IMMUNOLOGY

IMMUNOLOGY OF TRANSPLANTATION

You have to refer to the slides; only extra information is written in this sheet.

Slide 2:

- The individual you take the graft from is called the (donor) and the individual you place the graft into is the (recipient).
- The organ to be replaced usually suffers end stage organ disease.
- Transplanted tissues are divided according to the Ags they present (relationship between donor and recipient Ags) into:

1. Autografts:
   - tissues/ organs taken from an individual and transplanted into the same individual.
     - They are either AUTOTOPIC (the same anatomical site) or HETERO TOPIC (different anatomical sites)

2. Syngrafts [Isografts]:
   - [Syn-/Iso-] to indicate genetic relatedness
     - Transplanted between genetically identical individuals
     - Genetically identical mice (Syngenic mice) arise when siblings (brothers and sister mice) are allowed to mate for 20 generations.

3. Allografts:
   - Grafts that are taken from individuals, who are different genetically from the recipient.
     - They are the MOST COMMONLY UTILIZED transplants
**Slide 3:**

- Rejection:
  - The immune response mounted against the transplanted tissue
  - We may consider this an immune response against foreign Ags but this will not enable the understanding of what takes place in transplantation

**Slide 4:**

- Classical immunologic principles cannot be applied to understand the field of transplantation since 2 major differences are present:

**They exhibit extraordinary strength:**

- In any immune response to a foreign Ag, $10^{-4}$ to $10^{-5}$ T lymphocytes (1 from every 10,000 – 100,000 T lymphocytes) are activated
- In the case of transplantation, several thousand folds of lymphocytes are activated.
- Similar to SUPER-ANTIGENS

**They can be stimulated by 2 different sets of APCs; those of the donor and those of the recipient:**

- Both APCs of the donor and the recipient contribute to the immune response generated
Slide 5:

There are 2 methods to recognize Ags in Rejection

1. Direct:
   - If we have both MHC I and MHC II on the surface of the transplanted tissue.
   - For example: MACROPHAGES which are present in almost all tissues
   - T lymphocytes of the recipient are educated to recognize MHC
   - This configuration of MHC being expressed on the surface of the cell, is a configuration that has been introduced to T lymphocytes, so T lymphocytes will recognize this **directly without any requirement for Ag presentation**. Since both foreign MHC molecules and peptides loaded onto them are ready for stimulation.

2. Indirect
   - Both MHC class I and II undergo turnover and are shed
   - Shed MHC molecules are uptaken by host APCs → Processed and presented to T lymphocytes.

   - The molecules (MHC/TCR/CD8 or CD4 etc...) used in both cases are the same, except that:
     - **Direct Recognition**: no need for Ag presentation by HOST APCs because the MHC is already expressed with a peptide on DONOR APCs & the T cell can recognize it.
     - **Indirect Recognition**: Ags that are shed are uptaken, processed and then presented.

   - Direct Recognition represents a sort of **cross reactivity** between what was learned during the development of T cells & what’s presented by the donor’s APC.
   - In Direct Recognition, using **Anti-TCR Abs** blocks recognition indicating it is the function of TCR to deal with these Ags.
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Slides 10-12:

- The events that take place are a COMPLEX involving all effector mechanisms & that’s why the immune response mounted against transplanted tissue is very strong, and simple immunologic principles cannot be applied in the case of rejection reactions.

Slide 13:

- This response results in the destruction of the transplanted tissue
- Even in individuals that are MHC matched, which is very rare, this will not prevent rejection, rejection can still take place because of what is called **Minor Histo-Compatibility Ags**
- These are more than 30 in number that cause rejection of grafts even between MHC matched individuals.
- **REJECTION IS INEVITABLE**

Slide 14:

Mechanisms of Graft Rejection: Divided chronologically according to the Severity and Time Span required to mount the reaction into:

1. **Hyperacute**: Immediate Rejection
2. **Accelerated**: requires a limited period of time
3. **Acute**: takes place after a while
4. **Chronic**: develops after months- years after transplantation

Slide 15:

- **Preformed Antibodies**: like Abs against RBCs’ Ags [ABO blood group system is the major system with this regard].
- The expression of RBC Ags is not limited to the RBCs; they are also expressed on nucleated cells, secretions... etc.
These preformed Abs, can attack organ immediately after transplantation.

Organs susceptible to hyper-acute rejection are the **VASCULARIZED ORGANS**

So it does not involve skin transplantations for example since skin is not vascularized.

Heart & Kidney highly susceptible

**Slide 16:**
- Preformed Abs may also be present against MHC molecules, as a result of:
  - Pregnancy
  - Blood Transfusion
  - Previous Transplantation
- Complement Regulatory Proteins; down regulate complement activation

**Slide 17:**
- The target in hyperacute reactions is **the donor vascular endothelium**, because it expresses **RBC Ags** as well as **MHC Ags**; **originally expresses MHC I only, but may be induced to express MHC II too.**
- Now that we have Abs that are present in high concentrations & foreign Ags on endothelium, Ag- Ab complexes will form.
- Subsequent to Ag-Ab complexes formation, the complement is activated, and this will lead to the formation of the MAC

- **MAC (membrane attack complex)** is formed due to the activation of the complement by Ag-Ab complexes.
- MAC is essential for activating **endothelial cells** by **[Endothelial Activation Type I]** which is dependent on the formation of MAC to occur.
- Many molecules that are involved in down regulation of complement: [like: sCr1/ Decay Accelerating Factor (DAF/CD55), Membrane Cofactor Protein (MCP/ CD46) and CD59] act in different stages of complement activation to down regulate the complement.
Slide 18:
- Preformed anti-MHC Abs almost always result in hyperacute rejection, but RBC-Ags Abs are only responsible for Rejection in 25% of cases.
- Nevertheless, this doesn’t mean they are not important; ABO compatibility must be watched? (25:11) in all transplantations; transplantation should never be performed across ABO compatibility (without ABO matching) because this can lead to hyperacute reactions.
- In the case where the source of the organ is from a different species, the down regulation of complement fails, because of homologous restriction.
- This means that regulatory components or molecules of the complement of humans were immuned? (25:54) and those of animals were not immuned?
- Human Complement Regulatory proteins do not down regulate complement of foreign origin.

Slide 19:
- Endothelium express the Ag [RBC Ag(ABO) OR MHC class I/II Ag]
- Ab binds to it.
- The complement is activated (through Ag-Ab complexes)
- This leads to Endothelial Activation Type I and this will lead to the formation of an inflammatory response.
- And these complement regulatory proteins (on the right of the pic) will down regulate the cascade of activation.
- But if the source is an animal tissue, then we have a problem with homologous restriction and no down regulation of the complement will not occur.

Slide 20:
- Cell retraction will lead to: Hemorrhage and Edema
- Loss of anti-thrombotic molecules from the endothelium leads to: Intravascular Thrombosis
- The true major processes that are responsible for the death of the transplanted organ are the aforementioned: Hemorrhage, Edema, and Intravascular Thrombosis.
Slide 21:
- Abs bind endothelium Ags > activate complement > complement cleavage products > attract neutrophils and other cells to the site & this will cause the activation of **coagulation and clotting** inside BVs of the transplanted organ > perfusion disorders > death of transplanted tissue.

Slide 22:
- **No treatment**, only way to stop such reactions is by prevention by: testing individuals for the presence of **cytotoxic Abs** and for **ABO titer**, so individuals should be ABO identical and we should look for cytotoxic Abs that may be present from a previous transplantation/ pregnancy..etc.
- **Bone, Skin and Cartilage** are not vascularized > Resistant to hyper acute reactions
- **Liver** is remarkably **resistant** to hyper acute rejection (I’m not sure about this, since the liver is highly vascularized; should be highly susceptible)

Slide 24:
- This reaction is dependent on the development of Abs within a short period of time which normally require T cell help, T cell help will lead to a more serious type of rejection; that’s why scientists question the presence of such reactions (Accelerated Rejection)

Slide 25:
- **The MOST COMMON TYPE OF REJECTION**
  - HYPERACUTE > rare because of the precautions taken
  - ACCELERATED REJECTION > (introduction of Abs without T cell help) is questioned by scientists
- If an individual is transplanted with allogenic Ags, he usually mounts a response of rejection within 11-15 days (**First- set rejection**)  
- If the same individual is transplanted again from the **same** donor the reaction will take 6-8 days (**Second Set Rejection**)  
- If an individual who has already developed a **first set rejection** earlier, is transplanted again from a **different** donor a **first set rejection** is mounted again.

Slide 26:
- Sequence of activation of T- lymphocytes:
  - CD4 direct > CD4 indirect > CD8 direct > CD8 indirect
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- **Antigenic Disparity** MHC/HLA sharing between donor and recipient
- **DTH** (delayed type hypersensitivity)
- **NO** due to activation of macrophages

**Slide 27:**
- Transplanted organs can express different proteins on its surface which provides a target for cytotoxic T lymphocytes and that’s why despite the fact that individuals may share MHC, the difference in Minor HLA will result in the activation of CD8 T cells > destroy the organ within a short period of time.

**Slide 28:**
- **IMMUNOSUPPRESSIVE THERAPY** is given in all cases of transplantations to maintain/promote the survival of transplanted organs
- Transplantation is made across HLA incompatibility; in clinical practice we don’t have 100% matching between individuals, so a certain degree of matching is acceptable.
- Because of that immunosuppressive therapy is the factor that is relied upon most to prevent rejection of the graft rather than HLA matching.
- **Immunosuppressive therapy is the only way to maintain the function of transplanted organs.**

**Slide 29:**
- Immunosuppressive therapy can delay/prevent the rejection
- Those cases of rejection that develop over 3 months or more after transplantation due to immunosuppressive therapy (delays the onset of the reaction) are called **Chronic Rejection.**
- Acute rejection has been controlled in most of the cases of transplantation by immunosuppressive therapy, now those individuals on immunosuppressive therapy are not totally prevented from mounting a rejection reaction but the reaction is delayed for months- years instead.
- **Chronic rejection appears as a consequence of delaying an acute rejection by immunosuppressive therapy**
Slide 30:
- Strong acute reactions are associated with more common chronic reactions.
- He reads the first paragraph “The half life of renal transplants that have survived for 1 year has improved significantly from 40% to 98-100%, but the long term graft survival did not improve similarly in the last period of time” in slides “has not changed significantly”.

Slide 31:
- This slide shows the improvement in the 1 year graft survival over the past years.
- And the lack of improvement in the long term half life of grafts after 1 year.

IMMUNOSUPPRESSIVE THERAPY

Improved the first year survival of transplants.

Had no effect on the long term survival of transplants.

Slide 33:
- This slide shows the different types of rejection in the kidney.
- Chronic rejection is characterized by the occlusion of the blood vessels and ischemia that leads to the death of the organ.

Slide 35:
- In the case of transplantation of tissues, T lymphocytes become activated with the production of cytokines and effector cells of different nature are also activated [NK cells, Plasma cells...etc]

Slide 36:
- Management to prevent tissue rejection is achieved by: 1- Donor-Recipient matching 2- immunosuppressive therapy.
- 1- Donor-Recipient matching:
  - MHC matching improves the success rate but does not prevent rejection because of the presence of other antigens (minor histocompatibility antigens).
- We do HLA typing by histological methods but it is imprecise due to polymorphisms. HLA antigens are highly polymorphic with the presence of hundreds of haplotypes.

- No transplantation without immunosuppressive therapy, which is used to prevent acute rejection, if we don’t give immunosuppressive therapy acute rejections is inevitable, either by HLA antigens or minor histocompatibility antigens.

- So, immunosuppressive does not have any effect on chronic rejection, it is only used for acute rejection.

- Chronic rejection is acute rejection that has been delayed and thus, rejection is inevitable, even in HLA identical individuals, rejection takes place.

- Transplantation is a new field, and our aim in researches is to increase the years before the grafts is rejected and to increase the percentage for its acceptance.

**Slide 37:**

- The transplantation is usually made immediately when the donor is available, where there are a lot of people waiting for this organ.

- The time to identify a recipient is another problem (there is no time to do that), for example, a kidney is taken from a donor of a car accident, the decision of transplantation must be taken within few hours to maintain the viability of the transplanted tissue. So, there is no enough time to do the proper matching.

**Slide 38:**

- Regarding matching, we match for class I and class II HLA, and the products of the HLA-A, ALA-B, and HLA-DR alleles are the most important.

- The HLA-DR is the most important allele of class II because of linkage.
disequilibrium, so when we match the HLA-DR it will be easy to match HLA-P and HLA-Q.

-the matching could be 1 out of 6 or 2 out of 6..etc , the more matching the better the result of transplanting.

-MLR (mixed lymphocyte culture) is performed to determine the determinants that are not detected by antibodies (The doctor explained it in details in the MHC lecture).

-PCR is more accurate method and can replace the other methods (Antibodies and MLR)

**Slide 39:**

-in this figure, The HLA matching has been studied for more than ten years and the matching is classified into full house (HLA identical), excellent, good and fair matching, and as you see in the figure for the ten years the results are almost the same (I think the doctor means that the function of the graft is almost the same regardless of the MHC matching degree).

-The half life of the graft is 7 years, that's why chronic rejection is the major important problem in rejection.

**Slide 40:**

-cross matching is The last test in that is performed before transplantation, we take a serum from the recipient and mix it with a donor's tissue, this done to detect the presence of preformed antibodies that mediate the Hyper-acute rejection.

-So, we prevent the Hyper-acute rejection by ABO typing and the cross matching, and HLA matching and MC is performed to prevent the acute and chronic
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rejection.

**slide41:**

HLA typing is done by a test called (lymphocyte) microcytotoxicity assay which is performed by the use of microtiter case that has wells, each well has Ab attached to it (anti /HLA ab) 200 wells, 200 Ab for 200 HLA types we isolate lymphocytes from the donor and the recipient by simply taking a sample of peripheral blood and perform a differential centrifugation that will separate them, we wash them and if the lymphocyte has an antigen corresponding to the Ab in the well-a reaction will happen, then a complement is added, this will kill the reacted cells. We add dye (tryphan blue or eosin), the killed cells will take up the dye, the dead cells will appear red or blue depending on the dye, but other cells won't take the dye and will appear shiny, So we can determine the HLA for the lymphocytes killed We do this for the donor and the recipient and determine their HLA type Alternatively :PCR can do this. MLC: Irradiate donor's or recipient's lymphocytes (keeping donor's or recipient's lymphocytes activated and inactivating the other) then incubate together then add 3H thymidin coz if they recognize antigenic determinants on the other they will differentiate the amount of radioactivity determines whether the test is +ve or -ve MLC indicates histocompatibility We can detect graft vs. host disease by this reaction or anticipate it (the ability of donor cells to recognize recipient cells) , so we can use it as a measure to select the most suitable among multiple donors, e.g. if we had 5 donors, 3 of them have same HLA type we do MLC and choose the donor with the weakest response (reaction).

**slide 43:**

usually more than 1 is used, synergistic type of action.

**Slide 44-45:**

**Prevention By Metabolic Toxins that kill proliferating T cells**
This will inhibit maturation of lymphocytes and kill proliferating mature T cells. Can be used with Cyclosporine A

- **There are methods of promotion of graft survival and these include:**
  1. AB to CD3: recognition of the antigen by TCR depends on CD3, so if we prevent the CD3 we prevent the recognition of the antigen.
  2. Anti-CD25
  3. Anti CD4
  4. Anti CD8
  5. Anti ICAM

All these molecules are involved in the immune system, and by inhibiting them we can increase the survival of the graft, or decrease the rejection.

- **Anti Inflammatory agents** like Corticosteroids
- **Tolerance Induction:**
  - common on blood transfusion

**Slide 46:**

This is the usual CTLA-4 antigen which can bind to CD8\CD86 instead of binding to CD28. which will promote tolerance.

**slide 47:**

- T-regulatory cell is another mechanism >> can start a state of tolerance at the level of T helper and T cytotoxic.

**Slide 49:**

Transplantation can be promoted by different techniques that act at different levels during the recognition of antigens, so we have

- anti CD3
- CTLA-4 to block
- anti CD-25
Soluble CTLA-4 can promote tolerance by binding instead of CD28 to the B7-1.

- Anti-CD40 ligand AB which will prevent the CD40 binding
- Anti-IL-2 receptor, and MHC donor peptide.

**Blood transfusion**

- HLA haplotypes antigens tend to be reserved in population,

  - So if an individual (prepared for transplantation) is subjected to repeated transfusions of small amount of blood, and he is tested for cross matching after the transfusion each time.

  If he is negative, the transplantation is made (he is non-responder).

  If he is positive, the transplantation is excluded

- The advantage of this procedure is to exclude those who are positive (will reject the transplantation).

  - Its believed that the exposure of HLA antigens by blood transfusion causes this condition which is the tolerance to antigens present in the population.

**Slide 50-52:**

The Hindu surgeon Sushrutu (700 BC) used forehead flap to repair an amputated nose.

- Italian surgeons (15th century) began to practice rhinoplasty by flaps and extended the donor site to the patient’s arm.

- Skin grafting became an accepted practice in the late 1800’s.

- The results of these efforts led to a period of confusion in transplantation in the lack of coordination between those who used to utilize the transplantation,
which led to malpractice, like what happened in Dr. Serge Voronoff procedure because surgeons embarked on all sorts of transplants,

- Dr. Serge Voronoff used testicular transplantation from Apes to humans with the claim that this maintain manliness for long period of time, and this can't be accepted by the transplant recipient, but he attained sufficient fame and fortune because of his procedure which is mainly a fraud.

- Transplantation of internal organs wasn't possible until the development of techniques of vascular anastomosis (to connect the blood vessels together) by the mid of the 20th century. And that's why the first successful renal transplant was performed in 1954 in Boston using the kidney of an identical twin.

- Common transplants include; skin, cornea (47,000 corneas were transplanted in the developed countries in one year), kidney, heart (more than 200 transplants), lung (1400 were transplanted in 2005) or heart/lung, liver, bone marrow, blood (an estimated 14 million units used every year) small bowel, pancreas or islets, and brain cells. Now Stem cells are everywhere including the brain, spinal cord... (not only in bone marrow transplantation although it was the first indication for stem cell transplantation) and here some people are utilizing stem cells without ethical (standards) (I couldn't get the exact word that was said by the doctor), and without enough evidence of the benefits of transplantation by doctors who want to make fortune.

We'll take an example of vascularized organ, an example of organs that is resistant to hyperacute rejection which is the Liver transplant and also we will take bone marrow transplantation as an example.

**Kidney Transplantation**

- **Most common (>10⁴/year in USA).**
- **Patient survival after one year is expected to be better than 90%.**
- **The current likelihood of graft function at one year exceeds 85% even when organs from totally unrelated donors are used.**
  Even if the transplanted kidneys are obtained from cadavers or nonrelatives, the likelihood of graft function at one year is 85%!
- **Subsequent risk of loss to rejection is 3-5% in each subsequent year.**
  - That's why careful selection should be made.
Choice among multiple donors should be based on MLC [weak (90%) Vs strong (60%) survival in 1 haplotype matched]

In Jordan for example: the only permitted type of kidney transplant is living-donor donation (who's usually a relative), cadavers' kidneys are not transplanted in Jordan. So sometimes more than one donor is available in the family and then we have to apply certain criteria for donor selection, the best criteria to be applied is Mixed Lymphocyte Culture (MLC) -if they all have same degree of HLA matching-

MLC reaction can be labeled as strong, moderate or weak, depending on radioactivity (degree of reaction). If the Transplanted kidney was from a relative whose MLC was labeled as strong, the chance of success is only 60%, which can be increased to 90% by selecting from donors who mounted a weak response in MLC, indicating that incompatibly (histoincompatibility) of the second donor is minimal. This type of testing influences the chance of survival remarkably.

One year kidney graft function

<table>
<thead>
<tr>
<th>Type of Graft</th>
<th>1976</th>
<th>1986</th>
<th>1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-identical grafts (living-related)</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>One- haplotype matched grafts (living related)</td>
<td>78%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>Cadaver-donor grafts</td>
<td>58%</td>
<td>83%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Note the improving one year kidney function rate; This is due to improvements in immunosuppressive therapy.

Bone Marrow Transplantation
- It’s different from most other procedures as it involves the transplantation of a tissue that can mount an immune response against the host (recipient) !!

- The transplantation of pluripotent hemoatopoietic stem cells (Allogeneic Vs autologous).
  The transplanted marrow can be either Allogeneic or Autologous.

  In an allogeneic transplant, the patient receives bone marrow stem cells from another person - usually a sibling. On the other side, autologous transplant requires the extraction of stem cells from the patient him/herself.

- In the case of AUTOLOGOUS TRANSPLANT: bone marrow is aspirated(obtained) from sites that contain large amounts of bone marrow (hematopoietic bone sites: ribs, sternum or pelvic bones), then it's treated with a high-dose radio-chemotherapy to kill malignancies (if the patient has them), then conditioning of the patient takes place by being subjected to radio-chemotherapy to eradicate his malignant cells population, finally these stem cells are re-infused (transplanted).

- In the case of ALLOTRANSPLANT: stem cells can also be obtained from bone marrow aspirates. However, recent transplantation processes are more reliable on the use of peripheral blood as a source of stem cells. This is achieved by the administration of G-CSF(granulocyte colony stimulating factor); which increases the production of stem cells and mobilizes them from the donor's bone marrow into the peripheral circulation, then auto devices collect these cells from the donor's blood(similar to hemodialysis devices, meaning that the donor is connected to a machine where his blood pass through, and techniques like immunoprecipitationmagnetics remove and collect the wanted stem cells)

Peripheral blood stem cells are widely used nowadays, replacing the old aggressive procedure of bone marrow aspiration.

- It is general practice to transfer stem cells as part of an inoculum of total marrow cells collected by aspiration.
• However, treatment of donor with G-CSF can mobilize stem (CD34+) cells which are then isolated from peripheral blood.

• After transplantation (stem cells infusion), stem cells repopulate the recipient bone marrow with their differentiating progeny. These cells have the characteristic of homing, they repopulate the bone marrow and start differentiation into their progeny cells to provide the cells needed depending on the conditions of transplantation.

• Recipient must be nearly ablated to permit successful BMT (radiochemotherapy)
**Complications:**
(these complications are mainly due to the patient's ablation and radiochemotherapy)

1) **venoocclusive disease of the liver** (the most important complication)
   - It's a condition in which the small veins and venules of the liver are obliterated and blocked.
   - 20%, due to high doses of chemoradiotherapy.
   - 8-20 days after transplantation.
   - Fatal in 5-20%, resolves in 60% with no effective treatment (Spontaneous recovery).
   - Hepatitis is a risk factor.

2) **GVHD** (GravtVs Host Disease):
   - It's an important complication in bone marow transplantations that doesn't occur in other transplantation procedures, it happens because the transplanted tissue (bone marrow) has the potential to mount a response against the host.
   - Here we have 2 faces of the rejection reaction; the first mounted by the host immune system against the transplanted tissue, the second mounted by the transplanted tissue (which has the potential of mounting an immune response) against the host(recipient).
   - Transplant rejection usually refers to the conventional type of rejection; mounted by the host against the transplant. Here, as the rejection reaction being performed by both; the host and the transplant; it's better to refer to it as GVHD
   - It can be predicted by performing MLC in its both ways (mentioned in previous lectures)
   - It's a VERY SERIOUS reaction, it happens in most bone marrow transplantation, as it's very difficult to achieve complete matching between individuals (except in the case of identical twins).
   - usually against minor antigens
   - it takes place in 2 forms :
     a) **ACUTE** :
        - epithelial cell necrosis in skin, liver (biliary not hepatocytes), and GI tract causing skin rash, jaundice, diarrhea and GI hemorrhage
        - It usually target cells that express MHC-2 present in skin, liver & GIT
        - It could be the cause of failure of bone marrow transplantation
b) CHRONIC:
   - Characterized by fibrosis and atrophy of one or more of the same organs without evidence of acute cell necrosis (because unlike the acute, this chronic form develops SLOWLY)

3) Clinical Immunodeficiency
   - As a consequence of the use of immunosuppressive therapy that predisposes the recipient to infection and cancer.

Liver Transplantation

- **Long-term survival does not appear to be better when HLA matching is achieved.**
  - The liver, due to its large size and large vascular bed, has the capacity to accommodate Antibodies, so Antibodies cannot destroy the organ.
  - HLA matching is not a requirement for liver transplantations as it does not influence the long term survival.
  - So the donor can be any individual willing to donate, without the need of HLA matching.
    However, it’s important to test for blood group matching and cross-matching (to detect the presence of Anti-HLA Antibodies in particular, the presence of such influences the long term survival of the liver)

- **Rejection defined by histologic means** (by interpretation of lymphocytes as in the case of acute rejection) is common (75%) but it is easily reversed and does not influence long-term survival.
  - 75% of liver transplantations are associated with mononuclear cell infiltrate that does not influence the long term survival.

- **Living related liver lobe transplantation is now commonplace.**
  - Usually the right lobe is removed from a healthy living donor to be transplanted.
  - This is being more & more common worldwide, in Jordan we have 2 centres for transplantation; one at King Hussein Medical City & the other at Jordan hospital.
Problems of Transplantation

I. THERE ARE NO ENOUGH ORGANS
   • At least 150,000 patients in industrially developed countries badly need donor organs and tissues
   • Every 14 minutes another name is added to the national transplant waiting list.
   • About 16 people die because of the lack of available organs for transplant each day.

II. REJECTION:
   • When the immune system of the host detects foreign graft tissue, it launches an attack, resulting in tissue rejection. (Rejection can be manipulated by induction of tolerance & immunosuppressive therapy)

Gene technology as a solution

I. Gene technology offers the possibility to breed the desired organs in animals: Lack of organs is no longer a problem (Organ AVAILABILITY is solved)
II. Gene technology makes it possible to humanize (incorporate human genes into these bred tissues) the bred organs; the immune system identifies the organ as its own tissue: Immune system rejection is prevented (Organ REJECTION is solved)
From which animals are we able to transplant organs?

- The Baboon was utilized for heart transplantation BUT it has a problem in size.
- The best animal to breed organs for humans is the Pig!

Organ breeding
- A transgenic animal carries a foreign gene (which is of human origin) **inserted** into its genome.
- The transgenic animal shows the specific characteristics which are coded on the inserted gene
- A gene which is responsible for the construction of a human organ makes the organism produce the organ additionally.

The insert of a foreign gene into an animal:
I. DNA microinjection
The DNA is inserted into the cell with a small syringe
(this is commonly practiced in fertility issues)

II. Retrovirus gene transfer
The DNA is carried into a cell by a virus.
Retroviruses can incorporate the genome of humans, so they act as vehicles (carriers) for human genes to introduce them into an animal.

✓ This is the direction of research nowadays. It's concentrated on the area of utilizing animals to produce organs with human genes and antigens to be subsequently used in organ transplantation.

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