

Immunology

Lecture num. (21)

Transplantation

- Transplantation: removing an organ from donor and gives it to a recipient.
- Graft: transplanted organ.

Types of Graft (4 types):

Auto Graft

- From a person to himself.
- Same MHC and MiHC¹, so there is no possibility for immune rejection.
- Example: removing skin from one part of the body and put it on another (burned) part for cosmetic reasons.

Syngeneic Graft

- Between identical twins.
- Same MHC and MiHC¹. No possibility for immune rejection.

Allo Graft

- Most common type in clinical practice.
- From one to another within the same species.
- Cannot have complete matching (trying to match as possible).
- Two types of donors:

1. Living Donor

Like siblings or relatives. Living donors have more possibility to match HLA between them and their recipients. (For example in siblings we have 25% chance to have the same MHC, But with different MiHC).

2. Cadaveric Donor:

The possibility of matching is low (not necessarily always 100%). Actually there are waiting lists for recipients and once a cadaveric organ is offered, the most suitable person will be chosen by considering (MHC matching, waiting duration and other points).

¹ MiHC: Minor histocompatibility complex.

- Graft rejection is possible.

Xeno Graft

- Transplantation across the barrier of species.
- Not very well established (experimental).
- Example: talking heart valves from pigs.
- Other organs used in Xeno graft: Kidney, heart, liver.
- Animals used in Xeno graft trials: Pigs (similar to humans in their anatomy and MHC complexes), Monkeys, and Chimpanzees (98% of their DNA is similar to human DNA).

Immune Rejection

- There are a lot of similarities between graft rejection and inflammatory response, but they are not exactly the same.
- Transplant rejection is a strong and extended immune response (not like other immune responses; weak and short).
- Immune rejection is strong because up to 5% of lymphocytes in the body will be activated by this process. In contrast, just 0.1% or less of lymphocytes will be activated in any other immune response (against other foreign bodies).

Types of Immune rejection (4 types)

Hyper Acute Rejection

- Caused by the preformed antibodies in the recipient serum against ABO² and HLA antigens of the graft.
- Transplanted organ has two types of antigens:
 1. ABO antigens (on endothelial cells).
 2. HLA.
- HLA mismatching is more important and can cause severe graft rejection than ABO mismatching.
- Recipient serum may contain preformed antibodies (against HLA and ABO) because of:
 1. Previous transplant.
 2. Previous transfusion.
 3. Multiple pregnancies.
- Hyper acute rejection should not happen because:
 1. Doctors should match the antigens properly.

² Remember that: ABO antigens found on RBCs and other cells (like endothelial cells).

2. Doctors should screen the recipient serum for preformed antibodies against ABO and HLA antigens.
- If the recipient serum contains preformed antibodies, what will next is that:
As soon as the transplanted organ reach the recipient's body (minutes – half an hour), the antibodies will react with the antigens and the antigen-antibody complexes will activate the complement system. After that the inflammatory process will start in the endothelial cells and these cells will be retracted (but lysis does not always occur). At the end thrombosis of the blood supply will happen and the graft will die.
 - As a revision for hyper acute rejection:
 1. Caused by preformed antibodies.
 2. Has complement mediation.
 3. Rejection process: Cut of the blood supply and thrombosis.
 4. Result: Graft will die.

Acute Rejection

- Happened in few days after the transplantation (5-8days).
- Very similar to the immune response, but stronger than the inflammatory immune response.
- Involved cells: CD4 and CD8 T cells (consider the graft as foreign body).
- Both donor and recipient take part in the acute rejection.
- Donor's role in acute rejection:
 1. MHC molecules on the graft. Recipient T cells will recognize foreign MHC molecules and foreign peptides on them and they will react to them immediately without needing the antigen presentation process.
 2. APC (antigen presenting cells)of the donor –they are also called passenger cells³. Most of these cells are dendritic cells, so they will react with the recipient's MHC class 2 and with the peptides on them.
- Direct rejection: when APC of the donor take part in the immune rejection.
- Recipient's role in a acute rejection (mono immune response):
When APC of recipient (macrophages) react with HLA of the graft and initiate the antigen presentation process, so the antigens will be presented for T cells and an immune response will be activated against the donated organ.
- In acute rejection the organ might die, but doctors may deal with it and keep the existence of the graft by suppressing the recipient's immunity (they may use certain immunosuppressive drugs like: steroids, cyclosporine, anti CD3,...).For example : 80% of cadaveric transplanted kidney will still alive after 1 year from the transplantation.

³ Passenger cells: leukocytes that transfer with the graft (although grafts are washed before transplantation).Most of passenger cells are dendritic cells.

Accelerated Rejection

- Rare.
So if the recipient suffers from any problem after one week from transplantation, it is more likely to be acute rejection rather than accelerated rejection.
- Both humeral immunity and cell mediated immunity will take part in accelerated rejection.
- More severe than acute rejection but not as bad as hyper acute rejection (in hyper acute nothing can be done to stop the graft rejection even with immune suppression). So, it is difficult to treat accelerated rejection but it is not impossible.
- Please do not forget that any graft except (auto and syngeneic grafts) might be rejected because of MHC although the two haplotypes of MHC are matched properly.

Chronic Rejection

- Episodes of graft mal function without responding to immunosuppressants.
- Happens after years (mainly 10 years) from the transplantation.
- Improving methods of transplantation and Immune suppression can increase the survival of the graft within the first year. But after years graft rejection will occur (chronic rejection).
- Occurs despite good matching (ABO and HLA antigens) and despite immune suppression.
- Involved cells: CD4 (and cytokines activated by them), CD8, macrophages, NK cells.
It is like the delay type hypersensitivity reaction (according to the cell types that are involved in this type of rejection). Also, humeral immune response will be activated by: complement activation and ADCC. It will produce antibodies that will participate in the destruction of transplanted organ.
- Unknown mechanism.
Maybe the graft will be infiltrated with the cells (mentioned above). Fibrosis and narrowing of blood vessels will occur, then the blood supply will be destroyed completely and the graft will be fibrotic .At the end the graft will die.
- One of the chronic rejection mechanistic explanations is that it happens because of repair process (Fibrosis process).
- Although at the end of the 10 years the graft will die, but at least transplantation can afford the recipient more years with normal healthy life –instead of being on dialysis 3 times a week in patients with insufficient kidney, the transplantation is better and can offer longer and more healthy life-.
- Chronic rejection cannot be treated by increasing the dose of immunosuppressants – unlike acute rejection which can be treated with this way.

Organs used in transplantation:

- Kidney (most common).
- Heart and heart valves.
- Pancreas.
- Liver.
- Cornea.
- Bone marrow.

Kidney Transplantation

- First successful kidney transplantation was in 1954.
- Thousands of kidney transplantation procedures are done all over the world each year.
- In our countries it is easy for recipients to find living donors (siblings and relatives). In other countries it is difficult to find living donors, so the patient will wait until he found a suitable cadaveric donor.
- In living donors the possibility of matching will be higher than in cadaveric donors especially if there are more than one healthy sibling for the recipient. In cadaveric donor it is very hard to match one or both of the HLA haplotypes, but doctors should try to match at least one A or one B or DR (most important and most strong HLA antigens). Doctors can deal with the weak matching of antigens by increasing the dosage of the immunosuppressants.
- Certain criteria are used to choose one patient from the waiting list when a cadaveric kidney is available. (Matching, duration of waiting ...).
- The donor should be healthy with two well-functioning kidneys.⁴
- Before the transplantations doctors should check:
 1. ABO matching.
 2. Screen the recipient serum in order to make sure that he does not have anti HLA and ABO antibodies.
Screening method:
 - A. Lymphocytotoxicity testing
By taking serum from the recipient and mixing it with known HLA leukocytes. If the serum contains anti bodies, antigen-antibody complexes will be formed and will activate the complement .Cell lysis will occur. In this situation doctors will not make the transplantation at all.
If there is no cell lysis, then the serum does not contain antibodies. In order to make sure another test should be done which is cross matching test.

⁴ Note: 25% of our kidneys is sufficient for us to live healthy.

B. Cross matching test

This test is done by mixing the recipient serum with the lymphocytes of the donor, to detect if the donor's lymphocytes are killed by the serum of the recipient or not.

- Positive result, the transplantation will be contraindicated and hyper acute rejection will occur if the transplantation is done.
 - Negative result, transplantation can be done.
- Cadaveric kidney:
Kidney will be harvested after death, washed with saline and kept in ice for 2 days (maximum). Doctors can transfer the kidney to someone else within these two days. Early transplantation is favorable.

Heart transplant

- Heart cannot live outside the body for more than 6 hours, so you should transfer it from the donor to the recipient directly.
- Heart is not taken from cadaver, but it is often taken from a brain dead patient.
- ABO matching is needed.
- No need for HLA matching but the recipient should be screened against preformed antibodies.
- There are two options for any heart transplantation :
 1. Removing the patient's heart and put the donor's heart instead. It is dangerous because if the graft is rejected the patient will die directly.
 2. Putting the donor's heart next to the patient's heart. This option is safe, because the patient will not die directly if the heart is rejected.
- Most patients who need heart transplantation are in life or death situation, so they do not have a lot of choices (If they do not transplant a heart they will die. And also if they do transplantation, their bodies may accept or reject the transplanted hearts).

Liver Transplantation

- Most important factor in liver transplantation is the size; you cannot take an adult kidney and transplant it in a child.
- No need for HLA matching.
- Resistant to hyper acute rejection.
The liver is very large so the antibodies-in the recipient serum- which are against the transplanted liver will be diluted and cannot cause severe effects.
- Lobe transplantation is known. Not all the liver will be transplanted, just part of it.

- Some doctors said that in liver transplant if you mismatch HLA antigens, you will have better results!!

Pancreas Transplantation

- ABO and cross matching is needed. Also blood screening should be done.

Cornea Transplantation

- ABO and HLA matching not necessarily to be done because cornea is an avascular organ (no rejection) .
- ABO and HLA matching is needed in two situations (there might be a predisposition to rejection) :
 1. A person who received cornea before and reject it.
 2. A person who suffers from corneal vascularization.

Bone Marrow Transplantation

- Bone marrow transplantation is done for people who suffers from:
 1. Leukemia (aplastic bone marrow).
 2. Immune deficiency.
 3. Take drugs that cause aplastic anemia.
- All the bone marrow should be destructed by radiation (in leukemia or immune diffident patients), but people with inherited immunodeficiency do not need this previous step in their treatment because they do not have bone marrow.
- In bone marrow transplantation, doctors should match the antigens properly. For sure best results can be obtained if doctors can match the 2 haplotypes (by taking the bone marrow from siblings, sons, daughters, other relatives,...).
- G.V.H: graft versus host syndrome
This syndrome happens when HLA haplotypes are not well matched or are mismatched, so that the transplanted bone marrow will reject the recipient's tissues. (We called it GVH because here the graft will reject the host not as usual; when host rejects the transplanted organ).
- Mature T lymphocytes should be removed from bone marrow before the transplantation, because they are differentiated cells and may react with new body tissues as foreign bodies. Un Like new immature T lymphocytes that will go to the recipient's thymus and differentiate there.
But removing T lymphocytes alone without matching is not enough alone because we cannot be sure about removing all the mature T lymphocytes.

Wishing you all of the best 😊