Renal Block

Transplantation

Editing File

color index:

Black: Main text

Red: important

Gray: Notes & explanation

Immunology

MED438

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Objectives:

- To understand the diversity among human leukocyte antigens (HLA) or major histocompatibility 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.

Histocompatibility Complex and Transplantation

Major HLA genes

- 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.

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

Genes for HLA proteins are clustered in the MHC complex located on the short arm of chromosome 6

complement System related, not our interest this Lec.

MHC CLASS	I			II			III	
REGION	A	B	C	DP	DQ	DR	C4, C2, BF	
GENE PRODUCT	HLA-A	HLA-B	HLA-C	DP	DQ	DR	C' PROTEIN	TNF-α TNF-β
POLYMORPHISMS	47	88	29	MORE THAN 300 HLA-D				

MHC Class Proteins

Class I

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**.

Three genes HLA-A, HLA-B and HLA-C code for Class I MHC proteins.

Class II

MHC Class II glycoproteins are normally found on the surface of antigen presenting cells (macrophages, B cells, dendritic cells and Langerhans cells).

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

HLA-D loci encode for Class II MHC proteins ie, DP, DQ and DR.

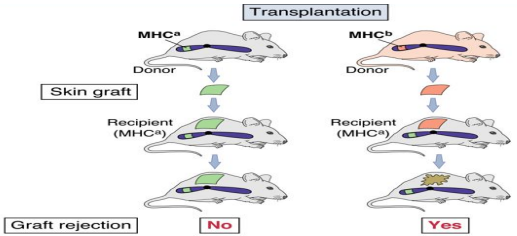
Minor HLA genes

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

MHC alleles control allograft rejection



Transplantation

Types of transplants:

- **Autografts**, Autologous grafts Donor and recipient are same individual 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**

Major Barrier to transplantation is the immune response

1. T cells play primary role.
2. B cells can/do play a role.
3. Classic adaptive/acquired immune response
   - Memory
   - Specificity.

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

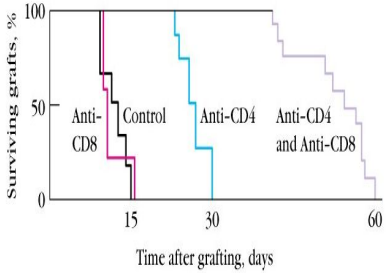
- Nude mice accept allografts (no T cells due to genetic modification resulting in absent thymus)
- B cell deficient mice reject allografts

Nude mouse has a transplant of rabbit skin

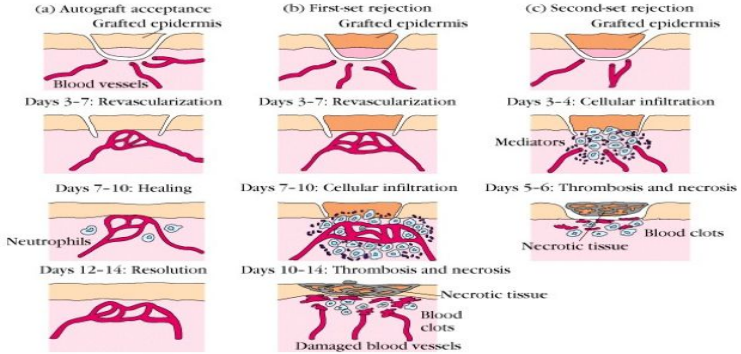
Role of CD4+ versus CD8 T+ cells

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

As the fig. Shows T cells play the primary role, CD8 cells have effective role when combined with CD4 cells effect, as shown here when both CD8&CD4 cell are depleted the graft had the longest survival time.But when only CD8 are depleted no change from control, unlike when CD4 only depleted a significant survival but isn't compared when both are depleted.



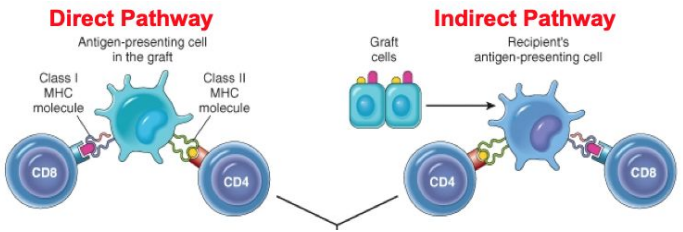
Transplantation (Rejection)



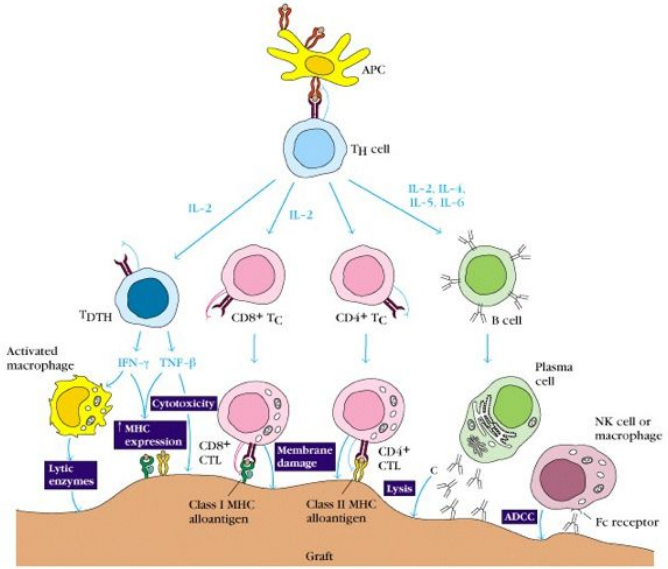
As can be seen in the fig. The memory property of our immunity facilitate faster necrosis of graft when re-exposed to the graft (second-set rejection).

Mechanisms involved in Graft Rejection

Antigen detection

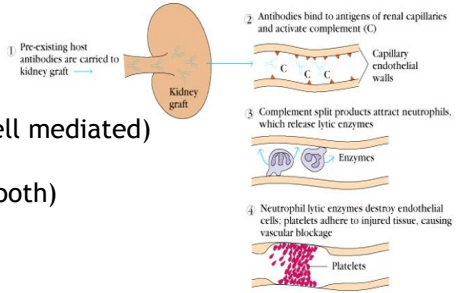


Rejection response



clinical manifestations of graft rejection

1. Hyperacute rejection: very quick
2. Acute rejection: about 10 days (cell mediated)
3. Chronic rejection: months-years (both)



Chronic Rejection

- This occurs months to years after engraftment
- Main pathologic finding in chronic rejection is <u>atherosclerosis</u> of the vascular endothelium
- Main cause of chronic rejection is not known
  - Minor histocompatibility antigen mismatch

Graft-versus-Host (GVH) Reaction

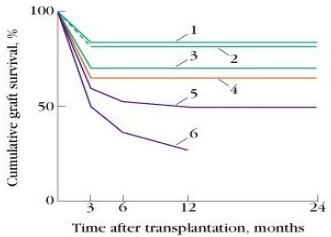
- Occurs in about two thirds of bone marrow transplants.
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction.
- Donor's Tc cells play a major role in destroying the recipient's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

Tissue Matching

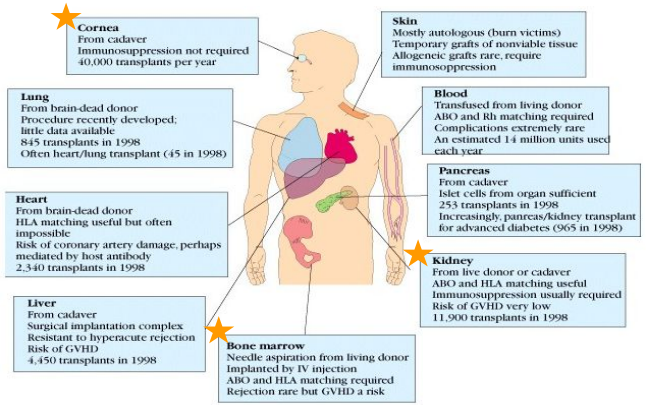
HLA Typing in the Laboratory

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

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



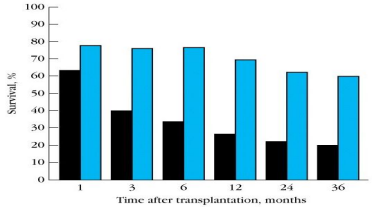
Curve no.	HLA mismatches (no.) Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2



Immunosuppression Therapy

General Immunosuppression Therapy

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



Transplant survival rates are shown over a 3-years period for 84 liver transplant patients immunosuppressed using a combination of azathioprine plus corticosteroids (black) compared with another 55 patients treated with cyclosporin A plus corticosteroids (Blue)

Specific Immuno-suppression therapy

A. Monoclonal antibodies against T cell components or cytokines
B. Agents blocking co-stimulatory signal (Cyclosporin)

Downsides Immuno-suppression therapy

1. Must be maintained for life
2. Toxicity
3. Susceptibility to infections
4. Susceptibility to tumors

Take Home Messages

- 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

Quiz:

1-: Depleting which of the following antibodies would allow for longest survival after grafting?
A- Anti-cytotoxic T-cells antibodies
B- Anti-T helper cells antibodies
C- Antineutrophil cytoplasmic antibody
D- Anti-CD8 & anti CD-14

2-: which of the following encode for class II MHC
A- HLA-A
B- HLA-B
C- HLA-C
D- HLA-D

3- : Atherosclerosis of the vascular endothelium is associated with which type of rejection?
A- Hyperacute rejection
B- acute rejection
C- Chronic rejection
D- both A and C

4-: Genes for HLA proteins are located on which of the following
A- long arm of chromosome 6
B- short arm of chromosome 6
C- long arm of chromosome 3
D- short arm of chromosome 3

5- :which one of the following is not considered as a general Immunosuppression therapy?
A- Cyclosporin
B- Corticosteroids
C- Mitotic inhibitor
D- Mitotic inducer

6-in (GVH) reaction, which one of the following play a primary role
A- donor CD4+ cells
B- donor CD8+ cells
C- Recipient Tc cells
D- donor T helper cells

1.B 2.D 3.C 4.B 5.D 6.B

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MORE

Good Luck !

إنّ الله يعطي أصعب المعارك لأقوى الجُنود فاستمر

Immunology
MED438

Team members▫

قلباً وقالباً

Girls*

*Sorry the names are in black you can’t see them

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RAYYAN MUSTAFA ALMOUSA

MOHAMMAD FAHD ALMAHJOMI

OMAR SAAD ALYABIS

HUSSAIN FAISAL ALKHARBOUSH

ABDULRAHMAN MOHAMMED ALOBAID

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KHALID OSAMA M ALRIYAMI

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BADER SALEH IBRAHIM ALMGHANNA

ABDULRAHMAN IBRAHIM ABDULAZIZ ALMEZAINI

SAMEH YOUSSEF TAWFIK YOUSSEF NASR

ZIYAD AYEDH SAID ALDOSARI

OMAR MUAZ HIDAR ALGHADIR

TALAL SAMEH MOHAMMED ABOZAID

SALMAN AGILA A ALAGILA

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MOHAMMED NASSER MOHAMMED ALHUQBANI

OMAR RIAB SAID ODEH

ABDULLAH MUSTAFA RAFIQ SHADID

ABDULRAHMAN MUSTAFA RAFIQ SHADID

YAZEN ABDULLAH SALMEN BALHEFER

IBRAHIM KHALID I ALDAWSIL

ABDULAZIZ FUAD M REDWAN

MOHAMMED ALI ALJASMARI

HAMMAD MOHAMMED ALAQEEL

ABDULLAH SAAD A ALTWAIM

MOHAMMED HASSAN M ALSHDIWI

KHALID ABDELRAHMAN SALEH ALBAHARDI

MOHAMMED KHALID M ALOTHMANI

ABDULLAH FAHAD A BIN MUAMMAR

BADER NASSER S ALAYYAR

MOHANNAD KHALID ABDULRAHMAN AHMAD

ABDULLAH BIN AHMED BIN A AL SUBAIHI

ABDULLAH KHALID M BASAMH

MOHAMMED NAWAF M ALMUTAIRI

ZIYAD FAHAD B ALJOFAN

LAITH MAZYAD S ALMAZYAD

KHALID ABDULHADI F ALDOSSARI

NAIF ABDULHADI F ALDOSSARI

FAISAL ABDULRAHMAN A ALZAHRANI

BASSAM TARIQ S ALKHUNAITIR

ALKASEEM AHMAD SULAIMAN BIN OBAID

RAKAN ABDULLAH E ALFAIFI

BADER HAMMAD M ALHARBI

BADR FADHEL Y ALSHDIWI

OMAR HAMAD A ALSHUNAYBIR

ABDULMOHSEN ALI HASSAN ALSHEHRI

NAIF NASSER S ALMUTAWA

MESHAAL KHALID M ALGHANIM

ALI GHAZI DAWOOD AL DAWOOD

MOHANNAD ADNAN A NAKKAWI

MOHAMMED ALHUNAIDI MOHAMMED ALOTAIBI

OMAR HAMAD S ALOMAR

ALWALEED KH M ALARABI

BADER MOHAMMED A ALQARNI

ABDULRAHMAN MOHAMMED A ALMUNAYYIR

NASSER MANSOUR NASSER AL BARRAN

HAMEED SUFIAN M HUMAID

ALBARAA MOHAMMED IBRAHIM ALSAIF

ABDULAZIZ SAAD A ALJORAID

-FAISAL -ABDULAH -N -ALSAMAD

ALWALEED ABDULRAHMAN S ALSALEH

ABDULLAH AHMED A ALEISA

MOHAMMED ABDULLAH M ALSHDIWI

FARIS RASHID A ALMUBARAK

MESHAL KHALID A ALGHAMDI

KHALID NABIL K NAGSHABANDI

*Group B is also in black you can't see them ▫