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## THE IMMUNOLOGY BEHIND TRANSPLANTATION

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**Abstract:** Transplantation is the process of moving cells, tissues or organs from one site to another for the purpose of replacing or repairing damaged or diseased organs and tissues. It saves thousands of lives each year. However, the immune system poses a significant barrier to successful organ transplantation when tissues/organs are transferred from one individual to another. Rejection is caused by the immune system identifying the transplant as foreign, triggering a response that will ultimately destroy the transplanted organ or tissue. Long term survival of the transplant can be maintained by manipulating the immune system to reduce the risk of rejection. Donor and recipient are carefully matched prior to transplantation to minimise the risk of rejection. They are matched based on their blood group, tissue typing, and how the recipient's blood serum reacts to donor cells. Immunosuppressive drugs are used to prevent and to treat transplant rejection by dampening the overall immune response. However, immunosuppressive drugs are non-specific and leave patients more susceptible to disease as well as being associated with numerous unwanted side effects. Further research on the immunological mechanisms of rejection will help improve cross matching, diagnosis and treatment, as well as facilitating the discovery of novel strategies for preventing transplant rejection.

**Index Terms -** transplantation, antigens; graft; immunology; immunosuppression; rejection; transplant; autograft; xenograft; stem cell; immunosuppression; lymphokines; MHC.

### I. INTRODUCTION

Transplantation is the introduction of biological material (organs or tissues) into an organism. The process of taking cells, tissues, or organs called a graft (transplant), from one part or individual and placing them into another (usually different individual). The donor is the individual who provides the graft and the recipient or host is the individual who receives the graft. The donor and recipient may be at the same location, or organs may be transported from a donor site to another location. Transplantation medicine is a challenging area of modern medicine. Sometimes there are problems of transplant rejection, during which the body has an immune response to the transplanted organ, leading to transplant failure and there is a need to immediately remove the organ from the recipient.

### II. HISTORY

Much of our early knowledge about transplantation rejection was gained during the Second World War when skin grafts were given to treat wounds. Animal experiments led to the first definition of antigens responsible for transplant rejection. Skin grafts were used to treat major wounds acquired during the Second World War, and it was from this experience that the early concept of transplantation rejection was founded. This led to the now widely known fact that transplantation of donor organs/tissues to another individual usually results in rejection, unless histocompatible tissues (based on specific tissue typing) and immunosuppression are used. Early experiments in mice in the 1950s and 60s defined the role of the major histocompatibility molecules in graft rejection. Transplantation is now common medical practice and many different organs/tissues are transplanted.

## Commonly transplanted organs/tissues

### Allografts

Kidney, pancreas, heart  
(heart/lung), skin, cornea,  
bone marrow, liver, blood

### Autografts

Skin, bone marrow

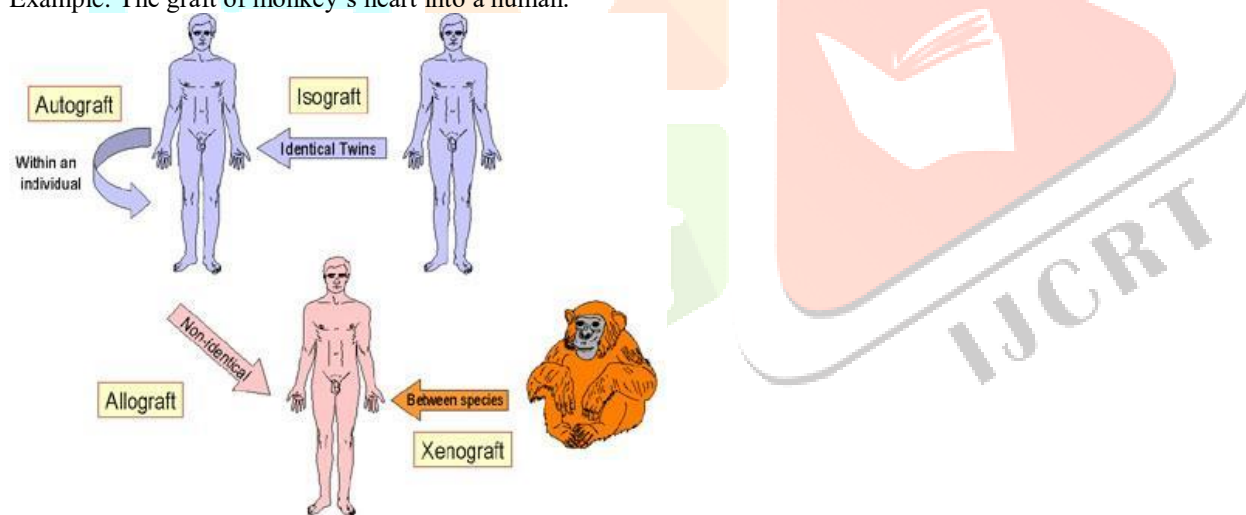
The first accounting of tissue transplantation comes from India, in the fifth century B.C. The legendary surgeon Sushruta (or Susruta) describes nose reconstruction that required collection and transfer of skin from one site to another. Although there is no documentation of success rates, today we know that this type of transfer, called an Autograft, is the most likely to succeed. It was not until 1908 that Alexis Carrel produced a systematic study of kidney transplantation in cats, some of which maintained urinary output for 25 days, establishing that a transplanted organ could carry out its normal function in a new recipient. Then, in 1954, Joseph Murray and colleagues in Boston successfully transplanted a kidney between identical twins. However, it was not until 1961 that success across the histocompatibility barrier was achieved, tackling the obstacle of MHC molecules, or alloreactivity. A team of surgeons led by Dr. Samuel Kountz, an African American transplant surgeon at Stanford, completed the first nontwin, living human transplant: a kidney, from mother to daughter. Their pioneering work with immune suppressants and a new kidney perfusion technique heralded a leap forward in the ability of physicians to imagine transplantation as a cure for disease.

Today, kidney, pancreas, heart, lungs, liver, bone marrow and cornea transplantations are performed among non-identical individuals with ever increasing frequency and success.

## III. CLASSIFICATION OF GRAFTS

The different types of transplant grafts include-

1. **Autograft:** In this type of graft, the tissue is transferred from one body site to another in the same individual.  
Example- Use of healthy blood vessels to exchange blocked coronary arteries.
2. **Isograft:** The transfer of tissue between genetically identical individuals is termed as isograft.  
Example- The transfer of kidney from one monozygotic twin to the opposite.
3. **Allograft:** During this sort of graft, the tissue transfer takes place between genetically non-identical members of same species.  
Example: Skin transplant between two individuals of various genotype.
4. **Xenograft:** The transfer of tissue or organ between different species is termed as xenograft.  
Example: The graft of monkey's heart into a human.



**Fig 1:** A diagrammatic representation of all the four types of grafts

Autografts and isografts are usually accepted, due to the genetic identity between donor and recipient. Tissues that share sufficient antigenic similarity, allowing transfer without immunologic rejection, are said to be histocompatible.

Other types of transplants involve-

**ABO incompatible transplant:** ABO is common term for blood type, which differs among individuals. The key strategy applied for the minimization of transplant rejection is that the matching of blood type between donor and recipient. However, the compatibility is usually not required for transplantations. For instance, ABO transplants are often administered in children with immature immune systems with minimized risk of transplant rejection.

**Stem cell transplant:** Stem cells are capable of giving rise to indefinitely more cells of same type, and from which different other cells arise by differentiation. Hematopoietic stem cell transplants are done to exchange damaged or worn out blood cells. Also, it's employed to treat various sorts of cancer, eg. Leukemia. These stem cells are often obtained either from cord blood or from bone marrow.

#### IV. TYPES OF DONOR

Organ donors could also be living or may have died of cerebral death or circulatory death. Most deceased donors are those who have been pronounced brain dead. Organ donation is feasible after cardiac death in some situations, primarily when the person is severely braininjured and not expected to survive without artificial breathing and mechanical support. Tissue could also be recovered from donors who die of either brain or circulatory death.

In **living donors**, the donor remains alive and donates a renewable tissue, cell, or fluid (e.g., blood, skin), or donates an organ or part of an organ in which the remaining organ can regenerate.

**Deceased donors** are people who have been declared brain-dead and whose organs are kept viable by ventilators or other mechanical mechanisms until they will be excised for transplantation. Apart from brain-stem dead donors, who have formed the bulk of deceased donors for the last 20 years, there's increasing use of donation-after-circulatory-death-donors to increase the potential pool of donors as demand for transplants continues to grow.

#### V. TRANSPLANTATION ANTIGENS

##### Blood type antigens

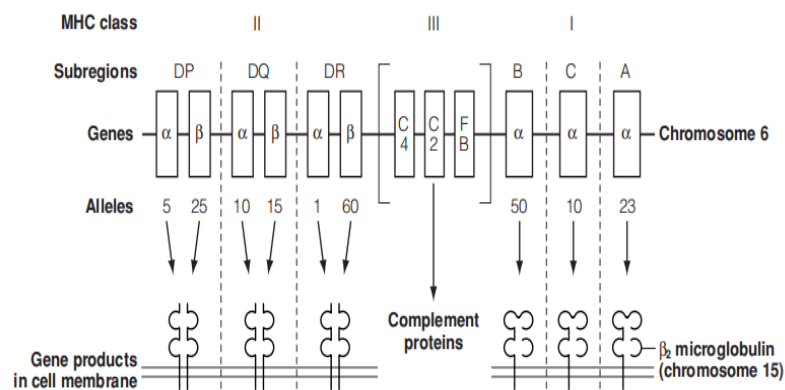
The major blood type ABO antigens are mainly present on the surfaces of erythrocytes and therefore the genes encoding them are polymorphic, i.e. there's more than one allele coding for the gene product. This is often in contrast to most proteins, e.g. albumin, which are coded for by nonpolymorphic genes or genes which lack allelic variation. The major blood type alleles A and B, code for enzymes which create different sugars on proteins and lipids on the surface of erythrocytes. Blood type O may be a null allele and doesn't add sugars. These alleles are inherited in a simple Mendelian inheritance pattern and are codominantly expressed (i.e. both allelic products are expressed on the erythrocyte surface). An individual can either be homozygous (the same) or heterozygous (different) for the inherited alleles. The main problem with transplanting blood is that all of us have antibodies (isohemagglutinins) to these blood type antigens (**Table 1**). The reason for development of these antibodies is unclear, but is perhaps due to cross-reactivity of AB antigens with those of certain ubiquitous microbes. Transplantation of blood to a recipient who has serum isohemagglutinins may result in a severe transfusion reaction mediated by a type II hypersensitivity reaction.

**Table 1:**

Blood group	A	B	AB	O
Genotype	AA or AO	BB or BO	AB	OO
Isohemagglutinins	Anti-B	Anti-A	None	Anti-A and B

##### Major histocompatibility complex antigens

These are the main barrier to transplantation of nucleated cells. MHC molecules are expressed on all nucleated cells of the body and their physiological function is to direct T cells to carry out their function. However, just like the locus coding for the main blood group antigens and unlike the majority of other gene products, genes coding for MHC molecules are polymorphic. In contrast to the ABO system, each MHC locus can encode for a very large number of different allelic forms and to further increase the complexity, there are six different loci. In humans, this locus is found on chromosome 6 and encodes HLA, since the antigens were first discovered in humans on leukocytes. The combinations of the many different allelic forms which are codominantly expressed means that the chances of two individuals having a totally identical set of alleles is extremely remote (1 in 35 million). Thus the different allelic products of the donor organ/tissue will be foreign to the recipient who does not have them and will therefore generate an immune response to them. An example of alleles which may be expressed by donors/ recipients is shown in the table below and the target of the recipient's immune system would be the products of the mismatched alleles.



**Fig 2:** The human major histocompatibility locus. Class I and Class II human leukocyte antigens (HLA) are encoded by three (A, B and C) and six genes (DP, DQ and DR), respectively. Each gene can be coded by many different alleles, the products of which, if different from self, are recognized as transplantation antigens. Thus, there are millions of different combinations of the different allelic products. The class III HLA locus encodes complement proteins.

**Table 2:** Human leukocyte antigens (HLA) alleles of a hypothetical donor and recipient

Locus	Donor	Recipient	Alleles to which the recipient's immune system responds
HLA-A	A2/A2	A6/A2	None*
HLA-B	B21/B26	B23/B8	B21, B26
HLA-C	C5/C8	C9/C4	C5, C8
HLA-DR	DR4/DR6	DR8/DR3	DR4, DR6
HLA-DP	DP3/DP1	DP2/DP1	DP3
HLA-DQ	DQ3/DQ3	DQ4/DQ2	DQ3

\* The recipient's immune system sees A2/A2 as self.

### Minor histocompatibility antigens

There are a number of minor transplantation antigens that include non-ABO blood groups and antigens associated with the sex chromosomes. These are usually 'weaker' than the MHC antigens, and are probably the antigens targeted by the immune system in late onset rejection.

## VI. REJECTION

Rejection is an immune-mediated destruction of transplanted tissue. Rejection are often classified by time-course (hyperacute, acute, or chronic rejection) or underlying mechanism (cell mediated, antibody-mediated). With early detection, treatment with increased immunosuppression is usually successful. Treatment depends on the type of rejection, its underlying cause, and severity. Although acute forms of rejection are usually divided into cellular and humoral types, there are sometimes components of both cellular and antibody-mediated damage in a single tissue specimen. When the immune system confronts a foreign organism, it prepares for attack against it in order to protect the body from infection. Foreign invaders appear in form of small molecules termed as antigens. These molecules, when presented to the immune system, triggers the immune reaction. It stimulates the production of antibodies specific to those antigens and amplifies the immune response. The group of genes that encodes proteins which identifies foreign agents to the immune system is termed as the Human Leukocyte Antigen (HLA) complex. These proteins act as 'self-markers' as they convey immune system not to trigger a response and are present on the surface of every cells. On the basis of genetic makeup, each individual shall have their own specific set of HLA proteins. Any cell unable to display HLA proteins will be identified as non-self by the immune system and will be further responded. The term histocompatibility is used to represent the degree of similarity between the HLA genes of the donor and the recipient. The compatibility between the donor and the recipient depends on the similarity of genetic makeup between them. However, there will always be some extent of rejection even if the donor and recipient are genetically identical. Non-self HLA proteins, other surface proteins on the donor graft can also be recognized as a foreign antigen and forbid an immune response.

### Types of Rejection:-

#### 1. Hyperacute rejection:

The presence of pre-existing antibodies of the recipient, that match the foreign antigens of the donor, triggers an immune response against the transplant and results in this type of rejection. These antibodies could have been produced due to result of previous blood transfusions, previous transplantations or multiple pregnancies. This takes place within minutes or hours after a transplantation. The blood clotting takes place, when antibodies react with cells in the blood vessels of the graft, which will prevent blood supply from the graft yielding an instantaneous rejection of the transplant.

#### 2. Acute rejection:

This takes place within the first 6 months after transplantation. Exception to identical twins, there prevails a point of acute rejections in all transplantations. There is a high risk for the first 3 months for recipients, however rejection can still take place at a later stage. Acute rejection is caused by the formation of antibodies following the detection of non-self antigens in the donated graft. If diagnosed early enough, acute rejection can be treated by suppressing the immune system and permanent damage to the graft can be avoided in some cases.

##### -Acute Cellular Rejection

Acute cellular rejection accounts for 90% of early rejection episodes (ie, those occurring in the first 3 months posttransplantation) and is mediated by the activation and proliferation of T cells. Use of induction antibody therapy may delay the onset of cellular rejection. Moreover, lack of adherence to or intentional withdrawal of maintenance immunosuppression can result in acute cellular rejection even years after transplantation.

##### -Acute humoral rejection

Acute humoral rejection can occur early after transplantation in highly sensitized patients (including those who have been treated with desensitization protocols) or any time after transplantation in patients who develop de novo DSAs. Symptoms are rare and patients usually present with either declining kidney function or an rise in urine protein excretion.

#### 3. Chronic rejection

Repeated episodes of acute rejection can ultimately lead to chronic rejection of the graft and failure of the transplant. Chronic rejection commonly manifests as scarring of the tissue or organ which can occur months to years after acute rejection has subsided. At present, there is no cure for chronic rejection aside from removal of the graft.

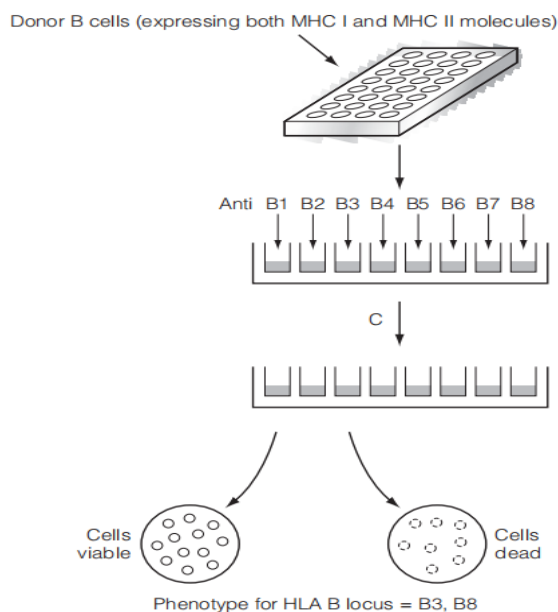
## Xenotransplant rejection

The inadequate supply of donor organs/tissues has led to consideration of animals as donors. In particular, the pig appears to be a suitable source of transplantable tissues since the dimensions of many of the internal organs is comparable with that of man. However, a major unforeseen problem is that pig cells have sugars which are not found on human cells and to which humans have serum IgM hemagglutinating antibodies (similar to the ABO isohemagglutinins). Thus, pig organs are going to be rejected through a hyperacute mechanism due to preformed hemagglutinins which activate complement resulting in lysis of the grafted cells. Strategies planned to prevent this include:

- Trying to inactivate the gene encoding the glycosyltransferase responsible for the sugar residues.
- Introducing genes into the pig which code for molecules which inhibit the lytic component of complement activation.

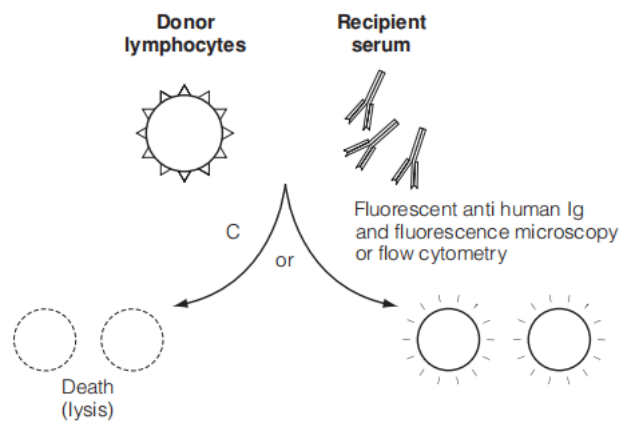
## Prevention of Rejection

- **ABO blood group compatibility-** The donor and recipient are tested for compatible blood groups. This is the first test to be carried out as the transplant will be rapidly rejected if the blood groups do not match. In some transplants, for example young children and also bone marrow transplants, ABO compatibility is not a necessity.
- **Tissue typing** – If a familial donor is not available, then the extent of the mismatches between alleles must be determined by tissue typing, in order to best match donor and recipient. In this context, one among the foremost useful assays involves cytotoxic antibodies (usually mAbs) to individual HLAs. The principal of the antibody method depends on the surface expression of the HLA. Donor and recipient blood for typing are enriched for B cells (they express both class I and II HLA) and specific cytotoxic antibodies are added. Binding of the antibody to a surface HLA in the presence of complement results in the direct killing of the B cells (**Fig. 3**). These can be microscopically scored. Using a panel of antibodies, it is possible to HLA type for the bulk of alleles. Many HLA typing labs are now turning to identification of the HLA genes inherited via molecular genetics based tests that utilize the restriction fragment length polymorphism (RFLP) or polymerase chain reaction (PCR) amplification techniques. These technologies determine the nucleotide sequence of the HLA genes in question and give unequivocal results. Outside its use in tissue typing for transplants, this technology has been particularly important in identifying minor polymorphisms within the HLA-D regions which could be related with susceptibility to particular kinds of diseases. Typing can also be done using the ‘mixed lymphocyte’ reaction also called ‘mixed lymphocyte response’, which primarily identifies HLA-D class II antigens. In this case, ‘typing cells’ (usually cell lines carrying specific homozygous HLA-D allelic products) are treated with a drug to inhibit their proliferation. They are then mixed with the potential recipient’s blood lymphocytes and cultured for 3–5 days. If the recipient’s T cells do not carry the typing cell’s HLA, they will proliferate in response to ‘foreign’ HLA since they will not have been eliminated by negative selection within the thymus. By using panels of typing cells, it is possible to determine the HLA type of the donor and recipient. Matching of HLA for liver transplants does not appear to be of major advantage, probably due to the weak expression of HLA by hepatic cells.



**Fig. 3:** Tissue typing. B cells obtained from the blood of the donor/recipient to be typed are placed in microplates and antibodies to the different MHC allelic products added together with complement.

- **Cross matching** – Blood samples are taken from both the recipient and donor, and therefore the cells of the donor are mixed with the blood serum of the recipient. If the recipient’s antibodies attack the donor cells, they are considered a positive match and transplantation will not be suitable due to increased risk of hyper-acute rejection. Cross-matching is employed to see that there are no preformed antibodies to donor HLA in the recipient. Blood lymphocytes from the donor are mixed with serum from the recipient (**Fig. 4**). Anti-donor antibodies are detected by lysis of the cells or by using fluorescent staining and flow cytometry. The presence of such antibodies is contradictory to the use of the tissues from that donor. Crossmatching for blood groups is also important for renal transplants.



**Fig. 4.** Cross-matching. Serum from the potential recipient is mixed with donor lymphocytes and is evaluated for lysis, in the presence of complement, or stained with fluorescent antibodies to human immunoglobulin and assayed by fluorescence microscopy or flow cytometry. Dead cells or positive fluorescence signifies the presence of antidonor antibodies which could lead to a hyperacute rejection of the graft. This is contradictory to the use of this donor/recipient combination. This assay identifies HLA antibodies in the recipient serum.

- **Panel reactive antibody test** – The blood serum of patients awaiting transplantation are tested for reactive antibodies against a random panel of cells. Previous exposure to foreign tissue, by blood transfusion, pregnancy or prior transplantations, are likely to increase the number of HLA antibodies in the blood. The more HLA antibodies present, the higher the panel reactive antibody (PRA) level denoted to the patient, and the greater the chance of graft rejection. If PRA levels are high, it may be more difficult to find a match and a better dosage of immunosuppressive drugs may be required.
- **Serology screening** – For patients undergoing stem cell transplantation they and their donor will undergo pre-transplant serology screening. This is undertaken to detect the immune status of both the donor and a potential recipient against a number of clinically significant infectious organisms, including viruses like HIV, Cytomegalovirus (CMV), and Epstein-Barr Virus (EBV), thus determining potential for re-infection or reactivation of the infection upon immunosuppression. Individuals are often matched according to the CMV and EBV status.

## VII. THE ROLE OF LYMPHOKINES IN REJECTION

In addition to the role of CD4<sup>+</sup> TH cells, a multiplicity of immunological mechanisms including lymphokines are involved in the process of rejection. The most important lymphokines in cellular rejection are interleukin-2 (IL-2), which is required for activation of T<sub>c</sub> cells, and IFN $\gamma$ , which induces MHC expression, increases APC activity, activates large granular lymphocytes and, in concert with lymphotoxin, activates macrophages. Macrophages, in turn, release TNF $\alpha$ , an important mediator of graft damage. Lymphokines (IL-4, -5 and -6) are also required for B-cell activation, leading to the production of anti-graft antibodies. These antibodies fix complement and cause damage to the vascular endothelium, resulting in haemorrhage, platelet aggregation within the vessels, graft thrombosis, lytic damage to cells of the transplant, and the release of the pro-inflammatory complement components, C3a and C5a. The critical targets are the vascular endothelium of the microvasculature and the specialized parenchymal cells of the organ, such as renal tubules, pancreatic islets of Langerhans or cardiac myocytes. IFN $\gamma$  can cause vascular endothelial cells to express high levels of class II MHC molecules, and can induce the expression of class I and II molecules on parenchymal cells, which usually express little or none of those. This upregulation of MHC expression on cells of the graft can provoke greater stimulation of the rejection response and provide a greater number of target molecules within the graft for antibodies and activated cells. Lymphotoxin and IFN $\gamma$  also upregulate the expression of adhesion molecules on vascular endothelium, these are required for the adhesion of blood-borne leucocytes to the walls of blood vessels prior to their migration across the endothelium into the tissues.

## VIII. THE ROLE OF T-HELPER CELLS IN REJECTION

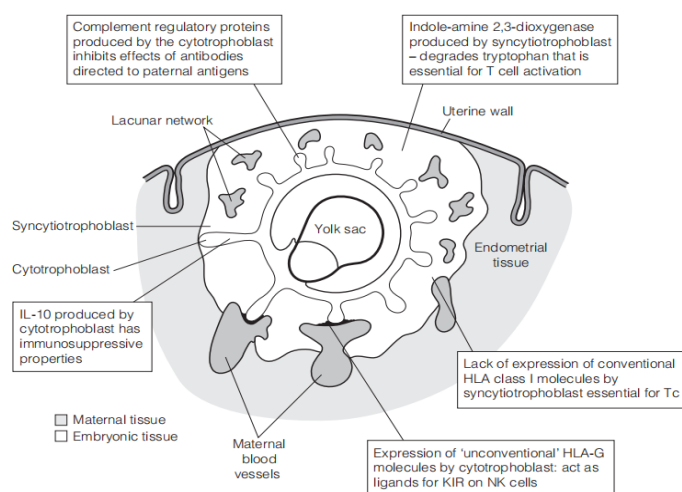
Injecting T cells of the CD4<sup>+</sup> subpopulation (TH cells) into nude or ATx. BM recipients leads to acute skin-graft rejection. Naïve, unsensitized CD8<sup>+</sup> T cells (T<sub>c</sub> cells) are unable to do this, but when CD8<sup>+</sup> T cells are mixed with a very low number of CD4<sup>+</sup> T cells, or are presensitized to graft antigens (i.e. taken from animals which have already rejected a graft), rapid graft destruction is then seen. Treating recipients with monoclonal anti-CD4<sup>+</sup> antibodies confirms the importance of TH cells in rejection. TH cells are activated by APCs derived from bone marrow and carrying MHC class II molecules. The APCs activating rejection can come from either the donor or the recipient. Those of donor origin are present within the graft as 'passenger leucocytes' (interstitial dendritic cells) and they cause 'direct' activation of the recipient's TH cells. Those of recipient origin are located in draining lymphoid tissues and acquire antigen that is shed from the transplant, and present it to the recipient's TH cells to cause 'indirect' activation. Direct activation is a more powerful stimulus to rejection than the so-called indirect route (**Figure-5**). Thus passenger cells may have a strong influence on graft survival.

A comparison of direct and indirect antigen presentation		
	Direct antigen presentation	Indirect antigen presentation
General comment	Abnormal situation restricted to recognition of transplanted tissues	Normal physiological route of antigen processing and presentation
Origin of antigen presenting cells	Donor	Recipient
Antigen recognised by recipient T cells	Donor MHC plus donor and 'neo-self' peptides	Recipient MHC plus donor peptide
Frequency of the activated T cells	1/1000 to 1/10 000	1/100 000 to 1/1000 000
Function of the activated T cells	Produce cytokines No cognate interaction with B cells	Produce cytokines Provide cognate help for B-cell activation and antibody formation
Tc cells	Can kill cells in the graft because they recognize donor MHC + peptide in the transplant	Cannot kill cells in the graft because they do not recognize antigens expressed on donor cells
Duration of stimulus	Donor APC (passenger leucocytes) are normally lost from the graft within days, therefore their influence is short-lived*	Continues for as long as the graft (source of donor peptide) survives, and can therefore stimulate chronic rejection

**Figure-5** Direct presentation of alloantigens stimulates a very powerful rejection response because of the large number of recipient T cells that may become activated. However, the T cells activated may act in different ways, and the stimulus through the direct route of alloantigen presentation is likely to be of limited duration.

## IX. FETAL TRANSPLANT

The fetus is a chimera carrying HLA alleles from both parents. It is therefore effectively an allograft in close apposition to maternal tissues. The main potential mechanisms for prevention of rejection are shown in the below figure for a recently implanted embryo (day 14), but also play an important role throughout gestation.



**Fig 6:** Mechanisms for preventing the rejection of an embryonic/fetal allograft. During pregnancy, there is a bias towards a Th2 response mediated through estrogen and progesterone, and this is also thought to contribute to the maintenance of the fetal allograft.

## X. IMMUNOSUPPRESSIVE THERAPY

### ❖ Generalized Immunosuppressive Therapy

Immunosuppressive therapy is widely used to aid organ transplants. Patients' bodies sense a foreign object and their immune system attacks it. The drugs help eliminate the risk of the patient rejecting the new organ. Immunosuppressive therapy is a drug regimen that patients use to lower their bodies' immune response. Immunosuppressants stop your immune system from damaging healthy cells and tissues. People with organ transplants and stem cell transplants take these medicines to prevent transplant rejections. The drugs also treat autoimmune disease symptoms. Immunosuppressants are powerful drugs that require careful monitoring to avoid problems. The body's immune system helps fight off infections that cause illness. But sometimes, the immune system mistakenly attacks healthy cells and tissues. Immunosuppressants can slow or stop this response.

When you have an autoimmune disease, the immune system mistakes healthy tissue and cells for foreign invaders (like germs). The immune system essentially turns against the body and attacks it. Depending on which part of the body is under attack, this response can lead to different types of autoimmune diseases. Immunosuppressants hold back the immune system, helping to prevent cell damage and inflammation. These drugs minimize symptoms. They can even put an autoimmune disease into remission (you have no signs of the disease).

You may need immunosuppressants if you have got one of these autoimmune diseases:

- Alopecia areata.
- Inflammatory bowel disease, including Crohn's disease and ulcerative colitis.
- Lupus.
- Multiple sclerosis.
- Psoriasis or psoriatic arthritis.
- Rheumatoid arthritis.

### Types of immunosuppressants include:

- Biologics such as adalimumab (Humira®) and infliximab (Remicade®).
- Calcineurin inhibitors such as tacrolimus

- Corticosteroids (prednisone).
- Inosine monophosphate dehydrogenase (IMDH) inhibitors such as mycophenolate mofetil (CellCept®).
- Janus kinase inhibitors such as tofacitinib (Xeljanz®).
- Mechanistic target of rapamycin (mTOR) inhibitors such as sirolimus (Rapamune®).
- Monoclonal antibodies such as basiliximab.

Immunosuppressants can have powerful effects on the body. The healthcare provider will order regular blood tests to make sure medication levels don't get too high. High doses can cause serious side effects. Side effects vary depending on the type of immunosuppressant. These drugs can cause:

- Acne.
- Diabetes.
- Fatigue.
- Hair loss or growth.
- Headaches. Trouble concentrating or remembering.
- High blood pressure.
- Mouth sores.
- Thinning bones (osteoporosis).
- Tremors.
- Weight gain.
- Stomach upset and nausea and vomiting.

### ❖ Specific Immunosuppressive Therapy

Immunosuppressive therapy is a drug regimen that patients use to lower their bodies' immune response. These drugs help doctors stop the immune system from overreacting and damaging transplanted organs and tissues. Most everyone has to take immunosuppressant drugs when receiving an organ transplant.

1. Calcineurin Inhibitors: Tacrolimus and Cyclosporine.
2. Antiproliferative agents: Mycophenolate Mofetil, Mycophenolate Sodium and Azathioprine.
3. mTOR inhibitor: Sirolimus.
4. Steroids: Prednisone.

Immunosuppressants can be divided into classes including calcineurin inhibitors, interleukin inhibitors, selective immunosuppressants and TNF alfa inhibitors. Immunosuppressants that do not fit into these classes are categorized as other immunosuppressants. Selective immunosuppressive agents are drugs that suppress the immune system due to a selective point of action. They are used to reduce the risk of rejection in organ transplants, in autoimmune diseases and can be used as cancer chemotherapy.

Immunosuppressive drugs can be classified into five groups:

- glucocorticoids
- cytostatics
- antibodies
- drugs acting on immunophilins
- 

Immunosuppressive drugs and their mechanisms of action and side effects:-

Immunosuppressive drug	Mechanism of action	Side effects
Antithymocyte globulin	Blocks T cell membrane proteins, resulting in T cell depletion	Cytokine-release syndrome Lymphopenia Increased risk of post-transplant lymphoma
Alemtuzumab (CAMPATH-1H)	Directed against CD52, thereby depleting T cells, B cells, NK cells and monocytes	Cytokine-release syndrome Lymphopenia Autoimmune phenomena
Rituximab	Directed against CD20, inducing B cell depletion	Infusion-related reactions
Basiliximab	Directed against CD25, thereby inhibiting IL-2-induced T cell proliferation	Hypersensitivity reactions
Daclizumab	Directed against CD25, thereby inhibiting IL-2-induced T cell proliferation	Withdrawn from market due to reports of serious inflammatory brain disorders
Belatacept	Blocks co-stimulation by binding to CD80 and CD86 receptors on APCs and thereby prevents binding to CD28 on the T cell	Increased risk of post-transplant lymphoproliferative disease Bone marrow suppression Hypertension Dyslipidemia
Azathioprine	Inhibits purine synthesis, resulting in reduced T cell proliferation	Leukopenia and thrombocytopenia Nausea and vomiting Hepatotoxicity Increased incidence of malignancies



## XI. GRAFT VS HOST REACTION

In some instance the graft tissue elicits an immune response against host antigen and that immune response is called graft versus host reaction. Graft versus host reaction brings damage to host cells and host. When grafted tissue has mature T cells, they will attack host tissue leading to Graft VS Host Reaction (GVHR). It is a major problem for bone marrow transplant.

### Methods to overcome GVHR:

- Treat bone marrow to deplete T cells.
- Use autologous bone marrow.
- Use umbilical cord blood

Graft-vs-host disease can occur in the special case in which immunocompetent tissue (fresh whole blood, thymus, or bone marrow) is transplanted into an immunocompromised host. T cells from the transplant recognize the host MHC molecules as nonself and attack the host. This is a type IV hypersensitivity reaction; antibody plays no role at all. Graft rejection is due to the reaction of the host to grafted tissue ( host – versus- graft response ) In contrary Graft mounts an immune response against the antigens of the host ( GVH ).

### GVH reaction occurs when:

- 1 The graft contains immunocompetent T cells
- 2 The recipient possesses transplantation antigens that are absent in the graft.



Fig 7: Graft vs Host Disease

### Mechanism of GVHR-

- Graft lymphocytes aggregate in the host lymphoid organs
- Graft lymphocytes are stimulated by the host lymphocyte
- Stimulated lymphocytes of graft produce lymphokines
- Lymphokines activate host T- cell which produce polyclonal b-cell activation
- Activated b-cell react with the self antigens and cause damage to the host cell

### Clinical Symptoms of GVHR-

- Skin rash
- Emaciation ( becoming thin)
- Retarded growth
- Diarrhoea
- Hepatomegaly
- Splenomegaly
- Increase in bilirubin production
- Bileducts are damaged
- Anaemia

## XII. FUTURE TRANSPLANT THERAPIES

The research in the nearest future is going to be focused on tolerance induction, inhibition of alloreaction in blood-group discordant transplants (in immunized patients) and xenografts. In parallel, studies on hybrid and totally artificial, implantable devices (artificial pancreas and liver) will be carried on. Kidney transplants are the most common type of transplant surgery; the least common single-organ transplants are the intestines.

Current methodologies of solid organ-derived cell transplant therapies introduce donor cells into hosts through a vascular route, a strategy modeled after hematopoietic therapies. These strategies fail due to inefficient engraftment, poor survival of the cells, and propensity for formation of life-threatening emboli. Transplant success necessitates grafting methods, requiring a mixture of appropriate cell sources embedded into or onto precise mixes of extracellular matrix components and then localized to the diseased or dysfunctional tissue, promoting necessary proliferation, engraftment, and vascularization. Grafting technologies are rapidly translatable to therapeutic uses in patients and provide alternative treatments for regenerative medicine.

**Organ bioengineering and regenerative medicine:** The field of tissue engineering is evolving rapidly and is opening new horizons for novel treatment opportunities. Tissue engineering and regenerative medicine includes artificial and biological materials. Whole organ decellularization and recellularization have gained importance in recent years. Decellularization, as the name implies, means the removal of all cellular components from the organ and at the same time, the micro and macro anatomy of the extracellular matrix is preserved. These scaffolds are repopulated with patient- derived cells or stem cells to construct an individual specific organ. Consequently immunosuppression is no more needed. Bioreactors are used for decellularization and recellularization. The technology used for organ bioengineering includes seeding cells on supporting scaffolding materials. A wide variety of human tissues and organs have been decellularized for tissue engineering. These include cartilage, bone, skeletal muscle, tendon, adipose tissue, heart, arteries and veins, gingiva, cornea, vocal folds, peripheral nerves, intestine, liver, pancreas, kidney, bladder, male and female reproductive systems, products of child birth and complex composite structures. Decellularization requires efficient removal of immunogenic cellular materials and maintenance of nonimmunogenic extracellular matrix. Human tissues are harvested from cadavers and surgery. An advantageous point is the fact that extracellular matrix derived from decellularization of a certain tissue may be used for tissue engineering of another tissue type. Organ bioengineering aims to develop extracorporeal systems to compensate or completely replace the functions of a diseased organ. As an example, an extracorporeal method designed to substitute liver function should have the capacity to detoxify, synthesize, and regulate. The artificial liver support system has beneficial effects on the prognosis of patients with acute-on-chronic failure. These beneficial effects are generated by improving jaundice, ameliorating hemodynamic instability, reducing portal hypertension, and improving hepatic encephalopathy.

### XIII. LAWS AND ETHICAL CONCERNS

The Indian government has had difficulty tracking the flourishing organ black market in their country, but in recent times it has amended its organ transplant law to form punishment more stringent for commercial dealings in organs. It has also included new clauses in the law to support deceased organ donation, such as making it mandatory to request for organ donation in case of brain death. Other countries victimized by illegal organ trade have also implemented legislative reactions. However, doctors in other countries, such as the United Kingdom, have accused China of abusing its high capital punishment rate. Despite these efforts, illegal organ trafficking continues to thrive and can be attributed to corruption in healthcare systems, which has been traced as high up as the doctors themselves in China and Ukraine, and the blind eye economically strained governments and health care programs must sometimes turn to organ trafficking.

The existence and distribution of organ transplantation procedures in developing countries, while almost always beneficial to those receiving them, raise many ethical concerns. Both the source and method of obtaining the organ to transplant are major ethical issues to consider, as well as the notion of distributive justice. The World Health Organization argues that transplantations promote health, but the notion of "transplantation tourism" has the potential to violate human rights or exploit the poor, to have unintended health consequences, and to provide unequal access to services, all of which ultimately may cause harm. Regardless of the "gift of life", within the context of developing countries, this might be coercive.

### XIV. CONCLUSION

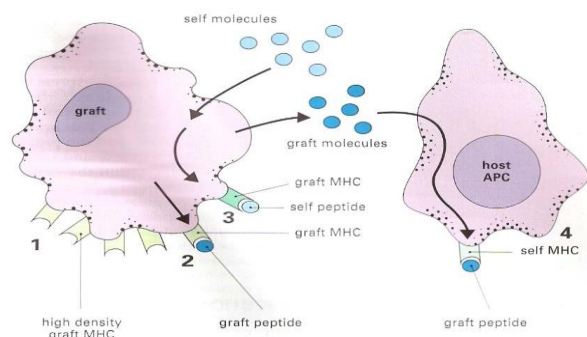
The immunobiology of transplantation is important for many reasons, in terms of both its impact on our understanding of immunological processes and its application in the development of clinical transplantation. It was the study of mouse skin-graft rejection that led to the discovery of the major histocompatibility complex (MHC) molecules, which function in the presentation of antigens to T cells. T cells are pivotal in transplant rejection, and much of our knowledge of T cell physiology and function, of self tolerance and autoimmunity, and of the role of the thymus in T cell destruction, is derived from studies of transplantation. Last, but not least, transplantation of tissues is very important clinically. The need to prevent transplant rejection has led to the development and use of new tolerance of the grafted tissues. These approaches also have a more general application in the treatment of various immune disorders, such as immune-mediated tissue damage in hypersensitivity and autoimmunity. In clinical practice, organs are transplanted to make good a functional deficit (**Table 3**)

**Clinical transplantation**

Organ transplanted	Exaples of disease
Kidney	End-stage renal failure
Heart	Terminal cardiac failure
Lung or heat/lung	Pulmonary hypertension, cystic fibrosis
Liver	Cirrhosis, cancer, biliary atresia
Cornea	Dystrophy, keratitis
Pancreas or islets	Diabetes
Bone marrow	Immunodeficiency, leukaemia
Small bowel	Cancer
Skin	Burns

**Table 3:** Organs and tissues are transplanted to treat various conditions. Each type of transplant has its own particular medical and surgical difficulties.

Unless the donor and recipient are genetically identical, the graft antigens will elicit an immunological rejection response. Transplantation can stimulate all of the various active mechanisms of humoral and cellular immunity, both specific and non-specific. This is a consequence of the recognition by the recipient's T cells of large numbers of foreign and 'neo-self' peptides associated with the foreign MHC molecules on the grafted cells and of graft-derived peptides bound to self MHC (**Figure-8**).



**Figure-8:** There are several ways in which grafts and graft antigens can be recognized by T cells in the host. This may account for the relatively high proportion of host T cells which is capable of responding to engrafted tissue.

1. A high density of graft MHC molecules, which individually react weakly with the TCR may generate a sufficient signal for T cell activation.
2. Graft MHC molecules can present the graft's own peptides including molecules from both major and minor histocompatibility antigens.
3. Graft MHC molecules can present processed antigens of host molecules. Because the graft MHC is different to self MHC it will present a different set of peptides to the host, and the host will not be tolerant of this MHC/antigen combination.
4. Allotypically different graft molecules, including histocompatibility antigens can be taken up by host antigen presenting cells, and be processed and presented on self MHC molecules. Also, a transplant can activate all the regulatory mechanisms that control immune responses causing a state of unresponsiveness to the graft. Hence, transplantation immunology encompasses virtually all aspects of immune function.

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