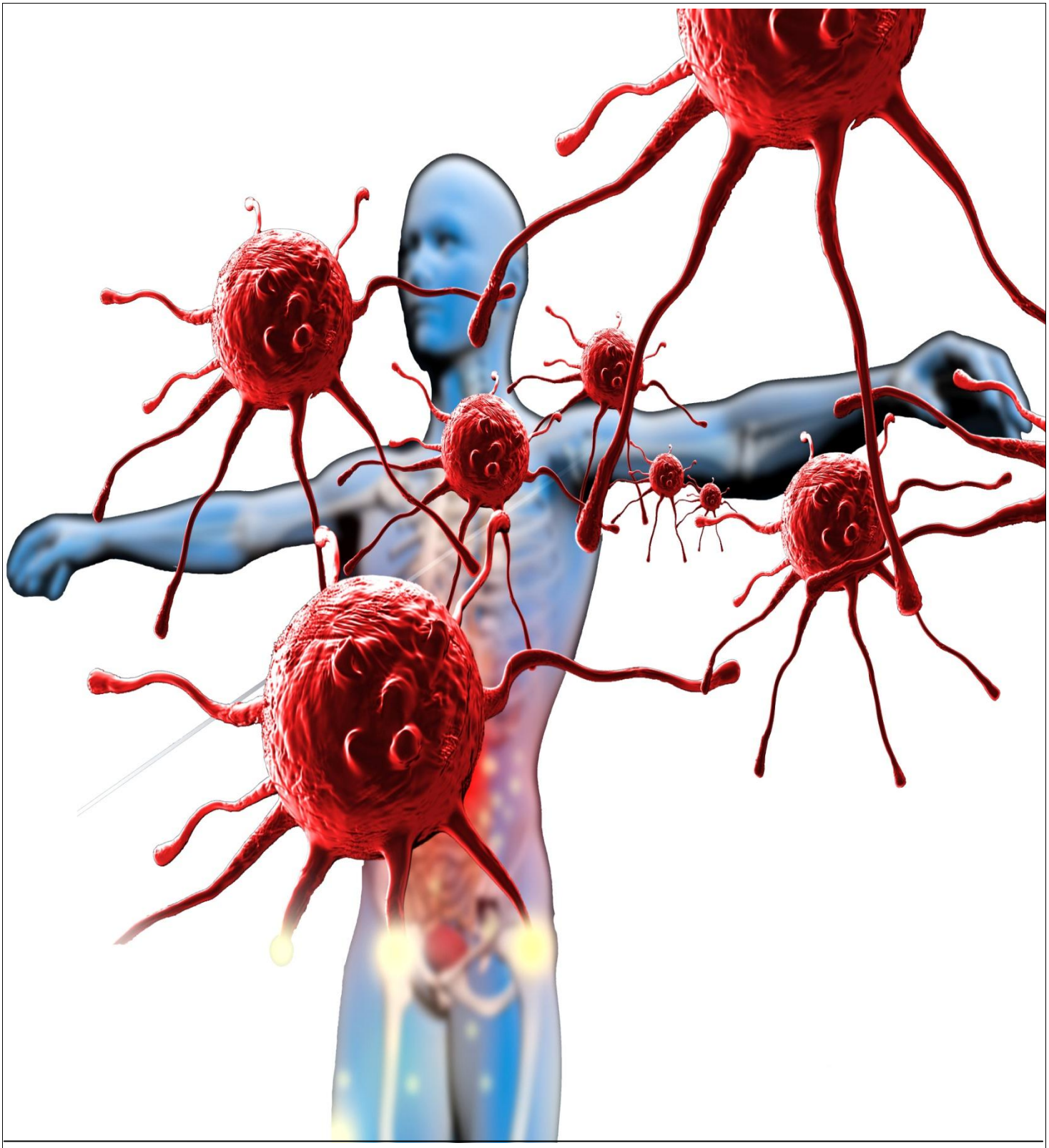

IMMUNOLOGY

Done By: Noor Hammad

#18

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By Mohammed Nawasreh

➢Tissue Transplantation

➢Transplantation: removing an organ /tissue from donor and gives it to a recipient**.**

➢Types of Graft:

-There are four types of graft

1- **AUTO GRAFT**

-From a person to himself.

-Same MHC and MiHC1 { MiHC: Minor histocompatibility complex }

- **No possibility for immune rejection**.

-Example: removing skin from one part of the body and put it on another (burned) part for cosmetic reasons.

2- **SYNGENEIC GRAFT OR SYN GRAFT**

-Between **identical twins.**

-Same MHC and MiHC1

-**No possibility for immune rejection**.

3-**ALLO GRAFT**

-Most common type in clinical practice.

-From one to another within the same species.

-Cannot have complete matching {they are not genetically related}

- Graft rejection is possible

4- XENOGRAFT

✓ **-XENO: MEANS Foreign**

✓ **-A surgical graft of tissue from one species to unlike SPECIES.**

✓ Transplantation across the barrier of species.

✓ Example: talking heart valves from pigs.

✓ Other organs used in Xenograft: Kidney, heart, liver.

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✓ Animals used in Xenograft trials: Pigs (similar to humans in their anatomy and MHC complexes), Monkeys, and Chimpanzees

➢ Immune Rejection

- The main problem in transplantation is that, the transplanted organ or tissue is usually considered as a foreign organism and there is an immune response against it in order to get rid of it. {Except for Syn-graft and auto-graft}.

- Immune rejection is **strong and INTENSE** because up to 5% of lymphocytes in the body will react with the transplanted organ/tissue. In contrast, 0.1% of lymphocytes will be activated in any other immune response against other foreign bodies.

- Both donor and recipient take part in the rejection.

1- **Donor's role in rejection**: "**Direct rejection** "

- **-** Recipient T cells will recognize foreign MHC molecules and foreign peptides on the donor organ /tissue and they will react to them.{MHC on the donor organ will be regarded as foreign organism }
- **-** APC (antigen presenting cells)of the donor –they are also called **passenger cells**. Most of these cells are **dendritic cells**, so they will pass to the host body and stimulate a measurable percentage of recipient T cells. {NO complete cleaning of the transplanted organ /tissue and some APC will pass to the recipient and act in the DIRECT REJECTION.}

2- RECIPIENT's role in rejection: INDIRECT REJECTION

- Host (recipient) dendritic cells process proteins from the transplanted graft, and trigger a T cell response.

➢ The main difference between **indirect** and **direct** rejection stems from the origin of the APC. In **direct** rejection, the involved dendritic cells are **donor derived**. In **indirect** rejection the dendritic cells (APCs) involved are **recipient** APCs.

➢ Types of Immune rejection

- **Once graft rejection has begun, it can be classified in one of three ways in humans, either hyperacute rejection, acute rejection, or chronic rejection. These categorizations are based on how quickly the rejection occurs.**

1- **HYPER ACUTE REJECTION**

✓ Caused by the **preformed antibodies** in the recipient serum before transplantation against **ABO** and **HLA antigens** of the graft.

✓ Transplanted organ has two types of antigens:

1- ABO antigens (can be found on both endothelial cells and RBCs)

2-HLA antigens .

Example: a recipient with type B blood would have antibodies targeted against "A" antigen of type A donor.

- ✓ **HLA mismatching** is **more important** and can cause severe graft rejection than **ABO mismatching**.
- ✓ Recipient serum may contain preformed antibodies (against HLA) because of:
  - Previous transplant.
  - Previous transfusion.
  - Multiple pregnancies.
- ✓ Hyper-acute rejection should not happen because:
  - We should match the antigens properly.
  - We should screen the recipient serum for preformed antibodies against ABO and HLA antigens.

➢ To sum up

{**There are several explanations for the preexisting antibodies that initiate hyperacute rejection. Recipients of blood transfusions sometimes develop antibodies to MHC antigens from the transfused blood. If some of these antigens match those in a graft, then hyperacute rejection may result. Multiple pregnancies may also expose the woman to the maternal antigens of the fetus, resulting in the creation of antibodies. Finally, prior recipients of transplants may have already formed antibodies to other MHC antigens, so they may be present at the time of a second transplant. Most of the time hyperacute rejection can be avoided by screening for anti-graft antibodies.**}

➢ Hyper-acute rejection is caused by preexisting host antibodies that bind to antigens present in the graft endothelium. Antigen recognition activates the **complement system**. The resulting inflammation prevents vascularization of the graft. The graft then suffers irreversible damage from ischemia.

➢ Hyper acute rejection:

- Immediate reaction {within minutes }
- Caused by preformed antibodies sticking to their antigens
- Leading to complement mediation.
- It is characterized by thrombotic occlusions and hemorrhage of the graft vasculature
- Result: Graft will die.

Note: during this type of rejection, the transplanted organ, we can say the Kidney for example will appear cyanotic {Blue in color} with stasis of blood and thrombosis.

2-**ACUTE REJECTION**

✓ Happened in few days after the transplantation (7-10 days).

✓ Very similar to the immune response, but *stronger than the Inflammatory immune response*.

✓ The Involved cells are: CD4 {**MAINLY**}, NK {can differentiate between self and non-self-antigens} and CD8 T cells.

✓ It occurs to some degree in **all transplants** (except between identical twins and auto- graft).

➢ **Accelerated Rejection**

✓ Accelerated rejection is a form of acute rejection *(but with more and increased antibodies)* that occurs within 2-4 days after the transplantation in patients already sensitized to donor antigen (previous pregnancy or blood transfusion).

✓ We 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*)

✓ 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

Hyper acute VS Accelerated

✓ Both of them are Antibody mediated rejection ,but if the rejection occurs **IMMEDIATELY** {PREFORMED antibodies } after the transplantation, it is **HYPERACUTE REJECTION** and it may be delayed by 2-4 days if sensitization to donor antigen has occurred in the remote past ,so it is **ACCERELATED REJECTION** {DE NOVO antibodies}

✓ ACCERELATED includes both cellular and humoral immunity.

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3- **CHRONIC REJECTION**

- ✓ Happens after years (2-6 years) from the transplantation.
- ✓ It is insidious process.
- ✓ Improving methods of transplantation and Immune suppression can increase the survival of the graft within the first year. But eventually after several years graft rejection will occur (chronic rejection).
- ✓ Occurs despite good matching (ABO and HLA antigens) and despite immune suppression.
- ✓ The Involved cells are s: CD4 (and cytokines activated by them), CD8, *macrophages*, NK cells.
- ✓ This is mainly a DTH (delayed type hypersensitivity) reaction (according to the cell types that are involved in this type of rejection). Also, humoral 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 (thickening) and narrowing of blood vessels will occur, then the blood supply will be destructed 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 immunosuppressant –unlike acute rejection which can be treated with this way.
- ✓ Any graft (except auto and syngeneic grafts) might be rejected because of MiHC although the two haplotypes of MHC are matched properly.
- ✓ The **severity** of the chronic rejection depends on whether you have a sever acute rejection at the beginning and how the exacerbation of the acute rejection you get over the time. {SEVERE acute rejection leads to **EARLY** chronic rejection, while the MILD acute rejection leads to **DELAYED** chronic rejection.
- ✓ If you have more than one episodes of acute rejection, the possibility of EARLY chronic rejection will be more and more.

❖ General Notes :

- When people transplant an organ from one to another, they should do the following :

➢ **1) TISSUE TYPING**: They should determine the type of HLA antigens present on the donor and recipient.

- One technique of tissue typing known as a **micro-cytotoxicity assay {serological method}**.

- In Serological method we utilize serum with known anti-HLA antibodies that recognize particular HLA loci (HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DQ, and HLA-DR) in order to match genetically similar individuals in hopes of performing tissue transplantation. In this technique a donor's blood cells are MHC typed by mixing them with serum containing the anti-HLA antibodies. If the antibodies recognize their epitope on the MHC then complement activation occurs and the cell will be osmotically lysed.

- **Molecular method** is another way for tissue typing and it is much more specific and accurate than serological method. It deals with DNA accesses.
- The most important antigens in immune rejection are HLA-A, HLA-B, HLA-DR and HLA-DQ
- HLA-C and HLA-DP are not important {they don't have a main role in REJECTION}
- When we match siblings for transplantation, the result will be either no matching or the matching is established in one or two haplotypes.

➢ 2)THE ABO MATCHING

- It should be taken in consideration , because if there is ABO incompatibility the organ /tissue
  Cannot be transplanted.

➢ 3) SCREENING FOR ANTI – HLA ANTIBODIES IN THE SERUM OF THE RECIPIENT.

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➢ 4- BLOOD CROSS MATCHEING TEST :

- By taking the serum of the recipient and reacting it with the lymphocytes of the donor {*lymphocytes are from the blood in case of living donor, from the spleen in case of cadaveric donor*}
- If there are antibodies against HLA antigens of the donor's leukocytes, the immune complex activates the complement system and the cells will die. This means that, the transplantation is contraindicated although, the HLA typing, ABO matching and screening are okay.

- **Positive result**, the transplantation will be contraindicated and hyper acute rejection will occur if the transplantation is done.
- **Negative result**, transplantation can be done.

❖ 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).

➢ **<u>Organs used in transplantation</u>**:

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

1) Kidney Transplantation

- ✓ Thousands of kidney transplantation procedures are done (*of course after successive testing and screening)* all over the world each year, and the complete matching is not very important because the effects of immunosuppressive agents are very significant.
- ✓ In living donors the possibility of matching will be higher than in cadaveric donors especially if there is more than one healthy sibling for the recipient.

➢ 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.

2) 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.**

  - ➢ **Note: Heart and Kidney are not resistant to HYPER-acute rejection.**

3) Liver Transplantation

- ✓ Most important factors in liver transplantation are 1- the size; you cannot take an adult kidney and transplant it in a child and 2- ABO matching.
- ✓ **No need for HLA matching.**
- ✓ Resistant to hyper acute rejection.{unknown mechanism}
- ✓ The expected explanations of the liver resistant are
- 1- 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.
- 2-The hepatocytes themselves are lacking or have few MHC molecules.

4) Pancreas or islet cells Transplantation

- ✓ ABO and cross matching is needed. Also blood screening, HLA typing and cross matching should be done.

5) Cornea Transplantation

✓ **ABO and HLA matching are not necessarily to be done because cornea is an avascular organ** (no rejection)

6) Bone Marrow Transplantation

✓ Bone marrow transplantation is done for people who suffers from:

- Leukemia.
- Immune deficiency.
- Aplastic anemia.

✓ In bone marrow transplantation, we should match the **HLA antigens properly**. For sure best results can be obtained if we can match the 2 haplotypes (by taking the bone marrow from identical twins).

✓ You can donate some of your stem cells in the bone marrow and store them in the hospital banks for years.

✓ In case of ALLOGRAFT, you have to be very careful about EXACT matching {HLA matching}.

GVH SYNDROME : 'graft versus host syndrome'

✓ This syndrome happens when **HLA haplotypes are not well matched or 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).

✓ Lymphocyte of the transplanted tissue/organ will recognize the host body as a foreign organism.

- ✓ This syndrome may affect a liver, skin and mucosal in the GIT which leads to vomiting and diarrhea, and sometimes people may die from GVH syndrome.

- ✓ There is acute GVH syndrome which occurs around months after transplantation, and for a long period there is chronic GVH syndrome.

FETUS GRAFT :

- ✓ Fetus is recognized as graft and can be rejected.
- ✓ The Natural mechanisms for avoiding "FETUS GRAFT REJECTION" are :
  - Most of the polymorphic MHC 1 class (A) Ags are lacking on the surface of fetally derived trophoblastic cells, so they can't be rejected by CD8+ cytotoxic T-cell.
  - Trophoblastic tissue expresses the human leukocyte antigen-G (HLA-G) which gives a non-classical MHC class I on their surface that gives a negative signal to NK cells rejection *(we know that NK cells attack any cell lacking MHC)*.

يعطيكم العافية
الشيت اهداء "خااص" ل "مرح قاسم"

وكل ما تبقى لان يصل هو : عليك ب" فكرك " فستسأل عن منهجيتك يوما ما , شتان بين متعلم يحاول الوصول وبين التبعية للواصلين أي كانت انتمائاتهم ومعتقداتهم . ف جوهر المرء هو " أفكاره ومبادئه " فان صلحت واستقامت لا تكترت لعواقب الزمان فهي مجرد عثرات شائكة في سراب زائل .

Written by نور حماد