Transplantation — Mechanisms and Therapies

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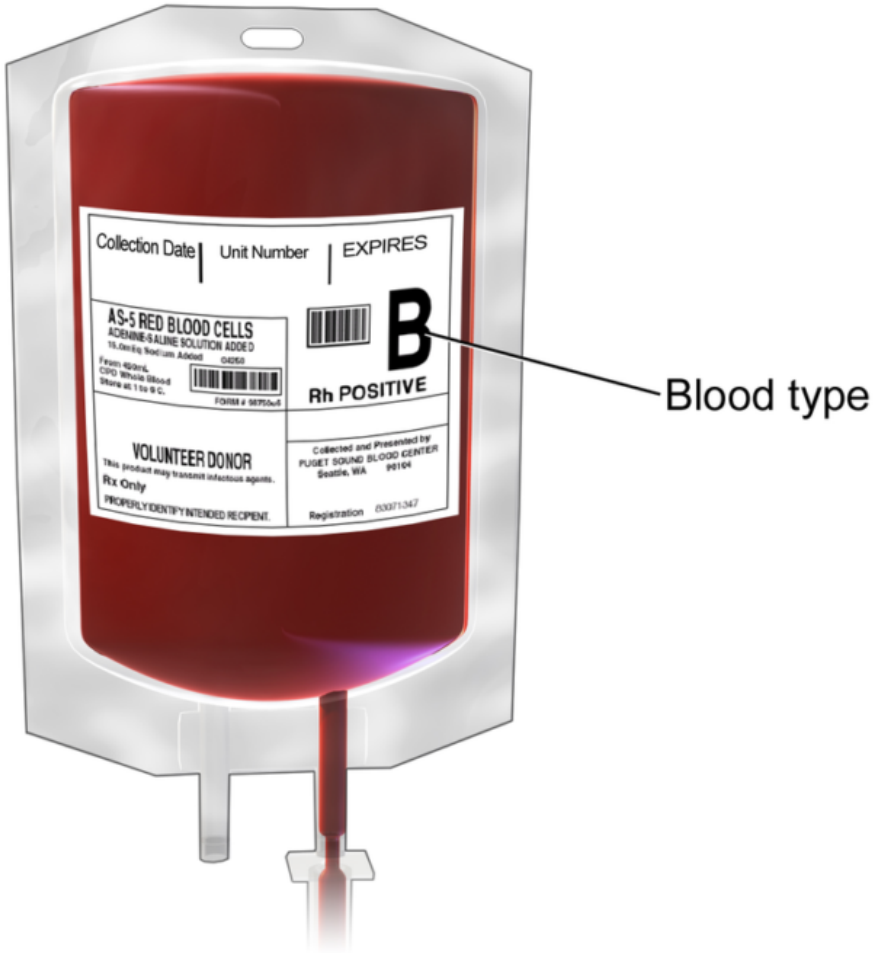
Transplantation medicine can be subdivided into solid organ transplantation and blood transfusion. Blood transfusion examples include packed red blood cells, plasma and platelets concentrates. Solid organ transplantation can be xenograft, autograft, isograft and allograft.



Labeled Blood Bag

Important Definitions in Transplantation Medicine

Xenografts

Xenografts were the first to be tried in transplantation medicine. They are described as the transplantation of a solid organ from a different species into the human body. A common example is pig heart valves. Non-human tissues are implanted into a human body and although a lot of controversies has been raised on the issue there have been many lives that have been changed through these procedures. This form of transplantation carried the highest risk of rejection until the introduction of **immunosuppressive drugs**.

They are used to ensure that the immune system does not overreact to the transplanted organ which was the major cause of rejection. They work by dampening the immune system's response to the foreign tissue or bone introduced to the body.

Their biggest disadvantage is their non-specific nature that leaves patients susceptible to diseases which can be a problem as it exposes them to several possible infections if care is not taken.

Autografts

They are grafts from the same individual. Examples include skin grafts and bone marrow transplantation from a previously stored cord blood sample. It involves transferring a patient's bone or tissue from one part of their body to another. It is very reliable, keeps the cells intact and has a high success rate as the tissues involved are live.

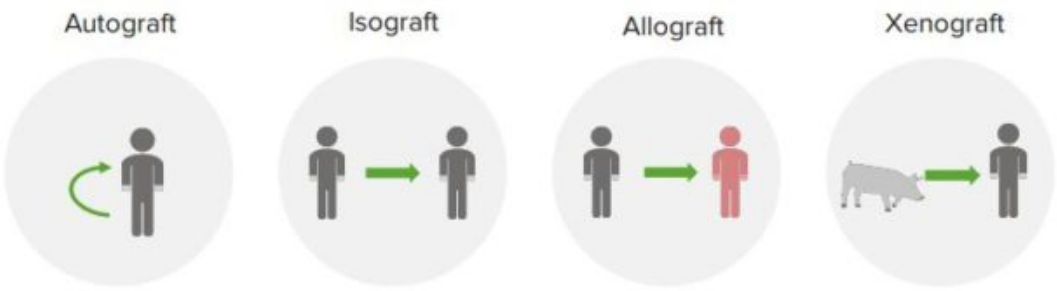
Isografts

They are transplants between two genetically identical individuals, monozygotic twins. They also run a risk of rejection seeing that there are cases of completely identical individuals are not always 100% guaranteed. Thus, even for identical twins immunosuppressant are indicated.

Allografts

They are the most common type of transplants nowadays. They include transplants between genetically non-identical individuals in the same species, human-to-human kidney transplant, for example. Allografts should be matched promptly to lower the risk of rejection, and immunosuppression is usually indicated. Allografts from approved donors are safe, available in large amounts and can readily be used if the two individuals agree on it.

This kind of grafting requires compatibility tests and some people have started it as a business to have tissue banks that have been relied on by many people seeking to find various parts of the body.



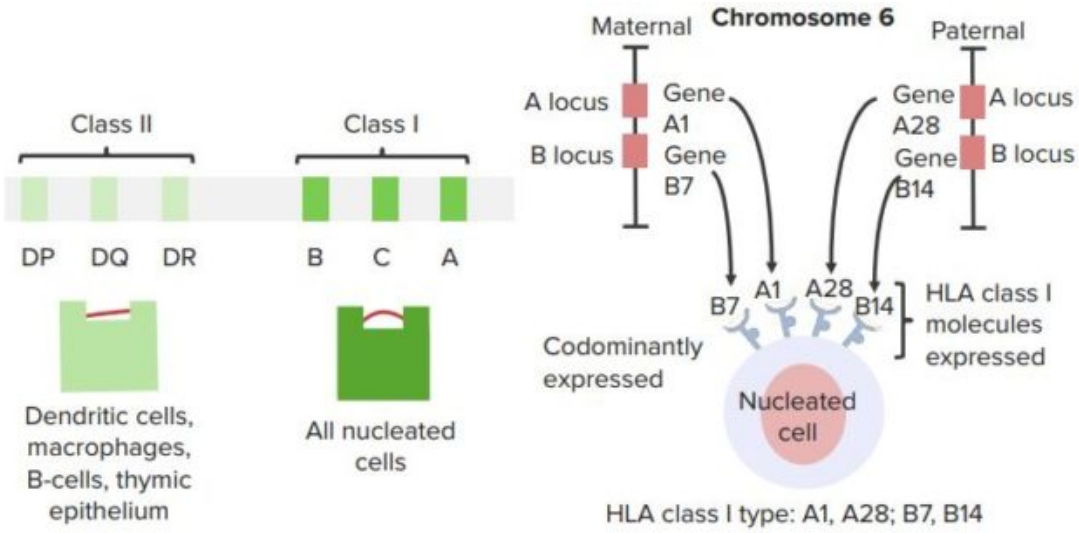
“Classification of Transplantation” Image created by Lecturio

Immunologic Matching Between Donor Organ and Recipient

It is paramount that improper matching is minimized as it will reduce graft rejection which is a loss of valuable tissue that could be implanted on another person. Thus, there is need for many factors for the donor and the recipient to be tested both before and after the transplant. The first identified **antigen** that plays a critical role in the rejection process of transplanted organs is the **major histocompatibility complex**, also known as the **human leukocyte antigen (HLA)**. Transplanted tissues have these surface antigens, which, if matched improperly, allow the recipient’s immune system to identify the tissue as foreign and to attack.

HLA can be classified into three main classes:

- **Class I HLAs** are present on the cell surface of all nucleated cells and are encoded by the HLA-A, HLA-B and HLA-C genes on chromosome 6.
- **Class II HLAs** are mainly present on immune cells such as activated B-cells, macrophages and activated T-cells. They can be also present on the endothelium and on epithelial cells. They are encoded by the HLA-D genes.
- **HLA class III antigens** determine the complement factors C2, C3, and B. Because the HLA-A to D genes are very close to each other, they are usually inherited as one block with minimal cross-over. 25% of siblings are therefore found to be genetically identical for the HLA classes.



"The Major Histocompatibility Complex" Image created by Lecturio

The **ABO system** plays an important role in **blood transfusion** reactions, but ABO incompatibility has a minimal role in solid organ rejection. Tissues that are **highly vascularized,** such as the kidneys, can undergo **hyperacute rejection** in case of ABO incompatibility, hence ABO matching for these transplants might be necessary. ABO matching is necessary as it ensures that there are reduced chances for rejection. With scientific developments, it is not required that people are of the same blood type. **Immunosuppressive therapy** ameliorates this problem.

Donor-recipient HLA matching is extremely important to lower the risk of graft rejection. First, it is important to identify which HLA antigens are expressed on the cell surface of leukocytes from the donor and the recipient and to confirm their matching. HLA proteins found on the surface of every cell and they direct the immune system doesn't trigger a reaction which can lead to a rejection. Each person has their own sets of HLA proteins that do not trigger the immune system but with the introduction of another set of HLA cells the immune system is likely to detect them and react.

Second, one should mix cells from the donor with recipient immune cells and look for any immunologic response to surface antigens. More recently, HLA matching is done via DNA typing which allows for rapid identification of the different HLA antigens the donor's organ might express. Testing cells on the surface and how they react with the introduction of another set is important to give Histocompatibility which in turn offer enough data to test for compatibility between donor and recipient.

To ensure **ABO compatibility**, it is important to do **serologic cross-matching** after HLA matching. The cause of hyperacute rejection, in the case of ABO incompatibility, is performed serum antibodies against ABO surface antigens, which are expressed on the surface of highly vascularized tissues such as the kidneys.

Serum from the recipient is mixed with cells from the donor's organ, and the pathologist should look for any signs of hyperacute rejection. If there is ABO incompatibility, but the patient needs the transplant urgently, and there are no other alternatives, **plasmapheresis** can be used to wash out any preformed antibodies, and the transplantation can be performed after that.

Transplantation of partially HLA compatible bone marrow into a recipient might cause **graft-versus-host-disease,** which can be fatal. This is caused by mature cells that are in the donor's graft that start attacking the recipient's cells. A donor who is

immune competent raises the risks for recipients in blood transfusions as well as stem cells transplants. Recent advances in depleting T-cells in the donor's bone marrow before transplantation lowered the risk of graft-versus-host-disease significantly.

Mechanisms of Transplant Rejection

A solid organ transplant might be rejected by **alloimmune antibodies**, **leukocytes mediated** or **cytokines mediated mechanisms**.

Preformed antibodies are responsible for hyperacute rejection of mismatched ABO organs or for patients undergoing a second transplant from the same donor. The preformed antibodies bind to HLA and ABO antigens in the endothelium, recruit complement factors and eventually lead to the formation of a **thrombus**. Multiple thrombi in the feeding vessels to the transplanted organ eventually result in **necrosis** and rejection.

In case of poorly matched HLA antigens, leukocytes identify the tissue as foreign, and a T-cell mediated immune response starts. T-cells get activated, release different proinflammatory cytokines and recruit CD4+ and CD8+ T-cells in addition to B-cells and other inflammatory cells.

The different immunologically active cells infiltrate the transplanted organ and eventually destroy it. This process can happen in months to years, in case of a partially HLA matched tissue; in weeks, in case of poorly matched tissues, and in days, if the patient had pre-existing anti-donor T-cells due to a previous transplant from the same donor.

Rejection Response

Rejection	Time post-transplant	Basis of rejection
Hyperacute	Minutes	Pre-existing anti-donor antibodies and complement activation
Accelerated acute	1-5 days	Pre-existing anti-donor T-cells
Acute	Weeks	Activation of naive T-cells
Chronic	Months-years	Diverse; can involve antibodies, immune complexes, T-cells, recurrence of disease

Transplantation Immunosuppression Therapy

Radiation therapy and the use of **anti-metabolite agents** usually target **hematopoietic stem cells**. They are recommended before a bone marrow transplantation. Before the transplanted bone marrow starts functioning, the patient is at an increased risk of opportunistic infections due to **cytopenia**. Additionally, patients are at an increased risk of **sterility** and **alopecia** because the formation of sperm and hair is dependent on highly metabolic active cells, which can be affected by anti-metabolite agents or radiation.

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Calcineurin inhibitors such as cyclosporine and tacrolimus are used to inhibit T-cell mediated rejection. Both drugs act by preventing the synthesis of different cytokines known to be responsible for activating and recruiting other leukocytes in the immune response initiated against the grafted organ.

Sirolimus blocks the action of different cytokine receptors, such as interleukin-2, interleukin-4, and interleukin-10 receptors. It can be used in combination with cyclosporine for a synergistic effect. This is a more recent way of suppressing the immune system in a manner that has a limited side effect. It has proven to be more effective in bringing a balance between overimmunosuppression and underimmunosuppression.

Immunosuppression Therapy for Specific Transplants

In **kidney transplantation**, **cyclosporine** is the immunosuppressive of choice to prevent acute and chronic rejection. In case of acute rejection, high dosage **methylprednisolone** can be used to salvage the transplanted kidney. Patients who develop hyperacute rejection should have the transplanted kidney removed.

Liver transplant recipients should be started on **tacrolimus,** followed by **mycophenolate combined with steroids**. This regimen improved survival in patients with liver transplants.

Patients undergoing a **heart transplantation** should be prescribed **prednisone** after the operation, which should be discontinued once the endomyocardial biopsy is completely normalized. **Tacrolimus** should be given after that time-point. It can be combined with **mycophenolate**.

In all the above cases, **anti-Interleukin-2-receptor antibodies** should be used for induction therapy before the transplantation. This has, however, not changed much statistics in terms of rejection rates or even short-term survival rates.

Patients undergoing **bone marrow transplantation** are at the highest risk of developing **graft-versus-host-disease**. It is important to prevent this process from happening in the first place because management of severe graft-versus-host-disease is usually futile.

Prevention is achieved by removing all T-cells from the donor’s bone marrow and blood before the transplantation. Treatment of mild to moderate graft-versus-host-disease includes **steroids**, **cyclosporine**, and **mycophenolate**.

A patient who has an acute rejection to the drug combinations should have it changed or dosage adjusted. It is important that the patient understands that immunosuppressant has very many side effects such as blood pressure.

References

Chinen J, Buckley RH. **Transplantation immunology: Solid Organ and bone marrow.** The Journal of allergy and clinical immunology. 2010;125(2 Suppl 2):S324-S335. doi:10.1016/j.jaci.2009.11.014.

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