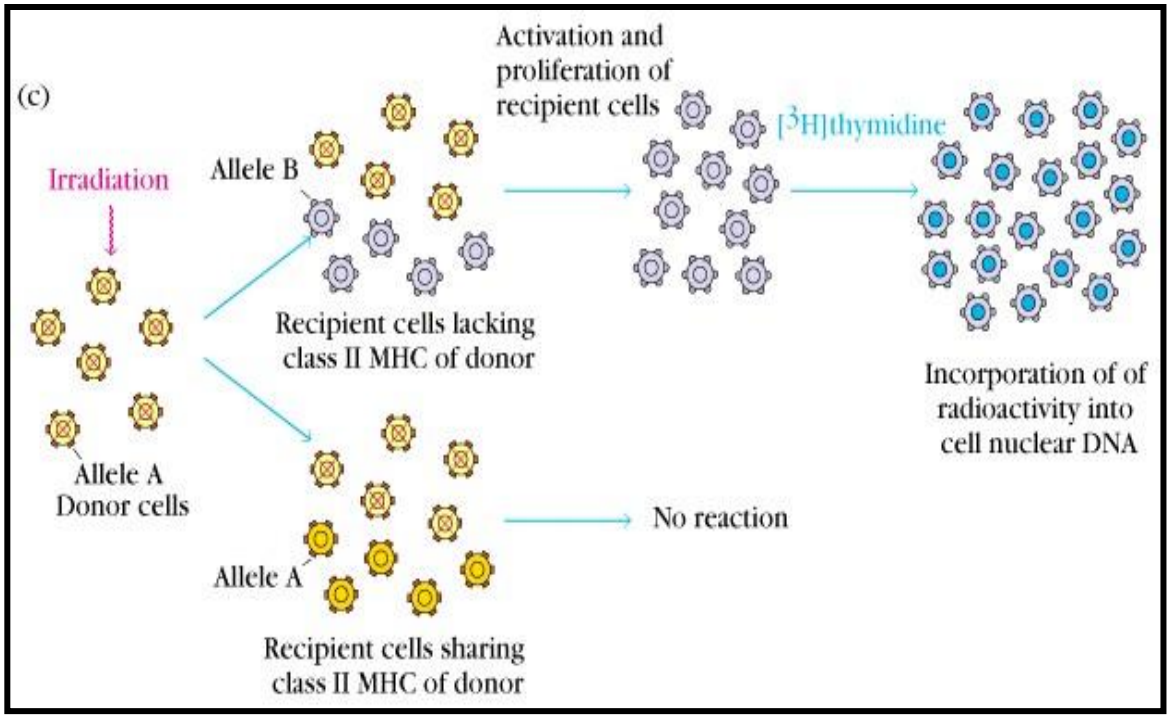
Tissue Matching:

Serological Method.

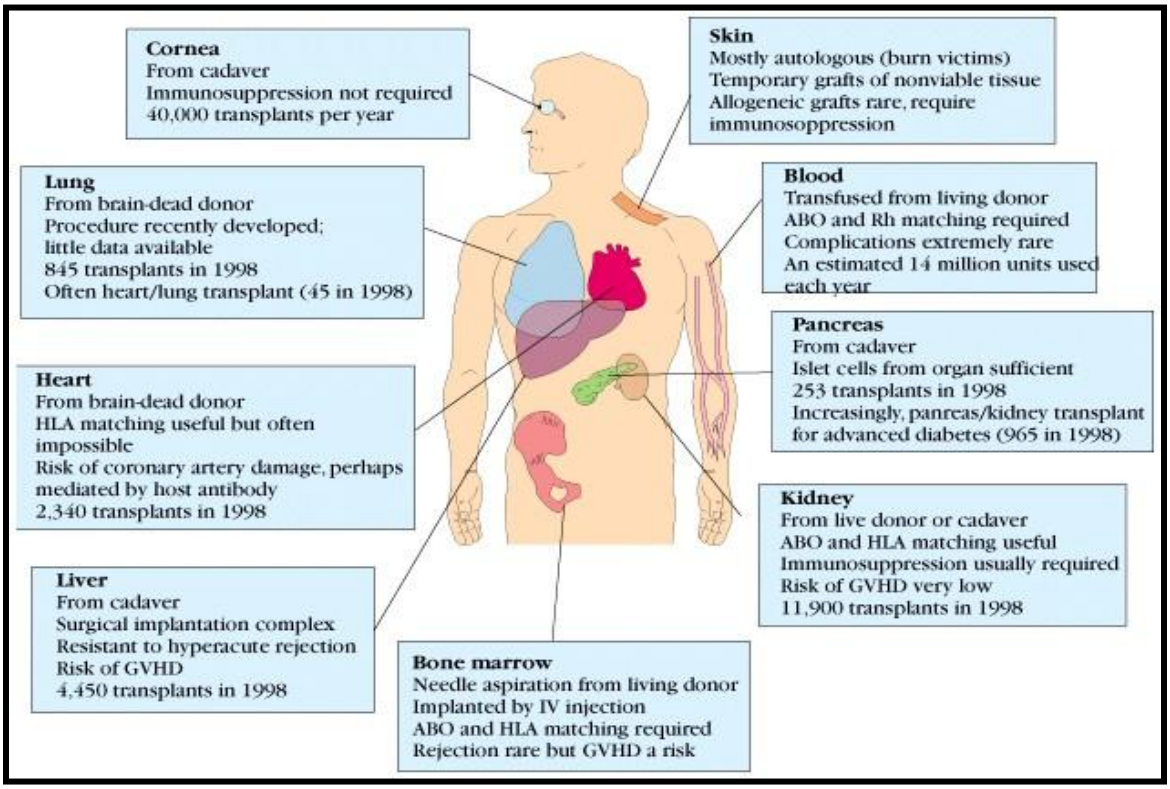


Tissue Matching:

Mixed Leukocyte Reaction (MLR).



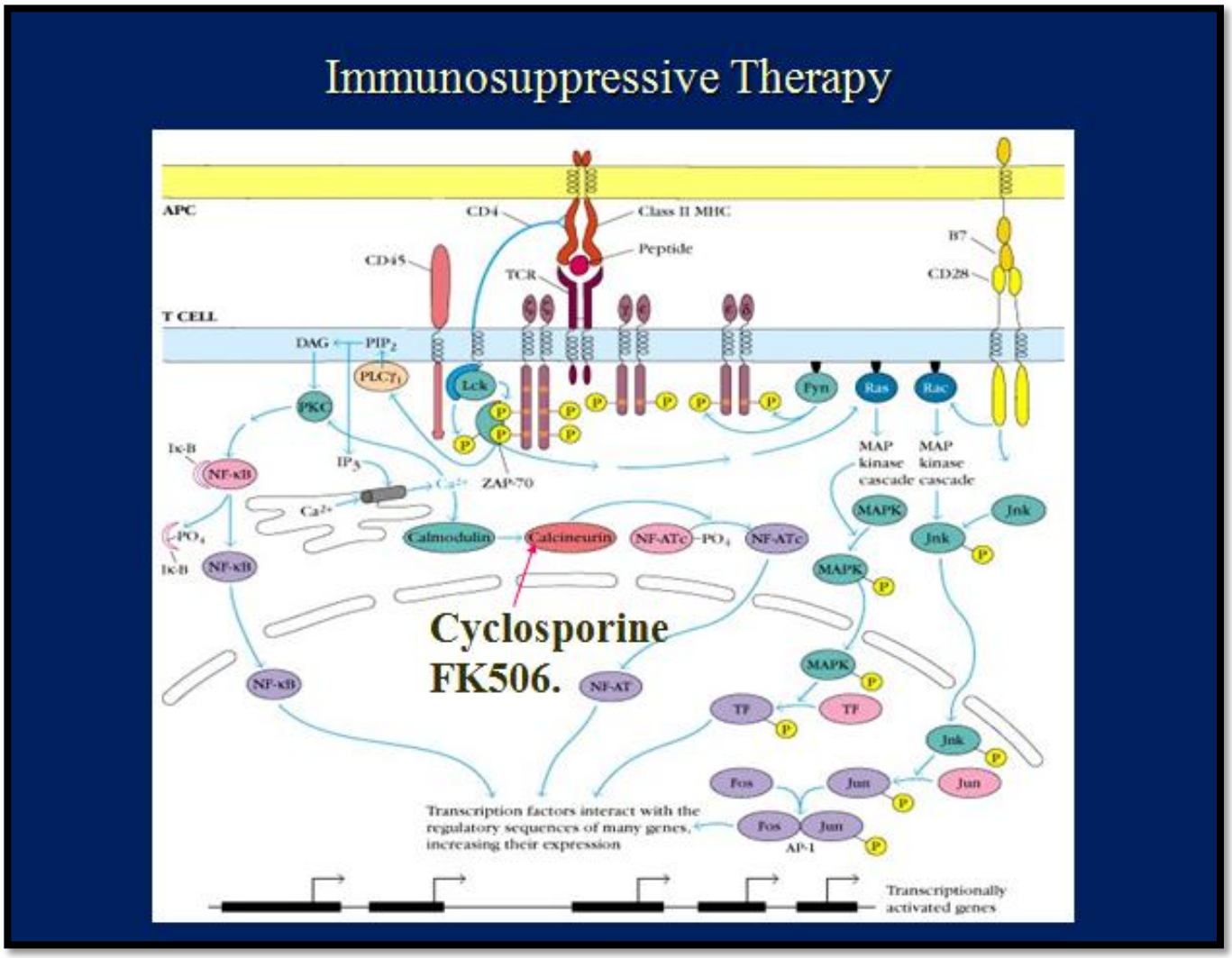
Organ and tissue grafts :



General Immunosuppressive Therapy.

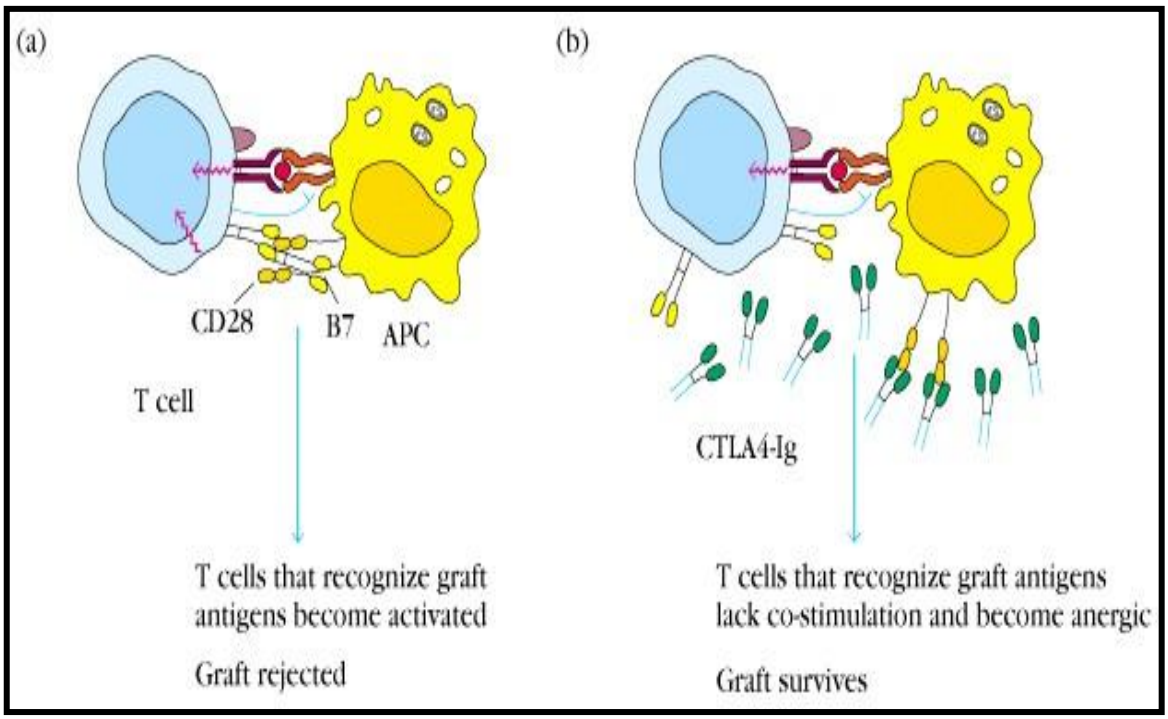
- Mitotic inhibitor: azathioprine (pre & post).
- Corticosteroids.
- Cyclosporine A, FK506: (inhibit IL-2 and IL-2R).
- Total lymphoid irradiation.

Immunosuppressive Therapy



Specific Immunosuppressive Therapy.

- Mabs to T cell components or cytokines.
- Agents that block co-stimulatory signal.



Immunosuppressive Therapy

Downsides:

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