L2: Immunology of Transplant

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

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Color coding:

Red= important gray : extra information

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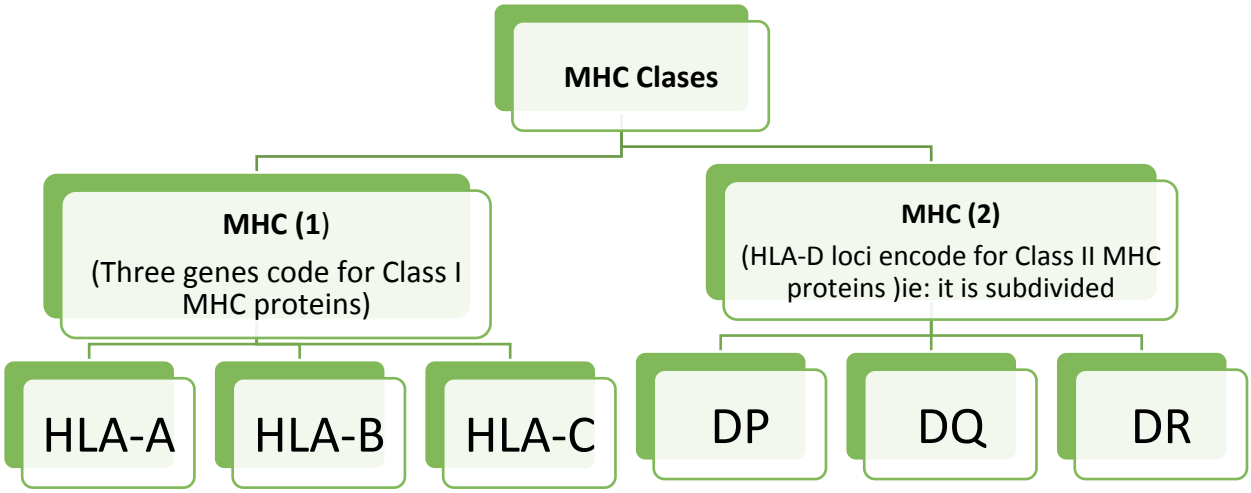
Major Histocompatibility Complex and Transplantation:

- 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) which are proteins encoded by HLA genes.
- These proteins are allo-antigens (Donor and recipient are same species, but genetically unrelated)
- The HLA Genes for HLA proteins are clustered in the MHC complex located on the short arm of chromosome 6.

- -NOTE: if MHCs or HLAs (HLA is a part of MHC , when we investigate for HLA it's like we're investigating for MHC but depends on which HLA we are investigating) 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.



MHC Class I are glycoproteins found on surface of virtually all the nucleated cells

Cytotoxic T cell (CD8) 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 (CD4) recognize antigen in association with class II MHC proteins

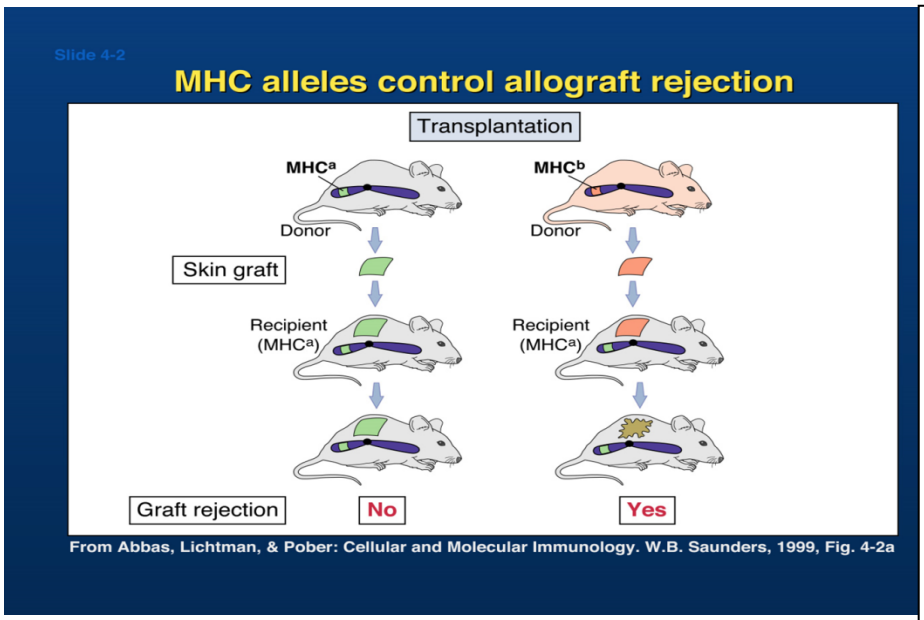
- Each individual has two "haplotypes[12]" i.e, two sets of these genes one paternal and one maternal.

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

Minor HLA genes and Transplantation:

- 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:



Note: in the first picture A piece of skin was taken from the mouse with same MHC type and grafted somewhere else in the same mouse so the result is there is no rejection (autograft).

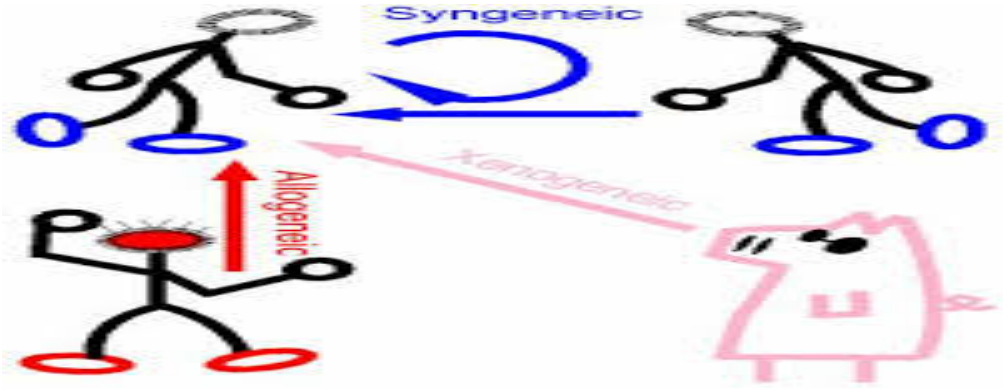
But in the second picture a piece of skin was taken from one mouse and grafted on another mouse with different MHC type and you can see there is rejection and necrosis. (allo-genic graft)

[1] Haplotypes: A set of alleles (an alternative form of a gene that can occupy a particular place on a chromosome) of a

Transplantation:

Types of transplants:

Autografts, Autologous grafts	• Donor and recipient are same individual • Tissue returning to same individual after a period outside the body – usually in a frozen state. • Common in skin grafting; bone marrow.
Syngeneic grafts or (isograft)	• Donor and recipient are genetically identical • Animal models; identical twins
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	- For example: prosthetic valves and artificial knees



Transplantation: - his immune response is the major barrier to transplantation.

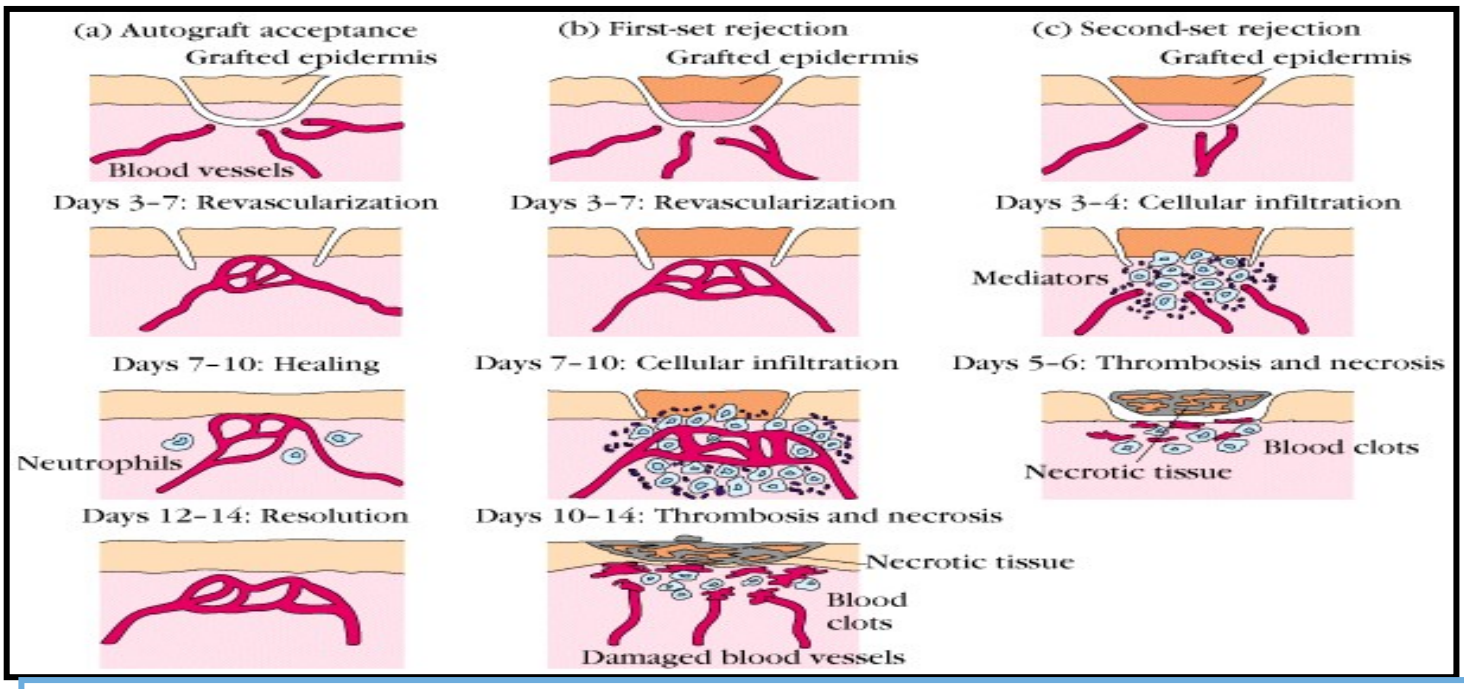
T cells play primary role . "which is the most important"

B cell (20-25%)

Classic adaptive/acquired immune response:

- Memory.
- specificity.

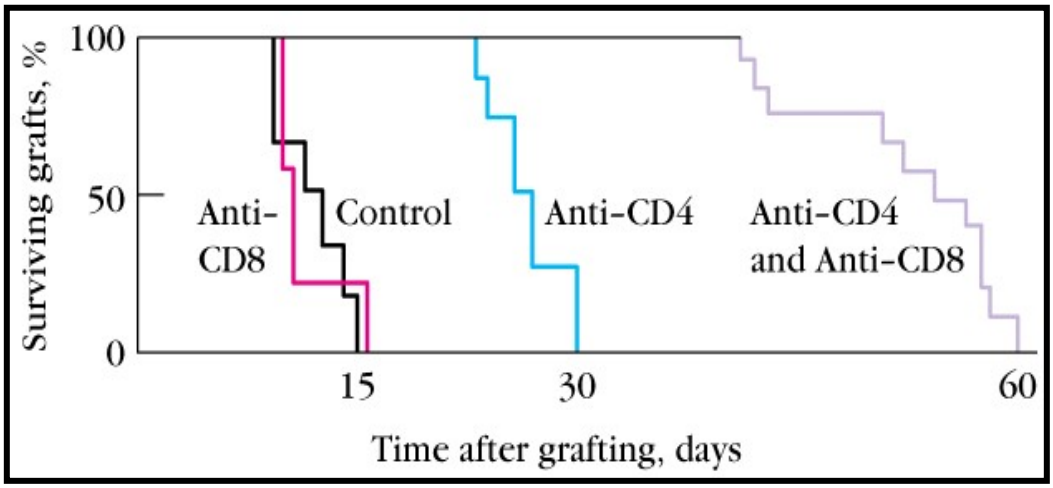
1st set versus 2nd set reactions: -



1- a) is an auto graft and no immune reactions will occur
2- (b) is an allograft for the first time for a person and immune reactions occur but it takes more time
3- (c) is an allograft but the second time on the same person who had the allograft in (b) (a previous allograft) immune reactions occur faster
And this is due to memory cells

Role of CD4+ versus CD8 T+ cells: -

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



Not that the role of CD4 is more effective than CD8, but both together is more effective than separated

Transplantation: -

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

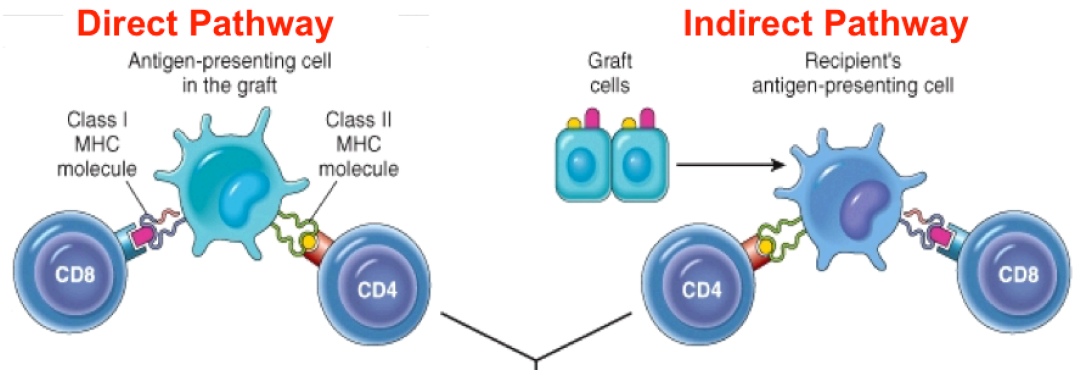
- Nude mice with no T cell (absent thymus) accept allografts.
- On the other hand mice with no B cell and with T cell will reject the allografts.

Nude mouse has a transplant of rabbit skin

From this we can understand that the T cell plays a more important role in the rejection of the transplant than B cells.

Mechanisms involved in Graft Rejection: -

https://youtu.be/CirqxHmRbjA -very useful video.



Direct: the Antigen presenting cells are from the Donor's immunity

Indirect: the Antigen presenting cells are from the recipient's immunity

AND THE REJECTION IN BOTH PATHWAYS ARE THE SAME PRECENTAGE

Clinical Manifestations of Graft Rejection:

Hyperacute rejection	Acute rejection	Chronic rejection
Very quick Minutes-hours (Humoral immunity)	10 days (Cell mediated)	Months-years (Both cell mediated & humoral)

Hyperacute: is due to preexisting antibodies carried to the Kidney graft the antibodies are already in the body before the transplantation such as in people with a lot of blood transfusions and even in women with multiple pregnancies (blood of the infant goes to the maternal blood and antibodies are produced)

Chronic Rejection:-

This occurs months to years after engrafment.

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.
- Side effects of immunosuppressive drugs

Graft-versus-Host (GVH) Reaction (in all the cases before " the host attacks the graft" but in this case it's the opposite)

- 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 T 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 " because most of the people who get this are already immunecompromised this is why we transplant bone marrows to them and 2/3 of them get GVH reactions

HLA Typing in the Laboratory:

- Prior to transplantation laboratory test commonly called as ***HLA typing* or *tissue typing*** to determine the closest MHC class one and class two (through their HLA protein) match between the donor and recipient is performed

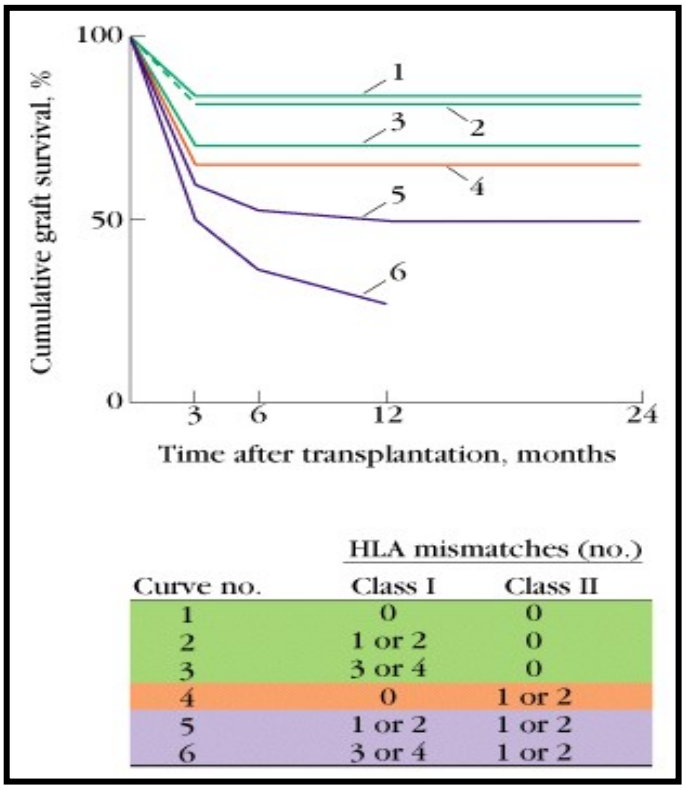
Methods of HLA Typing

- DNA sequencing by Polymerase Chain Reaction (PCR)
- Serologic Assays
- Mixed Lymphocyte Reaction (MLR)

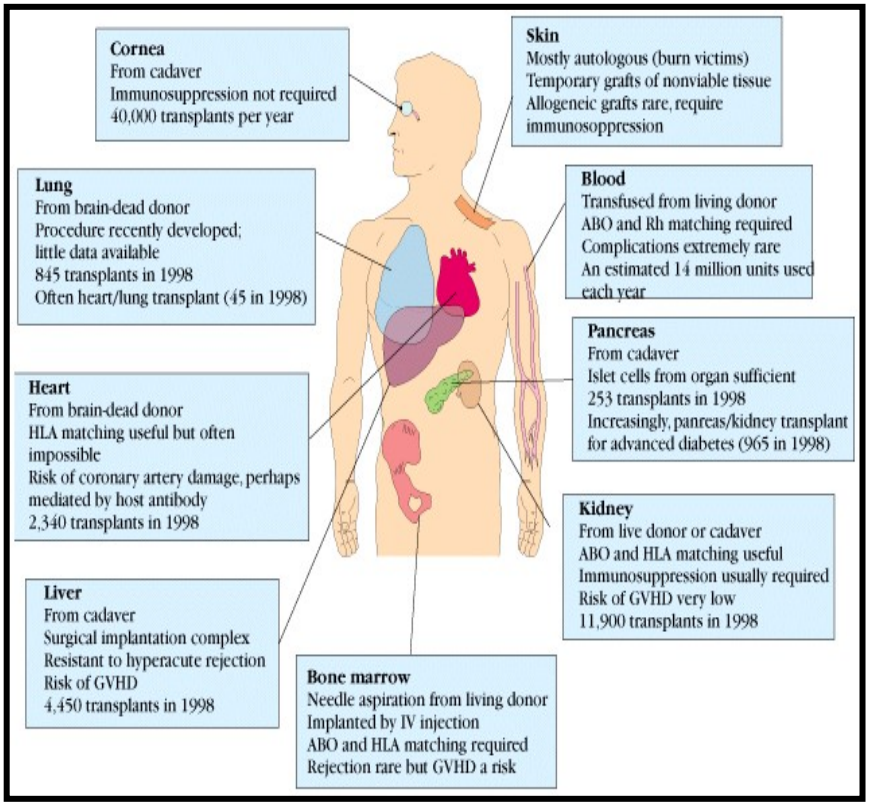
- Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.

Tissue Matching

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



	HLA mismatches (no.)	
Curve 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



ZERO mismatches in both classes is only in IDNETICAL TWINS

The point from this slide is to know that the cornea,lung, pancreas, liver ,heart(useful here but it's often impossible so they just transplant it) and skin do not need matching

Blood: needs ABO and RH matching

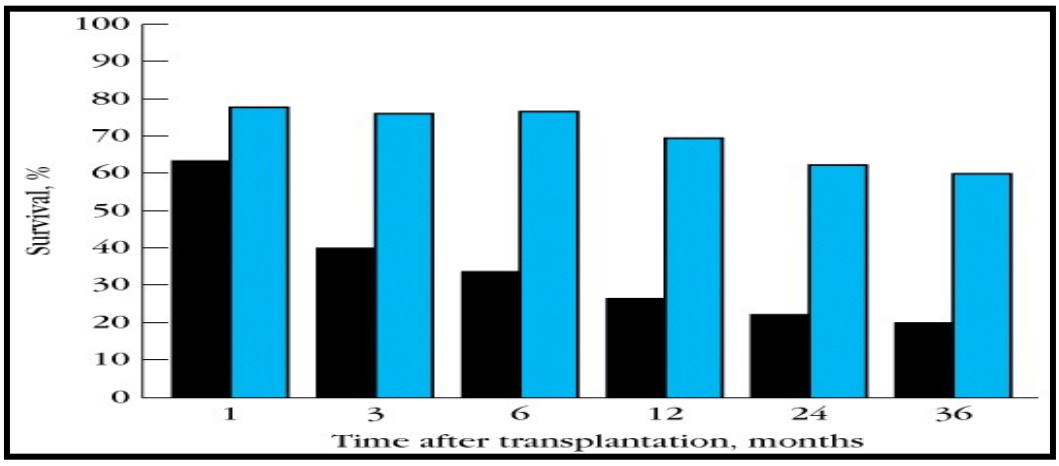
Kidney: needs ABO and HLA matching

Bone marrow: needs ABO and HLA matching

" The DR mentioned to read the small boxes for the kidney and bone marrow"

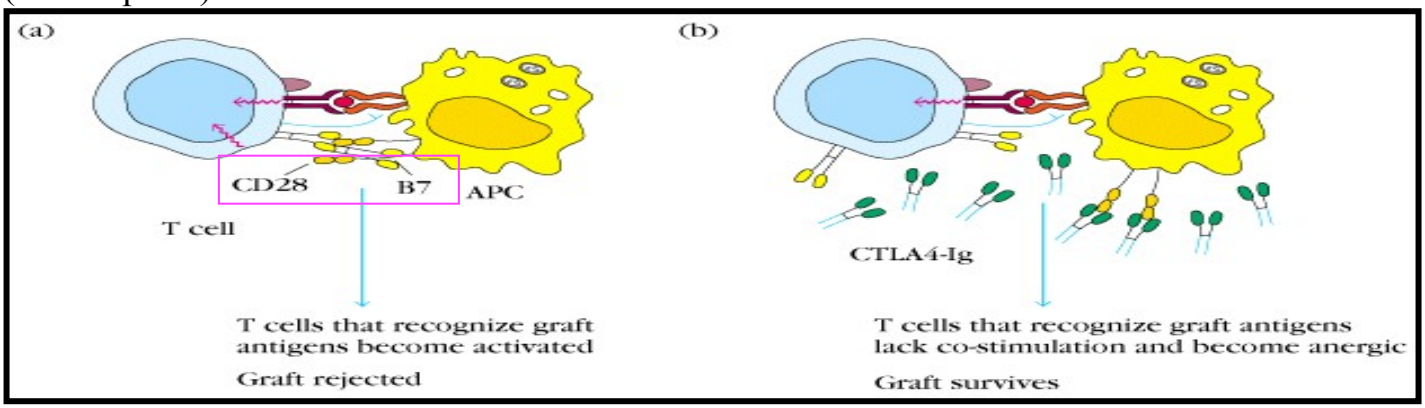
Immuno-suppresive Therapy (could be before during or after the transplant)

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



- The blue line is the patient who received immunosuppressive therapy and the black line is the patient who did not use immunosuppressive therapy.

How some immunosuppressive drugs work by inhibiting the action of T CELLS (azathioprine)



a) Monoclonal antibodies against T cell components or cytokines
b) Agents blocking co-stimulatory signal (between b7- Cd28)

Steps to activate T cells : 1- antigen in the body 2- APC 3- presenting of the peptide of the antigen to the t cell 4- binding of B7 (of the APC) to the CD28 (of the T cell) 5- ACTIVATION (Imp for understanding and having a concept of what is actually going on)

Downsides (Negative things about the immune-suppresive therapy)

-Must be maintained for life
-Toxicity
-they become Susceptible to infections
-they become Susceptible to tumors.

Summary:

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

HLA and MHC:

-Human Leukocyte Antigens (HLA) are genes that encode for the MHC protein, and are found on the short arm of chromosome 6.

-For a transplantation procedure to be successful, there has to be an MHC matching between the donor and the acceptor.

-MHC Class II has a stronger effect on tissue rejection than class I.

Types of transplantation:

1) Autografts
2) Isografts
3) Allogenic grafts
4) Xenogenic grafts
5) Artificial grafts.

Immune responses to transplantation (Rejection):

-**T Cells:** Has a major role (1st & 2nd set reactions). CD4 cells are more effective than CD8 cells.

-**Memory cells**: Activated as a type of a secondary response if the same graft is transplanted again (2nd set reaction).

-**B cells:** May play a role (Antibodies)

Rejection Response:

APC presents alloantigens to T Cells → Activates → CD4, CD8, and B Cells Secrete → cytokines and substances → attracting → Neutrophils Causes attraction of platelets leading to Necrosis, thrombosis and tissue dysfunction (Rejection).

Types of Rejection:

1) Hyper acute: immediate
2) Acute: ~ 10 days (Cell-mediated)
3) Chronic: months-years *Main Finding: Atherosclerosis.

Graft-versus-Host (GVH) Reaction:

- Donor's immunocompetent T Cells attack recipient's immunosuppressed cells.
- Symptoms: Maculopapular rash, Jaundice, Hepatosplenomegaly, and Diarrhea

Laboratory testing for HLA matching:

HLA\Tissue typing: To determine if donor and recipient's HLA match or not before transplantation

Methods:

1) DNA sequencing by PCR.
2) Serologic Assay.
3) MLR.
4) Cross-matching.

Immunosuppression therapy: Divided into:

1) General immunosuppression.
    A. Mitotic inhibitor: azathioprine (pre & post)
    B. Corticosteroids
    C. Cyclosporine
    D. Total lymphoid irradiation

2) Specific Immuno-suppression.
    i) Monoclonal antibodies against T cell components or cytokines
    ii) Agents blocking co-stimulatory signal (Anergy)

MCQS:

1-genes for HLA protein are clustered in (MHC complex) located on the short arm of which of the following:

a-chromosome 6

b-chromosome 17

c-chromosome 8

2-which of the following play a primary role in rejection reaction:

a-B cells

b-adaptive response

c-T cells

3-in Graft-versus-host (GVH) reaction which of the following play a primary role:

a-donor B cells

b-recipient Tc cells

c-donor Tc cells

4-which of the following is general immunosuppressive therapy:

a-antibody against T cell component

b-total lymphoid irradiation

c-blocking co-stimulatory signals

5-which of the following is a symptom in Graft-versus-Host reaction:

a-maculopapular rash

b-hepatospleenomegaly

c-all above

1-A 2-C 3-C 4-B 5-C

SAQS

1-minor HLA gene play a role in which type of rejection?

Ans: chronic rejection

2-which type of transplant the donor and recipient are same species but genetically unrelated?

Ans: Allogenetic graft

3-what is the main pathologic finding of chronic rejection?

Ans: Atherosclerosis of vascular epithelium

4-to determine the closest MHC match between the donor and recipient we use methods. Name two of them:

Ans: a-polymerase chain reaction(PCR)

b-serology assay

c-mixed lymphocyte reaction(MLR)

5-name three side effect of immunosuppressive therapy:

Ans: a-toxicity

b-susceptibility to infection

c-susceptibility to tumor